A STUDY OF DEMENTIA IN A RURAL POPULATION

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by

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DECLARATION

This study was designed and conducted by the author who personally interviewed and investigated all the subjects. Dr Paul Calloway conducted the Geriatric Mental State interviews on a subsample of the subjects. Mr Julian Lipscombe and Mrs Sue Edmonds entered the data. The assays of thyroid function and creatine kinase isoenzymes were carried out in the Department of Biochemistry and those of auto-antibodies in the Department of Immunology at Addenbrooke's Hospital, Cambridge. Analyses of haematology and biochemistry samples were performed as part of the routine laboratory service.

The term Alzheimer's disease and multi-infarct dementia have been used throughout, rather than a number of other terms used in the literature.

ABSTRACT

Dementia, in particular Alzheimer's disease, has been widely investigated in clinical settings. Moreover, many epidemiological studies have been carried out to estimate the prevalence and incidence of dementia and, less frequently, Alzheimer's disease. There have also been studies of ageing cohorts to examine mental changes associated with ageing. There has, however, been little research on unselected elderly populations which has been detailed enough to examine the relationship between normal and abnormal mental ageing. The aim of this study was to investigate the distribution of the indices of dementia in a rural population. This allowed investigation of the hypothesis that variables associated with dementia, in particular Alzheimer's disease, are distributed bimodally in the population and allowed investigation of possible associations with these distributions. It also provided prevalence estimates of dementia in a rural population.

A population sample of women aged 70 to 79 was selected from a rural Cambridgeshire health centre. Using the Cambridge Examination for Mental Disorders in the Elderly all aspects required for the diagnosis of dementia and tentative differential diagnosis were collected on 365 women. There was no evidence of bimodality in any of the derived scales, whether cognitive, behavioural or ischaemic. The prevalence of dementia of all types and levels, including mild, was 4.3% in the 70 to 74 age group and 11.7% in the 75 to 79 age group. For more severe dementia a prevalence of 2.8% was found in the 75 to 79 age group, and 0% in the 70 to 74 age group. The rates for more severe dementia were lower than other recent prevalence studies in the UK, whereas the rates for all levels of severity were higher. The tentative diagnosis of Alzheimer's disease accounted for 52% of the diagnoses of dementia and multi-infarct dementia for 31%.

Age, social class and education were all significantly and independently associated with scores on the longer cognitive scales (Mini-Mental State Examination and the CAMCOG scale of CAMDEX). Risk factors suggested in the literature for dementia, Alzheimer's disease

and cognitive impairment was also investigated. Few factors were associated with either cognitive function or dementia. Age was the only variable associated with both cognitive function and the diagnosis of dementia. Only small proportions of the population were exposed to postulated risk factors and these risk factors, if proven, would account for little population excess risk.

In this study no significant separation of performance on cognitive or behavioural scales between the demented and the non-demented was found. This could have been due to the small numbers in the tails of the frequency distributions but, if true, it is suggested that this observation might be related to the continuous distribution of underlying neuropathological lesions, such as plaques and tangles, noted in autopsy series of unselected populations. If so, current research into the mechanisms of the dementias may have implications for the understanding of cognitive decline noted in the non-demented elderly over time.

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INTRODUCTION

This century has seen a profound change in the structure of human populations. In Western societies the diagramatic representation of population age distribution has changed from a pyramid to a cylinder, with an increase in the proportion of the elderly. Developing countries do not have such aged populations but will experience similar demographic changes in the next century. These changes have arisen as a result of reduction in mortality in childhood, reduced birth rates and increased longevity at middle and older ages. Average life expectancy at birth has increased in the United Kingdom from 60 years in the last century to 75 years. The French demographer, Alfred Sauvey is quoted as saying that Europe could become "one enormous old peoples' home" (Pearce 1987). Age-associated disorders are of greater interest now than at any other time in the past. A major challenge to medical research has become the possibility of reducing morbidity in the older age groups and therefore improving quality as well as quantity of life (Fries 1983).

A further probable reason for the noted increase in chronic disorders of the aged is the improvement in treatment of previously fatal conditions such as pneumonia, which has been called the "failure of success" (Gruenberg 1977). The rise in prevalence of certain mental disorders as a result of these population changes has been called a pandemic (Kramer 1980). Dementia is an age specific disorder of particular importance because demented individuals require intensive care from statutory services, voluntary agencies and informal care networks such as family and neighbours. It has been estimated that there will be an increase in the numbers affected by dementia in less developed countries of 123% (7 million to 15 million), from 1975 to 2000, and in more developed countries of 54% (9 million to 14 million) (Brody 1985). Economically and socially this group of the population places a heavy burden on society. The elderly of different generations have widely differing expectations of services and the expectations of the future elderly are likely to be different from those of the past (Fox 1987). These changes will increase the need for services.

The quantity and quality of research into dementia over the last decade has increased dramatically. Attention has been directed to finding how much dementia there is in various communities, and also to the search for the causes of Alzheimer's disease, which is probably the commonest form of dementia in Western communities. There has been a separate initiative to elucidate the fundamental processes of ageing and associated mental changes. However, it has been difficult to link findings regarding normal and abnormal ageing despite the observation that in the area of mental health there is no evidence of a natural division between mentally ill and mentally healthy sections of elderly populations (Cooper and Sosna 1983).

Research into dementia in elderly populations has become increasingly structured in the last 20 years with development of diagnostic criteria and standardised instruments specifically for this purpose. Most epidemiological studies have measured limited aspects of dementia such as short measures of cognitive function, or have examined only selected groups in any detail. There has been a call to examine entire communities of elderly people and for development of valid means of classifying individuals according to cognitive ability/disability (Brody 1982), using sensitive instruments capable of detecting the early stages of dementia (Henderson 1986).

The epidemiological study described in this thesis examined a rural population of women in a defined age group (70 to 79 years) using a standardised psychiatric instrument specifically designed for the early detection of dementia in the elderly (CAMDEX: Cambridge Examination for Mental Disorders in the Elderly, Roth et al 1988). The results provide estimates of rural prevalence rates for dementia and compare different methods of case identification. They also describe the relationship of normal to abnormal cognitive function and behavioural measures in this population, and examine for associations between possible risk factors for cognitive impairment and dementia.

BACKGROUND

DEMOGRAPHIC CHANGES

The average age of mankind at death has risen since the early ages as shown below (Hayflick 1981,1984).

Early Bronze Age	18
Roman times	22
Middle Ages (UK)	33
Pre 1789 (USA)	35.5
19th Century (UK)	40.9
1900 (US)	49.2
1946 (US)	66.7

Ageing of large numbers of the population is a relatively new phenomenon. In 1950 there were 214 million people aged over 60, and by 2025 there will be a billion (Henderson 1986). In Europe by this time a quarter of the population will be aged over 60 years. The proportion of the elderly in the United Kingdom will remain stable in the next decades, but the proportion of those aged 75 and over will increase considerably into the next century (Pearce 1987). With these population changes, increasing numbers of demented individuals in society are expected, with increased demands upon the statutory services and informal sector.

DEMENTIA

Dementia is a complex disorder, which some claim should be considered to be a syndrome (Mahendra 1984), and others as a disease (Creasey and Rapoport 1985). It is difficult to diagnose in the early stages (Henderson and Huppert 1984), and difficult to make differential diagnoses. Validation of the diagnosis presents problems. The following section considers these areas, starting with the development of the concept of dementia, and our current definitions of the dementia disorders. This is followed by the methods used to identify demented individuals in the community, and concludes with a resume of the epidemiological findings.

For centuries age has been associated with decrepitude and melancholy, and by the sixteenth century it was commonplace to accept

the inevitability of these with age (Mahendra 1984). The separation of dementia from the ageing process began in the eighteenth century, with development of classifications such as ".. by degrees dull and at length foolish by mere declining age without any great errors of living... Great strokes, bruising of the head.. fall from high places.... Frequent drunkenness and surfeiting..." (Blancard's Medical Dictionary, Berrios 1987a). Clinicians from this time and into the early 19th century tended to refer to any mental illness which affected intellectual function as dementia, and mental handicap was only separated from this in the 19th century (Berrios 1987b). Georget included non-reversibility in the diagnosis in 1820 (Loo and Plas 1986). The more recent classification systems for dementia have reinforced the separation of dementia from normal ageing, such that is usually considered to be completely separate from the so-called normal ageing processes (Creasey and Rapoport 1985).

The concept of atherosclerotic dementia was not developed until the early nineteenth century when Griesinger suggested that senile dementia was caused by atherosclerosis (Mahendra 1984). In Kraepelin's classification of mental illness in 1883 "Insanities of the aged" was one category, and arteriosclerosis was thought to be a cause of mental impairment in 50% of these. In the late nineteenth century senile plaques were described in the brain of an aged epileptic, and were named miliary sclerosis. In 1907 Fisher found plaques in 12 out of 16 aged dements. At the same time Alzheimer published the neuropathology of a case of presenile dementia, which is now taken to be the classical description of Alzheimer's disease (Alzheimer 1907). Dementia then became separated into Alzheimer's disease and arteriosclerotic dementia. The term arteriosclerotic dementia was introduced by Alvarez, but the term was not entirely accepted and it was not until the last few decades that the category has been widely used. This type of dementia is now called multi-infarct dementia, a term coined by Hachinski (1975).

Diagnostic criteria for dementia

The Royal College of Physicians (UK) in a report in 1981 suggested the following definition of dementia:

> dementia is the global impairment of higher cortical function including memory, the capacity to solve the problems of day to day living, the performance of learned perceptuomotor skills, the correct use of social skills and control of emotional reactions, in the absence of gross clouding of consciousness, the condition is often irreversible and progressive.

Most definitions closely resemble this, and the most widely used sets of diagnostic criteria are now the Diagnostic and Statistical Manual of the American Psychiatric Association Third Edition (1980), which has been revised (DSM-III-R, American Psychiatric Association 1987) and the International Classification of Diseases, Tenth Revision, which is in preparation (WHO 1988). The criteria for dementia and the differential diagnosis of dementia of the instrument CAMDEX (see later) are also similar. A further important set of criteria are those from a work group on the clinical diagnosis of Alzheimer's disease established by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA). The criteria are presented in full in Appendix 1 and are summarised in Table 1.

Diagnosis in the community

The early community studies of dementia were conducted by clinicians. The methods were, on the whole, unstructured. Subsequently the methods became more structured, first with the introduction of diagnostic criteria, and later with the introduction of standardised methods of data collection before arriving at diagnoses. Some of the methods used are given in the following sections.

