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Vascular correlates of cognitive performance in a community based elderly population

Doctor in Medicine

2010

Dr. Ai- Vyrn Chin

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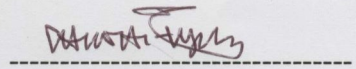

(Ai- Vyrn Chin)

1st January 2010

Vascular correlates of cognitive performance in a community based elderly population

Dr. Ai- Vyrn Chin

"A Thesis submitted for the degree of Doctor in Medicine in the faculty of Medicine, Trinity College, Dublin, Ireland"

1st January 2010

Abstract

Title

Vascular correlates of cognitive performance in a community based elderly population.

Introduction

Population studies suggest that cardiovascular risk factors may be associated with cognitive impairment. Epidemiological studies evaluating individual markers of vascular disease as a risk factor for cognitive dysfunction have yielded inconsistent results. Existing studies have largely examined individual vascular risks in isolation and have tended to ignore patient psychological status when adjusting for potential confounds and concentrated on patient biophysical factors.

Objective

The objective was to investigate the correlations between biomarkers and risk factors of vascular disease and cognition in a community dwelling non-demented elderly population while adjusting for vascular and non- vascular confounds.

Methods

A random sample of elderly subjects above 65 years were visited in their own homes on a single occasion. Each assessment included medical, psychiatric, social and neuropsychological evaluation. In addition blood samples were obtained for analysis.

Results

There were 466 subjects, 208 (44.6 %) male with mean (s.d.) age 75.45 (6.055) years. In addition to established covariates age, education and social class, other biophysical and psychosocial factors such as alcohol use, tea intake, depression, life satisfaction, past history of stroke, personality type, intake of fruit and use of psychotropic medication were all found to be associated with global cognitive performance.

Homocysteine was consistently associated with poorer performance in tests assessing visual memory, verbal recall and psychomotor processing speed. DM was independently associated with slower psychomotor processing speed and poorer global cognition. Higher total cholesterol levels and no previous history of BP were associated with poorer global cognition when psychosocial factors were adjusted for. There were no consistent significant correlations between CRP, glycosylated haemoglobin and smoking status and cognitive performance.

Conclusion

Homocysteine and DM were associated with poorer function in a number of domains on neuropsychological testing whereas higher total cholesterol and no previous history of BP were associated with poorer global cognition. This was independent of other vascular and non- vascular confounds. These potentially modifiable vascular biomarkers and risk factors may be important markers for cognitive dysfunction in the elderly. No other vascular factors were associated with cognitive performance. Other biophysical and psychosocial factors may need to be taken into account as potential confounds in future studies investigating cognition.

Acknowledgements

My thanks to

All the participants.

Dr. Henry O'Connell, Ms. Fiona Hamilton, Professors Davis Coakley, Bernard Walsh, Brian Lawlor, Drs. Robert Coen, Cathal Walsh, David Robinson and Ms. Irene Bruce.

Dr. Conal Cunningham

My Family

This study was funded by Mercer's Institute for Research on Ageing.

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Appendices

List of Tables/ Statistical models

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List of Diagrams

List of Abbreviations

ACCORD- MIND	Action to Control Cardiovascular Risk in Diabetes- The Memory in Diabetes substudy
AD	Alzheimer's Disease
AFIB	Atrial Fibrillation
APOE e4	Apolipoprotein E Epsilon 4
BMI	Body Mass Index
BP	Blood Pressure
↑BP	Hypertension
SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
CESD	Centre for Epidemiologic Studies Depression Scale
CI	Confidence Interval
CIG	Current Cigarette Smoker
CRP	C- Reactive Protein
DM	Diabetes Mellitus
DSC	Digit Symbol Coding
DWR	Delayed Word Recall test
EPI	Eyesenck Personality Inventory
FAS test	Letter (F,A,S) fluency test
GC	Global Measure of Cognitive Performance
HbA1c	Glycosylated Haemoglobin
HOM	Homocysteine
HPS	Heart Protection Study

IQ	Intelligence Quotient
Lipids HDL	High Density Lipoprotein
LDL	Low Density Lipoprotein
TC	Total Cholesterol
TG	Triglycerides
LNS	Letter Number Sequencing
LSI	Life Satisfaction Index
MCI	Mild Cognitive Impairment
MMSE	Mini Mental State Examination
NA	Data Not Available
NART	National Adult Reading Test
NIDDM	Non Insulin Dependent Diabetes Mellitus
NSAIDs	Non- Steroidal Anti-inflammatory Drugs
OR	Odds Ratio
PROSPER	Pravastatin in elderly individuals at risk of vascular disease trial
PROGRESS	Perindopril protection against recurrent stroke study
RIP	Passed away
SCID	Structured Clinical Interview for DSM Disorders
SD	Standard Deviation
SHEP	Systolic Hypertension in the Elderly Project
VaD	Vascular Dementia
WAIS-III	Wechsler Adult Intelligence Scale – III.
WMS-R	Wechsler Memory Scale – Revised.
WMS-III	Wechsler Memory Scale – III.

Chapter One

1.1 Introduction

"Except our own thoughts, there is nothing absolutely in our power.
I think; therefore I am."

Rene Descartes, Discourse on Methods [1]

These words, written over two centuries ago to try to prove the existence of self have become foundational elements in western philosophy. Personal identity, the identification of self, depends on one's self- awareness, which in turn depends on one's cognitive ability. If we lose our ability to think, we lose our personal identity. We remain the same person only if we are conscious of our past and future thoughts and actions in the same way as we are conscious of our present thoughts and actions [2]. Loss of identity however, is only one aspect of cognitive loss. Poor cognitive performance is associated with poorer physical functioning [3], increased risk of dementia [4] and subsequent loss of independence [5]. Cognitive impairment in the elderly contributes significantly to institutionalisation, independent of socio-demographic status, social network or functional status [6]. Increases in life expectancy these past decades have therefore brought a new challenge for the medical profession- a worldwide epidemic of cognitive decline in the ageing population.

It is paramount therefore to identify risk markers and suitable preventative strategies of cognitive decline. However, despite advances in our understanding of neurobiological and neurochemical changes in conditions associated with cognitive decline and dementia, the exact sequence of events resulting in cognitive impairment is still poorly understood.

Vascular disease, a common problem in the elderly, may be a possible risk factor for cognitive decline [7, 8]. There is evidence to suggest that vascular risk factors predispose to the development of vascular dementia and that they may also independently increase the risk of developing Alzheimer's disease [9] although this has not been universal [10]. Subjects with cardiovascular risks have been shown to have greater changes in brain morphology on MRI independent of age or genetic effects [11]. Traditional risk factors for cardiovascular disease in the elderly such as hypertension [12, 13], diabetes [14] and smoking [15] have been independently associated with an increased risk of Alzheimer's disease and vascular dementia [16-21]. In addition, biomarkers such as homocysteine [22], C- reactive protein [23, 24] cholesterol [25, 26], and glycosylated haemoglobin [27] which have been shown to be independent risks for vascular disease have also been associated with cognitive decline and dementia [28-33]. These findings challenge our current understanding of the pathogenesis of dementia and the role vascular disease may play in its aetiology.

There are few strategies available for the prevention of cognitive impairment in the older person. In view of the uncertainty as to the role vascular risk factors may play in cognitive performance and the development of cognitive impairment, modifying risk factors of vascular disease may be one such strategy. Biomarkers of vascular disease may therefore be important predictors of cognitive performance and potential decline. Although a number of studies have attempted to identify specific vascular risk factors for dementia in different communities, the majority of these studies have largely examined individual vascular risks in isolation. It is possible that individual vascular risk factors or biomarkers may influence each other [34, 35], leading to either over or under estimation of their individual effects on

cognition. In addition, attention needs to be paid to other patient factors that may also influence observed associations between vascular risks, vascular biomarkers and cognition. For example, medications used for prevention or treatment of vascular risks may also have an impact on cognitive performance [36] or other vascular risks [37, 38].

Furthermore, psychosocial and lifestyle factors have been shown to have an effect on cognition [39-41] as well as vascular risk factors [42-44]. While associations between vascular biomarkers and cognitive impairment have been described, the role of potential confounds such as lifestyle and personality, have not. The impact of vascular risk factors on cognition may therefore be mediated by psychosocial factors. Existing epidemiological studies have tended to ignore patient psychological status when adjusting for potential confounds and concentrated on patient biophysical factors. Therefore the possibility that the association between vascular risks and cognition identified in previous epidemiological studies were confounded or modified by other vascular risk factors or psychosocial factors cannot be excluded. This is important in light of evidence suggesting misidentification of beneficial effects of anti-oxidants and oestrogen hormone replacement therapy in vascular disease by several large epidemiological studies [45-47]. These most likely arose as a result of inadequate controlling for disease avoiding behaviours that were associated with use of vitamin supplementation or hormone replacement.

The potential for prevention of cognitive decline and dementia through modifying vascular risk factors is therefore dependent on understanding the effects of these factors on cognition both individually and collectively, taking into account potential confounders. Such information will provide insights into how risk factors

of vascular disease are associated with cognition. It may also help identify individuals at high risk of cognitive decline as well as primary and secondary interventional strategies important in the prevention of or delay in cognitive decline.

Although a large number of vascular risk factors have been identified [48], this study has concentrated on investigating risk factors and biomarkers which are highly prevalent in the elderly, strong risk factors for vascular disease (and therefore may account for a large proportion of the attributable risk for cognitive impairment) and amenable to modification, specifically hypertension, Diabetes Mellitus, smoking, homocysteine, C-reactive protein, cholesterol and glycosylated Haemoglobin. To date no published studies have looked at the interacting effects of all of the previously named vascular biomarkers and risk factors together while measuring aspects of lifestyle, personality and mood in addition to the more traditional factors such as education, social class, gender and age. This may be important as subjects are exposed to all these factors simultaneously and significant interaction between these factors may lead to attenuation (or negation) of any associations in practice.

This study was performed therefore to address these areas of uncertainty- to determine if cognition in a population sample of non- demented older Irish people living in the community is associated with cardiovascular risks (specifically Hypertension, Diabetes Mellitus and smoking) and biomarkers (specifically Homocysteine, C- Reactive Protein, Cholesterol and glycosylated Haemoglobin) independently of psychosocial and biophysical factors.

1.2 Aims

The Aim of this study:

To examine the relationship between vascular risk factors, vascular biomarkers and cognition in a population sample of older Irish people living in the community using a comprehensive battery of physical, social, psychological, biological and cognitive measures in order to determine if these vascular risk factors and biomarkers are associated with cognitive performance independent of psychosocial and biophysical factors.

The vascular risks investigated were hypertension, diabetes and smoking. The biomarkers investigated were homocysteine, C- reactive protein, lipid profiles and glycosylated haemoglobin. The physical and psychosocial factors investigated were age, gender, social class, education, depression, anxiety, life satisfaction, personality (introversion-extroversion, neuroticism), medications (statins, NSAIDs, antihypertensives, antipsychotropics), alcohol, tea, cardiovascular disease and stroke, exercise, body mass index and diet (fruits, fish, vegetables).

1.3 Objectives

The objectives of this study are to test the null hypotheses as stated below:

1. Vascular biomarkers and risk factors are not associated with cognitive performance.
2. Physical and psychosocial factors do not influence associations between vascular risk factors and biomarkers and cognition.

Chapter Two

Review of Literature

2.1 Vascular Biomarkers

2.1.1 Homocysteine

Homocysteine (2-amino-4 mercaptobutanoic acid) is a sulphur- containing amino acid that acts as an intermediate in methionine biosynthesis. Metabolism is via two pathways: remethylation and transulfuration (Diagram 1). Inborn errors of homocysteine metabolism are rare and were first described by Carson and Neill in 1962 who reported two siblings with homocystinuria whose clinical presentation included mental retardation, skeletal abnormalities and lens dislocation [49]. The normal range of plasma homocysteine is 5-15 μmol/ L. The prevalence of hyperhomocysteinaemia (plasma levels >15 μmol/ L) in the general population range between 5- 10% [50], increasing to 30% in the elderly [51]. High homocysteine levels have been associated with various factors such as increasing age, gender, smoking status, higher coffee consumption, lack of exercise, alcohol intake, serum creatinine levels, hypothyroidism and nutritional deficiencies in vitamin cofactors required for homocysteine metabolism such as folate, vitamins B12 and B6 [52-55].

Elevated total homocysteine is recognized as an independent risk factor for cerebrovascular disease [56] including silent brain infarcts [57, 58] and as such, has been implicated in vascular dementia. In addition, elevated homocysteine levels have been associated with brain atrophy in a healthy elderly population [59], supporting the suggestion that homocysteine has a neurotoxic effect, either directly or via its metabolites.

Case- control studies comparing homocysteine levels between subjects with dementia and healthy controls have all shown an association between higher homocysteine levels and dementia [60-63] except for one study that showed an association with VaD but not AD [64].

The majority of cross- sectional population based studies investigating the association between homocysteine and cognitive performance in non- demented individuals have shown an association between higher homocysteine levels and poorer cognitive performance [65-76]. However, three studies found no associations between homocysteine and cognition [77-79] whereas Ravaglia and colleagues [80] showed no correlations only in centenarians. One study evaluating homocysteine in individuals with cardiovascular disease also reported no associations between homocysteine levels and cognition [81]. Stewart and colleagues [82] found an association between homocysteine and cognitive performance only in those with less education in subjects born in a Caribbean nation residing in south London, attending primary care services, aged 55 to 75 years. Elias and colleagues [83] found an association only with an APOE e4 positive subset and two studies found an association between higher homocysteine levels and poorer cognitive scores only in older individuals [70, 84].

Associations between elevated homocysteine levels and Alzheimer's in prospective cohort studies have also been mixed with studies showing positive associations [28, 85-92] and others, no association with decline in cognition [93-97]. Seshadri and colleagues who assessed 1092 subjects from the Framingham study with a mean age of 76 years over a median period of eight years found that the relative risk of developing dementia was 1.4 (95%CI, 1.1 to 1.9) for each increase of 1 standard deviation in log- transformed homocysteine levels [28]. An

association between dementia and higher homocysteine levels was also reported by Ravaglia and colleagues [89] who followed 816 dementia free subjects over a period of four years. Haan and colleagues who evaluated a cohort of 1,779 Mexican- Americans over a period of 4.5 years showed an association between higher homocysteine levels and dementia as well as cognitive impairment [91]. Fasting total homocysteine levels were found to be significantly associated with cognitive decline by McCaddon and colleagues who assessed 32 healthy non-demented individuals with MMSE and ADAS-Cog over a period of 5 years [85]. Dufoil and colleagues [86] who followed 1,241 subjects over a period of 4 years and Tucker and colleagues [90] who assessed 321 men over a 3 year period also reported an association between higher homocysteine levels and cognitive decline whereas Nurk and colleagues who evaluated 2,189 subjects over a period of six years found an association between higher homocysteine levels and poorer memory [88]. Teunissen and colleagues [92] who assessed the cognitive performance of 144 normal ageing individuals at baseline and after six years found that elevated homocysteine levels at baseline correlated negatively with cognitive performance in memory as well as attention and information processing tests throughout the follow-up period.

Kado and colleagues [96] however showed an association between cognitive performance and homocysteine levels at baseline but not at follow up. Mooijaart and colleagues as part of the Leiden 85-plus study, assessed 599 elderly subjects aged 85 years over a period of four years found an association between cognitive impairment and elevated homocysteine levels but not with cognitive decline [97]. Kalmijn and colleagues who assessed 702 subjects over a mean period of 2.7 years as part of the Rotterdam study found no association between homocysteine levels

and cognitive decline as measured by MMSE scores [93]. Similarly, Luchsinger and colleagues [94] and Ramos and colleagues [95] reported no significant associations between homocysteine and cognitive performance or dementia. There was also no significant association between homocysteine and MCI in a study by Reitz and colleagues[98].

Cochrane reviews of studies assessing the effect of therapies that potentially modify Homocysteine levels (Folate, vitamin B6 and vitamin B12) have also not shown consistent evidence that such treatments have a beneficial effect on cognitive function [99-101].

As such, the association between Homocysteine and cognition remains inconclusive.

Table 1 Studies investigating associations between Homocysteine and cognition

Table 1.1 Homocysteine Case control studies

Study	Population	No.	Results
Clarke et al 1998[60]	UK	76(s) 108(c)	Elevated levels associated with AD
McCaddon et al 1998[61]	UK (Welsh)	30(s) 30(c)	Homocysteine level inversely related to cognitive scores

McIlroy et al 2002 [62]	Northern Irish	83-(s)AD 78-(s)VaD 64-(s)Non-demented stroke 71 (c)	Significant increase in plasma Homocysteine in all disease groups compared with controls. Moderately high plasma levels of Homocysteine associated with stroke, VaD and AD independent of age, sex, hypertension, cholesterol, smoking, creatinine, nutritional status and MTHFR genotype.
Miller et al 2002 [64]	North American	43(s) 37(c)	Elevated levels associated with vascular but not AD
Cascalheira et al 2009 [63]	European	19 (s) 36 (c)	High levels associated with AD

(s) = cases, (c) = controls

Table 1.2 Homocysteine Cross-sectional studies

Reference	Population	No.	Age (years)	Results
Riggs et al 1996[102]	Normative Aging Study	70	54- 81	>12.6umol/l poorer spatial copying skills
Stewart et al 2002[82]	African Caribbean	238	55- 75	>13.85 umol /L associated with cognitive impairment
Budge et al 2002[66]	UK Community	158	60-91	Higher Homocysteine per umol/l associated with lower scores
Duthie et al 2002[68]	Scottish mental survey Aberdeen Birth cohort	334	66	Homocysteine levels negatively associated with cognitive scores
Prins et al 2002[65]	Rotterdam scan study	1077	60-90	>14umol/l lower scores most marked psychomotor speed
Miller et al 2003[69]	Sacremento Area Latino study on aging	1789	>60	Inverse relation between Homocysteine levels and cognitive test scores
Ravaglia et al 2003[67]	Italian- normal cognitive function (Conselice)	650	>65	Inverse relationship between Homocysteine and MMSE scores

Garcia et al 2004 [103]	Community Volunteers	281	>65	Higher Homocysteine, lower cognitive scores
Wright et al 2004[70]	Triethnic North Manhattan study (Stroke free)	2871 of 3298	>40	Higher Homocysteine associated with lower MMSE in subjects> 65 years only
Schafer et al 2005[72]	Baltimore Memory Study Biethnic North American	1140	50-70	Homocysteine associated with poorer cognition across several domains
Clark et al 2005[73]	Post menopausal Australian women	200	56-67 (m=60)	Reduced verbal and working memory, learning for word lists
Elias et al 2005[84]	Framingham Offspring (Stroke and dementia free community)	2096	40-82	Homocysteine associated with multiple cognitive domains only in those > 60 years
Kado et al 2005[96]	MacArthur Studies of Successful Aging (cross-sectional arm)	499	70-79	Elevated Homocysteine independently associated with worse cognition (Similarly for low folate and B6)

Aleman et al 2005[71]	Dutch	400	40- 80	Positive association
Gunstad et al 2006[77]	North American Cardiovascular disease	126	NA	No association
Lei Feng et al 2006[74]	Singapore Longitudinal Ageing Study Singaporean Chinese	451	55-86	Associated with deficits in constructional ability and processing speed
Van Raamt et al 2006[75]	Second Manifestations of ARTerial disease Study Dutch	345	59	Positive association independent of extent and location of arterial disease- suggests non- vascular mechanisms for interaction
Fisher et al 2006[78]	Vienna	606	75	No association
Elias et al 2008[83]	Maine- Syracuse Study	911	26-98	Positive association with APOE e4 cohort only. Suggests APOE e4 modification of relation between Homocysteine and cognitive performance

Silbert et al 2008[81]	Australia Cardiovascular disease patients only (pre and post CABG)	264	NA	No association pre or post CABG

Table 1.3 Homocysteine Longitudinal studies *

Reference	Population	No.	Mean Age at onset (years)	Follow up (years)	Results
Kalmijn et al 1999[93]	Rotterdam	702	>55	2.7	No association between Homocysteine and cognitive impairment
McCaddon et al 2001[85]	Community dwelling	32	>65	5	Baseline Homocysteine level predicted MMSE and ADAS scores at 5 years
Seshadri et al 2002[28]	Framingham (Non demented)	1092	68-97	8	Homocysteine levels associated with increased risk dementia and AD
Teunissen et al 2003[92]	Dutch (Non demented)	144	30- 80	6	Homocysteine level inversely correlated with performance at baseline but not follow up.

Dufoil et al 2003[86]	EVA study	1241	>60	4	>15umol/l associated with cognitive decline. Odds 2.8 (95% CI 1.2-6.2)
Luchsinger et al 2004[94]	WHICAP North American (Washington) (Non demented)	679	NA	NA	No association between high Homocysteine and AD or decrease in memory scores
Garcia et al 2004 [104]	Canadian community	180	>65	2.3	Elevated Homocysteine and increases in Homocysteine associated with lower cognitive scores
Ramos et al 2005[95]	Sacremento Area Latino Study (Prospective arm)	1789	>60	Recruited 1998	No association
Kado et al 2005[96]	MacArthur Study (prospective arm)	499	70-79	7	Baseline H associated with poorer cognition Longitudinal only associated with low folate levels

Mooijaart et al 2005[97]	Leiden 85 Plus Study Dutch	599	>85	4	Association with cognitive impairment but not predictive of increased rate of decline
Nurk et al 2005[88]	Hordaland H Study Norwegian	2189	65-67	6	Positive association for memory decline
Ravaglia et al 2005[89]	Italian	816	74	4	Positive for AD and dementia
Tucker et al 2005[90]	Veterans Affairs Normative Aging Study North American (Boston) Men only	321	50-85	3	High Homocysteine predicted cognitive decline particularly spatial copying
Haan et al 2007[91]	Sacremento Area Latino study on aging	1779	60-101	4.5	Positive association with dementia and cognitive impairment

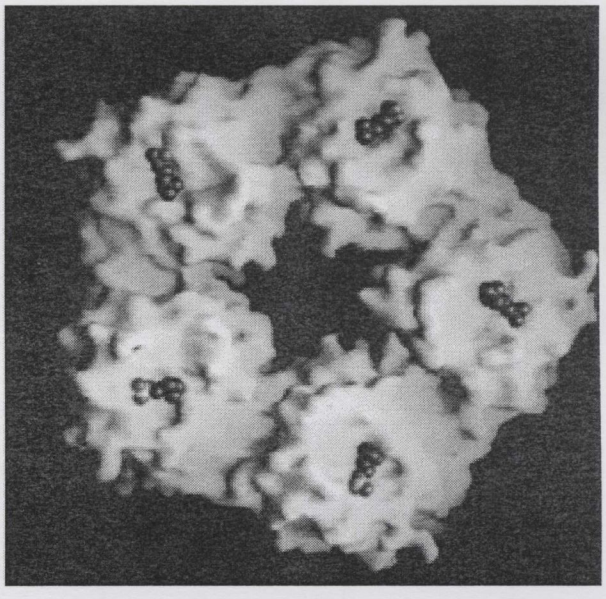
Reitz et al 2009[98]	North American (Medicare)	516	>65	5.2	No association with MCI

*For studies on the same cohort- most recent and/or comprehensive study shown unless results significantly different.

2.1.2 C- Reactive Protein

CRP is an acute phase reactant and non- specific marker of systemic inflammation that belongs to the pentraxin family of calcium dependent ligand-binding plasma proteins produced primarily by hepatocytes [105]. It was first described by Tillet and Francis and is characterized by its affinity for the phosphocholine moiety of the pneumococcal C- polysaccharide [106, 107]. The CRP molecule (M_r 115, 135) in human subjects is composed of five nonglycosylated polypeptide units (M_r 23, 027) which are identical [108]. Each of these units contain 206 amino acids and are non-covalently associated in an annular configuration (figure 1 below) [109].

Figure 1 Molecular structure and morphology of human CRP.



CRP levels in humans under normal conditions is low (1-5mg/l) with median concentrations of CRP in healthy young adults at 0.8 mg/l [110, 111] and levels at the 90^{th} centile 3.0 mg/l and the 99^{th} centile, 10 mg/l. The median

concentration doubles with age to approximately 2.0 mg/l in the elderly and can rise very rapidly in response to a variety of different stimuli such as infections, trauma or inflammation to more than 500 mg/l [111]. After the initial stimulus, de novo hepatic synthesis occurs with serum concentration levels rising above normal limits within 6 hours and peaking at 48 hours. CRP levels fall rapidly when the stimulus is removed. The plasma half- life of CRP is approximately 19 hours [112].

The exact role of CRP is unclear but it is likely that CRP has many pathophysiological roles in the inflammatory process and host defence mechanisms [113, 114]. Elevated levels of CRP have been shown to be an independent predictor for future cerebrovascular [115, 116], cardiovascular disease [23, 117-119], colorectal neoplasia [120], functional status [121, 122] and mortality [123, 124]. Individuals with raised basal levels of CRP also appear to be at higher risk for developing DM, supporting a possible inflammatory role for diabetogenesis [125, 126].

CRP may also have a role to play in cognitive decline. Inflammatory mechanisms have been suggested as having a role in the pathogenesis of Alzheimer's as well as vascular dementia [127]. Animal models show evidence of decreased neuronal survival when exposed to inflammatory markers [128]. Increased levels of cytokines and acute phase reactants have been found in blood and CSF of patients with AD compared with age- matched controls [129-131]. Additionally, an association between CRP and cognitive decline may also be mediated through increased ischaemic disease [132] or hypertension [34].

Results from cross-sectional studies investigating the association between CRP and cognition have been mixed. Gunstad and colleagues [77] showed an association between raised CRP and poorer cognition but no association was found

in three other studies [78, 81, 133]. Two prospective nested case control studies have suggested an association between raised CRP levels and dementia [29, 127]. The Honolulu- Asia Aging Study which studied 1050 Japanese- American men living in Hawaii beginning in 1965 reported that higher levels of CRP increased the risk of developing AD 25 years later [127]. The Rotterdam study also found increased levels of inflammatory proteins including CRP before the clinical onset of any dementia in a random subcohort of 727 subjects and 188 cases of dementia at follow-up from a source population of 6713 non-demented subjects at baseline.

Several longitudinal studies investigating the association between inflammatory processes and cognition have supported the association between CRP and dementia [134-137]. Yaffe and colleagues [134] studied 3,031 subjects enrolled in the Health, Aging and Body Composition Study over a two year period and found that subjects in the highest tertile of CRP were more likely to have cognitive decline compared with the lowest tertile (24 vs 19%; OR=1.41; 95% CI 1.10 to 1.79). Teunissen and colleagues [135] found that higher levels of CRP at baseline correlated negatively with cognitive performance in 93 subjects assessed over a six year period. Komulainen and colleagues reported similar findings in 97 women followed-up over a period of 12 years. Although there was no association between MMSE scores and baseline CRP levels in this cohort, higher baseline CRP levels were associated with poorer memory at 12 years follow-up as assessed by a detailed cognitive test battery [136]. Further data from the Honolulu- Asia Aging Study also showed an association between higher CRP levels and cognitive decline in later life in men [137].

Other longitudinal studies however, have failed to demonstrate an association between CRP and decline in cognitive performance [138-142]. Schram

and colleagues, who studied subjects from both the Rotterdam Study (3,874 subjects with mean follow-up 4.6 years) and the Leiden 85-plus Study (491 subjects with follow-up 5 years) found only a cross-sectional association between higher baseline CRP and global cognition and executive function in the Rotterdam cohort [138]. Dik and colleagues who assessed 1,284 subjects at baseline and at 3year follow-up [139] and Jordanova and colleagues [141] who evaluated 216 subjects of African-Caribbean descent over a 3 year period both found no association between CRP levels and cognitive decline. There was also no association found between CRP levels and cognitive impairment in the MacArthur Study of Successful Aging [142] nor was there any association found between CRP levels and risk of incident Alzheimer's disease in the Framingham Study [140].

One systematic review, which selected six studies, suggested that CRP was predictive of cognitive decline and dementia [143]. Kuo and colleagues were however unable to perform a meta- analysis on the studies selected due to the heterogenicity of the studies. The association between CRP and cognition therefore remains uncertain.

Table 2 Studies investigating associations between C- reactive protein and cognition

Table 2.1 C- reactive protein Cross sectional studies

Reference	Population	No.	Age at onset (years)	Results
Fisher et al 2006[78]	Vienna	606	75	No association
Gunstad et al 2006[77]	North American Cardiovascular disease	126		Positive association
Weuve et al 2006[133]	Women's Health Study	4231	60-90	No association
Silbert et al 2008[81]	Australia Cardiovascular disease patients only (pre and post CABG)	264	NA	No association pre or post CABG

Table 2.2 C- reactive protein Prospective nested case- control studies

Reference	Population	No.	Mean Age at onset (years)	Follow up (years)	Results
Schmidt et al 2002[127]	Honolulu-Asia Aging study Japanese American men	1050	55	25	Positive association between high CRP levels and dementia, AD, VaD
Engelhart et al 2004[29]	Rotterdam Study	727 188(s) 53(c)	NA	1.5	Elevated CRP associated with increased risk of dementia, AD, VaD

(s) = cases, (c) = controls

Table 2.3 C- reactive protein Longitudinal studies*

Reference	Population	No.	Mean Age at onset (years)	Follow up (years)	Results
Teunissen et al 2003[135]	Maastricht Aging Study	93	57	6	Elevated CRP at baseline negatively correlated with cognitive performance
Yaffe et al 2003[134]	Health, Aging and Body Composition Study African American and caucasians	3031	Mean age 74	>2	Positive association between high CRP and cognitive decline
Dik et al 2005[139]	Longitudinal Aging Study Amsterdam	1284	62-85	3	No association
Schram et al 2007[138]	Rotterdam Study (RS) and Leiden 85 Study (LS)	3874 (RS) 491 (LS)	Mean 72 (RS) all 85 (LS)	4.6 (RS) 5 (LS)	Higher CRP associated with worse global cognition. (RS). LS similar but not statistically significant

Komulainen et al 2007 [136]	Scandinavian Women only	97	60-70	12	Higher CRP levels predicted worse memory at follow up
Jordanova et al 2007[141]	UK African Caribbean	290	55-75	3	No association
Tan et al 2007 [140]	Framinham Study	691	49- 51	28-30	No association with AD
Alley et al 2008[142]	MacArthur Study of Successful Aging	851	70-79	At 3 years and 7 years	No association with cognitive change
Laurin et al 2008[137]	Honolulu-Asia Aging study Japanese American men	3734	53	31	Positive association between high CRP and dementia

*For studies on the same cohort- most recent and/or comprehensive study shown unless results significantly different.

2.1.3 Haemoglobin (HbA1c)

Glycation is the post- translational, non-enzymatic covalent linkage of glucose to proteins in tissue exposed to glucose. Glycated proteins form advanced glycation end products through a series of biochemical reactions [144]. Advanced glycation end products have been linked with the long term complication of poorly controlled glycaemia and have been found in subjects with Alzheimer's disease [145].

