

**PREDICTORS OF COGNITIVE DECLINE IN THOSE WITH
SUBJECTIVE MEMORY COMPLAINT**

A dissertation submitted for the degree of Doctor of Philosophy (PhD) at the
University of Western Australia

by

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DECLARATION

I declare that;

1. All sources are acknowledged; and
2. The thesis has not previously been accepted for any other degree in this or another institution; and
3. The thesis has been substantially accomplished during enrolment in the degree; and,
4. The thesis is wholly my own composition.
5. The main body of the thesis does not exceed 100,000 words

Roger M Clarnette

TABLE OF CONTENTS

VIII	Dedication
IX	Acknowledgements
XI	Abstract
XIV	Preamble

PART 1 - REVIEW

CHAPTER I - INTRODUCTION

<u>Pg</u>	<u>Chapter</u>	<u>Title</u>
1.	1.1	Ageing of the World's Population
2.	1.2	Ageing: Social, Economic and Health Consequences.
5.	1.3	Mental and Neurological Disorders: The Epidemic of the 21 st Century.
11	1.4	Common Causes of Dementia
23	1.5	Current Attempts to Control the Epidemic

CHAPTER 2 - HISTORY OF THE PRE-DEMENTIA SYNDROMES

<u>Pg</u>	<u>Chapter</u>	<u>Title</u>
25	2.1	Introduction
28	2.2	The Pre-dementia syndromes.
29	2.2.1	Benign Senescent Forgetfulness.
30	2.2.2	Severity Rating Scales that include Characterisation of Pre-dementia.
35	2.2.3	Age Associated Memory Impairment

39	2.2.4	Age Associated Cognitive Decline
40	2.2.5	Mild Cognitive Disorder
42	2.2.6	Mild Neurocognitive Disorder
44	2.2.7	Cognitive Impairment No Dementia
46	2.2.8	Mild Cognitive Impairment
65	2.2.9	Neuropsychological Predictors of Conversion to Dementia
71	2.2.10	Subjective Memory Complaint
85	2.3	Conclusions

CHAPTER 3 - RISK FACTORS FOR DEMENTIA

<u>Pg</u>	<u>Chapter</u>	<u>Title</u>
88	3.1	Dementia and Normal Ageing
96	3.2	Genetic Risk Factors for AD
103	3.3	Brain Structure and Function from Imaging as Risk Factors for AD
115	3.4	CSF Biomarkers as Risk Factors for Dementia
118	3.5	Cardiovascular and Metabolic Disease as Risk Factors for Dementia
121	3.6	Statins and AD Risk Reduction
122	3.7	Dietary Factors and the Risk of AD
124	3.8	Hormones and Risk of AD
127	3.9	Lifestyle Factors and Risk of AD
130	3.10	Anti-inflammatory Drugs and Risk of AD
131	3.11	Conclusions

PART 2 - STUDIES**CHAPTER 4, Study 1****CLINICAL CHARACTERISTICS OF INDIVIDUALS WITH SUBJECTIVE****MEMORY LOSS:**

<u>Pg</u>	<u>Chapter</u>	<u>Title</u>
133	4.1	Introduction
134	4.2	Objectives
134	4.3	Acquisition of the sample
136	4.4	Study procedures and timelines
137	4.5	Clinical Features
141	4.6	Cognitive and neuropsychological testing.
153	4.7	Neuroimaging protocol
158	4.8	Genetics
159	4.9	Homocysteine
159	4.10	Statistical Analysis
162	4.11	Results
176	4.12	Discussion

CHAPTER 5 - Study 2**LONGITUDINAL COGNITIVE CHARACTERISTICS OF INDIVIDUALS WITH
SUBJECTIVE MEMORY LOSS:**

<u>Pg</u>	<u>Chapter</u>	<u>Title</u>
189	5.1	Introduction
189	5.2	Objectives
190	5.3	Sample Acquisition and Methodology
197	5.4	Results
222	5.5	Discussion

CHAPTER 6 - Study 3**RISK FACTORS FOR MEMORY DECLINE AMONGST INDIVIDUALS WITH
AND WITHOUT SUBJECTIVE MEMORY COMPLAINT**

<u>Pg</u>	<u>Chapter</u>	<u>Title</u>
227	6.1	Introduction
227	6.2	Objectives
228	6.3	Sample Acquisition and Methodology
231	6.4	Results
255	6.5	Discussion

PART 3 - CONCLUSIONS**CHAPTER 7****SUMMARY OF FINDINGS**

<u>Pg</u>	<u>Chapter</u>	<u>Title</u>
260	7.1	Introduction
266		Reference

DEDICATION

This work is dedicated to my parents

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ABSTRACT

Background

Dementia, largely due to Alzheimer's disease (AD), is a major public health problem. The early identification of disease is an important challenge for clinicians because treatment of AD is now available. A simple and accurate means of stratifying risk for AD and identifying early disease is needed so that risk factor modification and treatment can occur optimally. To date, despite many attempts, an accurate means of standardising an approach to the assessment of subtle cognitive symptoms has not been developed. A subjective complaint of poor memory has been identified as a possible marker for underlying brain disease. This study examines the utility of neuropsychological scores, homocysteine levels, APOE genotyping and brain imaging as predictors of cognitive decline in individuals with subjective memory complaint (SMC).

Method

Eighty subjects with SMC were recruited from memory clinics and the community (MC: 1). Forty-two control subjects were also examined (MC: 0). CAMDEX was used to describe baseline clinical features. The CAMCOG was used as a global test of cognition and was administered annually for four years. At baseline, neuropsychological testing was administered. Cranial CT scanning, measurement of plasma homocysteine and APOE genotyping were completed. Categorical variables were analysed using chi-square according to Pearson's method. Continuous data was analysed using Student's *t*-tests and Mann-Whitney tests. A logistic regression model was used to identify independent contributors to the presence of memory complaint. Participants were then

matched for age, gender and time to follow-up (up for three years) to determine longitudinal predictors of cognitive decline.

Results

The groups were well matched for age (mean \pm SD, controls = 61.7 ± 11.0 years and complainers = 62.4 ± 10.3 years, $t=0.33$, $p=0.739$). There were more females in the complainer (MC:1) than in the control group (MC:0) (47.5% vs 62.5%, $\chi^2=2.50$, $p=0.114$). Mood and anxiety symptoms were more frequent in the MC:1 group than in the MC:0 group. Baseline CAMCOG scores were greater in the control group (MC:0 = 98.3 ± 2.8 , MC:1 94.2 ± 5.5 , $Z -4.46$, $p 0.000$). There were no differences in neuropsychological scores, concentration of total plasma homocysteine, APOE genotype or brain scan measurements. Using the Wald stepwise selection method, logistic regression could not be established due to non-convergence regardless of whether or not the continuous variables were re-coded into dichotomous variables.

A matching process that created 32 pairs of controls/subjects allowed follow-up analysis. The controls showed significant improvement with time on the CAMCOG unlike subjects (mean \pm SD, controls 1.5 ± 3.0 , $Z - 2.61$, $p 0.01$, subjects 0.2 ± 3.2 , $Z - 0.24$, $p 0.81$). The logistic regression analysis showed that group membership could not be defined by any single independent variable.

When group membership was abandoned and those with stable scores were compared to those who declined no clear meaningful independent predictors of decline apart from age were identified.

Conclusions

Methodological issues such as small sample size and inadequate follow up duration were identified that may have precluded identification of predictive factors for cognitive decline. The results indicate that complaints of memory problems are not associated with established risk factors for Alzheimer's disease and fail to predict objective cognitive decline over three years. Future studies should continue trying to identify robust predictors of cognitive decline in later life.

PREAMBLE

This dissertation examines subjective memory complaint as a possible manifestation of underlying brain disease. The central hypothesis is that subjective memory complaint predicts the presence of poor cognitive performance and is associated with evidence of cerebral atrophy. The motivation for the study is the pressing need to diagnosis Alzheimer's disease and other causes of dementia earlier than is currently possible.

Part 1, comprising chapters one to three, examines the background and literature that is fundamental to the topic. Part 2, comprising chapters four to six, describes the methodology and data analysis. Part 3 (chapter seven) concludes the dissertation.

PART 1 - REVIEW

CHAPTER I

INTRODUCTION

1.1 Ageing of the World's Population

The mean age of populations in most countries has increased significantly in the last century. The number of people aged over 65 years worldwide is increasing at an annual rate of 2.4% (Cooper 1994). This increase is primarily due to high fertility after World War II (Kinsella *et al* 2001). In addition, life expectancy, especially in Western countries, has increased particularly for those older than 80 years (Jacobzone 1999). A rise in life expectancy began in the 19th century and this occurred before better sanitation and was due to changes in the distribution and organisation of agricultural produce (Thomlinson 1976). In 1900 life expectancy at birth was 50 years in western countries and this has now risen to age 76 years as of 2000 (Katzman *et al* 1994). In Australia, average life expectancy is 77 years for men and 83 years for women (ABS 2002). This increase in life expectancy has been partly due to decline in infant mortality, infectious and parasitic disease and better nutrition (Kinsella *et al* 2001). Such a success is accompanied by significant social and economic challenges. The WHO report that arose from the 2nd United Nations World Assembly of Ageing in 2002 predicted that between 1970 and 2025 the proportion of people in the world over the age of 60 years will increase by 223% (WHO 2002). By 2050, there will two billion people aged 60 years or over and 80% of

these will be living in developing countries. At present, in developed countries, those over the age 80 years represent 3% of the population and this group is increasing at a greater rate than any other age category. Population ageing is seen by the World Health Organisation (WHO) as one of humanity's great triumphs (WHO 2002).

1.2. Ageing: Social, Economic and Health Consequences.

As fertility and mortality rates have fallen and populations have aged, more emphasis has been placed on quality of life for the elderly (Kinsella *et al* 2001). A WHO report from 1999 notes that in older population groups, non-communicable disease (NCD) has become the major reason for disability and mortality (WHO 1999). These diseases are often fully or partly preventable and there are social and economic consequences if measures are not taken to deal with them. Aboderin and colleagues state that there is considerable scope for prevention of the burden of disability of NCD if action is taken early in the life cycle (Aboderin *et al* 2002).

This situation is increasingly a problem not only for industrialised countries but also in the developing world. The WHO refers to the double burden of disease in these countries (WHO 2002). Not only is there the longstanding problem with infectious diseases, malnutrition and birth trauma, but also now with NCD. In 1990 it was estimated that 49% of the burden of disease in developing and newly industrialised countries was due to communicable disease (Murray *et al* 1996). By 2020 this is expected to decline to 22% as NCD rises with the ageing of the population. In

developed countries, it has been shown that the implementation of measures to reduce disability from NCD can be successful. This is exemplified by data from the USA that shows that age-specific disability rates declined between 1982 and 1999 (Manton 2001). As a result, the expected rise in absolute numbers of disabled Americans did not occur. This encourages health systems to continue the search for intervention programs to prevent chronic diseases. For those with chronic disease, attenuation of disability will continue to rely on community support and application of technology (Jacobzone 2000).

The WHO Assembly on Ageing report also pointed out the social needs of elderly disabled populations (WHO 2002). It makes the distinction between disablement and enablement. A focus on disablement tends to isolate individuals whereas enablement based programs increase participation and improve function.

The gender differences in ageing populations are yet another factor that has implications for health systems. Elderly women far outnumber elderly men (UN 2001). Female survival advantage is a feature of mortality trends, and as of 2000 women had an average 7 years survival advantage over men (US 2000). In addition, elderly widows make up a significant proportion of women over the age of 70 years (Botev 1999). The WHO report states that this is important because elderly women are at greater risk of poverty and social isolation (WHO 2002). Poverty has direct adverse effects on health outcomes (Wilkinson 1996), and the wealth gap that exists

in most countries needs to be addressed to prevent rising health costs and social fragmentation (Lynch *et al* 2000).

With respect to the cost of providing health care to those aged over 65 years, Organisation for Economic Cooperation and Development (OECD) data from 1993 is revealing. It shows that in nine developed countries where the elderly represented between 12 and 18% of the total population, this age-group expended between 32 and 42% of the total annual budget (OECD 1997). In Australia, however, there is a consistent view that health care costs will not rise significantly as the mean age of the population increases (Coory 2004). This is supported by data that Coory quotes from the Organisation for Economic Cooperation and Development. This shows that in countries where the elderly represent a greater percentage of the population than in Australia, expenditure on health is no greater as a percentage of GDP. One explanation for this is that the relationship between ageing and health care costs is confounded by time to death. This is known as the Fuch's effect (Fuchs 1984). In simple terms, it is the process of dying or health care costs in the last few years of life that is expensive and this is occurring at a later age (Van Weel 1997).

Nonetheless, there is evidence that the total expenditure on those over age 65 is rising. Among European countries in 1985, mean total health costs for the elderly was 37% of total budget (ILO 1991). This has been estimated to increase to 58% by 2015.

Disease burden and disability data give a different view of health than traditional mortality statistics. Australian data show that ischemic heart disease was the leading cause of death in 1996 at 25.4%. Dementia was sixth on the list at 3.0%. Other studies show that dementia predicts mortality as much as cancer does (Baldereschi *et al* 1999) (Katzman *et al* 1994).

In Australia, when non-fatal health outcomes are added to the mortality data, then mental disorders become the third biggest contributor to disease burden after cardiovascular disease and cancer (ABS 2002). Nervous system diseases are the fourth largest contributors. When the non-fatal disease burden is considered, then mental disorders and nervous system disorders are the leading causes in this category. For males in 1996, dementia was the fourth leading cause of disability burden, representing 4.4% of total disability. For women, dementia was the second leading cause, accounting for 6.8% of total disability (Mathers *et al* 1999).

1.3. Mental and Neurological Disorders: The Epidemic of the 21st Century.

1.3.1 Epidemiology

According to the WHO, 25% of people in developed and developing countries will suffer one or more mental or behavioural disorders during their life time (WHO 2001). Over 120 million people worldwide suffer from depression and 37 million from dementia. These conditions do not contribute greatly to mortality, but more significantly to the burden of disability. The clinical expression of dementia includes memory impairment, functional deficits, altered behaviour and psychological

symptoms. These directly affect ability to contribute to the workforce and the community.

In 2006 Access Economics referred to a World Health Organisation estimate that nearly 100 million disability adjusted life years are lost each year due to neuropsychiatric conditions worldwide (Access 2006). Only infectious and parasitic diseases cause more disability. Of the neuropsychiatric diseases, dementia is ranked sixth (5% overall) after depression, schizophrenia, alcohol abuse, bipolar disorder and mental retardation.

The Australian Institute of Health and Welfare (AIHW 2004) published a report in 2004 that identifies dementia as the greatest single contributor to burden of disease amongst the elderly (AIHW 2004). The report estimates that of 167,000 dementia sufferers in 2002, 113,000 had a profound core activity restriction, representing 1.1% of the population over the age of 35 years. Furthermore, the report estimates that this group will increase in absolute number by 60% by 2020. The prevalence of dementia doubles every 5.1 years after the age of 65 years (Henderson *et al* 1998). This figure was based on a meta-analysis by Jorm and is consistent with other published meta-analyses (Jorm *et al* 1987) (Hofman *et al* 1991) (Ritchie *et al* 1992). The prevalence of dementia in 2002 in Australia was 0.8% of the population (Access 2003). The Access Economics report states that half of the prevalent cases are over the age of 85 years. Hence the concern is that with increasing life expectancy, there will be a consequent epidemic of dementia sufferers requiring health care. In a further report in 2004,

Access Economics applied formulae as per Brookmeyer (Brookmeyer *et al* 1998) to estimate incidence and prevalence of AD in Australia (Access 2004). The incidence of AD is 0.08% at age 60 and increases to 12.1% at age 95. The prevalence of AD is 0.1% at age 60 and rises to 14.0% at age 95.

This is extant in other countries. In the United States, the annual mortality attributable to neuro-degenerative diseases was expected to rise 166% between 1990 and 2040 (Lilianfeld 1993). This increase will be largely due to dementia. In the USA, deaths due to Alzheimer's Disease represent 7.1% of all deaths, which is similar to stroke and therefore the third most common cause of death (Ewbank 1999). Brookmeyer concluded that the prevalence of Alzheimer's disease would rise fourfold in the next 50 years (Brookmeyer *et al* 1998). Projected incidence of the disease over this time will double, and most new incident cases will occur in those over the age of 80 years (Hebert 2001).

1.3.2 Health Care Service Consequences of Dementia.

The AIHW report included detailed data on the utilisation of resources across the spectrum of the health care system (AIHW 2004).

1.3.2.1 General Practice

In 2001-2 there were 505,000 encounters with patients with dementia. Of these 25% were thought to be related to Alzheimer's disease and 29.4% resulted in prescription of a medication.

1.3.2.2 Hospitals

Dementia has a significant effect on hospitals. It was the principle diagnosis in 0.16% of all separations (AIHW 2004). If the additional secondary diagnosis of dementia is considered then this frequency goes up to 1.2%. Length of stay (LOS) data also shows that dementia has a major effect. When same day separations in those with a principle diagnosis of dementia were excluded, the mean LOS for the dementia group was 32.6 days. The mean LOS for all separations was 6.5 days. When same day separations are included, the mean drops to 31.0 days. When the analysis includes patients with any diagnosis of dementia the mean LOS is 18.8 days.

1.3.2.3 Aged Care Assessment Teams

These teams are funded by the Commonwealth Government to assess patients for eligibility for residential care subsidies. Dementia was the most common diagnosis and represented 20% of all cases seen by the teams in 2000-1 (AIHW 2004).

1.3.2.4 Community Care

In late 2002, there were over 2,500 community aged care packages being delivered in Australia. These are designed to provide care for individuals who would otherwise need low level residential care. Elderly aged care in the home packages are designed to provide a higher level of support for individuals who would otherwise need high level residential care. Dementia sufferers contributed 20% and 33% to the total for packages and residential care respectively.

1.3.2.5 Residential Aged Care

Dementia has a significant effect on the utilisation of residential care beds and the level of care those residents need. In Australia in 2002, 31% of all residents in aged care facilities probably had dementia and 50% possibly had dementia (AIHW 2004). This approximation of probability was used because data on the clinical diagnosis of dementia is not systematically available for all residents of aged care facilities. Instead, the 20-item residential classification index was used for this approximation. In addition, for the occupied bed-days in the two highest care categories (there are eight in total), two thirds of these residents had probable dementia. Residents with possible or probable dementia occupied 80% of total bed-days.

Residents with dementia had an average length of stay of 169 weeks compared to 119 weeks for those without dementia (AIHW 2004). In this study period, those with probable dementia occupied more bed-days than the combined groups of possible dementia and no dementia. The AIWA report does not address the relevance of these data. However, one must assume that non-demented residents have diseases that adversely affect their survival.

1.3.3 Social Security Consequences of Dementia

In the last 50 years there has been a trend away from hospital-based long stay care for elderly people with dementia to non-clinical types of care (Cooper 1994). The proportion of the elderly now living in non-private households has therefore risen. In some countries, this is as high as 10.5% (Grundy 1984). The need to curtail the

costs of such care has led to the provision of other services like day care centres and home respite programs. These are designed to provide support to caregivers and allow dementia sufferers to stay at home for longer. The consequent health and economic effects on caregivers has driven a burgeoning interest in the field of caregiver research.

1.3.4 Cost of Dementia Care

Of the \$2.5 billion spent on dementia by the health and aged care sectors in Australia in 2001, 84% was allocated to residential aged care (AIHW 2004). In the 2003 financial year, of the \$4.3 billion spent on residential aged care, 66% of this was spent on care for dementia sufferers (Access 2003). The health system (excluding residential care) costs for dementia in 2001 was \$307 million, most of this for acute hospital care and pharmaceuticals (AIHW 2004). In addition, the cost of dementia to users of the system was \$360 million. This is consistent with data from other countries where social security rather than health insurance pays for the bulk of dementia care (Cooper 1994). It has been predicted that the direct cost of dementia care will rise to \$6 billion by 2011 (Access 2003).

The Access Economics report also includes an analysis of the total direct and indirect costs of dementia care in Australia in 2002. This includes mortality burden, lost earnings, income tax foregone (both patient and caregiver), costs of informal care by family members, aids and equipment and welfare payments. The total cost came to \$6.6 billion or just over \$40,000 for each patient (Access 2003).

1.3.5 Conclusion

It is apparent from the discussion so far that dementia is a huge world wide health issue. There is a pressing need to develop meaningful interventions that will reduce the incidence and prevalence of the diseases that cause dementia. Risk factor identification is crucial so that high-risk individuals can be targeted.

1.4. Common Causes of Dementia

Before risk factors are discussed, this section will present an overview of the common causes of dementia. Methods of diagnosis are emphasised.

1.4.1 Alzheimer's Disease (AD)

AD is the commonest cause of dementia in Western societies and accounts for 50-60% of all cases (Wahland 2003). Prevailing opinion is that the accumulation of the β -amyloid peptide is an early event (Selkoe 2000) leading to the hyperphosphorylation of microtubule associated tau protein (Alonso *et al* 1994). It is hypothesised that these set off an abnormal metabolic cascade leading to cell death and loss of synapses., Inflammatory factors, oxidative stress and altered calcium homeostasis are also important contributors to the pathogenesis of AD (Alafuzoff *et al* 2002). It is beyond the scope of this thesis to expand further on the molecular pathology of AD.

A deficit in new learning and encoding of newly presented information is the prominent and usually first cognitive symptom of AD (Knopman 2002). Other cognitive domains (eg language, executive function and visuospatial processing) are also affected early in the course of the disease (Knopman 2002).

Clinical diagnosis is based on symptoms and history, since neuropathological diagnosis is not practical in life and there are as yet no established biological markers to base diagnosis on. Chui and Lee (Chui *et al* 2002) examined the accuracy of the DSM-IV (APA 1994) and NINCDS (McKhann *et al* 1984) clinical criteria for AD. They found that “there is considerable room for improvement” in terms of distinguishing AD from other causes of dementia (Chui *et al* 2002). They found that the likelihood ratios generated from studies that correlated clinical diagnosis with post-mortem findings were small. In addition, no set of criteria showed both high sensitivity and specificity (Table 1.1).

Table 1.1Diagnostic Criteria for Alzheimer's Disease

Criteria	Number of Studies	PPV	NPV	Sensitivity	Specificity	Likelihood Ratio
NINCDS-ADRDA Prob/Poss (McKhann <i>et al</i> 1984)	10	0.84	0.66	0.90	0.56	2.9
NINCDS-ADRDA Probable (McKhann <i>et al</i> 1984)	5	0.91	0.45	0.65	0.76	4.4
DSM-III Dementia AD type (APA 1987)	3	0.86	0.58	0.53	0.88	4.8

Source (Chui *et al* 2002)

Similarly, other clinical and laboratory markers of disease (neurological signs, behaviour change, apolipoprotein E (*APOE*) genotype, CSF proteins, brain CT, or temporal lobe measurements on magnetic resonance imaging (MRI) did not have sufficiently high likelihood ratios to change pre-test probability to a significant post-test probability (Chui 2002).

With respect to neuropathology, the β -amyloid deposition and cytoskeletal pathology seen in AD are accepted as robust markers of disease, although they also occur in individuals who are not demented (Jellinger 2003). AD is not only clinically

but also a pathologically heterogeneous disorder. A number of pathological criteria exist that vary in approach. These are briefly outlined below.

1. Khachaturian (Khachaturian 1985). This approach uses plaque and tangle count per unit area of brain tissue and is corrected for age.
2. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) (Mirra *et al* 1991). This method uses a semi-quantitative plaque and tangle count adjusted for age and the clinical history of dementia to determine a likelihood of dementia.
3. Braak (Braak *et al* 1993). This method defines the pathology according to the spread of neurofibrillary tangles from the entorhinal cortex (early disease) to the isocortex (established disease) and pathology is graded in increasing severity from stage 1 to 6.
4. National Institute of Health and Reagan Institute of the Alzheimer's Association guidelines (Hyman 1997). These guidelines combine the CERAD and Braak criteria to give a probability of AD.

There is strong evidence that increased plaque, and in particular tangle load, correlate with decline in cognitive state (Berg *et al* 1998) (Cummings, BJ *et al* 1996) (Haroutunian *et al* 1998) (Haroutunian *et al* 1999). However, the number of these lesions cannot distinguish between cognitively normal, mild cognitive impairment and mildly demented cases (Jellinger 2003). It has been found that para-hippocampal tau pathology is more prominent in those with MCI than normals and correlates

with deficits in episodic memory (Mitchell *et al* 2002). In addition, there is evidence that plaques spread in a distinct sequence as the disease progresses, starting in the entorhinal cortex (Thal *et al* 2002).

There is impetus for these criteria to be re-evaluated because of the overlap between findings in cognitively normal individuals and those with AD. One study showed that of 59 cognitively normal subjects, only 17% were free of AD pathology (Davis, DG *et al* 1999). In addition, cerebral amyloid angiopathy was present in 75%. In another study that examined centenarians, there was little correlation between cognition and pathology (Silver *et al* 2002). Two of 14 subjects had no pathology to account for dementia and 2/14 had significant AD lesions with normal cognition. This raised the possibility that some individuals have brain reserve or increased protective factors or both of these features that overcomes considerable lesion load.

The concurrence of cerebrovascular pathology with AD lesions further compromises the usefulness of pathological criteria. In one study that examined 600 cases of clinically confirmed probable or possible AD, only 39% had 'pure' AD (Jellinger 2003). In this group, 30.3% had vascular lesions. Bowler and colleagues (Bowler *et al* 1998) argue that if correction is made for this concurrence of AD and vascular pathology, then the positive predictive value of a clinical diagnosis of AD is halved from 80 to 40%. Others have argued that pathological criteria *per se* should no longer be considered the 'gold standard' for diagnosis of a clinically defined syndrome (Pantoni 2002).

1.4.2 Vascular Dementia

There has been a long acknowledged association between dementia and cerebral lesions attributed to vascular pathology (Markesbury 2001) (Gustafson 2004). Historically, the medical profession has made a distinction between degenerative and vascular disease, and in the early 20th century cerebral arteriosclerosis was considered to be the leading cause of dementia (Kraepelin 1910). The description of this clinical entity has changed from multi-infarct dementia (Hachinski *et al* 1974) to vascular dementia, and latterly to vascular cognitive impairment (VCI)(Hachinski, Bowler 1993). At the time of writing, the term vascular dementia (VD) is the most common designation used by clinicians, although VCI is more in keeping with current knowledge of the condition (O'Brien *et al* 2004). VCI encompasses all forms of cerebrovascular disease, does not emphasise memory loss as the predominant symptom of the cognitive profile, and does not require the subject to be demented (Erkinjuntti *et al* 2002).

The diagnosis of VD has been the subject of considerable debate and a number of diagnostic criteria have been developed for research use that have limited usefulness in a clinical setting (Bowler 2004). One issue is that a diagnosis of AD requires exclusion of cerebrovascular disease, thus making it difficult to correlate the two conditions. More recently, the view that dementia due to a combination of both AD and vascular pathology is the commonest cause of dementia has gained credence (CFAS 2001). Hachinski and Munoz have suggested that the pathology of AD is intrinsically linked to vascular pathology (Hachinski, Munoz 1997). They point out

the abundant vessel pathology in AD including endothelial changes, disruption to the blood brain barrier and amyloid deposition in cerebral vessels.

There are currently four different sets of criteria available for clinicians and researchers. These are DSM IV (APA 1994), ICD-10 (WHO 1993), ADDTC (Chui *et al* 1992) and NINDS-AIREN (Roman *et al* 1993) (See appendix 1). The criteria are similar in that dementia is recognised as a syndrome, and the vascular cause of the dementia is detailed. However, they all differ in the definition of the essential elements for the diagnosis of VD (Erkinjuntti 2000). Sensitivity and specificity vary widely, with the NINDS-AIREN criteria being the most specific (Gold *et al* 1997). Erkinjuntti recommends that uniformity is needed by establishing new criteria that are based not on consensus, but on community studies and the natural history of the syndrome (Erkinjuntti 2000).

Skoog and Aevarsson (Skoog *et al* 2000) wrote that “often it is up to the investigator’s judgement to decide whether a stroke has caused the dementia, contributed to it or is just there by coincidence. The distinction is often difficult to make at autopsy. Depending on the investigator’s beliefs, these cases will be classified as VD, mixed dementia or AD”. Stewart’s opinion is that the use of categorical diagnoses (ie dementia) is problematic, and that the term vascular dementia has never been of any help in a clinical setting (Stewart, R 2004). This is supported by the view that the term has “outlived its usefulness” because criteria are based on an AD model and the requirement for dementia to be present, thus denying “the possibility of

identification and treatment to those who would benefit most from it" (Bowler *et al* 2002). Bowler and Hachinski have not considered establishing formal criteria for VCI because of the lack of adequate data to clearly characterise it.

These issues make the identification of VD difficult for clinicians and the true prevalence of VD is not known (Leys *et al* 2002). Some post mortem studies suggest that the prevalence of pure VD is low. The study by Snowden and Markesbury identified three cases of pure VD out of a total of 118 cases (Snowden 1999). A clinical study from Canada reports a rate of 12.1% (Rockwood *et al* 2000).

Given these misgivings, it may seem somewhat meaningless to consider data regarding the accuracy of the diagnostic criteria. The following table (Table 1.2) summarises available data.

Table 1.2Diagnostic Criteria for Vascular Dementia

	Hachinski Ischemic Score	DSM-III-R	ICD-10	DSM-IV	ADDTC	NINDS-AIREN	VCI
Diagnosis	MID	MID	VaD	VaD	VaD	VaD	VCI
Image	No	No	No	No	Yes for probable VaD.	Yes for probable VaD.	
Neuro-Pathology	No	No	No	No	No	No	
Neuro-Psychology	No	No	Unequal Distribution Of cognitive Loss	Unequal Distribution Of cognitive loss	2 cognitive domains impaired.	Memory + 2 other cognit' domains impaired.	

Evidence	<u>(Moroney et al 1997)</u> N=312 Sens 84% Spec 82% (Gold et al 1997) N-113 Sens 88-97% Spec 30-43%	<u>(Iellinger et al 1990)</u> N=677 Sens 80% Spec 89% <u>(Erkinjuntti et al 1988)</u> N=37 Sens 68% Spec 83%	(Gold et al 2002) Sens 20% Spec 94%	(Gold et al 2002) Sens 50% Spec 84%	(Gold et al 1997) Sens 58-63% Spec 64-88% (Gold et al 2002) Sens 25-70% Spec 78-91%	(Gold et al 1997) Sens 43-58% Spec 79-91% (Gold et al 2002) Sens 20-55% Spec 84-93%	
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DSM-III-R - Diagnostic and Statistical Manual, 3rd edition, revised. ICD-10 - International Classification of Disease, 10th edition. DSM-IV - Diagnostic and Statistical Manual, 4th edition.

1.4.3 Dementia with Lewy Bodies

The intra-cytoplasmatic inclusion described by Lewy is a key-pathological feature of Parkinson's Disease (Hughes, AJ *et al* 1993). However, Lewy bodies (LB) are also seen in other diseases and even in normal people (Forno 1982). The observation that dementia can be associated with the presence of LB in the cerebral cortex led to the systematic description of another type of dementia that is now known as dementia with Lewy bodies (DLB) (McKeith *et al* 1996). The consensus diagnostic criteria for probable DLB states that two of the following three features should be present:

- i Fluctuating cognition
- ii Recurrent visual hallucinations
- iii Motor features of Parkinsonism

Other features that are supportive of the diagnosis include:

- i Repeated falls
- ii Syncope
- iii Transient loss of consciousness
- iv Neuroleptic sensitivity

In addition, the pathology includes cortical and subcortical LB, Alzheimer lesions (ie plaques and tangles), Lewy related neurites, spongiform change and synapse loss (Londos *et al* 2003). There is considerable pathological overlap between DLB and AD. In one study, two thirds of those with clinical DLB met the criteria for AD (Londos *et al* 2003). In another, of 24 cases with a clinical diagnosis of probable DLB, 21 had a

secondary diagnosis of possible AD (McKeith *et al* 2000). In this study, 54% of 29 cases of pathologically proven DLB also had definite AD according to the CERAD criteria (Mirra *et al* 1994). In the Florida brain bank study, concomitant AD was found in 66% of DLB cases (Barker, WW *et al* 2002). Nevertheless, DLB appears to have distinct features, as evidenced by a different neuro-psychological profile and natural history (McKeith *et al* 2000).

The prevalence of DLB, according to neuro-pathological series, varies from 10 to 36% (Londos *et al* 2003) (McKeith *et al* 2000). The prevalence in the wider population remains unclear. The validity of the clinical criteria when correlated with neuropathology appears to be good. McKeith *et al* (McKeith *et al* 2000) reported that the sensitivity and specificity for the clinical diagnosis of probable DLB were 0.83 and 0.95 respectively. There is considerable overlap with other disorders.

1.4.4 Frontotemporal Dementia

The term fronto-temporal dementia encompasses a number of clinical disorders (including Pick's disease) that are due to variable pathology. Many cases have tau and ubiquitin inclusions, whilst others have no specific histological features (Miller 2004). About 40% of cases are familial, and 40% are the result of tau mutations (Rizzu *et al* 1999). This form of dementia accounts for no more than 1% of all types of dementia (Ritchie 2002).

Patients with fronto-temporal dementia are often cognitively distinct from AD, in that there is a relative preservation of episodic memory and visuospatial abilities (Rosen 2002). There are clinical criteria for this syndrome in DSM-IV (APA 1994) and ICD-10 (WHO 1992). The latter criteria include dementia, frontal lobe features (euphoria, emotional blunting, dysfunctional social behaviour and apathy) and less prominent memory loss early in the disease course. Further criteria were developed and modified (Neary 1998) and defined three syndromes of frontotemporal dementia. These are fronto-temporal dementia, progressive non-fluent aphasia and semantic dementia. These criteria have been shown to be reliable (Lopez *et al* 1999). However, to date there are no adequate clinico-pathological studies that inform us of the validity of these criteria and, as a result, they cannot be recommended for routine use in clinical practice (Chui *et al* 2002).

1.4.5 Other Conditions Causing Dementia

A number of other conditions cause dementia and deserve mention, but not detailed discussion. These are Parkinson's Disease, Huntington's disease, progressive supranuclear palsy, multisystems atrophy, corticobasal degeneration, Creutzfeld-Jacob disease and normal pressure hydrocephalus.

1.5 Current Attempts to Control the Epidemic

It is axiomatic that prevention is the best way of controlling disease. Primary prevention of infectious disease is a major public health success in the last century. Primary prevention of cardiovascular disease is also possible. For AD there is still a

need to understand the factors that influence the disease and how they can be modulated. This knowledge will assist with the development of preventive strategies.

PART 1 - REVIEW

CHAPTER 2 - HISTORY OF THE PRE-DEMENTIA SYNDROMES

2.1 Introduction

The manner of diagnosis is relevant in explaining how difficult it has been to clinically recognise brain disease in its early stages. Diagnosis is a summary of “what is known regarding symptoms, signs and clinical history.... How one clinical condition is related to or distinct from another” (Bamford 1988). According to Wulff, diagnosis of a condition can be based on four types of clinical information (Wulff 1976). These are:

1. Symptom: ‘the most primitive form of disease entity’
2. Syndromes: eg heart failure or dementia. Often there is no way of validating the presence of the disease.
3. Anatomically defined disease: eg fracture or tumour
4. Causally defined disease: eg infection

It was noted in chapter I that the diagnosis of the syndrome of dementia is based on clinical criteria. The two major criteria used for diagnosis are the Diagnostic and Statistical Manual (DSM) of the American Psychiatric Association (APA 1994) and the International Classification of Diseases (ICD) (WHO 1993). These are currently in their 4th and 10th iterations respectively. The application of these criteria in a clinical

setting requires skill and judgement on the part of the clinician. An individual with dementia does not become demented at a single point in time. It is a clinical syndrome that evolves. Therefore, the diagnosis of dementia is problematic for clinicians, especially when the symptoms are subtle. It is possible for two experienced clinicians to disagree about whether a person is demented. This is because the criteria for dementia are necessarily applied in a subjective fashion. Both DSM and ICD require a person with dementia to have a decline in occupational and social function from a previously attained level. Just what represents decline can be interpreted differently. Clinicians have therefore sought other means of diagnosing brain disease. Sophisticated brain imaging and neuro-psychological tests now allow the identification of altered brain function before the clinical syndrome of dementia is apparent (Jack *et al* 1999) (Grober *et al* 2000). In addition, biological markers for AD, such as tau and beta amyloid ($A\beta$), are now measurable in cerebrospinal fluid (Andreasen *et al* 2003).

Genetic risk factors for brain disease also exist. Pre-clinical prediction of the future development of AD is now possible for a small percentage of individuals with familial AD due to genetic mutations such as those in presenilin 1 (Schott *et al* 2002). These mutations causes an abnormality in the proteolytic processing of the amyloid precursor protein to generate the longer, more pathological form of $A\beta$, $A\beta_{42}$ (Schott *et al* 2002). When no family history exists, apolipoprotein E status determines risk of AD but is not determinative (Henderson *et al* 1995). Genetic risks will be discussed in chapter 3.

A problem in clinical practice is that by the time the diagnosis of dementia is made, a long pre-clinical phase is over suggesting that the underlying pathology is well-established (Linn *et al* 1995). Therefore, increased knowledge of the biological basis for brain disease has prompted an interest in the clinical, physiological and morphological manifestations of brain disease before dementia occurs.

In this section, the clinical aspects of early brain disease will be examined. The clinical manifestations can be thought of as pre-dementia syndromes. These can be memory, mood or behavioural in nature and are at present poorly characterised. Accurate early assessment of memory disorders has a number of advantages. It can provide reassurance for those with no evidence of dementia, while those with evidence of dementia may benefit from early intervention. The development of reliable, low cost methods of risk stratification based on clinical symptomatology and cognitive functioning is needed. If a pre-dementia syndrome can be identified accurately, then treatment can be given and risk factor modification can be started. The distinction between a pre-dementia syndrome and other clinical entities causing altered brain function is also important because prognosis may differ.

It is evident that current clinical diagnosis of dementia comes relatively late in the course of the disease. Researchers examining means of early diagnosis have focussed on cognitive symptoms in non-demented subjects. This is one way of selecting high risk subjects rather than undertaking expensive and time consuming population

based cohort studies. Early diagnosis is difficult and this is reflected in the many attempts to categorise cognitive symptoms not associated with dementia but not representative of normal ageing. This has caused great variability in inclusion criteria, prevalence and estimated rates of cognitive and functional decline.

2.2. The Pre-dementia syndromes.

There are a number of ways of presenting the vast literature on this topic. It is presented chronologically in part to give a sense of the development of the knowledge base over four decades. The information is also presented in accord with the approach of Bischkopf and colleagues who reviewed the topic in 2002 (Bischkopf *et al* 2002). In the latter review, the term mild cognitive impairment was used generically to refer to all cognitive changes. In this thesis, the term pre-dementia syndrome is preferred.

Bischkopf *et al* considered four categories of source material.

1. Theoretical discussions, ie not based on empirical data.
2. Diagnostic manuals.
3. Dementia scales that include a pre-clinical stage.
4. Additional concepts from empirical research.

Where relevant, this categorisation will be referred to in the remainder of this section.

2.2.1 Benign Senescent Forgetfulness.

Over 40 years ago the use of the term benign senescent forgetfulness (BSF) was the first attempt to conceptualise a mild form of cognitive decline not meeting the criteria for dementia (Kral 1962). Kral developed this idea from observing retirement home residents who had difficulty remembering details of an event, but could recall the event itself. These subjects acknowledged the problem and attempted to compensate for it. Kral classified his group of 162 patients into five groups:

1. Normal
2. Mild memory problem - benign forgetfulness
3. Psychosis but normal memory
4. Amnesic group - malignant memory impairment
5. Combined 3 and 4.

No formal cognitive examination was undertaken. Neurological findings on examination were common even in the normal group. A follow up study over four years reported on 94 subjects and showed a greater death rate in the amnesic group (Kral *et al* 1964).

This concept has not been operationalised and formal criteria were never proposed. Kral made no distinction between 'normals' and those with benign memory loss. It has never been demonstrated that BSF is objectively different from normal ageing, especially since the normals in the group were not in a community setting.

2.2.2 Severity Rating Scales that include Characterisation of Pre-dementia.

The next step in this intellectual process grew out of the need to develop global methods of staging dementia. In 1982 Reisberg proposed a seven point scale of deterioration, the Global Deterioration Scale (GDS) (Reisberg *et al* 1982). This was a retrospective correlative study using somatic and psychiatric complaints, psychometric scores, CT measurements and PET scan data. The stages were identified as follows:

1. No cognitive decline
2. Very mild cognitive decline. Subjective complaint only with no objective evidence on psychometric tests.
3. Mild cognitive decline. Objective evidence of memory deficiency that is obtained through an intensive interview. Psychometric scores were considered to be less than 1 standard deviation below normal for age group.

This stage is determined by requiring at least 2 of the following.

- i getting lost when travelling to an unfamiliar location.
- ii reduced work performance apparent to co-workers.
- iii word and name finding decline apparent to intimates.
- iv relatively little retention of material read.
- v reduced facility remembering names of newly introduced people.
- vi losing or misplacing an object of value
- vii decline in concentration apparent on clinical testing.

4. Moderate cognitive decline.

This stage is characterised by the following:

- i reduced knowledge of current events.
- ii reduced performance on serial subtraction.
- iii reduced ability to travel, handle finances and undertake complex tasks.
- iv possibly reduced memory of their own personal history.

5. Moderately severe cognitive decline.

6. Severe cognitive decline.

7. Very severe cognitive decline.

Determinants of stages 5,6, and 7 were not detailed.