TABLE 1

Criteria for dementia, Alzheimer's disease and multi-infarct dementia

	CAMDEX	DSM-III-R	NINCDS ADRDA
DEMENTIA	Global deterioration of intellectual, emotional, motivational behaviour in clear consciousness for 6/12. A. Progressive failure in everyday life B. Memory impairment C. Deterioration in one of following - intellectual ability; judgement; higher cortical function; deterioration of personality/general behaviour	A. Loss of intellectual abilities sufficient to interfere with social functions B. Memory impairment C. One of following - impairment of abstract thinking; deterioration in judgement; aphasia/apraxia; personality change D. Consciousness not clouded E. Other disorders excluded	Decline in memory and other cognitive function (history and examination), delirium excluded
ALZHEIMER'S DISEASE	Dementia A. Gradual onset B. Absence other aetiological factor C. Early dysphasia, agnosia, apraxia Cerebral atrophy Histopathological abnormality Not associated with signs of cerebrovascular disease	A. Dementia B. Insidious onset with uniformly progressive deteriorating course C. Exclusion of all other specific causes	Probable. Dementia (MMSE & Blessed dementia rating scale) Deficits 2 + areas cognition Progressive decline onset 40-90. Absence other aetiological disorders Possible. Dementia without other disorder Definite. Clinical criteria satisfied and histopathological evidence.
MULTI-INFARCT DEMENTIA	Dementia A. Sudden onset B. Stepwise deterioration C. One or more strokes or transient ischaemic attacks D. Focal signs E. Two of following - Patchy psychological deficits; Emotional liability; Insight loss; Depression/anxiety; Fits; Hypertension; Headache/dizziness; Gait abnormality	A. Dementia B. Stepwise deteriorating course. C. Focal neurolgical signs D. Evidence of significant cerebrovascular disease aetiologically related	Only as exclusion criteria AD unlikely if :- Sudden onset; Focal signs; Gait disturbance

Cognitive function

Measures of cognitive function are often employed in screening for and the diagnosis of dementia. Short cognitive scales have been developed in clinical settings and one of these has been used in large epidemiological studies of the elderly. The information/orientation test was been developed from the Clifton Assessment Procedure for the Elderly (Pattie and Gilleard 1979), and was found to distinguish demented subjects from normal controls in clinical settings, using experienced clinicians as the gold standard (McPherson et al 1975). This scale has been used widely in the community, in Melton Mowbray (Clarke et al 1984, 1986) and in Nottingham (Morgan et al 1987). The questions are basic and similar to those in other short cognitive scales such as the information-memory-concentration scale (Roth and Hopkins 1953), which was used in a prospective study of neuropathology and cognitive function (Tomlinson et al 1968). The original questions of the information-memory-concentration test have been shortened to 10 questions in the Abbreviated Mental Test (Hodkinson 1972). This test has been widely used in clinical but not community settings.

There are several longer scales which have been developed in clinical settings; the best known of these is the Mini Mental State Examination (MMSE, Appendix 2). This was developed as a practical method of grading the cognitive state of patients. It was validated on 206 patients with a variety of disorders and was considered to discriminate well between demented subjects and those with other disorders. It was found to have reasonable inter-rater reliability and test-retest stability and was acceptable to the tested population (Folstein et al 1975).

Premorbid intelligence

All diagnostic criteria for dementia mention decline in cognitive function. Since most studies are based on cross sectional data it has been suggested that an estimate of premorbid intelligence could help to identify decline. Measures of cognitive function are known to be affected by educational level (Richie 1988). The stability of verbal ability has been used to develop a simple test of pre-morbid intelligence called the National Adult Reading Test (NART). This was

based on the Schonell Graded Word Reading Test, and was developed on 98 controls aged 16-69 and 45 demented subjects aged 22 to 68 (Nelson and McKenna 1975). The result was compared with Wechsler Adult Intelligence Scale prediction of intelligence quotient (IQ). Reading ability was found to be a closer predictor of IQ than vocabulary level. There were no differences between the demented group and the normals in the reading ability. The test was later modified retaining only the most discriminating items and consists of reading out loud 50 irregular words (Nelson and O'Connell 1978) (see Appendix 2). The test has subsequently been validated in healthy volunteers (Ruddle and Bradshaw 1982), in demented subjects and controls in clinical settings (Nebes et al 1984), and has been found to be reliably recorded (O'Carroll 1987). No significant relationship between score, diagnosis and severity of dementia has been found in further studies (Nebes et al 1984, O'Carroll and Gilleard 1986, Crawford et al 1988). It was also found to be stable over time (Hart 1986). Other measures have been made, but the NART is the most widely used, although it has not been used in community studies.

Behavioural measures

Behavioural assessment is essential because of the important contribution of behaviour to all criteria for dementia. DSM-III-R criteria state that there should be loss of intellectual abilities severe enough to interfere with social functioning. Berrios (1989) has suggested that these criteria have emphasised cognitive decline too much, and that this prevents the criteria from differentiating other states with compromised cognitions if based on a single interview. Early dementia may be manifested by other disturbances such as those in motility, personality, organisation, emotional experience and volition. Such information is collected from an informant, which has the advantage of being more objective. Behavioural scales usually contain items which are relevant regardless of setting (Fillenbaum et al 1987). While systematic studies of behavioural change in the community are rare, such information has usually been collected in clinical series. The most widely used scale in the clinical setting has been the Blessed dementia rating scale (Blessed et al 1968). This scale consists of questions on change in performance in activities of daily living,

changes in habits, changes in personality, interests and drive. A standardised informant interview has been developed to assess change in memory and intelligence over 10 years (Jorm and Korten 1988). In the sample tested the informant history was less likely than the Mini-Mental State Examination to be affected by premorbid ability. The informant section correlated with overall health decline, not just mental decline. Some questions in such scales can be affected by physical impairment. The score can therefore be biased by health status. In some studies instructions to interviewers state that the interviewer makes a judgement about potential function (e.g. some applications of the Blessed dementia rating scale).

In the few community studies where both measures have been made an association between measures of cognitive function and daily activities has been found and much of the variance on the measure MMSE could be accounted for by activities of daily living (Teri et al 1988, Fillenbaum et al 1988). It has been suggested that a combined approach incorporating direct measures of cognitive function and indirect measures of change through questionning relatives would be a sensitive indicator of dementia in community samples (Fillenbaum et al 1988).

Despite the inclusion of personality in DSM-III-R criteria for dementia few systematic studies have been conducted on personality change in dementia or normal ageing in community settings, and there are no scales dealing with this area alone. In one study 44 demented subjects aged between 64 and 81 (selected out of 350) were followed for an average of 50 months and were compared with age, sex and social class matched controls. Informants were interviewed every 15 to 18 months. In 66% change towards less active, more "passive" behaviour was noted, in 30% "agitation", and in 34% "self centred behavioural change". These groupings were identified from a factor analysis of the data. The number of those agitated and self centred doubled over the observation period. 11% had all the features at outset, and 50% had developed all by the end (Rubin et al 1987). Thus substantial change was reported.

Depression

Depression should be considered in any discussion of dementia (Janowsky 1982), although they are usually distinct conditions in the elderly (Rabins et al 1984), with different outcomes and survival (Roth 1953, Blessed and Wilson 1982). The dementia syndrome ("pseudodementia") which can occur with depression does not progress and can reverse after treatment of the depression. The onset is described as relatively rapid, with short duration, rapid progression, antecedent psychiatric dysfunction, complaint of cognitive loss and emphasis on disability, strong sense of distress, pervasive affective change and variability of observed cognitive impairment (Mahendra 1985). However, symptoms of depression have been found to be ubiquitous in a group of demented patients (Lazarus 1987, Merriam et al 1988). In series of patients presenting to dementia clinics many patients who were initially diagnosed as depressed were found to have progressed to dementia (Kral 1983, Winstead and Mielke 1984, Reding 1985). These findings highlight the importance of including measures of depression in studies of dementia, with longitudinal study to confirm diagnoses.

Many scales are available for the measurement of depression. Some are diagnostic and others measure the level of depression. In clinical studies of dementia the Hamilton depression rating scale (Hamilton 1960) is the most frequently used scale to exclude subjects who may be suffering from pseudodementia. It is generally used to obtain an overall severity score and in many studies of dementia, individuals who score over a particular cutpoint are excluded from study. This introduces a possible bias into these studies which is rarely discussed. This scale was not developed for the elderly and other community studies have used a variety of scales (eg Morgan et al 1987, Livingston et al 1990).

Differential diagnosis

Criteria for Alzheimer's disease always contain an exclusion clause for multi-infarct dementia and confusional states. The most frequently used scale to attempt to exclude multi-infarct dementia is the Hachinski scale (Hachinski et al 1975). Results are not available from population samples. The relationship of this scale to underlying

neuropathology is described in the multi-infarct dementia section. As with the depression scales, cutpoints on the scale have been used to either exclude or include subjects in case series and case control studies. Acute confusional state is a category of some importance in the clinical setting. It is a transient global cognitive disorder due to organic aetiology, usually of abrupt onset and brief duration with disturbance of attention, sleep wake cycle and psychomotor disturbance. 35% of those aged over 65 admitted to hospital are said to be suffering from such a condition or develop it during their stay (Lipowski 1983). This group have a high mortality both immediately and up to one year after admission (Lipowski 1983, Rabins and Folstein 1982). Because of the nature of the disorder its prevalence in community studies would be expected to be low.

Combined interviews

The scales so far described refer to single aspects of dementia, such as cognition or behaviour. Clinically diagnosis is made on the basis of information about many different aspects of the patient, and in early epidemiological studies this was the type of unstructured diagnosis which was made by physicians or psychiatrists. Subsequently this changed to a diagnosis based on certain criteria. Clinicians could vary in the way in which they satisfied themselves that a criterion was fulfilled. As a result of this variability interviews have been developed to collect the necessary information for a diagnosis of dementia in a systematic fashion. The main such interviews are the Geriatric Mental State Examination (Copeland et al 1976) and the Cambridge Examination for Mental Disorders in the Elderly (Roth et al 1988). These are described below.

Geriatric Mental State Examination

The Geriatric Mental State Examination was developed in order to examine the full spectrum of mental disorders in the elderly in a standardised fashion. It is largely derived from the Present State Examination (PSE), a semistructured interview schedule developed by Wing and colleagues (1971). A Mental Status Schedule was added to the eighth revision of PSE and the instrument was first used in a cross-national study of the diagnoses of mental disorders in those aged over 65 years in institutions in New York and London (Copeland et al

1975). Twenty five independent factors arising from this study (Copeland et al 1976) were then tested on 100 elderly psychiatric in-patients and found to perform well in identifying different groups. There was some pre-selection before the analysis was conducted, which then agreed with the psychiatrists' clinical opinions (Gurland et al 1976). The GMS contains few items testing cognitive function, but has been expanded more recently to include the History and Aetiology Section, which is usually collected from an informant and a Social Status Section.

A computerised algorithm (AGECAT) for diagnoses of affective disorder, schizophrenia and paranoid states, organic psychoses, alcoholism, neuroses and personality disorders has been developed from this interview (Copeland et al 1986). For organic syndromes key items on observation and recall of simple items are included. An AGECAT organicity level 01 is a score of at least 2 on symptoms of mild memory disturbance such as forgetting the interviewer's name, miscalculating the time and the interviewer's impression of organic disorder. Level 02 is moderate memory disturbance with inability to calculate age, failure to recall the interviewer's name on a second occasion and misidentifying objects. Level 03 includes these errors as well as disorientation in time. Further levels of 04 and above are available for even more severely impaired individuals.

The original validation of AGECAT was performed with psychiatrists trained at the Maudsley Hospital. A further validation study has been reported on 647 subjects in 3 different community studies. Different versions of GMS were used, and different methods were used in the validation, such as repeat interviews and rating tapes. Kappa values, a measure of agreement which takes chance into account (Cohen 1960), for different diagnoses and levels of severity vary between 0.73 to 0.83 (Copeland et al 1988). These are reasonable measures of agreement, but they do reveal some disagreement which might be of importance in aetiological work.

Cambridge Examination for Mental Disorders of the Elderly (CAMDEX)

The Cambridge Examination for Mental Disorders of the Elderly (Roth et al 1986, 1988) was developed as a standardised clinical interview for use by clinicians in the differential diagnosis of mild to severe dementia in the elderly. The severity and extent of cognitive impairment and the rating of behaviour and activities of daily living were all seen as important components of the interview. These three areas were combined to provide a complete picture of the subject.

It consists of three main sections:

i) a structured clinical interview with the subject to obtain systematic information about the present state, past history and family history;

ii) a range of objective cognitive tests which constitute a mini-neuropsychological battery (CAMCOG, see below);

iii) a standardised schedule for recording observations of the present mental state, together with appearance and demeanour. These are as follows: self neglect, uncooperative behaviour, suspiciousness, hostility, bizzare behaviour, slowness, restlessness, anxiety, depressed affect, lability, flat affect, hallucinations, slurred, slow and restricted speech, rambling content of speech, perseveration, loss of insight, drowsiness, neologisms, talking to self, impaired ability to focus, sustain and shift attention, impaired judgement, hypochondriasis. These are rated as positive if markedly present;

iv) a structured interview with a relative or other informant to obtain independent information about the subject's present state, past history and family history;

v) a brief physical examination including neurological examination;

vi) an account of medical and laboratory investigations where appropriate.