In the course of the life span of a red blood cell (120 days), glucose molecules can link to haemoglobin to form glycosylated haemoglobin, which is expressed as a percentage of total Haemoglobin A. The abnormal haemoglobin, HbA1c is formed by the combination of glucose with the N- terminus of the beta chain, forming first a Schiff base which then undergoes a rearrangement to form a stable ketoamine (see diagram 2). Individuals with persistently elevated sugars, as in DM, have increased levels of HbA1c [146]. As such, HbA1c is a marker of glycaemic control and measurement of HbA1c assess the effectiveness of glucose regulation over the previous 1-3 months [147, 148]. Normal levels in healthy non-diabetic individuals vary but usually range from 4-5.9% [149]. Other proteins, such as collagen and albumin can be similarly altered often with disturbed function.

HbA1c has been shown to be independently associated with cardiovascular morbidity [27, 150]. HbA1c has also been associated with increased brain atrophy both cross-sectionally and longitudinally independent of DM [151].

The relationship between HbA1c and cognition is still unclear. There have been few studies directly evaluating the association between HbA1c and cognition in non- diabetic subjects. One small case control study showed an association between HbA1c and poorer cognitive performance [152]. Results from other case

control and cross- sectional studies in mixed populations (diabetic and non-diabetic) have been varied [78, 153-160]. One cross- sectional study in a Japanese population reported a U- shaped relationship between HbA1c and intellectual activity [161]. Three longitudinal studies have found positive associations between higher levels of HbA1c and the risk of developing dementia or cognitive decline. Yaffe and colleagues reported increased risk of dementia in both diabetics and non-diabetics with higher levels of HbA1c [162] whereas Gao and colleagues reported that levels of HbA1c greater than 7% in non- diabetics were associated with an increased risk of developing dementia [163]. Maggi and colleagues who evaluated 5,632 diabetic subjects over a period of 8 years as part of the Italian Longitudinal Study on Aging found that higher levels of HbA1c were associated with poorer cognitive performance on memory tests at follow-up [164].

Table 3 Studies investigating associations between Glycosylated Haemoglobin and cognition

Table 3.1 Glycosylated Haemoglobin Case Control studies

Study	Population	No.	Results
Cosway et al 2001 [157]	UK	38(s)/ 3(c)	No association
Lindeman et al 2001 [156]	USA (New Mexico)	414 (Hispanic) 469 (white) >65 years	No association

Table 3.2 Glycosylated Haemoglobin Cross sectional studies

Reference	Population	No.	Mean Age (years)	Results
Worrall et al 1996[155]	Canadian	77	67.6	No association
Amano et al 2005[161]	Akita prefecture Japan	935	>65	U shaped (highest and lowest tertile lower intellectual activity scores compared with middle tertile)

Fisher et al 2006[78]	Vienna	606	75	No association
Saczynski et al 2008[158]	AGES-reykjavik study Iceland	1917	76	No association between cognitive performance and HbA1c. Poorer cognitive performance in subjects with diabetes.
Okura et al 2009 [159]	Health and Retirement Study-USA	1097	69.2	Significantly higher HbA1c in the lowest quartile compared with highest quartile. Not significant when higher levels of social support corrected for.
Cukierman-Yaffe et al 2009 [160]	ACCORD-MIND trial USA	2977	62.5	Higher HbA1c associated with poorer cognitive function in diabetics

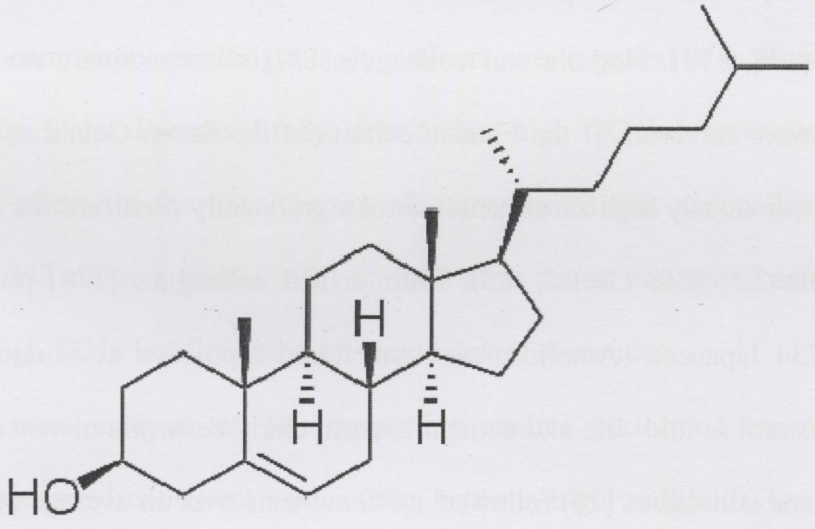
Table 3.3 Glycosylated Haemoglobin Longitudinal studies

Reference	Population	No.	Mean Age at onset (years)	Follow up (years)	Results
Yaffe et al 2006[162]	North American Osteoporotic Women	1983	67.2	4	Positive association for dementia and cognitive impairment in both diabetics and non-diabetics. Higher HbA1c levels associated with greater risk
Gao et al 2008[163]	UK England and Wales	1139	>69	5-6	HbA1c>7% without diabetes higher risk of developing dementia. Diabetes + HbA1c<7% similar dementia incidence to no diabetes + HbA1c <7%
Maggi et al 2009[164]	Italian Longitudinal study on Ageing	5632	65- 84	8	Higher HbA1c associated with poorer cognitive performance

2.1.4 Cholesterol

Cholesterol ($C_{27}H_{45}OH$) is a pearly, fatlike sterol, first identified in gallstones by François Poulletier de la Salle in 1769 [165], which is synthesized in the endoplasmic reticulum primarily from acetyl CoA via the HMG-CoA reductase pathway or absorbed from the diet. Approximately 20-25% of the cholesterol produced daily (~1 g/day) is synthesized by the liver. The remainder is produced in various organs such as the intestines, reproductive and adrenal glands.

Figure 2 Structure of Cholesterol



Cholesterol has many important roles including the maintenance of the integrity of cell membranes. Cholesterol metabolism has been linked with neurodegenerative diseases such as Alzheimer's disease in animal [166, 167] and autopsy studies [168, 169]. High levels of cholesterol also contribute to vascular disease. Benefits of reducing cholesterol may include plaque stabilisation and reduction of plaque rupture [170, 171] as well as improvements in endothelium-mediated responses and endothelial dysfunction including inflammatory effects

[172, 173]. This may be potentially beneficial cognitively as lipid dysfunction is a known risk factor for cerebrovascular disease and is implicated in vascular dementia. However, a Cochrane review assessing two randomized placebo-controlled trials (HPS [174] and PROSPER [175]) found no evidence to show that statins given in late life to subjects with risk factors of vascular disease had an effect in preventing AD or dementia [176].

The association between cholesterol levels and cognition therefore remains unclear. Studies investigating elevated total cholesterol in mid- life have shown consistent associations between high midlife total cholesterol and increased risk of AD [20, 177] as well as high midlife total cholesterol and increased risk of any dementia [178, 179]. Notkola and colleagues[177] retrospectively reviewed 444 men who were survivors of the Finnish cohorts of the Seven Countries Study and found that previously high serum cholesterol significantly predicted the prevalence of AD (OR=3.1; 95% CI=1.2, 8.5). Kalmijn and colleagues [178] prospectively studied 3734 Japanese –American men and found a positive association between total cholesterol in mid- life and dementia, particularly dementia of vascular origin. Kivipelto and colleagues [20] followed 1,449 subjects over an average period of 21 years and concluded that high serum cholesterol concentration (>/=6.5 mmol/l) in midlife significantly increased the risk of developing Alzheimer's disease in later life. Whitmer and colleagues[179] retrospectively assessed 8,845 subjects and found that high total cholesterol in mid life was associated with a 20- 40% increased risk of dementia. Solomon and colleagues [180] who followed 1,449 subjects over an average of 21 years also showed that higher cholesterol levels in mid- life was a risk factor for more severe cognitive impairment in later life. However, the association between elevated mid- life TC and cognitive impairment has not been universal,

with Tan and colleagues who followed 5,209 subjects from the Framingham Study finding no association between serum TC levels and risk for AD [181].

Studies evaluating the association between cognition and TC in later life have shown different results from studies assessing the effect of TC in mid-life. Romas and colleagues [182] found a weak association between decreased TC levels and the risk of AD. Moroney and colleagues [18] showed an association between elevated levels of LDL-cholesterol and VaD but not AD. Reitz and colleagues [183], Li and colleagues [184], Xiong and colleagues [185] and Raffaitin and colleagues [186] reported no association between late life TC and dementia or cognitive decline whereas Piquet and colleagues [187] who assessed 377 non-demented community dwelling elderly subjects over a period of 6 years as part of the Sydney Older Persons Study, found that high TC was associated with a protective effect for the development of dementia. Mielke and colleagues [188] evaluated 392 subjects from a 1901 to 1902 birth cohort and found an association between high TC in late life and a decreased risk of dementia.

A meta analysis of 18 prospective studies performed by Anstey and colleagues showed consistent associations between high midlife TC and increased risk of AD as well as increased risk for any dementia but no evidence supporting an association between late-life TC and AD or any dementia. There was also weak evidence for an association between high mid-life TC and cognitive decline. These results suggest that the effect of TC on dementia risk occurs in midlife but not late-life, and that there may be different cardiovascular risk factor profiles for different dementias [189].

The relationship between cholesterol and dementia may also be bidirectional. In addition to finding an association between mid-life TC and more

severe cognitive impairment in later life, Solomon and colleagues also reported that a moderate decrease in serum total cholesterol from mid- life to late- life (0.5 to 2 mmol/L) was found to be associated with a more impaired cognitive status in later life. Stewart and colleagues [190] assessed 1027 Japanese American men who had 5 serial TC measurements between 1965 and 1993 as part of the Honolulu- Asia Aging Study. Subjects diagnosed with dementia, particularly AD, had serum TC which had declined at least 15 years before the diagnosis and had lower TC levels than subjects without dementia throughout that period. Thus serum cholesterol levels may decline prior to the development of dementia, limiting the ability to accurately assess the effect of hypercholesterolaemia on cognition when measurements are made in later life. Furthermore, the effect of hypercholesterolaemia on cognition may be attenuated by APOE epsilon E status in certain populations [191, 192] although this has been inconsistent [182].

Table 4 Studies investigating associations between Cholesterol and cognition

Table 4.1 Cholesterol Longitudinal studies*

Table 4.1.1 Midlife serum Cholesterol and Alzheimer's disease or Dementia

Reference	Population	No.	Mean Age at onset (years)	Follow up (years)	Results
Notkola et al 1998 [177]	Seven Countries Study Finnish cohort	444	40-59	15-25	Positive association
Kalmijn et al 2000 [178] *Stewart et al 2007 [190]	Honolulu- Asia Aging study: Japanese American men	3734 *1027	53	25	Positive association *Subjects with TC measured on 5 occasions between 1965 and 1993. Decline in serum TC at least 15 years before associated with dementia
Kivipelto et al 2001 [20]	Finnish	1449	44-58	21	Positive association

Tan et al 2003 [181]	Framingham study	1026	NA	Recruited since 1950	No association
Whitmer et al 2005 [179]	Kaiser Permanente Medical Care Program (Retrospective study)	8845	40-47	27	Positive association 20- 40% increased risk
Solomon et al 2007[180]	Cardiovascular Risk Factors Aging and Dementia	1449	49.7	21	Positive association. Decreasing TC after mid life may be risk marker for late life cognitive impairment

Table 4.1.2 Late Life serum Cholesterol and Alzheimer's disease (AD), Vascular Dementia (VaD) or Mild Cognitive Impairment (MCI)

Reference	Population	No.	Mean Age at onset (years)	Follow up (years)	Results
Romas et al 1999[182]	North American (New York)	987	73	2.5	Risk of AD weakly associated with low cholesterol
Moroney et al 1999[18]	North American (New York Medicare)	1168	73	2.1	No association with AD. Risk of dementia with stroke associated with raised LDL-cholesterol
Piguet et al 2003[187]	Sydney Older persons study	377	75	5.8	Hypercholesterolaemia protective for dementia and cognitive decline
Reitz et al 2005[183]	North American (New York Medicare)	1147	78.4	7	No association
Li et al 2005 [184]	North American (Seattle)	2141	74.9	5.6	No association with dementia
Mielke et al 2005[188]	Swedish (Göteberg)	382	70	18	Dementia risk reduced with higher total cholesterol

Xiong et al 2006[185]	Duke Twins Study	282 pairs	72	12	No association with cognitive decline
Reitz et al 2008[193]	North American (New York Medicare)	854	>65	1.5	No association with MCI
Raffaitin et al 2009 [186]	French Three city cohort (3C)	7087	>65	4	Elevated TG but not TC associated with all cause and VaD

*For studies on the same cohort- most recent and/or comprehensive study shown unless results significantly different.

Table 4.2 Cholesterol Meta- Analysis of prospective studies

Reference	No of studies	No.	Follow up (years)	Results
Anstey et al 2008[189]	18	14331 AD 9458 VaD 1893 Cognitive decline 4793 Cognitive Impairment	3- 29	Consistent associations between high midlife TC and increased risk of AD, and high midlife TC and increased risk of any dementia. No evidence supporting an association between late-life TC and AD or any dementia. Weak evidence for an association between TC and cognitive decline.

2.2 Other Vascular Risk Factors

2.2.1 Hypertension

Hypertension, particularly isolated systolic hypertension, is one of the most common conditions seen in the elderly population. The prevalence of hypertension increases with age. Changes in the large arterial vasculature such as reduced elasticity and increased stiffness from atherosclerosis result in increasing systolic blood pressure with age whereas diastolic blood pressure tapers off in mid-life. As such, high systolic pressures in the elderly have traditionally been thought of as a product of ageing, requiring no intervention. Studies such as the Framingham study [194] however, have advanced our understanding of hypertension in recent decades. Hypertension in the elderly is far from a benign consequence of ageing, causing significant cardiovascular morbidity and mortality [195, 196]. The cardiovascular benefits of treating hypertension are well known [197, 198]. Although hypertension is an important risk factor for stroke [199], which is in turn a risk factor for vascular dementia, the precise effect that hypertension has on cognition in the elderly population remains uncertain.

Longitudinal studies examining mid- life hypertension and cognition have consistently shown an association between hypertension and poorer cognitive function in later life [7, 20, 179, 200-204] although one Japanese study found only an association with vascular dementia [205]. Swan and colleagues [202] found that subjects with persistently elevated SBP had reduced verbal learning and memory whereas individuals who experience a decrease in SBP did poorly in psychomotor speed.

Studies in the elderly have been mixed with studies showing an association with high blood pressure [206-208], low diastolic blood pressure [209, 210], no

association [187, 211-213] or a non linear association [187, 206, 208-215]. These discrepancies may be partly explained by differences in population groups, methodology and follow-up periods particularly if there is a long delay from exposure to clinical manifestation of cognitive decline. The use of antihypertensive medications may also have an impact on cognition with some studies suggesting that blood pressure reducing therapies may be protective for dementia [216, 217]. A Cochrane review however did not find convincing evidence that reducing blood pressure in elderly hypertensive subjects without cerebrovascular disease was cognitively beneficial although analysis of the studies included in this review was problematic due to the heterogeneity of the trials as well as the number of patients lost to follow- up. Many of the placebo subjects also received antihypertensive treatment [218]. Other possibilities include the fact that hypertension can be associated with certain subtypes of dementia and not others, that any relationship between hypertension and cognition may be age specific [219] or that the link may be complex [220, 221].

Table 5 Studies investigating associations between Hypertension and cognition

Table 5.1 Hypertension Longitudinal Studies*

Table 5.1.1 Hypertension in Mid life and Dementia (all subtypes), Cognitive Decline

Reference	Population	No.	Age at onset (years)	Follow up (years)	Results
Swan et al 1998 [202]	Western Collaborative Group Study	717	45	30	Positive association for 2 SBP subgroups- persistent high SBP associated with decreased verbal learning and memory, decrease in SBP during study at risk for decrease psychomotor speed.
Swan et al 1998[204]	National Heart, Lung and Blood Institute Twin Study	392	47	25	Midlife SBP associated with decline in cognitive function and decreased brain volume
Knopman et al 2001[7]	Atherosclerosis Risk in Communities cohort	8729 (w) 2234 (b)	47-70	6	Positive association with cognitive decline

	Biracial White (w) and Black (b)				
Kivipelto et al 2001[20]	Finnish	1449	44-58	21	Positive association for systolic blood pressure
Yamada et al 2003[205]	Radiation Effects Research Foundation Health Study, Hiroshima	1774	Born before Sept 1932	25-30	Positive association for systolic blood pressure with VaD only
Whitmer et al 2005[179]	Kaiser Permanente Medical Care Program	8845	40-47	27	Positive association 20- 40% increased risk

Table 5.1.2 Hypertension in Late life and Dementia (all subtypes), Cognitive Decline

Reference	Population	No.	Age at onset (years)	Follow up (years)	Results
Katzman et al 1989[222]	North American (New York)	434	75-85	5	No association
Yoshitake et al 1995[214]	Hisayama Study Japan	828	74	7	Positive association with VaD
Skoog et al 1996[206]	Longitudinal Population Study Goteborg, Sweden	382	70	15	Positive association with dementia with increased risk at age 79-85 with high SBP at 70 years or high DBP at ages 70 or 75
Elias et al 1997[223]	Framingham Study	1811	67	28-30	DBP>90 associated with worse immediate and delayed memory and word fluency. Risk increased further

					with DM
Glynn et al 1999[215]	Established Populations for the Epidemiologic Study of the Elderly (EPESE)	3657	74 (65-102)	6 years and 15 years	No linear association with cognitive decline but suggests a U shaped association
Morris et al 2001[224]	EPESE subset	634	72	6-15	No association with AD
Lindsat et al 2002[211]	Canadian	6434	>65	5	No association
Piquet et al 2003[187]	Sydney Older Persons Study	377	>75	6	Positive association with cognitive decline but not dementia
Verghese et al 2003[210]	North American Bronx Aging study	488	>75	21	Persistent low BP over 2 years at higher risk of developing dementia.
Hassing et al 2004[225]	OCTO-Twin Study	258	83	8	Positive association with cognitive decline

Luchsinger et al 2005[226]	North American (Manhattan, New York) Medicare	1138	76.2	5.5	Positive association with AD, increased when clustered with smoking and Diabetes
Xiong et al 2006[185]	Duke Twins Study	326 pairs	72	12	No association with cognitive decline
Li et al 2007[227]	North American (Washington)	2356	>65	8	High SBP associated with risk of dementia in younger elderly (<75 years) but not older subjects. Suggests adequate hypertension control may reduce risk of dementia
Rastas et al 2008[228]	Finnish	339	>85	9	History of hypertension associated with lower probability of dementia

*For studies on the same cohort- most recent and/or comprehensive study shown unless results significantly different.

2.2.2 Smoking

The deleterious effects of smoking have been well documented [229]. Smoking has been suggested however to have a protective effect on cognition. A review of 19 case control studies in 1994 showed a highly negative association between smoking and Alzheimer's disease [230]. However, more recent cohort studies evaluating the effect of smoking in mid-life on cognition have shown mixed results. Doll and colleagues [231] who assessed a cohort of 34, 439 male British doctors from 1951 found no significant association between smoking and AD or dementia. Knopman and colleagues [7] administered cognitive assessments which included the delayed word recall test (DWR), the digit symbol (DSC) and letter fluency (FAS) tests to 10,963 subjects on two occasions six years apart. Change in cognitive test scores was not found to be associated with smoking status. Yamada and colleagues [205] as part of the Radiation Effects Research Foundation Adult Health study also found no association between mid-life smoking status and either AD or VaD.

Kalmijn and colleagues [232] however, showed that psychomotor speed and cognitive flexibility were reduced in middle-aged subjects who were smokers. Whitmer and colleagues [179] also reported an increase risk of late- life dementia of 20-40% (HR 1.26, 95% CI 1.08 to 1.47) for subjects who smoked in mid-life. Tyas and colleagues [233] found that the risk of AD in smokers increased with the number of cigarettes smoked in pack years for individuals at medium and heavy smoking levels but not for very heavy smokers whereas Reitz and colleagues [234] who followed 6,868 subjects over a mean period of 7.1 years as part of the Rotterdam study found an association between current smokers at baseline and an

increased risk of dementia (HR 1.47, 95% CI 1.18 to 1.86) and AD (HR 1.56, 95% CI1.21 to 2.02) which was restricted to individuals without the APOEe4 allele. No association was found between current smoking at baseline and VaD or past smoking with an increased risk of any dementia in this study.

Studies evaluating the effect of smoking in late life on cognition have been equally mixed. Katzman and colleagues [222] who followed 434 subjects between 75 and 85 years of age over a 5- year period found no association between smoking and AD. Ford and colleagues [235], Lindsay and colleagues [211] and Piquet and colleagues [187] also found no association between smoking status and dementia. Ott and colleagues [31] however, in a European multi-centred study, found that after an average of 2.3 years, MMSE scores in non- demented elderly smokers declined greater than non- smokers with higher exposure in pack-years correlating significantly with a higher rate of decline. Smoking was also found to be associated with a higher risk of AD ($p<0.10$) in 1,138 subjects followed over a mean period of 5.5 years in a study done by Luchsinger and colleagues [226].

A meta- analysis of 19 prospective studies has suggested that current smokers at baseline had a greater risk for developing AD, Vascular dementia and for any dementia compared with subjects who never smoked. Current smokers at baseline showed greater declines in MMSE scores compared to those who never smoked [236].

As such, although it is likely that smoking has a negative impact on cognition, some uncertainty remains as not all results from previous studies have been conclusive.

Table 6 Studies investigating associations between Smoking and cognition

Table 6.1 Smoking Longitudinal studies*

Table 6.1.1 Smoking in Mid life and Dementia (all subtypes), Cognitive Impairment

Reference	Population	No.	Ave age at onset (yrs)	Follow up (years)	Results
Doll et al 2000 [231]	British Doctors (Male)	34439	32	49	No association
Knopman et al 2001[7]	Atherosclerosis Risk in Communities cohort Biracial White (w) and Black (b)	8729 (w) 2234 (b)	47-70	6	No association
Kalmijn et al 2002[232]	Dutch	1927	45-70	5	Positive association with cognitive impairment
Yamada et al 2003[205]	Radiation Effects Research Foundation Health Study (Hiroshima)	1774	Born before Sept 1932	25-30	No association

Tyas et al 2003[233]	Honolulu- Asia Aging Study Japanese American men	3734	53	25	Positive association except for very heavy smokers
Whitmer et al 2005[179]	Kaiser Permanente Medical Care Program	8845	40-47	27	Positive association 20- 40% increased risk
Reitz et al 2005[237]	North American (Manhattan, New York) Medicare	791	75.6 ±5.4	5	Positive association in current smokers>75 years. No association < 75 years
Reitz et al 2007[234]	Rotterdam Study	6868	>55	7.1	Positive association for current smoking only. Less pronounced for subjects with APOE e4

Table 6.1.2 Smoking in Late life and Dementia (all subtypes)

Reference	Population	No.	Age at onset (years)	Follow up (years)	Results
Katzman et al 1989[222]	North American (New York)	434	75-85	5	No association
Ford et al 1996[235]	North American (Cleveland, Ohio)	647	>74	4	No association
Lindsay et al 2002[211]	Canadian	6434	>65	5	No association
Piquet et al 2003[187]	Sydney Older Persons Study	377	>75	6	No association
Ott et al 2004[31]	Multi centre analysis EURODERM (Odense, Paquid, Rotterdam), MRC ALPHA	17610	>65	2.3	Positive association

Luchsinger et al 2005[226]	North American (Manhattan, New York) Medicare	1138	76.2	5.5	Positive association with AD

*For studies on the same cohort- most recent and/or comprehensive study shown unless results significantly different.

Table 6.2 Smoking - Meta- Analysis of prospective studies

Reference	**No of studies**	**No.**	**Follow up (years)**	**Results**
Anstey et al 2008 [236]	19	26374 17023	2-30 2-7	Elderly smokers higher risk for dementia

2.2.3 Non Insulin Dependent Diabetes Mellitus

NIDDM is a co-morbid risk for stroke disease [238] and as such, thought to be linked to vascular cognitive impairment. The presence of advanced glycation end- products and increased advanced glycation end- product receptor expression in the brains of patients with Alzheimer's disease [145] suggest that diabetes may have a role in influencing brain pathology in Alzheimer's disease. Insulin resistance [239] and high insulin levels [240] have also been associated with cognitive impairment.

Early case control studies showed no association between NIDDM [241] and cognitive impairment as well as relatively low rates of diabetes in Alzheimer's disease [242]. Almost all population based prevalence and prospective cohort studies however, have reported impaired cognitive function and greater cognitive decline in subjects with NIDDM and impaired glucose tolerance. Studies investigating the effect of DM in mid- life and cognition such as Ott and colleagues [243] who studied 6,370 subjects as part of the Rotterdam study, Knopman and colleagues [7] who conducted cognitive assessments on 10,963 subjects over six years, Schnaider Beeri and colleagues [244] who assessed survivors of the Israeli Ischaemic Heart Disease study cohort as well as Whitmer and colleagues [179] who performed a retrospective study on 8,845 subjects all found an association between DM in midlife and cognitive decline or dementia. Curb and colleagues [17] however found only an association between impaired glucose tolerance at baseline and vascular dementia but no association between DM and AD. There was also no association found between DM and dementia in the Adult Health study, a prospective cohort study of 1,774 subjects in Hiroshima, Japan [205].

Although all studies investigating the effect of DM on cognition in later life suggest a detrimental effect of DM on cognition, results have not been consistent. Three studies, Katzman and colleagues [222], Hassing and colleagues [245] and MacKnight and colleagues [246] found an association with vascular cognitive impairment and VaD but not AD. Raffaitin and colleagues[186] also reported an association between DM and VaD as well as all cause dementia. Arvanitakis and colleagues [247] however, showed a significant association between DM and an increased risk of AD (HR 1.65; 95% CI 1.10- 2.47) as well as a poorer cognitive performance at baseline and a decline in perceptual speed in 824 subjects followed over a period of 5.5 years. Yoshitake and colleagues [214], Brayne and colleagues [248] and Luchsinger and colleagues [226] also reported an association between AD and DM. Peila and colleagues [249] and Xu and colleagues [250] both showed an association between DM and AD as well as VaD. In the Framingham study, Akomolafe and colleagues [251] only found an association between DM and AD in subjects without APOE e4 or elevated Homocysteine levels.

Xiong and colleagues [185] who studied twin pairs over a twelve year period found an association between DM and greater cognitive decline particularly among older men. Four other studies also found an association between DM and cognitive decline [223, 225, 252, 253] whereas one other study showed an association between DM and amnestic MCI [254].

Age may be a possible explanation for these discrepancies. One study has suggested that the effect of diabetes on cognition may be age specific, with impaired cognition occurring only in subjects over the age of 70 years [185]. Other possible reasons for these discrepancies may be methodological differences. Endpoints in these studies have varied with some studies using Alzheimer's dementia as an

endpoint while others have used dementia regardless of aetiology. Furthermore, different definitions of diabetes have been used in these studies. In addition, studies evaluating diabetes from mid life may not have accounted for differences in drop-out rates between diabetics and non- diabetics or for incident diabetes [255].

Table 7 Studies investigating associations between Diabetes Mellitus and cognition

Table 7.1 Diabetes Mellitus Longitudinal studies*

Table 7.1.1 Diabetes in Mid life and Dementia (all subtypes), Cognitive Decline

Reference	Population	No.	Age at onset (years)	Follow up (years)	Results
Ott et al 1999[243]	Rotterdam Study	6370	>55	2.1	Positive association for dementia particularly for subjects on insulin treatment. Risk of dementia and AD doubled in DM patients
Curb et al 1999[17]	Hawaii	3774	45-68	15 and 25	No association with AD Positive association between impaired glucose tolerance and VaD
Knopman et al 2001[7]	Atherosclerosis Risk in Communities cohort	8729 (w) 2234 (b)	47-70	6	DM associated with cognitive decline

	Biracial White (w) and Black (b)				
Yamada et al 2003[205]	Radiation Effects Research Foundation Health Study, Hiroshima	1774	43 (Born before Sept 1932)	25-30	No association
Schnaider Beeri et al 2004[244]	Israeli Ischaemic Heart Disease Study	1892	40-65	30	Positive association
Whitmer et al 2005[179]	Kaiser Permanente Medical Care Program (Retrospective)	8845	40-47	27	Positive association 20- 40% increased risk

Table 7.1.2 Diabetes in Late life and Dementia (all subtypes), Cognitive Decline, Mild Cognitive Impairment (MCI)

Reference	Population	No.	Age at onset (years)	Follow up (years)	Results
Katzman et al 1989[222]	North American (New York)	434	75-85	5	Positive association with VaD. No association with AD.
Yoshitake et al 1995[214]	Hisayama Study Japan	828	74	7	Positive association with AD
Elias et al 1997[223]	Framingham Study	1811	67	28-30	DM associated with increased risk for poor visual memory. Duration of DM associated with poorer verbal memory and concept formation. Insulin treated DM higher risk of poorer cognitive performance than non insulin treated. Risk increased further with DM

Brayne et al 1998 [248]	UK	376	>75	2.4	Positive association with AD
Gregg et al 2000[253]	Study of Osteoporosis Fractures Research Group North American	9679	>65	3-6	Positive association with reduced cognitive performance and decline
Fontbonne et al 2001 [252]	Epidemiology of Vascular Aging Study Nantes,France	1389	59-71 (Born between 1922-32)	4	Diabetics worse on psychomotor speed, memory and attention
Hassing et al 2002[245]	Swedish	702	83	6	Positive association with VaD (twofold increase in risk) No association with AD
MacKnight et al 2002[246]	Canadian Study of Health and Aging	5574	74	5	No association with AD Positive association with vascular cognitive impairment

Peila et al 2002[249]	Honolulu- Asia Aging Study Japanese American men	2574	77	2.9	Positive association for AD, VaD particularly with APOE e4
Arvanitakis et al 2004[247]	North American (Chicago) Catholic order (Nuns, Priest, Brothers)	824	75	Mean 5.5	Positive association with AD (65% increase in risk) Positive association with cognitive impairment
Hassing et al 2004[225]	OCTO-Twin Study	258	83	8	Positive association with cognitive decline
Luchsinger et al 2005[226]	North American (Manhattan, New York Medicare)	1138	76.2	5.5	Positive association with AD
Xiong et al 2006[185]	Duke Twins Study	177 pairs	72	12	Positive association with cognitive decline

Akomale et al 2006[251]	Framingham Study	2210	70	12.7	No association with dementia except for subset without APOE e4 or elevated homocysteine, particularly in > 75 years
Xu et al 2007[256]	Swedish	1173	75	9	Positive association for dementia, AD and VaD, particularly in subjects with severe systolic hypertension or heart disease
Luchsinger et al 2007[254]	North American (Manhattan, New York) Minority (Hispanic, African American)	918	>80	>1	Positive association for amnestic MCI
Rastas et al 2008[228]	Finnish	339	>85	9	DM associated with higher probability of developing dementia

Raffaitin et al 2009[186]	French Three city cohort (3C)	7087	>65	4	DM associated with all cause and VaD

*For studies on the same cohort- most recent and/or comprehensive study shown unless results significantly different.