A later report confirmed that stage 3 or 'mild cognitive decline' had an 85% rate of stability over three years (Reisberg *et al* 1986). Others subsequently used the GDS in prospective studies. Flicker reported on a memory clinic population of 32 normals ie GDS stage 1/2 and 32 with GDS stage 3 (Flicker, C *et al* 1991). Neuro-psychological testing was done at baseline and after two years. Only 4 of the normals had progressed to stage 3. However 23 of those at stage 3 at baseline deteriorated to stage 4 or beyond at follow up. Twenty one of these 23 were considered to have either AD or VaD. Four tests done at baseline discriminated between decliners and non-

decliners. These were tests of verbal and visuo-spatial recall along with object identification and function recognition.

In the same year the terms 'limited dementia' and 'questionable dementia' were proposed (Gurland *et al* 1982) (Hughes, CP *et al* 1982). The latter used a five point scale, the Clinical Dementia Rating (CDR):

- 0 normal
- 0.5 questionable dementia (not healthy and not clearly demented)
- 1 mild dementia
- 2 moderate dementia
- 3 severe dementia.

This was based on a prospective study of community based patients who largely responded to advertisements in newspapers. Subjects underwent thorough clinical and psychometric assessment and a rating was given in six domains, namely:

1. Memory
2. Orientation
3. Judgement and problem solving.
4. Community affairs
5. Home and Hobbies
6. Personal care.

The authors found good correlation of the scale with scores on other tests and considered it to be reliable in staging dementia. They also offered guidelines to clinicians in how to operationalise the assessment thus improving reliability. The original study also reported on follow up of 90 cases that showed that a CDR score of 1 predicted subsequent cognitive decline.

Although the purpose of these scales was not to provide diagnostic criteria for a pre-dementia state, they raised awareness of pre-dementia phenotypes.

Independent studies provide further support to the potential usefulness of the CDR in predicting long term cognitive decline. Daly and colleagues prospectively examined a group of community dwellers over the age of 65 years using the CDR (Daly *et al* 2000). They were recruited through the print media. Forty two subjects with a CDR of 0 and 123 with a CDR of 0.5 were followed for three years. Thirty two of the normal group remained at CDR 0 at three years. Ten were categorised at 0.5 at follow up. Ninety one (73%) subjects with a CDR of 0.5 at baseline remained in this category at three years. Twenty three (19%) of this group had converted to probable AD at follow up. The likelihood of conversion was predicted by the total box score on the CDR. Those with a score of 2 or greater had more than 50% chance of converting. In addition, certain questions from the baseline interview were also predictive of conversion. These were questions related to decline in judgement and problem solving, ability to perform home duties/hobbies and personal care. The questions related to memory and orientation did not predict conversion. Overall, the

CDR box score combined with the responses to key interview questions identified 88.6% of those at baseline who converted. This occurred without any reference to neuro-psychological test scores.

The CAMDEX was also used to define minimal dementia (Roth *et al* 1986). The CAMDEX is a standardised structured interview and cognitive examination that identifies psychiatric syndromes in the elderly. Minimal dementia is defined by:

1. Limited and variable impairment in acquisition of new information and in recalling recent events
2. Increased tendency to misplace and lose possessions
3. Minor and variable errors in orientation.
4. Blunting in the capacity to follow or pursue a reasoned argument
5. Occasional errors in occupational tasks
6. Self care unimpaired
7. Preserved emotional life
8. Negative clinical examination

One study of minimal dementia found a prevalence of 16% in those over age 65 years (Cooper *et al* 1996).

In the Comprehensive Assessment and Referral Evaluation (CARE), the pre-dementia category is referred to as Limited Cognitive Disturbance (Gurland *et al*

1982). The CARE is a semi-structured interview that covers a comprehensive range of health and social issues. Limited Cognitive Disturbance is defined as:

1. Patient reported poor memory.
2. Increased reliance on notes and reminders.
3. Occasional (< once per week) forgetting of names and appointments and losing personal belongings.
4. Occasionally dangerous memory lapses, eg leaving gas stove running.
5. 1-2 errors on cognitive testing.

The first stage of established dementia in the CARE is referred to as pervasive cognitive disturbance. This is followed by the categories: dependent, regressed and deteriorated. In samples of subjects over age 65 years from New York and London, the prevalence of pervasive cognitive disturbance was 4.9% and 2.3% respectively (Gurland *et al* 1982). Rates for limited cognitive disturbance were not given.

2.2.3 Age Associated Memory Impairment

Historically, the next important concept was that of Crook and colleagues who used the term Age Associated Memory Impairment (AAMI) (Crook *et al* 1986). AAMI was created by a working group of the National Institute of Mental Health in the USA. Their brief was to establish criteria “to describe the memory loss that may occur in healthy elderly subjects”.

The criteria for AAMI are:

1. Age > 50.

2. Subjective memory decline compared to a younger age. This is reflected in every day tasks such as remembering names, misplacing objects and recalling a list of items to be purchased.

3. Performance > 1 standard deviation below mean scores for young adults.

Recommended tests are:

Benton Visual Retention test (Benton 1965, Benton 1974)

Logical Memory test from the Wechsler Memory Scale (Wechsler 1945)

Associated Learning sub-test from the Wechsler Memory Scale.

4. Intact global intellectual function and exclusion of dementia by virtue of a score of 24 or greater on the Mini-Mental State Examination (MMSE), a brief test of cognitive functioning (Folstein *et al* 1975).

5. Evidence of adequate intellectual function as determined by a scaled score of at least 9 on the vocabulary sub-test of the Wechsler Adult Intelligence Scale (WAIS-R) (Wechsler 1981).

Exclusion of other medical and psychiatric conditions that may contribute to memory loss is required.

Criticisms have been directed at these criteria (Blackford 1989). These include:

1. Lack of specification to the number of tests to be used. The more tests used the more likely a person will meet the criterion of a score below 1 standard deviation below normal.
2. The need for a scaled score of 9 on the WAIS-R vocabulary test excludes the bottom 37% of the population.
3. The MMSE is an inadequate means of excluding dementia.

It has been noted that AAMI does not distinguish between normal older adults and those with pathological AAMI since most elderly subjects will score less than 1 standard deviation below normal for young adults (Bamford 1988). This entity has attracted criticism including doubts about whether it actually represents a benign condition (O'Brien *et al* 1992). In addition, the criteria for validation have not been proposed according to accepted psychiatric methodology (Kendall, RE 1989). O'Brien and Levy concluded that AAMI is not a useful entity because it is too broad and lacks standardised criteria. Caine questioned its validity because of the inclusion of memory complaint as a criterion, particularly because at the time of writing the medical literature did not support the notion that memory complaint correlates with future cognitive decline (Caine 1993) (O'Brien *et al* 1992).

The reliability of AAMI has also been questioned (Smith, G *et al* 1991). Koivisto *et al* found a prevalence of AAMI of 38.4% and questioned the over inclusive nature of the criteria and its relevance as a research tool (Koivisto *et al* 1995). The study participants (n=1049) undertook the test battery as recommended by the original

protocol. The authors suggested that AAMI represented normal ageing rather than a discrete clinical entity. They also argued that the use of the MMSE to exclude dementia was inappropriate because of the test's poor sensitivity. In addition, the exclusion of those with medical problems excluded those who had normal cognitive function despite this. It was acknowledged at the time, that lack of follow up data was an impediment to validating the criteria.

Others have modified the criteria for AAMI and have extended the criteria to define age consistent memory impairment and late life forgetfulness (Blackford 1989). These categories are based on comparing test performance with young adult and age matched normal controls respectively using non-verbal and verbal tests of memory. An age limit of 50 to 79 years was proposed and the NINCDS-ADRDA criteria were recommended to exclude dementia (McKhann *et al* 1984). The IQ score on the WAIS-R should be normal. The categories were defined as follows (Blackford 1989):

Age Associated memory impairment.

Performance at least 1 standard deviation below the mean established for young adults on one or more tests.

Age consistent memory impairment.

Performance within +/- 1 standard deviation of the mean established for age on 75% of tests administered.

Late life forgetfulness

Performance between 1 to 2 standard deviations below the mean established for age on 50% or more of tests administered.

These criteria were not based on clinical data and no follow up reports have been published. These criteria do not consider another important limitation of the concept of AAMI, that of potential cohort effect. Comparing the cognitive performance of young and older cohorts cross sectionally may not be a valid comparison because of differences in education, nutrition and environment.

2.2.4 Age Associated Cognitive Decline

At an International Psychogeriatric Association working party in 1993, Levy and colleagues proposed age standardisation in their criteria for Ageing Associated Cognitive Decline (AACD) (Levy, R 1994). The criteria were:

1. Report from individual or informant of cognitive decline.
2. Gradual onset and present for at least six months.
3. Any cognitive domain affected.
4. Abnormal performance on a cognitive test for which norms are available.
Performance should be at least 1 standard deviation below the mean for an appropriate population.
5. Exclusion of other conditions known to cause cognitive decline.

The Working Party acknowledged that the criteria were preliminary and would likely need modification as research progressed.

Others examined the prevalence of AACD in a group of 403 volunteers between ages 68 and 78 years (Hanninen *et al* 1996). 26.6% of the group fulfilled the criteria for AACD. In the Euseria study, the prevalence was found to be 20.9% in a group over age 60 years (Ritchie *et al* 2001). The conversion rate of AACD has not been systematically investigated.

2.2.5 Mild Cognitive Disorder

The ICD-10 criteria for mild cognitive disorder (MCD) were published in 1992 and 1993 (WHO 1990, WHO 1993). The reason for including this new entity was to distinguish between a) memory loss not associated with dementia and b) dementia, c) amnesic disorder and d) delirium. The criteria require objective evidence of brain disease or systemic disorder known to cause cognitive loss. In one study the criteria for MCD were applied to a group of people living in the community in order to determine if MCD is a valid entity (Christensen *et al* 1995). The aim of the study was to assess the co-occurrence of the criteria and to assess if MCD was distinct from i) normality and ii) dementia based on measures of cognition and mood. The criteria for MCD and how the authors established them were:

- A. G1 Evidence of brain disease or systemic disease known to cause brain dysfunction eg stroke, TIA, Parkinson's disease, diabetes, renal disease, cancer and endocrine disorder.

G2 Relationship between disease and symptoms.

G3. Improvement in brain symptoms when the presumed disease is treated.

G4. Exclusion of other causes of the brain condition.

- B. The symptoms of brain disorder are present for at least two weeks and manifested by abnormalities in any cognitive domain. A subjective report of thinking difficulty or score over 4 on the IQCODE was required (Jorm, Korten 1988). The IQCODE is an informant rated instrument that is designed to detect changes in cognition over a ten year period.
- C. Abnormality or decline in cognitive functioning. Participants needed to score more than 1.5 standard deviations below normal on at least two of 12 neuropsychological tests. Alternatively evidence of decline in performance using the National Adult Reading Test (NART) and the Symbol Letter Modalities Test (SLMT)(Smith, A 1982) was considered sufficient evidence of abnormal cognition. The NART is an estimate of pre-morbid intelligence based on pronunciation of words (Nelson 1982). The SMLT is a test of executive function wherein the subject matches symbols and letters of the alphabet (Smith, A 1982).
- D. Exclusion of dementia and delirium using ICD-10 criteria.

Participants were recruited after sampling from the electoral roll (n=897). All were aged over 70 years. The prevalence of MCD was low. Only 36 (4%) met all four criteria. Correlations between the criteria were weak but significant. The biggest correlation was found between C and D ($r = -0.43$). This was thought to represent the

association between poor cognitive functioning and the presence of dementia. The authors felt that the weak correlations overall suggested that no syndrome exists. In particular, no correlation was found between physical disease and abnormal cognition. In addition, there was little difference in cognitive scores between controls and MCD.

Of note, most participants in the study could not meet the criteria G2, G3 and G4. Failure to meet these may have contributed to an under estimate of the prevalence of MCD, indicating that the disorder is rare. Furthermore, the authors suggested that use of categorical system in psychiatric disorders is flawed and that a “multi-dimensional” approach was needed.

Data on the same group was reported after 3.6 years of follow-up (Christensen *et al* 1997). Of those with MCD at baseline who were followed, 12% had dementia according to ICD-10 and DSM-III-R. The prevalence of DSM-III-R dementia at follow-up was the same in the baseline MCD and normal groups. The risk of ICD-10 dementia was increased among the original MCD cases. The authors concluded that “MCD...has little coherence as a clinical syndrome”.

2.2.6 Mild Neurocognitive Disorder

Mild neurocognitive disorder (MNCD) was proposed as a new entry in DSM-IV to meet the need for a milder category of memory loss than defined by delirium or dementia (Gutierrez *et al* 1993). The authors acknowledged that this entity was

similar to mild cognitive disorder, as listed in ICD-10 (WHO 1990, WHO 1993). The features of this condition are cognitive impairment that does not meet the criteria for delirium or dementia, and presence of a medical condition. The authors undertook a literature search to identify studies where neuro-psychological testing was undertaken amongst patients with medical, neurological and substance abuse problems. The literature search identified articles examining hypoxemia, autoimmunity, multiple sclerosis, renal dialysis, normal pressure hydrocephalus, cancer/therapy, HIV infection, thyroid disease, cardiac disease, metabolic disorders, chronic infection, intoxicants and epilepsy. The review showed that cognitive impairment frequently accompanies many medical conditions, but is often not severe enough to meet the criteria for delirium or dementia.

The proposed criteria for MNCD were:

- A. The presence of at least 2 of the following deficits lasting most of the time for at least 2 weeks:
 1. Reduced ability to learn or recall.
 2. Impaired executive function.
 3. Impaired attention and/or speed of information processing.
 4. Impaired perceptual motor ability.
 5. Impaired language.

- B. Evidence of a systemic illness or central nervous system dysfunction.

- C. Evidence of decline in performance from neuro-psychological testing.
- D. The cognitive deficit causes a mild impairment in social or occupational functioning and represents a decline in performance from a previous level.
- E. The cognitive deficit does not meet the criteria for any other disorder.

The proposal was included in appendix B of DSM-IV along with other categories that were considered to need further study (APA 1994). To date, no follow up studies of MNCD have been conducted to examine its epidemiology, etiology or prognosis.

2.2.7 Cognitive Impairment No Dementia

The Canadian Study of Health and Ageing (CSHA) sampled over 10,000 individuals in the community as well as in institutions (CSHA 1994). Names were drawn from electoral and health insurance records. The investigators designed the protocol to determine the presence of dementia and then make a specific diagnosis (Ebly *et al* 1995). The 3MS which was used as the initial cognitive examination is an expanded modification of the MMSE (Teng *et al* 1987). It includes four additional test items to broaden the range of cognitive domains examined and is scored out of 100. In the CSHA study, detailed clinical assessment was conducted on 2914 subjects (all those in institutions, those in the community with a 3MS score of <78 and a random sample of those with a score >78) who were categorised as:

1. no cognitive impairment (NCI) n=921

2. cognitive impairment no dementia (CIND) n=861
3. dementia. n=1132

Detailed neuro-psychological tests were done on all those with a 3MS score of 50 or greater. CIND was diagnosed clinically by exclusion of dementia and the belief that some form of cognitive deficit was evident. No specific criteria were applied. A number of CIND categories were defined including delirium, psychiatric disease, alcoholism and drug abuse. Therefore, inherently there was the potential for many of these CIND patients to improve cognitively if their underlying illness resolved.

Of note, functional loss, as a criterion for dementia, was defined as a deficit in eating, dressing, toileting or bathing. Therefore those with cognitive loss and with no deficits in these functional areas but functional deficits in instrumental domains would be labelled as CIND. Usually these individuals would be considered to be demented. In a later analysis of the CSHA data, the lack of operationalisation of functional deficits was commented on as a limitation of the study (Ingles *et al* 2003). The three categories showed clear differences in cognitive scores, age and rates of institutionalisation.

In the group of participants with CIND (n=841), only 35% met the criteria for any of AAMI, mild cognitive impairment according to DSM-III-R and ICD-10, ACCD, late life forgetfulness and age consistent memory loss. The authors felt that these diagnostic criteria, therefore, have limited usefulness because they fail to identify the majority of non-demented individuals who have cognitive deficits.

A follow up study five years later examined all those who were not demented in the initial cohort (Tuokko *et al* 2003). Clinical examination targeted memory, other cognitive domains, function and self-rating of health. Those with CIND at the initial assessment had a greater chance of dying and needing institutional care and were five times more likely to develop dementia (odds ratio 5.3, 95% confidence interval 3.8-7.4). Those identified as having AAMI or CIND due to identifiable co-morbid conditions all had similar risk of progressing to dementia. The authors suggest that use of specific criteria to aid the identification of those at risk of dementia is of limited usefulness.

2.2.8 Mild Cognitive Impairment

Mild Cognitive Impairment (MCI) is now the most popular term for the transitional period between normal brain function and early dementia in preference to previous terms. To date the MCI criteria that have gained most widespread use are those of Petersen and colleagues (Petersen *et al* 1995). The criteria are:

1. absence of dementia
2. normal general cognitive function
3. complaint of memory loss
4. impaired memory on a test of recall
5. normal activities of daily living.

The criteria have since been redefined into subcategories, ie amnestic, single non-memory and multiple cognitive domain MCI (Petersen 2004, Petersen *et al* 2001). It is likely that further refinements will occur. It is thought that MCI best represents the clinical manifestations of early brain disease, more so than other more inclusive entities (Petersen *et al* 2001). However, there are variations in how these criteria are applied and many patients with a label of MCI do not progress to develop dementia (Wolf *et al* 1998). Davis and Rockwood propose that ideally amnestic type MCI should include impairment of memory according to educational level as well as age (Davis, H, Rockwood 2004).

In 1978, ICD-9 introduced the term 'mild cognitive impairment not amounting to dementia' (WHO 1978). Of note, MCI was not included in ICD-10 (WHO 1993). Mild cognitive impairment (MCI) was initially used as a description of the extent of cognitive loss rather than a nosologic entity (Henderson, Huppert 1984) (Flicker, C *et al* 1991).

One of the earliest longitudinal reports on MCI was mentioned in section 2.2. Flicker and colleagues studied 32 subjects with a GDS rating of 3 and compared cognitive results with 32 age-matched normals (GDS rating 1 and 2) (Flicker, C *et al* 1991). The cross-sectional data showed that those with GDS rating 3 performed less well on tests of recent and remote memory, most language tasks, concept formation and visuo-spatial praxis. Other cognitive tests revealed no difference between scores in the two groups. Follow up data after two years showed that 23 of the impaired

group had deteriorated to GDS rating of 4 or more, whilst only 4 of the controls had deteriorated. Four baseline tests predicted which of the impaired group deteriorated at follow-up. These were tests of verbal recall, visuo-spatial recall, object function recognition and object identification. The authors concluded that mildly impaired subjects should not be considered to be normal as they have a greater risk of cognitive decline.

Zaudig proposed a number of categories of mild cognitive impairment (Zaudig 1992). These were derived from the DSM-III-R and ICD-10 criteria for dementia. A sample of 150 subjects from the community, clinic and residential home was examined. The SISCO is the cognitive examination component of the Structured Interview for the Diagnosis of Dementia (SIDAM) and was used as the principle cognitive test (Zaudig, Hiller 1991). This includes all the items of the MMSE. Cognitive scores were correlated with the CDR and the GDS (performed by an independent rater).

Two categories of MCI were created using the DSM-III-R dementia criteria (APA 1987). Three categories of MCI were created using ICD-10 criteria for dementia (WHO 1990). Analysis showed that the cognitive scores for patients in the MCI categories correlated with CDR 0.5 and GDS stages 2 and 3. The authors concluded that MCI as a category was validated by this means.

MCI soon began to replace previous terms and criteria were developed (Petersen *et al* 1995). In Petersen's study, subjects were identified from internal medical clinics at the Mayo Clinic. Patients were flagged as potential recruits if they, their family or attending physician expressed concern about memory performance. Comparisons between controls and a group with AD were made on comprehensive tests of cognition. In the impaired but not demented group (n=66), test performance tended to fall about 1.5 standard deviations below normal for age matched controls. This group was rated as 0.5 on the CDR ie questionable dementia. It should be noted that a memory score below the 1.5 standard deviations from the mean was not required as a criterion for MCI. In a later paper, Petersen states that the -1.5 standard deviation was a mean deficit and was not intended to be a cut point (Petersen 2004). When compared to 66 controls, the impaired group performed similarly on general tests of cognition, eg MMSE, but similarly to AD patients on tests of memory. In the impaired group deterioration to dementia was common.

Follow-up period	Conversion to dementia
18 months	16 (24%)
36 months	16 (44%)
54 months	12 (55%)

In Petersen's initial report apolipoprotein E (*APOE*) ϵ 4 genotype was the best predictor of conversion to dementia at follow-up (relative risk 4.36, 95% CI 1.41-

13.54) (Petersen *et al* 1995). The authors concluded that this impaired group could be categorised and defined by the aforementioned criteria

1. absence of dementia
2. normal general cognitive function
3. complaint of memory loss
4. impaired memory on a test of recall
5. normal activities of daily living.

In a follow up report, the same group divided subjects into four categories (Petersen *et al* 1997). Along with controls and established AD, the CDR 0.5 group was divided into MCI and mild AD. The mean CDR sum of the boxes for these two groups was 1.5 and 3.3 respectively. Those with MCI were found to have predominantly memory impairment, whereas those with AD and CDR 0.5 had other cognitive domains affected. The validity of the distinction was confirmed by greater rate of decline in the latter group. The authors stated that they “generally” used a score of less than 1.5 standard deviations below the normal range for age as the memory criterion for MCI. They acknowledged that this may include subjects who have always been poor performers and hence normal. After all, it is a statistical reality that for any normally distributed score in a normal population, a small percentage will score below this 1.5 standard deviation cut-off. In addition, the paper does not suggest that this criterion for MCI will not include those with declining memory that scored above the cut-off.

A group from Washington University used a similar approach in studying a group of 404 volunteers with both normal health and memory problems recruited through media advertisements (Morris, JC *et al* 2001). Again the CDR 0.5 designation was used to define pre-dementia, but Petersen's criteria for MCI were not used. Information from a "collateral source" about performance was the basis for determining dementia. The sub-categorisation of CDR 0.5 occurred without reference to neuro-psychological data. The 227 subjects with CDR 0.5 were categorised on clinical ground as:

1. AD - impaired memory (0.5 or more) and impairment in at least 3 of the 5 other domains.
2. Incipient AD - impaired memory (0.5 or more) and impairment in 2 or less remaining domains.
3. Uncertain dementia - usually only memory impaired at the 0.5 level. Of note, this category contained subjects who were doubtful and characterised as "worried well".

The study hypothesis was that MCI is unrecognised AD and to test this, follow up over a 9.5 year period occurred. Dementia was diagnosed based on clinical judgement using a variation of the NINCDS criteria for probable AD (McKhann *et al* 1984). Neuro-psychological data was not used to inform the clinical diagnosis. The five year rates of progression to CDR 1 were:

1. CDR 0	6.8%	(95% CI 2.2-11.3%)
2. CDR 0.5 uncertain AD	19.9%	(95% CI 8.0-31.8%)
3. CDR 0.5 incipient AD	35.7%	(95% CI 21.0-50.3%)
4. CDR 0.5 definite AD	60.5%	(95% CI 50.2-70.8%)

Clinico-pathologic correlations were done on 42 subjects.

<u>Category</u>	<u>N</u>	<u>AD at post-mortem exam</u>
1. CDR 0	8	1
(converted to dementia)	9	8
2. CDR 0.5 uncertain AD	6	6
3. CDR 0.5 incipient AD	8	7
4. CDR 0.5 definite AD	11	8

The authors drew the conclusion that CDR 0.5 equates to MCI and opined that, on this basis, that MCI represents very mild AD. They discussed the validity of this conclusion and compared their cohort with other MCI groups. However, because the 1.5 standard deviation cut point (as suggested by Petersen) was not used in this study, the CDR 0.5 group (also designated MCI) was in fact less cognitively impaired than Petersen's group (Petersen *et al* 1995). This is evident by the fact that only 52% of the CDR 0.5 definite AD group had memory scores less than 1.5 standard deviations below normal. The authors note further that early AD can be diagnosed if:

1. Clinicians accept that even mild impairment is abnormal and not part of normal ageing.
2. Impairment is operationalised as interference with normal performance, not complete loss of function in an activity of daily living.
3. Reliance is placed on informant's information and not on cognitive test scores.

These authors supported the view that AD can be diagnosed much earlier than is currently practiced and that the prevalence of AD is much higher than presently acknowledged (Morris, JC *et al* 2001). In a later editorial, Morris goes on to state "Arbitrarily drawing a line at some point along that continuum and labelling one side of that continuum as demented and the other side as not demented is inconsistent with the disease process" (Morris, JC 2006). He goes on to say that the need to use the term MCI represents the difficulty that clinicians have in making the distinction between early AD and other conditions, including the changes attributable to normal ageing.

Despite this view, researchers have continued to report on MCI and its distinction from AD. The Leipzig Longitudinal Study of the Aged examined the prevalence and incidence of MCI (Busse *et al* 2003). A sample of 1265 participants over age 75 years was drawn from the community. The SIDAM battery was used to test cognition. Normative values were derived from the data collected from the study group. The Petersen criteria for MCI were used and Aged Associated Cognitive Decline (AACD) was also included as a syndrome (Levy, R 1994). Caseness was identified by scores 1

standard deviation below the normal range for each age group. Deleting the need for subjective memory loss in the criteria modified both states. Baseline examination was completed on 929 subjects. The prevalence of MCI (3.1%) was lower than that observed for AACD (8.8%). When the need for subjective memory loss was deleted the rates were 5.1% and 19.1% respectively. Similarly, incidence rates were lower for MCI than for AACD, 5.3/1000 person years cf 32.7/1000 person years. Dementia developed in 89 subjects during the study. Receiver Operating Characteristic (ROC) curves were used to assess the power of each set of criteria to predict dementia. The modified AACD criteria had the best sensitivity and the MCI-amnestic criteria the worst. Of those who met the modified AACD criteria, 36% developed dementia within 2.6 years. In their conclusions the authors questioned the usefulness of including subjective impairment in criteria for prediction of dementia.

The Cardiovascular Health Study (CHS) assessed cognition in subjects 75 years or older based on information obtained from two examinations in 1991-94 and 1998-99 (Lopez *et al* 2003). Adjudication of high risk cases was carried out to determine prevalent and incident dementia, amnestic and multiple cognitive deficits MCI and probable/possible MCI. Standard criteria were not mentioned for dementia diagnosis and it seems this was based on clinician judgement. MCI was defined by neuro-psychological tests and results were deemed to be abnormal if scores were less than 1.5 standard deviations below normal for age group and education. How this was applied to the designation of MCI is not clear, but a decline from a previous level of performance in the study was required. Presumably, MCI designates had

cognition scores below the 1.5 SD cut-off point. MCI was classed as either amnesic (MCI-AT) or multiple cognitive domain type (MCI-MCDT). In addition, the adjudicators decided whether a case was probable or possible MCI based on whether or not the patient and informant were aware of cognitive deficits and how complete the evaluations were. Following adjudication, 18.8% of cases were found to have MCI. Of these, the possible MCI-MCTD type was most common.

The Alzheimer's Disease Cooperative Study Group developed operational criteria for distinguishing MCI from a) normal cognitive functioning and b) dementia (Grundman *et al* 2004). They recruited controls (n=107), those with a diagnosis of MCI (n=769) and demented subjects (n=305). The diagnosis of MCI was established by an experienced clinician and the following criteria were applied:

1. Memory complaint corroborated by an informant.
2. Abnormal memory manifested by a deficit in delayed recall from one paragraph of the Logical Memory II sub-test of the Wechsler memory scale. Age based norms were not used. Threshold scores were based on level of education.
3. Normal general cognitive function
4. No decline in ability to perform activities of daily living.
5. NINCDS criteria for Alzheimer's Disease not met.

At entry to the study, controls and those with MCI were assessed with the CDR and a neuro-psychological battery. In addition, patients recruited for an AD clinical trial were included in the analysis. The criteria were able to identify MCI as being distinct

from normal cognition and mild AD. This was evident on all neuro-psychological parameters used in the assessment of normal controls and MCI subjects. The CDR was used to distinguish these latter groups from two groups of patients with AD (CDR 0.5 and 1.0). The MCI group had a CDR global score of 0.5 but were not considered to have AD. The mean CDR sum of the boxes score for the MCI group was 1.8. For the group with a global CDR of 0.5 and designated to have AD, the mean sum of the boxes score was 3.0. In addition, hippocampal volumes measured by magnetic resonance images were significantly smaller in the MCI group than in the control group.

The Eugeria project recruited 397 subjects with cognitive difficulties from a general practice network in France (Ritchie *et al* 2001). Dementia was excluded by a trained general practitioner. Cognitive difficulties were identified through the use of a questionnaire completed by a regular contact of the subject. If the proxy felt that there was evidence of decline in at least one area of cognition over the past year and there was subjective memory complaint, then the subject was included in the study. A comprehensive computerised battery of tests was used. Those who met the criteria for MCI (Petersen *et al* 1997) and AACD (Levy, R 1994) were identified at baseline and at yearly follow-up. A baseline group of 308 subjects met the criteria of subjective memory complaint and preservation of general intellect. Of these, 103 met the criteria of having a decrement on memory score of more than one standard deviation below normal. At this point, those with a decrement in any other cognitive domain were apparently excluded from the study according to a strict interpretation

of Petersen's criteria (Petersen *et al* 1997). However, examination of the article in point shows that this exclusion is not specifically mentioned and perhaps not even implied. Nevertheless, this left 27 subjects with MCI and 174 with AACD. Follow up diagnoses showed that MCI, as was defined in the study, was unstable and totally unable to predict dementia status. AACD however had good discrimination ability based on ROC curve analysis. The authors concluded that MCI did not constitute a separate homogeneous syndrome, "showing neither temporal stability nor clear boundaries from normal subjects apart from the cognitive deficit that defines it". These researchers went on to suggest that the MCI criteria were too stringent in excluding subjects with deficits in other cognitive domains (Ritchie *et al* 2001).

This Eugeria cohort of 397 was further studied without recourse to categorisation after two years of follow up (Artero *et al* 2003). Subjects were included based on low scores on neuropsychological tests and exclusion of dementia. Dementia developed in 18% of cases. The authors used regression modelling to determine probability of dementia. Nine test variables were included in a stepwise logistic model. Then three were retained as representing the best combination for predicting AD. These variables were construction of an abstract figure, verbal fluency and delayed narrative recall. The sensitivity of predicting AD was 73% and the specificity was 99%. The likelihood ratio for a positive test was 18.25 and for a negative test 0.27. The scores for each item used to generate these figures were not mentioned in the paper. The authors state that use of these three tests (ten minute administration time) is suitable for general practice. This approach does not require any stratification or

categorisation of patients. Exclusion of dementia and presence of cognitive symptoms were the only entry criteria.

The Religious Orders Study enrolled 872 elderly volunteers from the Catholic clergy between 1994 and 2000 (Bennett *et al* 2002). Those with dementia were excluded and data were available on 798 subjects. Baseline and annual evaluations included thorough neuropsychological testing and clinical review. Educationally adjusted normal ranges for the tests were established. AD was diagnosed according to the NINCDS-ADRDA criteria (McKhann *et al* 1984) and MCI was diagnosed in those who were not demented but had abnormal tests scores according to the judgement of the clinician and neuropsychologist. The analysis focussed on the outcomes of death and conversion to AD. At baseline, 211 (26.4%) had MCI (mean age 78.6 years) while 587 (73.6%) had normal cognition (mean age 74.3 years). Over a mean follow-up period of 4.5 years, the death rate (adjusted for age, sex and education) was 29.9% in the MCI group and 12.8% in the normal group. The risk of dying in the MCI group was 1.74 times greater than in the normal group (95% CI 1.22-2.48). In the same period, conversion to AD occurred in 34% of the MCI group and 7.2% in the normal group. The risk was 3.17 times greater in the MCI group (95% CI 2.16-4.64). The study did not report the incidence of MCI in the 'normal' cognition group, nor did it report the rate of MCI reversion to 'normal' cognition. The authors commented that the results could not be generalised to the wider population.

Similar outcomes were reported by the PAQUID study (Larrieu *et al* 2002). This was a community based sample of 3,777 volunteers over age 65 years in France who had an initial cognitive evaluation by a psychologist. Suspected cases of dementia were then reviewed by a clinician. AD was diagnosed based on NINCDS-ADRDA criteria (McKhann *et al* 1984) and VaD was diagnosed based on the Hachinski score (Hachinski *et al* 1975). The final group analysed consisted of 2,084 volunteers who had been examined three times over a five year period. Dementia was determined according to DSM-III-R criteria (APA 1987). MCI was diagnosed by the following criteria:

1. No dementia.
2. Subjective memory complaint.
3. Normal general cognition, ie MMSE score higher than 1 standard deviation below the mean for education defined strata.
4. Score on the Benton Visual retention test (Benton 1965, Benton 1974) lower than 1.5 standard deviations below the mean for education and aged defined strata.
5. Autonomy in activities of daily living

Subjects were divided into four categories:

1. Normal (if they were not demented and scored above the cut offs for test scores used to diagnose MCI).
2. MCI.

3. Other cognitive impairment no dementia (OCIND). Most of these had scores on the MMSE lower than the chosen cut off so could not be considered normal and did not meet the five criteria for MCI. Subjects in this category would be labelled as non-amnesic MCI according to Lopez as mentioned previously (Lopez *et al* 2003).
4. Dementia.

The incidence of MCI was examined in 1,265 subjects who had normal cognition and after exclusion of those with missing data. The incidence of MCI was 9.9 cases/1000 person-years. The incidence rate did not increase with age. The incidence of dementia (100 person/years) in the MCI and OCIND groups was similar, 8.3 and 7.1 respectively. The rate in the normal cognition group was 1.7. Of note, the rate of reversion to normal cognition was high in both the MCI and OCIND groups at follow-up. The authors commented that this lack of predictive value for MCI might be because the diagnosis is based on psychometric test results and these “are subject to many sources of errors and variability”. They went on to say that widening the criteria for MCI would increase specificity and thus allow the screening of more subjects for risk of dementia.

The Canadian Study of Health and Aging (CSHA) also examined a group with MCI (Fisk *et al* 2003). This study has already been described in section 2.2.7. In this analysis the Petersen criteria for amnesic MCI were used (Petersen *et al* 1995) with the exception that psychometric cut points were not used to define cases. Instead,

clinical opinion was used to determine cognitive decline in the absence of dementia. In addition, cases had to have intact basic activities of daily living. MCI cases were analysed in an unusual fashion by creating four sub-groups:

1. All five Petersen criteria met. This group of 30 was then included in an analysis with sub-groups 2,3 and 4.
2. Those with MCI, but deficits in instrumental activities of daily living (IADL) were allowed, n=13.
3. Those with MCI, but absence of subjective memory complaint (SMC) was allowed, n= 27.
4. Those with deficits in IADL and absence of SMC, n=18.

The prevalence of MCI according to sub-category 1 was 1.0%. The elimination of the need for intact IADL and SMC raised the prevalence to 3.0% ie sub-group 4 (ie the least restrictive case definition). After five years of follow up, there were no differences between the groups in terms of risk of death, need for institutional care or conversion to dementia. Approximately half of the MCI cases converted to dementia, but nearly one-third were considered to be cognitively normal at five year follow-up. Of note, few were found to be stable in the MCI category at follow-up.

The authors felt that the inclusion of subjective memory complaint in the criteria for MCI may be unnecessarily restrictive and in population based studies lead to an

underestimate of the burden of MCI. In addition, they were not able to determine why one third of the MCI cases reverted to normal at follow-up.

More recently a group from Columbia University have questioned the use of conventional normative data in identifying MCI (Manly *et al* 2005). They state that normative data is usually collected from groups being screened for dementia at one point in time. Therefore, those with pre-clinical dementia are likely to be included in these so-called 'normative' samples. They advocate that the robust norms approach to collecting normative data will eliminate subjects from samples who will go on to develop dementia (Sliwinski *et al* 1996). Thus, the sensitivity of normative data to detect MCI will be improved. The Columbia group created a normative data set that excluded those that subsequently declined at follow-up. They applied this to a mixed racial group over age 65 years, in New York City (46.7% were Hispanic, 33.9% African-American and 19.4% Caucasian)(n = 1,698) and created sub-categories of MCI based on cognitive characteristics. The results show that the prevalence of all types of MCI was 28.3%, with amnesic MCI only representing 5.0%. Of the sample, 17% had MCI in a non-memory category, thus highlighting the importance of considering non-memory pre-dementia syndromes.

Markesbery and colleagues concentrated on the amnesic category of MCI and examined neuropathological features and compared them to controls (n=23) and early AD (n=10) (Markesbery *et al* 2006). Examination of neurofibrillary tangle and

neuritic plaque counts showed that MCI, from a neuropathological perspective, represents early AD.

A criticism of the manner of identifying MCI has come from work done at the University of Texas (Royall *et al* 2004). This group highlights the need to consider the role of executive control function (ECF) in causing functional decline. They found significant correlation between memory and ECF performance and suggest that if clinicians were aware of the deficits in ECF they would be more inclined to label many cases of MCI as dementia instead.

Table 2.1 presents a summary of the different ways that MCI has been operationalised based on the research summarised in this section.

Table 2.1
Criteria for Mild Cognitive Impairment.

Author	Criteria	Criteria
(Flicker, C <i>et al</i> 1991)	GDS stage 3	
(Zaudig 1992)	DSM-III-R	ICD-10
	Type 1: Short and long term memory impairment.	Type 1: Memory impairment
	Type 2: Short and long term memory impairment. Impairment in one or more of 1. Abstract thinking. 2. Judgement 3. higher cortical function 4. personality	Type 2: Memory impairment. Decline in intellectual ability
		Type 3: Memory impairment Decline in intellectual ability Decline in emotional control, behaviour or motivation.
(Petersen 2004, Petersen <i>et al</i> 1995)	Amnestic MCI	Revised criteria. 1. Amnestic MCI 2. Amnestic MCI multiple domain 3. Non-amnestic MCI single domain 4. Non-amnestic MCI multiple domain.
	1. Memory complaint 2. Memory deficit 3. Normal ADL 4. Normal general cognition 5. Not demented	1. Memory complaint 2. Cognitive deficit 3. Normal ADL 4. Normal general cognition 5. Not demented
(Morris, JC <i>et al</i> 2001)	CDR 0.5 (incipient and uncertain dementia)	
(Busse <i>et al</i> 2003)	Petersen criteria.	Memory loss >1 SD below normal.
(Lopez <i>et al</i> 2003)	Amnestic Multiple domain	Memory loss >1.5 SD below normal.
(Grundman <i>et al</i> 2004)	Petersen criteria-amnestic	Education based thresholds. Logical memory test.
(Ritchie <i>et al</i> 2001)	Petersen criteria-amnestic	Memory loss > 1 SD below normal
(Artero <i>et al</i> 2003)	Not demented Cognitive symptoms	
(Bennett <i>et al</i> 2002)	Not demented Cognitive impairment - clinical judgment	
(Larrieu <i>et al</i> 2002)	Petersen criteria-amnestic	MMSE > -1 SD below mean Benton test > 1.5 SD below normal
(Fisk <i>et al</i> 2003)	Petersen - amnestic	No cut points used. Clinical judgement
(Manly <i>et al</i> 2005)	Petersen - amnestic	Neuropsychological battery, -1.5 SD, robust norms
(Markesbery <i>et al</i> 2006)	Petersen-amnestic	CERAD word list -1.5 SD

2.2.9 Neuropsychological Predictors of Conversion to Dementia

A number of studies have focussed on examining neuropsychological predictors of cognitive decline in subjects who do not meet the criteria for dementia. The Framingham study highlighted the predictive value of cognitive assessment by showing that a deficit in secondary verbal memory predicts future AD (Linn *et al* 1995).

A group from Toronto (Tierney *et al* 1996) examined subjects with stage 2 or 3 rating on the GDS (Reisberg *et al* 1982). Those with a MMSE score below 24 (Folstein *et al* 1975) or a Mattis dementia rating score (Mattis 1973) below 123 were excluded, as were those with dementia as determined by experienced clinicians. A blinded psychometrician administered a comprehensive battery of tests. Testing and clinical assessment were done again at 12 and 24 months. After 24 months 29/123 had converted to dementia. The converters were found to have lower baseline scores on cognitive tests than non-converters. A test of delayed recall and the mental control subtest of the Wechsler memory scale (a measure of attention) (Wechsler 1945) were most predictive of conversion.

The Bronx Aging study (Grober *et al* 2000) examined a group of 264 subjects in whom dementia was excluded by clinical assessment and a Blessed Information Memory and Concentration score of 8 or less (Blessed *et al* 1968). The free and cued selective reminding test was used (Buschke 1973). Those with a free recall score of 24 or less out of 48 were considered to be memory impaired. Of the memory impaired

group, 31% were demented after five years, as were 0.5% of the normal group. The authors considered that free recall performance derived from the selective reminding test is a powerful predictor of future dementia. These researchers also suggested that the test controls for memory impairment due to other more general cognitive deficits and thus controls for cognitive impairment related to ageing.

Another group defined isolated memory impairment by using the AAMI criteria, exclusion of depression and a normal full scale IQ on the WAIS-R (Bozoki *et al* 2001). This was a retrospective analysis. Tests of memory were done along with tests of language, attention, visuospatial function and frontal lobe function. Subjects with deficits in memory and another cognitive domain were more than twice as likely to convert to dementia as those with memory impairment only.

The Baltimore Longitudinal Study of Aging examined visual memory as a predictor of risk for dementia (Kawas *et al* 2003). For the 1,425 participants, the mean length of follow up duration was 17.0 years at the time of analysis. It was found that those with >5 errors on the Benton Visual Retention Scale (BVRT) had almost twice the risk of Alzheimer's disease than those with 0-5 errors up to 15 years before diagnosis (RR 1.83, 95%CI 1.07-3.14).