At the end of the CAMDEX interview the interviewer makes a psychiatric diagnosis based on all relevant and available information according to operational diagnostic criteria (see Table 1 and Appendix 1). Guidelines for allocation of severity ratings are also

included with minimal, mild, moderate and severe levels of severity. Additional operational guidelines are given in the published version of CAMDEX (Roth et al 1988) which combine performance on cognitive, behavioural, depression and ischaemic scales with clinical assessment to arrive at operational probable and possible diagnoses.

CAMCOG, the mini-neuropsychological battery of CAMDEX, covers the range of cognitive functions mentioned in DSM-III-R, which requires the demonstration of a generalised loss of cognitive functions including language, praxis, perception, abstract thinking and constructional ability as well as memory (Roth et al 1986). In the original validation study its correlation with dementia severity was 0.68 (Roth et al 1986).

Information from someone who knows the subject well is essential in cross-sectional studies where diagnosis is attempted, as there is only one contact with the subject with no opportunity to observe deterioration over time. The informant section is therefore a key part of CAMDEX. There are some published data on this part of the intervew. In the Hughes Hall Project for Later Life informant interviews were available on 222 subjects with a diagnosis of dementia and 184 without (O'Connor et al 1989). Scales composed of informant items on orientation and memory were found to correlate with CAMCOG (0.61 and 0,67 respectively). If the observer section on rating present mental state was also added together this showed a correlation of 0.74 with the informant score. Where there was discrepancy between the informant interview content and the final diagnosis there was usually a clear reason, such as mental handicap or depression. There were no significant differences between informant scores for manual and non-manual social classes, nor for the different types of informant.

The use of this instrument has been described in several groups of patients and volunteers (Roth et al 1986). It was found to perform well in relation to prior clinical diagnoses. Embedded in the CAMDEX are several well-used scales, such as the ischaemic scale of Hachinski, the Blessed dementia rating scale and MMSE (see Appendix 2). In addition, following the validation study, scales were

constructed from the most discriminating individual items for organicity, ischaemia and depression. A further validation study has been conducted in the United States (Hendrie et al 1988). Inter-rater reliability was found to be satisfactory and CAMDEX was found to perform well as a diagnostic instrument. The scales constructed from CAMDEX items were significantly related to the appropriate diagnoses, so that those patients with a diagnosis of Alzheimer's disease had high mean scores on the organicity scale and those with a diagnosis of depression had high mean scores on the depression scale. Those with a diagnosis of multi-infarct dementia did not have higher mean scores on the ischaemia scale than those with Alzheimer's disease. The scales have not been validated against neuropathological diagnoses.

Diagnostic accuracy of dementia

The difficulties of accurate diagnosis of dementia, and the search for other causes of cognitive problems or reversible causes have been well reviewed (Gurland and Toner 1983). There are major difficulties in the identification of early dementia, since other conditions produce similar profiles (Henderson and Huppert 1984). In follow-up studies of diagnosed cases over various periods of time between 24% and 50% of subjects have been reported as not demented (Nott and Fleminger 1975, Ron et al 1979, Smith and Kiloh 1981, Shore et al 1983). Much higher validity of the clinical criteria for the diagnosis of dementia has been reported more recently in a longitudinal multicentre study (Joachim et al 1988). 55 consecutive patients who had suspected cognitive impairment from 3 different centres were evaluated by physicians using DSM-III-R criteria. Fifty two (95%) had the same diagnosis one year later. There is, therefore, some variation in the reported accuracy of the diagnosis of dementia. Some of this may be accounted for by the different entry criteria into studies, different methods of examination and variable length of follow up.

DIFFERENTIAL DIAGNOSIS OF DEMENTIA

Once dementia has been diagnosed in the clinical setting, a tentative differential diagnosis is usually made. In the community setting this presents more difficulties and few studies have attempted it. There are many other conditions which can lead to a dementia syndrome. Some examples of these are Pick's disease, Huntington's disease, Parkinson's disease, metabolic disturbances and toxic dementias. For some of the underlying causes of dementia, such as hypothyroidism and space occupying lesions, routine medical investigations will highlight the abnormality responsible. These types of dementia tend to be uncommon in the clinical setting and even rarer in the community setting. The diagnosis of multi-infarct dementia is less straightforward, based on a composite of historical features, physical findings and other investigations. The diagnosis of Alzheimer's disease cannot be made until other causes are excluded and cannot be made with certainty unless post-mortem is carried out. Even at post-mortem exact criteria for the diagnosis of Alzheimer's disease are not agreed.

A study of the diagnostic evaluation of 200 consecutive patients aged over 60 suspected of dementia revealed that the only investigations of major practical value were sodium, calcium, glucose and thyroid function tests. Frequently more than one illness appeared to contribute to the dementia, and many tests were abnormal. These had to be interpreted in the light of clinical knowledge and only 5 patients were found to have reversible dementia secondary to abnormalities identified in this way. Computerised axial tomography did not contribute to identifying underlying treatable pathologies (Larson et al 1986).

Because of the relative importance of Alzheimer's disease and multi-infarct dementia in epidemiological studies these are selected for special discussion.

Alzheimer's disease

Senile dementia of the Alzheimer's type and dementia of the Alzheimer's type have been extensively reviewed as Alzheimer's disease has become more prominent as a research area (Katzmann 1976, 1986, 1987, Dahl 1983, Henderson 1983, Donaldson 1984, Lauter 1985, Mesulam 1985, Gottfries 1986, Price et al 1985, Kwentus 1986, Pfeiffer 1988, Roberts 1988). Some of the diagnostic criteria for Alzheimer's disease are summarised in Table 1 and are given in full in Appendix 1 (DSM-III-R, CAMDEX clinical criteria and the NINCDS-ADRDA criteria). More recently in the United Kingdom a workshop was convened to agree on a minimum data set in research studies of Alzheimer's disease, instead of criteria (MRC 1987, Wilcock et al 1989). The clinical recommendations of this workshop are set out in Appendix 3.

It is said that Alzheimer's disease is a diagnosis of exclusion during life, and can only be confirmed post mortem. The pathological diagnosis of Alzheimer's disease rests on the demonstration of an abnormal accumulation of senile plaques in the cerebral cortex, with neurofibrillary tangles in some areas of the cortex, usually the archicortex as opposed to the neocortex. The exact distribution and frequency of these lesions is variable, despite many attempts to quantify these (Perry 1986). As a result of problems with set neuropathological criteria it has been suggested that the diagnosis can only be made with certainty from a combined clinicopathological approach (Khachaturian 1985).

Neuropathology and neurochemisty

Post mortem studies of brain changes with age have been conducted on selected samples, and the findings cannot be seen as representative of the population. It has been repeatedly found that the changes thought to be histopathognomic of Alzheimer's disease are to be found in many subjects who have not apparently suffered from the disorder during life (Mountjoy et al 1983). These lesions vary in quantity, quality and distribution (Newton 1948).

The closest to representative studies are the autopsy series in general hospitals, but there is still bias with regard to which patients are chosen for post mortem. In one such study of 199 individuals (representing 44% of all deaths in a general hospital), mainly aged over 65, the frequency of plaques and tangles was found to increase with age after 71 (Miller et al 1984). 12.7% of those over the age of 75 had enough plaques and tangles to fulfill some neuropathological criteria for Alzheimer's disease. There was a strong correlation similar for both sexes between the presence of one lesion and the other. It was concluded that the presence of plaques and/or tangles was clearly a function of age, occurring in a continuum, increasing with age without diminution and not affected by sex. Other autopsy series have reported higher proportions with plaques and tangles in younger age groups (e.g. Nakamura et al 1987, Ulrich 1982, 1985). In contrast to these studies Dayan (1970) reported finding no lesions in those aged under 60.

Few studies have been conducted on the very old. In one series, 31 subjects aged over 90, and 69 consecutive cases of Alzheimer's disease aged 65-89 came to post mortem (Ehrlich and Davis 1980). In all age groups most people with moderate to severe changes were not demented according to the medical notes, although dementia was more common in these groups than the group with no or mild changes. The exception to this was the finding that those aged 80-89 with no or mild changes were more likely to be diagnosed as demented. The functional significance of pathological changes such as plaques and tangles is largely unknown. Since low densities of plaques and tangles occur in at least the archicortex of many aged clinically normal individuals it has been suggested that these do not affect cerebral function (Perry 1986).

It has been suggested that Alzheimer's disease is a specific disorder of cholinergic innervation (Coyle et al 1983) and there is considerable evidence to support abnormalities in this system. It has been found that there is severe depletion of cholinergic activity in the cerebral cortex and in the limbic system in patients with Alzheimer's disease (Rossor et al 1984). Choline acetyltransferase activity has been shown to be reduced in proportion to the severity

of dementia (Perry et al 1978, Davies 1978). It has also been found to be reduced in widespread areas in Alzheimer's disease of early onset, whereas it appears to be reduced only in the temporal lobes significantly in late onset cases (Bird et al 1983, Rossor et al 1984). One post mortem study of dementia in the absence of substantial neuropathological changes of Alzheimer's disease found that there were abnormalities in the cortical cholinergic system possibly preceding neuropathological change (Perry et al 1985). However, in normal ageing and degenerative dementia the same kinds of neurochemical changes are found (Samotajski 1977, Bowen and Davison 1983, Gottfries 1986). Synthesis of whole brain acetylcholinesterase has been found to decline in two strains of senescent mice and the decline was found to correlate with the development of progressive behavioural deficits (Gibson et al 1981). Acetylcholinesterase studies in aged macaques and in subjects with Alzheimer's disease show similar changes (Price et al 1986). It has been suggested that the interest in cholinergic factors in Alzheimer's disease may reflect more the ease of their identification rather than any particular significance (Harrison 1986). Changes in other systems such as adrenergic neurotransmitters have been found to correlate with neuropathological changes of Alzheimer's disease, and the finding of histochemical demonstration of different peptide markers within plaques show that there are many changes, and that no single system can be regarded as responsible for the disorder (Mountjoy 1986).

The interpretation of these post mortem studies is hampered by the considerable variation between studies in terms of source, age, sex, the numbers of cases examined, differing diagnostic criteria with inclusion and exclusion criteria, the brain sections selected, the number and thickness of sections and the extent of the search as well as the magnification used, the stains used and the neuropathological criteria employed. They are also limited by information on the influence of premortem medication on most of the measures (Rossor et al 1984, 1986). Very few studies have been able to examine drug-free subjects. Other difficulties are found with choice of and access to controls and matching procedures. Mode of death and postmortem delay

may influence concentrations of neurotransmitters, as may shrinkage of tissues.

It does appear that in non-demented ageing populations considerable proportions will show some of the lesions and changes associated with the diagnosis of Alzheimer's disease, although generally in smaller quantities.

Clinicopathological studies

There have been relatively few clinicopathological studies. These involve testing cases before death and then examining their performance during life in relation to the changes found post mortem. Particular difficulty is found in obtaining brains from controls who have been studied during life, and no studies have been based on population samples. Techniques for standardising methods are difficult and studies are not always performed blind to the condition of the patient before death. The results of studies where quantitative correlations have been attempted are summarised below. From this table it can be seen that age appears to have a consistent relationship with several of the pathological indices of Alzheimer's disease in the brain. A relationship between plaques and measures of cognitive function has been reported in many studies, although this has not always been found to correlate with the degree of dementia when controls are excluded from the analysis (Molsa et al 1987). Tangles show a less consistent relationship with the degree of dementia or cognitive function. Other variables such as choline acetyl transferase, cell loss, area and length of temporal cortex, cellular smooth endoplasmic reticulum, low brain weight and tau antiserum have been reported in individual studies to be positively associated with various indicators of dementia.