2.3 Established and other risk factors, Epidemiological studies and misidentification of confounders

Age, gender and education are factors usually controlled for in the majority of studies assessing cognitive decline and dementia. Age is the strongest identified risk factor for dementia, particularly AD [228, 257, 258]. Hebert and colleagues reported that the incidence of AD was approximately 14 times higher in individuals older than 85 years compared with those between 65 and 69 years of age. The estimated annual incidence of AD in individuals between 65 to 69 years was 0.6%, 1.0% for individual aged between 70 to 74, 2.0% for individuals aged between 75 to 79 years, 3.3% for individuals aged 80 to 84 and 8.4% for individuals aged 85 and older [259]. This was supported by a prospective cohort study by Kukull and colleagues who followed 2581 subjects aged 65 years or older over a period of eight years from 1994. The incidence of dementia rose from 2.8 per 1000 person- years in the 65 to 69 year age group to 56.1 per 1000 person- years in the >90 years age group [260]. A meta- analysis of 23 studies reporting age specific incidence of dementia showed that the incidence of both AD and dementia increased exponentially up to the age of 90 years with no evidence of levelling off [261]. Although the incidence of vascular dementia varied from study to study, the general trend was also an exponential increase with age. Studies estimating dementia incidence in the very old have generally been limited by low numbers [261]. One study which enrolled 488 healthy non- demented community dwelling elderly aged 75 to 85 years and followed these individuals up to 21 years showed that the incidence of dementia continued to increase with age after 85 years but at a slower rate relative to that between 65 and 85 years [262].

The prevalence of dementia also increases with age. Jorm and colleagues who analysed studies of dementia prevalence from 1945 to 1985 found that the rates of dementia consistently doubled every 5.1 years [263]. The prevalence rate for individual aged from 65 to 69 was 1.4%. This increased to 23.6% for individuals over the age of 85 years.

In addition, the meta- analysis by Jorm and colleagues showed no gender difference in dementia incidence. Men however, tended to have a higher incidence of vascular dementia at younger ages whereas women tended to have a higher incidence of AD in very old age [261]. Kukull and colleagues also showed no appreciable gender difference in dementia incidence [260].

Many studies have assessed the relationship between educational attainments and dementia with most showing an association between lower education and an increased risk of dementia [260, 264-268] as well as faster cognitive decline in individuals with dementia [269]. This however has not been universal with some studies reporting associations between lower education and dementia only in women [270, 271]. Wilson and colleagues found an association between education and level of cognitive function in older residents of a south side Chicago community but not with cognitive decline. As such, the association between education and level of cognitive function may account for the correlation seen between education and the risk of dementia [272]. Measures used to assess cognitive performance are also highly influenced by pre-morbid ability [273]. Cervilla and colleagues found an association between pre-morbid IQ and poorer late life cognition but not education [274]. Another study suggested that poorer linguistic ability at a younger age was associated with poorer cognitive ability later

as well as AD [275]. As such, the confounding effect of pre-morbid ability needs to be taken into account when evaluating risks for cognitive decline.

Lifestyle and environmental factors such as physical exercise, diet and leisure activities may also be important confounders in studies evaluating risk factors of dementia and cognitive decline [276, 277]. Scarmeas and colleagues who assessed 1880 non- demented community dwelling elderly subjects living in New York over a period of 14 years found that adherence to a Mediterranean- type diet (high intake of fish, vegetables, legumes, fruits, cereals and monounsaturated fatty acids; relatively low intake of dairy products, meats and saturated fats; and moderate alcohol consumption) and higher physical activity were independently associated with a reduced risk for developing AD [41]. Higher adherence to a Mediterranean type diet was also associated with a reduced risk of MCI as well as conversion from MCI to AD [278]. Other studies have also reported similar findings as well as other factors found to attenuate the risk of dementia including consumption of seafood and fish [279-282], fruits and vegetables [283], tea [284], cognitive [285] and physical [286] activity, social engagement and support [287], occupation [288] and personality traits such as neuroticism and extroversion [289].

Epidemiological studies however have tended to focus on biophysical factors rather than lifestyle factors or psychosocial status when adjusting for potential confounds. Observational studies conducted to determine possible associations between adverse health- related outcomes and risk factors may be prone to systematic errors such as confounding bias. This may convey the appearance of an association where the confounding characteristic may be responsible for the observed association rather than the putative cause. Examples of the importance of confounding in epidemiological studies include studies

investigating the use of antioxidants and vitamin supplements. Such studies had suggested that the use of vitamin E and vitamin C may be beneficial in reducing the risk of cardiovascular disease [290]. However, randomised controlled trials not only showed no benefits but a potential for harm. The Physician's Health Study II was a randomised, double blind, placebo- controlled trial of vitamin A and vitamin C. 14,641 male physicians aged 50 years or older were randomised to either placebo or 400 IU of vitamin E on alternate days and 500mg of Vitamin C daily over a mean period of 8 years. There was no reduction in the risk of major cardiovascular with vitamin supplementation. Vitamin E was associated with an increased risk of haemorrhagic stroke [291]. A meta-analysis of seven randomised controlled trials on vitamin E also failed to find any benefits for vitamin E in reducing cardiovascular disease or mortality. A meta- analysis of eight studies on beta carotene found a small but significant increase in mortality and cardiovascular deaths [292].

This misidentification of beneficial effects of anti-oxidants in vascular disease most likely arose as a result of inadequate controlling for confounding factors such as disease avoiding behaviours associated with use of vitamin supplementation. Psychosocial factors including education, socioeconomic class and income have been shown to influence disease avoiding behaviour and therefore health [293].

Many factors may be confounders in any given study and the presence of confounding in epidemiological studies remains a common and important phenomenon. Although it is not possible to account for every single variable, failure to account for the most important confounders may limit the validity of observed associations. Identification of possible confounders and controlling for such

variables increases the validity of a study and reduces the chance that the observed association is spurious.

2.4 Cognitive and neuropsychological Assessment in Research

Neuropsychology is essentially the study of brain- behaviour relationships including the impairment of cognitive ability [294, 295]. The objective of neuropsychological assessment in clinical practice is to evaluate disturbances in mentation and cognitive ability in individuals with suspected brain dysfunction. Knowledge of the presence and characteristics of such cognitive impairments in relation to their neurological implications can aid in the diagnosis and clinical treatment of individuals with neurological disease as well as provide information on possible disease processes [296].

Cognitive impairment associated with advanced age was recognised as early as 2000 B.C. by the Egyptians. Neuropsychological testing however is largely a phenomenon of the twentieth century although rudimentary forms of testing have been recorded as far back as 2200 B.C. in China where officials were evaluated every three years to determine their fitness for office [297]. Much of current neuropsychological testing is influenced by late nineteen- century investigations by British and German experimentalists. Included in these were examinations conducted on the mentally ill as well as those on brain- injured individuals, which resulted in the development of many early non- standardised neuropsychological tests [298]. Although Wilhelm Wundt (1832- 1920) is credited with founding the first psychological laboratory [299], Sir Francis Galton (1822- 1911) is often regarded as the father of mental testing because of his efforts in devising practicable objective tests that obtained scores through standardised procedures [300]. His work was continued by James McKeen Cattell (1860- 1944) whose students in turn helped to further the development of neuropsychological testing [301]. In 1905, the first intelligence test was devised by Alfred Binet (1857- 1911) [301] in order to

identify children who would benefit from receiving special educational supports. This proved to be the springboard for the invention of the intelligence quotient as well as the development of other early, standardised neuropsychological tests that have helped shape current contemporary tests.

Like all tests, neuropsychological assessments are of limited use by themselves. Results of assessments need to be interpreted in the light of other clinical, radiological and haematological information available. In addition, other factors pertaining to test construction such as sensitivity, reliability and validity as well as factors associated with the subject being assessed such as age, gender, culture and educational status can have an impact on test outcomes [302].

Since neuropsychological assessments are dynamic processes that can be affected by extraneous factors, standardised procedures and conditions are essential elements of valid testing. However, there may be occasions where some degree of flexibility is required for example in situations where home assessments are necessary although test administration still need to follow carefully the standardised procedures for administration and scoring specified by the test publisher. Specifications regarding instructions to test takers, time limits, the form of item presentation, or response, and test materials or equipment have to be strictly observed. Exceptions should only be made on the basis of carefully considered professional judgement, primarily in clinical applications. An examiner requires considerable clinical experience and a familiarity with test procedures as well as test materials. Physical disabilities in subjects such as impairments in speech, vision or hearing commonly found in the elderly must be recognised by the examiner and appropriate corresponding adjustments to testing and scoring should be made [303]. The examiner should also be experienced in interacting with the elderly in order to

establish an appropriate rapport. Examiner factors such as gender and race are generally thought to have little effect on testing although there may be special situations where these may have a bearing on test outcomes [304]. Subject characteristics such as test anxiety and poor motivation may also have a bearing on test results and should be noted if thought to be significant [305]. Examiners have little impact on scoring if scoring criteria for tests are strictly adhered to. However care must be taken to avoid clerical scoring errors [306].

In order to assess current cognitive functioning, a neuropsychological assessment should typically evaluate multiple areas of cognitive function. The major cognitive domains usually assessed in neuropsychological assessments include: orientation, attention and concentration, learning and memory, language skills, executive function, visuospatial ability, sensory abilities and motor abilities [307]. In addition, assessments of activities of daily living, behaviour, mood and personality are also performed [294]. A battery of tests, either fixed or individualised to the subject, is commonly administered to assess the above domains as well as general cognitive function and various different tests suitable for administration to the elderly exist.

Ideally, assessments should be longitudinal to assess cognitive decline. However, in practice this is rarely available on the initial assessment. As such, additional tests based on vocabulary such as the National Adult Reading Test (NART) can be helpful as an indirect measure of pre-morbid ability and should be included in the test battery.

Prior to administration of the test battery however, a comprehensive history from the subject and a collateral history from an appropriate informant, if available, independently is desirable. The onset and course of any deterioration, family

history, risk factors particularly vascular risks, concomitant illnesses, medications and social history all have diagnostic relevance. Finally, a cognitive assessment is incomplete without a careful general neurological examination, noting subject alertness and cooperation as well as any findings which may be associated with cognitive disorders.

Chapter Three

Research Methods

3.1 Study population and design

This study was a community based cross- sectional analytical study of 466 non- demented elderly subjects, stratified for age (> or < 75 years), randomly selected from the patient lists of four General Practitioners in the catchment area of St. James's Hospital, Dublin. Data was collected between 2003 and 2005.

Inclusion criteria

Community dwelling subjects

Aged 65 and over

Willing to provide consent

Medically stable

Able to cooperate with neuropsychological testing.

Exclusion criteria

Dementia (DSM IV criteria [308]) as this would preclude cooperation with detailed testing.

3.2 Ethics Approval

Ethics approval was obtained from the Irish College of General Practitioners Research Ethics committee as well as the St. James's Hospital and Federated Dublin Voluntary Hospitals Joint Research Ethics committee.

3.3 Subject Recruitment

Subjects were contacted by mail and offered participation in the study. All community dwelling individuals aged over 65 years who were medically stable with no history of dementia and able to cooperate with neuropsychological testing were eligible for recruitment if they were able to provide consent. A total of 1349 letters to individuals were sent. Of these, 419 (31%) individuals refused participation. 159 (11.8%) did not meet inclusion criteria, 175 (13%) had passed away and 71 (5.3%) were no longer at their given address (table 8). There was no significant gender difference between those who participated in the study, those who refused participation and those who had passed away (p= 0.313). However, those who had passed away were more likely to be older and those who refused participation, younger than those who participated in the study (p< .009, mean rank 106.75, 71.44, 84.83)

Table 8 Reasons for non participation

	All Ages		65-75 years		>75 years	
	N	%	N	%	N	%
Refusal- Reason not given	368	27.3	195	32.8	173	22.9
Refusal- Health reasons	12	0.9	5	0.8	7	0.9
Refusal- Other reasons	24	1.8	11	1.9	13	1.7
Refusal – No reply	15	1.1	13	2.2	2	0.3
Not living at given address	71	5.3	23	3.9	48	6.4
Did not meet inclusion criteria	111	8.2	30	5.1	81	10.7
RIP	175	13	32	5.4	143	18.9
No longer on GP list	59	4.4	17	2.9	42	5.6
Participated	466	34.5	256	43.1	210	27.8
Total	1349	100	594	100	755	100

3.4 Assessment Procedure

A research psychologist and a doctor visited subjects who agreed to participate, in their own homes, on a single occasion. The duration of each assessment was approximately two hours.

A structured interview recorded self- reported information on demographic details, education, medical history, current medications, diet, smoking status, alcohol use, exercise, psychosocial history and family history. This included the use of a standardised psychiatric interview based on DSM IV: SCID [308], the CAGE alcohol screening questionnaire [309], the Centre for Epidemiologic Studies Depression Scale [310] and a measure of life satisfaction, the Life Satisfaction Index [311].

Cognitive status was assessed using the National Adult Reading Test [312] for pre- morbid intellect, Wechsler Adult Intelligence Scale –III Digit Symbol – Coding [313] for psychomotor processing speed, Verbal fluency (letter [FAS test] and category [animal] fluency) [314], Wechsler Memory Scale –III Serial Word Lists for verbal learning, interference, delayed recall and recognition [315], Wechsler Memory Scale – Revised Visual Reproduction for visuoconstruction, immediate and delayed visual memory [316] and the Wechsler Memory Scale –III Letter Number Sequencing [315] for working memory. Test scores were standardized (z- transformation- subject score minus sample mean divided by sample standard deviation) to enable comparison of tests with different matrices. A composite score consisting of the above tests was used as a global measure of cognitive performance (GC). In addition, the Mini Mental State Examination (MMSE) [317] was performed as a general index of cognitive functioning. Personality was measured using the Eysenck Personality Inventory [318] which

measures two important personality dimensions, Extroversion-Introversion and Neuroticism-Stability.

Biophysical measurements such as the subjects' height (cm), waist circumference (cm) and hip circumference (cm) were measured using a standard tape measure accurate to 1 mm. Weight (kg) was measured on a calibrated scale accurate to 0.5 kg with normal indoor clothing. Subjects' waist hip ratio (waist/hip) and body mass index (weight/ height^2) were calculated according to standard equations. Blood pressure measurements were performed with the subject sitting with a standard aneroid sphygmomanometer accurate to 3mmHg with the manometer placed at the same level as the cuff on the subject's upper arm. All clothing was removed from the arm before the cuff was applied with its lower border not less than 2.5 cm from the cubital fossa. The systolic reading was taken as the reading at which the first Korotkoff sounds occurred (phase one) and the diastolic as the reading when the sounds disappeared (fifth phase). Three readings were measured and the lowest reading taken as the subject's blood pressure. A comprehensive physical assessment of neurological status was performed. Further clinical assessments such as assessment of gait were performed if deemed necessary.

Social class was determined according to the Central Statistics Office of Ireland 2002 Social Class Census Classification [319]. Lifetime alcohol intake was estimated from self- report and calculated in number of units/ week. Exercise was estimated from self- report and calculated as number of minutes spent exercising in a fortnight. Smoking was defined as current smokers, ex- smokers (6 months) and non- smokers. Pack years were calculated by dividing the number of cigarettes smoked a day by 20 and multiplying this by the number of years smoked. Subjects

were considered to have hypertension if they had one of the following: use of antihypertensive medication or self- report of physician diagnosed hypertension. Diabetes mellitus was defined by use of insulin or oral hypoglycaemic agents, a non- fasting glucose of ≥ 11.1 mmol/L or a self- report of physician- diagnosed diabetes mellitus.

Blood samples were collected by venepuncture and non- fasting samples taken for homocysteine, glucose, glycosylated haemoglobin, lipid profile and C-reactive protein. All samples were measured by a commercial laboratory. Homocysteine samples were transported on ice, spun within 30 minutes and stored at –20° C or below until analysed. Quantitative measurement of L- Homocysteine in serum was by Fluorescence Polarization Immunoassay (Imx system; Abbott laboratories). Sensitivity of these assay were calculated to < 0.50umol/ L corresponding to upper limit of the 95% confidence interval. Precision of these assay were determined by assaying samples on 5 days, 2 runs per day across 10 instruments. Samples with mean value 5.9, 10.8, 21.6 μmol/L yielded within run coefficient of variation (CV) % of 2.2, 1.9 and 1.4 respectively and total CV% of 5.2%, 4.1% and 3.7% respectively. Glucose levels were determined enzymatically (bioMerieux) with CV range of 0.75% to 0.81%. Glycosylated Haemoglobin was measured using High-Performance Liquid Chromatography (Hi- AUTO A1c Analyser system) with a CV of 5 to 10%. Serum cholesterol, HDL and LDL were measured by enzymatic clearance assay (Randox Laboratories) using a Hitachi 737 or 747 with a CV range of 0.88% to 1.2% for HDL and CV 0.49% to 1.79% for LDL. Triglyceride levels were measured by the triglycerides liquicolor test (Human Gesellschaft fur Biochemica und Diagnostica mbH) with a CV range between 2.0%

and 3.5%. C- reactive protein was measured by particle enhanced immunonephelometry (BN Systems) with a CV range between 2.1% to 5.7%.

3.5 Study Instruments

3.5.1 Verbal fluency (letter [FAS test] and category [animal] fluency) [314]

Standard recommended instructions were used during the administration of the letter FAS and category (semantic association) fluency tests (appendix 3). This test took approximately 5-10 minutes. 1 minute, timed using a stopwatch, was allowed for each letter (F, A and S). Subjects were encouraged to continue trying to think of more words if they stopped before the allotted time. If a silence lasting for 15 seconds occurred, standard basic instructions were repeated. Actual words were written down in the order produced (or plus signs if words are produced too rapidly for verbatim recording) for scoring purposes. The category [animal] fluency test was administered immediately following the letter [FAS] fluency test. Standard recommended instructions were used for explaining the task. I minute was allowed for the task and the subject was encouraged to produce more names of animals if the subject discontinued before this period was up. Basic instructions were repeated if there was a delay of 15 seconds or more. Actual words were written down in the order they were produced. Scoring for the letter [FAS] fluency test was the sum of all admissible words for the three letters. Scoring for the category [animal] fluency test was the sum of all admissible words, which included extinct, imaginary and magic animals.

3.5.2 Word Lists (WMS-III; acquisition, interference, delayed recall, recognition) [313]

Standard recommended instructions were used to explain the task. List A from the record form (appendix 4) was read at approximately 1 seconds per word. For trial 1, subjects were then asked for as many words as they could remember. This was repeated for trial 2-4 using standard recommended instructions. A new list (list B) was read when all four trials of list A were completed. Again, standard recommended instructions were given and all words were read at approximately 1 seconds per word. All responses were recorded on the record form. Subjects were then asked to recall words on the first list (list A) for the subject's Short-Delay Recall. Responses were recorded. After a delay of 25-35 minutes, subjects were then asked to recall words on list A again for Retention and then asked using standard recommended instructions to identify words from list A read from the recognition list of 24 words for Recognition.

3.5.3 Visual Reproduction (WMS-R; visuoconstruction, immediate memory, delayed recall) [316]

Four visual reproduction cards (see figures 3-6 for cards A-D) were used for this assessment. The subject was asked, using standard recommended instructions, to look at each geometric design in turn for 10 seconds before drawing it from memory. After a delay of 25-35 minutes, the subject was asked to draw the geometric designs once more from memory. The drawings were scored for accuracy according to detailed standard criteria.

3.5.4 Letter Number Sequencing [315]

Standard instructions regarding the task were given to subjects. Subjects were then read a group of letters and numbers and required to place them in order with numbers first, starting with the lowest number followed by the letters in alphabetical order. Each combination was said at the rate of one number or letter per second and subjects were given ample time to respond. The following practice trials were administered prior to starting the actual task (correct answers in parentheses):-

6-F (6-F)

G-4 (4-G)

3-W-5 (3-5-W)

T-7-L (7-L-T)

1-J-A (1-A-J)

If the subject made an error in practice, the subject was corrected and the standard instructions were repeated if necessary. The task was performed even if the subject failed all the practice trials. A standard Record Form (appendix 7) was used and items were administered from the Record Form. All responses were recorded on the Record Form. The task was discontinued if the subject failed three to respond correctly to three consecutive letter number combinations.

3.5.5 CAGE [309]

The CAGE questionnaire (appendix 8) consists of four questions. Subjects were required to answer "Yes" or "No" to each answer with more "Yes" answers signifying greater problems with alcohol consumption and dependence.

3.5.6 Digit Symbol – Coding (WAIS-III; psychomotor / processing speed) [313]

Subjects were instructed using standard instructions to copy symbols paired with numbers. Using a key, subjects copied each symbol under its corresponding number (appendix 9) with the subject's score being the number of correctly drawn symbols within a 120 second time limit.

3.5.7 National Adult Reading Test (NART) [312]

The NART (appendix 10) comprises a list of 50 relatively short words "irregular" with respect to common rules of pronunciation to minimise phonemic decoding and arranged in order of increasing difficulty. Subjects were asked, using standard recommended instructions, to read the list of words aloud and errors were recorded on the NART answer sheet. Predicted IQs approximated to subject's premorbid IQs.

3.5.8 Centre for Epidemiologic Studies Depression Scale (CESD) [310]

The CESD (appendix 11) consists of 20 questions answered either Rarely (less than one day in a week), Sometimes (1-2 days in a week), Occasionally (3-4 days in a week) or Most of the time (5-7 days in a week) by the subject. Standard instructions to explain the task were given prior to commencement. Scoring was zero for Rarely, 1 for Sometimes, 2 for Occasionally and 3 for Most of the time. The range of scores was from 0-60 with higher scores indicating the presence of more depressive symptomatology.

3.5.9 Life Satisfaction Index A (LSIA) [311].

The LSIA (appendix 12) consists of 20 statements descriptive of satisfaction with one's life. Subjects are instructed to respond with "agree" or "disagree", indicating their feeling regarding the statement. Scoring was according to a standard template which identified the response indicative of satisfaction with life in that area. The potential score range was from 0 to 20 with higher scores indicating greater satisfaction with life.

3.5.10 Eysenck Personality Inventory (EPI) [318]

The EPI (appendix 13) is a measure of behaviour assessing two important personality dimensions, Extroversion- Introversion and Neuroticism- Stability. Subjects were asked to answer 57 "Yes" or "No" questions. Scoring was based on a standardised template. (appendix 14) Subjects with a higher "E" score had more extroverted tendencies. Subjects with a higher "N" had more neurotic tendencies . The "L" score assessed the honesty of the answers.

3.5.11 Mini Mental State Examination (MMSE) [317]

The MMSE (appendix 15) is a general index of global cognitive functioning. Subjects were asked to answer 11 questions over 5-10 minutes assessing 5 different domains of cognition including orientation, registration, attention and calculation, recall and language ability. The maximum score was 30.

3.5.12 Global Measure of Cognitive Performance (GC)

The cognitive tests were combined into a global composite score following the method employed by Dufouil and colleagues [320]. To give each test equal weighting in the composite score each individual test score was standardised (mean = 0, standard deviation = 1) by subtracting the score from the mean for all participants and dividing by the standard deviation. The tests included were Digit Symbol-Coding, Letter Number Sequencing, FAS test, animal fluency, combined immediate and delayed Visual Reproduction, WMS-III Word List delayed recall, and MMSE. The global composite score was computed as the mean of the sum of the standardised test scores.

3.6 Statistical Analysis

A sample size of 500 subjects was estimated to have 80% Power to detect approximately a quarter of a standard deviation for each of the vascular biomarkers with an alpha of 0.05. Standard deviations for each of the markers were obtained from published series of similar populations.

Table 9 Power calculations for vascular biomarkers

Vascular biomarker	SD	alpha	Power	N	Detectable difference
HbA1c	0.8	0.05	0.8	500	**0.2**
Glucose	0.5	0.05	0.8	500	**0.125**
Homocysteine	7	0.05	0.8	500	**1.8**
CRP	5.2	0.05	0.8	500	**1.25**
Total Cholesterol	1.1	0.05	0.8	500	**0.275**

A sample size of 500 subjects was estimated to have 95% Power to detect a 10-20% difference for each of the neuropsychological test measures with an alpha of 0.01. This was all less than 1 standard deviation for each test (generally accepted as the minimum for clinical significance in a neuropsychological test).

Table 10 Power calculations for neuropsychological tests

Test	Mean	SD	alpha	Power	% mean difference	Absolute difference detectable by study
DSST	54	17	0.01	0.95	11.9	6.4
WMS III Word lists recall	27.5	5.5	0.01	0.95	7.6	2.1
WSR R Visual Reproduction 1	27	7	0.01	0.95	9.8	2.6
WSR R Visual Reproduction 2	22	10	0.01	0.95	17.3	3.8
FAS test	35.6	12.5	0.01	0.95	13.2	4.7
Animals	16.4	4.3	0.01	0.95	9.8	1.6

Potential lifestyle, dietary, psychosocial and clinical confounders were introduced in backward regression models together with known covariates of cognitive performance such as age, gender, educational status and socio-economic class with the results of global cognitive assessments, MMSE and GC as outcomes (Model 1) to identify potential confounders. All categorical data was recoded as dummy variables prior to statistical analysis.

Multiple linear regression models were then used to investigate the relationship between vascular biomarkers (Homocysteine, C- reactive protein, glycosylated haemoglobin and Cholesterol) and risk factors (DM, Hypertension, Smoking status) and neuropsychological tests, controlling for covariates.

Neuropsychological test scores and vascular biomarkers and risk factors were initially modelled individually in base models controlling for established covariates (gender, age, social class and educational status) (Model 2).

In a higher order model, all potential confounders identified in Model 1 (use of psychotropic medications, intake of fruit, life satisfaction as measured by the LSI, extroversion, stroke, alcohol intake, tea intake and depression) were included as covariates together with the established covariates in the base models (Model 3).

In the final model, all vascular biomarkers and risk factors were included into the regression models simultaneously with all confounders identified in Model 1 and established covariates with specific neuropsychological test results, MMSE and GC as outcomes (Model 4).

All statistical analysis was performed using SPSS 13.0. (SPSS Inc, Chicago, IL).

3.7 Summary of Research Methodology

A summary of the research methodology used in this study is shown in sequence in the flow chart below:

Postal Contact

↓

Subjects meeting criteria and consenting to take part in the study recruited

↓

Assessment in subject's home

↓

Demographic and Medical history

↓

Verbal fluency (letter [FAS test] and category [animal] fluency)

↓

Word Lists I

↓

Visual Reproduction I

↓

Letter Number sequencing

↓

Standardised Psychiatric interview based on DSM IV:SCID

↓

CAGE

↓

Word List II

↓

Visual Reproduction II

↓

Digit Symbol Coding

↓

NART

↓

CESD

↓

LSI

↓

EPI

↓

Physical Examination and Biophysical Measurements

↓

MMSE

↓

Phlebotomy

Chapter 4

Results

4.1 Demographic Profile

A total of 466 subjects participated in the study. 258 (55.4%) were female; mean age was 75.45 years (± 6.06 SD). The mean age at which subjects left school was 14.88 ((± 2.15 SD). 15.7% were from social classes 1 and 2.

Table 11 shows the distribution of subjects by age, gender, education and social class.

Table 11 Demographic profile

	Subjects (n=466)
Demographic Characteristics	
Gender [n=females (%)]	258 (55.4)
Age [mean (SD)]	75.45 (6.06)
Education [mean year left school (SD)]	14.88 (2.15)
Social class 1+2 %	15.7

4.2 Clinical, Psychosocial and Lifestyle Characteristics

16.5% of the subjects were current smokers. Total exposure in pack years was 24.38 (± 35.57 SD). 22.1% drank no alcohol. 55.2% of the subjects had a history of hypertension. Mean systolic BP was156.70 (± 23.56 SD). Mean diastolic pressure was 82.15 (±13.37 SD). Nearly 10% of subjects had DM. 23.3% had a history of cardiovascular disease, 11.2% had had a previous stroke and 6% had atrial fibrillation. Mean Body Mass Index was 26.77 (± 4.88 SD). 16.8% of subjects were on psychotropic medications, 27.3% on a statin, 52.5% on an antihypertensive and 40% were on NSAIDs.

Mean Life Satisfaction Index A scores were 14.04 (±3.95 SD). Mean CESD scores were 7.73 (±10.32 SD). Case level anxiety was 2.6% whereas case level depression was 9%.

The average number of cups of tea drunk per day was 4.46 (±2.57 SD). The average number of portions of fish, vegetables and fruit consumed per week were 1.35 (±0.7 SD), 3.01 (±0.83 SD) and 2.57 (±1.23 SD) respectively. Mean number of minutes exercised per fortnight was 396 (±492.29 SD). Range for minutes exercised per fortnight was between none and 4 hours per day.

Table 12 summarizes the clinical characteristics of subjects who participated in the study whereas table 13 summarizes the psychosocial characteristics and table 14, the dietary and lifestyle characteristics.

Table 12 Clinical Characteristics

Clinical Characteristics	
Current smokers %	16.5
Pack years [mean (SD)]	24.38 (35.57)
Teetotalers %	22.1
Hypertension %	55.2
Systolic BP [mean (SD)]	156.70 (23.56)
Diastolic BP [mean (SD)]	82.15 (13.27)
NIDDM %	9.9
Cardiovascular disease %	23.3
Stroke %	11.2
Atrial fibrillation %	6.0
Body Mass Index [mean (SD)]	26.77 (4.88)
Psychotropic Medications %	16.8
Statins %	27.3
Antihypertensives %	52.5
NSAID %	40

Table 13 Psychosocial Characteristics

Psychosocial characteristics	
Life Satisfaction Index A [mean (SD)]	14.04 (3.95)
Depression scale (CESD) [mean (SD)]	7.73 (10.32)
Anxiety (case level) %	2.6
Depression (case level)%	9

Table 14 Dietary and Lifestyle characteristics

Dietary and lifestyle characteristics	**Mean (SD)**
Tea (cups/day)	4.46 (2.57)
Fish (portions/week)	1.35 (0.70)
Vegetables (portions/week)	3.01 (0.83)
Fruit (portions/week)	2.57 (1.23)
Exercise (minutes/ fortnight)	396 (492.29)

4.3 Biochemical test results

Mean Glucose was 6.02 (±3.14 SD) mmol/L whereas mean HbA1c was 5.98 (±0.81 SD) %. Mean Total Cholesterol, LDL, HDL and TG levels were 5.17 (±1.12 SD) mmol/L, 2.90 (±0.92 SD) mmol/L, 1.39 (±0.39 SD) mmol/L and 1.75 (±0.97 SD) mmol/L respectively. Mean Homocysteine was 13.86 (±6.11 SD) µmol/L. Mean CRP was7.29 (±14.1) mg/L.

Table 15 summarizes the biochemical test results

Table 15 Biochemical test results

Biochemical test results	Mean (SD)
Glucose (mmol/L)	6.02 (3.14)
HbA1c %	5.98 (0.81)
Total Cholesterol (mmol/L)	5.17 (1.12)
LDL (mmol/L)	2.90 (0.92)
HDL (mmol/L)	1.39 (0.39)
Triglycerides (mmol/L)	1.75 (0.97)
Homocysteine (µmol/L)	13.86 (6.11)
CRP (mg/L)	7.29 (14.1)

4.4 Neuropsychological test scores

Mean MMSE scores were 26.04 (±2.87 SD). Average Premorbid IQ as measured by the NART was 98.09 (±12.55 SD). Mean letter fluency score was 25.32 (±10.38 SD) whereas mean category fluency score was 13.68 (±4.38 SD). Mean Digit Symbol Coding (Psychomotor processing speed), Letter Number Sequencing (working memory) and Visual memory scores were 33.45 (±12.01 SD), 6.52 (±2.99 SD) and 33.50 (±14.99 SD) respectively. Mean scores for Verbal memory learning slope was 3.63 (±1.96 SD), Short delay recall 3.70 (±2.49 SD), Long delay recall 3.95 (±2.46 SD), Recognition 21.32 (±2.59 SD), Total recall list 23.23 (±6.17 SD), List B recall 4.12 (±1.56 SD), Proactive interference -0.45 (±1.74 SD) and Retroactive interference 3.62 (±2.25 SD)

Table 16 summarizes the neuropsychological test scores.