The BVRT was also used by the PAQUID investigators in their examination of cognitive predictors of AD (Amieva *et al* 2005). 1265 participants were followed for nine years and results supported the view that a long pre-dementia phase can be

identified. The cognitive tests all showed lower baseline scores for the demented group. In addition, in the dementia sub-group with higher education, scores were consistently greater than the lower education group but a more precipitous decline occurred closer to the time of diagnosis. The study confirmed that a deficit in episodic memory is evident years before the diagnosis of dementia.

A summary of studies of conversion of pre-dementia types to AD is presented in table 2.2. This is based on the format of a summary in a recent review of MCI (Bruscoli 2004). This review included studies that were longitudinal, prospective, had defined criteria for a pre-dementia state and had defined end points. Examination of the studies in question shows that one was retrospective (Bozoki *et al* 2001).

(Wolf <i>et al</i> 2000)	Psychological deficits/ no dementia	72.0	Clinic attenders	29	27	DSM-IIIIR dementia	12.2
(Ritchie <i>et al</i> 2001)	MCI-amnestic, score > 1 SD below mean for age AACD	>65	Community-living volunteers	24	308	DSM-IIIIR dementia	5.6
(Daly <i>et al</i> 2000)	CDR 0.5	72.2	Community-living volunteers	36	123	NINCDS-ADRDA AD	6.3
(Grober <i>et al</i> 2000)	Blessed information and concentration score < 9/no dementia	79.4	Community-living volunteers	60	68	DSM-IIIIR dementia	6.2
(Hogan <i>et al</i> 2000)	ICD-10 type 2 MCI	80.0	Community-living volunteers	60	210	DSM-IIIIR dementia	6.8
(Jack <i>et al</i> 1999)	CDR 0.5/ not demented	77.7	Community-living volunteers	33	80	NINCDS-ADRDA AD	12.4
(Johansson <i>et al</i> 1997)	Not demented, mild impairment on cognitive tests	84-90	Community-living volunteers	24	70	DSM-IIIIR dementia	18
(Kluger <i>et al</i> 1999)	Cognitively normal or mildly impaired (GDS 1-3)	70.5	Community-living volunteers	46	179	NINCDS-ADRDA AD	8.2
Li (2001)	MMSE 24-26, no dementia	68.7	Community-living volunteers	44	19	Clinical diagnosis AD	13.5
(Morris, JC <i>et al</i> 2001)	CDR 0.5/uncertain dementia	76.4	Community-living volunteers	61	53	CDR>=1	4.0
(Paykel <i>et al</i> 1998)	Minimal dementia	N/s	Community-living volunteers	28	22	CAMDEX dementia	17.8
(Visser <i>et al</i> 1999)	Minimal dementia	78.8	Community-living volunteers	13	36	NINCDS-ADRDA AD	23.1

(Tuokko <i>et al</i> 2003)	Cognitive impairment no dementia	80.61	Community living volunteers	60	801	Death, dementia (death certificate), admission to institution.	8.6
(Busse <i>et al</i> 2003)	1.MCI-Petersen Memory > 1 SD below age and education norms. 2.AACD-Levy Any Cognitive domain > 1 SD below age and education norms. 3.MMSE <27	1. 82.3 2. 83.3 3. 83.4	Community living volunteer	31	1.29 2.82 3.335	Dementia DSM-IV	1. 11 2. 15.7 3. 7.7
(Bennett <i>et al</i> 2002)	MCI based on clinical judgement.	78.6	Religious Community	54	211	Dementia (NINCDS-ADRDA) Death	7.6
(Larrieu <i>et al</i> 2002)	MCI-amnestic, memory < 1.5 SD below mean	>65	Community living volunteer	60	58	Dementia DSM-III-R	8.3
(Derouesne <i>et al</i> 1989, Fisk <i>et al</i> 2003)	MCI amnestic, no cut point used	80.7	Community living volunteer	60	88	DSM-III-R NINCDS-ADRDA	8.5

2.2.10 Subjective Memory Complaint

It is evident that the one clinical association in particular that has interested researchers and prompted numerous studies is the relationship between memory complaint and future risk of dementia. The rationale for this research is that there is sufficient evidence in the literature to suggest that an isolated complaint of poor memory is worthy of study both cross sectionally and prospectively. Early reports did not support a role for memory complaints in early diagnosis (Derouesne *et al* 1989, Kahn *et al* 1975, Larrabee *et al* 1986, Rabbitt *et al* 1991)(Bolla '91, Derouesne '99, Hanninen '94, O'Connor '90, O'Hara '86, Sunderland '86, Taylor '92) . In these studies, depression was found to be associated specifically with memory complaint, rather than with poor cognitive performance.

O'Connor and colleagues identified 2,889 people over the age of 75 years from general practice registries and were able to interview 2,616 (O'Connor *et al* 1990). Those who scored 23 or less on the MMSE and one in three of those who scored 24 and 25 (n=532) were examined using the CAMDEX. After subjects with severe dementia, major depression and respondents with missing data were excluded, analysis was carried out on 384 subjects. The CAMDEX and DSM-III-R criteria for dementia and depression were used. A memory complaint score (0 to 7) was generated from the seven CAMDEX questions that asked subjects to rate their mental performance. The memory complaint score correlated poorly with cognitive scores for normals and those

with depression. Normal subjects complained least and did best cognitively. The authors felt that "a person's assessment of their own abilities ...has little validity and should not be used to make even tentative diagnoses of dementia." No comments were made about the normal subjects with MMSE scores of 24 and above who were excluded from the analysis. It is possible that some cases of early dementia were in this group and not identified in the study.

Jorm and colleagues confirmed that depression is a more consistent determinant of memory complaint (Jorm *et al* 1994). The authors studied a community sample of 877 men and women. Both participants and a reliable informant were asked questions about memory and intellect in the participant. Subjects were asked whether their memory had declined since earlier in their life (62% responded yes) and if so whether the decline interfered with daily life (6.3% responded yes). In addition, the informant was asked about his or her own symptoms of depression and anxiety. Dementia was not identified in the study. The participant's reports had weak correlation with a brief test of episodic memory. In contrast, the informant's reports correlated better, suggestive of validity.

In a subsequent paper Jorm and colleagues reported on follow up data on the same sample (Jorm *et al* 1997). The analysis showed that global cognitive complaints and subjective memory decline did not predict dementia. The

authors concluded that cognitive complaints should not be included in diagnostic criteria for pre-dementia syndromes.

A cross sectional Austrian study concurs with this finding (Jungwirth *et al* 2004). Subjects of age 75 years (n=302) were recruited from the community and those with dementia were excluded. Memory performance was no different between complainers and non-complainers. Only 10.6% of the cohort had memory complaint and only 6.3% of those with poor memory had memory complaint. A score on the Fuld Object Memory Evaluation defined poor memory as worse than 1.5 standard deviations below the mean (Fuld 1977). The authors felt that the latter figure compromises the usefulness of diagnostic categories that require Subjective Memory Complaint (SMC) as a criterion.

Other studies reveal contrary findings. The Eastern Baltimore Mental Health Survey (Bassett *et al* 1993) interviewed 3481 volunteers and administered the MMSE (Folstein *et al* 1975) and the General Health Questionnaire (Goldberg 1978). Of these, 412 had evidence of a psychiatric diagnosis on the basis of the initial interview. The sample was augmented with 398 subjects who were normal on the initial interview and the combined group of 810 had an extensive clinical evaluation. After evaluation, 437 were deemed to be normal and 373 were categorised according to DSM-III. The limited cognitive examination used in the analysis was the three-word recall from the MMSE.

For the purposes of this study, a score of 0 or 1 was deemed poor performance and a score of 2 or 3 deemed normal performance.

Of this sample 22.1% complained of poor memory based on answering a single yes/no question about the presence of memory trouble. Poor recall occurred in 11.6% of the group. Overall, there was 68% agreement between memory trouble and poor performance. Of those who had a memory complaint, 29% also had poor performance as opposed to only 15 % of those with no memory complaint. Logistic regression showed that age, emotional distress measured on the GHQ and concomitant medical conditions were the significant predictors of memory complaint.

The authors concluded that the presence of memory complaint was associated with twice the likelihood of poor performance. They acknowledged the limitations of the memory test used and viewed the findings as preliminary.

Tobiansky and colleagues studied subjective memory impairment (SMI) in an area of inner London (Tobiansky *et al* 1995). Volunteers were recruited from a population register and 705 undertook memory testing and comprehensive assessment for memory and mood disorders. SMI was determined by responses to questions contained in a SMI scale. The nine question scale was derived from factor analysis of data from the community sample. The questions were similar to the items from the CAMDEX. Validation of the cut-

point of 3 on the 9 point scale was based on clinical judgement. The questions identify SMI in addition to probing functional aspects of the subject's life. At baseline in 1988, 25% of the sample had SMI.

Subjects with dementia and depression were not excluded and SMI was associated with both conditions. The odds ratio for dementia in the presence of SMI was 3.95 (95% CI 1.09-8.28) and for depression 2.85 (95% CI 1.85-4.36). The figures were similar in 1990 after two years follow up. It is not clear from the paper how a clinical diagnosis of dementia was made, however the CAMDEX was used as part of the assessment and this presumably formed the basis for the diagnosis (Roth *et al* 1986). Raw scores from the CAMCOG (the cognitive component of the CAMDEX) were not included in the paper. At follow up those with SMI had a five times greater risk of developing dementia and 2.5 times greater risk of developing depression than those without SMI. Of the SMI group at baseline, 8% had incident dementia over the two years. The authors concluded that SMI could not be considered a benign symptom.

The PAQUID study examined a population over age 65 years that was obtained from electoral lists (Gagnon *et al* 1994). Following exclusion of those with dementia, 2,726 were assessed for subjective memory complaint by responding to a single question regarding memory loss. Tests of visual and verbal memory were completed along with a depression scale. SMC was present in 33.5% of the group and was significantly more common in females,

in older age groups, in those with depression and those with no education. SMC correlated significantly with reduced scores on memory scales.

Similarly, the Amsterdam Study of the Elderly (AMSTEL) found a correlation between subjective memory complaint (SMC) and cognitive performance (Jonker *et al* 1996). Participants (n=4,051) aged between 65 and 84 years, in the Amsterdam Study of the Elderly (AMSTEL) were recruited from general practices. The CAMDEX was included in the mental status testing. Those with depressive symptoms and dementia were excluded from the analysis. The presence of SMC was based on answering a single question regarding the presence of memory complaint. In addition, subjects were asked whether they had problems due to their memory, eg forgetting where personal belongings are and forgetting names of family members. Four categories of SMC were created based on the presence of memory complaint and/or memory problem. The rates of SMC were:

Normals	22.1%
Depressed	36.7%
Demented	46.4%

In the normal group, SMC was significantly related to poorer performance on cognitive tests. Complaint status correlated with recall, factual memory, orientation and verbal fluency. Those with SMC and memory related

problems were the worst performers and scored at the lower end of the cognitive range.

The AMSTEL study also showed that self reported memory complaints confer greater risk of future dementia. Schmand and colleagues reported on the first longitudinal study of the predictive value of subjective memory complaint (SMC) (Schmand *et al* 1996). A sample of the AMSTEL cohort with a MMSE score greater than 23 and without dementia or other psychiatric diagnosis was invited to take part in a follow up study. The CAMDEX was used at yearly intervals and a SMC scale was created from the CAMDEX questions. Logistic regression analysis showed that SMC is predictive of future dementia (OR 1.25, 95% CI 1.03-1.52), but this was not as great as the predictive effect of age. Depressive symptoms did not influence the prediction, so the authors advised against attributing SMC to depression. This is despite a significant correlation between SMC and depression.

The AMSTEL sample were examined in another larger study that categorised 3,778 non-demented subjects as normal (MMSE 26-30) or borderline (MMSE 25 or less) (Geerlings *et al* 1999). The follow up period was 3.2 years and 2169 (57.4%) were available for interview, of whom 77 were diagnosed with AD. In this study, memory complaint was identified by the response to a single question "Do you have complaints about your memory?". The study found that memory complaint conferred a three times greater risk of AD based on

multivariate logistic regression analysis. This was not attributable to depression.

Another follow-up study examined a sample of elderly subjects recruited from health care facilities and local practitioners (Schofield *et al* 1997). A cognitive screening questionnaire was administered and those that were identified as at risk (n= 364) underwent neuropsychological testing. Those who scored below normal but were not demented were categorised as cognitively impaired according to a previously established paradigm. The study showed that in memory complainers with baseline cognitive impairment, there was greater risk of cognitive decline. Not surprisingly, dementia risk was increased for this group. The report did note that SMC predicted poor cognitive performance.

The Manitoba Study of Health and Ageing began in 1991 and examined SMC in 1,416 volunteers from the community (St John *et al* 2002). Subjects were designated SMC if they answered 'yes' to a single question about memory loss in the last year. The 3MS (Teng *et al* 1987) was used as the initial cognitive test and was followed by neuro-psychological testing. All those with a 3MS score below 78 were excluded and were deemed to be manifesting abnormal cognitive functioning. SMC was prevalent in 21% of the group and the SMC group was older and had slightly lower 3MS scores than non-complainers. SMC was associated with a higher risk of dementia and CIND after 5 years

follow-up. After adjusting for age, gender, health status and depression, the rates of conversion to dementia or CIND were:

	No SMC	SMC
3MS low tertile	35%	42%
3MS mid tertile	12%	22%
3MS high tertile	6%	11%

However, the authors stated that SMC is a poor predictor of dementia (insensitive and non-specific) and it should not be relied on as a clinical tool.

In another study, a population of 290 volunteers of African-Caribbean ethnicity was recruited from primary care team registration lists in London (Stewart, R *et al* 2001). Subjects were aged 55 to 75 years and there were no exclusions. The cohort did not include potential subjects not known to the care teams. Those with a MMSE score over 20 (n=243) were included in the analysis. The lower cut off was thought to be consistent with cultural differences in this group affecting performance on the test. SMC was assessed using questions from the Geriatric Mental State schedule (Copeland *et al* 1976) and a score out of 10 was generated. A score of 4 or more constituted SMC. A comprehensive range of cognitive tests was performed. Apart from significantly lower scores on the MMSE in the SMC group there were no differences on overall cognitive scores between the groups. There was a significant association with depression (odds ratio 5.57, 95% CI 2.58-12.00). Of

note, the prevalence of *APOE* $\epsilon 4$ was 69% in those with SMC and depression compared to 20% when depression was not accompanied by SMC. The authors felt that these data support the view that SMC should not be simply considered to be secondary to depression.

Another group examined a non-Caucasian population (Wang, PN *et al* 2000). Residents who were over age 65 years in a rural Taiwanese community were studied in 1993 (n=1736). After subjects with dementia, mental retardation and psychiatric disorders were excluded, 1,670 residents were examined. Subjects were asked "do you have trouble with your memory?" and a yes/no answer was recorded. The cognitive abilities screening instrument (CASI) was used. This instrument has long and short term memory items, along with items that assess other cognitive domains. Mood was assessed by use of a Chinese version of the Geriatric Depression Scale. All participants were examined by clinicians and at follow up in 1996, and dementia was diagnosed using DSM-III-R criteria. After subjects with missing data were excluded there were 543 available for analysis. The prevalence of SMC was 49% at baseline and 39% at follow up. Both poor long and short-term memory were associated with SMC at baseline, but performance in other cognitive domains was not. After stepwise logistic regression, only short-term memory was associated with SMC at baseline and only long-term memory was associated with SMC at follow-up. SMC was not associated with cognitive decline at follow-up, or

with incidence of dementia. There were 10 cases of the latter recorded. Depression was significantly associated with SMC.

A group from Chicago adopted a non-clinical approach to examining the relationship between SMC and Alzheimer's disease (Barnes *et al* 2006). Participants (n=90) were recruited from residential facilities and agreed to post-mortem examination at study entry. SMC was based on responses to questions about current ability to remember and a comparison to memory ability ten years previously. The responses most proximate to date of death were used in the analysis. Multiple linear regression showed that in the 67 subjects without dementia at time of death, AD pathology was related to memory complaints. The authors suggest that SMC may indicate self awareness of degenerative brain disease.

A summary of prevalence of SMC in community based studies is contained in table 2.3. Similarly, summaries of cross sectional and longitudinal data on SMC are contained in tables 2.4 and 2.5. The format of these tables is based on tables presented in a review of SMC by Jonker and colleagues in the Netherlands (Jonker *et al* 2000).

Table 2.3Prevalence of Subjective Memory Complaint in Community Studies

Reference	N	Age	Prevalence	Exclusions	Memory Test	Dementia	
O'Connor '90	384	>75	37%	MMSE >25 Severe dementia major depression	CAMDEX	CAMDEX DSM.III.R	CAMDEX Score 0-7.
Bassett '93	810	18-92	22%	NIL	MMSE	DSM III	Single question Y/N
Jorm '94	877	>70	6.3%	NIL	Episodic Memory	NIL	Scaled score 0-8.
Gagnon '94	2726	>65	33.5%	Dementia	Visual/verbal memory	NINCDS- ADRDA	Single question Y/N
Tobiansky '95	705	>65	25.0%	NIL	CAMDEX + others	CAMDEX	Scaled score -9 questions. SMC >3
Jonker '97	25-37	65-84	22.1%	Dementia depression	CAMDEX + others	CAMDEX	CAMDEX questions. 4 categories.
Blazer '97	3079	>65	56.0				
Jungwirth '04	302	75	47%	MMSE <24 AD.	FOME	DSM IV	Single question Y/N
St John '02	1416	>65	21%	3MS <78	3MS + others	DSM III.R	single question → followed by more questions. Score 0-8
Wang '00	543	>65	49%	Dementia Psychosis	CASI	DSM-III-R	Yes/No

Table 2.4Association between Subjective Memory Complaint, Depression and Cognitive Impairment – cross-sectional data.

Reference	n	Age	Sample	Association with depression	Association with cognitive impairment
(Sunderland <i>et al</i> 1986)	60	64-75	Volunteers	Not examined	No
(McGlone <i>et al</i> 1990)	28	>50	Referrals	Yes	No
(Christensen 1991)	64	53-75	Self-referrals	Not examined	Yes
(Bolla <i>et al</i> 1991)	199	39-89	Self referrals	Yes	No
(Barker, A <i>et al</i> 1995)	30	>50	Self referrals	Yes	No
(O'Connor <i>et al</i> 1990)	384	>75	Community		
(Bassett <i>et al</i> 1993)	810	18-92	Community	Yes	Yes
(Jorm <i>et al</i> 1994)	877	>70	Community	Yes	Weak
(Gagnon <i>et al</i> 1994)	2726	>65	Community	Yes	Yes
(Tobiansky <i>et al</i> 1995)	705	>65	Community	Yes	Yes
(Jonker <i>et al</i> 1996)	2537	65-84	Community	Excluded	Yes
(Blazer <i>et al</i> 1997)	3079	>65	Community	Yes	No
(Jungwirth <i>et al</i> 2004)	302	75	Community	Yes	No
(St John <i>et al</i> 2002)	1416	>65	Community	Yes	Yes
(Wang, PN <i>et al</i> 2000)	543	>65	Community	Yes	Yes
(Schofield <i>et al</i> 1997)	364	Mean 75.9	Registry	Yes	Yes
(Derouesne <i>et al</i> 1999)	183	>50	Self referrals	Yes	No

Table 2.5Subjective Memory Complaint as a predictor of Cognitive Decline in Longitudinal Studies

Reference	Study sample	n	Age mean (SD)	Follow-up (years)	Cognitive exclusion criterion	Outcome	Association with decline
(O'Brien <i>et al</i> 1992)	Referrals	64	67.2 (8.4)	3	MMSE >22	Dementia	Yes
(Taylor <i>et al</i> 1992)	Volunteers	43	67.5 (5.3)	4	MMSE >23	Word recall speed	Yes
(Flicker, C <i>et al</i> 1993)	Volunteers	59	68.7 (5.7)	3.5	GDS 2	Recall recognition speed	No
(Tobiansky <i>et al</i> 1995)	Community	705	74.6 (6.5)	2	Dementia	Dementia	Yes
(Schmand <i>et al</i> 1996)	Community	357	Not stated	3	MMSE > 23	Dementia	Yes OR 1.25 (95% CI- 1.03-1.52)
(Schmand <i>et al</i> 1997)	Community	2114	74.1 (5.5)	4	MMSE >23	Dementia	Yes
(Blazer <i>et al</i> 1997)	Community	3079	72.7 (6.1)	3	Nil	Cognitive test	No
(Schofield <i>et al</i> 1997)	Registry	364	75.9 (7.0)	1	Dementia	Cognitive decline	Yes
(Jorm <i>et al</i> 1997)	Community	721	Not stated (>70 years)	3.6	Dementia	Dementia Mortality	No Yes
(Geerlings <i>et al</i> 1999)	Community	3774		3.2	Dementia	Alzheimer's Disease	Yes OR 2.11 (95% CI- 1.19-3.71)
(St John <i>et al</i> 2002)	Community	1416	77.0 SMC 74.9 no SMC	5	Dementia CIND	Dementia CIND	Yes Yes
(Wang, PN <i>et al</i> 2000)	Community	543	75.4 (6.0)	3	Unclear	Cognitive decline	No

2.2.11 Conclusions

Chapter 2 of this thesis has dealt with cognitive signs and symptoms as risk factors for dementia. Overall, evidence suggests that subjective memory complaint, sub-normal cognitive performance and decline in cognitive performance are risk factors for dementia. It is extremely difficult to summarise cohesively the 40 years of pre-dementia research because of the numerous different methods employed in patient selection (clinic, response to advertisements, general community), variable application of the diagnosis of dementia and, in particular, hugely variable inclusion criteria for pre-dementia. The latter point is the most obvious reason for variability in outcomes.

Inclusion variables include:

1. A complaint of memory loss by an individual.
2. Observations of memory loss by a third party.
3. Deficits below a cut-off point on a global test of cognition eg the MMSE.
4. Deficit in cognition based on comparison to norms for younger adults.
5. Deficits below a cut point on a test of episodic memory (with numerous different tests employed).
6. Deficits below a cut-off point on tests of non-memory cognitive domains (with numerous different tests employed).
7. Deterioration over time in cognition.
8. Minor deficits in instrumental activities of daily living.

Another problem has been the desire to create clinical categories when it is not possible to accurately define 'normal' ageing and when degenerative brain disease progresses so slowly and in such a clinically subtle way. Degenerative brain disease may defy attempts to categorise early manifestations of the disease for these reasons. With respect to the category of dementia, the Canadian Study of Health and Aging designated a person as demented only if they had deficits in basic activities of daily living. Others have applied the more accepted deficits in instrumental activities of daily living as the benchmark for dementia threshold. Even this latter interpretation is subjective and can vary substantially from one clinician/researcher to another. One could argue that the literature indicates that careful exclusion of subjects with functional deficits, with less regard for scores on neuropsychological tests, will define a normal group (Morris, JC *et al* 2001). One reason that MCI outcomes are so unpredictable may be that the original criteria included normal subjects who happened to be poor performers. These subjects are unlikely to deteriorate cognitively or functionally, and may well improve as they learn how to do the tests. In addition, the original criteria excluded those high performers who, despite declining, still score above the arbitrary cut-off points used in the definition of MCI. Similarly, those with CIND may improve, because their cognitive deficit may be due to a reversible concomitant medical condition (as allowed by the definition of this entity).

For the present project, we chose to use subjective memory complaint (SMC) as the entry point into the study. At the time of recruitment of our volunteers, there was emerging evidence in the literature that SMC was a marker for those at risk of cognitive decline. It was considered that SMC was a convenient and inexpensive means of risk stratification, thus allowing recruitment of a cohort at significant risk of subsequent cognitive deterioration.

Chapter 3 will examine mainly non-cognitive risk factors.

PART 1 - REVIEW

CHAPTER 3 - RISK FACTORS FOR DEMENTIA

3.1. Dementia and Normal Ageing

Age is the strongest risk factor for dementia (CSHA 1994, Hofman *et al* 1991, Jorm *et al* 1987). This section on age as a risk factor will emphasise AD as the commonest and most researched form of brain pathology associated with dementia.

The distinction between a disease as opposed to a consequence of ageing is important. How is health separated from disease? Kendall says that it is often difficult to define this distinction (Kendall 1975). Established dementia is easily recognised and determined. However, there are difficulties defining more subtle brain symptoms. Ideally clinicians would like to establish a diagnosis that confers risk of adverse outcomes so that those in this category can be treated and those that are not in the category are not given treatment they do not need. An example of a disease that merges with normality is mild hypertension. Clinical trials have shown that treatment of mild hypertension is beneficial (Grassi *et al* 2005). There is a need for clinicians to use better tools to identify milder forms of brain failure and then determine if intervention is worthwhile.

If AD is considered to be at one end of the spectrum of normal ageing then it is inevitable that everyone will become demented if they live long enough. This notion may diminish the impetus to apply public health strategies to deal with dementia.

3.1.1 The History of AD

The term AD was first used by Kraepelin in 1910 following Alzheimer's report of a case of early onset dementia published in 1907 (Berrios 1994). Alzheimer described pathological findings. At this time, age and mechanisms associated with it were considered to be important in dementia. In the middle part of the 20th century, dementia was neglected both clinically and in research. Many of the major textbooks of the time gave it scant emphasis perhaps because there was little challenge diagnostically or therapeutically (Lishman 1994). It was the work of Roth and colleagues in Newcastle, England, beginning in the 1950's that prompted a comparison between AD and senile dementia and led to the conclusion that one disease could account for both (Blessed *et al* 1968) (Roth *et al* 1967). Previously, Alzheimer's was considered to be a disease of mid-life only. This prompted further research into the genetics and neuro-chemical aspects of dementia. This in turn promoted the medical model view of dementia.

3.1.2 The Distinction Between AD and Ageing

That age is the strongest risk factor for AD emphasises the difficulty that researchers have had with distinguishing between the subtle brain manifestations of normal ageing and the early symptoms of brain disease. Age is a tenable risk factor only if we accept that there is a distinction. There is evidence that normal brain function declines with age (Backman K 1999). One of the earliest aspects of brain function that declines is episodic memory (Backman K 1999). This is the ability to remember information acquired at particular place and time. A decline in episodic memory is also a feature of the cognitive profile of non-demented subjects who go on to develop AD, along with other cognitive deficits (Backman *et al* 2001, Small, BJ *et al* 2000). This point raises some questions that are central to the debate.

- (i) Is a decline in episodic memory solely an early manifestation of brain ageing or does it also represent one of the clinical manifestations of certain diseases?
- (ii) If it is a marker for either brain ageing or early disease, what are the precipitants in some people at a young age ie those who are considered to have AD?
- (iii) Is the deficit in episodic memory a life long phenomenon or did these individuals at one time perform as well as those who do not develop AD?

- (iv) Is it possible to identify these individuals and apply preventative measures to preserve brain function?

Huppert has pointed out that the medical model emphasises the categorical nature of disease as opposed to a continuity model (Huppert *et al* 1994). A categorical model works well for episodic conditions like infections and vascular events, but is less helpful for neuro-degenerative diseases that often have a long natural history. Huppert states that "The bulk of the evidence....is consistent with a continuum model of age-associated decline, where chronological age, intrinsic variables and environmental factors combine to determine when disability becomes manifested." So there is a view that perhaps AD is in fact brain ageing after all (Brayne *et al* 1988). In a similar vein, Khachaturian stated that "we are still uncertain whether AD is a specific, discrete, qualitative disorder such as an infectious process, endogenous or exogenous toxic disorder, or biochemical deficiency, or whether it is a quantitative disorder, in which an exaggeration and acceleration of the normal ageing processes occur and dementia appears when neural reserves are exhausted and compensatory mechanisms fail"(Khachaturian 1985). Drachman states that "..the primary etiologic mechanism causing late onset sporadic AD is the relentless erosion of biologic function and increasing neuronal vulnerability due to a combination of age related changes." (Drachman 2006)

There is evidence against this. Storandt and colleagues examined rates of cognitive decline in a group of subjects who were categorised as normal, incipient dementia, very mild dementia or mild dementia (Storandt *et al* 2002). Each category was then divided into four age groups, 52-64, 65-74, 75-84 and over age 85 years. There was no significant difference in the cognitive scores or rate of decline between the four groups even though there was a slight trend toward decline as age increased. This study carefully assessed the control group to ensure that there was no contamination with subjects with incipient dementia.

3.1.2.1 Neuropathology: Evidence for and against

Support for the brain ageing view comes from some neuropathological studies. Mann and colleagues have shown that plaque and tangle load in older AD patients is very similar to age matched controls (Mann *et al* 1985). Perry and Perry contend that the pathology of AD is not specific to the disease, ie it is also present in normal ageing (Perry *et al* 1998). Whereas dementia due to other pathologies such as Pick's, Huntingdon's and Creutzfeld-Jacob diseases all have unique pathology that is not seen in normal ageing.

However, the concept that AD is just brain ageing is countered by a study that show that non-demented centenarians have very little evidence of pathological change (Hauw *et al* 1986). Roth has argued that there is a clear

threshold effect between normal ageing and AD (Roth 1994). He cites threshold effects in other diseases and the absence of insoluble tau found in the core of neurofibrillary tangles in the brains of cognitively normal people. This abnormality is a feature of AD. Neuropathology, however, does not provide definitive answers. Jellinger has emphasised that there are a number of different criteria for the neuro-pathological diagnosis of AD (Jellinger 2003). In addition, current criteria cannot distinguish between definite and questionable dementia (Braak *et al* 1991).

The Vienna Prospective Dementia study shows that Braak stages V and VI only occur in subjects with severe dementia (Jellinger *et al* 1998). The Nun's study shows that neurofibrillary tangles (NFT) have a greater density in the limbic and temporal cortex in those with MCI and very mild AD than in normal subjects (Riley *et al* 2002). Density of NFT is significantly correlated with memory impairment (Mitchell *et al* 2002). These findings are tempered by a report that 9% of cognitively normal subjects have advanced pathology according to the Braak stages (Davis, DG *et al* 1999). Jellinger suggests that this represents the presence of neural reserve in some subjects (Jellinger 03), though other factors such as increased production of antioxidant enzymes may also contribute to prevent cognitive dysfunction.

3.1.2.2 The Cholinergic System

Perry and colleagues have mentioned problems with making a distinction between ageing and AD. These include the heterogeneity of the ageing process, which in turn may be due to superimposed disease. In addition, they raise the possibility that “functional disturbances may reflect changes in subtle neurophysiological mechanisms which, unlike relatively crude measures of neuron numbers, transmitter, enzyme or receptor levels, cannot be investigated readily” (Perry *et al* 1998).

Of the neurotransmitters, the cholinergic system has received most attention from laboratory researchers. The study by Drachman and Leavitt alerted researchers to the potential role of the cholinergic system in brain ageing (Drachman *et al* 1974). Young volunteers were given the anti-cholinergic chemical scopolamine and memory deficits similar to those seen in the elderly were observed. All the cholinergic parameters show a decline with ageing (Perry *et al* 1994). This knowledge prompted investigations into the use of cholinesterase inhibitors as the first effective treatment for AD. In 2001, the American Academy of Neurology, based on evidence at the time, concluded that the cholinesterase inhibitors should be standard treatment for AD (Doody *et al* 2001).

3.1.3 Conclusion

The argument discussed in this section is predicated on the veracity of the dichotomy between 'ageing' and 'disease'. The view that AD is brain ageing is countered by the knowledge that genetic mutations directly cause early onset AD in carriers that is clearly distinct from the ageing process.

The threshold versus continuum view of clinical phenomenon is academically an interesting debate. However, it obscures the possibility that less severe expressions of the underlying pathology or physiological changes are scientifically and clinically relevant. So there is a view that the threshold versus continuum debate is not important, in that examination of the common features of AD and ageing will provide important clues that will lead to the development of rational therapies (Perry *et al* 1998).

Normal ageing is probably not sufficient to cause dementia in everyone and does not explain all the clinical findings and natural history of AD. In the ten years since Huppert made her comment the accumulated evidence is less supportive of the view that AD represents the end of a continuum. This has been driven by the discovery of genetic mutations that cause AD in middle aged people and genetic risk factors that clearly influence age of onset of AD.

Is it possible to improve the ability to predict that a person will suffer dementia by investigating other risk factors? These factors will be examined more closely now.

3.2. Genetic Risk Factors for AD

It is apparent from studies of kindreds that genetic factors play a significant role in the genesis of neuro-degenerative disorders (Kennedy, JL *et al* 2003). This is supported by epidemiologic studies that show that first degree relatives of AD sufferers have approximately twice the risk of AD of the general population (Lautenschlager *et al* 1996). Genetic factors in the heritability of AD are complex due to involvement of multiple gene mutations and polymorphisms. Mutations are usually highly penetrant and transmitted in an autosomal dominant fashion, while polymorphisms are less penetrant and have more influence on age of onset (Bertram *et al* 2003).

A number of discoveries have given impetus to genetic research:

1. The identification of amyloid β peptide (A β) in cerebral blood vessels (Glenner *et al* 1984),
2. The identification of amyloid plaque cores (Masters *et al* 1985),
3. The link to Down's syndrome and the cloning of the gene on chromosome 21 that codes for the amyloid precursor protein (Kang *et al* 1987).

Further analysis has led to the knowledge that A β , tau protein and α -synuclein are implicated in the pathogenesis of AD, fronto-temporal dementias and Parkinson's disease respectively (Hardy 2003).

It is now known that in approximately 2% of AD cases inheritance occurs in an autosomal dominant pattern due to mutations in the amyloid precursor protein (APP), presenilin 1 (PS1) and 2 (PS2) genes (Schott *et al* 2002). Most of these familial autosomal cases are due to mutations occurring in the PS1 gene that are highly penetrant and occur in middle age. These cases exhibit the same neuropathological features as observed in sporadic late onset AD, though the degree of severity is greater in early-onset familial AD (EOFAD) (StGeorge-Hyslop 2000).

Mutations in the APP gene on chromosome 21 were the first AD causing mutations identified (Goate *et al* 1991). Penetrance is 100% by the seventh decade (Levy-Lahad *et al* 1998). Age of onset has been as early as 39 years. Similarly, the penetrance of the PS1 and PS2 mutations is extremely high with only rare cases of carriers not developing AD by the 8th decade (Levy-Lahad *et al* 1998). It has been estimated that mutations to these three dominant genes cause about 0.075% of all AD (Tol *et al* 1999) (Cruts *et al* 1998). Hence, screening for them has no value in risk assessment for the general population, but certainly has value for screening EOFAD where these known genes account for 50% of all affected families.

It is also known that the products of the presenilin genes facilitate the γ -secretase mediated cleavage of the APP protein (Citron *et al* 1997). Presenilin mutations lead to accumulation of A β . It has been suggested that presenilin 1 is the γ -secretase enzyme (Citron *et al* 1997). However, this enzyme is a multimeric complex of 4 proteins, each essential for its activity. The direct catalytic active site of the γ -secretase enzyme remains to be determined.

Other genetic analyses of neurological disorders including frontotemporal dementia, led to linkages with chromosome 17 close to the tau gene (Foster *et al* 1997) where mutations in this gene were identified. This knowledge showed that tau mutations cause tangle formation and are not associated with amyloid deposition (Hardy 2003).

Similar data exists for Parkinson's Disease and the mutation in the α -Synuclein gene on chromosome 4 (Polymeropoulos *et al* 1997). α -Synuclein is the principle component of the Lewy body (Spillantini *et al* 1997). Along with characteristic clinical features, Parkinson's disease is confirmed by the finding of loss of dopaminergic neurons in the substantia nigra and the presence of Lewy bodies at post-mortem examination (Cookson *et al* 2005).

Cummings has summarised the current knowledge of the molecular biology of these disorders and given it clinical context (Cummings, JL 2003). He cites

the increasing recognition that neurodegenerative disease is the result of abnormal protein metabolism principally involving A β , α -synuclein and tau. Other proteins are implicated less frequently eg prion protein (Prusiner 2001) and Huntingtin (Beal 2001). The proteotype is associated with certain phenotypes and regional vulnerability of neuronal populations. This allows for “proteotype-phenotype correlations”. In some cases, as mentioned above, genotype-phenotype correlations are possible.

Apolipoprotein E (*APOE*) is a susceptibility gene and the $\epsilon 4$ allele is associated with increased risk of disease and earlier age of onset of AD (Haines *et al* 2001). The $\epsilon 4$ allele occurs in a greater frequency in both early and late onset AD than in age-matched controls (Martins *et al* 1995). The *APOE* $\epsilon 4$ allele is not associated with a particular phenotype like the proteinopathies (Levy, ML *et al* 1999). *APOE* was identified in 1993 as risk factor for late onset familial AD and sporadic AD (Strittmatter *et al* 1993) (Saunders *et al* 1993). There are other susceptibility gene loci that have since been identified, but their contribution to AD is relatively minor compared to that associated with the *APOE* $\epsilon 4$ allele (Soinenin 03). The location or nature of these loci is yet to be determined. Other suggested genes may be located on chromosomes 1, 5, 6, 9, 10, 12, 15 and there are another 65 functional candidate genes reported (Bertram *et al* 2003).

APOE is universally confirmed as a risk gene. Farrer and colleagues published a meta-analysis that included 5,930 AD cases and 8,607 cognitively normal controls (Farrer *et al* 1997). In all racial groups the *APOE* $\epsilon 4$ allele was more common in the AD cases. It has been estimated that for $\epsilon 4$ heterozygotes the risk of AD is three times that of those who are $\epsilon 4$ negative, while for homozygotes the risk is nine times greater (Lindsay *et al* 2002) (Roses 1997).

It has also been shown that the *APOE* $\epsilon 4$ allele is more common in those with memory problems that do not meet the clinical criteria for dementia (Henderson *et al* 1995).

The risk associated with the *APOE* $\epsilon 4$ was further established by correlating genotype with brain metabolism in cognitively intact middle aged subjects with a first degree family member with AD (Reiman *et al* 1996). In this study, positron emission tomography (PET) in $\epsilon 4$ homozygotes showed significantly reduced glucose metabolism in brain areas typically affected in AD compared to controls.

This increased risk is also reflected in cognitive performance. The same group examined cognitive performance in a relatively young group of normal volunteers with mean age of 56 years (Caselli *et al* 1999). The purpose of the study was to examine the role of *APOE* $\epsilon 4$ in age of onset. Each of 25 *APOE* $\epsilon 4$ homozygotes was matched with one $\epsilon 3/\epsilon 4$ heterozygote and 2 subjects

lacking an APOE $\epsilon 4$ allele. All were cognitively normal and aged between 49 and 69 years. A 90 minute neuro-psychological battery was administered with emphasis on immediate memory and delayed recall. Mean memory scores in the three groups did not differ. However, in the homozygous group there was a negative correlation between age and scores on tests of immediate and delayed recall that was not seen in the other two groups. This finding supports the concept that *APOE* $\epsilon 4$ homozygosity contributes to memory decline at an earlier age.

In a further study involving a similarly aged group, $\epsilon 4$ carriers performed less well on multiple tests of verbal memory (Caselli *et al* 2004). Those with MCI were specifically excluded, as the purpose of this study was to determine the pre-clinical effects of *APOE* genotype. The authors concluded that those carrying the $\epsilon 4$ allele displayed a modest decline in memory performance before the age of 60, compared to non- $\epsilon 4$ carriers.

Other studies support this data. AMSTEL study participants (n=511) (referred to in part 2) were divided into normals, minimal dementia and dementia and had genotyping performed (Jonker *et al* 1998). This group had been selected from the original general practice sample of 4051. The participants were stratified according to scores on the mini-mental state examination, 27-30, 22-26 and <22. Annual review using the CAMDEX occurred for three years. The finding of more severe cognitive decline in those with *APOE* $\epsilon 4$ and normal

baseline cognition was not seen in those with minimal and manifest dementia. This suggests that once dementia is evident, *APOE* ϵ 4 status has less influence over rate of decline than previously thought. The age adjusted odds ratios for prevalent and incident dementia were 2.65 and 2.66 respectively with confidence intervals of 1.53-4.60 and 1.27-5.58.

Another Dutch study recruited from municipal registries and reported on 1297 volunteers (Dik *et al* 2000). An inclusion criteria of MMSE score >21 was used to exclude subjects with dementia and an age of 62 years or older. The Rey auditory verbal learning test was used. The group was divided into 'cognitively impaired' (MMSE 21-26) and 'cognitively normal' (MMSE 27-30). Memory decline over a three year follow-up period was greater in the cognitively impaired group than in the normal group and those over age 75 years were most at risk of cognitive decline. A deficiency of this study was that clinical assessment of dementia was not carried out. It is therefore possible that the cognitively impaired group included some subjects with dementia - in which case it is not unexpected that more rapid decline was observed among these individuals.

Further evidence shows that *APOE* genotype influences risk of conversion from pre-dementia states to AD. The Canadian Study of Health and Aging included a nested case control study of *APOE* genotypes and its effect on conversion of cognitive impairment no dementia (CIND)(see part II) to

dementia (Hsiung *et al* 2004). A total of 1469 subjects had genotyping done and of these 296 had CIND at baseline. At five year follow-up it was found that the $\epsilon 4$ allele was a significant predictor of conversion from CIND to AD and VaD after adjustment for age, sex, ethnicity and level of education. The odds ratio for incident AD and VaD were 2.89 (CI 1.96-4.28) and 3.13 (CI 1.76-5.55) respectively. The *APOE* $\epsilon 4$ status did not influence the risk of development of CIND in those designated as normal.

However, not all reports concur with these findings. A cross-sectional study from Florida showed that there was no evidence of an influence of *APOE* $\epsilon 4$ on cognition (Small, BJ *et al* 2000). This finding may have been influenced by a low frequency of $\epsilon 4$ homozygotes ($n=8/413$), accompanied by a total $\epsilon 4$ allele frequency of 11.99%.