The methodology of these studies has varied considerably. The range can be illustrated with the sources of patients. These have included psychiatric, psychogeriatric and geriatric facilities (Roth et al 1966, Blessed et al 1968), acute medical units and psychogeriatric wards (Perry et al 1978, 1985), hospital patients (Wilcock and Esiri 1982), resident's nursing homes (Katzman et al 1983, 1988), referral from physicians (Merskey et al 1985), patients known to a dementia

service (Martin et al 1987), Alzheimer's disease from the community (Molsa et al 1987) and selected biopsied cases (Mann et al 1987). Therefore it is not surprising that there is relatively little consistency in the results reported.

Summary of correlations reported

Age: plaques 0.55
: hippocampal plaques 0.40
: histopathological dementia score 0.51
: brain weight -0.47 (Alafuzoff et al 1987)

Plaques:dementia score
:overall score 0.78 (Roth et al 1966)
0.15-0.43 (Wilcock & Esiri 1982)
(hippocampal-occipital)
0.73 (Katzman et al 1986)
+++ (Molsa et al 1987)
++ (Neary et al 1986)

:Information-Memory-Concentration -0.591 (Roth et al 1966)
:I-M-C long -0.60
short -0.54 (Katzman et al 1986)
:retrieval score -0.70 (Katzman et al 1986)
:Token Test -0.77 ( )
:Controlled (Martin et al 1987)
Oral Word test -0.62 ( )
:MMSE -0.70 ( )

Tangles: degree of dementia

0.19 to 0.59 (H1 hippocampal-temporal) (Wilcock & Esiri 1982)
+++ (Molsa et al 1987)
++ (Neary et al 1986)

Choline acetyl transferase

: Mental Test score 0.81 (Perry et al 1978)

: Mental Test score in Parkinson's Disease 0.76 (Perry et al 1985)

: Cognitive test score ++ (Neary et al 1986)

Cell loss

: Mental Test score -0.53 - -0.71 (Neary et al 1986)

Area and length of temporal cortex

: Blessed Dementia Scale (Duyckaerts et al 1985)

Smooth Endoplasmic Reticulum

: Reaction time ++ (Sumpter et al 1986)

Low Brain Weight

: Degree of dementia +++ (Katzman et al 1988)

Tau antiserum

: intellectual deficit ++ (Delaere et al 1989)

Diagnosis during life

Primitive reflexes have been found to be increased in the demented population compared to normal controls in some studies (Molsa 1980, Tweedy et al 1982, Shibayama et al 1986, Huff et al 1987). The pout reflex was found to correlate with the degree of ventricular enlargement shown on computerised axial tomography. Increasing pathological signs were also found to be related to increasing cognitive impairment (Tweedy et al 1982). Hyperreflexia, paralysis, dysarthria and tremor (Shibayama et al 1986), gait disorder, impaired stereognosis and graphaesthesia (Huff et al 1987) have also been reported in Alzheimer's disease. Aphasia and apraxia were noted, particularly in subjects with a family history of dementia, by one group of researchers (Breitner and Folstein 1984). Many of these studies have used controls who were younger than the subjects. Furthermore many of these signs were not specific and were associated with increasing age in the controls (Huff et al 1987), making the findings difficult to interpret.

It has been suggested that examination of the cranial nerves in detail might enable a more accurate diagnosis of Alzheimer's disease (Knupfer and Spiegel 1986). In one longitudinal study olfactory, gustatory and auditory functions were found to deteriorate in

subjects with Alzheimer's disease, whereas little change was found in controls (Waldton 1974). A dissociation between recognition and detection of olfaction in mildly demented subjects has been reported (Rezek et al 1987), and another found a significant difference between those with a diagnosis of Alzheimer's disease and multi-infarct dementia (Knupfer and Spiegel 1986). These findings appear to be non-specific since olfactory deficits have also been found in those aged over 80, head trauma, Korsakoff's disorder, Parkinson's disease. Furthermore, many patients cannot be assessed because their cognitive function is too profoundly impaired to understand and respond to the necessary instructions (Rezek et al 1987).

There have been various reviews of the search for antemortem markers of Alzheimer's disease. Cholinergic, somatostatin, amine, aluminium, parathyroid hormone, glucose, pituitary hormone, somatomedin, immunological, genetic, radiological and neurophysiological measures have been examined but none found to be adequately sensitive or specific (Thienhaus et al 1985, Sherman et al 1986, Carlsson 1986, Hollander et al 1986, Blass et al 1985). Promising areas were seen as the difference in the choline ratio between red blood cells and plasma between subjects with Alzheimer's disease and age matched controls, and the decreased binding capacity of lymphocytes for choline muscarinic receptors (Rabey et al 1986). However the former was not confirmed by a subsequent larger study where no differences were found (Houck et al 1988). No differences have been reported between cholinesterase activity in cerebrospinal fluid between subjects with Alzheimer's disease and normals (Elbe et al 1987). Protein markers, such as Alz 50, have been identified and claimed as specific for Alzheimer's disease, but as yet none have been proven to be of value in diagnosis during life (Wolozin et al 1986, Davies and Wolozin 1987, Love et al 1989)

Multi-infarct dementia

Multi-infarct dementia has been described as vascular damage unevenly distributed through the brain, ranging from scattered micro-infarcts to macro-infarcts. The type of damage can range from multiple small areas of cystic degeneration to the massive destruction of tissue that can result from occlusion of a major artery (Corsellis 1977). In

a classical post-mortem study of subjects with dementia including those with multi-infarct dementia Tomlinson et al (1968) reported that in 20 patients with cerebral infarction volumes affected ranged from 2 to 91 mls. A threshold of infarction before dementia is present was suggested, with a critical volume of damage of 50mls (Hachinski 1983). The type and location of lesions seem to be important also (Tomlinson et al 1968, Ladurner et al 1982, Roth 1986, Kase 1986). Areas known to be affected in Alzheimer's disease have not been found to be affected in multi-infarct dementia. An example of this is the nucleus basalis of Meynert in which no significant difference from controls was found in one post mortem series (Mann et al 1986). There remains some debate as to whether the clinical syndrome should be called dementia if only single infarcts are present (Hachinski 1983). In clinical evaluation, therefore, these subjects tend to have aphasias, apraxias, amnesias, neglect, disorders of visuomotor and visuospatial systems (Fields 1986).

The causes of multi-infarct dementia can include almost any condition which causes vascular damage. These include thromoboembolism, recurrent severe hypotension, collagen vascular disease, temporal arteritis, Takawasu disease, central nervous system angioendotheliosis, Moyamoya disease and generalised small vessel thromboses.

The diagnosis of multi-infarct dementia

Cerebral blood flow and metabolic studies in subjects with clinically diagnosed multi-infarct dementia show many infarcts of varying size and location. Computerised tomography is often recommended in the differential diagnosis of dementia, but this is complicated by the fact that it is not possible to tell whether vascular lesions are the cause of the dementia syndrome or merely a coincidental finding. A major problem with the diagnosis of multi-infarct dementia is that up to 30% of the normal elderly over 85, and significant proportions of those younger, are found to have evidence of single acute or healed cerebral infarcts (Perl and Pendlebury 1986). Diagnosis cannot therefore be made on the basis of computerised tomography and one author has commented that "even with sophisticated measures of cerebral atrophy computerised axial tomography is unable to

discriminate among common causes of cognitive dysfunction in the elderly.... optimal clinical prediction rules remain to be developed" (Martin et al 1987). Magnetic resonance imaging provides an alternative, and provides better images of the periventricular small white matter lesions called leukoaraiosis (Johnson et al 1987). In a comparison of the two methods magnetic resonance imaging was found to identify early non specific lesions, and computerised tomography more definite abnormalities (Gupta et al 1988). It was originally thought that this method would enable the differentiation of multi-infarct dementia from Alzheimer's disease, but many early high signal abnormalities were subsequently found in subjects with Alzheimer's disease and controls (Fazekas et al 1987) and have cast doubt on the usefulness of this method. The machines used for this are not standardised and thus the methods used in each study tend to be different.

The ischaemic scale

As an adjunct to the clinical history and examination Hachinski et al (1975) developed a scale to aid the differentiation of multi-infarct dementia from Alzheimer's disease. This has become widely used in clinical series. It is based on a combination of historical features, physical symptoms and signs (see Appendix 2). Many studies have been performed comparing its accuracy with clinical diagnosis based on full investigation (Harrison et al 1979), but rarely with histopathological diagnosis. One such study found that Alzheimer's disease and multi-infarct dementia were reasonably well differentiated by the scale but that it was difficult to differentiate multi-infarct dementia and the mixed condition of multi-infarct dementia and Alzheimer's disease (Rosen et al 1980). In this study the post mortem diagnoses were not made blind to the diagnoses during life. In a further small autopsy study questionnaires were mailed to relatives of 36 subjects (Kukull and Larson 1989). These contained sufficient questions to arrive at a Hachinski ischaemic scale score and DSM-III diagnosis. The sensitivity of this method for Alzheimer's disease was 93% and specificity 43%. Using a standard cutpoint the Hachinski scores classifed 40% of pure Alzheimer's disease as multi-infarct dementia. The authors concluded that the scale cannot be used on its own to

differentiate the two disorders, although they acknowledge that the results of this study may be a result of non clinicians filling in clinical rating scales. This suggests that the use of such a scale in differential diagnosis is more due to the bias and subtle interpretation of clinicians than the items as stated. This interpretation is supported by the finding of poor inter-rater reliability for the ischaemic scale (Small 1985).

Neuropsychology

Attempts have been made to differentiate between Alzheimer's disease and multi-infarct dementia by means of neuropsychological profiles. Varying success has been reported with high classification rates reported in one group, followed by poor rates in the next. A correct classification rate of 70% was reported in one study using logistic memory, the Wechsler memory test, trail making and word fluency. Subjects with Alzheimer's disease were identified in 96% of cases and only 7% normals were misclassified (Tierney et al 1987). Recent memory and lexical semantic memory were the most frequent deficits in another group of subjects with probable Alzheimer's disease who had been preselected according to educational level and ischaemic score. 96% of the cases were correctly identified using selected cognitive tests, with a specificity of 86% (Huff et al 1987). Several studies have been conducted using the Wechsler adult intelligence scale, and verbal ability has been found to be a "hold" test, that is, which does not decline with other tests in dementia (Crookes 1974). It has been suggested that there are "positive" profiles on the Wechsler adult intelligence scale for Alzheimer's disease (Fuld et al 1982), but this was only found in 22% of 41 subjects with probable Alzheimer's disease (Filley et al 1987). The Wechsler adult intelligence scale profile was only able to identify 13 out of 23 subjects with Alzheimer's disease and 32 out of 39 subjects with multi-infarct dementia in a further study (Brinkman and Braun 1984). These studies are all based on current diagnosis and differential diagnosis can only be made with fair confidence at post mortem. This approach also ignores the common ground between dementias which has to be present in order to fulfill the initial diagnostic criteria for dementia.

Accuracy of differential diagnosis

If strict criteria such as the NINCDS-ADRDA are employed, a pure group of Alzheimer's disease can be selected for study in which high concordance of diagnosis during life with diagnosis after death is found. The proportion of cases correctly identified has ranged from 82% to 100% in the few studies where subjects have come to postmortem (Sulkava et al 1983, Fox et al 1985, Joachim et al 1988). However, Table 2 shows the sensitivity and specificity of the clinical diagnosis when compared with post mortem diagnosis in a variety of clinical series. It appears that in ordinary clinical settings the diagnosis of Alzheimer's disease and multi-infarct dementia during life is likely to be imprecise, although studies with multiple exclusion criteria and longitudinal study are more likely to achieve a high level of accuracy. How relevant these findings are to the general population is debatable. In an extensive review of the literature, Liston and La Rue (1983a and b) concluded that the literature "fails to provide sufficient support for the ante-mortem differentiation of primary degenerative dementia from multi-infarct dementia on the basis of clinical criteria".