Table 16 Neuropsychological test scores.

Neuropsychological test scores	**Mean (SD)**
MMSE	26.04 (2.87)
Premorbid IQ (NART)	98.09 (12.55)
Letter fluency (FAS)	25.32 (10.38)
Category fluency (Animals)	13.68 (4.38)
Psychomotor processing speed (WAIS-III Digit Symbol Coding)	33.45 (12.01)
Working Memory (WMS-III Letter Number Sequencing)	6.52 (2.99)

Visual Memory (immediate & delayed) (WMS-R Visual Reproduction)	33.50 (14.99)
Verbal Memory (WMS-III Serial Words)	
Learn slope	3.63 (1.96)
Short delay recall	3.70 (2.49)
Long delay recall	3.95 (2.46)
Recognition	21.32 (2.59)
Total recall list 1-4	23.23 (6.17)
List B recall	4.12 (1.56)
Proactive interference	-0.45 (1.74)
Retroactive interference	3.62 (2.25)

4.5 Correlations between physical and psychosocial factors and global cognition

Backward regression analysis of biological and psychosocial factors (Model 1) showed that age, lower education, lower social class, increased use of psychotropic medications, lower intake of fruit, reduced satisfaction with life as measured by the LSI, a less extroverted personality, a previous history of stroke, lower intake of alcohol, lower intake of tea and increasing severity of depression were significantly associated with poorer global cognition (as measured by a composite of the neuropsychological test battery, GC and the MMSE).

Model 1 Hierarchical multiple regression analysis of biological and psychosocial factors with only factors significant at $p<0.05$ remaining with MMSE and GC as dependents

Psychosocial and Biophysical Factors	**Dependent-GC**	
	Beta	Sig.
Age	-.266	<.001
Education	.264	.001
Social class	-.205	<.001
Psychotropic Medications	-.119	.046
Fruit portions	.135	.028
Extroversion	-.170	.006
Life satisfaction Index	.164	.009
Stroke	-.146	.012

Psychosocial and Biophysical Factors	Dependent- MMSE (DRLOW)	
	Beta	Sig.
Social class	-.112	.049
Alcohol	.115	.030
Tea Intake	.107	.042
Life satisfaction	.141	.021
Depression	-.128	.028
Psychotropic medications	-.105	.046

4.6 Correlations between vascular biomarkers and risk factors and cognition

Hierarchical multiple regression analysis with adjustment for established covariates age, gender, educational level and social class showed that higher Homocysteine levels were associated with poorer verbal memory, visual memory, slower psychomotor speed and MMSE (model 2). Additional adjustment for other biophysical and psychosocial covariates (alcohol, tea intake fish intake, stroke, use of psychotropic medications, depression and life satisfaction) identified in model 1, together with established covariates only marginally attenuated these relationships and showed that higher Homocysteine levels remained significantly associated with poorer verbal memory, visual memory and slower psychomotor speed independent of established and possible novel covariates (model 3). However, Homocysteine was no longer significantly correlated with MMSE. In the final model, the correlations between Homocysteine and the above cognitive domains remained significant even with the additional adjustment for vascular co-morbidities.

DM was significantly correlated with slower psychomotor speed and poorer global cognition independent of established covariates. These relationships remained significant with the addition of other identified covariates in model 1 as well as vascular co-morbidities. DM was also significantly associated with subsets of visual memory but these were not consistent.

Smoking status was associated with slower psychomotor speed independent of established covariates. However with the addition of other identified covariates in model 1, this association was rendered insignificant. Smoking status was also significantly associated with subsets of verbal memory although this was not consistent.

BP and Cholesterol were not associated with any measures of cognitive performance in Model 2. However, a previous history of BP was associated with better MMSE scores and higher Cholesterol levels were associated with poorer global cognition, GC in both model 3 and 4 when identified covariates and vascular co-morbidities were included.

There were no consistent significant correlations between CRP, HbA1c and cognition.

Model 2

Vascular biomarkers and risk factors individually, adjusted for covariates age, gender, education, social class, with neuropsychological test results, MMSE and GC as outcomes

Cognitive test	**Vascular Risk Factors and Biomarkers**						
	HOM	**CRP**	**HbA1c**	**CHOL**	**DM**	**↑BP**	**CIGS**
	Beta *Sig.*	Beta *Sig.*	Beta *Sig.*	Beta *Sig.*	Beta *Sig.*	Beta *Sig.*	Beta *Sig.*
FAS	.010 *.836*	.023 *.637*	.013 *.797*	-.001 *.975*	-.051 *.280*	.054 *.258*	.018 *.717*
Animals	-0.31 *.504*	-.042 *.361*	.066 *.153*	.046 *.371*	-.037 *.412*	.040 *.372*	.019 *.680*
Visual reproduction1	-.127 *.008**	.021 *.656*	.005 *.921*	-.054 *.276*	-.039 *.405*	.012 *.802*	-.030 *.530*
Visual reproduction2	-.127 *.008**	.033 *.700*	-.025 *.594*	-.033 *.513*	-.089 *.052*	.041 *.377*	-.002 *.964*
Visual Reproduction savings	-.136 *.006**	.018 *.357*	-.093 *.058*	-.029 *.589*	-.126 *.008**	.028 *.559*	.021 *.671*
vrcombo	-.131 *.006**	.028 *.601*	.004 *.930*	-.044 *.366*	-.059 *.193*	.032 *.493*	-.016 *.728*

Letter number sequencing	-.078 *.144*	-.040 *.446*	-.027 *.608*	-.067 *.210*	-.074 *.146*	-.012 *.810*	.007 *.895*
Digit symbol score	-.134 *.006**	-.073 *.130*	-.503 *.268*	-.024 *.627*	-.098 *.037**	.001 *.981*	-.129 *.007**
Verbal Short delay recall	-.057 *.243*	-.017 *.720*	-.019 *.692*	.001 *.978*	-.026 *.578*	-.031 *.506*	.068 *.159*
Verbal Free recall	-.086 *.080*	.029 *.546*	.012 *.812*	.019 *.716*	-.053 *.260*	-.013 *.783*	.045 *.350*
Verbal Recognition	-.076 *.129*	-.034 *.497*	.023 *.643*	-.076 *.157*	-.009 *.846*	.012 *.798*	.044 *.376*
Verbal learning slope	-.052 *.309*	.040 *.421*	.046 *.360*	.073 *.196*	-.003 *.958*	-.009 *.850*	.078 *.115*
Verbal recall total	-.144 *.002**	-.053 *.248*	.023 *.610*	.001 *.985*	.003 *.942*	.038 *.396*	-.063 *.163*
Verbal list B recall	-.125 *.011**	-.048 *.320*	.026 *.587*	-.077 *.146*	>.001 *.996*	-.050 *.292*	-.109 *.023**
Verbal proactive Interference	>.001 *.998*	-.047 *.354*	-.041 *.408*	.021 *.703*	.015 *.760*	.059 *.229*	.003 *.945*
Verbal retroactive Interference	-.071 *.160*	-.018 *.722*	.053 *.286*	.015 *.795*	.035 *.468*	.041 *.406*	-.081 *.104*
Composite global score	-.105 *.053*	-.017 *.758*	.018 *.741*	-.101 *.050*	-.116 *.025**	.040 *.447*	-.022 *.685*

MMSE	-.107	.014	-.078	.011	-.044	.059	-.068
(DLROW)	*.025**	*.772*	*.098*	*.826*	*.335*	*.199*	*.149*

*significant at $p<0.05$

Model 3

Vascular biomarkers and risk factors individually, adjusted for covariates age, gender, education, social class, alcohol, tea intake, depression, extroversion, life satisfaction, use of psychotropic medications, stroke, fruit intake with neuropsychological test results, MMSE and GC as outcomes

Cognitive test	**Vascular Risk Factors and Biomarkers**						
	HOM	**CRP**	**HbA1c**	**CHOL**	**DM**	**↑BP**	**CIGS**
	Beta *Sig.*	Beta *Sig.*	Beta *Sig.*	Beta *Sig.*	Beta *Sig.*	Beta *Sig.*	Beta *Sig.*
FAS	.033 *.511*	.021 *.675*	.029 *.562*	-.013 *.804*	-.048 *.322*	.091 *.070*	.004 *.936*
Animals	-.009 *.852*	-.029 *.524*	.078 *.088*	.043 *.374*	-.033 *.466*	.090 *.053*	.086 *.072*
Visual reproduction1	-.119 *.014**	.028 *.552*	>.001 *.994*	-.051 *.317*	-.043 *.365*	.018 *.716*	.003 *.955*
Visual reproduction2	-.115 *.016**	.047 *.313*	-.021 *.658*	-.034 *.494*	-.086 *.065*	.068 *.155*	.054 *.272*
Visual Reproduction savings	-.124 *.014**	.032 *.511*	-.083 *.095*	-.036 *.499*	-.115 *.017**	.065 *.199*	.074 *.152*

vrcombo	-.120	.040	.005	-.044	-.059	.051	.031
	*.012**	*.398*	*.920*	*.381*	*.201*	*.288*	*.534*
Letter number sequencing	-.071	-.043	-.028	-.074	-.076	.002	.023
	.193	*.422*	*.607*	*.197*	*.148*	*.968*	*.685*
Digit symbol score	-.109	-.057	-.040	-.032	-.088	.062	-.063
	*.021**	*.219*	*.395*	*.520*	*.054*	*.190*	*.194*
Verbal Short delay recall	-.042	-.016	-.014	-.007	-.026	.005	.106
	.393	*.743*	*.765*	*.896*	*.581*	*.921*	*.035**
Verbal Free recall	-.074	.035	.017	.014	-.055	.026	.086
	.135	*.471*	*.723*	*.784*	*.244*	*.595*	*.090*
Verbal Recognition	-.076	-.033	.017	-.076	-.018	.020	.067
	.136	*.506*	*.732*	*.154*	*.721*	*.692*	*.198*
Verbal learning slope	-.058	.038	.043	.068	>.001	-.004	.109
	.265	*.453*	*.396*	*.211*	*.999*	*.940*	*.040**
Verbal recall total	-.143	-.054	.027	-.009	.006	.076	-.037
	*.002**	*.235*	*.564*	*.856*	*.898*	*.103*	*.443*
Verbal list B recall	-.139	-.042	.027	-.085	.006	-.039	-.077
	*.005**	*.381*	*.572*	*.098*	*.901*	*.426*	*.126*
Verbal proactive Interference	.021	-.053	-.035	.020	.014	.085	-.018
	.687	*.299*	*.487*	*.717*	*.780*	*.099*	*.728*
Verbal retroactive Interference	-.087	-.022	.051	.013	.040	.033	-.091
	.091	*.658*	*.311*	*.806*	*.424*	*.525*	*.083*

Composite	-.092	-.035	.024	-.110	-.118	.088	.078
global score	*.091*	*.508*	*.647*	*.053*	*.023**	*.102*	*.157*
MMSE	-.076	.033	-.061	.011	-.039	.109	-.046
(DLROW)	*.117*	*.486*	*.198*	*.832*	*.399*	*.023**	*.350*

*significant at $p<0.05$

Model 4

All vascular biomarkers and risk factors together adjusted for covariates age, gender, education, social class, alcohol, tea intake, depression, extroversion, life satisfaction, use of psychotropic medications, stroke, fruit intake with neuropsychological test results, MMSE and GC as outcomes

Cognitive test	**Vascular Risk Factors and Biomarkers**						
	HOM	**CRP**	**HbA1c**	**CHOL**	**DM**	**↑BP**	**CIGS**
	Beta *Sig.*	Beta *Sig.*	Beta *Sig.*	Beta *Sig.*	Beta *Sig.*	Beta *Sig.*	Beta *Sig.*
FAS	.031 *.543*	.020 *.689*	.075 *.223*	-.018 *.734*	-.105 *.087*	.087 *.099*	.006 *.913*
Animals	-.015 *7547*	-.019 *.687*	.114 *.044**	.035 *.480*	-.105 *.061*	.093 *.053*	.096 *.057*
Visual reproduction1	-.116 *.022**	.025 *.605*	.036 *.545*	-.052 *.320*	-.079 *.189*	.017 *.747*	.009 *.862*
Visual reproduction2	-.117 *.018**	.048 *.310*	.025 *.662*	-.034 *.500*	-.119 *.040**	.075 *.132*	.073 *.163*
Visual Reproduction savings	-.128 *.013**	.033 *.505*	-.045 *.460*	-.036 *.503*	-.109 *.075*	.081 *.120*	.099 *.071*
vrcombo	-.119	.039	.049	-.044	-.105	.052	.043

	*.016**	*.419*	*.404*	*.391*	*.071*	*.296*	*.415*
Letter number sequencing	-.066 *.245*	-.045 *.406*	.020 *.762*	-.094 *.109*	-.104 *.118*	-.001 *.984*	.027 *.655*
Digit symbol score	-.108 *.029**	-.060 *.208*	-.029 *.622*	-.044 *.394*	-.126 *.033**	.061 *.226*	-.070 *.185*
Verbal Short delay recall	-.046 *.360*	-.010 *.835*	-.021 *.733*	-.007 *.898*	-.014 *.820*	.014 *.785*	.114 *.035**
Verbal Free recall	-.078 *.124*	.044 *.379*	.054 *.371*	.014 *.794*	-.090 *.137*	.033 *.526*	.091 *.094*
Verbal Recognition	-.075 *.156*	-.038 *.461*	.027 *.665*	-.080 *.144*	-.045 *.472*	.021 *.698*	.073 *.192*
Verbal learning slope	-.062 *.243*	.052 *.314*	.034 *.586*	.071 *.203*	-.014 *.827*	.008 *.889*	134 *.019**
Verbal recall total	-.143 *.003**	-.058 *.211*	.035 *.535*	-.003 *.945*	-.031 *.585*	.076 *.120*	-.026 *.612*
Verbal list B recall	-.128 *.012**	-.050 *.308*	.063 *.296*	-.094 *.075*	-.043 *.470*	-.056 *.274*	-.094 *.084*
Verbal proactive Interference	.015 *.779*	-.057 *.276*	-.071 *.265*	.029 *.609*	.048 *.446*	.092 *.090*	-.004 *.948*
Verbal retroactive Interference	-.082 *.124*	-.026 *.619*	.054 *.389*	.015 *.792*	-.003 *.967*	.025 *.647*	-.081 *.152*
Composite	-.089	-.037	.120	-.131	-.216	.083	.077

global score	*.101*	*.482*	*.064*	*.021**	*.001**	*.134*	*.186*
MMSE	-.082	.027	-.058	.029	-.021	.120	-.028
(DLROW)	*.100*	*.576*	*.325*	*.576*	*.720*	*.018**	*.603*

*significant at $p<0.05$

Chapter 5

Discussion of Results

5.1 Correlations between vascular biomarkers and risk factors and cognition

This study found that raised homocysteine concentrations were significantly associated with a poorer performance in neuropsychological tests assessing visual memory and verbal recall. Elevated homocysteine levels were also initially associated with poorer MMSE scores in Model 2 when adjusted for established covariate age, gender, education and social class. However this association was no longer significant when identified covariates alcohol, tea intake, depression, extroversion, life satisfaction, use of psychotropic medications, stroke, fruit intake in model 1 were adjusted for.

Hyperhomocysteinaemia has previously been implicated in the pathogenesis of arteriosclerosis and a number of epidemiological studies have shown a relationship between vascular disease and homocysteine concentrations [321]. As such, high homocysteine levels may contribute to cognitive decline through silent brain infarcts [322]. Studies on cultured neurons have shown that homocysteine potentiates Beta amyloid peptide neurotoxicity [323] and that potentiation of Beta amyloid peptide induced neuronal apoptosis may be enhanced by Homocysteine levels that are themselves benign [324-327]. Homocysteine also appears to sensitize hippocampal neurons to Beta amyloid peptide induced damage and also enhance B amyloid peptide generation by induction of a stress protein located in the endoplasmic reticulum [328]. As such homocysteine may play a more direct role in the pathogenesis of neurodegenerative disorders rather than through cerebrovascular damage [75, 329].

The results from this study support neurodegenerative aetiology over cerebrovascular damage. Deficits in visual and verbal memory suggest bilateral hippocampal and temporal dysfunction. The hippocampus is a limbic structure known to play a special role in memory and appears to be part of a complex memory circuit that consolidates new experiences into long- term memory [330]. Loss of the left hippocampus or temporal lobe impairs verbal memory [331] whereas right hippocampal damage results in dysfunction of auditory and pictorial memory, particularly with visual and auditory patterns [332, 333].

The findings of this study are consistent with the majority of cross- sectional studies [65-67, 69, 70, 72-75, 82, 84, 96, 102, 334], which have reported an association between homocysteine and cognitive dysfunction in the elderly. Three studies [77, 78, 81] however found no association whereas one study found an association only in an APOE subset [83]. Two of the negative studies [77, 81] were in populations with significant cardiovascular morbidity. Silbert and colleagues evaluated patients scheduled for coronary artery bypass grafting while Gunstad assessed 126 subjects with cardiovascular disease. As such population differences may account for the discrepancy. Most of the longitudinal studies [28, 85, 86, 88-91, 97, 334] have shown an association between elevated homocysteine levels and cognitive dysfunction but this has not been universal [93, 94]. Three longitudinal studies showed an association between homocysteine levels at baseline but not on follow up [92, 95, 96]. Methodological differences such as that found in the WHICAP study [94] may be responsible for the discrepancies. The Rotterdam study [93] used only one measure of cognition, the MMSE and as would not have been able to assess other domains of cognition adequately.

Although publication bias cannot be discounted, the weight of the evidence

suggests that it is likely that elevated homocysteine levels are associated with cognitive dysfunction. However, whether elevated levels of homocysteine is a causative factor in cognitive dysfunction (either by vascular damage or neurotoxicity) or merely a marker heralding cognitive decline is still uncertain. Interventional studies aimed at lowering homocysteine particularly in cardiovascular disease [335] have not shown that lowering homocysteine has an impact on reducing cardiovascular disease. A recent double blind placebo controlled trial investigating homocysteine lowering and cognitive performance conducted by McMahon and colleagues [336] concluded that there was no evidence showing that lowering homocysteine improved cognitive performance. However, the mean MMSE of the subjects in the study was high at baseline (mean MMSE 29.19 out of a possible 30), homocysteine levels at baseline were low and the duration of this study was short (2 years). Furthermore, subjects showed no cognitive deterioration during the trial period. As such the question of causality remains unanswered and further trials of longer duration in appropriate populations may prove informative.

DM was significantly correlated with slower psychomotor speed and poorer global cognition independent of established covariates (age, gender, education, social class), other identified covariates in model 1 (alcohol, tea intake, depression, extroversion, life satisfaction, use of psychotropic medications, stroke, fruit intake) as well as vascular co-morbidities (homocysteine, CRP, HbA1c, total cholesterol, BP, smoking status). DM was also significantly associated with subsets of visual memory but these were not consistent. The correlation between DM and cognitive dysfunction found in this study mirrors the majority of longitudinal studies evaluating associations between DM and cognition or dementia in midlife [7, 17, 179, 243, 244] and late life [185, 214, 223, 226, 228, 245-250, 253, 254]. However,

some studies have shown no associations between DM and cognition [205, 222, 251]. Discrepancies between studies may be due to a number of reasons. Study populations varied ethnically and were recruited in different ways from different backgrounds. The assessment of DM also varied from one study to another. Some studies diagnosed DM based on medical records only with implications for non-responders and dropouts. As DM is commonly undiagnosed in the elderly, dependence on medical records may also erroneously assign a substantial percentage of undiagnosed diabetics to non-diabetic groups. Longitudinal studies that assessed DM only at baseline may also have missed incident cases of DM. This is particularly important in studies with long follow-up durations or studies assessing a more elderly population [337] particularly as the fasting plasma glucose criteria to diagnose DM was lowered in 1998 [338] increasing the number of individuals diagnosed as DM [339]. Long intervals between DM assessment and assessment for dementia may also be biased by selective survival, with a higher drop out rate due to mortality before repeat assessments more likely in DM.

Although it is likely that DM is associated with cognitive dysfunction, the process by which this occurs is still unclear. DM is an accepted risk factor for cerebrovascular and microvascular disease. The possibility that the impairment of cognition is caused mainly by ischaemic cerebrovascular damage is supported by studies showing associations only with VaD [17, 245, 246] but not AD. Psychomotor slowing has been noted in other studies of middle aged and older adults with DM [252, 340] and has been linked to retinopathy [341, 342] which in turn is an indicator of cerebrovascular abnormalities [343, 344]. As such this study supports a vascular aetiology for the cognitive dysfunction found associated with DM.

Total cholesterol was significantly associated with poorer global cognition and BP was associated with better MMSE scores when identified covariates in model 1 (alcohol, tea intake, depression, extroversion, life satisfaction, use of psychotropic medications, stroke, fruit intake), were adjusted for. This association remained significant even when other vascular biomarkers and risk factors were added to the model. With numerous neuropsychological variables and multiple significance testings, several statistical tests may be expected to result in spurious significance at the conventional α level of $p<0.05$. However, in view of the strict exclusion criteria and rigorous control for confounding used in this study, the results may potentially be biased by over-adjustment towards showing null associations and therefore significant associations should not be dismissed lightly. Furthermore, despite the wide range of cognitive domains measured, the associations remained consistent and as such are plausible. Therefore, it is possible that total cholesterol and BP may be correlated with global cognition and that the effects of total cholesterol and BP on cognition may be attenuated by biophysical and psychosocial factors.

The life- long effect of total cholesterol levels on cognition however, remains uncertain. Cholesterol appears to have a central role in the biology of amyloid precursor protein and the production of beta amyloid [345]. Elevated total cholesterol levels appear likely to have a negative impact on cognition in midlife. Almost all longitudinal studies assessing midlife cholesterol and cognition [20, 177-180] have found an association between higher midlife cholesterol levels and a higher risk of developing Alzheimer's disease, dementia or cognitive dysfunction. The only exception has been the Framingham study [181], which used cumulative

time averaged cholesterol levels, making it more difficult to detect significant associations.

Longitudinal studies assessing the association between cholesterol in later life and cognition however, have been mixed with studies showing no association with dementia [184] or AD [18], a higher risk of AD with lower cholesterol [182, 183] or an association with dementia only in the oldest old [185]. One meta-analysis of 18 studies showed that there were consistent associations between high midlife TC and increased risk of AD, and high midlife TC and increased risk of any dementia. There was no evidence supporting an association between late-life total cholesterol and AD or any dementia with weak evidence for an association between TC and cognitive decline [189].

Autopsy studies performed by Papolla and colleagues [168] showed that high cholesterol correlated strongly with increased amyloid deposition in younger subjects (40-55 years). Hypercholestrolaemia almost tripled the risk of developing amyloid. However this risk disappeared with increasing age. The relationship between total cholesterol and amyloid load was not linearly correlated suggesting that although total cholesterol may be a risk factor in the development of AD pathology, other factors were also involved in amyloid accumulation. As such, discrepancies between the studies investigating cholesterol in late life may be due to several factors. It is increasingly accepted that dementia is not just a late life disease. Risk of dementia appears to be life-long, a combination of genetic susceptibility and exposure to harmful or protective environmental factors which may change over time. Increased public awareness with regards to healthy living, increased use of cholesterol lowering medications and selective survival (individuals with high cholesterol are more likely to die before reaching old age)

may result in fluid cholesterol levels over time where cholesterol increases in midlife and decreases with age. The total cholesterol levels in this study population were relatively low (5.12 mmol/L) compared to other studies showing contrasting results [181, 188] which may be due to lifestyle measures or the high penetrance of cholesterol lowering medications in this population. The relationship between cholesterol may also be bidirectional, particularly in dementia [180]. High cholesterol may therefore be a factor in the development of dementia but total cholesterol levels may fall when dementia is established. Differences in population characteristics such as racial makeup, marked differences in lifestyle, diet and use of medications may also explain the discrepancies seen. The results found in this study remains consistent with current evidence suggesting that high serum total cholesterol is associated in the initial development of cognitive dysfunction. Following this non- demented elderly population sample over time may cast more light on what happens to cholesterol levels as cognitive performance change.

The association between BP and cognition is likely to be complex as well. Hypertension in midlife, particularly if untreated, appears to have a negative impact on cognition. Studies assessing the effect of midlife BP on cognition have consistently showed an association between ↑BP in midlife and higher risk of cognitive dysfunction in later life [7, 20, 202, 204] although one Japanese study showed an association only with VaD [205]. However, hypertension in midlife is unlikely to have a similar effect on cognition as hypertension in later life. Similarly with total cholesterol, factors such as life style changes, use of antihypertensive medications and selective survival may have an impact on BP and cognition over time. Studies evaluating hypertension in later life and cognitive dysfunction have been inconsistent with studies showing no association between BP and cognitive

function [211, 222, 224], an association with VaD only [214], an association with either elevated SBP or DBP depending on age [206, 227], an association with elevated DBP only [223], an association with cognitive decline but not dementia [187], an association with either dementia or cognitive decline [185, 225, 226], an association only with low BP [210], a u shaped association [215] or a lower probability of developing dementia with ↑BP [228]. The heterogenecity of the results shown reflect the differences in study design and methodology such as populations studied, duration of follow-up, covariates controlled for and the definitions of ↑BP. This study showed that subjects with a history of hypertension were associated with higher MMSE scores when identified covariates were adjusted for. This remained significant even when other vascular biomarkers and risk factors were added to the model. Methodological differences particularly in the definition of BP may explain discrepancies between the results of this study and that seen in others. The definition of BP in this study was based on patient self- reporting of medical history and medications taken (medications were inspected in all cases). All subjects with physician diagnosed ↑BP or who had been prescribed antihypertensives were defined as having a history of ↑BP. Thus almost all subjects defined as having ↑BP were on antihypertensives (only 2.7% of subjects with ↑BP were not on medications). Although the average BP in the ↑BP group remained higher (SBP 161.21± 23.56 DBP 83.55±13.27) compared to the non- ↑BP group (SBP 153.37±21.29 DBP 82.32±12.50), this was not statistically significant.

Several studies evaluating the effects of treatment of ↑BP on cognition have shown that treatment with antihypertensive medication appear to be protective with subjects on antihypertensive therapy at lower risk of cognitive impairment and AD [216, 217, 346-348]. However the Systolic Hypertension in the Elderly Project

(SHEP) trial [349], which enrolled subjects over 60 years (mean age 71.6 years) with isolated systolic hypertension found no benefits cognitively with antihypertensive treatment. No significant effect of antihypertensive therapy on cognitive function was also seen in a Medical Research Council (MRC) Trial [350]. The Hypertension in the Very Elderly Trial (HYVET-COG) [351], a double-blinded, placebo- controlled trial which enrolled non- demented subjects aged 80 years or older at baseline, found no statistical reduction in the incidence of dementia between participants randomly assigned to receive 1.5 mg slow release indepamide with the option of Perindopril (n=1687) or placebo (n=1649).

A further analysis of the SHEP trial [352] however suggested that participants experiencing either functional or cognitive decline were more likely to drop out of the study and were unavailable for follow-up assessments resulting in a bias toward a null effect. The MRC trial was of shorter duration and may have been unable to detect an association particularly if, as the studies assessing BP in midlife show, the effect of BP on cognition is exerted over a long period of time. The HYVET-COG trial was also of short duration (mean 2.2 years) as it was terminated early after interim analysis showed significant reductions in stroke and total mortality. Of note, when data from the HYVET-COG trial was combined in a meta-analysis, the results supported the possibility that antihypertensive treatment may reduce the incidence of dementia.

As such, it is possible that antihypertensive therapy may be cognitively beneficial and that the results shown in this study may be due to the effect of antihypertensive medication use. This is supported by post mortem studies showing evidence of substantially reduced AD neuropathology in brain specimens of subjects on antihypertensive treatment compared to subjects without a diagnosis of

hypertension [353]. There may be different mechanisms of action of antihypertensive medications in the prevention of cognitive decline. In PROGRESS, a post stroke study, treatment with angiotensin converting enzyme inhibitors with or without diuretics reduced the risks of dementia and cognitive decline associated with recurrent stroke but not dementia without stroke [348]. The use of dihydropyridine calcium antagonists were associated with a decreased risk of cognitive impairment and AD independent of blood pressure levels in other studies, suggesting a neuroprotective effect [217, 346]. Another possibility however is that subjects on antihypertensives may also be more aware with regards to health issues and the association seen in this study between BP and cognition may be a reflection of lifestyle with disease avoiding behaviour.

There were no associations shown between cognition and other vascular biomarkers or risk factors. Similar to results reported in other case control [156, 157] and cross-sectional studies [78, 155], no association between HbA1c and cognition was found in this study. One cross sectional study [161] reported a U shaped association. This discrepancy may be due to ethnic differences as the population studied by Amano and colleagues were Japanese whereas the other studies investigated caucasian populations. Three longitudinal studies [162-164] have reported an association between elevated HbA1c levels and cognitive dysfunction. Populations studied and methodology in these studies were however, very dissimilar. Yaffe and colleagues [162] investigated the development of mild cognitive impairment or dementia as part of an ancillary study in postmenopausal women with osteoporosis. Gao and colleagues [163] investigated mortality and other outcomes of raised HbA1c in participants flagged for death notification whereas Maggi and colleagues evaluated subjects with type 2 Diabetes [164].

HbA1c, a measure of glycaemic control over a period of one hundred and twenty days, may be affected by factors resulting in reduced or increased red cell survival. HbA1c may also fluctuate with time for example, with changes in diet and exercise patterns. In addition, survival bias may also explain the discrepancy between cross-sectional and longitudinal study outcomes. Recent studies focusing on glycaemic control in diabetic subjects have shown that although tight glycaemic control in newly diagnosed younger patients with type 2 DM may have cardiovascular benefits in later life, tight glycaemic control in older patients with established or subclinical cardiovascular disease has no impact on cardiovascular outcomes and may increase the risk of mortality and morbidity [354]. As such, although it is possible that glycaemic dysregulation may be associated with cognitive impairment, this study does not support a cross sectional association.