Several mechanisms have been suggested to explain the role of *APOE* $\epsilon 4$ in the pathogenesis of AD (Huang, Y 2006). These include modulation of $A\beta$ deposition and clearance, impairment of anti-oxidative defences, impairment of neuronal signalling and increased phosphorylation of tau.

3.3 Brain Structure and Function from Imaging as Risk Factors for AD

In chapter 1, the difficulty with the diagnosis of early dementia was explored. It is possible for two experienced clinicians to disagree about whether a

person has dementia. This is because the criteria for dementia are necessarily applied in a subjective fashion. Both DSM and ICD require a person with dementia to have a decline in occupational and social function from a previously attained level. Just what represents decline can be interpreted differently. Clinicians have therefore sought more objective means of diagnosing brain disease. Sophisticated brain imaging now allows the identification of brain disease before the clinical syndrome of dementia is apparent (Reiman *et al* 1996).

Accurate definition of brain morphology with sophisticated imaging techniques has prompted many studies that have examined the role of brain imaging in early identification of brain disease. It is useful to consider changes in brain morphology along with neuro-psychological and clinical parameters for pre-clinical identification of degenerative cerebral pathology. Performance on neuro-psychological tests can fluctuate due to emotional and educational factors. Therefore, it is sensible to have structural information about the brain as well. Most interest has centred on the medial temporal lobe structures and in particular the hippocampus (the hippocampus forms the floor of the temporal horn of the lateral ventricle, its dimensions being approximately 4 x 2 x 1.5 cm). Post mortem studies show that AD pathology starts and is most severe in this area of the brain (Braak *et al* 1993). In addition, episodic memory, the earliest affected cognitive process in AD, is clearly subserved by the medial temporal lobe (Eichenbaum *et al* 1996). Additional support for a

clinical and research focus on the medial temporal lobe is that loss of neurones and atrophy within the entorhinal cortex (which forms the anterior part of the hippocampus) occurs in those with MCI (Kordower *et al* 2001). Neuropathological evidence shows that even before neuron loss occurs in the entorhinal cortex and hippocampus, there is accumulation of tau and A β pathology in these brain regions.

In a review of the topic, Chetalet and Baron make the point that the medial temporal lobe is complex, with distinct structures that are small and with ill defined boundaries that are often difficult to delineate on brain images (Chetelat *et al* 2003). They also state that accurate measurement of the entorhinal and perirhinal cortices is very time consuming and even then not always reproducible. More recently, automated methods have been proposed

3.3.1 Computerised Tomography

Before the advent of computerised tomography (CT), it was considered acceptable to correlate intellectual impairment with cerebral atrophy (Nielsen *et al* 1966). This was found not to be the case as ventricular and sulcal enlargement on CT images correlated weakly with the presence of AD (Earnest *et al* 1979). Thus, atrophy may be identified on the scans of healthy individuals and cannot be identified in some with manifest dementia. Other studies have confirmed that CT is not predictive of intellectual function independent of age (Kaszniak *et al* 1979) (Hughes, CP *et al* 1981).

It is apparent that CT assessment of cerebral atrophy cannot distinguish between normal individuals and those with dementia and certainly cannot define those at risk of dementia. However measurement of the temporal lobe provided some hope of increasing the diagnostic validity of CT with a study in 1989 showing that AD patients were much more likely to have widening of the temporal horn ($>3\text{mm}$)(Kido *et al* 1989). Widening of the Sylvian fissure based on a subjective measurement was less specific but more sensitive. This approach was refined by George and colleagues by scanning every 10 mm with contiguous 5mm images at a 20° angle caudal to the standard baseline (George *et al* 1990). This allows visualisation of the peri-hippocampal fissure, which widens in early AD. This study showed that lower hippocampal volumes in the cognitively normal subjects were associated with lower scores on tests of delayed recall. (See appendix 3 for a coronal depiction of the relevant structures.)

Diaz-Guzman and colleagues reviewed the utility of CT in diagnosing dementia (Diaz-Guzman *et al* 2002). In terms of diagnosing AD, the positive likelihood ratios for CT parameters are modest and therefore do not significantly change post test probabilities. Problems were also identified with patient selection biases, inappropriate reference standards and unblinded evaluations. The review did not address the usefulness of CT measurements as a predictor of future cognitive decline.

de Leon and colleagues from New York University, did test the hypothesis that widening of the peri-hippocampal fissure in non-demented elderly subjects predicts future onset of AD (de Leon *et al* 1993). At baseline there were 54 volunteers with GDS stage 1 or 2 and 32 with GDS stage 3. All had CT scans performed according to the protocol described above. Hippocampal CSF was rated subjectively as absent, questionable, mild-moderate or severe. Four years later the scans were repeated. There were 25 subjects who converted to AD during this time and 23 of these were from the GDS stage 3 group. The baseline measurement of hippocampal CSF had a sensitivity of 91% and specificity of 89% for conversion at four years in the GDS stage 3 group. For the control group the specificity of the hippocampal CSF rating was 88%. This equates to six controls with hippocampal CSF who did not convert to AD in the follow-up period. The likelihood ratio for the rating of hippocampal CSF is 8.3 (Diaz-Guzman *et al* 2002). The study also shows that the imaging data is a better predictor of decline than the neuropsychological test scores.

The Oxford Project to Investigate Memory and Aging (OPTIMA) study examined medial temporal lobe thickness in 44 AD patients, ten with dementia due to other causes and in 75 controls using cranial CT (Jobst *et al* 1992). The cases of AD had established disease and the mean MMSE score was 9.3. The temporal lobe thickness was half that of controls. The clinical

diagnosis was confirmed by post mortem examination in all cases. The AD cases in this study all had established dementia with a mean MMSE of 9.3. Therefore this study did not contribute to the need for an imaging parameter that will increase specificity of tests in at risk populations.

3.3.2 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has advantages over CT that makes it a more useful technique in the investigation of AD. It provides images without bone artefacts, allows greater resolution of structures in the medial temporal lobe and provides better estimates of brain parenchyma and CSF volumes (Rusinek *et al* 1991).

Another report by the group from New York University using magnetic resonance images (MRI) showed that medial temporal lobe structures were consistently smaller in AD subjects than non-demented controls (Convit *et al* 1993). Hippocampal volume was the only measure to discriminate between those with mild cognitive impairment and controls.

A series of papers from Jack and colleagues illustrates how imaging has contributed to our understanding of early brain disease. In an early study, 62 AD patients and 125 controls were examined (Jack *et al* 1998b). MR hippocampal volume was normalised and a score based on deviation from population based norms was determined. These were designated 'W values'.

The difference in these values between *APOE* $\epsilon 4$ negative and positive controls was insignificant, a result that surprised the investigators. They expected to observe a difference based on the presence of sub-clinical AD in the control subjects who were $\epsilon 4$ positive. Similarly there was no statistically significance difference between the $\epsilon 4$ positive and negative AD patients. Using logistic regression, both the *W* score and *APOE* $\epsilon 4$ status were independently and significantly related to likelihood of AD. The odds ratio for the *W* value was 0.196 and for *APOE* $\epsilon 4$, 3.581.

The same group studied another sample of 48 subjects aged between 70 and 89 years, half of whom had AD (Jack *et al* 1998a). Recruitment came from an AD clinic. These were matched with similarly aged cognitively normal controls. Of the AD group, 11 had a CDR score of 0.5. MR measurements included total intracranial volume, hippocampal and temporal horn volumes. Baseline images were followed by repeat images after 12 months. The rate of hippocampal volume loss and temporal horn enlargement was greater in the AD group. When normalised by considering differences in individual head size the differences were still significant. The rates of volume change were not related to *APOE* $\epsilon 4$ status, use of estrogen or vascular risk factors.

In yet another study from the same clinic, 80 cases of MCI were studied and followed (Jack *et al* 1999). Hippocampal volumes were measured from baseline MRI scans. Clinical and cognitive examinations were done annually

for three years. Conversion to dementia ('crossover' is the descriptor used in the paper) was based on DSM-III-R and NINCDS-ADRDA criteria. W scores as previously mentioned were derived with a score of zero indicative of hippocampal volume at the 50th centile. The W scores were distributed and conversion to AD occurred as follows:

W score	N	Conversion
≥ 0	13/80	2/13
0 to -2.5	54/80	19/54
< -2.5	13/80	6/13

Age and scores on cognitive tests were also predictive of conversion. Bivariate analysis showed that hippocampal volume remained an independent predictor of conversion. For each one unit increase in W score the relative risk of conversion reduced by 31%. The authors concluded that MRI based hippocampal volume measurement represents a marker of incipient AD.

A follow-up study in 2000 reported on 129 subjects who were classified as normal, mild cognitive impairment (MCI) or demented. MCI was defined by a CDR score of 0.5 (Jack *et al* 2000). No test score cut offs were used. In addition, controls and those with MCI were identified as stable or a decliner ie changed category. Clinical and MR follow up occurred about three years after baseline assessment. The annualised rate of decline in W score was greatest in the AD

group and in those with MCI who progressed to AD. The least decline was observed in those controls that remained stable. Of note, the rate of decline in stable MCI patients was significantly greater than in stable control patients. This suggests that MCI is a clinically important entity and that even though a patient may be clinically stable, underlying disease is progressing. The study also suggests that rate of change in hippocampal volume correlates well with decline in cognition.

A review of longitudinal studies of 'at risk subjects' has shown that hippocampal atrophy does have moderate but significant predictive value for conversion to AD (Chetelat *et al* 2003). The same authors state that "...the initial degree of hippocampal (Hcp) atrophy and also the combination of a reduced temporal neocortex and an atrophied Hcp or anterior cingulate cortex may be the most significant predictors of progression to AD". Others argue that structural imaging alone is not specific enough to accurately predict AD risk and separate it from other diseases eg frontotemporal dementia (de Leon *et al* 2004).

More recently, it has been shown that a decline in volume of particular brain regions correlates with decline in specific cognitive functions. A study from California included predominantly normal or slightly impaired subjects with evidence of subcortical cerebrovascular disease (Mungas *et al* 2005). Follow-up over five years showed that baseline hippocampal volume correlated with

decline in memory only and not executive function, whilst baseline atrophy of cortical grey matter correlated with executive function loss. Of note, a decline in hippocampal volume with time correlated with both memory decline and executive function loss, suggesting that executive function loss is a cognitive component of AD and not only cerebrovascular disease.

The other important structural abnormality seen on MR images in the elderly is white matter disease (WMD) seen as hyperintense signals on T2 weighted images (Gunning-Dixon *et al* 2000). WMD is associated with age, hypertension and other vascular risk factors (Basile *et al* 2006). Although traditionally considered to be ischemic in nature the pathology is often non-specific (Erkinjuntti *et al* 1996). The exact relationship to AD is still not known and there is a complex relationship between AD pathology and vascular related pathology (Burns *et al* 2005). It is acknowledged that the concurrence of vascular pathology and AD pathology leads to greater cognitive deficits than would be present with either pathology alone (Snowdon *et al* 1997). The presence of WMD is not considered a risk factor for AD at this time.

3.3.3 Functional Imaging of the Brain

Another surrogate marker for brain disease is imaging of brain function as opposed to the structural approach with CT and MRI as described above. It is thought that functional changes occur before structural change hence the

considerable research interest in this area and potential advantage of these techniques in early disease detection.

It has been known for over 20 years that measurement of brain glucose metabolic rate shows reduced utilisation in the parietal and frontal cortex in AD (Phelps *et al* 1979). Small amounts of molecular probes are injected that contain short-lived isotopes that emit positrons (Phelps *et al* 1979). This allows for targeting of a molecule in the tissue of interest. PET allows quantification of other physiological processes including cerebral blood flow and neurotransmitter and receptor function (Nordberg *et al* 2001). Cross sectional studies have shown abnormal glucose metabolism in at risk groups including those with APP mutations (Wahlund *et al* 1999), PS1 mutations (Kennedy, AM *et al* 1995), carriers of the APOE ϵ 4 allele (Small, GW *et al* 1995) and MCI (Jelic *et al* 2000).

Longitudinal studies now show that reduced glucose metabolism in normal subjects predicts conversion to MCI. The New York University group studied 144 volunteers with GDS scores of 1 or 2 who had MRI and PET scans done at baseline and three years later (de Leon *et al* 2001). Decline was defined by a GDS score of 3 or more. Reduced baseline metabolism in the entorhinal cortex predicted conversion to MCI. In those who converted, follow up scans showed metabolic decline in the temporal neocortex and the hippocampus.

An Italian study has shown that there is variability in the distribution of hypometabolism on PET scans of subjects with amnesic MCI (Anchisi *et al* 2005). Those with poor scores on a test of episodic memory were at significant risk of conversion to AD. These individuals had the typical AD pattern of hypometabolism in the parietal and posterior cingulate cortex.

Single photon emission computed tomography (SPECT) is another technique that employs injected radionuclides. It produces images with less resolution than PET and measures blood flow in a qualitative way. One study showed that temporal perfusion ratios on SPECT could distinguish between normals and those with AD (Eberling *et al* 1992). However, a review of the use of SPECT in the diagnosis of AD concluded that the technique has no advantage over clinical diagnosis and that a prospective study following all subjects to autopsy is needed (Jagust W 2002).

MRI can also be applied to determining brain function. This technique relies on the measurement of an increase in regional MR signals when deoxygenated hemoglobin levels are relatively reduced during complex cognitive processes, due to the enhanced flow of oxygenated blood into an active brain region. This is referred to as, measured as blood oxygen level dependent brain response (BOLD) (Sperling 2003). The advantage of functional MRI (fMRI) is that no injection is needed and measurements are taken while the patient is performing a task that is clinically meaningful. A

number of different activation paradigms can be used. To date, results have been conflicting and this is likely due to subject selection differences (Bondi *et al* 2005). In one study patients with MCI have been shown to display increased activity in the parahippocampal gyrus during cognitive activity (Sperling 2003). However, in another study medial temporal lobe activation was found to be greater in controls than both MCI and AD subjects (Machulda *et al* 2003). In this last study, there were no differences observed between the latter two groups, suggesting that the technique can detect change in the prodrome of AD. Bondi and colleagues feel that the differences seen between *APOE* ϵ 4 positive and negative subjects in their study “are consistent with a compensatory hypothesis wherein *APOE* ϵ 4 persons appear to require additional cognitive effort to achieve the same level of performance” (Bondi *et al* 2005). They also report that fMRI shows a diffuse response in AD subjects indicative of the need to recruit other brain regions to subserve memory.

FMRI may yet prove to be a cost effective method of early detection.

3.4 CSF Biomarkers as Risk Factors for Dementia

Biochemical changes in the brain are reflected in the CSF because it is in direct contact with the extracellular space of the brain. It is known that tau and A β pathology ie tangles and plaques, is present in the hippocampal formation

before neuronal loss occurs(Price *et al* 2001). It follows then that measurement of these proteins in CSF offers some hope for identifying those at risk for future cognitive decline and also for monitoring treatment effects.

3.4.1 CSF Tau

Tau is a protein that is a component of the microtubules in neuronal axons (Buee L 2000). In a review, de Leon and colleagues state that “many studies demonstrate elevated CSF levels of total-Tau in AD and in MCI” (de Leon *et al* 2004). De Leon claims that total tau is not specific for AD and there is further evidence that it does not predict which MCI patients will progress to AD (Andreasen *et al* 1999). However, Blennow and Hampel reviewed the literature and found a specificity of total-tau of 90% and a sensitivity of 81% in distinguishing 2459 AD cases from 1332 controls (Blennow *et al* 2003). In a later paper, Blennow indicates that many other neurological conditions eg Parkinson’s disease, alcoholic dementia, depression and progressive supranuclear palsy, are not associated with increased CSF total-tau (Blennow 2004). However, he notes that most Creutzfeld-Jacob disease cases and some VaD and frontotemporal cases have elevated levels of total-tau. So the specificity for total-tau in distinguishing AD from other causes of dementia is less.

AD is associated with an abnormally hyperphosphorylated form of tau (P-tau) that is found in the paired helical filaments that are a pathological feature

of the disease (Grundke-Iqbal *et al* 1986). P-tau has greater specificity for distinguishing AD from other causes of dementia. It is not elevated in VaD or frontotemporal dementia (Blennow 2004).

3.4.2 CSF A β

Reduced levels of A β 42 in subjects with AD in comparison to controls have been found in several studies (Blennow *et al* 2001). However, levels of A β 40 remain stable (Kanai *et al* 1998). It may be that the ratio of A β 42 to A β 40 may be a better diagnostic marker. In Blennow's review of reduced A β 42 levels as a diagnostic test for AD from 13 studies, he found a sensitivity of 85% and specificity of 90% (Blennow *et al* 2003).

Combining low CSF A β 42 and raised total-tau has been useful. In one study, 90% of MCI cases that progressed to dementia had this combination of CSF findings whereas this finding was occurred in only 10% of those that did not progress to AD (Riemenschneider *et al* 2002). This has been confirmed recently by Hansson and co-workers (Hansson *et al* 2006). Using cut-off values of T-tau>350 ng/L and A β 42<530 ng/L, they found in a group with MCI that the combined test had a sensitivity of 95% and a specificity of 83%.

One study has suggested that measurement of tau, A β 42 and ubiquitin in CSF allows for determination of phenotypes (Iqbal *et al* 2005).

3.5 Cardiovascular and Metabolic Disease as Risk Factors for Dementia

In part 1 the difficulties of distinguishing between AD and VaD were mentioned. This has focussed attention on the notion that vascular risk factors may also be risk factors for AD. Longitudinal population based studies have consistently shown that midlife hypertension increases the risk of future AD (Skoog *et al* 1996) (Launer *et al* 2000) (Forette *et al* 2002, Kivipelto *et al* 2001b). Similarly, high serum cholesterol has been found to be associated with greater risk of AD in some studies (Kivipelto *et al* 2001b, Notkola *et al* 1998). Others have found no such association (Tan *et al* 2003) or a reduced risk of dementia (Mielke *et al* 2005). Mielke and colleagues studied 392, 70 year old subjects and followed them for 18 years (Mielke *et al* 2005). They considered that the reduced AD risk with higher cholesterol may reflect the fact that the relationship between cholesterol and dementia depends on “when cholesterol is measured over the life course, or alternatively, in relation to the underlying course of the disease”. They go on to say that cholesterol may be protective in late life and consideration should be given to adopting different attitudes to managing lipid disorders in the elderly.

Kivipelto and colleagues also examined vascular risk factors and the subsequent development of MCI (Kivipelto *et al* 2001a). Elevated serum cholesterol was found to be a significant risk factor for MCI, odds ratio 1.9, (95% CI, 1.2-3.0). In another study, use of anti-hypertensive medication was

associated with preservation of cognitive function (Murray MD 2002). Low diastolic blood pressure has also been identified as a risk factor (Qiu *et al* 2003). In this Swedish study, subjects over age 75 were studied over a six year period. Those with a diastolic pressure below 65 mm Hg had a relative risk of AD of 1.7 (95% CI, 1.1-2.4).

The group from Sweden also examined diabetes as a risk factor for dementia (Xu *et al* 2004). 1,301 subjects free of dementia at baseline were again followed for six years. Diabetes was associated with hazard ratios of 1.5 for dementia (95% CI, 1.0-2.1, P=0.04). The risk was greater for VaD than AD. Diabetes is also a component of the metabolic syndrome along with abdominal obesity, hypertriglyceridemia, low levels of high density lipoproteins and hypertension (NCEP 2001). Yaffe and colleagues have shown that those with the metabolic syndrome and high levels of inflammation at baseline had a relative risk of 1.66 (95% CI, 1.19-2.32) of cognitive impairment after five years (Yaffe *et al* 2004).

It has even been proposed that AD could be considered as diabetes type 3 (Pilcher 2006). This is based on animal model data that shows reduced insulin gene expression in AD accompanied by reduced choline acetyltransferase and neuroinflammation.

Another vascular risk factor is plasma homocysteine. Elevated plasma homocysteine is associated with most forms of vascular pathology (Seshadri *et al* 2002). Cross-sectional studies have shown higher homocysteine levels in subjects with dementia than controls (Morris, MC *et al* 2003, Smith, AD 2002). In a prospective study of the Framingham population, 1092 non-demented subjects were followed for a median period of eight years (Seshadri *et al* 2002). The relative risk of AD was 1.8 (95% CI, 1.3-2.5) for those with a homocysteine level one standard deviation above the mean at baseline. This association has been replicated by the Hordaland homocysteine study (Nurk *et al* 2005). A group of 2,189 subjects from a community sample were assessed at baseline and underwent a test of episodic memory after six years. A definitive clinical diagnosis of probable AD was not performed. There was a correlation between memory deficit and increasing homocysteine quintiles.

In another study, no association was found between hyperhomocysteinemia and incident AD over 3206 person years of follow-up (Luchsinger *et al* 2004). The authors of this study point out that B12 and folate are needed for the conversion of homocysteine to methionine and B6 is needed for the conversion of homocysteine to cysteine. Therefore deficiency in these vitamins may offer further clues to risk of AD. Wang and colleagues examined 370 non-demented subjects aged over 75 years based on previous reports of vitamin deficiency in AD (Wang, HX *et al* 2001). Follow-up occurred after three years and showed a significant association between B12

and folate deficiency and relative risk of AD (RR 2.1, 95% CI, 1.2-3.5). The authors considered the possibility that B12 and folate deficiency causes neurotoxicity due to elevated levels of homocysteine. A recent report has shown a positive correlation between plasma homocysteine levels and plasma A β 40 levels suggesting that homocysteine induces A β accumulation leading to neurotoxicity (Flicker, L *et al* 2004).

3.6 Statins and AD Risk Reduction

HMG-Co A reductase inhibitors, also known as statins, decrease mortality from heart disease and stroke by inhibiting cholesterol synthesis (Li *et al* 2004). In the introduction to their report, Li and colleagues summarise the postulated role of cholesterol metabolism in AD. In a brief review of the literature on the role of statins in prevention of AD, they indicate that there is lack of consistent data. Their study recruited 2356 subjects over the age of 65 years who were followed for 13,110 person-years. Statin use was determined from health maintenance organisation databases and dementia assessments were carried out every two years. The analysis showed no relationship between statin use and incident AD. Differences in study design (cross-sectional versus longitudinal), analysis and indication bias were thought to account for the positive relationship found in other reports (Rockwood *et al* 2002, Yaffe *et al* 2002a).

At present, based on available data, there is no consensus about whether statins reduce risk of AD.

3.7 Dietary Factors and the Risk of AD

There is evidence that high saturated fat intake may increase the risk of dementia (Kalmijn *et al* 1997). This prompted the Chicago Health and Aging Project to examine 815 subjects over age 65 years from a community sample (Morris, MC *et al* 2003). Participants completed a food frequency questionnaire and were followed for a mean period of 3.9 years. Those in the upper quintile of intake of saturated fat had a relative risk of AD of 2.2 compared to those in the lowest quintile (95% CI, 1.1-4.7). Those with a high intake of trans-unsaturated fat also had an increased risk of AD, relative risk of 2.4 (95% CI, 1.1-5.3). Intake of unsaturated fat was thought to be possibly protective.

In a follow up study of the same population, the investigators examined fish consumption over a six year period (Morris, MC *et al* 2005). They found that fish intake was associated with a lower rate of cognitive decline but no clear association with ω 3 polyunsaturated fat intake.

Section 1.4.1 of the introduction described that oxidative stress is thought to play a role in AD pathology. This has prompted a number of studies

examining the role of ingested anti-oxidants in reducing risk of AD. The Rotterdam study followed 5395 subjects for a mean of six years (Engelhart *et al* 2002). High intake of vitamins C and E, as determined by dietary records, was associated with lower AD risk based on one standard deviation greater intake (RR 0.82 and 0.82, 95% CI, 0.68-0.99 and 0.66-1.00 respectively). The authors were not convinced that this relationship was causal. Morris *et al* published two reports in 2002 based on food frequency questionnaires in a cohort from the community. In the first paper, cognitive change was the outcome (Morris, MC *et al* 2002b) while in the second paper it was incident AD (Morris, MC *et al* 2002a). These studies showed that cognitive decline is attenuated by vitamin E intake from food or supplements and that AD incidence is reduced by vitamins from food only. The latter association was found only for those who were *APOE* ϵ 4 negative. Again the authors state that this data does not indicate a causal relationship. Conflicting data comes from a study that examined 980 volunteers from a community setting (Luchsinger *et al* 2003). There was no association between anti-oxidant intake from food or supplemental sources and risk of AD.

Another aspect of the role of anti-oxidants is their presence in some alcoholic beverages. It has been hypothesised that wine reduces the risk of AD by virtue of its flavonoid content and their anti-oxidant activity (Ott *et al* 1998). The Copenhagen City Heart Failure researchers were able to conduct a nested case-control in a cohort study and examine whether amount or type of alcohol

affects AD risk (Truelsen *et al* 2002). They found that weekly or monthly intake of wine was associated with a reduced risk of AD. The same was not found for beer or spirits. The authors commented that other dietary intake of anti-oxidants was not known and that perhaps wine drinkers had healthier diets than beer and spirit drinkers. A Finnish study also used dementia as an outcome as well as MCI (Anttila *et al* 2004). 1,464 men and women were followed for up to 23 years. Those who abstained and those who drank frequently had twice the risk of MCI compared to those that drank infrequently. In *APOE* $\epsilon 4$ carriers the risk of dementia increased as drinking increased. Therefore the risk of dementia in *APOE* $\epsilon 4$ carriers may be exacerbated by increasing alcohol intake *APOE*. The authors urged caution with respect to making recommendations about alcohol intake as a factor in reducing risk of dementia. The mechanisms for such effects remain unknown.

3.8 Hormones and Risk of AD

There are theoretical reasons why estrogen should be protective against AD. These include promotion of cholinergic function, acting as a cofactor with nerve growth factor and reversal of glucocorticoid damage (Jorm, A 2002). A meta-analysis of observational studies shows an odds ratio of 0.71 for those who take exogenous estrogen (Yaffe *et al* 1998). Shumaker has commented on the methodologic deficiencies of most of these trials in a report of data from the Women's Health Initiative Memory Study (WHIMS) (Shumaker *et al*

2003). This was an ancillary study to the Women's Health Initiative study that was stopped prematurely due to the increased risk in those on estrogen and progestin replacement of heart disease, stroke, pulmonary embolism and breast cancer. The WHIMS data shows that the hazard ratio for dementia in the treatment group was 2.05 (95% CI, 1.21-3.48). Also, MCI was not prevented in the treatment group. The authors confirmed that the risks of treatment outweigh the benefits.

Schumaker further reported on the estrogen only arm of the WHIMS study (Schumaker *et al* 2004). A group of 1464 women were treated with estrogen and 1483 were randomised to placebo. The hazard ratio for dementia in the treatment group was 1.5 (95% CI, 0.8-2.7). The hazard ratio for dementia plus mild cognitive impairment was 1.4 (95% CI, 1.0-1.9). When the two treatment groups from the study were analysed together, it was found that there was a significant risk of dementia compared to those treated with placebo (HR 1.8, 95% CI 1.2-2.6).

Flaws have been identified in the methodology of the WHIMS study however (Almeida *et al* 2005). Prevalent cases of dementia may have inadvertently been included at baseline and there was a significantly lower mean baseline cognitive score in the treatment group compared to the control group. This may have biased the outcome in favour of the placebo group. In addition, the age group recruited was 65-79 years. The biological effect of hormone

treatment may be different for a younger group of women. There is evidence that the benefits of hormone therapy occur immediately after menopause (Shumaker *et al* 2004). The point has been made that treatment of elderly women with hormone therapy with the expectation of preventing dementia within five years may represent secondary prevention and not primary prevention (Schneider 2004). This is because those with incident dementia would likely have had subclinical neuro-degeneration at entry into the trial. Schneider also states that other forms of estrogen delivered in more physiological doses may yet prove to be beneficial.

Endogenous estrogen exposure correlates with reproductive period. A study of this shows that a longer reproductive period does not reduce the risk of dementia or AD specifically (Geerlings *et al* 2001).

The interest in hormone supplementation as a treatment for AD has also focussed on testosterone. Several studies have shown a positive correlation between testosterone and cognition (Barrett-Connor *et al* 1999) (Yaffe *et al* 2002b) (Yaffe *et al* 2003). In the laboratory it has been shown that testosterone diminishes A formation from amyloid precursor protein (Gouras *et al* 2000) and reduced phosphorylation of tau (Papasozomenos *et al* 2002). To date, there has been little evidence to support the contention that testosterone supplementation benefits cognition. Lu and co-workers conducted a randomised trial using testosterone in the form of a dermal gel and placebo in

16 subjects with AD and 22 controls (Lu *et al* 2006). They found an improvement in quality of life scores in the treatment group but no difference in cognition. There was however a trend to cognitive improvement in the treated AD group.

3.9 Lifestyle Factors and Risk of AD

It has been shown that physical activity has a protective effect against cardiovascular disease (Hu *et al* 2000, Tanasescu *et al* 2002). This is supported by experiments in laboratory animals that demonstrate enhanced angiogenesis with physical activity (Black *et al* 1990, Isaacs *et al* 1992). In addition, exercise in a mouse model has been shown to reduce amyloid load (Adlard *et al* 2005). Given that cardiovascular disease, particularly stroke (de la Torre 2006) is a risk factor for dementia, there has been interest in examining physical activity as a risk modifier in AD. In addition, other vascular risk factors including diabetes, hypercholesterolemia and hypertension are known to respond to physical activity (Criqui 2004).

Yaffe and colleagues examined the protective effect of physical activity, being prompted by methodological inadequacies in previous studies (Yaffe *et al* 2001). Nearly 6000 women were recruited and activity was measured by recording self reported blocks walked each week. Over a six to eight year follow-up period it was shown that a progressive increase in risk of cognitive

decline occurred as activity diminished. The odds ratio for decline in the highest activity quartile compared to the lowest was 0.66 (95%CI, 0.54-0.82). It was felt that possible explanations include benefits of an overall healthy lifestyle, reduction in vascular risk factor effect or a direct effect on neurones.

Larson and colleagues followed 1740 participants over the age of 65, recruited from a health maintenance organisation for a mean period of 6.2 years (Larson *et al* 2006). Survival estimates showed that those who exercised more than three times each week had better dementia free survival, the hazard ratio was 0.44 (95% CI, 0.44-0.86, p=0.004).

Observational studies examining exercise and dementia risk do not always show similar results. A report from Chicago shows a non-significant effect of physical activity on cognition over six years of follow up (Sturman *et al* 2005). Unlike previous studies, the potential confounding effect of concurrent participation in cognitively stimulating activities was factored into the analysis. Cognitive decline was slowed in those most active however this was not significant. The authors acknowledge that the level of physical activity in the majority of this group was less than in other studies and this may have attenuated the true benefit.

Two meta-analyses of the effect of exercise on dementia risk confirm that observational studies show a benefit (Fratiglioni *et al* 2004, Heyn *et al* 2004).

An editorial that reviewed the study by Larson, states that “it is still uncertain whether this association is causal or whether physical activity is just a proxy measure for "life engagement," for other cognitive activities, or for other lifestyle or socio-demographic characteristics associated with dementia” (Podewils *et al* 2006). Intervention trials are needed to resolve this.

Scarmeas *et al* reported on the effect of leisure activity on risk of incident dementia due to AD (Scarmeas *et al* 2001). Non-demented residents of New York City (n=1772) were given a leisure score based on their participation in a range of 13 different activities. Mean follow up was 2.9 years. The risk of dementia was reduced in those with high leisure scores, relative risk 0.62 (95%CI, 0.46-0.83). Another study also using a group recruited from New York City confirms this finding (Verghese *et al* 2003). The researchers split leisure into cognitive and physical activity scales - only higher scores on the cognitive scale were associated with reduced risk of AD, hazard ratio 0.93(95%CI, 0.90-1.00). An example extrapolated from the data is that a person who does crosswords four times a week has a risk of dementia that is 47% lower than a person who does crosswords only once a week.

Further evidence for a role for intellectual activity comes from a study from Alabama where 2832 volunteers aged between 65 and 94 years were assigned to one of three cognitive training groups or to a non-intervention group (Ball *et al* 2002). All targeted cognitive abilities improved in the intervention groups

compared to baseline. However, there were no differences in everyday function between the intervention groups and non-intervention group.

More recently, the role of social networks in protecting against AD has been examined (Bennett *et al* 2006). In a prospective study of 89 elderly subjects, it was shown that brain pathology at post-mortem examination is modified by degree of social networks. As stated above, it is still to be determined if these lifestyle effects are 'proxy' determinants of other factors.

3.10 Anti-inflammatory Drugs and Risk of AD

Inflammatory mechanisms may play a role in the etiology of AD (Aisen *et al* 1994, McGeer *et al* 1995). Some epidemiological studies show that there is an inverse relationship between risk of AD and prior use of aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) (McGeer *et al* 1996) (Stewart, WF *et al* 1997). The protective effect is thought to be secondary to inhibition of cyclo-oxygenase, thus diminishing the inflammatory reactions considered to play a role in AD (Aisen *et al* 2003). In contrast, the Kungsholmen project showed an increased risk of AD in aspirin users without the APOE ϵ 4 allele (Cornelius *et al* 2004). There was no explanation evident for this unexpected finding. There was a trend towards reduced risk with NSAIDs (relative risk 0.23 95%CI 0.03-1.68). The authors felt that the study may not have had sufficient statistical power and that dual disease mechanisms may play a role in explaining these results.

A meta-analysis has shown that the relative risk of AD from pooled results of six cohort studies and three case-control studies was 0.72 (95% CI, 0.56-0.94) (Etminan *et al* 2003). The authors mention that the potential for publication bias and unsuspected sources of confounding limit how much significance can be attached to the findings. Another meta-analysis confirmed these findings using data from prospective studies (Szekely *et al* 2004). The risk estimate in the three studies where exposure to NSAIDs was two years or greater was 0.42 (95% CI 0.26-0.66). Both authors agree that a randomised controlled trial of prevention of AD using these agents is needed. Given that treatment trials of AD using NSAIDs have been unsuccessful (Scharf *et al* 1999), (Aisen *et al* 2003), it seems that use of NSAIDs early in the natural history of the disease is most important.

3.11 Conclusions

Despite increasing knowledge about the cause of AD, there is still need for a specific low cost method of predicting who will develop AD. In this section, a range of risk factors have been reviewed that reveal information about risk but also pathogenesis. Many of the risk factors are only available for identification in research settings and are not applicable in the clinic eg volumetric analysis of MR images and measurement of CSF biomarkers. Clinicians need a simple method of stratifying risk of brain disease that allows

for efficient use of resources along with diagnostic algorithms that yield high likelihood ratios for increasing post-test probability of disease. In the next section the methodology of the current study is described and data presented.

Chapter 4

Study 1

CLINICAL CHARACTERISTICS OF INDIVIDUALS WITH SUBJECTIVE MEMORY LOSS:

4.1 Introduction

Dementia is a major public health problem. The availability of effective symptomatic treatment for Alzheimer's disease (AD) over the last ten years and the prospect of further advances in therapy have focussed interest on early diagnosis. Chapter 2 reviewed the relationship between memory complaint in non-demented individuals and the future risk of dementia. Rather than examine the validity of concepts that attempt to characterise subclinical cognitive impairment, this study examined individuals with a complaint of memory loss. Chapters 1, 2 and 3 showed that a diagnostic test for AD is still lacking. In this context, examination of cognitive, mood, imaging, genetic and biochemical profiles of those with subjective symptoms of brain dysfunction may provide predictive information. This in turn, may allow risk stratification and facilitate early therapeutic intervention.

The discussion in chapter 3 indicated that cognitive test results, APOE genotype and specific brain imaging parameters confer risk of subsequent cognitive decline. The literature review in chapter 2 showed that those with

subjective memory complaints also have greater risk of subsequent cognitive decline. These factors determined the rationale for the current study.

4.2 Objectives

This cross-sectional study aimed to test the following hypotheses:

In comparison with healthy controls with no complaint of memory loss, individuals with subjective memory impairment show significantly:

1. Worse cognitive performance on the CAMCOG, MMSE and selected neuropsychological tests assessing memory performance.
2. More severe brain atrophy, as determined by linear CT scan measurements, particularly of medial temporal lobe structures.
3. Higher frequency of APOE ϵ 4 genotype.
4. Higher frequency of mood and anxiety symptoms.
5. Higher concentration of total plasma homocysteine.

4.3 Acquisition of the sample

Individuals with subjective memory complaint, hereafter referred to as MC:1, were recruited from the Memory Clinics at Osborne Park Hospital and Hollywood Specialist Centre in Perth, Western Australia. Additional participants were self-referred after responding to an advertisement in the local newspaper. Recruitment occurred in 1997 and 1998. Control subjects,

hereafter referred to as MC:0, were recruited through newspaper advertisements. In addition, some spouses of memory complainers were recruited to the study and included in the control group.

Inclusion criterion (MC:1)

Any subject over age 40 years of age who responded 'yes' to the question:
Do you have a problem with your memory?

Exclusion criteria (MC:0 and MC:1)

1. Dementia due to any cause as defined by DSM-IV criteria (APA 1994), clinically evident major depression or other psychiatric condition (as defined by DSM IV criteria) that clearly contributes to cognitive symptoms (eg poor concentration).
2. Previous stroke, as determined by clinical history.
3. Mini-Mental State Examination score <24 (Folstein *et al* 1975).
4. Any unstable medical condition that may contribute to cognitive symptoms, including, but not restricted, to cardiac failure, chronic airflow limitation, diabetes, renal failure, liver failure, epilepsy, vasculitis, chronic infection.
5. Communication problem that prevents participation in cognitive testing (e.g. dysphasia, dysarthria).

6. Lack of fluency in written and spoken English

In addition, a group of 21 patients with established dementia were included for the purpose of analysis of their CT scans to compare with MC:0 and MC:1. No cognitive or laboratory data was collected on these patients as part of the study. Dementia in these individuals was diagnosed at the Memory Evaluation Unit at Osborne Park Hospital according to DSM IV criteria for Alzheimer's disease.

4.4 Study procedures and timelines

Approval to conduct the study was obtained from the Committee for Human Rights, University of Western Australia.

Study visit 1:

The research nurse obtained informed consent from each participant. CAMDEX patient interview and cognitive examination (CAMCOG) were then performed.

Study visit 2:

Clinical assessment. All participants were reviewed clinically by the author. A medical history was taken, drug regimen recorded and a physical and neurological examination conducted.

Study visit 3:

Acquisition of CT brain images.

Study visit 4:

Neuropsychological tests performed.

Study visits 1, 2 and 3 were conducted within three months of recruitment.

Study visit 4 was conducted within 12 months of recruitment.

4.5 Clinical Features

4.5.1 Cerebrovascular Function

A composite score was created from the four items related to cerebrovascular function in the CAMDEX (CDX 19-22). Subjects who answered 'yes' to at least one question were considered to have evidence of cerebrovascular dysfunction.

4.5.2 Sleep

Similarly, a composite score was created from the three items related to sleep in the CAMDEX (CDX 23-25). Subjects who answered 'yes' to at least one question were considered to have a sleep disorder.

4.5.3 Depressed Mood and Anxiety

Clinical review of the subjects did not identify any that were suffering major depression or being treated for this condition. However, it was considered to be important that the degree of depressive symptomatology be quantified, since these symptoms may confound the expression of memory related symptoms. The CAMDEX items that inform the ICD-10 criteria for severe depression were therefore used to create new variables ('depression A', 'depression B' and 'major depression').

Criteria A: Mood depressed, sad or irritable and loss of capability for enjoyment which is a) abnormal for the person concerned and b) lasts for at least two weeks.

CDX 30 and 36 were used to create a variable for criteria A, designated 'depression A'. CDX 30 asks "Have you lost pleasure or interest in doing things you usually cared about or enjoyed?". CDX 36 asks "Do you feel sad or depressed or miserable?". Responses are recorded as 'No'= 0, 'sometimes'=1 or 'most of the time'=2, for both items. If a subject scored '2' for both items then criteria A were met.

Criteria B: At least three of the following must be present most of the time for at least two weeks:

1. Depressed mood unvarying from day to day and uninfluenced by circumstances
2. Consistent improvement in mood as the day goes on
3. Recurrent thoughts of suicide or a suicide attempt
4. Delusions of guilt, worthlessness, bodily disease, impending disaster
5. Prominent ideas of guilt or worthlessness
6. Severe insomnia, worse in second half of night
7. Loss of appetite and loss (without dieting) of over 5% of body weight within a month
8. Restless pacing or inability to sit still
9. Slowing of bodily movements or slow and monotonous speech
10. Auditory hallucinations in the form of derisive or condemnatory comments about patient

The items in the CAMDEX that correspond to these symptoms were used to create a new variable for criteria B, designated 'depression B'. Nine variables were used and these were:

1. A weight change variable using CDX 26 (have you lost your appetite or become much more hungry than usual?) and 27 (have you lost or gained a lot of weight in the last six months?). For CDX 26, responses are recorded as 'No'= 0, 'sometimes'=1 or 'most of the time'=2. For CDX 27, responses are recorded as 'No'= 0, 'some change'=1 or 'considerable change'=2. If a subject responded '2' for both items then these criteria were met.

2. CDX 34: 'Do you find you talk more slowly than normal for you?' 'No'=0, 'Yes'=1.
3. CDX 40: 'When you are feeling depressed can anything cheer you up?' 'able to cheer up'=0 and 'not able to cheer up'=1
4. CDX 41: 'Is there any particular time of day when this is worse?' 'No'=0 and 'Yes' (if morning)=1.
5. CDX 43: 'Do you feel worthless or guilty or sinful about some of the things you did or mistakes you made in the past?' 'No'=0, 'sometimes'=1 and 'most of the time'=2. If a subject responded '2' then this criteria was met.
6. CDX 46: 'Have you felt so low that you thought of ending it all (committing suicide)?' 'No'=0, 'occasionally'=1, 'recurrent thoughts'=2, 'suicide attempt'=3. If a subject responded '2' or '3' then this criteria was met.
7. Sleep function: The composite score described in section 5.3 was used.
8. CDX 72: 'Have you any peculiar feelings with regard to your body?' 'No'=0, 'Yes'=1.
9. CDX 85: 'Have you ever had emotional or nervous illness requiring treatment?' 'No'=0, 1 or more episodes of illness=1.