One of the main deficiencies of the studies noted above is the lack of control data from truly representative populations. Other areas of difficulty include differences in diagnostic criteria, both clinical and neuropathological, and the biased population who come to post mortem. Examples of this variation are to be found in the range of neuropathological criteria employed for Alzheimer's disease. The criteria have ranged from the demonstration of abundant neurofibrillary tangles and senile plaques in the hippocampus and moderate to large numbers of neurofibrillary tangles and senile plaques in the neocortex (Sulkava et al 1983) to demonstration of neurofibrillary tangles only (Wade et al 1987). One study examined the effect of such different neuropathological criteria, including exclusion criteria for multi-infarct dementia (Tierney et al 1988). Total agreement between clinical diagnosis and pathological diagnosis was between 81-88%. Sensitivity varied between 64% and 86%. Because marked changes can be present in the brain without manifest dementia, it has been suggested that Alzheimer's disease should only be

diagnosed with certainty when both clinical history and neuropathological diagnoses tally (Henderson and Jorm 1987).

Table 2 Post Mortem Validation Studies

Disorder	Se(%)	Sp(%)	No.	First author
Alzheimer's disease	40	19	776	Todorov 1975
	28	43		
	71	73	58	Molsa 1985
	78	87	65	Wade 1987
	63	46	55	Alafuzoff 1987
	100	67	27	Homer 1988
Multi-infarct	75	39		Todorov
	73	77		Molsa
	54	67		Alafuzoff
	56	91		Homer
Mixed type	30	48		Todorov
	17	92		Molsa

Se=sensitivity Sp=specificity

DEMENTIA IN THE POPULATION

Mortality

The different codes in the Ninth Edition of the International Classification of Diseases which can be used for dementia are listed in Appendix 4. This indicates some of the difficulties in studies of dementia which rely on death certification. Comparison of standardised mortality ratios for different areas of the United Kingdom have showed that those areas with the highest ratios were those where long-stay institutions were situated (Martyn and Pippard 1988). Analysis of mortality statistics in the United States for the years 1968 to 1973 has shown that age adjusted rates were 5.2 per million for presenile dementia and 3.9 per million for senile dementia (Jordan and Schoenberg 1986). This appears to be markedly lower than the numbers expected if prevalence rates are used as a guide to dementia in the population. Another study of routine statistics in the US noted that there has been a secular change in the reporting of dementia and senility, with the former becoming more commonly reported and the latter less commonly. It was also found that for dementia male rates exceeded female and white rates exceeded black rates with the converse for senility (Chandra et al 1986). It seems likely that these observations are more likely to be due to inaccuracies of reporting than true underlying trends.

In a detailed study of a psychogeriatric clinic in England fewer than 25% of demented subjects had dementia noted as an underlying cause of death on their death certificate, although dementia or a related condition was noted in 75% somewhere on the certificate (Martyn and Pippard 1988). It seems, therefore, that mortality statistics are of limited value at present in the understanding of dementia, largely because of under reporting and inaccuracy. Unlike other disorders where, despite large errors, some comparison across areas and countries using routine statistics is possible, these appear to be too influenced by differences in reporting practices as well as differences in diagnostic practices to be of use.

Differential diagnosis in clinical settings

The proportions of all dementia accounted for by different diagnoses in hospital settings vary enormously between studies. Some examples of this type of study are shown in Table 3. Further workers have reported specifically on reversible causes and the proportion of multi-infarct dementia found in different studies. Between 5% and 14% of dementias from various clinical settings have been reported as due to multi-infarct dementia (Freemon 1976, Victoratos et al 1977, Marsden and Harrison 1972, Maletta et al 1982). In a study of elderly outpatients on a register for Alzheimer's disease 21% were found to have abused alcohol. The author suggests that the proportion of dementia due to alcohol abuse may have been seriously underestimated in previous studies (King 1986).

These studies are based on a variety of clinical services. Considerable variation would therefore be expected. It is not possible to estimate the prevalence of different aetiologies of dementia in the community. Even in those studies in which the series is taken from a facility serving a defined population the influences determining which patients present, or are referred, to a particular service will tend to bias the final estimates. Despite these limitations, it is seems that reversible dementias appear to contribute only a small proportion to the total, which would be even less in community settings.

Table 3 Differential diagnosis in clinical settings (%)

First author	AD	MID	Other	Comment
Molsa (1980)	44.9	31.6		Turku city
Delaney(1982)	49	17	23	Consecutive referrals
Erkinjuntti (1986)	34.9	72.4	4.5	Admissions to med dept.
Ojeda (1986)	77.7	-	-	Metropolitan hospital
Larson (1986)	74.5	-	15	Consecutive admissions
Kokmen (1987)	72	0.3	-	Autopsy series
Erkinjuntti (1988)	16.1	69.4	14.5	Admissions to med dept

Population studies

Methods

Population studies of dementia have been carried out using widely differing methods from sample definition to assessments. Such differences could lead to wide differences in reported prevalence rates, which hampers comparison of these rates. This section considers the major differences in methodologies.

Sampling frames. Some research studies have used routine census statistics for estimates of the denominator. Other approaches have involved enumerating the exact numbers in the whole population before sampling and case identification. Electoral rolls (eg Kay et al 1964), door to door calling (eg Livingston et al 1990), or Family Practitioner Committee/ general practice registers (eg Copeland et al 1987a, O'Connor et al 1989) have been used as the sampling frame. Geographically-based samples have sometimes included people in institutions within the area. Door to door calling has usually excluded them. Some studies have been conducted entirely on institutional samples (eg Ames et al 1988). Types of institution have ranged from private retirement homes for the relatively fit elderly to long-stay psychogeriatric hospitals.

Sampling procedures. Many investigators have taken complete population samples in a given age range (eg Clarke et al 1984, O'Connor et al 1989). Others have selected subjects using randomisation procedures (eg Epidemiologic Catchment Area study - Eaton and Kessler 1986) or systematic sampling (eg O'Connor et al 1989). Stratification has been used, usually by age, with sub-selection within strata (eg Morgan et al 1987). A less population based method has been the use of attenders in general practice, taking as a sample all those people of a particular age willing to take part (Griffiths et al 1987). Sampling is of particular importance when comparing studies of age-related conditions, since the population estimates reported are based on a wide range of age and sex distributions.

Case identification. Some reported estimates have been based on cases known to health or social services, relating these numerators to the numbers estimated in the base population from other sources such as the census (eg Adelstein et al 1968). This information has been used in two ways. The figures have either been presented unchanged or there has been a review of cases using criteria defined by the individual study, using case records or interviewing to confirm diagnosis. The other method of case identification has been to interview all the population in the sample in a single or multi-stage study as described below.

Measurement. The main approaches to case identification have been described above in the diagnosis section. Early small studies relied on unstandardised clinical interviews. Diagnostic criteria were then introduced, but without standardised methods of examining subjects. More recently, such interviews have been developed. Those particularly widely used in the community are the Geriatric Mental State (GMS) and the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX). Many investigators, however, construct new standardised instruments.

Single stage study. Screening for case identification depends on the type of scale used. For example using cutpoints on the information/orientation scale of the Clifton Assessment Procedure for the Elderly or MMSE leads to estimates of rates of cognitive impairment. Using measures of activities of daily living would include rates of physical disability. Screening usually involves measuring one dimension, such as cognitive function (eg Clarke et al 1984), but some population studies have combined two approaches including both cognitive and behavioural (Cooper and Sosna 1983). Ideally this initial screening wave should be as sensitive and specific as possible in relation to the final outcome measure. The validity of these tests has usually been based on highly selected populations, such as in-patients (eg Anthony et al 1982). In some surveys the GMS has been applied to whole populations as a case finding instrument and a special version of the interview has been developed for this purpose. This is administered by trained lay

interviewers. The need for clinical diagnosis is avoided by the use of computerised algorithms.

Two stage study. A two stage design is more frequently used where the population is screened using a shorter instrument such as the Mini Mental State Examination (MMSE), with or without a further interview of selected individuals to confirm diagnosis (eg Sulkava et al 1985, O'Connor et al 1989).

Diagnostic methods. As described above diagnosis can be made using computer algorithms. Other studies have used a combination of scales, making an algorithm from cognitive questions, ICD 9 criteria questions and clinical severity scores (Cooper and Sosna 1983). Algorithms for various criteria were constructed from the GMS interview and MMSE for a study in Hobart (Kay et al 1985), but difficulties in setting levels for decisions were found. CAMDEX uses a somewhat similar approach for an alternative operational diagnosis - with a combination of clinical diagnoses and cutpoints on internal scales (Roth et al 1988).

Method of contact. There are two main methods of contacting subjects in epidemiological studies of the elderly, either via general practitioners or direct approach by the research team. There have been recent studies in the UK using both approaches. The Melton Mowbray, the Liverpool study and the Cambridge city study were introduced to the subjects by a letter from the general practitioners (Clarke et al 1984, Copeland et al 1987a, O'Connor et al 1989). The Nottingham study approached subjects directly (Morgan et al 1987).

Interviewers and training. Different types of interviewers have been employed ranging from those with no experience of medicine or social science to paramedically trained and medical doctors. Training can take the form of classroom teaching, or working in the field under supervision or a combination of the two. Assessment or diagnostic interviews have usually been conducted by geriatricians, psychogeriatricians, psychiatrists and nurses. Some of these interviews have been structured as described above, but some have not been (eg Morgan et al 1987).

Interview administration. It is possible to conduct some research in the area of dementia by postal questionnaire. This has been attempted successfully in the development of informant scales (Jorm et al 1988, 1989), and has also been used in case control studies for collecting information on risk factor exposure (Shalat et al 1987). However, most interviews have been conducted by trained interviewers. Informant interviews can be conducted by telephone. A review of the literature showed that, although the face to face interviews were marginally better than telephone interviews, the gap was narrow (McCann et al 1984).

Interview location. Subjects have usually been interviewed in their own homes. Other possibilities have been the use of bases such as local health centres, specially designated research centres or central research units in hospitals or university buildings. This last option has applied in multi-stage designs, where at the second or third assessments specific investigations, such as CT scanning or EEG, have been performed. All options present particular problems. In the home setting standardisation of some measures such as lighting and ambient temperature are not possible. The other options tend to lower response rates, particularly the central research centre.

Period of data collection. The period of data collection has depended on the type and resources of the survey. Some studies based on institutions or reviews of routine statistics have provided true point prevalence estimates. Large population surveys with single phases, short interviews and many interviewers have conducted data collection over short periods such as weeks or a few months (eg Clarke et al 1984). Many studies, however, have had few interviewers, long interviews and have taken many months to be completed (eg O'Connor et al 1989). These latter studies do not provide period prevalence, but a staggered point prevalence of an ageing cohort. The effect of this lag between sample definition and subject interview on prevalence figures has rarely been discussed. It is possible that the effect of loss of severe cases through death before interview, and the identification of incident cases after sample definition could

balance in numbers but the estimates of severity would tend to be biased towards milder disease.