There was also no consistent correlation found between CRP and cognition in this study although an association between CRP and cognition is biologically plausible. CRP appears to have a proatherogenic role and may be an active participant in the development of atherogenesis [355, 356] by mediation of LDL cholesterol uptake and facilitating the formation of foam cells [357], stimulating the recruitment of monocytes [358], promoting vascular smooth vessel cell proliferation and migration [359] as well as causing endothelial dysfunction by attenuating the production of Nitric oxide [360]. As such, raised CRP levels may be a risk factor for micrangiopathic and macroangiopathic cerebrovascular disease although some animal studies do not support an aetiological role for CRP in early atherogenesis [361]. There is also some evidence that elevated CRP levels may be directly neurotoxic in vitro [362]. Immunohistochemical studies have shown evidence of immunoreactivity for CRP in the brains of patients with Alzheimer's disease [363,

364]. However, results from observational studies have been inconsistent. Three cross sectional studies found no association between CRP and cognition [78, 81, 133] although Gunstad and colleagues [77] reported an association between cognitive performance and higher CRP levels in subjects with cardiovascular disease. Results from longitudinal studies have also been mixed with some studies showing an association between cognition and elevated CRP levels [29, 127, 134, 135, 137, 138] and others, no association [139-142]. There are several possible explanations for the observed lack of association between CRP levels and cognition in this study. Although local inflammatory processes in the brain have been shown to be associated with systemic inflammation peripherally [365], the reverse is not necessarily true. Increased circulating levels of inflammatory cytokines such CRP due to systemic inflammation may not be mirrored by intracerebral inflammatory responses due to the presence of the blood brain barrier. As such, raised CRP levels measured peripherally may not equate to inflammatory processes in the brain. Furthermore, analysis of inflammatory marker levels at one time point such as in this study may be influenced by other factors such as a concomitant illness. In addition, systemic factors unrelated to degenerative processes such as ageing can also influence circulating CRP levels. Temporarily elevated levels, if affecting subjects randomly, may potentially lead to an underestimation of possible correlations between CRP and cognition. Survival bias may also contribute to the discrepancies found between studies as individuals with higher CRP levels have a greater risk of mortality [124]. A response bias would also account for discrepancies. It is possible that non- participants may be more unwell and thus more likely to have elevated CRP levels. Exclusion would therefore bias towards the null hypothesis.

Smoking status was associated with slower psychomotor speed when adjusted for established covariates age, gender, educational status or social class. However with the addition of other identified covariates (alcohol, tea intake, depression, extroversion, life satisfaction, use of psychotropic medications, stroke, fruit intake), this association was no longer significant. Smoking status was also significantly associated with subsets of verbal memory although this was not consistent. Results from early small case-control studies suggested that smoking had a protective effect on dementia. However, longitudinal studies investigating smoking in mid life and cognition have either shown no associations between smoking and dementia [7, 205, 231] or an increased risk of cognitive dysfunction [179, 232-234]. Studies investigating late life smoking status and cognition have shown similar results with some studies showing no association [187, 211, 222, 235] and others, an increase in dementia risk [31, 226]. One study reported an association only in the older old (subjects>75 years) [237]. A meta-analysis of 19 studies suggested that elderly smokers were more at risk for developing dementia compared to non- smokers [189].

The discrepancy between longitudinal studies and cross-sectional studies is most likely because of survival bias (where smokers were less likely to survive to show the negative effects of smoking) or loss to follow –up due to non participation [366]. Methodological differences such as study duration, definitions of smoking status and follow up periods may account for the mixed results reported by longitudinal studies. Study populations were also varied. Most of the studies relied on self- reporting for smoking status whereas some studies reviewed medical notes. Adjustment for confounding was also variable with the majority of studies adjusting only for established covariates. The impact of secondhand smoke on cognition

remains uncertain and may also need to be adjusted for in non- smokers [367]. This study does not support a cross- sectional association between smoking status and cognition. This study does however suggest that biophysical and psychosocial factors attenuate associations between smoking status and cognition and as such need to be taken into account as possible confounders.

The results from this study support an association between elevated levels of homocysteine, higher total cholesterol, DM, BP and cognitive dysfunction but not an association between raised HbA1c, CRP or smoking status and cognitive performance. This study also shows that biophysical and psychosocial factors attenuate associations between cognition and vascular biomarkers and risk factors particularly homocysteine, total cholesterol, BP and smoking status.

5.2 Correlations of biophysical and psychosocial factors and cognition

This study showed that in addition to established covariates such as age, gender, social class and educational status, other factors such as alcohol, tea intake, depression, extroversion, life satisfaction, use of psychotropic medications, stroke, fruit intake were independent associations of cognitive performance in this elderly community dwelling non- demented population. Lifestyle differences in different socio-economic groups such as leisure activities, diet, nutrition, or other environmental factors may prove to be important in maintaining cognition [368, 369].

Findings in this study, for example, the association between psychotropic medication use and poorer cognitive function are consistent with that shown in other studies [370-372] although Vignola and colleagues as well as Allard and colleagues have suggested that the use of psychotropic medications may be benign cognitively [373, 374] if patients with prodromal dementia are taken into account. Stroke is a risk factor for vascular dementia [375] and may have a role to play in Alzheimer's disease [9]. A number of studies have found a significant association between cognition and depression [376, 377] although results have been less consistent in elderly population studies [378-380]. Several researchers have suggested that cognitive impairment associated with depression in elderly individuals may reflect underlying organic brain disease [381, 382]. Increments in life satisfaction in the elderly has also been shown to be associated with cognitive performance by Rabbitt and colleagues [383]. The impact of alcohol on cognition in the elderly remains controversial [384]. Studies on tea have shown evidence that it may be of benefit in reducing cardiovascular disease and improvements in cognitive performance [284, 385]. Studies assessing the effects of diet on cognition have however, been

generally inconclusive due to methodological difficulties particular with accurate reporting of dietary habits over a period of time [386]. It is plausible however that fruit intake may be associated with cognitive performance [387, 388] although, in contrast to this study, two other studies have found an association between better cognitive function and high intake of vegetables but not fruit [389, 390]. Another possibility is that a higher fruit intake reflects changes towards a healthier lifestyle [391].

This study supports the possibility that biophysical and psychosocial factors may have an impact on cognition and as such should be taken into account in studies assessing cognitive performance.

5.3 Limitations and strengths

Limitations of this study include a single timed measurement of vascular biomarkers, which lends itself to measurement error. This, if non- differential, could have contributed to an underestimation of the effect of vascular biomarkers on cognitive performance. Furthermore, analysis of CRP could have been affected by concomitant illnesses such as a viral infection which may elevate levels. Homocysteine and TC samples in this study were also obtained from non- fasting subjects. However, this may not be significant. Although fasting TC levels may be slightly lower than random nonfasting TC, fasting and nonfasting TC levels are highly correlated and any difference is usually not clinically relevant [392]. Studies have also found no significant difference between levels of plasma homocysteine measured and postprandial levels in the same subject [393]. Therefore, any increase in variability in homocysteine or TC values is likely to be random and unlikely to have altered the results.

Pyridoxine (B6) levels and renal status were not adjusted for in this study and as such may be possible confounding factors. Subjects with chronic renal failure have higher levels of homocysteine [394]. Pyridoxine deficiency can also lead to higher homocysteine levels. However, homocysteine has been reported as a risk factor for coronary and cerebrovascular events [395] as well as cognitive decline [90] independent of pyridoxine.

The population studied was an urban community population and as such the findings may not be applicable to rural or other ethnic populations. Although the response rate in this study was comparable to other studies, the possibility of a response bias potentially reducing an association between vascular factors and cognitive performance cannot be out-ruled. This study depended on self- reporting for medical history including vascular risks such as smoking and lifestyle factors such as alcohol use, diet and exercise, which may have resulted in some misclassification and would have tended to reduce any associations with cognitive dysfunction. Due to the cross sectional nature of this study, the possibility that a survival bias as seen with smoking, or yet unknown confounding factors may have modified the result could not be discounted nor is this study able to determine cause and effect. Finally, this study did not study genetic risk factors such as epsilon 4 allelle of lipoprotein E [396].

Strengths of this study would include a homogenous non- demented population sample, use of an extensive cognitive battery, consistency and expertise in neuropsychological assessments in the elderly and a comprehensive physical assessment.

5.4 Study instruments

Numerous fixed neuropsychological test batteries are available, well validated and widely used. However, in specific situations such as research purposes, a tailored test battery is often more appropriate, taking into account the population being tested, the environment in which the test will be administered, the time available for testing and the hypotheses under examination. If possible, the test battery should include both tests of general intellectual function and tests that evaluate specific domains. As such, a test battery to evaluate cognitive deficits in non- demented community dwelling elderly subjects with regards to vascular risks should include tests to assess general cognition as well as attention, memory especially recall and recognition, language, executive function, visuospatial ability and psychomotor speed. The tests selected should be standardised and well validated for use in the elderly. The selection of tests for this study's neuropsychological test battery reflects the abovementioned issues, enabling a short but comprehensive assessment covering general cognition as well as the important domains within a limited time in the subjects' own homes.

5.5 Recommendations

5.5.1 Further research

Further areas of study which may be of benefit include:

a) Genetic testing

It is likely that genetic susceptibility and environmental risk factor interactions play a role in the aetiology of cognitive dysfunction and vascular disease. As such, genetic factors such as APOE may be important considerations when studying cardiovascular risk factors on cognitive decline in the elderly [397].

APOE appears to mediate neuronal repair as well as neuronal protection and remodelling and may affect early beta- amyloid deposition [398]. Epidemiological studies have shown an association between APOE and dementia risk [396, 399]. Individuals homozygous for APOE e4 appear to be more likely to develop cognitive impairment [399]. APOE e4 has also been linked to the severity of AD [400], the age of onset of the disease [401, 402], increased hippocampal atrophy [403], decreased survival [404], increased Alzheimer's type neuropathology on autopsy [405] as well as increased associated psychiatric complications [406].

It is still uncertain as to how APOE influences the development of AD. APOE e4 has been shown to affect plasma lipid levels and is associated with an increased risk of atherosclerosis [407, 408] However other studies have suggested that dyslipidaemia and vascular disease may not be the primary mechanism of action [409-411] although it may mediate the effect of vascular risk factors such as LDL cholesterol on AD risk [412]. APOE genetic polymorphism also appears to affect the interaction of other vascular risk factors such as smoking [413], hyperhomocysteinaemia [83], as well as DM [414] and hyperglycaemia [397]. As such, APOE status may need to be considered and controlled for when assessing vascular risk factors and AD risk in population studies.

b) Evaluation of Folate and vitamin B12 levels and correlations with homocysteine and cognition.

Homocysteine is a thiol- containing amino acid that links the methionine cycle with the folate cycle and may be a marker for folate and vitamin B12 deficiency [415]. There is evidence to suggest that folate and vitamin B12 may have an effect on cognitive function [74, 88, 95, 416]. Since homocysteine is closely

linked to folate and vitamin B12 bio-chemically, it would be informative to assess the effect homocysteine on cognition independent of folate and B12. Trials to ascertain the potential benefits of homocysteine lowering therapy on cognition would also be informative.

c) Longitudinal assessment

A longitudinal arm assessing subjects annually or bi-annually would give further information regarding factors associated with the progress of cognitive dysfunction and the development of clinical conditions such as MCI and dementia. It will also allow conclusions about cause and effect as well as provide greater statistical power and capability to estimate a greater range of conditional probabilities. However the disadvantages of extending the study would include greater cost and the possibility that cognitive decline may be masked by a learning effect and other factors associated with repeated testing.

5.5.2 Clinical

The results from this study suggest that appropriate treatment of DM and TC might be of benefit cognitively in the elderly although the extent of glycaemic control remains uncertain. Use of antihypertensive therapy in subjects diagnosed with ↑BP also appears to be beneficial in terms of cognitive performance. Interventions to lower homocysteine levels may potentially be of benefit cognitively although further clinical trials in suitable populations need to be performed to ascertain this.

Chapter 6

Conclusion

In this elderly non- demented community population, elevated homocysteine concentrations were significantly associated with a poorer performance in neuropsychological tests assessing visual memory and verbal recall. DM was significantly correlated with slower psychomotor speed and poorer global cognition, a history of ↑BP was associated with better MMSE scores and higher total cholesterol levels were associated with poorer global cognition when biophysical and psychosocial factors were adjusted for. There were no consistent associations found between CRP, HbA1c and smoking status with cognition. In addition, aside from the established confounds of cognitive performance such as age, educational status and social class, other potential psychosocial and biophysical covariates were identified.

An increased use of psychotropic medications, a lower intake of alcohol, fruit and tea, reduced satisfaction with life, a less extroverted personality, a previous history of stroke and severity of depression were associated with poorer global cognition. These psychosocial covariates significantly attenuated the associations found between homocysteine, BP and TC and global cognitive performance.

Although this study supports an association between homocysteine, DM, BP and TC and cognitive performance but not CRP, HbA1c or smoking status, not all studies have shown similar results. Potential explanations for discrepancies include methodological and population differences between studies. Age may also be an important factor. Subjects with adverse outcomes related to vascular risks and biomarkers may not have survived to inclusion in studies or may have become ineligible. It is also possible that vascular risks and biomarkers are related to

cognitive performance in younger individuals only. Furthermore, risks and levels of biomarkers at the age of entry may not necessarily reflect risks and levels earlier in life. In addition, it is possible that residual and uncontrolled confounding could have influenced previous reports.

This study identifies further areas of research including genetic testing as well as the need to evaluate associations between homocysteine, folate, vitamin B12, proteins involved in vitamin B12 transportation and cognition. A longitudinal arm would enable study of the development of clinical conditions such as MCI and dementia and allow conclusions about cause and effect. The results from this study also suggest that appropriate treatment of DM and TC, and the use of antihypertensive therapy in subjects diagnosed with ↑BP might be of benefit cognitively in the elderly. Interventions to lower homocysteine levels may also potentially be of benefit cognitively.

Finally, this study suggests that psychosocial factors need to be taken into account in future studies investigating associations between vascular factors and cognition.

References

1. Descrates, R., Laurence J. Lafleur (trans.), *Discourse on Method and Meditations*. 1960, New York: The Liberal Arts Press.
2. Locke, J., *Works*. 1975: Clarendon.
3. Aguero-Torres, H., et al., *The impact of somatic and cognitive disorders on the functional status of the elderly.* J Clin Epidemiol, 2002. **55**(10): p. 1007-12.
4. Unverzagt, F.W., et al., *Prevalence of cognitive impairment: data from the Indianapolis Study of Health and Aging.* Neurology, 2001. **57**(9): p. 1655-62.
5. Greiner, P.A., D.A. Snowdon, and F.A. Schmitt, *The loss of independence in activities of daily living: the role of low normal cognitive function in elderly nuns.* Am J Public Health, 1996. **86**(1): p. 62-6.
6. Tuokko, H., et al., *Five-year follow-up of cognitive impairment with no dementia.* Arch Neurol, 2003. **60**(4): p. 577-82.
7. Knopman, D., et al., *Cardiovascular risk factors and cognitive decline in middle-aged adults.* Neurology, 2001. **56**(1): p. 42-8.
8. Singh-Manoux, A., A.R. Britton, and M. Marmot, *Vascular disease and cognitive function: evidence from the Whitehall II Study.* J Am Geriatr Soc, 2003. **51**(10): p. 1445-50.
9. Snowdon, D.A., et al., *Brain infarction and the clinical expression of Alzheimer disease. The Nun Study.* Jama, 1997. **277**(10): p. 813-7.
10. Launer, L.J., et al., *AD brain pathology: vascular origins? Results from the HAAS autopsy study.* Neurobiol Aging, 2008. **29**(10): p. 1587-90.

11. Carmelli, D., et al., *Midlife cardiovascular risk factors and brain morphology in identical older male twins.* Neurology, 1999. **52**(6): p. 1119-24.

12. Stamler, J., R. Stamler, and J.D. Neaton, *Blood pressure, systolic and diastolic, and cardiovascular risks. US population data.* Arch Intern Med, 1993. **153**(5): p. 598-615.

13. Blake, G.J., et al., *Blood pressure, C-reactive protein, and risk of future cardiovascular events.* Circulation, 2003. **108**(24): p. 2993-9.

14. Stamler, J., et al., *Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial.* Diabetes Care, 1993. **16**(2): p. 434-44.

15. Neaton, J.D. and D. Wentworth, *Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. Overall findings and differences by age for 316,099 white men. Multiple Risk Factor Intervention Trial Research Group.* Arch Intern Med, 1992. **152**(1): p. 56-64.

16. Hofman, A., et al., *Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam Study.* Lancet, 1997. **349**(9046): p. 151-4.

17. Curb, J.D., et al., *Longitudinal association of vascular and Alzheimer's dementias, diabetes, and glucose tolerance.* Neurology, 1999. **52**(5): p. 971-5.

18. Moroney, J.T., et al., *Low-density lipoprotein cholesterol and the risk of dementia with stroke.* Jama, 1999. **282**(3): p. 254-60.

19. Breteler, M.M., *Vascular involvement in cognitive decline and dementia. Epidemiologic evidence from the Rotterdam Study and the Rotterdam Scan Study.* Ann N Y Acad Sci, 2000. **903**: p. 457-65.

20. Kivipelto, M., et al., *Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study.* Bmj, 2001. **322**(7300): p. 1447-51.

21. Singh-Manoux, A. and M. Marmot, *High blood pressure was associated with cognitive function in middle-age in the Whitehall II study.* J Clin Epidemiol, 2005. **58**(12): p. 1308-15.

22. Wald, D.S., M. Law, and J.K. Morris, *Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis.* Bmj, 2002. **325**(7374): p. 1202.

23. Ridker, P.M., et al., *Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events.* N Engl J Med, 2002. **347**(20): p. 1557-65.

24. Pai, J.K., et al., *Inflammatory markers and the risk of coronary heart disease in men and women.* N Engl J Med, 2004. **351**(25): p. 2599-610.

25. Manolio, T.A., et al., *Cholesterol and heart disease in older persons and women. Review of an NHLBI workshop.* Ann Epidemiol, 1992. **2**(1-2): p. 161-76.

26. Lloyd-Jones, D.M., et al., *Lifetime risk of coronary heart disease by cholesterol levels at selected ages.* Arch Intern Med, 2003. **163**(16): p. 1966-72.

27. Khaw, K.T., et al., *Association of hemoglobin A1c with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk.* Ann Intern Med, 2004. **141**(6): p. 413-20.

28. Seshadri, S., et al., *Plasma homocysteine as a risk factor for dementia and Alzheimer's disease.* N Engl J Med, 2002. **346**(7): p. 476-83.

29. Engelhart, M.J., et al., *Inflammatory proteins in plasma and the risk of dementia: the rotterdam study.* Arch Neurol, 2004. **61**(5): p. 668-72.

30. Logroscino, G., J.H. Kang, and F. Grodstein, *Prospective study of type 2 diabetes and cognitive decline in women aged 70-81 years.* Bmj, 2004. **328**(7439): p. 548.

31. Ott, A., et al., *Effect of smoking on global cognitive function in nondemented elderly.* Neurology, 2004. **62**(6): p. 920-4.

32. Luchsinger JA, R.C., Honig LS, Tang MX, Shea S, Mayeux R, *Aggregation of vascular risk factors and risk of incident Alzheimer disease.* Neurology, 2005. **65**(4): p. 545- 551.

33. Kuo, H.K., et al., *Effect of blood pressure and diabetes mellitus on cognitive and physical functions in older adults: a longitudinal analysis of the advanced cognitive training for independent and vital elderly cohort.* J Am Geriatr Soc, 2005. **53**(7): p. 1154-61.

34. Sesso, H.D., et al., *C-reactive protein and the risk of developing hypertension.* Jama, 2003. **290**(22): p. 2945-51.

35. Wildman, R.P., et al., *Lipoprotein levels are associated with incident hypertension in older adults.* J Am Geriatr Soc, 2004. **52**(6): p. 916-21.

36. Richards, S.S., et al., *The association between vascular risk factor-mediating medications and cognition and dementia diagnosis in a*

community-based sample of African-Americans. J Am Geriatr Soc, 2000. **48**(9): p. 1035-41.

37. Amery, A., et al., *Influence of anti-hypertensive therapy on serum cholesterol in elderly hypertensive patients. Results of trial by the European Working Party on High blood pressure in the Elderly (EWPHE).* Acta Cardiol, 1982. **37**(4): p. 235-44.

38. Prince, M.J., et al., *Metabolic effects of hydrochlorothiazide and enalapril during treatment of the hypertensive diabetic patient. Enalapril for hypertensive diabetics.* Arch Intern Med, 1988. **148**(11): p. 2363-8.

39. Singh-Manoux, A., M. Richards, and M. Marmot, *Leisure activities and cognitive function in middle age: evidence from the Whitehall II study.* J Epidemiol Community Health, 2003. **57**(11): p. 907-13.

40. Weuve, J., et al., *Physical activity, including walking, and cognitive function in older women.* Jama, 2004. **292**(12): p. 1454-61.

41. Scarmeas, N., et al., *Physical activity, diet, and risk of Alzheimer disease.* Jama, 2009. **302**(6): p. 627-37.

42. Marti, B., et al., *[Total cholesterol, HDL-cholesterol and blood pressure in relation to life style: results of the first population screening of the Swiss MONIKA Project].* Schweiz Med Wochenschr, 1990. **120**(51-52): p. 1976-88.

43. Burke, V., et al., *Association of lifestyle and personality characteristics with blood pressure and hypertension: a cross-sectional study in the elderly.* J Clin Epidemiol, 1992. **45**(10): p. 1061-70.

44. Palatini, P., et al., *[The relationship between overweight, life style and casual and 24-hour pressures in a population of male subjects with mild*

hypertension. The results of the HARVEST study]. G Ital Cardiol, 1995. **25**(8): p. 977-89.

45. Vivekananthan, D.P., et al., *Use of antioxidant vitamins for the prevention of cardiovascular disease: meta-analysis of randomised trials.* Lancet., 2003. **361**(9374): p. 2017-23.

46. Waters, D.D., et al., *Effects of hormone replacement therapy and antioxidant vitamin supplements on coronary atherosclerosis in postmenopausal women: a randomized controlled trial.* Jama., 2002. **288**(19): p. 2432-40.

47. Manson, J.E., et al., *Estrogen plus progestin and the risk of coronary heart disease.* N Engl J Med., 2003. **349**(6): p. 523-34.

48. Pearson, T.A., et al., *AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update: Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients Without Coronary or Other Atherosclerotic Vascular Diseases. American Heart Association Science Advisory and Coordinating Committee.* Circulation, 2002. **106**(3): p. 388-91.

49. Carson, N.A. and D.W. Neill, *Metabolic abnormalities detected in a survey of mentally backward individuals in Northern Ireland.* Arch Dis Child, 1962. **37**: p. 505-13.

50. Booth, G.L. and E.E. Wang, *Preventive health care, 2000 update: screening and management of hyperhomocysteinemia for the prevention of coronary artery disease events. The Canadian Task Force on Preventive Health Care.* Cmaj, 2000. **163**(1): p. 21-9.

51. Selhub, J., et al., *Vitamin status and intake as primary determinants of homocysteinemia in an elderly population.* Jama, 1993. **270**(22): p. 2693-8.

52. Refsum, H., et al., *Homocysteine and cardiovascular disease.* Annu Rev Med, 1998. **49**: p. 31-62.

53. Nygard, O., et al., *Major lifestyle determinants of plasma total homocysteine distribution: the Hordaland Homocysteine Study.* Am J Clin Nutr, 1998. **67**(2): p. 263-70.

54. Hussein, W.I., et al., *Normalization of hyperhomocysteinemia with L-thyroxine in hypothyroidism.* Ann Intern Med, 1999. **131**(5): p. 348-51.

55. Jacques, P.F., et al., *Determinants of plasma total homocysteine concentration in the Framingham Offspring cohort.* Am J Clin Nutr, 2001. **73**(3): p. 613-21.

56. Yoo, J.H., C.S. Chung, and S.S. Kang, *Relation of plasma homocyst(e)ine to cerebral infarction and cerebral atherosclerosis.* Stroke, 1998. **29**(12): p. 2478-83.

57. Matsui, T., et al., *Elevated plasma homocysteine levels and risk of silent brain infarction in elderly people.* Stroke, 2001. **32**(5): p. 1116-9.

58. Kim, N.K., et al., *Hyperhomocysteinemia as an independent risk factor for silent brain infarction.* Neurology, 2003. **61**(11): p. 1595-9.

59. den Heijer, T., et al., *Homocysteine and brain atrophy on MRI of non-demented elderly.* Brain, 2003. **126**(Pt 1): p. 170-5.

60. Clarke, R., et al., *Folate, vitamin B12, and serum total homocysteine levels in confirmed Alzheimer disease.* Arch Neurol, 1998. **55**(11): p. 1449-55.

61. McCaddon, A., et al., *Total serum homocysteine in senile dementia of Alzheimer type.* Int J Geriatr Psychiatry, 1998. **13**(4): p. 235-9.

62. McIlroy, S.P., et al., *Moderately elevated plasma homocysteine, methylenetetrahydrofolate reductase genotype, and risk for stroke, vascular*

dementia, and Alzheimer disease in Northern Ireland. Stroke, 2002. **33**(10): p. 2351-6.

63. Cascalheira, J.F., et al., *Serum Homocysteine: Interplay with other circulating and genetic factors in association to Alzheimer's Type Dementia.* Clin Biochem, 2009.

64. Miller, J.W., et al., *Homocysteine, vitamin B6, and vascular disease in AD patients.* Neurology, 2002. **58**(10): p. 1471-5.

65. Prins, N.D., et al., *Homocysteine and cognitive function in the elderly: the Rotterdam Scan Study.* Neurology, 2002. **59**(9): p. 1375-80.

66. Budge, M.M., et al., *Total plasma homocysteine, age, systolic blood pressure, and cognitive performance in older people.* J Am Geriatr Soc, 2002. **50**(12): p. 2014-8.

67. Ravaglia, G., et al., *Homocysteine and cognitive function in healthy elderly community dwellers in Italy.* Am J Clin Nutr, 2003. **77**(3): p. 668-73.

68. Duthie, S.J., et al., *Homocysteine, B vitamin status, and cognitive function in the elderly.* Am J Clin Nutr, 2002. **75**(5): p. 908-13.

69. Miller, J.W., et al., *Homocysteine and cognitive function in the Sacramento Area Latino Study on Aging.* Am J Clin Nutr, 2003. **78**(3): p. 441-7.

70. Wright, C.B., et al., *Total homocysteine and cognition in a tri-ethnic cohort: the Northern Manhattan Study.* Neurology, 2004. **63**(2): p. 254-60.

71. Aleman, A., et al., *Vascular risk factors and cognitive function in a sample of independently living men.* Neurobiol Aging, 2005. **26**(4): p. 485-90.

72. Schafer, J.H., et al., *Homocysteine and cognitive function in a population-based study of older adults.* J Am Geriatr Soc, 2005. **53**(3): p. 381-8.

73. Clark, M.S., J.R. Guthrie, and L. Dennerstein, *Hyperhomocysteinemia is associated with lower performance on memory tasks in post-menopausal women.* Dement Geriatr Cogn Disord, 2005. **20**(2-3): p. 57-62.

74. Feng, L., et al., *Homocysteine, folate, and vitamin B-12 and cognitive performance in older Chinese adults: findings from the Singapore Longitudinal Ageing Study.* Am J Clin Nutr, 2006. **84**(6): p. 1506-12.

75. van Raamt, A.F., et al., *Homocysteine level and cognitive function in patients with arterial disease: the second manifestations of ARTerial Disease Study.* J Am Geriatr Soc, 2006. **54**(4): p. 575-9.

76. Tassino, M., T.F. Campos, and R.O. Guerra, *Homocysteine (Hcy) and cognitive performance in a population sample of elderly Brazilians.* Arch Gerontol Geriatr, 2009. **48**(2): p. 142-5.

77. Gunstad, J., et al., *C-reactive protein, but not homocysteine, is related to cognitive dysfunction in older adults with cardiovascular disease.* J Clin Neurosci, 2006. **13**(5): p. 540-6.

78. Fischer, P., et al., *Relation between vascular risk factors and cognition at age 75.* Acta Neurol Scand, 2006. **114**(2): p. 84-90.

79. Hengstermann, S., et al., *Total serum homocysteine levels do not identify cognitive dysfunction in multimorbid elderly patients.* J Nutr Health Aging, 2008. **12**(6): p. 411-6.

80. Ravaglia, G., et al., *Elevated plasma homocysteine levels in centenarians are not associated with cognitive impairment.* Mech Ageing Dev, 2000. **121**(1-3): p. 251-61.

81. Silbert, B., et al., *Homocysteine and C-reactive protein are not markers of cognitive impairment in patients with major cardiovascular disease.* Dement Geriatr Cogn Disord, 2008. **25**(4): p. 309-16.

82. Stewart, R., B. Asonganyi, and R. Sherwood, *Plasma homocysteine and cognitive impairment in an older British African-Caribbean population.* J Am Geriatr Soc, 2002. **50**(7): p. 1227-32.

83. Elias, M.F., et al., *Homocysteine and cognitive performance: modification by the ApoE genotype.* Neurosci Lett, 2008. **430**(1): p. 64-9.

84. Elias, M.F., et al., *Homocysteine and cognitive performance in the Framingham offspring study: age is important.* Am J Epidemiol, 2005. **162**(7): p. 644-53.

85. McCaddon, A., et al., *Homocysteine and cognitive decline in healthy elderly.* Dement Geriatr Cogn Disord, 2001. **12**(5): p. 309-13.

86. Dufouil, C., et al., *Homocysteine, white matter hyperintensities, and cognition in healthy elderly people.* Ann Neurol, 2003. **53**(2): p. 214-21.

87. Schafer, J.H., et al., *Homocysteine and cognitive function in a population-based study of older adults.* J Am Geriatr Soc, 2005. **53**(3): p. 381-8.

88. Nurk, E., et al., *Plasma total homocysteine and memory in the elderly: the Hordaland Homocysteine Study.* Ann Neurol, 2005. **58**(6): p. 847-57.

89. Ravaglia, G., et al., *Homocysteine and folate as risk factors for dementia and Alzheimer disease.* Am J Clin Nutr, 2005. **82**(3): p. 636-43.

90. Tucker, K.L., et al., *High homocysteine and low B vitamins predict cognitive decline in aging men: the Veterans Affairs Normative Aging Study.* Am J Clin Nutr, 2005. **82**(3): p. 627-35.

91. Haan, M.N., et al., *Homocysteine, B vitamins, and the incidence of dementia and cognitive impairment: results from the Sacramento Area Latino Study on Aging.* Am J Clin Nutr, 2007. **85**(2): p. 511-7.

92. Teunissen, C.E., et al., *Homocysteine: a marker for cognitive performance? A longitudinal follow-up study.* J Nutr Health Aging, 2003. **7**(3): p. 153-9.

93. Kalmijn, S., et al., *Total homocysteine and cognitive decline in a community-based sample of elderly subjects: the Rotterdam Study.* Am J Epidemiol, 1999. **150**(3): p. 283-9.

94. Luchsinger, J.A., et al., *Plasma homocysteine levels and risk of Alzheimer disease.* Neurology, 2004. **62**(11): p. 1972-6.

95. Ramos, M.I., et al., *Low folate status is associated with impaired cognitive function and dementia in the Sacramento Area Latino Study on Aging.* Am J Clin Nutr, 2005. **82**(6): p. 1346-52.

96. Kado, D.M., et al., *Homocysteine versus the vitamins folate, B6, and B12 as predictors of cognitive function and decline in older high-functioning adults: MacArthur Studies of Successful Aging.* Am J Med, 2005. **118**(2): p. 161-7.

97. Mooijaart, S.P., et al., *Homocysteine, vitamin B-12, and folic acid and the risk of cognitive decline in old age: the Leiden 85-Plus study.* Am J Clin Nutr, 2005. **82**(4): p. 866-71.

98. Reitz, C., et al., *Plasma homocysteine and risk of mild cognitive impairment.* Dement Geriatr Cogn Disord, 2009. **27**(1): p. 11-7.