Depression B was scored as follows: 9 item sum between 0-3 = 0, 4 or more =

1. Depression was considered present based on these criteria if both depression A and depression B were scored as '1'.

Two subjects were identified as having depression in the MC:1 group based on this criterion, although neither met ICD-10 criteria for a depressive episode after clinical review. As the presence of depressive symptoms was not an exclusion from participation in the study, these two subjects were included in the data analysis.

Considering responses to CDX47 to CDX52 created the variable 'anxiety'. These questions explore the presence of tension, worry, irritability, panic, fearfulness and phobias. If any of these variables had a value of 1, the value for the variable 'anxiety' was 1. If all these variables had a value of 0, the value for the variable 'anxiety' was 0.

4.6 Cognitive and neuropsychological testing.

Ms Athena Paton, a registered nurse and member of the research team, interviewed all participants using the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX) (Roth *et al* 1986). The CAMDEX includes standardised patient and informant interviews and a cognitive examination. The cognitive component of the CAMDEX (CAMCOG) includes tests of orientation, memory, language, praxis, attention, calculation, abstract thinking and visual perception. Scores can range from 0 to 107. The majority of those with dementia score below 80 on the CAMCOG (Roth *et al* 1986). The MMSE score can be calculated from questions included

in the CAMCOG. In addition, the interview components of the CAMDEX gather demographic information and recent and remote medical history.

Trained psychologists under the supervision of Dr Johanna Badcock of the University of WA carried out the neuropsychological testing. The battery consisted of tests of attention, memory, language and frontal lobe function. These tests were chosen largely on the basis of data from Masur and colleagues who identified neuropsychological predictors of risk of dementia in a group of elderly subjects (Masur *et al* 1994). Four variables from the cognitive test battery were shown by a multi-variate test model to predict dementia. These were the Fuld Object Memory Evaluation (delayed recall subtest) (Fuld 1977), the Digit Symbol sub-test from the WAIS-R (Wechsler 1981), the Buschke Selective Reminding test (Buschke 1973) and a test of verbal fluency.

In addition, frontal lobe functions were assessed using a test of temporal order discrimination. The frontal lobes are involved in the organisational aspects of memory (Baddeley 1992). Frontal dysfunction can cause problems with temporal order judgements, so that a subject may have difficulty knowing which of more than one stimuli occurred first (Milner *et al* 1985). Correlations have been found between memory performance and tests of frontal lobe functions, although results in the literature have been inconsistent (Fabiani *et al* 1997).

Two test sessions were conducted on one day. All tests are described in detail below and appear in appendix 1.

Table 4.1**Session 1 - Duration approximately 1 hour**

<u>Task</u>	<u>Trial</u>	<u>Delay to next trial</u>	<u>Duration</u>
Temporal order discrimination	(1) 8 pictures	30 mins	2 mins
Logical Memory	(1) Immediate recall	30 mins	8 mins
Fuld object memory evaluation	(1) Trial 1	10 mins	12 mins
Digit span forwards and backwards or; Digit span forwards only or; Break if necessary			8 mins
Fuld object memory evaluation	(2) Trial 2		2 mins
Temporal order discrimination	(2) 8 pictures	2 mins	2 mins
Conversation +/- or fluency tasks			2 mins
Temporal order discrimination	(3) 32 pictures ID		4 mins
Logical memory	(2) Delayed recall		5 mins
Break			15 mins

Session 2 - Duration approximately 1 hour

<u>Task</u>	<u>Trial</u>	<u>Delay to next trial</u>	<u>Duration</u>
Temporal order discrimination	(1) 8 pictures	30 mins	2 mins
Cued Recall-Pictures and categories	(1) Immediate recall	15 mins	15 mins
Trail making tests	A/B		10 mins
Conversation and fluency tasks			3 mins
Temporal order discrimination	(2) 8 words	2 mins	2 mins
Cued Recall-Pictures and categories	(2) delayed recall		2 mins
Temporal order discrimination	(3) 32 words ID task		4 mins
Break if necessary			10 mins
Verbal paired associates			5 mins

4.6.1 Cognitive Testing

Muriel Lezak views memory as the “complex of systems by means of which an organism registers, stores, retains and retrieves some previous exposure to an event or experience” (Lezak 1995). She describes two major memory systems, declarative and procedural.

Declarative memory can be defined as the ability to remember information, objects and events and consciously retrieve information in the form of propositions, statements or images. With respect to its temporal characteristics, declarative memory can be divided into three sequential stages.

(i) Registration or sensory memory.

Information is held briefly in a sensory store and is either passed into short term memory or it decays quickly.

(ii) Immediate memory

This represents temporary neuronal activation which serves as a limited capacity, short term storage and retrieval system. It has been characterised as ‘working memory’ by some researchers (Baddeley 1992). Working memory is described as having a central executive, a phonological loop and a visuo-spatial sketch pad. In addition, a fourth component, the episodic memory buffer was added more recently. This is proposed as ‘a limited capacity system that provides

temporary storage of information held in a multimodal code, which is capable of binding information from the subsidiary systems, and from long-term memory, into a unitary episodic representation'. The separate functional characteristics of these components of working memory were developed by Baddeley (Baddeley 2000).

(iii) Long term or secondary memory.

This refers to the ability to store information over a longer time period (e.g. weeks, months, years or even decades). The distinction between short and long term memory is best exemplified by the amnesic states where immediate memory is intact but long term is not. Long term memory is somewhat analogous to information that is stored on the 'hard drive' of a computer, whereas working memory is more analogous to the computer's RAM store. Long term memory can be recent and remote. Permanent changes occurring at the cellular level (such as long term potentiation) are thought to subserve long term memory.

Procedural memory refers to the ability to remember actions, behaviours and skills such as walking, talking and dressing. So this is akin to a habit system (Mishkin 1984). This type of memory is preserved in most amnesic patients. Others use the term implicit memory as perhaps synonymous with procedural memory and define it as "knowledge that is expressed in performance without the subject's phenomenal awareness that they possess

it" (Schacter 1988). For example, some people may be able to type rapidly via procedural or implicit memory, without being able to express the location of specific keys via explicit memory.

4.6.1.1. Logical Memory Test

The logical memory test from the Wechsler Memory Scale Revised involves the telling of two stories by the examiner and subsequent recall by the subject (Wechsler 1987). Each story, (story A followed by story B) containing 25 items of information each, is read aloud by the examiner. The subject is then asked to immediately recall as much of each story as possible. The raw score is recorded out of 50 and a centile rating is also derived. The latter is based on age matched norms. After 30 minutes delay, the subject is asked to recall each story again with the same scoring method being used.

The logical memory test is a test of recent, long term, declarative memory. The test has been used to identify subjects at risk of dementia (Storandt *et al* 1986).

4.6.1.2. Fuld Object Memory Test

The Fuld Object-Memory Evaluation is designed to assess storage, retention and retrieval of information (Fuld 1977). Again, it is a test of recent, long term, declarative memory.

- Ten common objects are placed in a bag and the subject is asked to place his/her hand in the bag and identify each object by tactile sense. Left and right hands are used alternatively.
- The object is then visually identified and the subject asked to remember it.
- A brief distraction task is then employed.
- After 60 seconds the subject is asked to recall the objects.
- The subject is reminded about all objects that are not recalled.
- A distraction period of 10 minutes is filled with a structured interview.
- Recall of all items in the bag is requested. Multiple choice recognition is asked for items not remembered.

The test also provides information on stereognosis, left-right orientation and verbal fluency.

4.6.1.3. Digit Span

Digit span is a test of attention, concentration and mental tracking that is incorporated in both the Wechsler Memory and the Wechsler Adult Intelligence Scales (Wechsler 1981, Wechsler 1987). Digit span is used to measure attentional capacity, specifically in the context of short term memory capacity. There are two different components of the task, digits forwards and digits backwards. Both consist of random number sequences read aloud by the examiner, requiring auditory attention and short term

retention capacity (Lezak 1995). Digits backwards also involves working memory. Forward span requires each sequence to be repeated exactly as it is heard. The next longest number sequence is presented following correct performance on the previous shorter sequence. The digits backward task requires the subject to say the number string presented in exactly the reverse order. This requires double tracking in that both memory and reversing procedures have to proceed simultaneously (Lezak 1995).

4.6.1.4. Trail Making

The Trail Making Test was originally developed by the US army (Lezak 1995). Firstly, the subject connects consecutively numbered circles and then numbered circles combined with letters. Scoring is based on time to completion in seconds. The test requires visual scanning, monitoring and motor control.

4.6.1.5. Cued Recall

The Cued Recall procedure is a test of visual declarative memory using appropriate strategies to ensure that processing has been carried out according to the selective reminding strategy of Buschke (Buschke 1984, Tuokko *et al* 1989). The authors state that use of cues, controls for inefficient use of strategies, impaired attention, reduced processing capacity and impairment of other cognitive domains.

In this task, subjects are shown 12 pictures of common objects to scan and remember. Subjects are then given a semantic category cue (e.g. a piece of furniture) and asked to point to and name the previously presented item from that category. This is done for each of the 12 presented pictures.

Distraction is then employed – the subject is asked to count backwards from 100 for 60 seconds. The subject is then asked to freely recall as many of the objects as possible. After a 20-second period in which no items are recalled, semantic category cues are used to prompt recall of those items not previously retrieved under free recall. Three trials of free and cued recall are administered. Three scores are derived:

- (i) Retrieval, the number of items remembered without cueing over the three learning trials.
- (ii) Acquisition, the number of items remembered without and with cueing over the three trials.
- (iii) Retention, the number of items recalled after a delay combining free and cued recall.

In a study of 45 elderly participants the retrieval score on Cued Recall was found to be a robust predictor of the onset of dementia after a follow up period of 18 months (Tuokko *et al* 1991).

4.6.1.6. Verbal Paired Associates

The Verbal Paired Associates is another verbal memory test from the Wechsler Memory Scale Revised. It is a word learning test with built in cueing. A list of eight paired words is read and then the examiner states one of the words from each pair. The subject is asked to complete the pair. Three trials were administered; hence the maximum score was 24.

4.6.1.7. Temporal Order Discrimination

The temporal order discrimination tasks were based on the work of Milner and assess frontal lobe function (Milner *et al* 1991). Normal ageing is associated with decline in performance 'on tasks requiring the retrieval and organisation of contextual information' (Fabiani *et al* 1997). Therefore, a subject may have difficulty remembering the circumstances of acquisition of information (e.g. temporal or spatial context) despite being able to recall the target information. As an example from every day life, a face may be remembered without recall of the location or time when the face was encountered. This test was created by Dr Badcock using established paradigms (Fabiani *et al* 1997). Subjects were shown eight abstract pictures, each exposed for two seconds on an A4 size piece of paper. Thirty minutes later, eight new pictures were displayed for two minutes. Following a two minute distraction conversation, 32 pictures were shown that included the 16 pictures not previously shown and the 16 target pictures that had been previously shown. The subject was asked to discriminate between those that

had previously been seen and those that had not previously been seen. Of those pictures that had been previously seen, the subject was asked the order of presentation. An identical sequence was used for the temporal discrimination task that was used in session 2, but this time words were used as stimuli rather than pictures.

4.6.1.8 Fluency

Retrieval tasks were designed to measure verbal fluency and fill in time to facilitate the other components of the battery of tests. The verbal fluency task comprised measurement of the number of words the subject could think of starting with the letters 'F', 'A' and 'S' in 60 seconds (i.e. phonemic fluency). In addition, the number of supermarket items remembered in 60 seconds was recorded (semantic fluency).

Table 4.2Cognitive Tests and Cognitive Domains Examined

<u>Test</u>	<u>Cognitive Domain</u>
Temporal Order Discrimination	Frontal lobe functions
Logical Memory	Verbal declarative memory
Fuld Object Memory Evaluation	Visual/Verbal declarative memory
Fluency	Language, attention and frontal lobe functions
Digit span	Attention, short term and working memory
Cued recall	Visual declarative memory
Trail making	Attention, visual scanning and motor control
Verbal paired associates	Verbal declarative memory

The cognitive tests record sheets are included in appendix 1.

4.7 Neuroimaging protocol

Chapter 3 identified MRI as the preferred modality for assessing brain morphology. The use of MRI scans in this study was not possible because of funding constraints. Hence, CT scans were performed in this study. These

were acquired at Perth Radiological Clinic in Subiaco, Western Australia under the supervision of Dr Stephen Davis, neuroradiologist.

The scanner was a GE Prospeed Helical CT (120KV, 160mA, three second rotation time, FOV 21 cm), 5mm slice thickness at 1mm interval were acquired. A standard algorithm (cantho-meatal line) at 3:1 pitch was used. Images were then re-formatted at 20 degrees negative to standard baseline, with the meatus as the fulcrum, using software at the Radiology Department at Sir Charles Gairdner Hospital. The intention of the re-formatting was to provide better views of the temporal lobes and allow measurement of the medial temporal lobe width.

The CT features that were measured are described in the work of George et al who examined 34 Alzheimer patients and 20 controls (George *et al* 1990). The subjects with AD had a mean Global Deterioration Score of 4.47 ie they had mild to moderate dementia. The researchers described five measures of atrophy, as follows:

1. Temporal horn enlargement

This is rated as normal if its side to side diameter is no more than 5 mm at the level of the choroid fissure. A width of >10mm is considered severely enlarged. The scans obtained in this study did not allow identification of the

choroid fissure consistently so the measurement was taken on the slice where the temporal horn was seen most distinctly. The width was rated as follows:

1. <5mm i.e. normal
2. 5-10mm
3. >10mm

2. Medial cortical atrophy (Sylvian fissure)

This is an assessment of the Sylvian fissure and the peri-mesencephalic cisterns. The scans obtained in this study did not allow identification of the peri-mesencephalic cisterns so the Sylvian fissures only were rated.

0. no fissure apparent
1. <5mm
2. >5mm

3. Lateral cortical atrophy

This is based on the size of the lateral sulci. This measurement was not included because in this group of patients without dementia and of a relatively young age, prominent lateral sulci were not apparent.

4. Presence and severity of hippocampal lucency

This is defined as a focal area of reduced attenuation that involves the medial temporal lobe parenchyma and is located medial to the temporal horn. Again this structure was not consistently visible on the re-formatted images and was therefore not recorded as a variable in the current study.

5. Overall temporal lobe atrophy

This score is a combination of the other scores and is based on the degree of atrophy of the most affected region. In the study by George et al, two raters used a five point scale (1='normal', 2='minimal', 3='mild', 4='moderate' and 5='severe') (George *et al* 1990). It was not possible to generate this measure from our scans because of the difficulty identifying the hippocampal lucency.

George et al also described a more conventional measure of ventricular size – the composite linear measure (George *et al* 1990). This is obtained by summing the following:

- bi-caudate diameter
- transverse diameter of the right frontal horn
- transverse diameter of the left frontal horn

- width of the third ventricle measured 1 cm anterior to the pineal gland.

This sum is divided by the maximal width of the skull, measured from inner table to inner table at the level of the third ventricular measurement. George et al found that the composite linear measurement had a sensitivity of 68%, specificity of 85% and overall accuracy of 74% with respect to identifying those with dementia. The composite linear measure (CLM) was also calculated on the CT scans of 21 subjects with mild to moderate dementia. This was done to provide reassurance that the measurement discriminated between those with disease and the two study groups. This was found to be so. The mean CLM for the dementia groups was 0.298 ± 0.06 , compared to 0.193 ± 0.06 and 0.191 ± 0.06 for the control and subjective complaint groups respectively.

Measurement of medial temporal lobe width was also included. This was based on the work of Jobst et al (Jobst *et al* 1992). As reported, this measurement requires firstly identification of the margin of the temporal horn of the lateral ventricle. Secondly, it requires identification of the medial structures ie the hippocampal fissure and the tentorial edge. Jobst found that identification of these structures presented no difficulty, however the reformatted images did not facilitate easy definition of the temporal horn of the lateral ventricle. This was despite production of multiple slices through

the temporal lobes. Therefore the medial temporal lobe measurement data in this study is not as accurate as was initially planned.

The reliability of the CT measurement protocol was examined by training another rater, Justin Fonte. Both raters (i.e. RC and JF) measured a selection of 27 scans with names of patients de-identified. One measurement of the relevant parameters was done on each scan.

The re-formatted images were measured by using Efilm, a software program that was available from its website (www.merge.emed.com).

4.8 Genetics

Genotyping was carried out at the McCusker Foundation laboratory at Hollywood Private Hospital. For the determination of Apolipoprotein E (APOE) alleles, genomic DNA was extracted from blood samples and subjected to PCR amplification, essentially as described by Hinson and Vernier (Hixson *et al* 1990) using oligonucleotide primers described by Wenham *et al* (Wenham 1991). The amplified products were digested using the restrictive enzyme Hha1. Digested products were then placed on non-denaturing polyacrylamide gels, stained with ethidium bromide and visualised by UV illumination to reveal DNA fragments with electrophoretic migration patterns unique to each allele.

4.9 Homocysteine

Total plasma homocysteine assays were also carried out at the McCusker Foundation laboratory at Hollywood Private Hospital. Homocysteine was measured by fluorescence polarisation immunoassay on an IMx automated analyser (Leino 1999). The coefficient of variance for this assay was 5-7%.

4.10 Statistical Analysis

The data were analysed using the Statistical Package for the Social Sciences (SPSS 14.0 for Windows). Likelihood ratio analysis of contingency tables (Pearson's method) was used in the investigation of categorical data, the statistical result being distributed as chi-squared (χ^2) (the degrees of freedom for this test equals one unless otherwise stated). Student's *t*-test (*t*) was applied to determine between-group differences in the means of continuous non-skewed data (the degrees of freedom for the *t*-tests equal the total number of subjects minus 2, unless stated otherwise). Most variables were not normally distributed, even after logarithmic transformation. Hence, baseline characteristics for MC:1 and MC:0 were compared using independent non-parametric Wilcoxon tests for ordinal variables (Mann-Whitney, *Z* statistic). Descriptive summary statistics for continuous and ordinal variables appear as mean \pm standard deviation. To maintain consistent reporting of the data, standard deviations were used for data that was not normally distributed. Strictly, interquartile ranges are recommended for such data however the

standard deviation still provides a description of the distribution of variables and this approach was considered to be appropriate. Non-parametric tests were used for analysis in these cases.

The variables found to differ between MC:0 and MC:1 in the univariate analysis were entered into a logistic regression model to investigate the independent contribution of clinical symptoms and cognitive scores to the presence of memory complaints. Ninety five per cent confidence intervals were calculated for the means, difference between means and odds ratios (CI_{OR}).

In order to find the meaningful model with the best fit, different factor selection and coding methods were used. Two methods were used to select factors in the logistic regression analysis. The first method included all factors in the model (full model) regardless of whether these factors had a significant influence on the assignment to MC:0 or MC:1. The second method involved systematically screening those factors that exerted a significant influence on the assignment to MC:0 or MC:1. In this case, the Wald method was used for a forward stepwise factor selection.

In order to derive odds ratios (OR) for all factors, recoding of continuous variables into dichotomous variables was attempted. Medians of each continuous variable were utilised as a dividing point to categorise all values

for each continuous variable into two categories - those lower than the median (new value = 0) and those higher or equal to the median (new value = 1). Then these newly created variables were entered into the analysis along with other discrete variables.

4.11 Results

A total of 108 subjects with complaints of memory difficulties were enrolled in the study. Eleven participants were excluded because their MMSE score was less than 24 (N=7) or because they had prior history of stroke (N=4). Two subjects reported a history of stroke, however, brain imaging failed to confirm this and there was no clinical evidence for stroke. Therefore, they were included in the study. Another 17 subjects were excluded because they did not have cranial CT scans performed.

One hundred and twenty two subjects were included in this analysis. This group consisted of 80 memory complainers and 42 controls. These subjects all had both the CAMCOG administered and cranial CT scans performed. The groups were well matched for age (mean \pm SD, controls = 61.7 \pm 11.0 years and complainers = 62.4 \pm 10.3 years, $t=0.33$, $p=0.739$). There were more females in the complainer (MC:1) than in the control group (MC:0), but this was not statistically significant (47.5% vs 62.5%, $\chi^2=2.50$, $p=0.114$). The CAMDEX questionnaire does not record number of years of education, rather, age at leaving school and years of education after leaving school. The number of years of education was therefore calculated by subtracting six from the age at school leaving (CAMDEX 16) and adding the number of years of education after leaving school (CAMDEX 17). The age of starting school in Australia for this cohort was assumed to be six years. There was no difference between the

groups in relation to the number of years of education (mean \pm SD, MC:0 = 12.6 ± 3.9 years and MC:1 = 11.5 ± 3.5 years, p 0.078)(Table 4.3).

4.11.1 Cerebrovascular Function

The MC:1 group had a significantly greater proportion of positive responses (MC:0 = 11.9%; MC:1 = 28.8%, p 0.036).

4.11.2 Sleep

The MC:1 group had a significantly greater proportion of positive responses (MC:0 = 19.0%; MC:1 = 53.8%, p 0.000).

4.11.3 Depressed Mood and Anxiety

Table 4.3 shows the results for the two groups for these variables.

Table 4.3

Demographic and Clinical characteristics of controls (MC:0) and memory complainers (MC:1) according to Section A of the CAMDEX

Variable	MC:0 n = 42	MC:1 n = 80	Statistic	P
Age mean (SD)	61.7 (11.0)	62.4 (10.3)	T -0.33	0.739
Female (%)	47.6	62.5	χ^2 2.49	0.114
Marital status (%)	92.9	72.5	χ^2 7.01	0.008
Yrs Education mean (SD)	12.6 (3.9)	11.5 (3.5)	Z -1.77	0.078
Age left school mean(SD)	15.7 (1.3)	15.7 (1.6)	T -0.07	0.821
TIA (%)	4.8	11.3	χ^2 1.41	0.235
Cerebrovascular function (%)	11.9	28.8	χ^2 4.40	0.036
Sleep function (%)	19.0	53.8	χ^2 13.60	0.000
Anxiety (%)	23.9	76.1	χ^2 8.27	0.004
Use money (%)	0	8.8	χ^2 3.90	0.048
Household tasks (%)	0	2.5	χ^2 1.07	0.302
Bladder (%)	0	22.5	χ^2 11.09	0.001
Depression A (%)	0	5.0	χ^2 2.17	0.141
Depression B (%)	0	10.1	χ^2 4.55	0.033
Major depression (%)	0	2.5	χ^2 1.08	0.298

MC:0 = controls; MC:1 = memory complainers; Numbers with brackets are means with SD; Z = statistic for non-parametric Mann-Whitney test; χ^2 = chi square test statistic; T = *t* test statistic.

Table 4.4

Clinical characteristics of controls (MC:0) and memory complainers (MC:1)
according to Section A of the CAMDEX

Variable	MC:0 N = 42	MC:1 N = 80	Statistic	P
Lose items (%)	16.7	86.3	χ^2 56.77	0.000
Forget names (%)	2.4	50	χ^2 27.99	0.000
Lost (%)	0	5	χ^2 2.17	0.141
Talk about past (%)	9.5	32.5	χ^2 7.84	0.005
Word finding (%)	35.7	77.5	χ^2 20.66	0.000
Hypertension (%)	16.7	21.3	χ^2 0.37	0.545
Smoker %	33.3	30	χ^2 0.14	0.706
Heavy drinker %	9.5	21.3	χ^2 2.66	0.103
Nervous person %	9.5	32.5	χ^2 7.84	0.005
Emotional illness (%)	2.4	19.0	χ^2 6.59	0.010
Family History Poor Memory (%)	43.9	57.5	χ^2 2.01	0.156

MC:0 = controls; MC:1 = memory complainers; Numbers with brackets are means with SD; χ^2 = chi square test statistic.

The responses to the CAMDEX items related to low mood and anxiety were almost all significantly more positive in the MC:1 group than in the MC:0 group (Table 4.3). The only item that was not significantly different between these two groups was CDX 48 "have you felt more irritable lately (eg intolerant of noise)". The MC:1 group was also more likely to consider themselves to be a 'nervous person' - CDX 84 (Table 4.4).

4.11.4 Memory symptoms

As already noted, the two groups were distinguished by their response to CDX 58 "do you have any difficulty with your memory?" Hence, the MC:0 group responded in the negative to this question and the MC:1 group

responded positively. As expected, the MC:1 group had a greater positive response to (Table 4.4):

- CDX 59 “do you forget where you have left things more than you used to?”
- CDX 60 “do you forget the names of close friends or relatives?”
- CDX 65 “do you tend to think and talk about the past more than recent events?”
- CDX 66 “when speaking do you have difficulty finding the word you want or do you sometimes say the wrong word?”

The duration of the complaint of memory loss in the MC:1 group varied from six months to greater than 120 months. The mean duration of memory symptoms was 35.3 months (SD 3.6). Of the 80 memory complainers, 74 stated that the problem had started gradually as opposed to suddenly. Only two of the memory complainers felt that the problem had improved since it commenced, while 48 felt that the problem had not worsened and 30 felt that their memory had worsened.

There were no significant differences in smoking or alcohol consumption between the two groups (Table 4.4).

4.11.5 CAMCOG Scores

At baseline, the total CAMCOG score was not normally distributed in either group. Hence, a non-parametric analysis was performed (Table 4.5). The MC:1 group performed less well than the MC:0 group on the total CAMCOG score and all sub-scale scores except the praxis sub-scale.

The CAMCOG scores were adjusted by deleting CDX 167 - 'draw a large clock face and put all the numbers in...now set the hands to 10 past 11'. Review of the source CAMCOG documents showed that the psychometrician had systematically administered this item incorrectly. Therefore, the CAMCOG total score was adjusted to a maximum of 104 rather than 107.

Table 4.5

CAMCOG and CAMCOG Subscales in controls (MC:0) and memory complainers (MC:1)

Variable	MC:0 N = 42 Mean (SD)	MC:1 N = 80 Mean (SD)	Statistic	P
Baseline CAMCOG Total N = 122	98.3 (2.8)	94.2 (5.5)	Z -4.46	0.000
Orientation subscale	10.0	9.8	Z -2.55	0.011
Language subscale	29.0 (1.2)	28.3 (1.5)	Z -2.55	0.011
Memory subscale	23.5 (2.0)	21.6 (2.7)	Z - 3.60	0.000
New learning subscale	14.0 (1.7)	12.4 (2.3)	Z - 3.43	0.001
Attention subscale	6.9 (0.3)	6.5 (0.9)	Z -2.30	0.022
Praxis subscale	8.9 (0.3)	8.9 (0.4)	Z - 0.75	0.452
Abstraction subscale	7.5 (0.9)	6.9 (1.6)	Z - 2.31	0.021

MC:0 = controls; MC:1 = memory complainers; Numbers with brackets are means with SD; Z = statistic for non-parametric Mann-Whitney test;

4.11.6 Neuropsychological Test Scores

Ninety four subjects attended for neuropsychological testing, MC:0, n=25 and MC:1, n=69.

4.11.6.1 Fuld Object Memory Evaluation

The Mann-Whitney non-parametric test showed that MC:0 performed better than MC:1 on this test. However, only the 'storage 1', 'retrieval 1' (the trial 1 scores for storage and retrieval are always identical) and 'repeat retrieval' scores were statistically significant (Table 4.6).

4.11.6.2 Temporal Order Discrimination

This test did not discriminate between the groups, except for the total 'hit' score on the word component of the test, where MC:0 scored significantly better (Table 4.6).

Table 4.6

Fuld/Temporal Order Discrimination in controls (MC:0) and memory complainers (MC:1)

Variable	MC:0 n = 25 Mean (SD)	MC:1 n = 69 Mean (SD)	Statistic	P
Fuld Storage 1	8.0 (1.4)	7.3 (1.5)	Z - 1.99	0.047
Fuld Storage 2	9.5 (0.8)	9.0 (1.6)	Z - 1.58	0.114
Fuld Retrieval 1	8.0 (1.4)	7.3 (1.5)	Z - 1.99	0.047
Fuld Retrieval 2	8.6 (1.2)	8.0 (1.7)	Z - 1.46	0.144
Fuld Repeat Retrieval	7.1 (1.7)	6.2 (2.1)	Z - 1.96	0.05
Fuld Ineffective reminders	0.5 (0.8)	0.8 (1.1)	Z - 1.45	0.149
Fuld Number named	23.6 (4.4)	22.4 (5.6)	Z - 1.25	0.211
Temporal Order Pictures - Hits	14.4 (1.4)	13.9 (2.3)	Z - 0.74	0.457
Temporal Order Pictures - Correct rejection	11.3 (2.8)	12.0 (2.6)	Z - 1.08	0.281
Temporal Order Pictures - % order correct	76.7 (13.0)	77.3 (12.3)	Z - 0.28	0.781
Temporal Order Words - Hits	15.1 (1.3)	13.4 (3.0)	Z - 3.44	0.001
Temporal Order Words - Correct rejection	13.0 (3.2)	14.1 (2.3)	Z - 0.35	0.082
Temporal Order Words - % order correct	76.6 (13.5)	72.7 (22.2)	Z - 0.35	0.725

MC:0 = controls; MC:1 = memory complainers; Numbers with brackets are means with SD; Z = statistic for non-parametric Mann-Whitney test;

4.11.6.3 Wechsler Memory Scale (WMS-R)

The parts of the WMS used in testing did not discriminate between the groups (Table 4.7). MC:0 had higher scores on all sub-tests but none of these were significantly better.

Table 4.7

Wechsler Memory Scale of controls (MC:0) and memory complainers (MC:1)

Variable	MC:0 n = 25 Mean (SD)	MC:1 n = 69 Mean (SD)	Statistic	P
Logical Memory 1	24.2 (6.5)	21.6 (7.8)	Z - 1.24	0.214
Centile	58.7 (26.8)	49.7 (30.2)	Z - 1.34	0.180
Logical Memory 2	18.6 (8.3)	16.3 (8.1)	Z - 1.14	0.256
Centile	55.0 (29.1)	48.0 (28.1)	Z -1.09	0.275
Verbal Paired Associates Total	16.8 (3.3)	16.5 (4.3)	Z - 0.08	0.938
Verbal Memory index	102.2 (13.9)	96.3 (20.0)	Z - 1.17	0.242
Digit span forward centile	65.8 (30.7)	62.7 (28.5)	Z - 0.55	0.580
Digit span backwards centile	59.3 (33.4)	56.6 (27.7)	Z - 0.70	0.485
Digit span total	15.4 (4.0)	15.0 (3.5)	Z - 0.71	0.479

MC:0 = controls; MC:1 = memory complainers; Numbers with brackets are means with SD; Z = statistic for non-parametric Mann-Whitney test;

4.11.6.4 Cued Recall

There were no differences in performance between the MC:0 and MC:1 groups identified using this test (Table 4.8).

4.11.6.5 Fluency tests

MC:1 subjects performed marginally better on the tests of phonemic and semantic fluency but again no significant differences were found between the two groups (Table 4.8).

4.11.6.6 Trails

MC:0 completed the trails tests more quickly than MC:1 but these differences were not statistically significant (Table 4.8).

Table 4.8

Cued Recall/Fluency test/ Trails in controls (MC:0) and memory complainers (MC:1)

Variable	MC:0 n = 25 Mean (SD)	MC:1 n = 69 Mean (SD)	Statistic	P
Cued recall retrieval	30.1 (2.9)	28.2 (5.9)	Z -0.69	0.492
Cued recall acquisition	36	35.5	NA	NA
Cued recall retention	12	12	NA	NA
Cued recall - delayed free recall	10.9 (1.0)	10.0 (2.8)	Z - 0.56	0.577
Fluency - F	11.5 (4.2)	12.4 (4.2)	Z - 0.84	0.402
Fluency - A	10.6 (4.3)	11.4 (5.3)	Z - 0.45	0.656
Fluency - S	14.8 (5.0)	15.0 (5.1)	Z - 0.23	0.822
Fluency - Supermarket items	26.0 (6.5)	23.5 (6.1)	Z - 1.67	0.095
Trails A	36.0 (13.1)	42.0 (35.5)	Z - 0.77	0.443
Trails B	89.8 (35.4)	111.7 (86.9)	Z - 1.08	0.281

MC:0 = controls; MC:1 = memory complainers; Numbers with brackets are means with SD; Z = statistic for non-parametric Mann-Whitney test;

4.11.7 Brain measurements

The inter-rater correlation of the brain CT measurements was found to be excellent, except for that of the medial temporal lobes (table 4.9).

None of the brain measurements could discriminate MC:0 from MC:1 (Table 4.10). The measurements were not normally distributed, so transformation to natural logs was performed. However, these analyses failed to show any difference between the groups, except for the left medial temporal lobe width that approached significance ($p = 0.054$).

Table 4.9Reliability between raters of CT measurements

Measurement	Test	Value	P
Medial Temporal R	Spearman's	0.58	0.002
Medial Temporal L	Spearman's	0.46	0.015
Temporal Horn R	Spearman	1.00	0.000
Temporal Horn L	Spearman	0.97	0.000
Medial Atrophy R	Spearman	0.60	0.001
Medial Atrophy L	Spearman	0.62	0.001
3 rd Ventricle	Spearman's	0.90	0.000
Brain width	Spearman's	0.93	0.000
Bicaudate diameter	Spearman's	0.99	0.000
Frontal horn R	Spearman's	0.95	0.000
Frontal horn L	Spearman's	0.94	0.000
Linear measure	Spearman's	0.99	0.000

Table 4.10

Brain measurements of controls (MC:0) and memory complainers (MC:1)

Variable Mean (SD)	MC:0 n=42 Mean (SD)	MC:1 n=80 Mean (SD)	Statistic	P
Medial Temporal lobe width R	18.3 (2.4)	19.0 (2.7)	Z - 1.24	0.215
Medial Temporal lobe width L	17.8 (2.9)	18.1 (2.7)	Z - 1.72	0.085
Temporal fissure R	1. 38 2. 2 3. 2	1. 73 2. 6 3. 1	χ^2 1.70	0.428
Temporal fissure L	1. 40 2. 2 3. 0	1. 72 2. 8 3. 0	χ^2 0.94	0.333
Third Ventricle	3.86 (1.8)	3.64 (2.3)	Z - 1.02	0.309
Cranial Diameter	127.8 (5.1)	127.6 (4.9)	Z - 0.25	0.802
Sylvian fissure R	0. 14 1. 19 2. 9	0. 18 1. 46 2. 16	χ^2 2.04	0.361
Sylvian fissure L	0. 13 1. 21 2. 8	0. 18 1. 47 2. 15	χ^2 0.38	0.826
Bicaudate distance	13.5 (3.3)	13.0 (3.1)	Z - 0.66	0.512
Lateral ventricle R	3.0 (2.3)	3.4 (2.2)	Z - 1.38	0.167
Lateral ventricle L	4.3 (2.3)	4.4 (2.1)	Z - 0.48	0.635
Ratio	0.193 (0.06)	0.191 (0.06)	Z - 0.14	0.893

MC:0 = controls; MC:1 = memory complainers; Numbers with brackets are means with SD; Z = statistic for non-parametric Mann-Whitney test; χ^2 = chi square test statistic.

4.11.8 Homocysteine and APOE

No differences were found between MC:0 and MC:1 in plasma homocysteine levels or APOE allele distribution. The mean homocysteine level in MC:0 (n=36) was 12.9 ± 5.0 $\mu\text{g/l}$, in MC:1 (n=72) mean 12.0 ± 4.9 , (Z 0.88, p=0.378). The APOE allele frequencies were analysed as a proportion of all alleles in the two groups. In MC:0 (n=15) the ϵ_2 , ϵ_3 , ϵ_4 allele frequencies were 6.3%, 73.4% and 20.3% respectively, while in MC:1 (n=48) they were 6.6%, 69.1% and 24.3% (ϵ_2 - χ^2 0.01, p = 0.926; ϵ_3 - χ^2 0.59, p = 0.744; ϵ_4 - χ^2 0.76, p = 0.683).

4.11.9 Logistic Regression

Logistic regression was carried out as a post hoc and exploratory analysis, i.e. it was not hypothesis driven. The outcome variable was group membership i.e. MC:0 or MC:1. Table 4.11 shows each step of the logistic regression using the Wald stepwise forward selection method. In step 1, CDX66 (word finding) was identified as a significant variable. In step 2, TOWH (temporal order words hits) was also found to be significant variable along with CDX66. In step 3, CCNL (CAMCOG new learning subscale) was identified as a significant variable and valid OR and its 95% CI were calculated. Although in step 4 CDX56 (bladder control) was also selected into the model, no valid OR and its 95% CI were produced by the program. Therefore, only the results as far as step 3 should be used as the final results for the regression model.

The results from step 3 demonstrated that the value of 1 for CDX66 (word finding) was significantly associated with the presence of memory complaint. Participants with a value of 1 for CDX66 had a 7.5 times greater risk of experiencing memory complaint compared with those with a value of 0.

Contrarily, patients with a value of 0 for both CCNL (CAMCOG new learning subscale) and TOWH (Temporal Order Words Hits) were 3.5 ($=1/0.284$) and 5.5 ($=1/0.183$) times more likely respectively, to have a memory complaint, compared with those with a value of 1 for these variables.

Full models, including all variables or using the Wald stepwise selection method, could not be established due to non-convergence of the logistic regression regardless of whether or not the continuous variables were recoded into dichotomous variables.

The results from Wald forward stepwise selection using the original values of continuous variables were similar to those in Table 4.11, and therefore were not presented separately.

Table 4.11Logistic regression

Step	Variable	B	SE	Wald	P	OR	95.0% C.I.for OR	
							Lower	Upper
Step 1(a)	Word finding(1)	1.83	0.42	18.98	0.000	6.20	2.73	14.09
	Constant	-0.41	0.30	1.78	0.183	0.67		
Step 2(b)	Word finding(1)	1.91	0.46	17.07	0.000	6.77	2.73	16.76
	Temporal Order Word Hits(1)	-1.74	0.46	14.18	0.000	0.18	0.07	0.43
	Constant	0.41	0.38	1.12	0.289	1.50		
Step 3©	Word finding(1)	2.02	0.49	17.14	0.000	7.53	2.90	19.58
	Camcog New Learning(1)	-1.26	0.48	7.00	0.01	0.28	0.11	0.72
	Temporal Order Word Hits(1)	-1.70	0.48	12.59	0.000	0.18	0.07	0.47
	Constant	0.91	0.45	4.18	0.04	2.49		
Step 4(d)	Bladder control(1)	20.40	8720.91	0.00	0.998	726189756.40	0.00	.
	Word finding(1)	1.83	0.50	13.32	0.000	6.23	2.33	16.64
	Camcog New Learning(1)	-1.42	0.50	8.01	0.010	0.24	0.09	0.65
	Temporal Order Word Hits (1)	-1.62	0.50	10.40	0.001	0.20	0.07	0.53
	Constant	0.79	0.49	2.55	0.11	2.20		
A	Variable(s) entered on step 1: Word finding.							
B	Variable(s) entered on step 2: Temporal Order Word Hits.							
C	Variable(s) entered on step 3: Camcog New Learning.							
D	Variable(s) entered on step 4: Bladder control.							
Stepwise procedure stopped because removing the least significant variable result in a previously fitted model.								

B = Coefficient for the variable; SE = standard error for the coefficient; Wald =Wald statistic; OR = exponentiation of the B coefficient, which is the odds ratio. CCNL = CAMCOG new learning, TOWH = temporal order discrimination task word hits

4.12 Discussion

4.12.1 Cognitive Test Findings

In this study, the mean scores on the CAMCOG were relatively high within the normal range in both groups. This was expected, as participants were recruited on the basis of having no objective cognitive impairment. However, the MC:1 group manifested significantly worse scores on the CAMCOG than did the MC:0 group (table 4.5). This was not seen with the neuropsychological test scores. The finding of lower scores on a global test of cognition (ie the CAMCOG) amongst memory complainers has not been a consistent finding in previous studies. In section 2.2.10, a number of reports examining subjective memory complaint (SMC) were reviewed. Different methods of selecting the target population and identifying memory complainers have been used in the past. In addition, a review of the relevant literature indicates substantial variation in the extent and types of cognitive testing done. Comparisons are therefore difficult.

Amongst previous cross-sectional studies, O'Connor et al used the MMSE to define the population and found that a complaint of poor memory correlated poorly with MMSE scores (O'Connor *et al* 1990). Those with a MMSE score of 26 or greater were excluded from this study and only one-third of those with a MMSE score of 24 or 25 were included. From this community sample, normal participants were identified. The mean MMSE score in the 'normal'

group was 21.5. It could be argued that this score is in the impaired range. Hence, it is inappropriate to compare these 'normal' subjects to the MC:0 or MC:1 groups in this study.

Hanninen and co-workers also found no association between SMC and a global test of cognition, in this case the MMSE (Hanninen *et al* 1994). A similar lack of association was found for the neuropsychological tests that were also performed. A self-rated memory questionnaire was used to create a score that categorised subjects as complainers or non-complainers. Those with 'normal cognition' as defined by a MMSE score over 24 were included in the study. An association was found between memory complaint and high scores on the Minnesota Multiphasic Personality Inventory.

Some reports of cross-sectional data that have used global tests of cognition do show a correlation with SMC. Grut *et al* identified memory complainers in a similar fashion to the current study (Grut *et al* 1993). Participants were asked to rate themselves as experiencing 'no memory complaint', 'occasional complaint', or 'marked complaint'. The sample of 436 was population based and included 157 demented subjects. The group was aged over 75 years. Non-demented memory complainers had lower scores on the MMSE than non-complainers. In accord with the current data and other reports, low mood was also positively associated with memory complaint.