Screening scale cutpoints. The purpose of cutpoints in the screening phase of a two stage study is to provide a selected sample with a high probability of being demented. Cutpoints have been applied to populations when they have been validated on a different type of population. This is of uncertain validity (Little et al 1987). Several cutpoints have been suggested for the MMSE, initially 23/24 (Folstein et al 1975), followed by 21/22 (Anthony et al 1982). The most widely used cutpoint remains 23/24 for mild cognitive impairment, and 17/18 for more severe impairment. Some studies have used several scales measuring different axes applying cutpoints for each "diagnosis". In one such exercise (Morgan et al 1987) diagnostic categories of depression and cognitive scales from an identified subsample with a few controls had an agreement of 81.5% with experienced psychogeriatricians, and a kappa of 0.73. For dementia the agreement was 92.3%, with a kappa of 0.83 and for depression the kappa was lower at 0.66. The subsample was made up of 20 subjects failing the cutpoint on CAPE information/orientation scale, 14 borderlines, 25 failing the depression cutpoint and 20 normals. Sliding scale cutpoints have been suggested in order to adjustment for influences such as education on the scores that individuals achieve, but these have not been adopted so far in population surveys. Table 4 shows the sensitivities and specificities reported for various scales, and the gold standard against which they have been measured. Concurrent clinical diagnosis has often been the "gold standard", whereas to fulfill diagnostic criteria, the relation of scales to established progression would be of greater interest. The lack of independence is particularly marked in the case of the Organic Depression Index, which is part of the GMS (McWilliam et al 1988). The AGECAT diagnostic algorithm was the gold standard for this comparison and contains many of the same items. High apparent performance is therefore expected.

TABLE 4

SCALE VALIDITY

AUTHOR	TEST	SE (%)	SP (%)	GOLD STANDARD	SAMPLE TYPE
Kay et al 1977	Memory Inf. Test 10/11	78.3	97.7	Clinical diagnosis	community 65+
	15/16	80.2	95.7	Clinical diagnosis	community 65+
Anthony et al 1982	MMSE 23/24	87.0	82.0	Clinical diagnosis	Medical admission
Cooper & Bickel 1984	MSQ	predictive values 81.7%-92.3%		Clinical diagnosis	279 male in-patient
Kay et al 1985	MMSE 23/24	100	85.0	DSM III/Psychiatry moderate/severe	community 65+
Spagnoli et al 1986	OBS Subscale care	77.0	96.0	Clinical diagnosis	institutions
Roth et al 1986	MMSE				mixed, hospital
	21/22	96.0	80.0		subjects &
	23/24	94.0	85.0	Camdex clinical	volunteers
	CAMCOG			criteria	17 N, 26 SDAT
	79/80	92.0	96.0		13 MID, 7 mixed
					5 clouded, 12 dep.
Morgan et al 1987	I/O subscale of CAPE	89.8	87.5	Psychogeriatrics	community 65+
McWilliam 1988	ODI	90.0	98.0	AGECAT	community 65+

MSQ = Mental Status Questionnaire
IMC = Information Memory
MMSE = Mini Mental State Examination
I/O = Information Orientation Subscale
ODI = Organic Depression Index

Differential diagnosis. Differential diagnosis in the community can be attempted using cutpoints on scales such as those described in the earlier sections, or by applying diagnostic criteria after interview. A further method is review of the interview material (gathered by non-clinicians) by a clinician with allocation of diagnosis. Some tests such as venepuncture can be carried out in the home setting. More detailed investigation of specified subgroups can be undertaken in multi-stage studies by transporting identified groups to the research centre. This tends to lead to large drop out rates such as in one such study, where a response rate of 39% was reported for the third stage of the study (Folstein et al 1985). The intensity with which investigation for differential diagnosis is pursued is therefore variable.

Quality control

Reliability. Inter-rater reliability studies can be conducted in several ways. Interviews can be conducted by one interviewer with one or more others rating at the same time. Alternatively the interview can be recorded, with audio or videotape, and rated later by others. A further approach is for a different interviewer to see the subject using the same instrument on a subsequent occasion, and, finally, for a different interviewer to see the same subject using a different instrument. However, this type of comparison does not test inter-rater reliability alone. Reliability measures can be applied to individual items, scales and overall diagnosis. The measures used can include simple percentage agreement, detailed description of where the
disagreements lie, and statistical assessment of these.
Phi is one measure used, but it does not take into account chance agreement. The most popular measure of reliability at present is kappa (Cohen 1960), which incorporates an adjustment for chance agreement.

Item reliability. It has been said that "inter-rater reliability appears to be ensured by the highly structured nature of the questionning and recording responses" (Cooper and Bickel 1984). Whilst this may be true with the intensive training methods now used

in psychiatric research it cannot be accepted without some investigation. The following studies have attempted in some manner or other to examine this important area. It would appear that for interviewer-observer studies, that is those studies in which an interviewer delivers a question and both interviewer and observer record the response, correlation for individual items is high, but that questions to the interviewer requiring interpretation such as observations on mental state are less reliable. In the social interview section of the Gothenburg cohort of 70 year olds two nurses were found to show considerable variation in responses for certain questions such as fear of going out alone. It was concluded that subjective ratings were not very useful, and that objective measures, such a blood pressure, were preferred (Rinder et al 1975). In another study 25 psychiatric patients were given a short test of cognitive function, observed by three psychiatrists. More than chance agreement was reported on 19 items, and a correlation of over 0.8 for 14 items (Taylor et al 1980). Agreement between observations by psychiatrists of 20 severely demented institutionalised females based on a single interview, such as presence of delusions and hostility, was found in another such study to be very variable, ranging from 0.16 to 0.81 (Winslow et al 1985), a finding also noted in another study of consecutive psychiatric admissions (Helzer et al 1977). In the CAMDEX validation study (Roth et al 1986) agreement on individual items between observer raters, all psychiatrists, in 40 patients was found to be good, with the worst figures in the observer ratings. Correlations of 0.87 within an interview for positive ratings on GMS items were found and 0.78 between interviews (Copeland et al 1976). Mean item kappa was 0.73 for the interviewer/ observer interviews and 0.48 for the interview/ reinterview.

Agreement in this kind of study is greater than that from repeat interviews with different interviewers. In this type of study improvement in scores on cognitive scales, as well as interviewer variation, has been noted i.e. a "practice effect". Such studies have found that there was improvement between the first and second assessment in functional and mildly impaired organic disorders, but none in the moderately to severely affected organic disorders (Hodkinson 1972, Little et al 1987). It seems that these scales are

moderately reliable in terms of test-retest, although there remain uncertainties about the effect of time between testing, type of interview and effect of diagnosis.

Diagnostic reliability. Measures of reliability between diagnosticians have been quoted in several studies. Agreement of 92% for the category organic brain syndrome was reported by one group (Helzer et al 1977). This study was based on 101 consecutive psychiatric admissions with independent diagnostic ratings based on two structured interviews 24 hours apart. The kappa value was much lower at 0.29, but organic brain syndrome only formed 6% of the total sample. Most conditions were found to have a kappa of more than 0.75. There was a considerable range of experience amongst the interviewers in this study, and the highest concordance was in the two least experienced members of the team. In the CAMDEX validation study (Roth et al 1986), the inter-rater reliability according to main diagnostic groupings was found to be good for observed interviews, with complete agreement on whether subjects were normal or demented. This is not entirely unexpected since the sample was drawn from two disparate groups - hospital based and volunteers from the University of the Third Age in Cambridge. Differential diagnosis showed less agreement with a phi of 0.63. Inter-rater reliability for the GMS was found to be high with a phi of 0.84 in psychiatric day patients, although reliability was lower when two interviewers interviewed subjects independently with a phi of 0.56 (Henderson et al 1983). In a study in London, the agreement between psychiatrists using GMS was found to be 17 out of 20 for observer and interviewer, and 11 out of 20 for interview and reinterview (Copeland et al 1975). In a comparison of American and British psychiatrists complete agreement was 38% and on principal categories 73% (Copeland et al 1976). In a more recent study of 396 community residents using the GMS, AGECAT case levels were compared with the psychiatrists' assessments. Cohen's kappa was 0.74 for all diagnoses, it was 0.80 for depression, 0.88 for organic brain syndrome and 0.74 for non caseness (Copeland et al 1987a). When a replication study was conducted concordance was 89% and kappas for depression were 0.71, organic brain syndrome 0.73 and non-caseness 0.77 (Copeland et al 1988).

Prevalence Studies

Overall rates

Table 5 shows prevalence rates reported for dementia in the UK from 1948 to the present for both urban and rural settings. These studies were mostly based in large towns. Rates quoted are either levels of cognitive impairment or diagnoses with severity, and vary accordingly. The lowest rate is 2.5% for Melton Mowbray (Clarke et al 1984) and the highest 24% for Edinburgh (Williamson et al 1964). Neither of the rates included subjects in institutions. The only rural study is difficult to comment on, since this was based on a volunteer sample who were attending their health centre (Griffiths et al 1987).

Variations in methodology, most notably differences in age structures, make valid comparisons between different areas or time periods very difficult, if not impossible. The higher estimates of the clinically based studies are to be expected, since the short cognitive tests are cruder and less sensitive to milder levels of severity. The more recent studies of the 65 and over age group based on short cognitive scales or AGECAT case levels appear to provide broadly similar estimates of between 3.2% and 7.3%. However, if this two-fold variation were true it would have major implications for service provision and possibly indicate different aetiological mechanisms.

Table 6 shows prevalence rates for Europe apart from the UK, and some stability of rates around 5% is seen. Table 7 shows the figures for the United States. These rates are based mainly on the MMSE and the wide variation is influenced by the differences in the age structure of the populations examined. In Table 8 estimates from other areas are shown. There is wide variation in the rates. The figure of 45% for Korean women is based on failure on cutpoints on MMSE or a shorter information memory scale and is most likely to be due to problems with literacy and cultural effects than to the dementia syndrome itself.

TABLE 5

DEMENTIA PREVALENCE UK

First Author	Published	Age group	Nos	%	Degree	Comment
URBAN						
SHELDON	1948	65+	369	3.9	Severe	
				14.0	All	
PRIMROSE	1962	65+	222	4.5	Severe	Period prevalence/GP
				5.4	All	
KAY	1964	65+	443	5.6	Severe	Psychiatrist
				4.1	Mild	
				4.6	Overall	
WILLIAMSON	1964	65+	200	8.0	Severe	Psychiatrist
				15.5	Mild	
PARSONS	1965	65+	228	14.8	Severe	Psychiatrist
				24.9	Mild	
KAY	1970	65+	461	6.2		Psychiatrist
HERBST	1980	70+	253	16.0		
CLARKE	1984	75+	1800	4.5	included institutions. SCS	
				2.5	community only	
COPELAND	1987	65+	1070	5.2		GMS:AGECAT
MORGAN	1987	65+	1042	3.2		SCS
O'CONNOR	1989	75+	2616	5.3	Mod&severe	included
				10.5	Mild&mod&severe	institutions
						MMSE & Psychiatrist
LIVINGSTON	1990	65+	813	5.0		Short Care
RURAL						
GRIFFITHS	1987	65+	200	10.0	Community volunteers. SCS.	
URBAN/RURAL						
GILMORE	1974	65+	300	8.24		Clinical diagnosis
BROE	1976	65+	808	3.8	Severe	Clinical diagnosis
				4.3	All	
KEMP	1985	75+	1000	4.2	75-84	SCS
				7.5	85+	

SCS = Short Cognitive Scale

TABLE 6

DEMENTIA PREVALENCE-EUROPE

First Author	Published	Country	Age Group	Nos	%	Degree	Comment
BREMER	1951	Norway	60+	119	2.5	Severe	GP
ESSEN-MOLLER	1956	Sweden		443	5.0	Severe	Psychiatrist
					15.8	All	
NIELSEN	1962	Samso(R)	65+	978	3.1		Known to services
JENSEN	1963	(R)	65+	546	1.1		GP
AKESSON	1969	Sweden(R)	60+	4198	0.95		Psychiatrist
HAGNELL	1970	Sweden			16.1		Psychiatrist
SVANBORG	1977	Sweden(U)	70/75	1000	1.3	Severe	Psychiatrist
					6.3	All	
STERNBERG	1978	USSR(U)	60+	1020	2.8	All	
MOLSA	1980	Finland(U)	65+		65-74	0.36	Known to services
					75+	1.05	
NIELSEN	1982	Odense	70+	1683	Female	2.8	51% severe dem.
					Male	2.3	80+
COOPER	1983	FRG(U)	65+	519	6.0	Severe	Interview
					10.2	All	
WEYERER	1983	FRG(R)	65+	295	8.8		Psychiatrist
ENZELL	1983	Sweden(U)	69	4930	1.0	Mild/moderate	
SULKAVA	1985	Finland(U/R)	65+	8000	6.7	Severe	Neurologist
GAVRILOVA	1987	USSR(U)	60+	1704	4.2	All	Psychiatrist
					1.5	Mild	
					3.1	Min.	
					(all ages)		