99. Malouf, R. and J. Grimley Evans, *The effect of vitamin B6 on cognition.* Cochrane Database Syst Rev, 2003(4): p. CD004393.

100. Malouf, R. and A. Areosa Sastre, *Vitamin B12 for cognition.* Cochrane Database Syst Rev, 2003(3): p. CD004326.

101. Malouf, R. and J. Grimley Evans, *Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people.* Cochrane Database Syst Rev, 2008(4): p. CD004514.

102. Riggs, K.M., et al., *Relations of vitamin B-12, vitamin B-6, folate, and homocysteine to cognitive performance in the Normative Aging Study.* Am J Clin Nutr, 1996. **63**(3): p. 306-14.

103. Garcia, A.A., et al., *Metabolic markers of cobalamin deficiency and cognitive function in normal older adults.* J Am Geriatr Soc, 2004. **52**(1): p. 66-71.

104. Garcia, A., et al., *Increases in homocysteine are related to worsening of stroop scores in healthy elderly persons: a prospective follow-up study.* J Gerontol A Biol Sci Med Sci, 2004. **59**(12): p. 1323-7.

105. Pepys, M.B. and G.M. Hirschfield, *C-reactive protein: a critical update.* J Clin Invest, 2003. **111**(12): p. 1805-12.

106. Tillett, W.S. and T. Francis Jr, *Serological reactions in pneumonia with a nonprotein somatic fraction of pneumococcus.* J Exp Med 1930. **52**: p. 561-585.

107. Pepys, M.B., *C-reactive protein fifty years on.* Lancet, 1981. **1**(8221): p. 653-7.

108. Shrive, A.K., et al., *Structure solution of C-reactive proteins: molecular replacement with a twist.* Acta Crystallogr D Biol Crystallogr, 1996. **52**(Pt 6): p. 1049-57.

109. Thompson, D., M.B. Pepys, and S.P. Wood, *The physiological structure of human C-reactive protein and its complex with phosphocholine.* Structure, 1999. **7**(2): p. 169-77.

110. Shine, B., F.C. de Beer, and M.B. Pepys, *Solid phase radioimmunoassays for human C-reactive protein.* Clin Chim Acta, 1981. **117**(1): p. 13-23.

111. Hutchinson, W.L., et al., *Immunoradiometric assay of circulating C-reactive protein: age-related values in the adult general population.* Clin Chem, 2000. **46**(7): p. 934-8.

112. Vigushin, D.M., M.B. Pepys, and P.N. Hawkins, *Metabolic and scintigraphic studies of radioiodinated human C-reactive protein in health and disease.* J Clin Invest, 1993. **91**(4): p. 1351-7.

113. Gabay, C. and I. Kushner, *Acute-phase proteins and other systemic responses to inflammation.* N Engl J Med, 1999. **340**(6): p. 448-54.

114. Volanakis, J.E., *Human C-reactive protein: expression, structure, and function.* Mol Immunol, 2001. **38**(2-3): p. 189-97.

115. Ford, E.S. and W.H. Giles, *Serum C-reactive protein and self-reported stroke: findings from the Third National Health and Nutrition Examination Survey.* Arterioscler Thromb Vasc Biol, 2000. **20**(4): p. 1052-6.

116. Everett, B.M., et al., *The relative strength of C-reactive protein and lipid levels as determinants of ischemic stroke compared with coronary heart disease in women.* J Am Coll Cardiol, 2006. **48**(11): p. 2235-42.

117. Danesh, J., et al., *Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies.* Jama, 1998. **279**(18): p. 1477-82.

118. Bansal, S. and P.M. Ridker, *Comparison of characteristics of future myocardial infarctions in women with baseline high versus baseline low levels of high-sensitivity C-reactive protein.* Am J Cardiol, 2007. **99**(11): p. 1500-3.

119. Ridker, P.M. and J.D. Silvertown, *Inflammation, C-reactive protein, and atherothrombosis.* J Periodontol, 2008. **79**(8 Suppl): p. 1544-51.

120. Erlinger, T.P., et al., *C-reactive protein and the risk of incident colorectal cancer.* Jama, 2004. **291**(5): p. 585-90.

121. Figaro, M.K., et al., *Diabetes, inflammation, and functional decline in older adults: findings from the Health, Aging and Body Composition (ABC) study.* Diabetes Care, 2006. **29**(9): p. 2039-45.

122. McDermott, M.M., et al., *Circulating blood markers and functional impairment in peripheral arterial disease.* J Am Geriatr Soc, 2008. **56**(8): p. 1504-10.

123. Ridker, P.M., *Inflammatory biomarkers and risks of myocardial infarction, stroke, diabetes, and total mortality: implications for longevity.* Nutr Rev, 2007. **65**(12 Pt 2): p. S253-9.

124. Reuben, D.B., et al., *Peripheral blood markers of inflammation predict mortality and functional decline in high-functioning community-dwelling older persons.* J Am Geriatr Soc, 2002. **50**(4): p. 638-44.

125. Pradhan, A.D., et al., *C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus.* Jama, 2001. **286**(3): p. 327-34.

126. Dehghan, A., et al., *Risk of type 2 diabetes attributable to C-reactive protein and other risk factors.* Diabetes Care, 2007. **30**(10): p. 2695-9.

127. Schmidt, R., et al., *Early inflammation and dementia: a 25-year follow-up of the Honolulu-Asia Aging Study.* Ann Neurol, 2002. **52**(2): p. 168-74.

128. Campbell, I.L., et al., *Neurologic disease induced in transgenic mice by cerebral overexpression of interleukin 6.* Proc Natl Acad Sci U S A, 1993. **90**(21): p. 10061-5.

129. Licastro, F., et al., *Increased serum alpha 1-antichymotrypsin in patients with probable Alzheimer's disease: an acute phase reactant without the peripheral acute phase response.* J Neuroimmunol, 1995. **57**(1-2): p. 71-5.

130. Singh, V.K. and P. Guthikonda, *Circulating cytokines in Alzheimer's disease.* J Psychiatr Res, 1997. **31**(6): p. 657-60.

131. Licastro, F., et al., *Increased plasma levels of interleukin-1, interleukin-6 and alpha-1-antichymotrypsin in patients with Alzheimer's disease: peripheral inflammation or signals from the brain?* J Neuroimmunol, 2000. **103**(1): p. 97-102.

132. van Exel, E., et al., *Interaction of atherosclerosis and inflammation in elderly subjects with poor cognitive function.* Neurology, 2003. **61**(12): p. 1695-701.

133. Weuve, J., et al., *High-sensitivity C-reactive protein and cognitive function in older women.* Epidemiology, 2006. **17**(2): p. 183-9.

134. Yaffe, K., et al., *Inflammatory markers and cognition in well-functioning African-American and white elders.* Neurology, 2003. **61**(1): p. 76-80.

135. Teunissen, C.E., et al., *Inflammation markers in relation to cognition in a healthy aging population.* J Neuroimmunol, 2003. **134**(1-2): p. 142-50.

136. Komulainen, P., et al., *Serum high sensitivity C-reactive protein and cognitive function in elderly women.* Age Ageing, 2007. **36**(4): p. 443-8.

137. Laurin, D., et al., *Midlife C-reactive protein and risk of cognitive decline: A 31-year follow-up.* Neurobiol Aging, 2008.

138. Schram, M.T., et al., *Systemic markers of inflammation and cognitive decline in old age.* J Am Geriatr Soc, 2007. **55**(5): p. 708-16.

139. Dik, M.G., et al., *Serum inflammatory proteins and cognitive decline in older persons.* Neurology, 2005. **64**(8): p. 1371-7.

140. Tan, Z.S., et al., *Inflammatory markers and the risk of Alzheimer disease: the Framingham Study.* Neurology, 2007. **68**(22): p. 1902-8.

141. Jordanova, V., et al., *Markers of inflammation and cognitive decline in an African-Caribbean population.* Int J Geriatr Psychiatry, 2007. **22**(10): p. 966-73.

142. Alley, D.E., et al., *Inflammation and rate of cognitive change in high-functioning older adults.* J Gerontol A Biol Sci Med Sci, 2008. **63**(1): p. 50-5.

143. Kuo, H.K., et al., *Relation of C-reactive protein to stroke, cognitive disorders, and depression in the general population: systematic review and meta-analysis.* Lancet Neurol, 2005. **4**(6): p. 371-80.

144. Makita, Z., et al., *Hemoglobin-AGE: a circulating marker of advanced glycosylation.* Science, 1992. **258**(5082): p. 651-3.

145. Brownlee, M., H. Vlassara, and A. Cerami, *Nonenzymatic glycosylation and the pathogenesis of diabetic complications.* Ann Intern Med, 1984. **101**(4): p. 527-37.

146. Rahbar, S., O. Blumenfeld, and H.M. Ranney, *Studies of an unusual hemoglobin in patients with diabetes mellitus.* Biochem Biophys Res Commun, 1969. **36**(5): p. 838-43.

147. Koenig, R.J., et al., *Correlation of glucose regulation and hemoglobin AIc in diabetes mellitus.* N Engl J Med, 1976. **295**(8): p. 417-20.

148. Larsen, M.L., M. Horder, and E.F. Mogensen, *Effect of long-term monitoring of glycosylated hemoglobin levels in insulin-dependent diabetes mellitus.* N Engl J Med, 1990. **323**(15): p. 1021-5.

149. Nathan, D.M., et al., *The clinical information value of the glycosylated hemoglobin assay.* N Engl J Med, 1984. **310**(6): p. 341-6.

150. Singer, D.E., et al., *Association of HbA1c with prevalent cardiovascular disease in the original cohort of the Framingham Heart Study.* Diabetes, 1992. **41**(2): p. 202-8.

151. Enzinger, C., et al., *Risk factors for progression of brain atrophy in aging: six-year follow-up of normal subjects.* Neurology, 2005. **64**(10): p. 1704-11.

152. MacLullich, A.M., et al., *Glycosylated hemoglobin levels in healthy elderly nondiabetic men are negatively associated with verbal memory.* J Am Geriatr Soc, 2004. **52**(5): p. 848-9.

153. Gradman, T.J., et al., *Verbal learning and/or memory improves with glycemic control in older subjects with non-insulin-dependent diabetes mellitus.* J Am Geriatr Soc, 1993. **41**(12): p. 1305-12.

154. Mogi, N., et al., *Cognitive function in Japanese elderly with type 2 diabetes mellitus.* J Diabetes Complications, 2004. **18**(1): p. 42-6.

155. Worrall, G.J., P.C. Chaulk, and N. Moulton, *Cognitive function and glycosylated hemoglobin in older patients with type II diabetes.* J Diabetes Complications, 1996. **10**(6): p. 320-4.

156. Lindeman, R.D., et al., *A biethnic community survey of cognition in participants with type 2 diabetes, impaired glucose tolerance, and normal glucose tolerance: the New Mexico Elder Health Survey.* Diabetes Care, 2001. **24**(9): p. 1567-72.

157. Cosway, R., et al., *Cognitive function and information processing in type 2 diabetes.* Diabet Med, 2001. **18**(10): p. 803-10.

158. Saczynski, J.S., et al., *Cognitive impairment: an increasingly important complication of type 2 diabetes: the age, gene/environment susceptibility--Reykjavik study.* Am J Epidemiol, 2008. **168**(10): p. 1132-9.

159. Okura, T., M. Heisler, and K.M. Langa, *Association between cognitive function and social support with glycemic control in adults with diabetes mellitus.* J Am Geriatr Soc, 2009. **57**(10): p. 1816-24.

160. Cukierman-Yaffe, T., et al., *Relationship between baseline glycemic control and cognitive function in individuals with type 2 diabetes and other cardiovascular risk factors: the action to control cardiovascular risk in diabetes-memory in diabetes (ACCORD-MIND) trial.* Diabetes Care, 2009. **32**(2): p. 221-6.

161. Amano, H., et al., *Glycated hemoglobin levels and intellectual activity in an aged population.* J Am Geriatr Soc, 2005. **53**(12): p. 2128-34.

162. Yaffe, K., et al., *Glycosylated hemoglobin level and development of mild cognitive impairment or dementia in older women.* J Nutr Health Aging, 2006. **10**(4): p. 293-5.

163. Gao, L., et al., *An investigation of the population impact of variation in HbA1c levels in older people in England and Wales: from a population based multi-centre longitudinal study.* BMC Public Health, 2008. **8**: p. 54.

164. Maggi, S., et al., *Diabetes as a risk factor for cognitive decline in older patients.* Dement Geriatr Cogn Disord, 2009. **27**(1): p. 24-33.

165. Olson, R.E., *Discovery of the lipoproteins, their role in fat transport and their significance as risk factors.* J Nutr, 1998. **128**(2 Suppl): p. 439S-443S.

166. Refolo, L.M., et al., *Hypercholesterolemia accelerates the Alzheimer's amyloid pathology in a transgenic mouse model.* Neurobiol Dis, 2000. **7**(4): p. 321-31.

167. Ghribi, O., *Potential mechanisms linking cholesterol to Alzheimer's disease-like pathology in rabbit brain, hippocampal organotypic slices, and skeletal muscle.* J Alzheimers Dis, 2008. **15**(4): p. 673-84.

168. Pappolla, M.A., et al., *Mild hypercholesterolemia is an early risk factor for the development of Alzheimer amyloid pathology.* Neurology, 2003. **61**(2): p. 199-205.

169. Lesser, G.T., et al., *Serum lipids are related to Alzheimer's pathology in nursing home residents.* Dement Geriatr Cogn Disord, 2009. **27**(1): p. 42-9.

170. Fuster, V., et al., *Atherosclerotic plaque rupture and thrombosis. Evolving concepts.* Circulation, 1990. **82**(3 Suppl): p. II47-59.

171. Cheng, G.C., et al., *Distribution of circumferential stress in ruptured and stable atherosclerotic lesions. A structural analysis with histopathological correlation.* Circulation, 1993. **87**(4): p. 1179-87.

172. Treasure, C.B., et al., *Beneficial effects of cholesterol-lowering therapy on the coronary endothelium in patients with coronary artery disease.* N Engl J Med, 1995. **332**(8): p. 481-7.

173. Omoigui, S., *Cholesterol synthesis is the trigger and isoprenoid dependent interleukin-6 mediated inflammation is the common causative factor and therapeutic target for atherosclerotic vascular disease and age-related disorders including osteoporosis and type 2 diabetes.* Med Hypotheses, 2005. **65**(3): p. 559-69.

174. Collins, R., R. Peto, and J. Armitage, *The MRC/BHF Heart Protection Study: preliminary results.* Int J Clin Pract, 2002. **56**(1): p. 53-6.

175. Shepherd, J., et al., *Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial.* Lancet, 2002. **360**(9346): p. 1623-30.

176. McGuinness, B., et al., *Statins for the prevention of dementia.* Cochrane Database Syst Rev, 2009(2): p. CD003160.

177. Notkola, I.L., et al., *Serum total cholesterol, apolipoprotein E epsilon 4 allele, and Alzheimer's disease.* Neuroepidemiology, 1998. **17**(1): p. 14-20.

178. Kalmijn, S., et al., *Metabolic cardiovascular syndrome and risk of dementia in Japanese-American elderly men. The Honolulu-Asia aging study.* Arterioscler Thromb Vasc Biol, 2000. **20**(10): p. 2255-60.

179. Whitmer, R.A., et al., *Midlife cardiovascular risk factors and risk of dementia in late life.* Neurology, 2005. **64**(2): p. 277-81.

180. Solomon, A., et al., *Serum cholesterol changes after midlife and late-life cognition: twenty-one-year follow-up study.* Neurology, 2007. **68**(10): p. 751-6.

181. Tan, Z.S., et al., *Plasma total cholesterol level as a risk factor for Alzheimer disease: the Framingham Study.* Arch Intern Med, 2003. **163**(9): p. 1053-7.

182. Romas, S.N., et al., *APOE genotype, plasma lipids, lipoproteins, and AD in community elderly.* Neurology, 1999. **53**(3): p. 517-21.

183. Reitz, C., et al., *Impact of plasma lipids and time on memory performance in healthy elderly without dementia.* Neurology, 2005. **64**(8): p. 1378-83.

184. Li, G., et al., *Serum cholesterol and risk of Alzheimer disease: a community-based cohort study.* Neurology, 2005. **65**(7): p. 1045-50.

185. Xiong, G.L., et al., *Vascular risk factors and cognitive decline among elderly male twins.* Neurology, 2006. **67**(9): p. 1586-91.

186. Raffaitin, C., et al., *Metabolic syndrome and risk for incident Alzheimer's disease or vascular dementia: the Three-City Study.* Diabetes Care, 2009. **32**(1): p. 169-74.

187. Piguet, O., et al., *Vascular risk factors, cognition and dementia incidence over 6 years in the Sydney Older Persons Study.* Neuroepidemiology, 2003. **22**(3): p. 165-71.

188. Mielke, M.M., et al., *High total cholesterol levels in late life associated with a reduced risk of dementia.* Neurology, 2005. **64**(10): p. 1689-95.

189. Anstey, K.J., D.M. Lipnicki, and L.F. Low, *Cholesterol as a risk factor for dementia and cognitive decline: a systematic review of prospective studies with meta-analysis.* Am J Geriatr Psychiatry, 2008. **16**(5): p. 343-54.

190. Stewart, R., et al., *Twenty-six-year change in total cholesterol levels and incident dementia: the Honolulu-Asia Aging Study.* Arch Neurol, 2007. **64**(1): p. 103-7.

191. Evans, R.M., et al., *Serum cholesterol, APOE genotype, and the risk of Alzheimer's disease: a population-based study of African Americans.* Neurology, 2000. **54**(1): p. 240-2.

192. Hall, K., et al., *Cholesterol, APOE genotype, and Alzheimer disease: an epidemiologic study of Nigerian Yoruba.* Neurology, 2006. **66**(2): p. 223-7.

193. Reitz, C., et al., *Plasma lipid levels in the elderly are not associated with the risk of mild cognitive impairment.* Dement Geriatr Cogn Disord, 2008. **25**(3): p. 232-7.

194. Vokonas, P.S., W.B. Kannel, and L.A. Cupples, *Epidemiology and risk of hypertension in the elderly: the Framingham Study.* J Hypertens Suppl, 1988. **6**(1): p. S3-9.

195. Forette, F., et al., *The prognostic significance of isolated systolic hypertension in the elderly. Results of a ten year longitudinal survey.* Clin Exp Hypertens A, 1982. **4**(7): p. 1177-91.

196. Cushman, W.C., *The burden of uncontrolled hypertension: morbidity and mortality associated with disease progression.* J Clin Hypertens (Greenwich), 2003. **5**(3 Suppl 2): p. 14-22.

197. Amery, A., et al., *Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly trial.* Lancet, 1985. **1**(8442): p. 1349-54.

198. Wang, J.G. and J.A. Staessen, *The benefit of treating isolated systolic hypertension.* Curr Hypertens Rep, 2001. **3**(4): p. 333-9.

199. Lawes, C.M., et al., *Blood pressure and stroke: an overview of published reviews.* Stroke, 2004. **35**(3): p. 776-85.

200. Launer, L.J., et al., *The association between midlife blood pressure levels and late-life cognitive function. The Honolulu-Asia Aging Study.* Jama, 1995. **274**(23): p. 1846-51.

201. Kilander, L., et al., *Hypertension is related to cognitive impairment: a 20-year follow-up of 999 men.* Hypertension, 1998. **31**(3): p. 780-6.

202. Swan, G.E., D. Carmelli, and A. Larue, *Systolic blood pressure tracking over 25 to 30 years and cognitive performance in older adults.* Stroke, 1998. **29**(11): p. 2334-40.

203. Kivipelto, M., et al., *Midlife vascular risk factors and late-life mild cognitive impairment: A population-based study.* Neurology, 2001. **56**(12): p. 1683-9.

204. Swan, G.E., et al., *Association of midlife blood pressure to late-life cognitive decline and brain morphology.* Neurology, 1998. **51**(4): p. 986-93.

205. Yamada, M., et al., *Association between dementia and midlife risk factors: the Radiation Effects Research Foundation Adult Health Study.* J Am Geriatr Soc, 2003. **51**(3): p. 410-4.

206. Skoog, I., et al., *15-year longitudinal study of blood pressure and dementia.* Lancet, 1996. **347**(9009): p. 1141-5.

207. Guo, Z., Fratiglioni, L, Winblad, B, Viitanen, M, *Blood pressure and performance on the Mini-Mental State Examination in the very old. Cross-sectional and longitudinal data from the Kungsholmen Project.* Am J Epidemiol 1997(145).

208. Tzourio, C., et al., *Cognitive decline in individuals with high blood pressure: a longitudinal study in the elderly. EVA Study Group. Epidemiology of Vascular Aging.* Neurology, 1999. **53**(9): p. 1948-52.

209. Qiu, C., et al., *Low blood pressure and risk of dementia in the Kungsholmen project: a 6-year follow-up study.* Arch Neurol, 2003. **60**(2): p. 223-8.

210. Verghese, J., et al., *Low blood pressure and the risk of dementia in very old individuals.* Neurology, 2003. **61**(12): p. 1667-72.

211. Lindsay, J., et al., *Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging.* Am J Epidemiol, 2002. **156**(5): p. 445-53.

212. Posner, H.B., et al., *The relationship of hypertension in the elderly to AD, vascular dementia, and cognitive function.* Neurology, 2002. **58**(8): p. 1175-81.

213. Hebert, L.E., et al., *Blood pressure and late-life cognitive function change: a biracial longitudinal population study.* Neurology, 2004. **62**(11): p. 2021-4.

214. Yoshitake, T., et al., *Incidence and risk factors of vascular dementia and Alzheimer's disease in a defined elderly Japanese population: the Hisayama Study.* Neurology, 1995. **45**(6): p. 1161-8.

215. Glynn, R.J., et al., *Current and remote blood pressure and cognitive decline.* Jama, 1999. **281**(5): p. 438-45.

216. Guo, Z., et al., *Occurrence and progression of dementia in a community population aged 75 years and older: relationship of antihypertensive medication use.* Arch Neurol, 1999. **56**(8): p. 991-6.

217. Forette, F., et al., *The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study.* Arch Intern Med, 2002. **162**(18): p. 2046-52.

218. McGuinness, B., et al., *Blood pressure lowering in patients without prior cerebrovascular disease for prevention of cognitive impairment and dementia.* Cochrane Database Syst Rev, 2009(4): p. CD004034.

219. Elias, P., Elias, MF, Robbins, MA, Budge, MM, *Blood pressure-related cognitive decline: does age make a difference?.* . Hypertension, 2004(44).

220. Morris, M.C., et al., *Association between blood pressure and cognitive function in a biracial community population of older persons.* Neuroepidemiology, 2002. **21**(3): p. 123-30.

221. Elkins, J., Yaffe, K, Cauley, JA, et al, *Pre-existing hypertension and the impact of stroke on cognitive function.* Ann Neurol 2005(58).

222. Katzman, R., et al., *Development of dementing illnesses in an 80-year-old volunteer cohort.* Ann Neurol, 1989. **25**(4): p. 317-24.

223. Elias, P.K., et al., *NIDDM and blood pressure as risk factors for poor cognitive performance. The Framingham Study.* Diabetes Care, 1997. **20**(9): p. 1388-95.

224. Morris, M.C., et al., *Association of incident Alzheimer disease and blood pressure measured from 13 years before to 2 years after diagnosis in a large community study.* Arch Neurol, 2001. **58**(10): p. 1640-6.

225. Hassing, L.B., et al., *Comorbid type 2 diabetes mellitus and hypertension exacerbates cognitive decline: evidence from a longitudinal study.* Age Ageing, 2004. **33**(4): p. 355-61.

226. Luchsinger, J.A., et al., *Aggregation of vascular risk factors and risk of incident Alzheimer disease.* Neurology, 2005. **65**(4): p. 545-51.

227. Li, G., et al., *Age-varying association between blood pressure and risk of dementia in those aged 65 and older: a community-based prospective cohort study.* J Am Geriatr Soc, 2007. **55**(8): p. 1161-7.

228. Rastas, S., et al., *Vascular risk factors and dementia in the general population aged >85 years Prospective population-based study.* Neurobiol Aging, 2008.

229. LaCroix, A.Z. and G.S. Omenn, *Older adults and smoking.* Clin Geriatr Med, 1992. **8**(1): p. 69-87.

230. Lee, P.N., *Smoking and Alzheimer's disease: a review of the epidemiological evidence.* Neuroepidemiology, 1994. **13**(4): p. 131-44.

231. Doll, R., et al., *Smoking and dementia in male British doctors: prospective study.* Bmj, 2000. **320**(7242): p. 1097-102.

232. Kalmijn, S., et al., *Cigarette smoking and alcohol consumption in relation to cognitive performance in middle age.* Am J Epidemiol, 2002. **156**(10): p. 936-44.

233. Tyas, S.L., et al., *Mid-life smoking and late-life dementia: the Honolulu-Asia Aging Study.* Neurobiol Aging, 2003. **24**(4): p. 589-96.

234. Reitz, C., et al., *Relation between smoking and risk of dementia and Alzheimer disease: the Rotterdam Study.* Neurology, 2007. **69**(10): p. 998-1005.

235. Ford, A.B., et al., *Smoking and cognitive impairment: a population-based study.* J Am Geriatr Soc, 1996. **44**(8): p. 905-9.

236. Anstey, K.J., et al., *Smoking as a risk factor for dementia and cognitive decline: a meta-analysis of prospective studies.* Am J Epidemiol, 2007. **166**(4): p. 367-78.

237. Reitz, C., et al., *Effect of smoking and time on cognitive function in the elderly without dementia.* Neurology, 2005. **65**(6): p. 870-5.

238. Stegmayr, B. and K. Asplund, *Diabetes as a risk factor for stroke. A population perspective.* Diabetologia, 1995. **38**(9): p. 1061-8.

239. Abbatecola, A.M., et al., *Insulin resistance and executive dysfunction in older persons.* J Am Geriatr Soc, 2004. **52**(10): p. 1713-8.

240. Stolk, R.P., et al., *Insulin and cognitive function in an elderly population. The Rotterdam Study.* Diabetes Care, 1997. **20**(5): p. 792-5.

241. Atiea, J.A., J.L. Moses, and A.J. Sinclair, *Neuropsychological function in older subjects with non-insulin-dependent diabetes mellitus.* Diabet Med, 1995. **12**(8): p. 679-85.

242. Nielson, K.A., et al., *Apolipoprotein-E genotyping of diabetic dementia patients: is diabetes rare in Alzheimer's disease?* J Am Geriatr Soc, 1996. **44**(8): p. 897-904.

243. Ott, A., et al., *Diabetes mellitus and the risk of dementia: The Rotterdam Study.* Neurology, 1999. **53**(9): p. 1937-42.

244. Schnaider Beeri, M., et al., *Diabetes mellitus in midlife and the risk of dementia three decades later.* Neurology, 2004. **63**(10): p. 1902-7.

245. Hassing, L.B., et al., *Diabetes mellitus is a risk factor for vascular dementia, but not for Alzheimer's disease: a population-based study of the oldest old.* Int Psychogeriatr, 2002. **14**(3): p. 239-48.

246. MacKnight, C., et al., *Diabetes mellitus and the risk of dementia, Alzheimer's disease and vascular cognitive impairment in the Canadian Study of Health and Aging.* Dement Geriatr Cogn Disord, 2002. **14**(2): p. 77-83.

247. Arvanitakis, Z., et al., *Diabetes mellitus and risk of Alzheimer disease and decline in cognitive function.* Arch Neurol, 2004. **61**(5): p. 661-6.

248. Brayne, C., et al., *Vascular risks and incident dementia: results from a cohort study of the very old.* Dement Geriatr Cogn Disord, 1998. **9**(3): p. 175-80.

249. Peila, R., B.L. Rodriguez, and L.J. Launer, *Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: The Honolulu-Asia Aging Study.* Diabetes, 2002. **51**(4): p. 1256-62.

250. Xu, W.L., et al., *Diabetes mellitus and risk of dementia in the Kungsholmen project: a 6-year follow-up study.* Neurology, 2004. **63**(7): p. 1181-6.

251. Akomolafe, A., et al., *Diabetes mellitus and risk of developing Alzheimer disease: results from the Framingham Study.* Arch Neurol, 2006. **63**(11): p. 1551-5.

252. Fontbonne, A., et al., *Changes in cognitive abilities over a 4-year period are unfavorably affected in elderly diabetic subjects: results of the Epidemiology of Vascular Aging Study.* Diabetes Care, 2001. **24**(2): p. 366-70.

253. Gregg, E.W., et al., *Is diabetes associated with cognitive impairment and cognitive decline among older women? Study of Osteoporotic Fractures Research Group.* Arch Intern Med, 2000. **160**(2): p. 174-80.

254. Luchsinger, J.A., et al., *Relation of diabetes to mild cognitive impairment.* Arch Neurol, 2007. **64**(4): p. 570-5.

255. Biessels, G.J., A. Koffeman, and P. Scheltens, *Diabetes and cognitive impairment. Clinical diagnosis and brain imaging in patients attending a memory clinic.* J Neurol, 2006. **253**(4): p. 477-82.

256. Xu, W., et al., *The effect of borderline diabetes on the risk of dementia and Alzheimer's disease.* Diabetes, 2007. **56**(1): p. 211-6.

257. Evans, D.A., *The epidemiology of dementia and Alzheimer's disease: an evolving field.* J Am Geriatr Soc, 1996. **44**(12): p. 1482-3.

258. Hebert, L.E., et al., *Annual incidence of Alzheimer disease in the United States projected to the years 2000 through 2050.* Alzheimer Dis Assoc Disord, 2001. **15**(4): p. 169-73.

259. Hebert, L.E., et al., *Age-specific incidence of Alzheimer's disease in a community population.* Jama, 1995. **273**(17): p. 1354-9.

260. Kukull, W.A., et al., *Dementia and Alzheimer disease incidence: a prospective cohort study.* Arch Neurol, 2002. **59**(11): p. 1737-46.

261. Jorm, A.F. and D. Jolley, *The incidence of dementia: a meta-analysis.* Neurology, 1998. **51**(3): p. 728-33.

262. Hall, C.B., et al., *Dementia incidence may increase more slowly after age 90: results from the Bronx Aging Study.* Neurology, 2005. **65**(6): p. 882-6.

263. Jorm, A.F., A.E. Korten, and A.S. Henderson, *The prevalence of dementia: a quantitative integration of the literature.* Acta Psychiatr Scand, 1987. **76**(5): p. 465-79.

264. Butler, S.M., J.W. Ashford, and D.A. Snowdon, *Age, education, and changes in the Mini-Mental State Exam scores of older women: findings from the Nun Study.* J Am Geriatr Soc, 1996. **44**(6): p. 675-81.

265. Kalaria, R.N., et al., *Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors.* Lancet Neurol, 2008. **7**(9): p. 812-26.

266. Zhou, D.F., et al., *Prevalence of dementia in rural China: impact of age, gender and education.* Acta Neurol Scand, 2006. **114**(4): p. 273-80.

267. Caamano-Isorna, F., et al., *Education and dementia: a meta-analytic study.* Neuroepidemiology, 2006. **26**(4): p. 226-32.

268. Ngandu, T., et al., *Education and dementia: what lies behind the association?* Neurology, 2007. **69**(14): p. 1442-50.