Bassett and Folstein used the three-object recall item in the MMSE to assess memory performance (Bassett *et al* 1993). Memory complainers were twice as likely to have poor performance on this item as non-complainers. Poor performance was designated as a score of 0 or 1 out of 3 on the object recall component of the MMSE. Again, this result is difficult to compare to other studies as the memory outcome is relatively crude – as acknowledged by the authors.

The AMSTEL study also used the CAMDEX to identify memory complainers (Jonker *et al* 1996, Schmand *et al* 1996). A population sample was used, unlike in this current study. Baseline MMSE and CAMCOG scores were found to be lower for those who later developed dementia. Three-year follow up data showed that objective memory performance was a better predictor of dementia risk than subjective memory complaint.

In a separate cross-sectional study of the same population, those characterised by memory complaint, normal cognition and normal mood performed less well on the CAMCOG than did non-complainers with normal cognition and normal mood (Jonker *et al* 1996). Geerlings and colleagues reported longitudinal follow-up on this population (Geerlings *et al* 1999). At baseline there was no difference in MMSE scores between complainers and non-complainers. Over the 3.2 years of follow-up however, the complainers had nearly a three times greater risk of developing AD (OR 2.78, CI 1.49-5.18). The

authors commented that this was a striking result in view of the use of such a general question that did not refer specifically to a memory related problem. In addition, they commented that these subjects lived at home and had likely not sought attention for their memory complaint. Further, they commented that “it is possible that these people correctly perceived deterioration in their memory or cognitive functioning that could not yet be validated by objective test performance”. One qualification made was that the failure to detect an association between incident dementia and baseline impaired cognition may have been due to the high drop out rate in this group.

The Manitoba Health and Ageing study reported similar findings to Geerlings (St John *et al* 2002). The 3MS (a global cognitive test) was used. Baseline scores were lower in the SMC group. The risk of incident dementia in the three baseline tertiles of the 3MS over the five years of follow-up was greater in the SMC group based on regression models. The author’s opinion is that those with SMC are “experiencing early pre-clinical cognitive loss which is also apparent as a lower 3MS score”. They argue that SMC is a valid complaint and that those with SMC need to be followed over time despite the low rate of progression to dementia.

Some studies have employed tests of episodic memory (see section 4.6.1) in their neuro-psychological test battery exclusively, rather than global tests of cognition. Bolla and colleagues used a metamemory questionnaire that

consisted of nine questions related to self-perception of performance and rated according to a five point Likert scale (Bolla *et al* 1991). All of the participants were recruited from newspaper advertisements. In keeping with the results in section 4.10.6, there was no clear correlation between SMC and neuropsychological test scores.

An Austrian study reported on a group of 75-year-old subjects from the community and used performance on the Fuld Object Memory Evaluation as the determinant of poor memory. No association with SMC was found (Jungwirth *et al* 2004). This is similar to the findings with this test reported in section 4.10.6.1, although the Austrian study reported the total recall score only as opposed to the component scores mentioned in 4.10.6.1. The PAQUID study however did find a cross-sectional association between SMC and neuropsychological test scores (Gagnon *et al* 1994).

In New York a cohort that was identified as being at risk through attendance at health care facilities was studied (Schofield *et al* 1997). The cross-sectional analysis showed no association between SMC and impaired cognition. Global tests of cognition were not used and there was no difference between complainers and non-complainers on the neuropsychological tests at baseline. At variance with the findings of Geerlings, this study found that SMC combined with cognitive impairment predicted further cognitive decline and incident dementia. However, the cohort acquisition was quite different, as

was the method of assignment of the diagnosis of dementia and duration of follow-up period. It is therefore questionable if valid comparison of these two studies can be made.

More recently another group from New York have reported on seven year outcomes of a cohort with Global Dementia Stage (GDS) stage 2 ie subjective memory complaint without evidence of cognitive decline (Prichep *et al* 2006) (see chapter 2.2.2). Of 44 subjects at GDS stage 2 at baseline, 27 (61.4%) had deteriorated to stages 3, 4 or 5 at year seven post-baseline. The focus of the paper was to discuss the utility of using abnormal quantitative EEG as a marker of mild underlying brain disease, so no comparative data were provided about progress of those in stage 1. Previous longitudinal reports have shown that GDS stage 2 cases do not deteriorate (Flicker, C *et al* 1993), however the follow-up period was significantly longer in the study by Prichep and colleagues (7 vs 3.4 years).

How representative of the normal population is the self-selected group in this current study? Williams *et al* have identified normative values for the CAMCOG from the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS)(Williams *et al* 2003). The results were based on a population-based sample of 13,009 subjects over the age of 65 years. The original version of the CAMCOG was used, as was the case in this study. Three items were deleted from the standard interview to accommodate the

circumstances of the study. Hence, the maximum score was 103. In our study the maximum score was 104 due to the removal of the clock drawing item. Therefore comparison of scores between the two samples cannot be made accurately. However, a comparison can indicate, with some limitations, as to how representative of the 'normal' population the subjective memory loss group in this current study is.

Williams et al defined their normal sample as comprising anyone without dementia. A score on the AGE-CAT of 03 or greater (Copeland *et al* 1986) defined dementia. The median score on the CAMCOG for the non-demented group was 89. In the current study the median score for the whole sample was 97. The difference can be accounted for partly by the exclusion in the current study of any subject with objective evidence of a cognitive deficit, ie mild cognitive impairment. By comparison, the 'normal' population described in Williams et al would have almost certainly included subjects with mild cognitive impairment, because only those with established dementia were excluded. Hence, this is likely to explain the lower scores in the MRC CFAS study.

The only neuropsychological test that showed a significant difference between the two groups in the current study was the Fuld Object Memory Evaluation (FOME). Again, there are few studies that are comparable. The study by Jungwirth examined a similar population, but reported the total recall score

on the FOME and not the subscales as reported here and identified in the Masur study (Jungwirth *et al* 2004). The FOME has been shown to be a robust test of episodic memory that is not influenced by educational or ethnic status (La Rue *et al* 1999, Marcopulos *et al* 1999). The FOME has been shown to have very good utility in differentiating dementia amongst a group of African-Americans (Mast *et al* 2001).

There are a number of possible reasons why the neuropsychological tests administered in this study did not reveal differences between the controls and memory complainers in the presence of a clear difference in the total CAMCOG score. Individual components of neuropsychological tests may manifest ceiling effects in this population, precluding discrimination of subtle differences in brain function. Perhaps the tests employed in this study were insufficiently sensitive to detect a difference. Given the quality of the clinical psychology input to the study it is unlikely that maladministration of the neuropsychological tests was a factor. Why a global test would provide discrimination between the groups is not clear. Alternatively, the difference in the CAMCOG score may be spurious and in fact there may be no disparity in brain function between the two groups.

4.12.2 Clinical Features

O'Connor found that depression was more closely linked to SMC, as do others (Christensen 1991, Jorm *et al* 1994, Jorm *et al* 1997, O'Hara *et al* 1986).

The data in this current study also confirm strong correlations between depressive symptoms and SMC. The findings in this study are therefore not unexpected. Jorm however did not compare memory complainers and controls (Jorm *et al* 1994). Rather, they compared memory complainers and their informants. In a follow-up study they showed that memory complaint did not predict cognitive loss or incident dementia over a three year period (Jorm *et al* 1997).

In addition to reduced cognitive scores, the memory complainers in our study were more likely to complain of word-finding difficulty. This finding was not supported by the rapid retrieval task – a test of verbal fluency (Table 4.6). There was no difference between the two groups on these tests.

Those in MC:1 were more likely to be single. A positive family history of a memory disorder was more frequent amongst memory complainers but not significantly so. It may be that demographic and clinical characteristics of this group are not sufficiently representative of the population.

4.12.3 CT findings

The use of CT for brain imaging in the current study was clearly inadequate with respect to delineation of differences in brain morphology between the two groups. The linear method of measuring key structures has been shown to distinguish established Alzheimer's disease from normal (George *et al*

1990). The lack of resolution with CT in the current study suggests that this technique is unlikely to show differences between normal subjects and those with, at most, very early cerebral degeneration.

The failure of the CT measurements to differentiate the two groups in the current study is not surprising given the technique's relatively modest positive likelihood ratios for diagnosing established AD (Diaz-Guzman *et al* 2002). Magnetic resonance imaging is considered a better technique for examining the medial temporal lobe and the basal forebrain structures (Leys *et al* 2002).

It is also possible that there are no real differences in medial temporal morphology between cognitively intact people who complain and do not complain of memory loss.

4.12.4 Genetic/Biochemical Features

The frequency of APOE ϵ 4 genotype did not explain the presence of memory complaints in our sample. The frequency of the APOE ϵ 4 allele in the two groups (20.31% and 24.34%) is greater than that observed in other non-demented Caucasian populations. In an early study the frequency was 15% (Zannis *et al* 1993). A meta-analysis of 40 studies that included all racial groups (n=14,537) showed that in Caucasian populations the APOE ϵ 4 frequency was 13.7% in control subjects and 36.7% in AD case subjects (Farrer

et al 1997). The frequencies in the MC:0 and MC:1 groups in the current study are therefore not typical of either normal subjects or cases according to the meta-analysis. The small sample size in the control group likely accounts for the discrepancy. Selection bias may also account for this finding, i.e. volunteers with a strong family history of memory problems were recruited.

Similarly, homocysteine levels did not distinguish between the MC:0 and MC:1 groups in the current study. Based on a previous population based study, the homocysteine levels in the two groups are 'normal' (Seshadri *et al* 2002). Homocysteine has been evaluated as a risk factor for early stage brain disease (Lehmann *et al* 1999). This Swedish study was clinic based and included a group with normal cognition but also with subjective memory complaint. This group's mean homocysteine level was used as the reference point for the cognitively impaired groups. All other groups had higher levels than the reference group. Unfortunately no control group was included, so no direct comparison is possible with the current study. If homocysteine is a true risk factor for AD, it may be that the metabolic changes are not reflected in changes in plasma levels at the early stage of brain disease represented in the memory complaint group in this study.

4.12.5 Conclusions

There are limitations in the methodology employed in this study. The means of acquiring the participant samples may have been inappropriate.

Specifically, a self-selected, heterogeneous, convenience sample might not have been representative of the general elderly population. In addition, the number of control subjects was small. The use of 14 spouses of subjects as controls means that the samples may not have been entirely independent. The high frequency of APOE ϵ 4 genotype amongst the control subjects suggests biased acquisition. Another potential problem is that the ascertainment of memory complaint was based on the answer to a simple single question. The sample as defined may not, therefore, have been 'at risk'. However, this was a recruitment technique used by many other investigators. In addition, the young age of this cohort suggests that the number of incident dementia cases is likely to be small during the follow up period.

Despite the considerations above, these data add to the accumulating evidence that a subjective complaint of memory loss should not be dismissed (Geerlings *et al* 1999, Schofield *et al* 1997, St John *et al* 2002), (Prichep *et al* 2006). The findings confirm that those with memory complaints have lower scores on global tests of cognition. There is also histopathological data that shows greater numbers of plaques and tangles in those with subjective memory complaint (Barnes *et al* 2006).

Furthermore, longitudinal data suggests that age related decline in memory function is less than previously reported from cross-sectional studies (Unger *et al* 1999). These finding supports the notion that even subtle deterioration in

cognition needs to be considered as clinically relevant and worthy of follow-up and hence gives impetus to identifying the symptomatic manifestations of such deterioration.

Chapter 5

Study 2

LONGITUDINAL COGNITIVE CHARACTERISTICS OF INDIVIDUALS WITH SUBJECTIVE MEMORY LOSS:

5.1 Introduction

The work of Morris and colleagues (Morris, JC *et al* 2001) suggests that those with uncertain dementia have a higher risk of deterioration to dementia over five years of follow up compared to control subjects. This group included those considered to be 'worried well', which equates to the group being examined in the current study. Similarly, the work of Schmand (Schmand *et al* 1996) and Geerlings (Geerlings *et al* 1999) supports the view that subjective memory complaint may be a risk factor for cognitive decline as described in chapter 2. Therefore, it is expected, that in our group, deterioration in cognition over time should be demonstrated.

5.2 Objectives

This study aimed to test the following hypothesis:

In comparison with healthy controls with no complaint of memory loss, individuals with subjective memory impairment show-

- Greater deterioration over time in cognitive performance on the CAMCOG.

A secondary outcome of interest of this study was to examine differences in the at baseline in the MC:0 and MC:1 groups after matching for age and sex on:

- Clinical characteristics
- Cognition
- Brain measures
- Laboratory parameters

5.3 Sample Acquisition and Methodology

The recruitment of subjects was described in chapter 4. The same research nurse attempted to repeat the CAMCOG on the anniversary of the baseline CAMCOG. However, this was not always possible. As a result, variation in the length of follow-up occurred. To allow for this, to deal with missing data and to facilitate a better baseline comparison of the two groups, a matching procedure was undertaken.

5.3.1 Matching process

Eighty patients (MC:1) with subjective memory complaint (SMC) were matched with forty-two controls (MC:0) using the following three variables:

- **Sex:** MC:1 and MC:0 had the same sex;
- **Age** in years: A gradual matching algorithm described below was utilised to match ages between MC:1 and MC:0.

- **Follow-up duration** in days: A gradual matching algorithm was utilised, together with age to match follow-up duration periods between MC:1 and MC:0. Follow-up duration was defined as the time lapsed between the 1st and subsequent cognitive examinations in days. For example, the follow-up duration between the 1st and 2nd examinations was recorded in the variable daysd1d2. The follow-up duration between the 1st and 3rd examinations and between the 1st and 4th examinations was determined accordingly using the existing variables daysd2d3 and daysd3d4.

A gradual matching algorithm was utilised to find suitable candidate(s) for the control group. As there were more cases than controls, it was possible that more than one case were suitable matches for a control based on the specified matching criteria. Only one candidate case was chosen as a final match for each control. The processes were as follows:

In the first round, patients in MC:1 were matched with patients in MC:0 with the same sex, an age difference less than or equal to (+/-) 5 years and a difference in follow-up duration between the 1st and 2nd examinations less than 60 days, resulting in 27 pairs. If there was more than one candidate case per control, the candidate case with the least difference in follow-up duration between the 1st and 2nd examinations was chosen as the final match for the case. Matched pairs were then put aside as final pairs whilst unmatched cases and controls remained in a pool for further matching.

In the second round, remaining patients in MC:1 were matched with remaining patients in MC:0 with the same sex, an age difference +/- 10 years and a difference in follow-up duration between the 1st and 2nd examinations less than 120 days, resulting in two pairs. If there was more than one candidate case for a control, the candidate case with the least difference in follow-up duration between the 1st and 2nd examinations was chosen as a final match. Matched pairs were again put aside as final pairs and unmatched cases and controls were included in the further matching process.

In the 3rd to 5th rounds, the process in the 2nd round was repeated using the following criteria:

- 3rd round – same sex, an age difference +/- 10 years and a difference in follow-up duration between the 1st and 2nd examinations less than 150 days, resulting in one pair.
- 4th round – same sex, an age difference +/- 15 years and a difference in follow-up duration between the 1st and 2nd examinations less than 150 days, resulting in one pair.
- 5th round – same sex, an age difference +/- 15 years and a difference in follow-up duration between the 1st and 2nd examinations less than 210 days, resulting in one pair.

A total of 32 pairs (32 MC:1 and 32 MC:0) were identified. No further matching rounds were attempted. It was considered that as the differences in either ages or follow-up duration became greater, the resulting matches might not be clinically meaningful.

Similar matching processes were utilised to match MC:1 and MC:0 in terms of the difference in follow-up duration between the 1st and 3rd examinations. The following two rounds of matching were carried out:

- 1st round – same sex, an age difference +/- 5 years and a difference in follow-up duration between the 1st and 3rd examinations less than 150 days, resulting in 19 pairs.
- 2nd round – same sex, an age difference +/- 10 years and a difference in follow-up duration between the 1st and 3rd examinations less than 210 days, resulting in two pairs.

A total of 21 pairs (21 MC:1 and 21 MC:0) were identified. The patients in each pair matched for the 1st and 3rd examinations might not be the same as those patient pairs in the matching between the 1st and 2nd examinations. Thus the baseline characteristics for the two groups with different follow-up periods could be different. For this reason, baseline characteristics were systematically taken into account in the analyses.

No further matching rounds were attempted, as the total number of available controls with valid follow-up duration was only 23. Hence, matching cases could not be found for the remaining two controls.

Matching was not conducted for MC:1 and MC:0 in terms of the difference in follow-up duration between the 1st and 4th examinations because there were only 8 available controls with valid follow-up duration. The number was too small for robust results to be obtained.

5.3.2 Statistical analysis

The data were analysed using the Statistical Package for the Social Sciences (SPSS 14.0 for Windows). Likelihood ratio analysis of contingency tables (Pearson's method) was used in the investigation of categorical data, the statistical result being distributed as chi-squared (χ^2). Paired McNemar non-parametric tests were used to compare before-after changes for the same subjects for categorical variables. Student's *t*-test (*t*) was applied to determine between-group differences in the means of continuous non-skewed data. For those variables with a non-normal distribution, independent or paired non-parametric Wilcoxon tests were applied depending upon whether the tests were for a before-after comparison for the same subjects.

The following statistical analyses were conducted for the data from the matching results in terms of the difference in follow-up duration between the 1st and 2nd examinations.

5.3.2.1 Basic characteristics of the two groups

Basic characteristics with respect to the three matching variables for MC:1 and MC:0 were compared using chi-square test for categorical variable (sex), t test for normally distributed variables (age) and independent non-parametric Mann-Whitney tests for variables with a skewed distribution (duration between the 1st and 2nd examinations).

5.3.2.2 Baseline comparison between the two groups

Baseline characteristics for MC:1 and MC:0 were compared using independent non-parametric Mann-Whitney tests for continuous variables as all variables to be analysed were not normally distributed, even after logarithmic and other forms of transformations. Chi-square tests were used for categorical variables.

5.3.2.3 2nd examination comparison between the two groups

CAMCOG scores at the 2nd examination for MC:1 and MC:0 were compared using the independent non-parametric Mann-Whitney test.

5.3.2.4 Change from baseline to 2nd examination for each group

Change in CAMCOG scores for MC:1 and MC:0 from the baseline to 2nd examination were compared using the paired non-parametric Wilcoxon test for continuous variables.

Similar statistical analyses including baseline characteristics were conducted for the data from the matching results in terms of the difference in follow-up duration between the 1st and 3rd exams.

5.3.2.5 Comparison of MC cases included and excluded in the 1st match

In order to clarify whether the matched sample was representative of the original inception sample, further analyses were carried out. Memory complaint cases who were matched with controls in the first match (M:1) and memory complaint cases who were NOT matched with controls in the first match (M:0) were also compared.

5.3.2.6 Logistic Regression Methodology:

Similar to the analysis reported in Chapter 4, the factors that potentially influenced whether or not participants would have memory complaints were entered into a logistic regression analysis if the variable showed a statistically significant difference between the MC:0 and MC:1 groups in the univariate analysis.

In order to find the meaningful model with the best fit, different factor selection and coding methods were tried. Two methods were used to select factors in the logistic regression analysis. The first was to include all factors in the model (full model) regardless of whether they had significant influence on the assignment to MC:0 or MC:1. The second method was to stepwisely screen those factors that posed significant influence on the assignment to MC:0 or MC:1. In this case, the Wald method was used for a forward stepwise factor selection.

In order to derive odds ratio for all factors, recoding of continuous variables into dichotomous variables was attempted. The median of each continuous variable was utilised as a dividing point to categorise all values for each continuous variable into two categories - those lower than the median (new value = 0) and those higher or equal to the median (new value = 1). Next, these newly created variables were entered into the analysis along with other discrete variables.

5.4 Results

The 32 matched pairs as described in section 5.3.1 naturally had identical sex. The pairs were well matched for age (mean \pm SD, MC:0 = 62.3 \pm 11.6 years and MC:1 = 62.4 \pm 10.7 years, $t=0.03$, $p = 0.973$). The follow up duration in days between the baseline and second examinations was also well matched (mean \pm SD, MC:0 = 406.9 \pm 74.9 days and MC:1 = 397.2 \pm 64.6 years, $Z=1.42$, $p 0.154$).

Tables 5.1 and 5.2 show the identical demographic and clinical data contained in tables 4.1 and 4.2, for the 32 matched pairs. Sleep function and bladder symptoms were significantly different between the two groups.

Table 5.1

Demographic and Clinical characteristics of matched controls and memory complainers according to Section A of the CAMDEX

Variable	MC:0	MC:1	Statistic	P
	N=32	N=32		
Marital status - married (%)	90.6	75.0	χ^2 2.74	0.098
Yrs Education (Years, Mean (SD))	12.6 (4.1)	11.5 (3.5)	Z -1.04	0.297
Age left school (Years, Mean (SD))	15.7 (1.2)	15.7 (1.6)	T 0.00	1.000
TIA (%)	6.3	9.4	χ^2 0.22	0.641
Cerebrovascular function (%)	15.6	31.3	χ^2 2.18	0.140
Sleep function (%)	21.9	50.0	χ^2 5.50	0.019
Anxiety	41.0	59.0	χ^2 3.22	0.073
Use money (%)	0.0	6.3	χ^2 2.07	0.151
Household tasks (%)	0.0	0.0	χ^2 -	-
Bladder (%)	0.0	28.1	χ^2 10.47	0.001
Depression A (%)	0.0	3.1	χ^2 1.02	0.313
Depression B (%)	0.0	9.7	χ^2 3.25	0.071
Major depression (%)	0.0	3.2	χ^2 1.05	0.306

MC:0 = controls; MC:1 = memory complainers; Z = statistic for non-parametric Mann-Whitney test; χ^2 = chi square test statistic; T = t test statistic
 - = not available.

Table 5.2

Clinical characteristics of matched controls and memory complainers
according to Section A of the CAMDEX

Variable	MC:0 N=32	MC:1 N=32	Statistic	P
Lose items (%)	18.8	93.8	χ^2 36.57	0.000
Forget names (%)	3.1	43.8	χ^2 14.72	0.000
Lost in own neighbourhood(%)	0.0	6.3	χ^2 2.07	0.151
Talk about past (%)	9.4	34.4	χ^2 5.58	0.010
Word finding (%)	37.5	62.5	χ^2 4.00	0.046
Hypertension (%)	18.8	21.9	χ^2 0.10	0.756
Smoker - > 20 cigarettes/day for > one year (%)	37.5	31.3	χ^2 0.28	0.599
Heavy drinker %	9.4	28.1	χ^2 3.69	0.055
Nervous person %	9.4	31.3	χ^2 4.73	0.030
Emotional illness (%)	3.1	12.5	χ^2 1.95	0.162
Family History Poor Memory (%)	9.7	21.9	χ^2 1.75	0.185

MC:0 = controls; MC:1 = memory complainers; χ^2 = chi square test statistic.

5.4.1 Cognitive, Neuropsychological, Brain, Genetic and Biochemical Data for the 32 matched pairs

Tables 5.3 to 5.8 show the results for the baseline CAMCOG and its subscales (Table 5.3) and the neuropsychological tests (Tables 5.4 to 5.6). Significant differences between controls and complainers were found on the total CAMCOG score and the orientation and attention sub-scales. Significant differences were also found on the Fuld, (1st storage and 1st retrieval trial) and the temporal order test (number of correct hits in both the word and picture form of the test). Otherwise there were no significant differences on any other variable.

Comparison of brain measurements showed no significant differences between the groups (Table 5.7). Similarly, there were no differences in APOE genotype or homocysteine levels (Table 5.8)

Table 5.3CAMCOG and CAMCOG Sub-scale scores of matched controls and memory complainers

Variable	MC:0 N=32	MC:1 N=32	Statistic	P
Baseline CAMCOG Total	98.1 (2.9)	95.1 (5.0)	Z -2.57	0.010
Orientation subscale	10.0 (0.2)	9.8 (0.5)	Z -2.00	0.046
Language subscale	29.1 (1.1)	28.7 (1.3)	Z -1.46	0.143
Memory subscale	23.4 (2.1)	21.9 (3.0)	Z -1.83	0.068
New learning subscale	14.0 (1.9)	12.8 (2.5)	Z -1.77	0.077
Attention subscale	6.9 (0.3)	6.5 (1.0)	Z -2.26	0.024
Praxis subscale	8.9 (0.2)	8.9 (0.2)	Z 0.00	1.000
Abstraction subscale	7.4 (0.9)	6.9 (1.2)	Z -1.63	0.104

MC:0 = controls; MC:1 = memory complainers; * = Mean (SD); Z = statistic for non-parametric Mann-Whitney test.

Table 5.4Fuld/Temporal Order Discrimination scores of matched controls and memory complainers

Variable	MC:0 N=32	MC:1 N=32	Statistic	P
Fuld Storage 1	8.0 (1.5)	7.1 (1.4)	Z -1.99	0.047
Fuld Storage 2	9.5 (0.9)	9.1 (1.1)	Z -1.58	0.114
Fuld Retrieval 1	8.0 (1.5)	7.1 (1.4)	Z -1.99	0.047
Fuld Retrieval 2	8.7 (1.2)	8.1 (1.6)	Z -1.46	0.144
Fuld Repeat Retrieval	7.2 (1.7)	6.1 (2.0)	Z -1.96	0.050
Fuld Ineffective reminders	0.6 (0.9)	0.9 (1.2)	Z -1.45	0.149
Fuld Number named	23.7 (4.3)	22.5 (5.5)	Z -1.25	0.211
Temporal Order Pictures - Hits	14.5 (1.4)	13.3 (2.4)	Z -2.21	0.027
Temporal Order Pictures - Correct rejection	11.6 (2.8)	12.1 (2.7)	Z -0.73	0.467
Temporal Order Pictures - % order correct	77.8 (13.1)	77.7 (13.1)	Z -0.11	0.917
Temporal Order Words - Hits	15.1 (1.1)	12.9 (3.2)	Z -3.78	0.000
Temporal Order Words - Correct rejection	13.0 (3.4)	14.2 (2.4)	Z -1.58	0.115
Temporal Order Words - % order correct	76.9 (14.2)	73.1 (20.1)	Z -0.66	0.511

MC:0 = controls; MC:1 = memory complainers; * = Mean (SD); Z = statistic for non-parametric Mann-Whitney test.

Table 5.5Wechsler Memory Scale scores of matched controls and memory complainers

Variable	MC:0 N=32	MC:1 N=32	Statistic	P
Logical Memory 1	24.9 (6.6)	22.5 (8.0)	Z -1.05	0.295
Centile	62.0 (26.0)	51.2 (31.7)	Z -1.16	0.246
Logical Memory 2	19.1 (8.7)	16.2 (8.6)	Z -1.17	0.242
Centile	57.2 (29.7)	46.0 (29.4)	Z -1.33	0.183
Verbal Paired Associates Total	16.9 (3.4)	15.6 (4.0)	Z -1.17	0.244
Verbal Memory index	103.7 (14.0)	94.5 (24.1)	Z -1.55	0.121
Digit span forward centile	68.1 (30.4)	61.0 (27.9)	Z -1.06	0.290
Digit span backwards centile	62.4 (30.3)	51.5 (24.3)	Z -1.75	0.081
Digit span total	15.8 (4.6)	14.6 (2.8)	Z -1.45	0.148

MC:0 = controls; MC:1 = memory complainers; * = Mean (SD); Z = statistic for non-parametric Mann-Whitney test.

Table 5.6Cued Recall/Rapid Retrieval/ Trails scores of matched controls and memory complainers

Variable	MC:0 N=32	MC:1 N=32	Statistic	P
Cued recall retrieval	30.4 (3.0)	28.5 (5.2)	Z -1.00	0.315
Cued recall acquisition	36.0 (0.0)	35.9 (0.3)	Z -1.24	0.213
Cued recall retention	12.0 (0.0)	12.0 (0.0)	Z 0.00	1.000
Cued recall - delayed free recall	11.0 (0.9)	10.3 (2.4)	Z -0.73	0.467
Fluency - F	11.7 (4.5)	12.0 (4.3)	Z -0.12	0.901
Fluency - A	10.9 (4.3)	10.7 (5.5)	Z -0.33	0.745
Fluency - S	15.1 (5.2)	14.4 (4.4)	Z -0.26	0.798
Fluency - Supermarket items	26.5 (6.5)	23.1 (6.0)	Z -1.88	0.061
Trails A	34.0 (11.1)	50.1 (52.5)	Z -1.07	0.088
Trails B	88.4 (35.4)	124.5 (120.5)	Z -1.28	0.199

MC:0 = controls; MC:1 = memory complainers; * = Mean (SD); Z = statistic for non-parametric Mann-Whitney test.

Table 5.7Brain measurements of matched controls and memory complainers

Variable	MC:0 N=32	MC:1 N=32	Statistic	P
Medial Temporal Lobe Width R	18.5 (2.5)	19.0 (2.7)	Z -0.51	0.610
Medial Temporal Lobe Width L	17.8 (3.0)	19.0 (2.6)	Z -1.62	0.105
Temporal Fissure R (% abnormal rating)	12.5	9.4	χ^2 0.16	0.689
Temporal Fissure L (% abnormal rating)	6.3	15.6	χ^2 1.34	0.247
Third Ventricle	3.9 (1.8)	4.0 (2.4)	Z -0.17	0.864
Cranial Diameter	127.5 (5.2)	128.9 (4.2)	Z -1.17	0.241
Sylvian Fissure R (% abnormal rating)	68.8	84.4	χ^2 2.18	0.140
Sylvian Fissure L (% abnormal rating)	71.9	84.4	χ^2 1.46	0.226
Bicaudate Distance	13.4 (3.6)	13.6 (3.1)	Z -0.66	0.700
Lateral Ventricle R	3.0 (2.4)	4.1 (2.7)	Z -1.63	0.104
Lateral Ventricle L	4.3 (2.4)	4.7 (2.3)	Z -0.75	0.454
Ratio	0.2 (0.1)	0.2 (0.1)	Z -0.63	0.532

MC:0 = controls; MC:1 = memory complainers; Numbers with brackets are means with SD; Z = statistic for non-parametric Mann-Whitney test; χ^2 = chi square test statistic. Temporal horn rating of 2 or 3 and Sylvian fissure rating of 1 or 2 were considered to be abnormal for the purpose of this analysis.

Table 5.8APOE ϵ 4 allele frequencies and Homocysteine of matched controls and memory complainers

Variable	MC:0 N=32	MC:1 N=32	Statistic	P
Homocysteine (μ g/l)	13.0	12.9	Z -0.14	0.885
APOE ϵ 4 (%)	19.0	26.6	χ^2 0.99	0.319

MC:0 = controls; MC:1 = memory complainers; χ^2 = chi square test statistic. Z = statistic for non-parametric Mann-Whitney test.

5.4.2 Comparison of Inception and Matched Cohorts for Cases

The matching process created a sub-group of 32 controls from the original group of 80. The 48 MC:1 cases that were excluded from this first matching process were compared to the sub-group that was matched. The results (Tables 5.9-5.16) show that overall cases that were matched with controls were representative of all cases. In almost all comparisons between cases matched and cases not matched there were no significant differences.

Table 5.9

Basic Characteristics of the Cases (MC:1) included and excluded from the First Match with Controls

Variable	Included N = 32	Excluded N = 48	Statistic	P
Sex: Female (%)	53.1	27.1	χ^2 5.56	0.018
Age in Years, Mean (SD)	62.4(10.2)	62.3(10.7)	T -0.03	0.976
Whole Follow-up Duration in Years, Mean (SD)	2.4 (0.8)	2.5 (0.9)	Z -0.54	0.590
Total Education Years, Mean (SD)	11.5(3.5)	11.4(3.5)	Z -0.24	0.812
Age in Years when Left School, Mean (SD)	15.6(1.6)	15.7(1.6)	Z -0.48	0.632
Marital status (%)	75.0	70.8	χ^2 0.17	0.683
TIA (%)	9.4	12.5	χ^2 0.19	0.665
Cerebrovascular function (%)	31.3	27.1	χ^2 0.16	0.687
Sleep function (%)	50.0	56.3	χ^2 0.30	0.583
Anxiety (%)	71.9	64.6	χ^2 0.47	0.495
Use money (%)	6.3	10.4	χ^2 0.42	0.518
Household tasks (%)	0.0	4.2	χ^2 1.37	0.242
Bladder (%)	28.1	18.8	χ^2 0.97	0.325
Depression A (%)	3.1	6.3	χ^2 0.40	0.530
Depression B (%)	9.7	10.4	χ^2 0.01	0.915
Major depression (%)	3.2	2.1	χ^2 0.10	0.752

M:1 = In the 1st match; M:0 = Not in the 1st match; * = Mean (SD); T = t test statistic; Z = Mann-Whitney non-parametric test statistic; χ^2 = chi-square test statistic;

Table 5.10

Clinical characteristics of cases (MC:1) included and excluded from the first match with controls

Variable	Included N=32	Excluded N=48	Statistic	P
Talk about past (%)	34.4	31.3	χ^2 0.09	0.770
Word finding (%)	62.5	87.5	χ^2 6.88	0.009
Hypertension (%)	21.9	20.8	χ^2 0.01	0.911
Smoker %	31.3	29.2	χ^2 0.04	0.842
Heavy drinker %	28.1	16.7	χ^2 1.51	0.220
Nervous person %	31.3	33.3	χ^2 0.04	0.845
Emotional illness (%)	12.5	25.0	χ^2 1.88	0.171
Fam Hist Poor Mem (%)	21.9	37.5	χ^2 2.18	0.140

M:1 = In the 1st match; M:0 = Not in the 1st match; χ^2 = chi square test statistic.

Table 5.11

CAMCOG and CAMCOG Subscale scores of cases (MC:1) included and excluded from the first match with controls

Variable	Included N=32	Excluded N=48	Statistic	P
Baseline CAMCOG	95.1 (5.0)	93.6 (5.8)	Z -0.90	0.370
Total				
Orientation subscale	9.8 (0.5)	9.7 (0.6)	Z -0.07	0.942
Language subscale	28.7 (1.3)	28.1 (1.5)	Z -1.68	0.092
Memory subscale	21.9 (3.0)	21.5 (2.6)	Z -1.13	0.259
New learning subscale	12.8 (2.5)	12.2 (2.2)	Z -1.38	0.168
Attention subscale	6.5 (1.0)	6.5 (0.9)	Z -0.28	0.777
Praxis subscale	8.9 (0.2)	8.8 (0.5)	Z -1.18	0.237
Abstraction subscale	6.9 (1.2)	6.8(1.8)	Z -0.30	0.765

M:1 = In the 1st match; M:0 = Not in the 1st match; * = Mean (SD); Z = statistic for non-parametric Mann-Whitney test.

Table 5.12

Fuld/Temporal Order Discrimination scores of cases (MC:1) included and excluded from the first match with controls

Variable	Included N=32	Excluded N=48	Statistic	P
Fuld Storage 1	7.1 (1.4)	7.4 (1.6)	Z -0.72	0.472
Fuld Storage 2	9.1 (1.1)	9.0 (1.8)	Z -0.34	0.732
Fuld Retrieval 1	7.1 (1.4)	7.4 (1.7)	Z -0.72	0.472
Fuld Retrieval 2	8.0 (1.6)	8.0 (1.7)	Z -0.09	0.931
Fuld Repeat Retrieval	6.1 (2.0)	6.2 (2.2)	Z -0.22	0.829
Fuld Ineffective reminders	0.9 (1.2)	0.8 (1.1)	Z -0.70	0.482
Fuld Number named	22.5 (5.5)	25.3 (5.7)	Z -0.16	0.874
Temporal Order Pictures - Hits	13.2 (2.1)	14.3 (2.1)	Z -2.41	0.016
Temporal Order Pictures - Correct rejection	12.1 (2.7)	11.9 (2.6)	Z -0.49	0.624
Temporal Order Pictures - % order correct	77.8 (13.1)	76.9 (11.9)	Z -0.12	0.903
Temporal Order Words - Hits	12.8 (3.2)	13.8 (2.8)	Z -1.58	0.114
Temporal Order Words - Correct rejection	14.2 (2.4)	14.0 (2.2)	Z -0.70	0.486
Temporal Order Words - % order correct	73.1 (20.1)	72.3 (23.8)	Z -0.19	0.847

M:1 = In the 1st match; M:0 = Not in the 1st match; * = Mean (SD); Z = statistic for non-parametric Mann-Whitney test.

Table 5.13

Wechsler Memory Scale of cases (MC:1) included and excluded from the first match with controls

Variable	Included N=32	Excluded N=48	Statistic	P
Logical Memory 1	22.5 (8.0)	21.0 (7.7)	Z -0.69	0.488
Centile	51.2 (31.7)	48.5 (29.4)	Z -0.37	0.715
Logical Memory 2	16.2 (8.6)	16.4 (7.9)	Z -0.21	0.836
Centile	46.0 (29.4)	49.5 (27.5)	Z -0.50	0.618
Verbal Paired Associates Total	15.5 (4.0)	17.1 (4.4)	Z -1.70	0.090
Verbal Memory index	94.5 (24.1)	97.6 (16.6)	Z -0.40	0.693
Digit Span Forward Centile	61.0 (27.9)	64.0 (29.2)	Z -0.57	0.571
Digit Span Backwards Centile	51.5 (24.3)	60.4 (30.0)	Z -1.49	0.137
Digit Span Total	14.6 (2.8)	15.3 (4.0)	Z -0.71	0.479

M:1 = In the 1st match; M:0 = Not in the 1st match; * = Mean (SD); Z = statistic for non-parametric Mann-Whitney test.

Table 5.14

Cued Recall/Rapid Retrieval/ Trails of cases (MC:1) included and excluded from the first match with controls

Variable	Included N=32	Excluded N=48	Statistic	P
Cued recall retrieval	28.5 (5.2)	28.0 (6.5)	Z -0.02	0.985
Cued recall acquisition	35.9 (0.3)	35.2 (3.8)	Z -0.50	0.619
Cued recall retention	12.0 (0.0)	12.0 (0.3)	Z -0.85	0.395
Cued recall - delayed free recall	10.3 (2.4)	9.9 (3.0)	Z -0.26	0.796
Rapid Retrieval - F	12.0 (4.3)	12.6 (4.2)	Z -0.75	0.453
Rapid Retrieval - A	11.0 (5.5)	11.9 (5.1)	Z -1.37	0.172
Rapid Retrieval - S	14.4 (4.4)	15.4 (5.6)	Z -0.63	0.530
Rapid Retrieval - Supermarket items	23.1 (6.0)	23.8 (6.3)	Z -0.41	0.683
Trails A	50.7 (52.54)	35.8 (11.0)	Z -1.28	0.201
Trails B	124.5 (120.5)	102.5 (50.4)	Z -0.63	0.527

M:1 = In the 1st match; M:0 = Not in the 1st match; * = Mean (SD); Z = statistic for non-parametric Mann-Whitney test.

Table 5.15

Brain measurements of cases (MC:1) included and excluded from the first match with controls

Variable	Included N=32	Excluded N=48	Statistic	P
Medial Temporal Lobe Width R	19.0 (2.7)	19.0 (2.8)	Z -0.18	0.885
Medial Temporal Lobe Width L	19.0 (2.6)	18.7 (2.7)	Z -0.64	0.524
Temporal Fissure R(% abnormal rating)	9.4	8.3	χ^2 0.03	0.872
Temporal Fissure L(% abnormal rating)	15.6	6.3	χ^2 1.88	0.171
Third Ventricle	4.0 (2.4)	3.4 (2.3)	Z -1.10	0.273
Cranial Diameter	128.9 (4.2)	127.0 (5.2)	Z -2.01	0.044
Sylvian Fissure R (% abnormal rating)	84.4	72.9	χ^2 1.45	0.229
Sylvian Fissure L (% abnormal rating)	84.4	70.8	χ^2 1.94	0.163
Bicaudate Distance	13.6 (3.1)	12.6 (3.1)	Z -1.30	0.194
Lateral Ventricle R	4.1 (2.7)	3.0 (1.7)	Z -1.46	0.145
Lateral Ventricle L	4.7 (2.3)	4.2 (1.9)	Z -0.60	0.551
Ratio	0.2 (0.1)	0.2 (0.1)	Z -1.19	0.236

M:1 = In the 1st match; M:0 = Not in the 1st match; Numbers with brackets are means with SD; Z = statistic for non-parametric Mann-Whitney test; χ^2 = chi square test statistic. Temporal horn rating of 2 or 3 and Sylvian fissure rating of 1 or 2 were considered to be abnormal for the purpose of this analysis.

Table 5.16

APOE ϵ 4 allele frequency and Homocysteine levels of cases (MC:1) included and excluded from the first match with controls

Variable	Included N=32	Excluded N=48	Statistic	P
APOE ϵ 4 (%)	26.6	21.6	χ^2 0.51	0.477
Homocysteine (μ g/l)	12.9 (4.6)	11.4 (5.1)	Z -1.39	0.166

M:1 = In the 1st match; M:0 = Not in the 1st match; χ^2 = chi square test statistic; Z = statistic for non-parametric Mann-Whitney test.

5.4.3 Changes in CAMCOG scores from the 1st to 2nd Exam

Table 5.17 shows that there was a statistically significant change (ie, increase) from the 1st to the 2nd exam in terms of CAMCOG Scores for the control group (MC:0) but there was no significant change for the complainers group (MC:1).

Table 5.17

Changes in CAMCOG Scores from the 1st to the 2nd Examination for the Two Matched Groups

Period	MC:0 N=32	MC:1 N=32
1 st Exam *	98.1 (2.9)	95.1 (5.0)
2 nd Exam *	99.6 (2.4)	95.3 (5.5)
Difference between the 1 st and 2 nd Exam *	1.5 (3.0)	0.2 (3.2)
Z	-2.61	-0.24
P	0.01	0.81

MC:0 = controls; MC:1 = memory complainers; * = Mean (SD); Z = Wilcoxon paired non-parametric test statistic (sub-test of Mann-Whitney test).