TABLE 7

DEMENTIA PREVALENCE-USA

First Author	Published	Country	Age Group	Nos	%	Degree	Comment
GRUENBERG	1961				6.8		
HOLZER	1984	(U)	65+	1977	65-74	1.1	MMSE
					75+	4.0	
ROBINS	1984	New Haven	All	3058	1.3		MMSE
	1984	Baltimore	All	3481	1.3		
	1984	St.Louis	All	3004	1.0		
KRAMER	1985	(U)	65+		65-74	3.0	
					75+	9.3	
FOLSTEIN	1985	ECA	65+	564	65-74	2.1	Community MMSE
					75+	11.7	
					(6.1)		
BLAZER	1985	Baltimore(U)	65+	3921	1.8	All	MMSE
		Baltimore(R)	65+	3921	2.5	All	MMSE
SCHOENBERG	1985	(U)	40+	8994		40+	1.0
					80+	7.0	
PFEFFER	1987		65+	817	15.3	All grades	SCS
					80+	35.8 all	
						12 age adjacent	
MAGAZINER	1987		65+	783	10.0		MMSE

TABLE 8 DEMENTIA PREVALENCE IN OTHER COUNTRIES

First Author	Published	Country	Age Group	Nos	%	Degree	Comment
CAMPBELL	1983	New Zealand (U)	65+	559	Inst 7.7 2.4 Severe 5.3 Mild		
KAY	1985	Australia (U)	70-79	158	3.8 Mild 2.5 Moderate 0 Severe	} DSM Interview	
					10.8 Mild 1.3 Moderate	} Psychiatrist	
			80+	116	17.2 Mild 6.9 Moderate 0.9 Severe		
HAGESAWA	1986	Japan		1800	4.8		
SHIBAYAMA	1986	Japan(U/R)		3105	5.2 All 2.2 Mod./severe 3.6 Mild		No institutional subjects
PARK	1988	Korea	65+	549	Male 25.0 Female 45.0		No institutional subjects
					Male 8.0 Female 19.0		
JENSEN	1988	Palau(R/U)	90+	31	25.0 Mild 42.0 Moderate/severe		

Age and sex specific rates

In all studies where age specific rates have been examined, a sharp increase in the rates of cognitive impairment and dementia have been found with age. This is demonstrated for one study of cognitive impairment in New Zealand in Figure 1 (Campbell et al 1983). The same pattern is seen in both sexes, and this is demonstrated in Figure 2 by the results of Pfeffer et al's study (1987). A six fold difference was found between the over 85 age group and the 75-79 age group in Melton Mowbray in the rates of failure on the information/orientation scale. Yet detailed age breakdown of rates has often not been provided, and standardisation has rarely been performed despite different age structures in samples. This is partly because few studies examine enough individuals in each age group to compare age-specific rates.

Several studies with different case identification methods have found higher rates for dementia or cognitive impairment in women than men (Weyerer 1983, Sulkava et al 1985, Koukoulik 1986, Morgan et al 1987). Others have reported equal rates (Campbell et al 1983, Weissman et al 1985, Griffiths et al 1987). Only a few studies have reported higher rates for men than women (Pfeffer et al 1987). The comparisons were often not made using age- standardised rates. Since there are more older women than men in many of these populations, even within age stratified groups, age differences could account for the differences found. There are also differences in patterns of mortality and institutionalisation between the sexes which would have to be accounted for before any conclusions about true differences could be drawn (Weissman et al 1985). In the large meta analysis of prevalence studies Jorm et al (1987) found that only 3 studies permitted statistical comparison between the rates of Alzheimer's disease between the sexes. When all relevant factors were adjusted the difference between women and men remained significant (Akesson 1969, Kaneko 1975, Molsa et al 1982). There was no difference in overall rates of dementia between the sexes. Further examination of the difference in the prevalence Alzheimer's disease, by examining incidence and mortality, has shown that the difference is most probably due to the longer survival of the women (Henderson 1989).

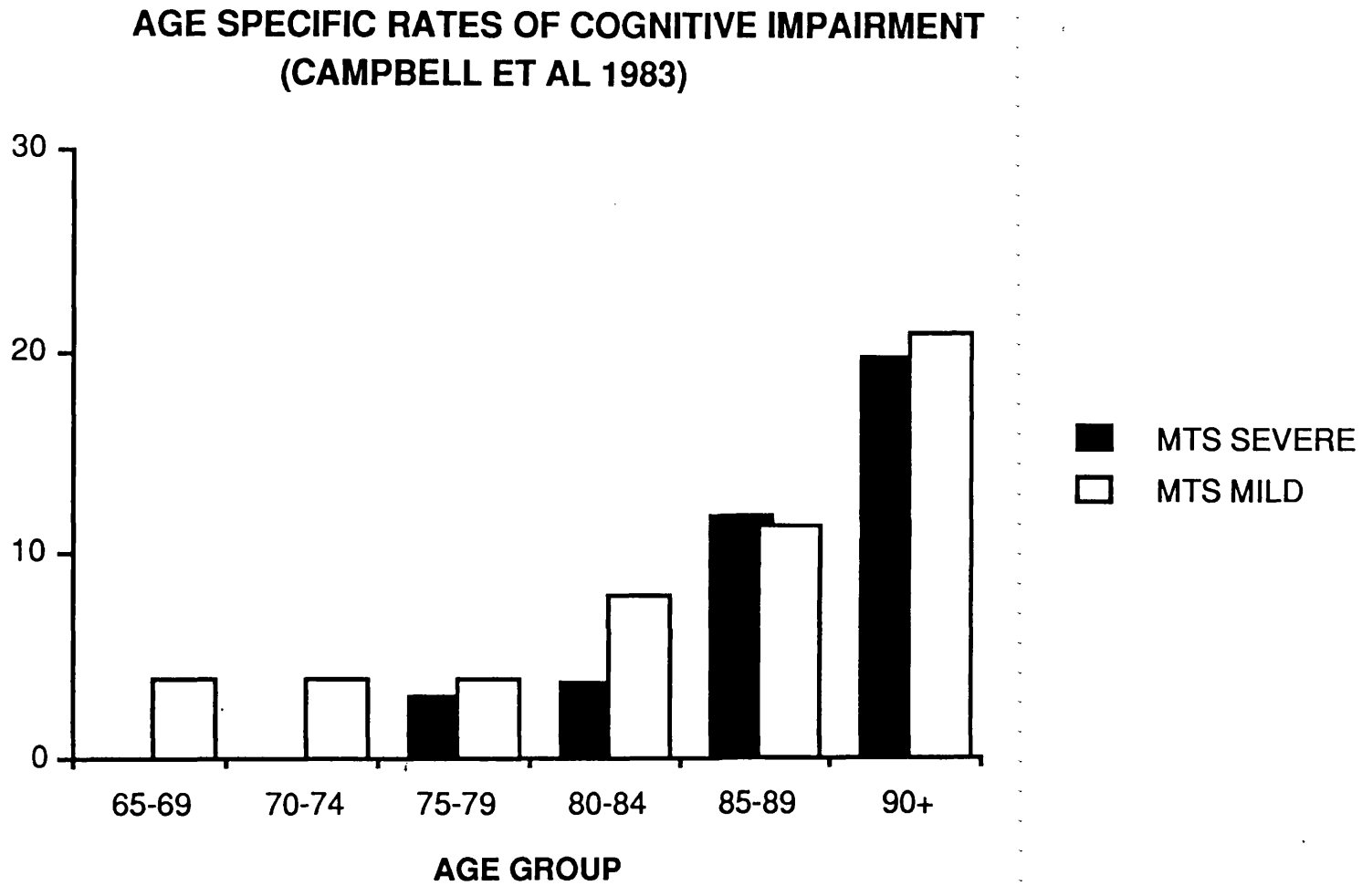
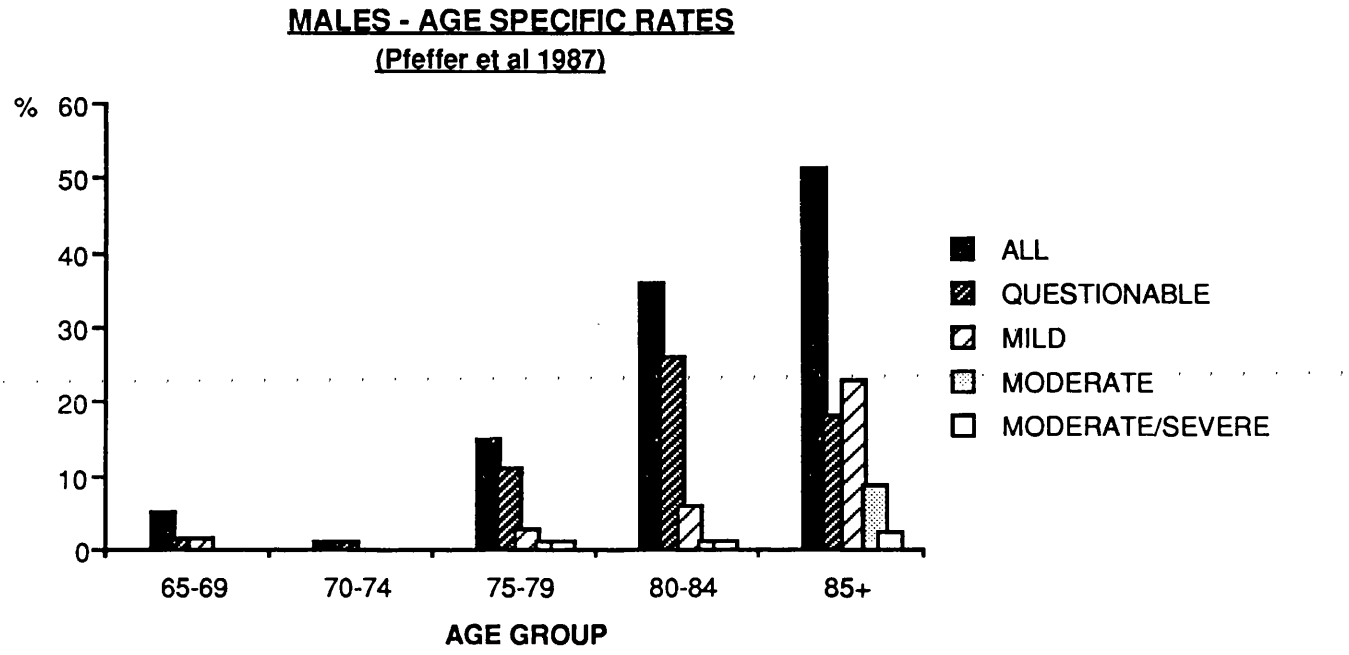
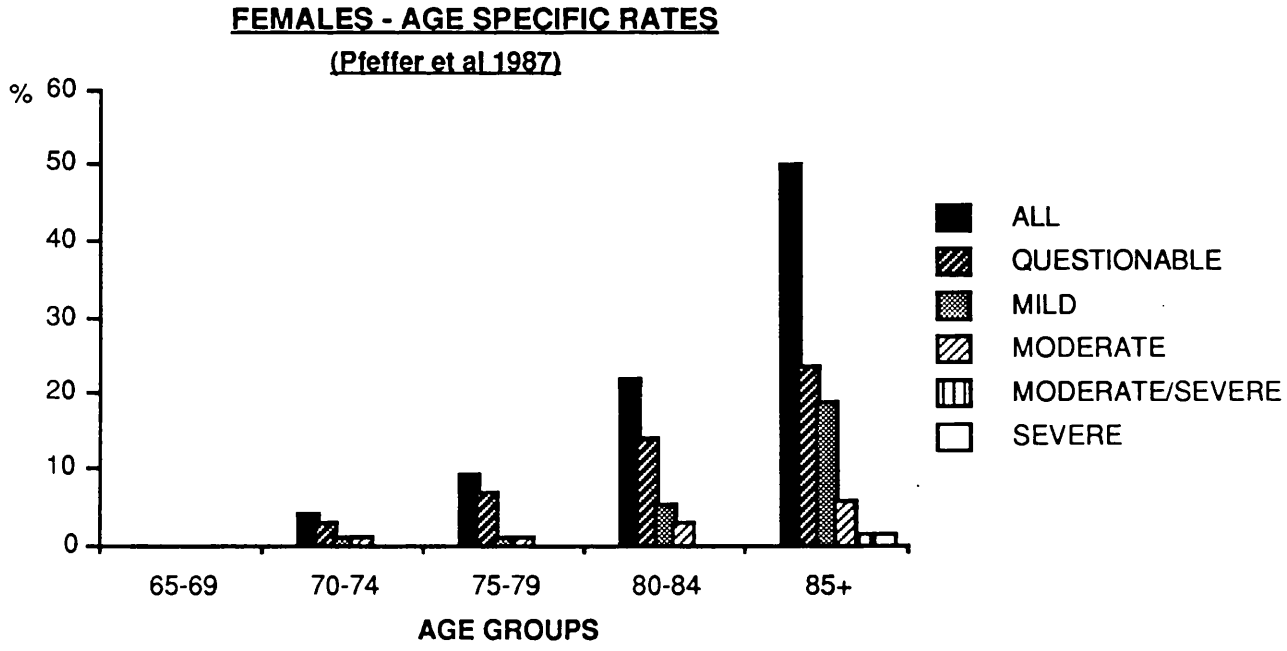