269. Scarmeas, N., et al., *Education and rates of cognitive decline in incident Alzheimer's disease.* J Neurol Neurosurg Psychiatry, 2006. **77**(3): p. 308-16.

270. Ott, A., et al., *Education and the incidence of dementia in a large population-based study: the Rotterdam Study.* Neurology, 1999. **52**(3): p. 663-6.

271. Letenneur, L., et al., *Education and the risk for Alzheimer's disease: sex makes a difference. EURODEM pooled analyses. EURODEM Incidence Research Group.* Am J Epidemiol, 2000. **151**(11): p. 1064-71.

272. Wilson, R.S., et al., *Educational attainment and cognitive decline in old age.* Neurology, 2009. **72**(5): p. 460-5.

273. O'Carroll, R. and K. Ebmeier, *Education and prevalence of Alzheimer's disease and vascular dementia. Premorbid ability influences measures used to identify dementia.* Bmj, 1995. **311**(6997): p. 125-6.

274. Cervilla, J.A., et al., *Long-term predictors of cognitive outcome in a cohort of older people with hypertension.* Br J Psychiatry, 2000. **177**: p. 66-71.

275. Riley, K.P., et al., *Early life linguistic ability, late life cognitive function, and neuropathology: findings from the Nun Study.* Neurobiol Aging, 2005. **26**(3): p. 341-7.

276. Wang, H.X., et al., *Late-life engagement in social and leisure activities is associated with a decreased risk of dementia: a longitudinal study from the Kungsholmen project.* Am J Epidemiol, 2002. **155**(12): p. 1081-7.

277. Scarmeas, N., et al., *Influence of leisure activity on the incidence of Alzheimer's disease.* Neurology, 2001. **57**(12): p. 2236-42.

278. Scarmeas, N., et al., *Mediterranean diet and mild cognitive impairment.* Arch Neurol, 2009. **66**(2): p. 216-25.

279. Larrieu, S., et al., *Nutritional factors and risk of incident dementia in the PAQUID longitudinal cohort.* J Nutr Health Aging, 2004. **8**(3): p. 150-4.

280. Nurk, E., et al., *Cognitive performance among the elderly and dietary fish intake: the Hordaland Health Study.* Am J Clin Nutr, 2007. **86**(5): p. 1470-8.

281. Huang, T.L., et al., *Benefits of fatty fish on dementia risk are stronger for those without APOE epsilon4.* Neurology, 2005. **65**(9): p. 1409-14.

282. Morris, M.C., et al., *Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease.* Arch Neurol, 2003. **60**(7): p. 940-6.

283. Barberger-Gateau, P., et al., *Dietary patterns and risk of dementia: the Three-City cohort study.* Neurology, 2007. **69**(20): p. 1921-30.

284. Hindmarch, I., et al., *The effects of black tea and other beverages on aspects of cognition and psychomotor performance.* Psychopharmacology (Berl), 1998. **139**(3): p. 230-8.

285. Valenzuela, M. and P. Sachdev, *Can Cognitive Exercise Prevent the Onset of Dementia? Systematic Review of Randomized Clinical Trials with Longitudinal Follow-up.* Am J Geriatr Psychiatry, 2009. **17**(3): p. 179-87.

286. Laurin, D., et al., *Physical activity and risk of cognitive impairment and dementia in elderly persons.* Arch Neurol, 2001. **58**(3): p. 498-504.

287. Krueger, K.R., et al., *Social engagement and cognitive function in old age.* Exp Aging Res, 2009. **35**(1): p. 45-60.

288. Kroger, E., et al., *Is complexity of work associated with risk of dementia? The Canadian Study of Health And Aging.* Am J Epidemiol, 2008. **167**(7): p. 820-30.

289. Wang, H.X., et al., *Personality and lifestyle in relation to dementia incidence.* Neurology, 2009. **72**(3): p. 253-9.

290. Jha, P., et al., *The antioxidant vitamins and cardiovascular disease. A critical review of epidemiologic and clinical trial data.* Ann Intern Med, 1995. **123**(11): p. 860-72.

291. Sesso, H.D., et al., *Vitamins E and C in the prevention of cardiovascular disease in men: the Physicians' Health Study II randomized controlled trial.* Jama, 2008. **300**(18): p. 2123-33.

292. Vivekananthan, D.P., et al., *Use of antioxidant vitamins for the prevention of cardiovascular disease: meta-analysis of randomised trials.* Lancet, 2003. **361**(9374): p. 2017-23.

293. Kanjilal, S., et al., *Socioeconomic status and trends in disparities in 4 major risk factors for cardiovascular disease among US adults, 1971-2002.* Arch Intern Med, 2006. **166**(21): p. 2348-55.

294. Kolb, B. and I. Whishaw, *Fundamentals of human neuropsychology (3rd Ed.).* 1990: New York: Freeman.

295. *What is Neuropsychology?* Clinical Neuropsychology: A Guide for Patients and their families. 2003: Public Interest Advisory Committee, Division 40, American Psychological Association.

296. Shallice, T., *From Neuropsychology to Mental Structure.* 1988.

297. Chaffee, J.W., *The thorny gates of learning in Sung China: A social history of examinations.* 1985: Cambridge: Cambridge University Press.

298. Bondy, M., *Psychiatric antecedents of psychological testing (before Binet).* Journal of the History of the Behavioral Sciences, 1974(10): p. 180-194.

299. Diamond, S., *Wilhem Wundt and the making of a scientific psychology.* 1980: New York: Plenum Press.

300. Pearson, K., *The life, letters and labours of Francis Galton.* 1930, Cambridge: Cambridge University Press.

301. Fancher, R.E., *The intelligence men: Makers of the IQ controversy.* 1985: New York: Norton.

302. Sattler, J.M., *Age effects on Wechsler Adult Intelligence Scale -Revised.* Journal of Consulting and Clinical Psychology, 1982(50): p. 785- 786.

303. AERA, APA, and NCME, *Standards for educational and psychological testing*. 1985: Washington DC: American Psychological Association.

304. Terrell, F., S. Terrell, and J. Taylor, *Effect of race of examiner and cultural mistrust on the WAIS performance of black students.* Journal of Consulting and Clinical Psychology, 1981.

305. Sarason, I.G., *Test anxiety,experimental instructions and verbal learning.* American Psychologist, 1961. **16**: p. 374.

306. Gregory, R.J., *Adult Intellectual Assessment*. 1987: Boston: Allyn & Bacon.

307. Bennett, T., *Use of the Halstead-Reitan Neuropsychological Test Battery in the assessment of head injury.* Cognitive Rehabilitation, 1988. **6**: p. 18-25.

308. *Diagnostic Criteria for DSM IV*. 1994, Washington: American Psychiatric Association.

309. Ewing, J.A., *Detecting alcoholism: The CAGE questionnaire.* JAMA, 1984(252): p. 1905-07.

310. Radloff, L.S., *The CES-D Scale: A Self-Report Depression Scale for research in the general population.* Appl. Psychol. Meas, 1997(1): p. 385-401.

311. Wood, V., Wylie, M.L. and Sheafor, B, *An analysis of a short self report measure of life satisfaction: Correlation with rater judgements.* J. Gerontol, 1969(24): p. 465-469.

312. Nelson, H., *National Adult Reading Test.* 2nd ed. 1991, Windsor: NFER-NELSON.

313. Wechsler, D., *WAIS-III Administration and Scoring Manual.* 1997: The Psychological Corporation, San Antonio, TX.

314. Benton, A.L., *Differential behavioural effects of frontal lobe disease.* Neuropsychologia, 1968(6): p. 53-60.

315. Wechsler, D., *Wechsler Memory Scale – Third Edition.* 1997: The Psychological Corporation, San Antonio, TX.

316. Wechsler, D., *Wechsler Memory Scale – Revised manual.* 1987: The Psychological Corporation, San Antonio, TX.

317. Folstein, M.F., S.E. Folstein, and P.R. McHugh, *"Mini-mental state". A practical method for grading the cognitive state of patients for the clinician.* J Psychiatr Res, 1975. **Nov;12**(3): p. 189-98.

318. Eysenck, H. and S. Eysenck, *Manual of the Eysenck Personality Inventory.* 1964: Hodder & Stoughton, Kent.

319. *Social Class Census Classification.* 2002: Central Statistics Office.

320. Dufouil, C., P. Ducimetiere, and A. Alperovitch, *Sex differences in the association between alcohol consumption and cognitive performance. EVA Study Group. Epidemiology of Vascular Aging.* Am J Epidemiol, 1997. **146**(5): p. 405-12.

321. Perry, I.J., *Homocysteine and risk of stroke.* J Cardiovasc Risk, 1999. **6**(4): p. 235-40.

322. Matsui, T., et al., *Plasma homocysteine and risk of coexisting silent brain infarction in Alzheimer's disease.* Neurodegener Dis, 2005. **2**(6): p. 299-304.

323. Lipton, S.A., et al., *Neurotoxicity associated with dual actions of homocysteine at the N-methyl-D-aspartate receptor.* Proc Natl Acad Sci U S A, 1997. **94**(11): p. 5923-8.

324. Woo, K.S., et al., *Hyperhomocyst(e)inemia is a risk factor for arterial endothelial dysfunction in humans.* Circulation, 1997. **96**(8): p. 2542-4.

325. Chan, N.N., *Homocysteine and insulin levels in type 2 diabetic patients.* Diabetes Care, 2000. **23**(7): p. 1041-2.

326. Woo, K.S., et al., *Hyperhomocyst(e)inemia is a risk factor for arterial endothelial dysfunction in humans.* Circulation, 2000. **101**(12): p. E116.

327. Kruman, II, et al., *Homocysteine elicits a DNA damage response in neurons that promotes apoptosis and hypersensitivity to excitotoxicity.* J Neurosci, 2000. **20**(18): p. 6920-6.

328. White, A.R., et al., *Homocysteine potentiates copper- and amyloid beta peptide-mediated toxicity in primary neuronal cultures: possible risk factors in the Alzheimer's-type neurodegenerative pathways.* J Neurochem, 2001. **76**(5): p. 1509-20.

329. Obeid, R. and W. Herrmann, *Mechanisms of homocysteine neurotoxicity in neurodegenerative diseases with special reference to dementia.* FEBS Lett, 2006. **580**(13): p. 2994-3005.

330. Mishkin, M. and T. Appenzeller, *The anatomy of memory.* Scientific American, 1987. **256**: p. 80-89.

331. Rami, L., et al., *Naming is associated with left temporal pole metabolite levels in neurodegenerative diseases.* Dement Geriatr Cogn Disord, 2008. **25**(3): p. 212-7.

332. Smith, M. and B. Milner, *The role of the right hipocampus in the recall of spatial location.* Neuropsychologia, 1981. **19**: p. 781-793.

333. Jones- Gotman, M. and B. Milner, *Right temporal lobe contribution to image mediated verbal learning.* Neuropsychologia, 1978. **16**: p. 61-71.

334. Garcia, A., Zanibbi, K, *Homocysteine and cognitive function in elderly people.* CMAJ, 2004(171).

335. Bonaa, K.H., et al., *Homocysteine lowering and cardiovascular events after acute myocardial infarction.* N Engl J Med, 2006. **354**(15): p. 1578-88.

336. McMahon, J.A., et al., *A controlled trial of homocysteine lowering and cognitive performance.* N Engl J Med, 2006. **354**(26): p. 2764-72.

337. Wahi, P.W., et al., *Diabetes in older adults: comparison of 1997 American Diabetes Association classification of diabetes mellitus with 1985 WHO classification.* Lancet, 1998. **352**(9133): p. 1012-15.

338. Albert, K.G. and P.Z. Zimmet, *Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1:diagnosis and classification of diabetes mellitus provisional report of a WHO consultation*

Diabet Med, 1998. **15**(7): p. 539-53.

339. Dinneen, S.F., et al., *Effects of changing diagnostic criteria on the risk of developing diabetes.* Diabetes Care, 1998. **21**(9): p. 1408-13.

340. Ryan, C.M. and M.O. Geckle, *Circumscribed cognitive dysfunction in middle-aged adults with type 2 diabetes.* Diabetes Care, 2000. **23**(10): p. 1486-93.

341. Wong, T.Y., et al., *Retinal microvascular abnormalities and cognitive impairment in middle-aged persons: the Atherosclerosis Risk in Communities Study.* Stroke, 2002. **33**(6): p. 1487-92.

342. Ryan, C.M., M.O. Geckle, and T.J. Orchard, *Cognitive efficiency declines over time in adults with Type 1 diabetes: effects of micro- and macrovascular complications.* Diabetologia, 2003. **46**(7): p. 940-8.

343. Wong, T.Y., et al., *Cerebral white matter lesions, retinopathy, and incident clinical stroke.* Jama, 2002. **288**(1): p. 67-74.

344. Wong, T.Y., et al., *Relation of retinopathy to coronary artery calcification: the multi-ethnic study of atherosclerosis.* Am J Epidemiol, 2008. **167**(1): p. 51-8.

345. Wolozin, B., *Cholesterol and the biology of Alzheimer's disease.* Neuron, 2004. **41**(1): p. 7-10.

346. Hanon, O., et al., *Relationship between antihypertensive drug therapy and cognitive function in elderly hypertensive patients with memory complaints.* J Hypertens, 2006. **24**(10): p. 2101-7.

347. Skoog, I., et al., *Effect of baseline cognitive function and antihypertensive treatment on cognitive and cardiovascular outcomes: Study on COgnition and Prognosis in the Elderly (SCOPE).* Am J Hypertens, 2005. **18**(8): p. 1052-9.

348. Tzourio, C., et al., *Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease.* Arch Intern Med, 2003. **163**(9): p. 1069-75.

349. Probstfield, J.L., et al., *The Systolic Hypertension in the Elderly Program (SHEP): an intervention trial on isolated systolic hypertension. SHEP*

Cooperative Research Group. Clin Exp Hypertens A, 1989. **11**(5-6): p. 973-89.

350. Prince, M.J., et al., *Is the cognitive function of older patients affected by antihypertensive treatment? Results from 54 months of the Medical Research Council's trial of hypertension in older adults.* Bmj, 1996. **312**(7034): p. 801-5.

351. Peters, R., et al., *Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial.* Lancet Neurol, 2008. **7**(8): p. 683-9.

352. Di Bari, M., et al., *Dementia and disability outcomes in large hypertension trials: lessons learned from the systolic hypertension in the elderly program (SHEP) trial.* Am J Epidemiol, 2001. **153**(1): p. 72-8.

353. Hoffman, L.B., et al., *Less Alzheimer disease neuropathology in medicated hypertensive than nonhypertensive persons.* Neurology, 2009.

354. Lund, S.S. and A.A. Vaag, *Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association: response to Skyler et al.* Diabetes Care, 2009. **32**(7): p. e90-1; author reply e92-3.

355. Wilson, A.M., M.C. Ryan, and A.J. Boyle, *The novel role of C-reactive protein in cardiovascular disease: risk marker or pathogen.* Int J Cardiol, 2006. **106**(3): p. 291-7.

356. Torzewski, J., et al., *C-reactive protein frequently colocalizes with the terminal complement complex in the intima of early atherosclerotic lesions of human coronary arteries.* Arterioscler Thromb Vasc Biol, 1998. **18**(9): p. 1386-92.

357. Zwaka, T.P., V. Hombach, and J. Torzewski, *C-reactive protein-mediated low density lipoprotein uptake by macrophages: implications for atherosclerosis.* Circulation, 2001. **103**(9): p. 1194-7.

358. Torzewski, M., et al., *C-reactive protein in the arterial intima: role of C-reactive protein receptor-dependent monocyte recruitment in atherogenesis.* Arterioscler Thromb Vasc Biol, 2000. **20**(9): p. 2094-9.

359. Wang, C.H., et al., *C-reactive protein upregulates angiotensin type 1 receptors in vascular smooth muscle.* Circulation, 2003. **107**(13): p. 1783-90.

360. Verma, S., et al., *A self-fulfilling prophecy: C-reactive protein attenuates nitric oxide production and inhibits angiogenesis.* Circulation, 2002. **106**(8): p. 913-9.

361. Torzewski, M., et al., *No effect of C-reactive protein on early atherosclerosis in LDLR-/- / human C-reactive protein transgenic mice.* Thromb Haemost, 2008. **99**(1): p. 196-201.

362. Duong, T., P.J. Acton, and R.A. Johnson, *The in vitro neuronal toxicity of pentraxins associated with Alzheimer's disease brain lesions.* Brain Res, 1998. **813**(2): p. 303-12.

363. Iwamoto, N., et al., *Demonstration of CRP immunoreactivity in brains of Alzheimer's disease: immunohistochemical study using formic acid pretreatment of tissue sections.* Neurosci Lett, 1994. **177**(1-2): p. 23-6.

364. McGeer, P.L., E.G. McGeer, and K. Yasojima, *Alzheimer disease and neuroinflammation.* J Neural Transm Suppl, 2000. **59**: p. 53-7.

365. Eikelenboom, P., et al., *Distribution pattern and functional state of complement proteins and alpha 1-antichymotrypsin in cerebral beta/A4 deposits in Alzheimer's disease.* Res Immunol, 1992. **143**(6): p. 617-20.

366. Sabia, S., et al., *Smoking history and cognitive function in middle age from the Whitehall II study.* Arch Intern Med, 2008. **168**(11): p. 1165-73.

367. Llewellyn, D.J., et al., *Exposure to secondhand smoke and cognitive impairment in non-smokers: national cross sectional study with cotinine measurement.* Bmj, 2009. **338**: p. b462.

368. Coulson, I., et al., *Knowledge and lifestyle behaviors of healthy older adults related to modifying the onset of vascular dementia.* Arch Gerontol Geriatr, 2004. **39**(1): p. 43-58.

369. Evans, D.A., et al., *Education and other measures of socioeconomic status and risk of incident Alzheimer disease in a defined population of older persons.* Arch Neurol, 1997. **54**(11): p. 1399-405.

370. Dealberto, M.J., et al., *Psychotropic drug use and cognitive decline among older men and women.* Int J Geriatr Psychiatry, 1997. **12**(5): p. 567-74.

371. Paterniti, S., C. Dufouil, and A. Alperovitch, *Long-term benzodiazepine use and cognitive decline in the elderly: the Epidemiology of Vascular Aging Study.* J Clin Psychopharmacol, 2002. **22**(3): p. 285-93.

372. Hogan, D.B., et al., *Prevalence and potential consequences of benzodiazepine use in senior citizens: Results from the Canadian Study of Health and Aging.* Can J Clin Pharmacol, 2003. **10**(2): p. 72-7.

373. Vignola, A., et al., *Effects of chronic insomnia and use of benzodiazepines on daytime performance in older adults.* J Gerontol B Psychol Sci Soc Sci, 2000. **55**(1): p. P54-62.

374. Allard, J., S. Artero, and K. Ritchie, *Consumption of psychotropic medication in the elderly: a re-evaluation of its effect on cognitive performance.* Int J Geriatr Psychiatry, 2003. **18**(10): p. 874-8.

375. Ivan, C.S., et al., *Dementia after stroke: the Framingham Study.* Stroke, 2004. **35**(6): p. 1264-8.

376. Lyness, S.A., E.M. Eaton, and L.S. Schneider, *Cognitive performance in older and middle-aged depressed outpatients and controls.* J Gerontol, 1994. **49**(3): p. P129-36.

377. Biringer, E., et al., *The association between depression, anxiety, and cognitive function in the elderly general population-the Hordaland Health Study.* Int J Geriatr Psychiatry, 2005. **20**(10): p. 989-97.

378. Fuhrer, R., et al., *Depressive symptomatology and cognitive functioning: an epidemiological survey in an elderly community sample in France.* Psychol Med, 1992. **22**(1): p. 159-72.

379. van Ojen, R., et al., *Late-life depressive disorder in the community. I. The relationship between MMSE score and depression in subjects with and without psychiatric history.* Br J Psychiatry, 1995. **166**(3): p. 311-5, 319.

380. Clark, M.S., et al., *Normative verbal and non-verbal memory test scores for Australian women aged 56-67.* Aust N Z J Psychiatry, 2004. **38**(7): p. 532-40.

381. van Oijen, M., et al., *Atherosclerosis and risk for dementia.* Ann Neurol, 2007. **61**(5): p. 403-10.

382. Geerlings, M.I., et al., *History of depression, depressive symptoms, and medial temporal lobe atrophy and the risk of Alzheimer disease.* Neurology, 2008. **70**(15): p. 1258-64.

383. Rabbitt, P., et al., *Unhappiness, health and cognitive ability in old age.* Psychol Med, 2008. **38**(2): p. 229-36.

384. Peters, R., et al., *Alcohol, dementia and cognitive decline in the elderly: a systematic review.* Age Ageing, 2008.

385. Gardner, E.J., C.H. Ruxton, and A.R. Leeds, *Black tea--helpful or harmful? A review of the evidence.* Eur J Clin Nutr, 2007. **61**(1): p. 3-18.

386. Van Dyk, K. and M. Sano, *The impact of nutrition on cognition in the elderly.* Neurochem Res, 2007. **32**(4-5): p. 893-904.

387. Ortega, R.M., et al., *Dietary intake and cognitive function in a group of elderly people.* Am J Clin Nutr, 1997. **66**(4): p. 803-9.

388. Martin, A., et al., *Effects of fruits and vegetables on levels of vitamins E and C in the brain and their association with cognitive performance.* J Nutr Health Aging, 2002. **6**(6): p. 392-404.

389. Morris, M.C., et al., *Associations of vegetable and fruit consumption with age-related cognitive change.* Neurology, 2006. **67**(8): p. 1370-6.

390. Kang, J.H., A. Ascherio, and F. Grodstein, *Fruit and vegetable consumption and cognitive decline in aging women.* Ann Neurol, 2005. **57**(5): p. 713-20.

391. Stables, G.J., et al., *Changes in vegetable and fruit consumption and awareness among US adults: results of the 1991 and 1997 5 A Day for Better Health Program surveys.* J Am Diet Assoc, 2002. **102**(6): p. 809-17.

392. Craig, S.R., et al., *Blood cholesterol screening influence of fasting state on cholesterol results and management decisions.* J Gen Intern Med, 2000. **15**(6): p. 395-9.

393. Thirup, P. and S. Ekelund, *Day-to-day, postprandial, and orthostatic variation of total plasma homocysteine.* Clin Chem, 1999. **45**(8 Pt 1): p. 1280-3.

394. van Guldener, C., *Homocysteine and the kidney.* Curr Drug Metab, 2005. **6**(1): p. 23-6.

395. Vanuzzo, D., et al., *Both vitamin B6 and total homocysteine plasma levels predict long-term atherothrombotic events in healthy subjects.* Eur Heart J, 2007. **28**(4): p. 484-91.

396. Myers, R.H., et al., *Apolipoprotein E epsilon4 association with dementia in a population-based study: The Framingham study.* Neurology, 1996. **46**(3): p. 673-7.

397. Carmelli, D., et al., *Midlife cardiovascular risk factors, ApoE, and cognitive decline in elderly male twins.* Neurology, 1998. **50**(6): p. 1580-5.

398. Horsburgh, K., et al., *The role of apolipoprotein E in Alzheimer's disease, acute brain injury and cerebrovascular disease: evidence of common mechanisms and utility of animal models.* Neurobiol Aging, 2000. **21**(2): p. 245-55.

399. Slooter, A.J., et al., *The impact of APOE on myocardial infarction, stroke, and dementia: the Rotterdam Study.* Neurology, 2004. **62**(7): p. 1196-8.

400. Martins, C.A., et al., *APOE alleles predict the rate of cognitive decline in Alzheimer disease: a nonlinear model.* Neurology, 2005. **65**(12): p. 1888-93.

401. Hsiung, G.Y., A.D. Sadovnick, and H. Feldman, *Apolipoprotein E epsilon4 genotype as a risk factor for cognitive decline and dementia: data from the Canadian Study of Health and Aging.* Cmaj, 2004. **171**(8): p. 863-7.

402. Goldstein, F.C., et al., *Apolipoprotein E and age at onset of Alzheimer's disease in African American patients.* Neurology, 2001. **57**(10): p. 1923-5.

403. Mori, E., et al., *Accelerated hippocampal atrophy in Alzheimer's disease with apolipoprotein E epsilon4 allele.* Ann Neurol, 2002. **51**(2): p. 209-14.

404. Dal Forno, G., et al., *APOE genotype and survival in men and women with Alzheimer's disease.* Neurology, 2002. **58**(7): p. 1045-50.

405. Tiraboschi, P., et al., *Impact of APOE genotype on neuropathologic and neurochemical markers of Alzheimer disease.* Neurology, 2004. **62**(11): p. 1977-83.

406. Olarte, L., et al., *Apolipoprotein E epsilon4 and age at onset of sporadic and familial Alzheimer disease in Caribbean Hispanics.* Arch Neurol, 2006. **63**(11): p. 1586-90.

407. Mahley, R.W. and S.C. Rall, Jr., *Apolipoprotein E: far more than a lipid transport protein.* Annu Rev Genomics Hum Genet, 2000. **1**: p. 507-37.

408. Burman, D., et al., *Relationship of the ApoE polymorphism to plasma lipid traits among South Asians, Chinese, and Europeans living in Canada.* Atherosclerosis, 2009. **203**(1): p. 192-200.

409. Slooter, A.J., et al., *The effect of APOE on dementia is not through atherosclerosis: the Rotterdam Study.* Neurology, 1999. **53**(7): p. 1593-5.

410. Kivipelto, M., et al., *Apolipoprotein E epsilon4 allele, elevated midlife total cholesterol level, and high midlife systolic blood pressure are independent*

risk factors for late-life Alzheimer disease. Ann Intern Med, 2002. **137**(3): p. 149-55.

411. Mortimer, J.A., D.A. Snowdon, and W.R. Markesbery, *The effect of APOE-epsilon4 on dementia is mediated by Alzheimer neuropathology.* Alzheimer Dis Assoc Disord, 2009. **23**(2): p. 152-7.

412. Tascilar, N., et al., *Relationship of apoE polymorphism with lipoprotein(a), apoA, apoB and lipid levels in atherosclerotic infarct.* J Neurol Sci, 2009. **277**(1-2): p. 17-21.

413. Merchant, C., et al., *The influence of smoking on the risk of Alzheimer's disease.* Neurology, 1999. **52**(7): p. 1408-12.

414. Irie, F., et al., *Enhanced risk for Alzheimer disease in persons with type 2 diabetes and APOE epsilon4: the Cardiovascular Health Study Cognition Study.* Arch Neurol, 2008. **65**(1): p. 89-93.

415. Refsum, H., et al., *Facts and recommendations about total homocysteine determinations: an expert opinion.* Clin Chem, 2004. **50**(1): p. 3-32.

416. Quadri, P., et al., *Homocysteine, folate, and vitamin B-12 in mild cognitive impairment, Alzheimer disease, and vascular dementia.* Am J Clin Nutr, 2004. **80**(1): p. 114-22.

Appendix 1- Patient information sheet

Patient information sheet

1. Title of study:

The Dublin Healthy Ageing Study.

2. Introduction:

The aim of this study is to examine the relationship between lifestyle factors and health in older people. We hope by doing so we can identify factors that will allow older people to stay healthy and live independently for longer. We are also interested in factors that can affect the memory as people get older.

3. Procedures:

In order to be eligible for this part of the study you must be:

Willing to give an additional blood sample.

In order to avoid having to take further blood specimens, some of the cells may be kept frozen at the Mercer's Institute for Research on Ageing or the Vitamin Laboratory in St. James's Hospital. These samples may be used for further studies designed only for the detection of genes in memory difficulties and the types of studies may take a number of forms. All information is completely confidential and blood samples are anonymous for purposes of genetic testing.

4. Benefits:

Participants in this study do not gain any direct benefit from taking part, however they and others may benefit from future advances in treatment and prevention of

illnesses which are based on the results of current research. Genetic results will not be available to participants or their families on an individual basis.

5. Risks:

An experienced doctor or nurse will take a blood sample from you who has done this numerous times before. If you have a tendency to faint after blood tests please tell the person taking the sample and he/she will make sure you are sitting down. The blood test may be a little uncomfortable and, may, in a small number of people result in a little bruising.

6. Exclusion from participation: *Your doctor has told you that you cannot be in this study if any of the following are true*:

If you are under 65 years.

7. Alternative treatment: Not applicable.

8. Confidentiality:

Your identity will remain confidential. Your name will not be published and will not be disclosed to anyone outside the hospital.

9. Compensation:

Your doctors are covered by standard medical malpractice insurance. No other compensation is available.

10. Voluntary Participation: You have volunteered to participate in this study. You may quit at any time. If you decide not to participate, or if you quit, you will not be penalised and will not give up any benefits that you had before entering the study.

11. Stopping the study: ***You understand that your doctor may stop your participation in the study at any time without your consent.***

.

12. Permission: This trial has hospital and GP Ethical Committee approval

13. Further information: You can get more information or answers to your questions about the study, your participation in the study, and your rights, from

Dr. Ai- Vyrn Chin

Mercer's Institute for Research on Ageing,

St. James's Hospital,

Dublin 8

Phone: 01 – 416 2641

Email: **achin@stjames.ie/ achin@tcd.ie**

Appendix 2- Consent Form

ST JAMES'S HOSPITAL AND FEDERATED DUBLIN VOLUNTARY HOSPITALS JOINT RESEARCH ETHICS COMMITTEE CONSENT FORM

Title of research study:

The Dublin Healthy Ageing Study.

This study and this consent form have been explained to me. My doctor has answered all my questions to my satisfaction. I believe I understand what will happen if I agree to be part of this study.

I have read, or had read to me, this consent form. I have had the opportunity to ask questions and all my questions have been answered to my satisfaction. I freely and voluntarily agree to be part of this research study, though without prejudice to my legal and ethical rights. I have received a copy of this agreement.

I agree that I can give a sample of blood for research in the above project. I understand how the sample will be collected, that giving a sample for this research is voluntary and that I am free to withdraw my approval for use of the sample at any time without giving a reason and without my medical treatment or legal rights being affected.

I give permission for my medical records to be looked at by responsible people from Mercer's Institute or from regulatory authorities where it is relevant to the research.

I understand that my doctor will be informed if any of the results of the memory tests/other information gathered as a part of the research are important for my health.

I am satisfied that my welfare and interests have been properly safeguarded in asking me to donate blood samples for research in the above project.

I understand that I will not benefit financially if this research leads to the development of a new treatment or medical test.

I know how to contact the research team if I need to.

I understand that future research using the sample may include genetic research aimed at understanding the genetic influences on disease, but that the results of these investigations are unlikely to have any implications for me personally.

I agree that the sample that I have given can be looked after and stored at the Mercer's Institute for Research on Ageing, St James's Hospital, Dublin, and used in future projects. I understand that some of these projects may be carried out by researchers other than those who ran the first project, including researchers working for commercial companies.

PARTICIPANT'S NAME: _____

PARTICIPANT'S SIGNATURE: _____

DATE: _____

Where the participant is incapable of comprehending the nature, significance and scope of the consent required, the form must be signed by a person competent to give consent to his or her participation in the research study (other than a person

who applied to undertake or conduct the study). If the subject is a minor (under 18 years old) the signature of parent or guardian must be obtained: -

NAME OF CONSENTOR, PARENT or GUARDIAN:

_____

SIGNATURE:

_____

RELATION TO PARTICIPANT:

_____

Where the participant is capable of comprehending the nature, significance and scope of the consent required, but is physically unable to sign written consent, signatures of two witnesses present when consent was given by the participant to a registered medical practitioner treating him or her for the illness.