5.4.4 Difference in CAMCOG scores for the 2nd Exam between the two Groups

There was a statistically significant difference between the two groups at the 2nd exam in terms of CAMCOG Scores. The MC:0 group had significantly higher CAMCOG scores than the MC:1 group (mean \pm SD, MC:0 = 99.6 \pm 2.4, MC:1 = 95.3 \pm 5.5, Z = 3.90, p = 0.000)

5.4.5 Baseline Clinical Characteristics of Individuals with Subjective Memory Complaint and Matched Controls in Terms of the Follow-up Duration between the 1st and 3rd Exams

There were 21 matches between case (MC:1) and control (MC:0) groups in terms of age, sex and the difference in follow-up duration between the 1st and 3rd exams. (This is referred to as "the 2nd Matching").

The 21 matched pairs again had identical sex. The pairs were well matched for age (mean \pm SD, MC:0 = 64.3 \pm 11.5 years and MC:1 = 64.2 \pm 11.9 years, $t=0.03$, p 0.979). The follow up duration in days between the baseline and second examinations was also well matched (mean \pm SD, MC:0 = 969.4 \pm 198.8 days and MC:1 = 989.8.2 \pm 228.8 years, $Z=0.06$, p 0.950).

Note that the numbers of cases (MC:1) and controls (MC:0) in Tables 5.19-5.26 are 21 each. These results again show no differences between groups apart from similar variables identified in the first matching ie the total Camcog score and the orientation sub-scale. Significant differences were also found on the Fuld, (1st storage and 1st retrieval trial) and the temporal order test (number of correct hits in both the word form of the test).

Table 5.18

Demographic and Clinical characteristics of controls and memory complainers according to Section A of the CAMDEX: The 2nd Matching

Variable	MC:0 N=21	MC:1 N=21	Statistic	P
Marital status (%)	85.7	71.4	χ^2 1.27	0.259
Yrs Education (Years, Mean (SD))	12.9 (4.0)	11.8 (4.1)	Z -1.01	0.312
Age left school (Years, Mean (SD))	15.8 (1.3)	15.9 (1.9)	T -0.28	0.781
TIA (%)	0.0	9.5	χ^2 2.10	0.147
Cerebrovascular function (%)	9.5	28.6	χ^2 2.47	0.116
Sleep function (%)	28.6	52.4	χ^2 2.47	0.116
Sleep (%)	14.3	42.9	χ^2 4.20	0.040
Anxiety	38.1	66.7	χ^2 3.44	0.064
Lose control (%)	0.0	9.5	χ^2 2.10	0.147
Use money (%)	0.0	4.8	χ^2 1.02	0.311
Household tasks (%)	0.0	0.0	χ^2 -	-
Bladder (%)	0.0	33.3	χ^2 8.40	0.004
Depression A (%)	0.0	0.0	χ^2 -	-
Depression B (%)	0.0	5.0	χ^2 1.08	0.300
Major depression (%)	0.0	0.0	χ^2 -	-

MC:0 = controls; MC:1 = memory complainers; Z = statistic for non-parametric Mann-Whitney test; T = t test statistic

- = not available.

Table 5.19

Clinical characteristics of controls and memory complainers according to Section A of the CAMDEX: The 2nd Matching

Variable	MC:0 N=21	MC:1 N=21	Statistic	P
Lose items (%)	28.6	95.2	χ^2 19.79	0.000
Forget names (%)	4.8	28.6	χ^2 4.29	0.038
Lost in own neighbourhood(%)	0.0	4.8	χ^2 1.02	0.311
Talk about past (%)	14.3	19.0	χ^2 0.17	0.679
Word finding (%)	42.9	61.9	χ^2 1.53	0.217
Hypertension (%)	19.0	28.6	χ^2 0.53	0.469
Smoker - > 20 cigarettes/day for > one year (%)	52.4	42.9	χ^2 0.38	0.537
Heavy drinker %	19.0	23.8	χ^2 0.14	0.707
Nervous person %	9.5	33.3	χ^2 3.54	0.060
Emotional illness (%)	4.8	14.3	χ^2 1.11	0.293
Fam Hist Poor Mem (%)	4.8	38.1	χ^2 6.93	0.008

MC:0 = controls; MC:1 = memory complainers; χ^2 = chi square test statistic.

Table 5.20

Camcog and Camcog Subscale scores of controls (MC:0) and memory complainers (MC:1): The 2nd Matching

Variable	MC:0 N=21	MC:1 N=21	Statistic	P
Baseline CAMCOG Total	98.6 (2.7)	95.1 (5.7)	Z -2.22	0.027
Orientation subscale	10.0 (0.0)	9.8 (0.4)	Z -2.35	0.019
Language subscale	29.3 (0.8)	28.5 (1.2)	Z -2.32	0.020
Memory subscale	23.4 (2.3)	22.1 (3.1)	Z -1.24	0.217
New learning subscale	13.9 (2.0)	12.8 (2.7)	Z -1.20	0.231
Attention subscale	7.0 (0.2)	6.7 (0.7)	Z -1.78	0.075
Praxis subscale	9.0 (0.2)	9.0 (0.2)	Z 0.00	1.000
Abstraction subscale	7.7 (0.7)	6.9 (1.2)	Z -2.23	0.026

MC:0 = controls; MC:1 = memory complainers; * = Mean (SD); Z = statistic for non-parametric Mann-Whitney test.

Table 5.21

Fuld/Temporal Order Discrimination scores of controls (MC:0) and memory complainers (MC:1): The 2nd Matching

Variable	MC:0 N=21	MC:1 N=21	Statistic	P
Fuld Storage 1	8.2 (1.3)	7.1 (1.4)	Z -2.05	0.045
Fuld Storage 2	9.5 (0.9)	9.1 (1.2)	Z -1.43	0.209
Fuld Retrieval 1	8.2 (1.3)	7.1 (1.4)	Z -2.05	0.045
Fuld Retrieval 2	8.9 (1.3)	7.8 (1.4)	Z -2.23	0.030
Fuld Repeat Retrieval	7.6 (1.4)	5.9 (1.9)	Z -2.59	0.010
Fuld Ineffective reminders	0.5 (0.9)	1.0 (1.3)	Z -1.45	0.195
Fuld Number named	24.2 (4.0)	23.0 (6.8)	Z -0.54	0.596
Temporal Order Pictures - Hits	14.2 (1.6)	13.1 (2.9)	Z -1.27	0.223
Temporal Order Pictures - Correct rejection	12.1 (2.1)	12.0 (2.8)	Z -0.02	1.000
Temporal Order Pictures - % order correct	79.5 (14.0)	73.5 (12.3)	Z -1.19	0.238
Temporal Order Words - Hits	15.2 (1.5)	12.7 (3.9)	Z -2.53	0.014
Temporal Order Words - Correct rejection	13.8 (2.2)	14.2 (2.2)	Z -0.87	0.404
Temporal Order Words - % order correct	78.7 (9.6)	71.9 (22.8)	Z -0.73	0.472

MC:0 = controls; MC:1 = memory complainers; * = Mean (SD); Z = statistic for non-parametric Mann-Whitney test.

Table 5.22

Wechsler Memory Scale scores of controls (MC:0) and memory complainers (MC:1): The 2nd Matching

Variable	MC:0 N=21	MC:1 N=21	Statistic	P
Logical Memory 1	26.3 (6.2)	22.1 (8.5)	Z -1.33	0.195
Centile	69.5 (21.9)	52.0 (31.9)	Z -1.56	0.126
Logical Memory 2	20.4 (8.0)	15.8 (8.9)	Z -1.46	0.147
Centile	63.9 (24.8)	47.1 (29.0)	Z -1.59	0.117
Verbal Paired Associates Total	17.9 (2.6)	16.2 (4.5)	Z -0.94	0.362
Verbal Memory index	108.3 (12.0)	94.0 (27.5)	Z -1.77	0.077
Digit span forward centile	68.5 (28.8)	60.8 (28.9)	Z -0.66	0.520
Digit span backwards centile	71.8 (25.0)	56.0 (26.0)	Z -1.92	0.054
Digit span total	16.4 (3.2)	14.5 (3.2)	Z -1.56	0.126

MC:0 = controls; MC:1 = memory complainers; * = Mean (SD); Z = statistic for non-parametric Mann-Whitney test.

Table 5.23

Cued Recall/Rapid Retrieval/ Trails scores of controls (MC:0) and memory complainers (MC:1): The 2nd Matching

Variable	MC:0 N=21	MC:1 N=21	Statistic	P
Cued recall retrieval	30.9 (2.9)	27.7 (5.5)	Z -1.56	0.126
Cued recall acquisition	36.0 (0.0)	36.0 (0.2)	Z -0.83	0.821
Cued recall retention	12.0 (0.0)	12.0 (0.0)	Z 0.00	1.000
Cued recall - delayed free recall	11.3 (0.9)	9.9 (2.8)	Z -1.79	0.087
Fluency - F	11.2 (4.4)	12.0 (4.1)	Z -0.31	0.762
Fluency - A	10.3 (3.8)	10.8 (5.1)	Z -0.02	1.000
Fluency - S	14.5 (4.8)	13.8 (4.9)	Z -0.52	0.623
Fluency - Supermarket items	26.9 (8.3)	22.3 (6.7)	Z -1.83	0.071
Trails A	29.9 (9.2)	58.2 (63.8)	Z -2.63	0.008
Trails B	82.5 (33.3)	143.8 (143.8)	Z -2.07	0.037

MC:0 = controls; MC:1 = memory complainers; * = Mean (SD); Z = statistic for non-parametric Mann-Whitney test.

Table 5.24

Brain measurements scores of controls (MC:0) and memory complainers (MC:1): The 2nd Matching

Variable	MC:0 N=21	MC:1 N=21	Statistic	P
Medial Temporal Lobe Width R	18.9 (2.1)	18.8 (3.0)	Z -0.51	0.627
Medial Temporal Lobe Width L	17.8 (3.0)	18.8 (1.9)	Z -1.04	0.309
Temporal Fissure R(% abnormal rating)	19.0	19.0	χ^2 0.00	1.000
Temporal Fissure L(% abnormal rating)	5.0	9.5	χ^2 0.31	0.578
Third Ventricle	4.0 (1.9)	4.1 (2.6)	Z -0.08	0.939
Cranial Diameter	127.7 (5.8)	128.4 (4.6)	Z -0.29	0.772
Sylvian Fissure R (% abnormal rating)	57.1	81.0	χ^2 2.79	0.095
Sylvian Fissure L (% abnormal rating)	66.7	76.2	χ^2 0.47	0.495
Bicaudate Distance	13.8 (3.9)	13.8 (3.7)	Z -0.16	0.869
Lateral Ventricle R	3.0 (2.6)	4.3 (3.3)	Z -1.24	0.214
Lateral Ventricle L	4.5 (2.4)	4.7 (2.6)	Z -0.46	0.647
Ratio	0.2 (0.7)	0.2 (0.1)	Z -0.32	0.753

MC:0 = controls; MC:1 = memory complainers; Numbers with brackets are means with SD; Z = statistic for non-parametric Mann-Whitney test; χ^2 = chi square test statistic. Temporal horn rating of 2 or 3 and Sylvian fissure rating of 1 or 2 were considered to be abnormal for the purpose of this analysis.

Table 5.25

APOE ϵ 4 allele frequencies and Homocysteine levels scores of controls (MC:0) and memory complainers (MC:1): The 2nd Matching

Variable	MC:0 N=21	MC:1 N=21	Statistic	P
APOE ϵ 4 (%)	17.5	23.8	χ^2 0.50	0.481
Homocysteine (μ g/l)	13.0 (5.9)	14.3 (5.1)	Z -0.90	0.368

MC:0 = controls; MC:1 = memory complainers; χ^2 = chi square test statistic. Z = Mann-Whitney non-parametric test statistic.

5.4.6 Changes in CAMCOG scores from the 1st to 3rd Examination

Table 5.26 shows that there was a statistically significant change (ie, increase) from the 1st to the 3rd examination in terms of CAMCOG scores for the control group but there was no significant change for the memory complainer group.

Table 5.26

Changes in CAMCOG Scores from the 1st to the 3rd Examination for the Two Groups

Period	MC:0 N=21	MC:1 N=21
1 st Examination *	98.6 (2.7)	95.1 (5.7)
3 rd Examination *	101.0 (1.9)	95.1 (6.5)
Difference between the 1 st and 3 rd Examination *	2.4 (2.8)	0.1 (4.7)
Z	-3.09	-0.67
P	0.002	0.505

MC:0 = controls; MC:1 = memory complainers; * = Mean (SD); Z = Wilcoxon paired non-parametric test statistic (sub-test of Mann-Whitney test).

5.4.7 Difference in CAMCOG Scores for the 3rd Examination between the Two Groups

There was a statistically significant difference between the two groups at the 3rd examination in terms of CAMCOG Scores. The scores for the control group were significantly higher than those in the case group (mean \pm SD, MC:0 = 101.0 \pm 1.9, MC:1 = 95.1 \pm 6.5, Z = 3.68, p = 0.000)

5.4.8 Summary of Changes in CAMCOG Scores for the Two Groups

Figure 5.1 shows the changes in CAMCOG scores over different examination points during follow-up. The case groups show a stable trend while the control groups demonstrate an upward trend. That is, the performance improved over time for the controls.

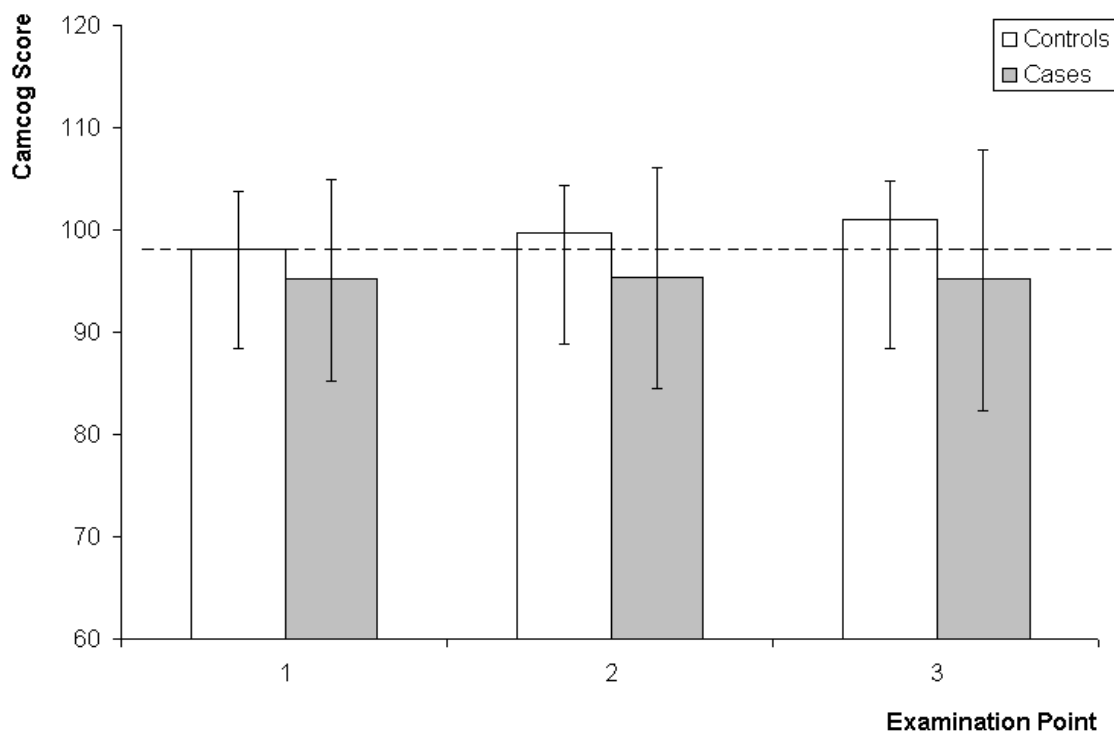


Figure 5.1. Changes in CAMCOG Scores over Different Examination Points during Follow-up (The reference dot line indicates the mean score at the first examination point for controls). The vertical bars represent the standard error of the mean.

5.4.9 Logistic Regression Analysis

Table 5.27 lists the logistic regression results using the Wald forward stepwise selection method. In Step 1, TOWH (Temporal Order Words Hits) was also found to be a significant predictor variable. In Step 2, bladder control was also identified as a significant predictor but no valid OR and associated 95% CI were calculated by the SPSS program. Thus, only the results from Step 1 of the logistic regression model should be used as the final results from the model and only one significant variable (TOWH) was identified to influence the occurrence of memory complaint.

The results from Step 1 of the regression analysis demonstrated that the value of 0 for TOWH (Temporal Order Words Hits) was more than 7.8 ($=1/0.127$) times more likely to be associated with memory complaint compared with those with a value of 1.

Table 5.27

Logistic regression results using Wald forward stepwise selection method and after recoding of continuous variables

Step	Variable	B	SE	Wald	P	OR	95.0% CI for OR	
							Lower	Upper
Step 1(a)	Temporal Order Word Hits(1)	-2.06	0.57	12.94	0.000	0.13	0.04	0.391
	Constant	0.92	0.37	6.00	0.014	2.50		
Step 2(b)	Bladder Control(1)	21.42	12600.40	0.00	0.999	2014617129.77	0.00	
	Temporal Order Word Hits (1)	-2.070	0.63	10.68	0.001	0.13	0.04	0.44
	Constant	0.59	0.39	2.22	0.136	1.80		
A	Variable(s) entered on step 1: Temporal Order Word Hits.							
B	Variable(s) entered on step 2: Bladder control.							

Stepwise procedure stopped because removing the least significant variable result in a previously fitted model.

B = Coefficient for the variable; SE = standard error for the coefficient; Wald = Wald statistic; OR = exponentiation of the B coefficient, which is the odds ratio

The full models by including all variables or using Wald stepwise selection method could not be established due to non-convergence of the logistic regression. This was the case regardless of whether or not the continuous variables were recoded into dichotomous variables.

5.5 Discussion

The cross-sectional comparisons of the matched pairs revealed little difference from the same analysis of the entire cohort as described in chapter 4. The matching process employed in this chapter resulted in a loss of power due to the loss of subjects. However, the analysis revealed no major differences from the unmatched analysis. This corroboration of the findings reported in chapter 4 is reassuring.

The univariate analysis shows consistently that the MC:1 group performed worse than the MC:0 group on the CAMCOG. This is so in comparisons of the entire groups and also for matched pairs. The logistic regression analysis however, shows that group membership cannot be defined by any single independent variable. Why did these risk factors not provide a means of identifying group membership? It may be that cognitive decline is a less useful endpoint than dementia.

The longitudinal data analysed in this chapter did show an improvement on repeated testing in the MC:0 group and lack of improvement in the MC:1 group on CAMCOG scores. This is at odds with previous reports using this test as discussed below.

There are relatively few longitudinal observational studies of cognition in normal populations using the CAMCOG in the literature. A study from Cambridge examined women over the age of 70 years at baseline and five years later (Brayne *et al* 1997). At baseline, there were 29 cases of dementia identified in the group (n=365). The non-demented group in this study was not stratified according to memory complaint and the mean CAMCOG score for this sub-group is not recorded. The mean score for the whole group was 84.4/106 declining to 79.3 at follow-up five years later. This decline of 5.1 points was reduced to 4.7 points when prevalent dementia cases were excluded. At follow-up, mean CAMCOG scores for those that remained non-demented were not mentioned in the analysis. It is likely that the non-demented group contained subjects with mild cognitive impairment. Furthermore, it is possible that the learning effect seen in the data in this chapter would have been attenuated by the long interval between examinations in the study conducted by Brayne and colleagues.

The same Cambridge based research group, examined 135 subjects who completed CAMCOGs at two interviews, 3.9 years apart as part of a study of

a community sample aged over 75 years (Cullum *et al* 2000). The cohort was again not stratified according to memory complaint. The mean decline in the total score was 6 points with an annual rate of change of -1.6 points. Of note, only seven of the 135 participants showed no decline in any of the CAMCOG sub-scales. The mean age of the sample was 81.5 years. Again, the sample likely contained cases of mild cognitive impairment. The authors acknowledge that prodromal dementia may have contributed to the decline in scores. Direct comparisons with the current study are not possible, as the age groups are disparate and men were excluded from the study by Cullem and colleagues.

The increasing CAMCOG scores in the MC:0 group in the current study suggests that the participants learnt how to do the test as it is repeated annually. The failure of the MC:1 to show a decline in test scores over the course of the current investigation means that the null hypothesis must be accepted i.e. that subjective memory complaint is not associated with cognitive decline over time. It is possible that selection bias played a role in the performance of the MC:1 group. The relatively high scores on the CAMCOG suggest that this group is highly performing and that the length of follow-up was insufficient for decline to occur if indeed this group were ever to deteriorate. Dropout bias is another possible contributor to the lack of decline observed in the MC:1 group. If some in the MC:1 group failed to attend follow-up visits as a result of declining memory then this would

attenuate any decline in the group as a whole. A population-based approach to recruitment may have reduced the potential recruitment biases in the study. The participants were all from the western suburbs of metropolitan Perth and hence from a predominantly 'white collar' background. This may help to explain the high baseline scores on the CAMCOG.

The approach of the Paquid study investigators may also shed some light on the data seen in the current study. In their report on follow-up of 1265 subjects over age 65 years they excluded baseline cognitive data (Amieva *et al* 2005). Hence, they used the second examination result as the reference point. This methodology was based on a previous study that showed an improvement in cognitive scores between first and second examinations (Jacqmin-Gadda *et al* 1997). The authors considered that stress at the initial assessment and/or a learning effect at the subsequent assessment meant that the initial scores were not useful in assessing change over time.

An explanation for the failure of the MC:1 group to improve, as the MC:0 did, is not apparent. Does this represent evidence of a learning deficit in the MC:1 group or is the learning effect in the control group abnormal and unrepresentative of a normal group of individuals? Other prospective studies of subjective memory complaint do not report cognitive scores for control groups and so do not help with resolution of this question (Geerlings *et al*

1999, Jorm *et al* 1997, Schmand *et al* 1996, Schofield *et al* 1997, St John *et al* 2002, Tobiansky *et al* 1995).

Despite the above considerations, the data reported in this chapter have identified a difference in cognitive scores between the two groups and this is consistent with the literature review as described in chapters 2 and 4. When matched for gender, age and duration of follow-up, the differences in scores between the groups were still evident. It seems therefore that the role of subjective memory complaint remains potentially important in clinical medicine as a marker of emotional, psychological and cognitive disorders.

Chapter 6

Study 3

RISK FACTORS FOR MEMORY DECLINE AMONGST INDIVIDUALS WITH AND WITHOUT SUBJECTIVE MEMORY COMPLAINT

6.1 Introduction

The study described in chapter 5 showed that those with a subjective complaint of memory loss (MC:1) have consistently lower scores than non-complainers (MC:0) over a three year period on a global test of cognition (CAMCOG). However, both groups showed stable CAMCOG scores (indeed improvement in the control group) over the period of follow-up. This suggests an ability of some to learn how to perform well on the CAMCOG or, alternatively, the failure to benefit from learning to improve performance.

6.2 Objectives

This post hoc analysis aimed to determine the best predictors of:

- Cognitive decline as demonstrated by the CAMCOG.

6.3 Sample Acquisition and Methodology

The recruitment of subjects was described in chapter 4. The same research nurse repeated the CAMCOG at the follow-up assessments. All subjects with a valid second or third or fourth CAMCOG score were included in the analysis when comparing those subjects with a decline in CAMCOG scores (DC:1) and those without (DC:0). A decline in CAMCOG scores was defined as a subject having a decrease in CAMCOG scores from the first test to the last test. Those subjects without any change or with an increase in CAMCOG scores were grouped into DC:0.

In addition, the distribution of 'change in scores' was analysed. The change was measured by subtracting the first score of a subject from his or her final score. Then subjects were divided into two groups based on scores above (DC1=0) and below (DC1=1) the median change in score. A comparison of subjects within the upper (DC2=0) and lower (DC2=1) quartiles was also conducted where subjects in the middle two quartiles were excluded from the analysis.

The literature review in chapters two and three identified a number of risk factors for cognitive decline. These include subjective memory complaint (Bassett *et al* 1993, Gagnon *et al* 1994, Jonker *et al* 1996, Tobiansky *et al* 1995) and other categories of pre-dementia syndrome such as mild cognitive

impairment (Bennett *et al* 2002, Larrieu *et al* 2002), deficits in neuropsychological test scores (Bozoki *et al* 2001, Grober *et al* 2000, Kawas *et al* 2003, Tierney *et al* 1996), hippocampal atrophy (de Leon *et al* 1993, George *et al* 1990, Jack *et al* 1998a) and *APOE* genotype (Farrer *et al* 1997, Haines *et al* 2001, Petersen *et al* 1995), to name a few. In this study variables from the CAMDEX were chosen that are consistent with these known risk factors.

A variable designated 'Neuro' was created to reflect acquired brain disease an/or injury. This included:

1. The variable 'TIA' used in studies 1 and 2 and taken from the CAMDEX ie item 22 'have you ever had weakness, or difficulty with speech, memory or vision which got better?'
2. CAMDEX item 76, ie 'have you ever been told by a doctor that you have had a stroke?'
3. CAMDEX item 77, ie 'have you ever had a serious head injury and been unconscious after it?'

If any of these items was scored as 1 then the variable 'neuro' was scored as

1. Otherwise, it was scored as 0.

The characteristics of the groups, as described above, were compared using univariate analyses. Finally, a Cox regression analysis was conducted to evaluate the effect of each statistically significant factor from the univariate analysis on the decline or non-decline in CAMCOG scores. This was adjusted for the potential confounding effects of total follow-up duration,

age, sex and other factors. In this analysis, total follow-up duration was defined as the interval between the 1st and the last test dates. Survival was defined as subjects not having decline in CAMCOG scores during the follow-up period from the 1st to the last examination.

6.4 Results

6.4.1 Basic characteristics of the No-decline (DC1=0) and Decline (DC1=1) groups

One hundred and six subjects had valid second, third or fourth CAMCOG scores with a minimum and maximum follow-up duration of 315 days and 1,428 days (equivalent to 3.91 years) respectively.

Table 6.1

Basic Characteristics of the No-decline in Cognition (DC:0) and Decline in Cognition (DC:1) Groups

Variable	DC:0 n = 83	DC:1 n = 23	Statistic	P
Sex: Female (%)	47.0	30.4	χ^2 2.0	0.156
Age in Years, Mean (SD)	60.6 (9.9)	66.9 (11.5)	T -2.58	0.011
Follow-up Duration in Years, Mean (SD)	2.4 (0.9)	2.2 (0.9)	Z -0.86	0.391
Total Education Years, Mean (SD)	12.0(3.8)	11.4(3.7)	Z -0.66	0.512
Age in Years when Left School, Mean (SD)	15.7(1.5)	15.7(1.4)	Z -0.23	0.816
Hypertension (%)	16.9	34.8	χ^2 3.51	0.061
Smoker %	32.5	34.8	χ^2 0.04	0.839
Heavy drinker %	19.3	13.0	χ^2 0.48	0.490
Neuro %	24.1	30.4	χ^2 0.38	0.537
Poor memory %	67.5	69.6	χ^2 0.04	0.849
Depression A (%)	4.8	0.0	χ^2 1.15	0.283
Depression B (%)	8.5	0.0	χ^2 2.10	0.147
Anxiety	60.2	65.2	χ^2 0.19	0.665

DC:0 = Without decline; DC:1 = With decline; * = Mean (SD); T = t test statistic; Z = Mann-Whitney non-parametric test statistic; χ^2 = chi-square test statistic. χ^2 = chi square test statistic

The group that declined was significantly older than the group that showed no decline. There were no other significant differences between the two groups with respect to other lifestyle risk factors.

6.4.2 Cognitive Scores

There were no differences between the groups on the total CAMCOG score or its sub-scales at baseline.

Table 6.2

CAMCOG and CAMCOG Subscales for the No-decline in Cognition (DC:0) and Decline in Cognition (DC:1) Groups

Baseline scores	DC:0 n = 83	DC:1 n = 23	Statistic	P
CAMCOG Total	95.4 (4.9)	96.6 (5.0)	Z -0.34	0.735
Orientation subscale	9.9 (0.4)	9.8 (0.5)	Z -0.18	0.861
Language subscale	28.6 (1.4)	28.6 (1.3)	Z -0.09	0.930
Memory subscale	22.2 (2.5)	22.5 (2.8)	Z -0.25	0.805
New learning subscale	12.9 (2.2)	13.2 (2.3)	Z -0.26	0.795
Attention subscale	6.6 (0.9)	6.8 (0.6)	Z -1.19	0.234
Praxis subscale	8.9 (0.4)	8.9 (0.3)	Z -0.33	0.744
Abstraction subscale	7.1 (1.4)	6.9(1.7)	Z -0.32	0.747

DC:0 = Without decline; DC:1 = With decline; * = Mean (SD); Z = statistic for non-parametric Mann-Whitney test.

Significant differences between the groups were identified on the Fuld object memory evaluation. Storage2 is the total number of objects remembered after the second attempt at recalling the objects, including those in trial 1. An ineffective reminder is when the subject cannot recall the object on two successive trials. The group that declined scored worse than the group that

did not decline on these two variables. There were no differences on the temporal order discrimination test.

Table 6.3

Fuld/Temporal Order Discrimination for the No-decline in Cognition (DC:0) and Decline in Cognition (DC:1) Groups

Baseline scores	DC:0 n = 83	DC:1 n = 23	Statistic	P
Fuld Storage 1	7.7 (1.4)	7.1 (1.4)	Z -1.92	0.055
Fuld Storage 2	9.3 (1.5)	8.9 (1.1)	Z -2.05	0.041
Fuld Retrieval 1	7.7 (1.4)	7.1 (1.5)	Z -1.92	0.055
Fuld Retrieval 2	8.4 (1.4)	7.8 (1.5)	Z -1.70	0.089
Fuld Repeat Retrieval	6.7 (1.9)	6.0 (1.9)	Z -1.53	0.127
Fuld Ineffective reminders	0.6 (0.9)	1.2 (1.1)	Z -2.29	0.022
Fuld Number named	23.2 (5.4)	22.0 (4.6)	Z -0.99	0.324
TO Pictures - Hits	14.0 (2.2)	14.6 (1.5)	Z -0.96	0.340
TO Pictures Correct rejection	12.2 (2.5)	10.8 (3.3)	Z -1.65	0.099
TO Pictures % order correct	78.3 (12.7)	73.5 (12.5)	Z -1.56	0.119
TO Words Hits	13.9 (2.5)	14.0 (2.5)	Z -0.56	0.576
TO Words Correct rejection	14.1 (2.1)	12.6 (3.7)	Z -1.40	0.161
TO Words % order correct	76.0 (19.5)	72.5 (16.4)	Z -1.12	0.265

DC:0 = Without decline; DC:1 = With decline; * = Mean (SD); Z = statistic for non-parametric Mann-Whitney test.

Comparison of scores on the Wechsler memory scale and Cued Recall/Rapid Retrieval/ Trails revealed no differences between the two groups.

Table 6.4Wechsler Memory Scale for the No-decline in Cognition (DC:0) and Decline in Cognition (DC:1) Groups

Baseline scores	DC:0 n = 83	DC:1 n = 23	Statistic	P
Logical Memory 1	23.1 (7.2)	22.0 (8.0)	Z -0.87	0.382
Centile	55.2 (28.6)	50.2 (30.1)	Z -0.63	0.532
Logical Memory 2	17.7 (7.9)	16.4 (9.0)	Z -0.93	0.353
Centile	51.8 (28.5)	49.3 (27.8)	Z -0.39	0.698
Verbal Paired Associates Total	16.8 (4.1)	16.0 (3.9)	Z -0.99	0.321
Verbal Memory index	98.9 (19.4)	98.5 (16.2)	Z -0.51	0.614
Digit span forward centile	64.6 (31.0)	61.5 (22.6)	Z -1.11	0.266
Digit span backwards centile	57.1 (29.7)	57.9 (27.0)	Z -0.05	0.960
Digit span total	15.3 (3.9)	14.8 (3.0)	Z -0.56	0.578

DC:0 = Without decline; DC:1 = With decline; * = Mean (SD); Z = statistic for non-parametric Mann-Whitney test.

Table 6.5Cued Recall/Rapid Retrieval/ Trails for the No-decline in Cognition (DC:0) and Decline in Cognition (DC:1) Groups

Baseline scores	DC:0 n = 83	DC:1 n = 23	Statistic	P
Cued recall retrieval	29.4 (5.1)	27.5 (5.6)	Z -1.71	0.088
Cued recall acquisition	35.6 (2.7)	36.0 (0.2)	Z -0.18	0.861
Cued recall retention	12.0 (0.2)	12.0 (0.0)	Z -0.55	0.585
Cued recall - delayed free recall	10.5 (2.3)	9.7 (2.9)	Z -1.10	0.273
Fluency - F	12.5 (4.2)	11.3 (5.0)	Z -1.04	0.300
Fluency - A	11.6 (5.6)	10.6 (3.2)	Z -0.70	0.482
Fluency - S	15.2 (5.4)	15.3 (4.4)	Z -0.06	0.951
Fluency - Supermarket items	25.1 (5.7)	22.9 (7.9)	Z -2.14	0.033
Trails A	40.2 (36.2)	38.9 (10.5)	Z -1.45	0.147
Trails B	101.7 (84.1)	109.6 (51.9)	Z -1.12	0.263

DC:0 = Without decline; DC:1 = With decline; * = Mean (SD); Z = statistic for non-parametric Mann-Whitney test.

The only variable significantly different on brain measurements was width of the left medial temporal lobe, which was greater in the group that declined.

Table 6.6

Brain measurements for the No-decline in Cognition (DC:0) and Decline in Cognition (DC:1) Groups

Baseline measurements	DC:0 n = 83	DC:1 n = 23	Statistic	P
Medial Temporal lobe width R	18.7 (2.5)	19.5 (3.3)	Z -0.60	0.546
Medial Temporal lobe width L	18.3 (2.7)	20.0 (2.3)	Z -2.75	0.006
Temporal fissure R(% abnormal rating)	10.8	4.3	χ^2 0.89	0.346
Temporal fissure L(% abnormal rating)	7.3	8.7	χ^2 0.05	0.826
Third Ventricle	3.8 (2.2)	3.8 (2.2)	Z -0.20	0.839
Cranial Diameter	127.6 (5.3)	128.4 (3.9)	Z -0.51	0.609
Sylvian fissure R (% abnormal rating)	73.5	78.3	χ^2 0.22	0.642
Sylvian fissure L (% abnormal rating)	72.3	78.3	χ^2 0.33	0.565
Bicaudate distance	13.1 (3.2)	13.2 (3.8)	Z -0.34	0.735
Lateral ventricle R	3.3 (2.2)	3.6 (2.4)	Z -0.69	0.448
Lateral ventricle L	4.4 (2.2)	4.2 (2.2)	Z -0.12	0.904
Ratio	0.2 (0.1)	0.2 (0.1)	Z -0.08	0.936

DC:0 = Without decline; DC:1 = With decline; Numbers with brackets are means with SD; Z = statistic for non-parametric Mann-Whitney; χ^2 = chi square test statistic. Temporal horn rating of 2 or 3 and Sylvian fissure rating of 1 or 2 were considered to be abnormal for the purpose of this analysis.

Table 6.7APOE and Homocysteine for the No-decline in Cognition (DC:0) and Decline in Cognition (DC:1) Groups

Baseline Measurements	DC:0 n = 83	DC:1 n = 23	Statistic	P
Homocysteine (µg/l)	12.3 (4.9)	13.4 (5.6)	Z -0.58	0.563
APOE ε4 (%)	22.8	21.4	χ ² 0.03	0.852

DC:0 = Without decline; DC:1 = With decline; χ² = chi square test statistic. Z = statistic for non-parametric Mann-Whitney

6.4.3 Cox Regression Analysis Results

Table 6.8 shows the Cox regression analysis results. Subjects with reduced width of the left temporal lobe (LTL) had a greater chance ($1/0.895=1.12$ times) of having a decline than those with a greater width.

Table 6.8

Cox Regression Analysis Results: Wald Stepwise Forward Factor Selection

Method

Cox Regression Analysis (Results 1) for the No-decline in Cognition (DC:0) and Decline in Cognition (DC:1) Groups
:All factors included in the model

Factor	Coefficient t(B)	Standard error for B	Wald statistic	P value	OR	95% CI for OR	
						Lower	Upper
AGE	.063	.026	5.86	.015	1.07	1.01	1.12
FULDS2	1.57	1.26	1.54	.215	4.78	.40	56.63
FULDIR	1.64	1.19	1.89	.170	5.16	.50	53.58
RAPRSN	-.01	.05	.02	.897	0.99	.91	1.09
LTL	.16	.09	3.27	.071	1.17	.99	1.39

Cox Regression Analysis Results 2:Wald Stepwise Forward Factor Selection Method

Factor	Coefficient (B)	Standard error for B	Wald statistic	P value	OR	95% CI for OR	
						Lower	Upper
AGE	.07	.02	8.01	.005	1.07	1.02	1.12
LTL	.18	.08	4.44	.035	1.19	1.01	1.40

The results show that greater age is associated with a greater chance of decline in cognitive scores. Paradoxically, the same applies to greater width of the left medial temporal lobe, ie with a larger LTL measure (width) the subject

has greater chance of a decline in CAMCOG score compared with subjects with smaller LTL measure.

Other factor selection methods have also been tried and no factors were found to be significant.

Figure 6.1 shows that in the first two years of follow-up, only a small proportion (less than 10%) of subjects had a decline in CAMCOG scores. However after two years, especially after 2.5-3 years, the proportion declining (of those remaining in the study) increased dramatically.

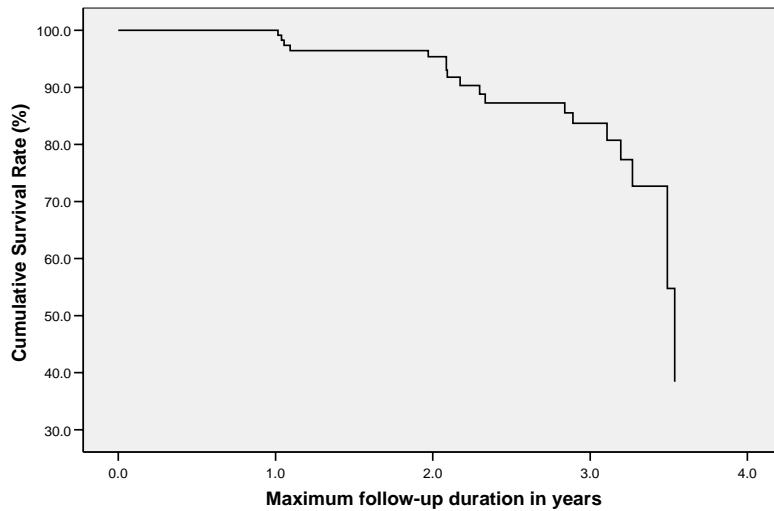


Figure 6.1. Cumulative survival rate of subjects with and without decline in CAMCOG scores over time.

6.5 Comparison of subjects above (DC1=0) and below (DC1=1) median change on the CAMCOG

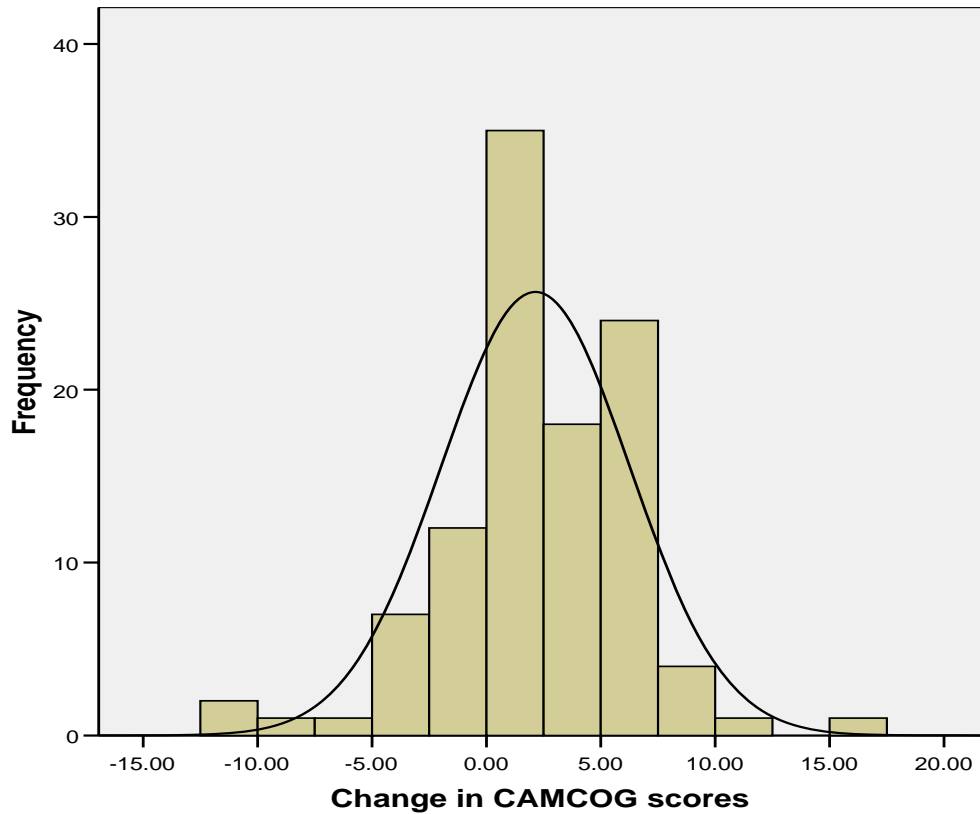


Figure 6.2 Distribution of change in CAMCOG scores

(0 represents no change in CAMCOG score over time)

(Super-imposed curve is a normal distribution curve.)