NAME OF FIRST WITNESS:_____

SIGNATURE:_____

NAME OF SECOND WITNESS:_____

SIGNATURE:_____

Statement of investigator's responsibility: I have explained the nature, purpose, procedures, benefits, risks of, or alternatives to, this research study. I have offered to answer any questions and fully answered such questions. I believe that the participant understands my explanation and has freely given informed consent.

Physician's signature: _____Date:_____

Appendix 3– Verbal fluency (letter [FAS test] and category [animal] fluency)

VERBAL FLUENCY:

ANIMALS	FRUITS	VEGETABLES	F	A	S

TOTAL=____ TOTAL=____

Appendix 4– Word Lists I

6. Word Lists I (Optional)

RECORDING:
Place a tick (✓) next to each word recalled.
Write intrusions verbatim.

SCORING RULE:
0–1 pt. for each item

List A	Trial 1 Responses	Trial 2 Responses	Trial 3 Responses	Trial 4 Responses
Target				
Finger				
Sunset				
Crocodile				
Pound				
Yard				
Student				
Traffic				
Broom				
Ocean	✓			
Wing	✓			
Giant	✓			
Intrusions				

[ ] + [ ] + [ ] + [ ] = [ ]

Trial 1 Recall Range = 0 to 12

Trial 2 Recall Range = 0 to 12

Trial 3 Recall Range = 0 to 12

Trial 4 Recall Range = 0 to 12

Recall Total Score Range = 0 to 48

1st Recall Total Score Range = 0 to 12

List B	List B Responses	List A (Do not read)	Short-Delay Responses
Diamond		Target	
Garden		Finger	
Court		Sunset	
Hero		Crocodile	
Sand		Pound	
Kitten		Yard	
Branch		Student	
Kitchen		Traffic	
Daisy		Broom	
Lake		Ocean	
Gorilla		Wing	
Jail		Giant	
Intrusions			

List B Recall Range = 0 to 12 [ ]

Short-Delay Recall Range = 0 to 12 [ ]

Contrast 1 Calculation

[ ] − [ ] = [ ] Contrast 1

Trial 1 Recall Range = 0 to 12 — List B Recall Range = 0 to 12 — Range = -12 to +12

Learning Slope Calculation

[ ] − [ ] = [ ] Learning Slope

Trial 4 Recall Range = 0 to 12 — Trial 1 Recall Range = 0 to 12 — Range = -12 to +12

Contrast 2 Calculation

[ ] − [ ] = [ ] Contrast 2

Trial 4 Recall Range = 0 to 12 — Short-Delay Recall Range = 0 to 12 — Range = -12 to +12

Appendix 5– Word List II

16. Word Lists II (Optional)

ADMINISTER 25–35 MINUTES AFTER WORD LISTS I.

Recall

RECORDING:
Place a tick (✔) for each word recalled. Write intrusions verbatim.

SCORING RULE:
0–1 pt. for each item

List A (Do not read)	Response
Target	
Finger	
Sunset	
Crocodile	
Pound	
Yard	
Student	
Traffic	
Broom	
Ocean	
Wing	
Giant	
Intrusions	

Recall Total Score
Range = 0 to 12 [ ]

Recognition

RECORDING:
Circle Y or N.

SCORING RULE:
0–1 pt. for each item

Item	Circle Y or N	Score 0 or 1	Item	Circle Y or N	Score 0 or 1
1. Magazine	Y **N**		13. Smile	Y **N**	
2. Pound	**Y** N		14. Ocean	**Y** N	
3. Carpet	Y **N**		15. House	Y **N**	
4. Nest	Y **N**		16. Wing	**Y** N	
5. Traffic	**Y** N		17. Student	**Y** N	
6. Doctor	Y **N**		18. Breakfast	Y **N**	
7. Target	**Y** N		19. Feather	Y **N**	
8. Broom	**Y** N		20. Crocodile	**Y** N	
9. Village	Y **N**		21. Yard	**Y** N	
10. Finger	**Y** N		22. Shoelace	Y **N**	
11. Market	Y **N**		23. Sunset	**Y** N	
12. Giant	**Y** N		24. Hotel	Y **N**	

Recognition Total Score
Range = 0 to 24 [ ]

Percent Retention Calculation

[ ] ÷ [ ] x 100 = [ ]

Percent Retention
Range = 0 to 100%

Word Lists II
Recall Total Score
Range = 0 to 12

Word Lists I
Trial 4 Recall
Range = 0 to 12

Appendix 6- Visual Reproduction 1 & 2

Card A
Card B
Card C
Card D

Appendix 7– LNS

8. Letter–Number Sequencing

DISCONTINUE RULE:
After scores of 0 for all three trials of an item

RECORDING:
All responses verbatim

SCORING RULE:
0–1 pt. for each trial

Item/Trial	(Correct Response)/Response	Score 0 or 1
1. Trial 1	1–2 (2–L)	
Trial 2	6–F (6–P)	
Trial 3	8–6 (6–8)	
2. Trial 1	F–7–L (7–F–L)	
Trial 2	R–4–D (4–D–R)	
Trial 3	H–1–8 (1–8–H)	
3. Trial 1	T–9–A–5 (5–9–A–T)	
Trial 2	V–1–J–5 (1–5–J–V)	
Trial 3	7–N–4–L (4–7–L–N)	
4. Trial 1	8–D–6–G–1 (1–6–8–D–G)	
Trial 2	K–2–C–7–8 (2–7–C–K–8)	
Trial 3	6–P–3–Y–9 (3–6–9–P–Y)	
5. Trial 1	M–4–E–7–Q–2 (2–4–7–E–M–Q)	
Trial 2	W–8–H–5–F–J (J–5–8–F–H–W)	
Trial 3	6–Q–9–A–2–5 (2–6–9–A–Q–5)	
6. Trial 1	R–3–B–4–2–1–C (1–3–4–B–C–R–2)	
Trial 2	5–T–9–J–2–X–7 (2–5–7–9–J–T–X)	
Trial 3	E–1–H–8–R–4–D (1–4–8–D–E–H–R)	
7. Trial 1	6–H–9–5–2–N–8–A (2–5–6–8–A–H–N–S)	
Trial 2	D–1–R–9–B–4–K–3 (1–3–4–9–B–D–K–R)	
Trial 3	7–M–2–1–6–F–1–Z (1–2–6–7–F–M–T–Z)	

Total Score
Range = 0 to 21

Appendix 8– CAGE questionnaire

1. Have you ever felt you should **C**ut down on your drinking?
2. Have people **A**nnoyed you by criticising your drinking?
3. Have you ever felt bad or **G**uilty about your drinking?
4. Have you ever taken a drink first thing in the morning (**E**ye opener) to steady your nerves or get rid of a hangover?

Appendix 9- DSC

Digit Symbol—Coding

Sample Items

2	1	3	7	2	4	8	2	1	3	2	1	4	2	3	5	2	3	1	4

5	6	3	1	4	1	5	4	2	7	6	3	5	7	2	8	5	4	6	3

7	2	8	1	9	5	8	4	7	3	6	2	5	1	9	2	8	3	7	4

6	5	9	4	8	3	7	2	6	1	5	4	6	3	7	9	2	8	1	7

9	4	6	8	5	9	7	1	8	5	2	9	4	8	6	3	7	9	8	6

2	7	3	6	5	1	9	8	4	5	7	3	1	4	8	7	9	1	4	5

7	1	8	2	9	3	6	7	2	8	5	2	3	1	4	8	4	2	7	6

Appendix 10- NART

National Adult Reading Test (NART)

SECOND EDITION

Answer/Record Sheet

Name:..... **Date of test:**.....

	Errors		Errors
CHORD		SUPERFLUOUS	
ACHE		SIMILE	
DEPOT		BANAL	
AISLE		QUADRUPED	
BOUQUET		CELLIST	
PSALM		FACADE	
CAPON		ZEALOT	
DENY		DRACHM	
NAUSEA		AEON	
DEBT		PLACEBO	
COURTEOUS		ABSTEMIOUS	
RAREFY		DETENTE	
EQUIVOCAL		IDYLL	
NAIVE		PUERPERAL	
CATACOMB		AVER	
GAOLED		GAUCHE	
THYME		TOPIARY	
HEIR		LEVIATHAN	
RADIX		BEATIFY	
ASSIGNATE		PRELATE	
HIATUS		SIDEREAL	
SUBTLE		DEMESNE	
PROCREATE		SYNCOPE	
GIST		LABILE	
GOUGE		CAMPANILE	

Appendix 11 – CESD

Center for Epidemiologic Studies Depression Scale (CES-D), NIMH

Below is a list of the ways you might have felt or behaved. Please tell me how often you have felt this way during the past week.

	During the Past Week			
	Rarely or none of the time (less than 1 day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of time (3-4 days)	Most or all of the time (5-7 days)
1. I was bothered by things that usually don't bother me.	☐	☐	☐	☐
2. I did not feel like eating; my appetite was poor.	☐	☐	☐	☐
3. I felt that I could not shake off the blues even with help from my family or friends.	☐	☐	☐	☐
4. I felt I was just as good as other people.	☐	☐	☐	☐
5. I had trouble keeping my mind on what I was doing.	☐	☐	☐	☐
6. I felt depressed.	☐	☐	☐	☐
7. I felt that everything I did was an effort.	☐	☐	☐	☐
8. I felt hopeful about the future.	☐	☐	☐	☐
9. I thought my life had been a failure.	☐	☐	☐	☐
10. I felt fearful.	☐	☐	☐	☐
11. My sleep was restless.	☐	☐	☐	☐
12. I was happy.	☐	☐	☐	☐
13. I talked less than usual.	☐	☐	☐	☐
14. I felt lonely.	☐	☐	☐	☐
15. People were unfriendly.	☐	☐	☐	☐
16. I enjoyed life.	☐	☐	☐	☐
17. I had crying spells.	☐	☐	☐	☐
18. I felt sad.	☐	☐	☐	☐
19. I felt that people dislike me.	☐	☐	☐	☐
20. I could not get "going."	☐	☐	☐	☐

SCORING: zero for answers in the first column, 1 for answers in the second column, 2 for answers in the third column, 3 for answers in the fourth column. The scoring of positive items is reversed. Possible range of scores is zero to 60, with the higher scores indicating the presence of more symptomatology.

Appendix 12- LSIA

The Life Satisfaction Index A

1) As I grow older, things seem better than I thought they would be

☐ agree

☐ disagree

2) I have gotten more of the breaks in life than most people I know

☐ agree

☐ disagree

3) This is the dreariest time of my life

☐ agree

☐ disagree

4) I am just as happy as when I was younger

☐ agree

☐ disagree

5) My life could be happier than it is now

☐ agree

☐ disagree

6) These are the best years of my life

☐ agree

☐ disagree

Appendix – LSIA (continued)

7) Most of the things I do are boring or monotonous

☐ agree

☐ disagree

8) I expect some interesting and pleasant things to happen to me in the future

☐ agree

☐ disagree

9) The things I do are as interesting to me as they ever were

☐ agree

☐ disagree

10) I feel old and somewhat tired

☐ agree

☐ disagree

11) I feel my age, but it does not bother me

☐ agree

☐ disagree

12) As I look back on my life, I am fairly well satisfied

☐ agree

☐ disagree

13) I would not change my past life even if I could

☐ agree

☐ disagree

14) Compared to people my age, I've made a lot of foolish decisions in my life.

☐ agree

☐ disagree

15) Compared to other people my age, I make a good appearance

☐ agree

☐ disagree

16) I have made plans for things I'll be doing in a month or a year from now

☐ agree

☐ disagree

17) When I think back over my life, I didn't get most of the important things I wanted

☐ agree

☐ disagree

18) Compared to other people, I get down in the dumps too often

☐ agree

☐ disagree

19) I've gotten pretty much what I expected out of life

☐ agree

☐ disagree

Appendix – LSIA (continued)

20) In spite of what some people say, the lot of the average man is getting worse, not better

- ☐ agree
- ☐ disagree

Appendix 13- EPI

E ○ N ○ L ○ ☐☐☐☐☐☐☐☐☐☐

FORM A

		YES	NO
1.	Do you often long for excitement?	○	○
2.	Do you often need understanding friends to cheer you up?	○	○
3.	Are you usually carefree?	○	○
4.	Do you find it very hard to take no for an answer?	○	○
5.	Do you stop and think things over before doing anything?	○	○
6.	If you say you will do something do you always keep your promise, no matter how inconvenient it might be to do so?	○	○
7.	Does your mood often go up and down?	○	○
8.	Do you generally do and say things quickly without stopping to think?	○	○
9.	Do you ever feel "just miserable" for no good reason?	○	○
10.	Would you do almost anything for a dare?	○	○
11.	Do you suddenly feel shy when you want to talk to an attractive stranger?	○	○
12.	Once in a while do you lose your temper and get angry?	○	○
13.	Do you often do things on the spur of the moment?	○	○
14.	Do you often worry about things you should not have done or said?	○	○
15.	Generally, do you prefer reading to meeting people?	○	○
16.	Are your feelings rather easily hurt?	○	○
17.	Do you like going out a lot?	○	○
18.	Do you occasionally have thoughts and ideas that you would not like other people to know about?	○	○
19.	Are you sometimes bubbling over with energy and sometimes very sluggish?	○	○
20.	Do you prefer to have few but special friends?	○	○
21.	Do you daydream a lot?	○	○
22.	When people shout at you, do you shout back?	○	○
23.	Are you often troubled about feelings of guilt?	○	○
24.	Are *all* your habits good and desirable ones?	○	○
25.	Can you usually let yourself go and enjoy yourself a lot at a lively party?	○	○
26.	Would you call yourself tense or "highly-strung"?	○	○
27.	Do other people think of you as being very lively?	○	○

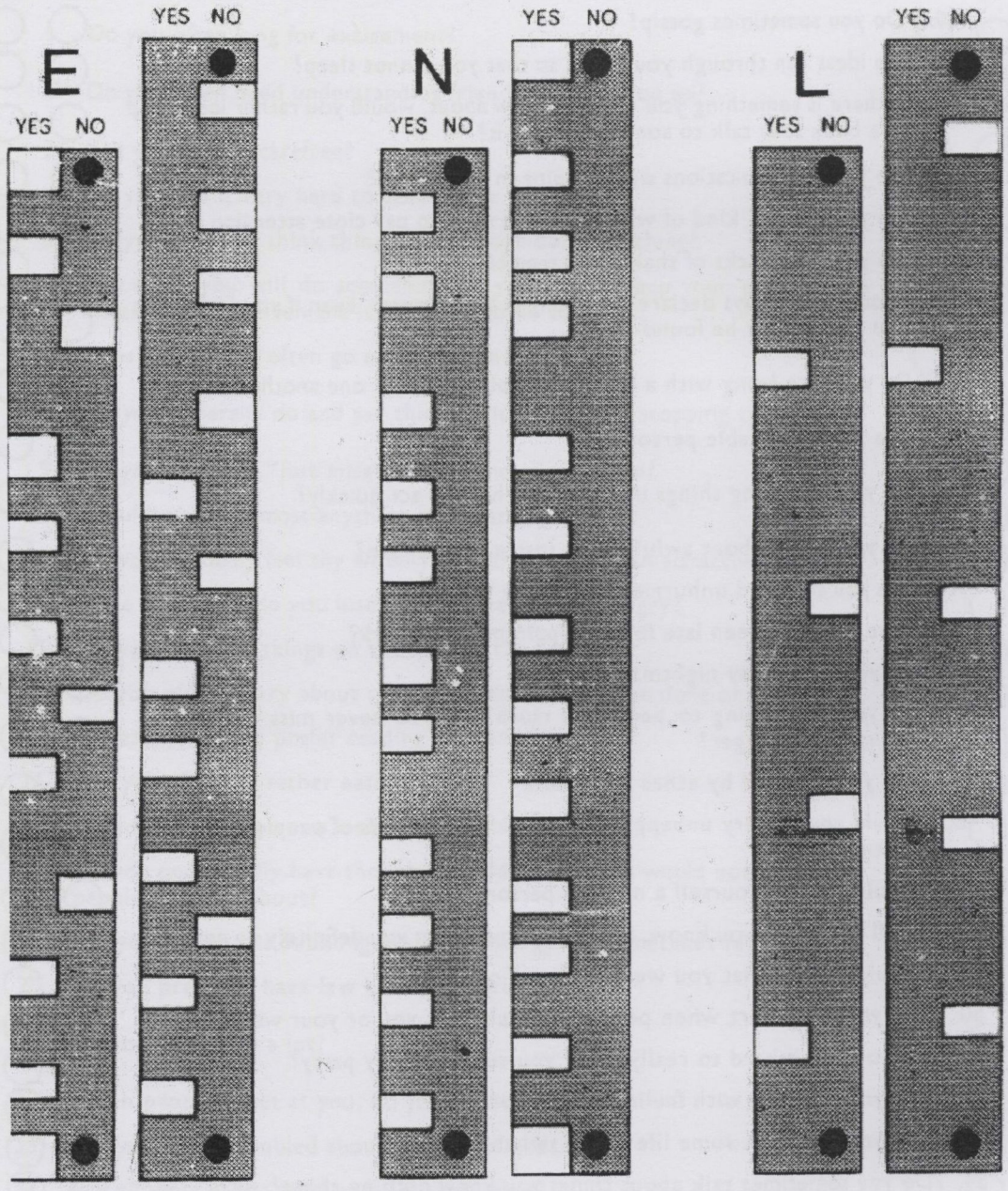
		YES	NO
28.	After you have done something important, do you often come away feeling you could have done better?	○	○
29.	Are you mostly quiet when you are with other people?	○	○
30.	Do you sometimes gossip?	○	○
31.	Do ideas run through your head so that you cannot sleep?	○	○
32.	If there is something you want to know about, would you rather look it up in a book than talk to someone about it?	○	○
33.	Do you get palpitations or thumping in your heart?	○	○
34.	Do you like the kind of work that you need to pay close attention to?	○	○
35.	Do you get attacks of shaking or trembling?	○	○
36.	Would you always declare *everything* at the customs, even if you knew that you could never be found out?	○	○
37.	Do you hate being with a crowd who play jokes on one another?	○	○
38.	Are you an irritable person?	○	○
39.	Do you like doing things in which you have to act quickly?	○	○
40.	Do you worry about awful things that might happen?	○	○
41.	Are you slow and unhurried in the way you move?	○	○
42.	Have you ever been late for an appointment or work?	○	○
43.	Do you have many nightmares?	○	○
44.	Do you like talking to people so much that you never miss a chance of talking to a stranger?	○	○
45.	Are you troubled by aches and pains?	○	○
46.	Would you be very unhappy if you could not see lots of people most of the time?	○	○
47.	Would you call yourself a nervous person?	○	○
48.	Of all the people you know, are there some whom you definitely do not like?	○	○
49.	Would you say that you were fairly self-confident?	○	○
50.	Are you easily hurt when people find fault with you or your work?	○	○
51.	Do you find it hard to really enjoy yourself at a lively party?	○	○
52.	Are you troubled with feelings of inferiority?	○	○
53.	Can you easily get some life into a rather dull party?	○	○
54.	Do you sometimes talk about things you know nothing about?	○	○
55.	Do you worry about your health?	○	○
56.	Do you like playing pranks on others?	○	○
57.	Do you suffer from sleeplessness?	○	○

PLEASE CHECK TO SEE THAT YOU HAVE ANSWERED ALL THE QUESTIONS

Appendix 14- EPI Scoring Key

Scoring Key

DIRECTIONS Place this key over each scoring column in turn. For each column, register the heavy circles at the top and bottom right with the corresponding circles on the questionnaire. Obtain the score by counting one point for each answer appearing through the 'windows'. Enter the total scores for each category E, N and L (both columns) in the large circles provided on the questionnaire.

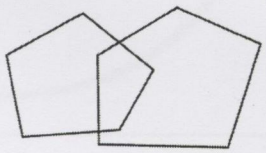


Appendix 15– MMSE

MINI MENTAL STATE EXAMINATION (MMSE)

Patient's name:

Hospital number:

ONE POINT FOR EACH ANSWER	DATE			
ORIENTATION				
Year Month Day Date Time	___/5	___/5	___/5	___/5
Country Town District Hospital Ward	___/5	___/5	___/5	___/5
REGISTRATION Examiner names 3 objects (eg apple, table, penny) Patient asked to repeat (1 point for each correct). THEN patient to learn the 3 names repeating until correct.	___/3	___/3	___/3	___/3
ATTENTION AND CALCULATION Subtract 7 from 100, then repeat from result. Continue 5 times: 100 93 86 79 65 Alternative: spell "WORLD" backwards - dlrow.	___/5	___/5	___/5	___/5
RECALL Ask for names of 3 objects learned earlier.	___/3	___/3	___/3	___/3
LANGUAGE Name a pencil and watch.	___/2	___/2	___/2	___/2
Repeat "No ifs, ands, or buts".	___/1	___/1	___/1	___/1
Give a 3 stage command. Score 1 for each stage. Eg. "Place index finger of right hand on your nose and then on your left ear".	___/3	___/3	___/3	___/3
Ask patient to read and obey a written command on a piece of paper stating "Close your eyes".	___/1	___/1	___/1	___/1
Ask the patient to write a sentence. Score if it is sensible and has a subject and a verb.	___/1	___/1	___/1	___/1
COPYING Ask the patient to copy a pair of intersecting pentagons: 	___/1	___/1	___/1	___/1
TOTAL	___/30	___/30	___/30	___/30

Appendix 16- Publications

Vascular biomarkers of cognitive performance in a community- based elderly population: The Dublin Healthy Ageing study.

Ai- Vyrn Chin, David J. Robinson, Henry O' Connell, Fiona Hamilton, Irene Bruce, Robert Coen, Bernard Walsh, Davis Coakley, Anne Molloy, John Scott, Brian A. Lawlor, Conal J. Cunningham.

*Age & Ageing 2008 Sept 37(5):559-564**

*Only vascular biomarkers were investigated in this paper (homocysteine, C-reactive protein, glycosylated haemoglobin and LDL- cholesterol). The associations between the vascular biomarkers and neuropsychological test scores were initially modelled individually in base models controlling for gender, age, social class and educational status before significant confounders determined in exploratory analyses were adjusted for in the final multivariate analysis.

Figures

Figure 3: Visual Reproduction Card A

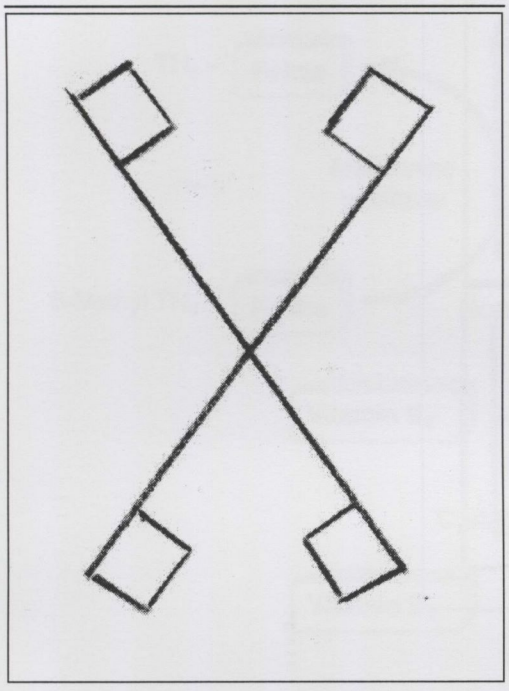


Figure 4: Visual Reproduction Card B

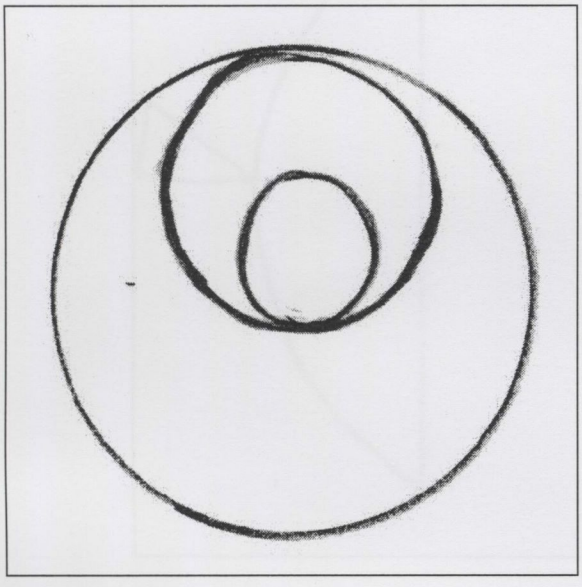


Figure 5: Visual Reproduction Card C

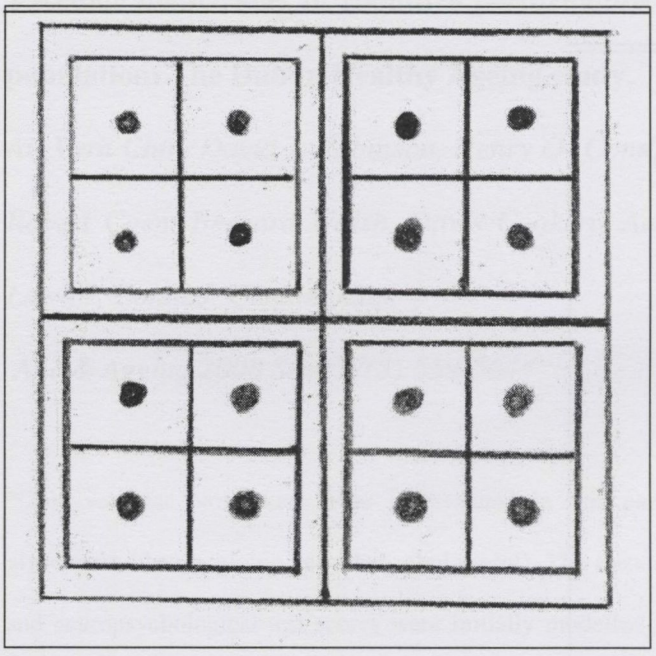


Figure 6: Visual Reproduction Card D

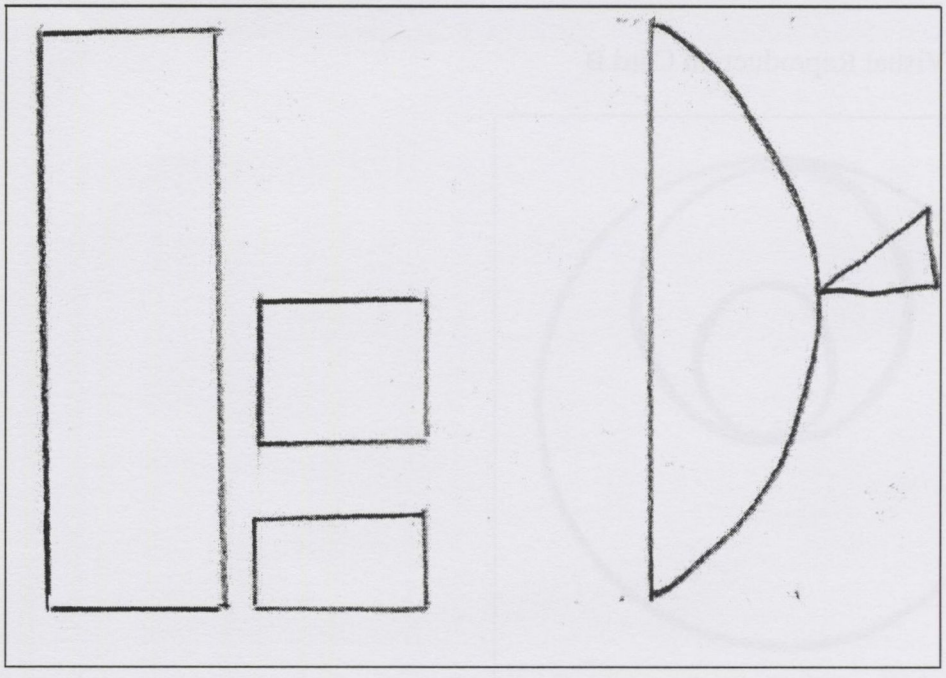


Diagram 1 Homocysteine Metabolism

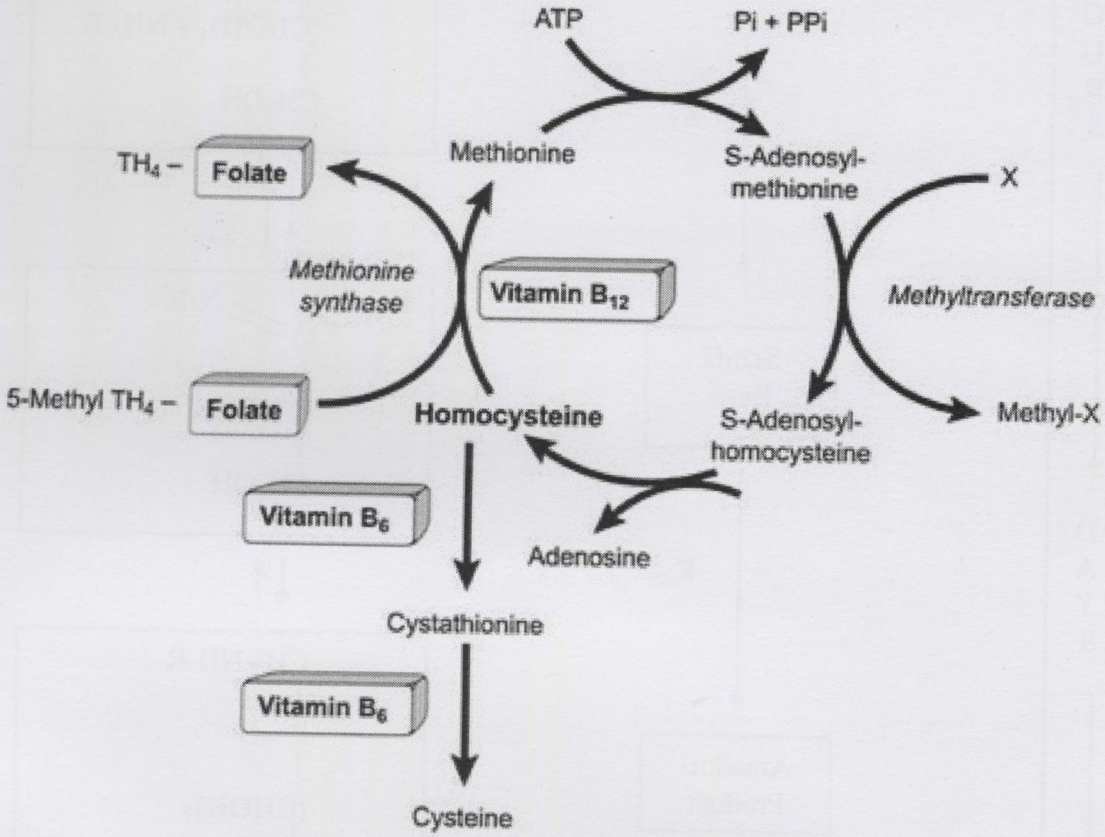


Diagram 2: Schematic representation of the formation of advanced glycosylation end products in the presence of persistent hyperglycaemia