The distribution of change in CAMCOG scores was approximately normal with a mean of 2.14, standard deviation of 4.12, minimum of -11 and maximum of +17. The majority of subjects had either stable or improved scores.

12.3.1 Basic characteristics of the two groups

Table 6.9

Basic Characteristics of the Two Groups: Above median change (DC1:0) and below median change (DC1:1) on the CAMCOG

Variable	Above median n = 58	Below median n = 48	Statistic	P
Sex: Female (%)	46.6	39.6	χ^2 0.52	0.471
Age in Years, Mean (SD)	61.6(10.4)	62.5(10.7)	T -0.45	0.653
Follow-up Duration in Years, Mean (SD)	2.2 (0.9)	2.5 (0.9)	Z -1.75	0.080
Total Education Years, Mean (SD)	12.1(4.1)	11.6(3.3)	Z -0.23	0.815
Age in Years when Left School, Mean (SD)	15.8(1.4)	15.6(1.6)	Z -0.84	0.404
Hypertension (%)	20.7	20.8	χ^2 0.00	0.986
Smoker %	34.5	31.3	χ^2 0.12	0.725
Heavy drinker %	20.7	14.6	χ^2 0.67	0.415
Neuro	29.3	20.8	χ^2 0.99	0.319
Poor memory	69.0	66.7	χ^2 0.06	0.801
Depression A (%)	1.7	6.3	χ^2 1.48	0.224
Depression B (%)	5.3	8.3	χ^2 0.40	0.530
Anxiety	60.3	62.5	χ^2 0.05	0.821

DC1:0 = change \geq median; DC1:1 = change $<$ median; * = Mean (SD); T = t test statistic; Z = Mann-Whitney non-parametric test statistic; χ^2 = chi-square test statistic. χ^2 = chi square test statistic

12.3.2 Cognitive Scores

There were significant differences between the groups on the total CAMCOG score and several sub-scales at baseline.

Table 6.10

CAMCOG and CAMCOG Subscales for the two groups: Above median change (DC1:0) and below median change (DC1:1) on the CAMCOG

Baseline scores	Above median n = 58	Below median n = 48	Statistic	P
CAMCOG Total	96.9 (4.5)	94.0 (4.9)	Z -3.25	0.001
Orientation subscale	9.8 (0.5)	9.9 (0.3)	Z 0.00	1.000
Language subscale	28.9 (1.3)	28.3 (1.5)	Z -2.37	0.018
Memory subscale	22.9 (2.5)	21.5 (2.5)	Z -2.85	0.004
New learning subscale	13.4 (2.2)	12.4 (2.2)	Z -2.31	0.021
Attention subscale	6.7 (0.7)	6.6 (0.9)	Z -1.01	0.312
Praxis subscale	8.9 (0.2)	8.8 (0.5)	Z -1.96	0.050
Abstraction subscale	7.1 (1.4)	7.0(1.5)	Z -0.78	0.435

DC1:0 = change \geq median; DC1:1 = change $<$ median; * = Mean (SD); Z = statistic for non-parametric Mann-Whitney test.

Comparison of scores on the Fuld Object Memory Evaluation and the temporal order tests revealed no differences between the two groups.

Table 6.11

Fuld/Temporal Order Discrimination for the two groups: Above median change (DC1:0) and below median change (DC1:1) on the CAMCOG

Baseline scores	Above median n = 58	Below median N = 48	Statistic	P
Fuld Storage 1	7.4 (1.3)	7.8 (1.5)	Z -1.06	0.288
Fuld Storage 2	9.0 (1.6)	9.4 (1.1)	Z -1.19	0.234
Fuld Retrieval 1	7.4 (1.3)	7.8 (1.5)	Z -1.06	0.288
Fuld Retrieval 2	8.2 (1.4)	8.5 (1.5)	Z -1.17	0.243
Fuld Repeat Retrieval	6.4 (1.8)	6.8 (2.0)	Z -1.21	0.226
Fuld Ineffective reminders	1.0 (1.0)	0.6 (1.1)	Z -0.96	0.337
Fuld Number named	23.4 (4.7)	22.3 (5.9)	Z -1.01	0.312
TO Pictures - Hits	14.3 (1.5)	13.8 (2.6)	Z -0.43	0.666
TO Pictures Correct rejection	11.4 (2.9)	12.4 (2.4)	Z -1.65	0.099
TO Pictures % order correct	78.0 (12.2)	76.0 (13.5)	Z -0.65	0.514
TO Words Hits	14.1 (2.0)	13.7 (2.9)	Z -0.37	0.709
TO Words Correct rejection	13.4 (3.1)	14.2 (1.8)	Z -0.80	0.423
TO Words % order correct	74.4 (17.3)	76.2 (20.6)	Z -0.88	0.378

DC1:0 = change \geq median; DC1:1 = change $<$ median; * = Mean (SD); Z = statistic for non-parametric Mann-Whitney test.

Comparison of scores on the Wechsler memory scale and Cued Recall/Rapid Retrieval/ Trails revealed no differences between the two groups.

Table 6.12

Wechsler Memory Scale for the two groups: Above median change (DC1:0) and below median change (DC1:1) on the CAMCOG

Baseline scores	Above median n = 58	Below median n = 48	Statistic	P
Logical Memory 1	23.5 (7.8)	22.1 (6.8)	Z -0.87	0.387
Centile	56.1 (29.8)	51.7 (27.9)	Z -0.76	0.448
Logical Memory 2	18.3 (8.6)	16.4 (7.5)	Z -0.99	0.320
Centile	53.6 (28.4)	48.5 (28.1)	Z -0.78	0.438
Verbal Paired Associates Total	16.9 (3.8)	16.2 (4.5)	Z -0.83	0.409
Verbal Memory index	101.1 (16.8)	96.1 (20.5)	Z -0.93	0.351
Digit span forward centile	67.0 (26.4)	60.3 (32.1)	Z -0.53	0.596
Digit span backwards centile	59.2 (29.0)	55.1 (29.0)	Z -0.56	0.579
Digit span total	15.7 (3.2)	14.7 (4.0)	Z -1.30	0.192

DC1:0 = change \geq median; DC1:1 = change $<$ median; * = Mean (SD); Z = statistic for non-parametric Mann-Whitney test.

Table 6.13

Cued Recall/Rapid Retrieval/ Trails for the two groups: Above median change (DC1:0) and below median change (DC1:1) on the CAMCOG

Baseline scores	Above median n = 58	Below median N = 48	Statistic	P
Cued recall retrieval	29.0 (4.6)	28.8 (6.4)	Z -0.25	0.801
Cued recall acquisition	36.0 (0.2)	35.4 (3.5)	Z -0.67	0.506
Cued recall retention	12.0 (0.0)	12.0 (0.3)	Z -1.08	0.278
Cued recall - delayed free recall	10.5 (2.2)	10.1 (2.7)	Z -0.91	0.364
Fluency - F	12.1 (4.5)	12.3 (4.2)	Z -0.07	0.945
Fluency - A	11.3 (4.3)	11.4 (6.0)	Z -0.09	0.929
Fluency - S	15.6 (4.4)	14.7 (5.9)	Z -0.87	0.383
Fluency - Supermarket items	24.2 (6.4)	25.0 (6.2)	Z -1.00	0.318
Trails A	34.7 (10.6)	46.1 (45.5)	Z -1.14	0.255
Trails B	93.7 (41.0)	115.2 (105.2)	Z -0.68	0.496

DC1:0 = change \geq median; DC1:1 = change $<$ median; * = Mean (SD); Z = statistic for non-parametric Mann-Whitney test.

Comparison of brain measurements, homocysteine levels and APOE

genotype revealed no differences between the two groups.

Table 6.14

Brain measurements for the two groups: Above median change (DC1:0) and below median change (DC1:1) on the CAMCOG

Baseline measurements	Above median n = 58	Below median n = 48	Statistic	P
Medial Temporal lobe width R	19.3 (3.0)	18.4 (2.3)	Z -1.15	0.249
Medial Temporal lobe width L	19.0 (3.0)	18.4 (2.3)	Z -1.55	0.122
Temporal fissure R(% abnormal rating)	10.3	8.3	χ^2 0.12	0.724
Temporal fissure L(% abnormal rating)	8.8	6.3	χ^2 0.235	0.628
Third Ventricle	3.6 (2.0)	4.0 (2.4)	Z -0.88	0.381
Cranial Diameter	127.9 (5.0)	127.7 (5.2)	Z -0.10	0.921
Sylvian fissure R (% abnormal rating)	67.2	83.3	χ^2 3.58	0.058
Sylvian fissure L (% abnormal rating)	69.0	79.2	χ^2 1.41	0.236
Bicaudate distance	13.0 (3.1)	13.3 (3.5)	Z -0.65	0.517
Lateral ventricle R	3.0 (2.1)	3.7 (2.5)	Z -1.44	0.149
Lateral ventricle L	4.1 (2.1)	4.6 (2.2)	Z -0.88	0.381
Ratio	0.2 (0.1)	0.2 (0.1)	Z -0.96	0.336

DC1:0 = change \geq median; DC1:1 = change $<$ median; Numbers with brackets are means with SD; Z = statistic for non-parametric Mann-Whitney; χ^2 = chi square test statistic. Temporal horn rating of 2 or 3 and Sylvian fissure rating of 1 or 2 were considered to be abnormal for the purpose of this analysis.

Table 6.15

Homocysteine and APOE for the two groups: Above median change (DC1:0) and below median change (DC1:1) on the CAMCOG

Baseline measurements	Above median n = 58	Below median n = 48	Statistic	P
Homocysteine ($\mu\text{g/l}$)	12.4 (5.1)	12.7 (5.0)	Z -0.10	0.918
APOE $\epsilon 4$ (%)	21.7	23.4	χ^2 0.08	0.773

DC1:0 = change \geq median; DC1:1 = change $<$ median; χ^2 = chi square test statistic. Z = statistic for non-parametric Mann-Whitney test

13.3.3 Cox Regression Analysis Results

Table 6.16

Cox Regression Analysis Results:

Cox Regression Analysis Results 1: All factors included in the model (full model)

Factor	Coefficient t(B)	Standard error for B	Wald statistic	P value	OR	95% CI for OR	
						Lower	Upper
Cam1score	-.06	.06	1.05	.306	.94	.83	1.06
CC Language	-.04	.16	.06	.810	.96	.71	1.31
CC Memory	-.10	.16	.37	.545	.91	.66	1.25
CC NL	.17	.17	1.03	.311	1.18	.86	1.63
CC Praxis	-.44	.32	1.86	.173	.64	.34	1.21

Cox Regression Analysis Results 2:Wald Stepwise Forward Factor Selection Method

Factor	Coefficient (B)	Standard error for B	Wald statistic	P value	OR	95% CI for OR	
						Lower	Upper
LTL	-.06	.03	5.47	.019	.94	.90	.99

12.4 Comparison of subjects with change above 75th percentile (DC2:0) and below 25th percentile (DC2:1)

12.4.1 Basic characteristics of the two groups

Table 6.17

Basic Characteristics of the Two Groups: Top quartile of change (DC2:0) and bottom quartile of change (DC2:1) on the CAMCOG

Variable	Lower quartile n = 32	Upper quartile n = 30	Statistic	P
Sex: Female (%)	34.4	43.3	χ^2 0.52	0.469
Age in Years, Mean (SD)	64.9(10.8)	62.0(10.1)	T -1.08	0.284
Follow-up Duration in Years, Mean (SD)	2.2 (0.9)	2.7 (0.8)	Z -2.32	0.020
Total Education Years, Mean (SD)	11.0(3.4)	11.3(3.3)	Z -0.37	0.711
Age in Years when Left School, Mean (SD)	15.5(1.3)	15.5(1.7)	Z -0.43	0.668
Hypertension (%)	31.3	20.0	χ^2 1.02	0.312
Smoker %	37.5	30.0	χ^2 0.39	0.533
Heavy drinker %	15.6	13.3	χ^2 0.07	0.798
Neuro	28.1	30.0	χ^2 0.03	0.871
Poor memory	75.0	63.3	χ^2 0.99	0.319
Depression A (%)	0.0	3.3	χ^2 1.08	0.298
Depression B (%)	3.2	6.7	χ^2 0.39	0.534
Anxiety	62.5	73.3	χ^2 0.83	0.362

DC2:0 = change \leq 25th percentile; DC2:1 = change \geq 75th percentile; * = Mean (SD); T = t test statistic; Z = Mann-Whitney non-parametric test statistic; χ^2 = chi-square test statistic. χ^2 = chi square test statistic; NA= not available.

12.4.2 Cognitive Scores

There were significant differences between the groups on the total CAMCOG score and the memory sub-scale at baseline (Table 6.18).

Table 6.18

CAMCOG and CAMCOG Subscales: Top quartile of change (DC2:0) and bottom quartile of change (DC2:1) on the CAMCOG

Baseline scores	Upper quartile n = 32	Lower quartile n = 30	Statistic	P
CAMCOG Total	96.4 (5.3)	93.3 (4.9)	Z -2.32	0.020
Orientation subscale	9.8 (0.4)	9.9 (0.3)	Z -0.35	0.729
Language subscale	28.6 (1.4)	28.2 (1.4)	Z -1.15	0.251
Memory subscale	22.7 (2.8)	21.1 (2.1)	Z -2.41	0.016
New learning subscale	13.3 (2.4)	12.2 (2.0)	Z -1.85	0.064
Attention subscale	6.7 (0.7)	6.4 (1.0)	Z -1.79	0.074
Praxis subscale	8.9 (0.2)	8.8 (0.5)	Z -1.62	0.104
Abstraction subscale	7.0 (1.6)	7.0(1.7)	Z -0.45	0.656

DC2:0 = change \geq 75th percentile; DC2:1 = change \leq 25th percentile; * = Mean (SD); Z = statistic for non-parametric Mann-Whitney test.

There were significant differences between the groups on the FULD storage2 and Fuld ineffective reminder scores at baseline. No differences were identified on the temporal order tests (Table 6.19).

Table 6.19

Fuld/Temporal Order Discrimination: Top quartile of change (DC2:0) and bottom quartile of change (DC2:1) on the CAMCOG

Baseline scores	Upper quartile n = 32	Lower quartile N = 30	Statistic	P
Fuld Storage 1	7.2 (1.5)	7.9 (1.6)	Z -1.45	0.147
Fuld Storage 2	8.7 (2.0)	9.5 (1.1)	Z -2.37	0.018
Fuld Retrieval 1	7.3 (1.5)	7.9 (1.6)	Z -1.45	0.147
Fuld Retrieval 2	7.3 (1.5)	7.9 (1.6)	Z -1.55	0.121
Fuld Repeat Retrieval	6.2 (1.9)	7.0 (2.0)	Z -1.25	0.211
Fuld Ineffective reminders	1.0 (1.1)	0.5 (1.1)	Z -2.08	0.037
Fuld Number named	22.9 (4.9)	23.8 (5.1)	Z -0.76	0.449
TO Pictures - Hits	14.4 (1.5)	13.7 (2.9)	Z -0.75	0.456
TO Pictures Correct rejection	11.0 (3.0)	11.9 (2.8)	Z -1.03	0.305
TO Pictures % order correct	75.4 (12.1)	76.7 (14.0)	Z -0.30	0.762
TO Words Hits	13.8 (2.3)	13.6 (3.4)	Z -0.14	0.893
TO Words Correct rejection	13.1 (3.5)	14.1 (1.6)	Z -0.32	0.751
TO Words % order correct	73.3 (16.4)	72.6 (20.9)	Z -0.32	0.748

DC2:0 = change \geq 75th percentile; DC2:1 = change \leq 25th percentile; * = Mean (SD); Z = statistic for non-parametric Mann-Whitney test.

Comparison of scores on the Wechsler memory scale and Cued Recall/Rapid Retrieval/ Trails revealed no differences between the two groups (Tables 6.20 and 6.21).

Table 6.20

Wechsler Memory Scale: Top quartile of change (DC2:0) and bottom quartile of change (DC2:1) on the CAMCOG

Baseline scores	Upper quartile n = 32	Lower quartile n = 30	Statistic	P
Logical Memory 1 Centile	22.3 (8.4)	20.8 (4.5)	Z -0.84	0.400
Logical Memory 2 Centile	53.0 (30.6)	45.5 (21.7)	Z -0.95	0.340
Verbal Paired Associates Total	17.3 (8.9)	14.8 (5.6)	Z -1.00	0.316
Verbal Memory index	52.5 (29.0)	42.6 (23.4)	Z -1.21	0.227
Digit span forward centile	16.2 (3.9)	15.9 (4.3)	Z -0.03	0.977
Digit span backwards centile	99.1 (17.3)	92.0 (21.1)	Z -1.19	0.234
Digit span total	60.9 (26.7)	61.1 (32.1)	Z -0.45	0.656
	57.2 (28.7)	54.7 (28.0)	Z -0.17	0.865
	14.9 (3.5)	14.5 (4.0)	Z -0.14	0.887

DC2:0 = change \geq 75th percentile; DC2:1 = change \leq 25th percentile; * = Mean (SD); Z = statistic for non-parametric Mann-Whitney test.

Table 6.21

Cued Recall/Rapid Retrieval/ Trails: Top quartile of change (DC2:0)
and bottom quartile of change (DC2:1) on the CAMCOG

Baseline scores	Upper quartile n = 32	Lower quartile n = 30	Statistic	P
Cued recall retrieval	28.3 (5.1)	29.4 (4.9)	Z -0.97	0.334
Cued recall acquisition	36.0 (0.2)	35.9 (0.3)	Z -0.69	0.487
Cued recall retention	12.0 (0.0)	12.0 (0.0)	Z -0.00	1.000
Cued recall - delayed free recall	10.1 (2.7)	10.0 (2.4)	Z -0.63	0.528
Fluency - F	11.6 (4.9)	12.4 (4.2)	Z -0.58	0.564
Fluency - A	11.2 (4.1)	11.2 (5.3)	Z -0.28	0.784
Fluency - S	15.4 (4.8)	14.3 (6.7)	Z -0.55	0.583
Fluency - Supermarket items	22.8 (7.1)	25.9 (5.8)	Z -2.17	0.030
Trails A	38.2 (9.8)	45.7 (51.2)	Z -0.90	0.369
Trails B	105.8 (46.7)	117.7 (125.7)	Z -0.52	0.604

DC2:0 = change \geq 75th percentile; DC2:1 = change \leq 25th percentile; * = Mean (SD); Z = statistic for non-parametric Mann-Whitney test.

No differences in brain measurements, homocysteine levels or APOE genotype were identified between the two groups (Tables 6.22 and 6.23).

Table 6.22

Brain measurements: Top quartile of change (DC2:0) and bottom quartile of change (DC2:1) on the CAMCOG

Baseline scores	Upper quartile n = 32	Lower quartile N = 30	Statistic	P
Medial Temporal lobe width R	19.4 (2.9)	18.7 (2.3)	Z -0.71	0.477
Medial Temporal lobe width L	19.6 (2.5)	18.5 (3.1)	Z -1.27	0.204
Temporal fissure R(% abnormal rating)	9.4	10.0	χ^2 0.01	0.934
Temporal fissure L(% abnormal rating)	6.3	3.3	χ^2 0.29	0.593
Third Ventricle	3.6 (2.0)	3.9 (2.4)	Z -0.38	0.704
Cranial Diameter	128.5 (4.6)	127.2 (5.4)	Z -0.78	0.437
Sylvian fissure R (% abnormal rating)	68.8	80.0	χ^2 1.02	0.312
Sylvian fissure L (% abnormal rating)	68.8	80.0	χ^2 1.02	0.312
Bicaudate distance	12.8 (3.4)	13.0 (3.5)	Z -0.40	0.692
Lateral ventricle R	3.3 (2.3)	3.8 (2.0)	Z -1.12	0.263
Lateral ventricle L	4.3 (2.3)	4.4 (2.1)	Z -0.17	0.869
Ratio	0.2 (0.1)	0.2 (0.1)	Z -0.66	0.507

DC2:0 = change \geq 75th percentile; DC2:1 = change \leq 25th percentile; Numbers with brackets are means with SD; Z = statistic for non-parametric Mann-Whitney test; χ^2 = chi square test statistic. Temporal horn rating of 2 or 3 and Sylvian fissure rating of 1 or 2 were considered to be abnormal for the purpose of this analysis.

Table 6.23

Homocysteine and APOE: Top quartile of change (DC2:0) and bottom quartile of change (DC2:1) on the CAMCOG

Baseline scores	Upper quartile n = 32	Lower quartile n = 30	Statistic	P
Homocysteine (µg/l)	13.0 (5.7)	12.3 (5.4)	Z -0.44	0.663
APOE ε4 (%)	20.0	19.0	χ ² 0.02	0.887

DC2:0 = change \geq 75th percentile; DC2:1 = change \leq 25th percentile; χ^2 = chi square test statistic. Z = statistic for non-parametric Mann-Whitney test;

12.4.3 Cox Regression Analysis Results

Table 6.24

Cox Regression Analysis Results:

Cox Regression Analysis Results 1: All factors included in the model (full model)

Factor	Coefficient (B)	Standard error for B	Wald statistic	P value	OR	95% CI for OR	
						Lower	Upper
Cam1score	-.12	.05	4.51	.034	.89	.80	.99
CC	.12	.12	.97	.325	1.13	.89	1.43
Memory	.21	2.13	.01	.920	1.24	.02	79.97
FULDS2	-.12	2.13	.00	.954	.88	.01	57.86
RAPRSN	.07	.04	3.03	.082	1.07	.99	1.15

Further Cox Regression analysis using Wald stepwise forward factor Selection method produced no results due to non-convergence of the regression.

6.5 Discussion

The univariate analysis comparing those who were stable with those who declined in cognitive scores, revealed significant differences in five variables. Greater age was more likely at baseline in those who declined and the width of the left medial temporal lobe was greater at baseline in this group. At baseline, three neuropsychological test variables were significantly better in the stable group. The baseline total CAMCOG score and sub-scale scores did not distinguish the groups. The Cox regression analysis also produced a paradoxical result in that narrower medial left temporal lobe width was more likely in the group that showed no decline in CAMCOG score. The finding of significance for the width of the left medial temporal lobe on the regression analysis is inconsistent with the premise that subtle memory decline indicates the presence of brain disease. The difficulty in measuring medial temporal width, as mentioned in chapter 4, probably explains this result. In addition, a single measure is far less significant than longitudinal data so this result cannot be taken seriously. The magnetic resonance imaging literature highlights how important follow-up measurements of brain morphology are. The approach used in this study was probably unhelpful.

Overall, the baseline data do not show any clear meaningful independent predictors of decline apart from age.

There are relatively few studies of the prospective use of the CAMCOG in cognitively normal elderly subjects. A Cambridge University study examined 365 females between the ages of 70 and 79 of whom 237 were re-examined a mean of four years later (Brayne *et al* 1997). The mean baseline CAMCOG was 84.4/106, however this included 29 participants with dementia. Twelve demented subjects were included in the follow-up interviews that showed the mean CAMCOG score to be 79.3/106. Further analysis of scores from the non-demented subjects was not recorded in the paper. This and the greater mean age of the cohort make it difficult to compare studies.

A later study by the group from Cambridge University used the CAMCOG to determine change in normal ageing (Cullum *et al* 2000). They reported on 135 subjects without dementia who had decline of 6 points in CAMCOG scores over the four years of follow-up. The group included a number of participants with low MMSE scores. The authors acknowledge this by suggesting that inclusion of cases of pre-dementia may have accounted for some of the decline along with regression to the mean of CAMCOG scores. The mean score at baseline of 87.7/106 is considerably below the mean in this study as detailed in chapter 4 as is the mean age of 81.5 years. The Cambridge study did not examine variables that independently predicted cognitive decline.

The AMSTEL study examined change in the CAMCOG in a group of 405 subjects with a range of cognitive deficits (Jonker *et al* 1998). The sample was

chosen on the basis of MMSE score and those with a score of <22 were all selected along with subjects with borderline cognition. Only 215 subjects were included with a MMSE score of 27 or above. Of the group, 317 were designated as having normal cognition and the mean CAMCOG score in this group was 87.6/107. The group designated as minimal dementia was considered to be consistent with CDR score of 0.5. For this group the mean CAMCOG score was 72.6/107. The mean age of the total sample was 75.6 years. Over the four year follow-up period the decline in the CAMCOG score was 1.48 points in the cognitively normal group. The subjects in the AMSTEL study are manifestly different from those in the current study. They are older and the minimal dementia group appears to be quite impaired. This raises the possibility that the cognitively normal group may include some cases of pre-dementia.

Another group from the Netherlands investigated 37 memory clinic attenders and 28 control subjects, recruited through newspaper advertisements, for a mean period of 1.8 years (van der Flier *et al* 2005). The purpose of the study was to determine if MRI measurements predict cognitive decline, however of interest here is that the CAMCOG was the cognitive measure used. Of the 37 clinic patients, 20 had subjective memory complaint and 17 met the Petersen criteria for mild cognitive impairment (MCI). The original version of the CAMCOG was used at baseline and follow-up. At baseline the score was 96/107 in the control group, 93/107 in the subjective memory complaint

group and 83/107 in the MCI group. This differential between the control and memory complaint groups is similar to the findings in chapter 4. At follow up medial temporal lobe volume as measured with MRI was independently associated with the baseline CAMCOG score, a similar finding to the result presented from the current study in this chapter. Unfortunately, follow-up CAMCOG scores for the control group were not mentioned. However, no subjects progressed to dementia in the follow-up period.

One can conceptualise categories of brain function designated as:

1. normal
2. subjective memory complaint
3. mild cognitive impairment
4. dementia.

The disparate means of determining allocation to each category means the data presented in the current study are not directly comparable to data from other studies. Indeed, most studies appear to be unique in their methodology and none can be compared with another directly. The purpose of the current study was not principally to monitor changes in diagnostic categories. Therefore, clinical follow-up of cases did not occur. So the incidence of mild cognitive impairment and dementia was not determined. The mean follow-up scores suggest that these outcomes would have been unlikely during the length of the study. Previous studies using the CAMCOG examined subjects with seemingly greater cognitive impairment than in this cohort.

Consideration of what constitutes a normal score is relevant. The robust norms method of identifying normative data is rarely used (Sliwinski *et al* 1996), i.e. norms are derived from subjects who have stable cognitive function over time. Failure to do so overestimates the effect of age on cognitive function. It could be argued that norms for the CAMCOG are unknown. Williams *et al* did not use this method to derive their normative scores (Williams *et al* 2003). One outcome of the current study is that it may provide more robust norms for future reference.

This exploratory examination of CAMCOG scores and change over a three-year period has failed to show robust predictors of decline apart from age. The small sample size, relatively young age of the sample, short follow-up period and sub-optimal brain imaging are factors that may explain this. Ideally, magnetic resonance imaging should have been employed to provide the baseline assessment of brain morphology (Bosscher *et al* 2002).

Part 3

Chapter 7

SUMMARY OF FINDINGS

7.1 Introduction

Dementia is a common clinical syndrome that causes significant harm to individuals, their families and to the wider community. In Australia and other developed countries, it is believed that increasing prevalence rates seen in recent decades will continue and place considerable burden on health care systems. In Australia, most dementia care is provided by informal caregivers and nursing homes are 81% occupied by those with possible or probable dementia (AIHW 2004). This amounts to large personal and financial costs.

Following the advent of cholinesterase inhibitor treatment ten years ago for Alzheimer's disease (AD), there has been a focus on diagnosing AD earlier in the course of the disease. This is based on the premise that earlier treatment is more beneficial than later treatment. There is an opinion emerging that even with current practice, the cholinesterase inhibitors are being used too late in the disease process (Mori *et al* 2006, Nordberg 2006). With this greater medical focus on AD, as opposed to a social one, there has been great interest in diagnosing brain disease at a time when subtle symptoms of brain failure are emerging.

The need to diagnose degenerative brain disease early has led to a host of clinical scales, criteria and syndromes being proposed. These were detailed in chapter 2. In addition, sophisticated imaging techniques have been examined in research centres to detect changes in key brain structures. For the clinician, a simple office method of identifying at risk patients as early as possible in the course of the disease is needed. This study aimed to determine if the simple complaint of subjective memory loss, in the absence of objective evidence of cognitive decline, leads to identification of at risk individuals.

How Useful in a Clinical Setting is a Complaint of Memory Loss?

The univariate analysis showed that memory complainers had a significantly lower score on a global cognitive test. The variables found to be different between the groups in the univariate analysis failed to converge in the logistic regression models. When cases and controls were matched according to age, sex and length of follow-up, only one significant variable (Temporal Order Word Hits) was shown to influence the occurrence of memory complaint.

These data suggest that the complaint of memory loss is not helpful in a clinical setting in terms of identifying those with significant cognitive impairment.

How Useful is 'Risk Factor' Determination in Identifying at-risk Individuals?

The radiological and laboratory parameters used in this study failed to distinguish complainers from controls. Greater age identified those who declined on the CAMCOG. Paradoxically, greater left medial temporal lobe width identified those who declined on the CAMCOG, but this group included complainers and controls.

These results suggest that complaints of memory problems are not associated with established risk factors for Alzheimer's disease and fail to predict objective cognitive decline over three years.

Limitations of this Study

The previous chapters have identified methodological problems with the conduct of the study. These include:

- The small numbers in each group compromised the power of the study.
- The relatively young age of the sample yielded a low prior probability of detectable early brain disease in the memory complaint group.
- The control group may not have been independent because of use of spouses of complainers.
- Cases may not have been representative of a population sample as they largely came from a high socio-economic region of WA. In addition, the complainers in this study actively sought medical attention and this may have led to selection bias.

- The follow-up period may have been inadequate to observe the expected changes.
- The study did not include ascertainment of incidence of dementia in the follow-up period, but cognitive decline. Incidentally, none of the participants converted to dementia during follow up.
- The imaging modality was clearly inadequate, as it was difficult to reliably define the medial temporal lobe structures on the CT scans.

Ideal study methodology

- Population representative case ascertainment to overcome selection bias.
- Control group acquisition independent of cases.
- Use of MR for brain imaging.
- Longer follow-up period. This would allow the discretion to exclude the baseline scores from analysis to diminish the effects of stress at first examination and learning at the second.
- Determination of incident MCI and dementia or conversion from CDR 0 to 0.5/1.0
- Larger sample size

The literature review suggests that subjective memory complaint is a valid trigger for assessment of presence of early brain disease. Neuropsychological testing is the preferred method of determining risk, as it is inexpensive. Data is robust for tests of episodic memory.

While the imaging approach used in the current study was not beneficial clinically, the advent of more sensitive technologies such as amyloid imaging offers the promise of more definitive and early diagnosis. This knowledge should serve as the basis for developing diagnostic blood tests that may eventually be used routinely in clinical practice.

Examination of the literature to put this study into appropriate context has revealed a number of issues relevant to current clinical practice. There are concerns regarding how a diagnosis of dementia is made when there are no standardised means of defining function loss. A recent position paper advocates revision of the NINCDS-ADRDA criteria (Dubois *et al* 2007). In the proposed criteria, function loss is not included and diagnosis is largely based on the presence of a carefully assessed deficit in episodic memory in addition to evidence of a biological manifestation of disease.

There is uncertainty regarding the evidence available to determine the veracity of nosological entities. Mild cognitive impairment is still not uniformly defined. If the revision of the NINCDS-ADRDA criteria gains acceptance then there may be less of a need to identify such an entity. Controversy stills exists about whether brain atrophy is a disease or the physiological effects of normal ageing. Very few studies can be compared directly, as the methodologies used are so varied. Differences exist in

participant acquisition, definition of caseness, diagnosis of target condition, exclusions and tests used.

The quest for a simple clinical marker of early brain disease remains unfulfilled. Despite this, the work of Morris and Petersen suggests that careful consideration of informant information, targeted use of robust tests of episodic memory and applying good clinical judgment will allow risk stratification and use of effective treatment when it becomes available.

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Appendix 1

NINCDS-ADRDA Clinical Diagnosis of probable Alzheimer's Disease

The criteria for the clinical diagnosis of probable Alzheimer's disease include all of the following.

1. Dementia, established clinically.
2. Deficits in two or more areas of cognition.
3. Progressive worsening of memory and other cognitive functions.
4. No disturbance of consciousness.
5. Onset between ages 40 and 90.
6. Absence of other systemic disorders or brain diseases that in themselves could account for the progressive deficits in memory and cognition.

Features supporting the diagnosis

The diagnosis of probable AD is supported by the following:

1. Progressive deterioration of specific cognitive functions such as language (aphasia) motor skills (apraxia) and perception (agnosia).
2. Impaired activities of daily living and altered patterns of behaviour.
3. Family history of similar disorders, particularly if confirmed neuropathologically.
4. Laboratory results of:
 - Normal lumbar puncture as evaluated by standard techniques
 - Normal pattern or non-specific changes in EEG such as increased slow-wave activity; and
 - Evidence of cerebral atrophy on CT with progression documented by serial observation

Features consistent with diagnosis

Other clinical features consistent with the diagnosis of probable AD, after exclusion of causes of dementia other than AD, include the following.

1. Plateaus in the course of the progression of the illness.
2. Associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional or physical outburst, sexual disorder or weight loss.
3. Other neurological abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder.
4. Seizures in advanced disease.
5. CT normal for age.

Features making diagnosis uncertain

Features that make the diagnosis of probable AD uncertain or unlikely include the following.

1. Sudden, apoplectic onset.
2. Focal neurologic findings such as hemiparesis, sensory loss, deficits in visual field and in coordination early in the course of the illness.
3. Seizures or gait disturbance at the onset or very early in the course of the illness.

DSM-IV Definition for VaD

- Focal neurological signs and symptoms (for example, exaggeration of deep tendon reflexes, extensor plantar responses, pseudobulbar palsy, gait abnormalities, weakness of an extremity, etc)

Or

- Laboratory evidence of focal neurological damage (eg multiple infarctions involving cortex and underlying white matter)
- The cognitive deficits cause significant impairment in social or occupational functioning and represent a significant decline from a previously higher level of functioning
- The focal neurological signs, symptoms and laboratory evidence are judged to be aetiologically related to the disturbance
- The deficits do not occur exclusively during the course of delirium
- The course is characterized by sustained periods of clinical stability punctuated by sudden significant cognitive and functional losses

The ICD-10 Criteria for VaD

- Unequal distribution of deficits in higher cognitive functions with some affected and others relatively spared. Thus memory may be quite markedly affected while thinking, reasoning and information processing may show only mild decline
- There is evidence for focal brain damage, manifest as at least one of the following: unilateral spastic weakness of the limbs, unilaterally increased tendon reflexes, an extensor plantar response, pseudobulbar palsy
- There is evidence from the history, examination or test of significant cerebrovascular disease, which may reasonably be judged to be aetiologically related to the dementia (history of stroke, evidence of cerebral infarction)

The ADDTC Criteria for Probable ischaemic vascular Dementia (IVD)

- A The criteria for the clinical diagnosis of probable IVD include all of the following:
 - 1. Dementia
 - 2. Evidence of two or more ischaemic strokes by history, neurological signs and/or neuroimaging studies (CT or T1-weighted MRI), or occurrence of a single stroke with a clearly documented temporal relationship to the onset of dementia
 - 3. Evidence of at least one infarct outside the cerebellum by CT or T1-weighted MRI
- B The diagnosis of probable IVD is supported by:
 - 1. Evidence of multiple infarcts in brain regions known to affect cognition
 - 2. A history of multiple transient ischaemic attacks
 - 3. History of vascular risk factors (for example, hypertension, heart disease, diabetes mellitus)
 - 4. Elevated Hachinski ischaemic score (original or modified version)
- C. Clinical features that are thought to be associated with IVD, but await further research, include
 - 1. Relatively early appearance of gait disturbance and urinary incontinence
 - 2. Periventricular and deep white matter changes on T2-weighted MRI that are excessive for age
 - 3. Focal changes in electrophysiological studies (eg EEG, evoked potentials) or physiological neuroimaging (eg SPECT, PET, MRI spectroscopy)
- D. Other clinical features that do not constitute strong evidence either for or against a diagnosis of probable IVD include
 - 1. Periods of slowly progressive symptoms
 - 2. Illusions, psychosis, hallucinations, delusions
 - 3. Seizures
- E. Clinical features that cast doubt on a diagnosis of probable IVD include
 - 1. Transcortical sensory aphasia in the absence of corresponding focal lesions on neuroimaging studies
 - 2. Absence of central neuroimaging symptoms/signs, other than cognitive disturbance

The NINDS-AIREN criteria for probable VaD

The criteria for the clinical diagnosis of probable VaD include all of the following:

1. Dementia
2. Cerebrovascular disease, defined by the presence of focal signs on neurological examination, such as hemispheric, lower facial weakness, Babinski sign, sensory deficit hemianopsia, dysarthria etc, consistent with stroke (with or without a history of stroke) and evidence of relevant CVD by brain imaging (CT or MRI) including multiple large vessel strokes or a single strategically placed infarct (angular gyrus, thalamus, basal forebrain, PCA or ACA territories) as well as multiple basal ganglia and white matter lacunes or extensive periventricular white matter lesions or combinations thereof
3. A relationship between the above two disorders manifested or inferred by the presence of one or more of the following:
 - a. Onset of dementia within 3 months following a recognized stroke
 - b. Abrupt deterioration in cognitive functions; or fluctuating , stepwise progression of cognitive deficits

Clinical features consistent with the diagnosis of probable vascular dementia include the following.

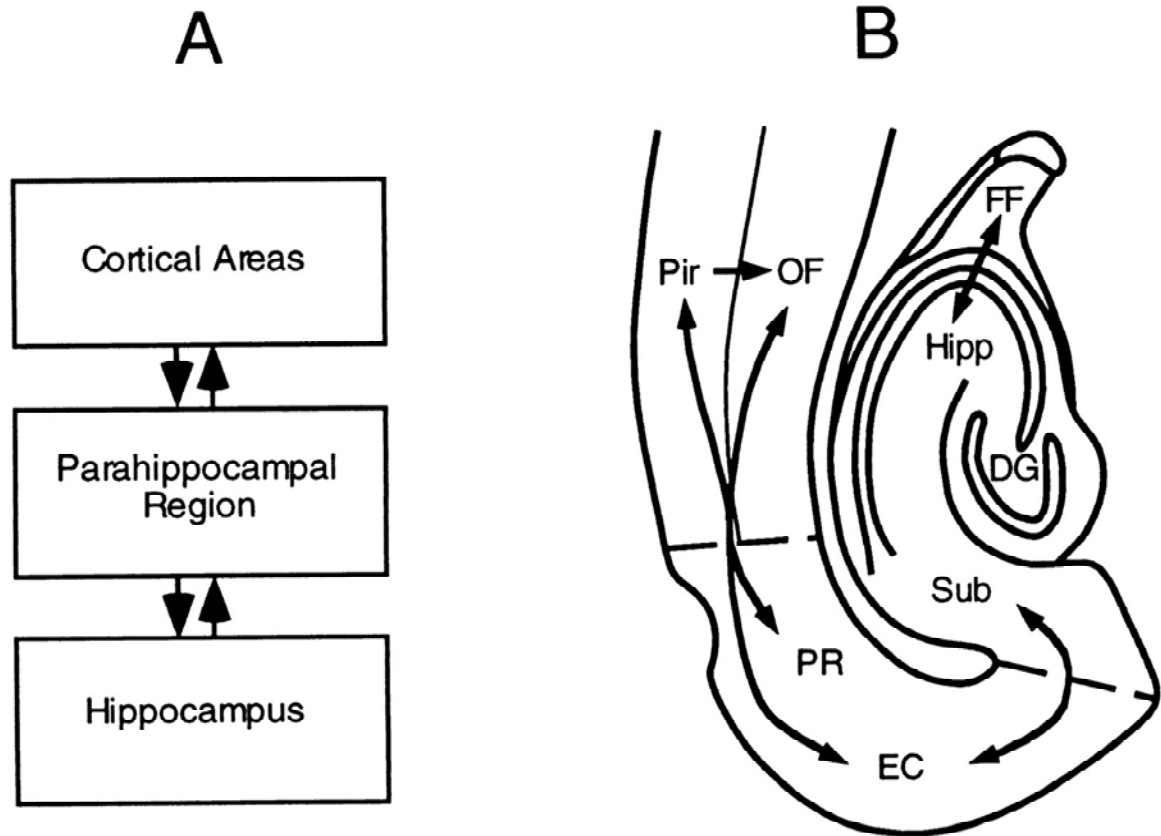
1. Early presence of a gait disturbance (small step gait or *marche á petits-pas*, magnetic, apraxic, ataxic or Parkinsonian gait).
2. History of unsteadiness and frequent, unprovoked falls.
3. Early urinary frequency, urgency, and other urinary symptoms not explained by urological disease.
4. Personality and mood changes, abulia, depression, emotional incontinence, other subcortical deficits including psychomotor retardation and abnormal executive function.

Features that make the diagnosis of vascular dementia uncertain or unlikely include:

1. Early onset of memory deficit and progressive worsening of memory and other cognitive functions such as language (transcortical sensory aphasia), motor skills (apraxia), and perception (agnosia), in the absence of corresponding focal lesions on brain imaging.
2. Absence of focal neurological signs, other than cognitive disturbance.
3. Absence of cerebrovascular lesions on brain CT or MRI.

Appendix 2

Neuropsychological test Protocol

Appendix 3

Hipp = hippocampus, Sub = subiculum, EC = entorhinal cortex

Rapid Retrieval Task

I would like you to tell me as quickly as you can all the words you can think of that begin with the letter

F

I would like you to tell me as quickly as you can all the words you can think of that begin with the letter

A

I would like you to tell me as quickly as you can all the words you can think of that begin with the letter

S

I would like you to tell me as quickly as you can all the things you can think of that you would find in a supermarket