AGE SPECIFIC RATES OF COGNITIVE IMPAIRMENT
(CAMPBELL ET AL 1983)
30
20
10
0
65-69
70-74
75-79
80-84
85-89
90+
AGE GROUP
MTS SEVERE
MTS MILD

FIGURE 1

FIGURE 2


MALES - AGE SPECIFIC RATES
(Pfeffer et al 1987)
%
60
50
40
30
20
10
0
65-69
70-74
75-79
80-84
85+
AGE GROUP
ALL
QUESTIONABLE
MILD
MODERATE
MODERATE/SEVERE


FEMALES - AGE SPECIFIC RATES
(Pfeffer et al 1987)
%
60
50
40
30
20
10
0
65-69
70-74
75-79
80-84
85+
AGE GROUPS
ALL
QUESTIONABLE
MILD
MODERATE
MODERATE/SEVERE
SEVERE

In Table 9 prevalence estimates are shown for those studies where age specific rates were given for women. There is considerable variation in the rates given for cognitive impairment between populations. There is also considerable variation in the estimates of dementia. Most of these estimates are based on very small numbers in the specific age groups, and consequently confidence limits are wide.

Jorm et al (1987) performed a meta-analysis of prevalence rates reported between 1945 and 1985. The authors coded for methodological differences between studies such as sampling, age groups, case definition, rural or urban settings, sex and differential diagnosis. Refusal rates, sex ratios, inclusion and exclusion of institutionalised subjects did not influence rates. Complete samples tended to report lower rates than stratified samples. The prevalence rates where a mild category of dementia was included tended to report lower rates for moderate to severe dementia than studies where only moderate to severe levels were measured. The authors found that the baseline rates given below were a reasonable reflection of 22 out of 27 studies entered into this analysis. The doubling time averaged 5.1 years.

Rates of best fit for 27 studies in meta-analysis

	Median age	%
60-64	62.5	0.7
65-69	67.5	1.4
70-74	72.5	2.8
75-79	77.5	5.6
80-84	82.0	10.5
85-89	87.0	20.8
90-95	91.5	38.6

(Jorm et al 1987)

TABLE 9 A comparison of prevalence estimates for women aged 70 to 79 of cognitive impairment and dementia (%)

Cognitive impairment

Author	Method	Location	Rates 70-74	75-79
Park	MMSE <= 23	Korea	56	74
	<= 17		14	25
	or equivalent			
			65-74	75+
Clarke	CAPE <= 7	Melton Mowbray		1.8 (2.5 Unclass)
Morgan		Nottingham	2.1	7.2
Weissman	MMSE <= 17	New Haven	1.1	4.3 (both sexes)
Kramer		Baltimore	1.5	10.2

Dementia

				70-74	75-79
Copeland	AGECAT	Liverpool		4.1	8.5
Pfeffer		California AD	Questionable	2.2	6.8
			Mild	1.1	1.1
			Mod/severe	1.1	1.1
Jorm	Meta-analysis	World		2.8	5.6
Nielsen		Sweden		13.0	17.0
Hofman	Meta-analysis	Europe		3.9	6.7
				70-79/80	
Akesson		Sweden	AD 1%	MID 0.4%	no diff sexes
Schoenberg		Mississippi		1.7%	
Hofman	Meta-analysis	Europe	AD	2.8%	
				65-74	75-84
Molsa		Finland	AD	3.6	22.3
			MID	1.7	17.1
Broe		UK		2.4	11.8
Sulkava		Finland	AD	1.6	7.3
			MID	1.7	4.7
			All	3.3	12.0

Differential diagnosis in community

In studies of Western populations where differential diagnosis has been attempted the prevalence of Alzheimer's disease has usually been found to be higher than that of multi-infarct dementia. This is demonstrated in Figure 3 for a study from Finland (Sulkava et al 1985).

The rates of multi-infarct dementia appear to stabilise with age in many studies (Figure 4) resulting in an increase in the ratio of Alzheimer's disease to multi-infarct dementia (Table 10). This may be due to shorter survival of cases of multi-infarct dementia than Alzheimer's disease. In Japan multi-infarct dementia has been found to be more common than Alzheimer's disease using DSM-III and ICD-9 criteria (Shibayama et al 1986, Hagesawa et al 1986). In Jorm et al's meta-analysis of 16 prevalence studies where differential diagnosis was attempted during life, Japan and the Soviet Union were the only countries where the rates of multi-infarct dementia were significantly higher than Alzheimer's disease, although this has been queried as a diagnostic artefact (Jorm et al 1987, Henderson 1988). In Finland and the United States they were not significantly different, and in other countries, mainly European, rates of Alzheimer's disease were lower than those of multi-infarct dementia. Overall the ratio of Alzheimer's disease to multi-infarct dementia was 1.3. It has been suggested that the incidence of multi-infarct dementia should be declining in those countries where stroke incidence is declining (Glatt and Katzmann 1984), but valid estimates confirmed by neuropathology are not available over time from any country.

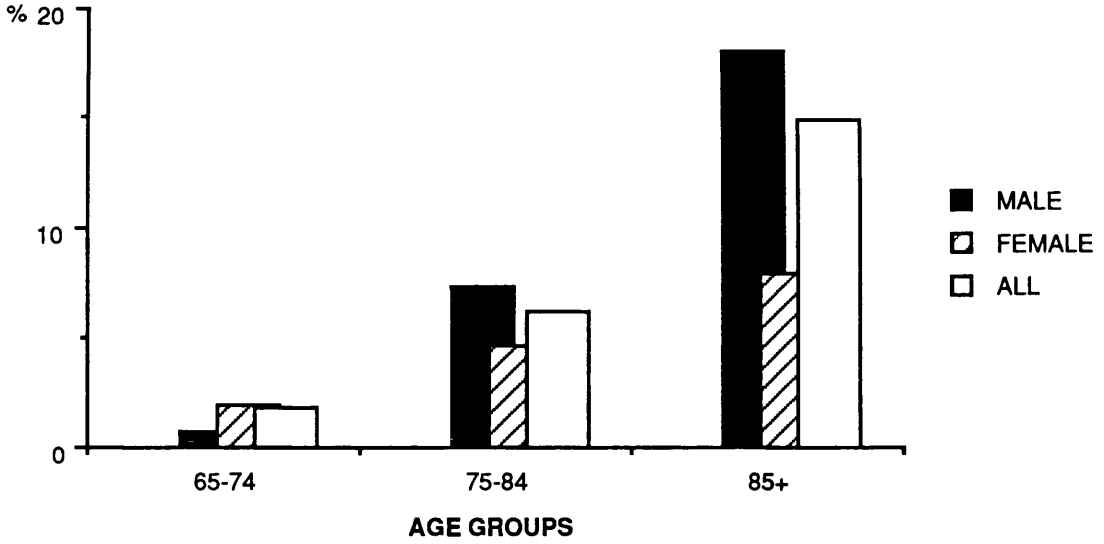
Urban and Rural rates

Pure rural community studies tend to have lower rates than urban studies (Nielsen 1962, Jensen 1963 and Akesson 1969 - an observation by Jorm 1987). A study in Redmont, North Carolina, measuring cognitive function found higher rates of impairment in rural than urban areas (Blazer et al 1985). The difference disappeared once other confounding variables such as education were controlled. Higher rates of dementia in rural areas have also been reported in a

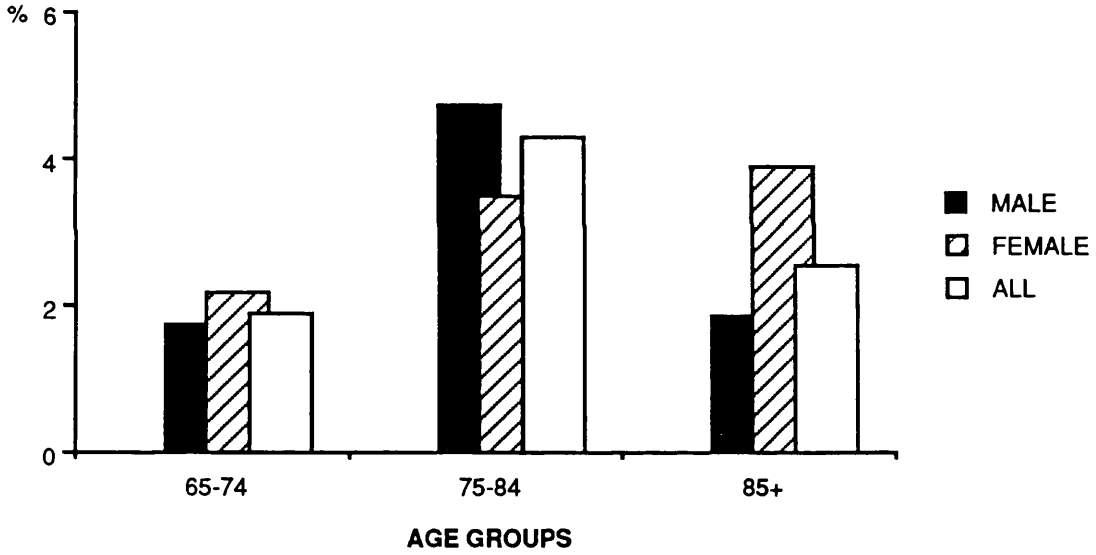
Japanese study, but no attempt at examining possible confounding factors such as age structure of the populations were made (Shibayama et al 1986). The rural prevalence of dementia and its determinants remain relatively understudied.

FIGURE 9

DIFFERENTIAL DIAGNOSIS IN THE COMMUNITY: DEMENTIA



DIFFERENTIAL DIAGNOSIS IN THE COMMUNITY: VASCULAR DEMENTIA



(Sulkava et al 1985)

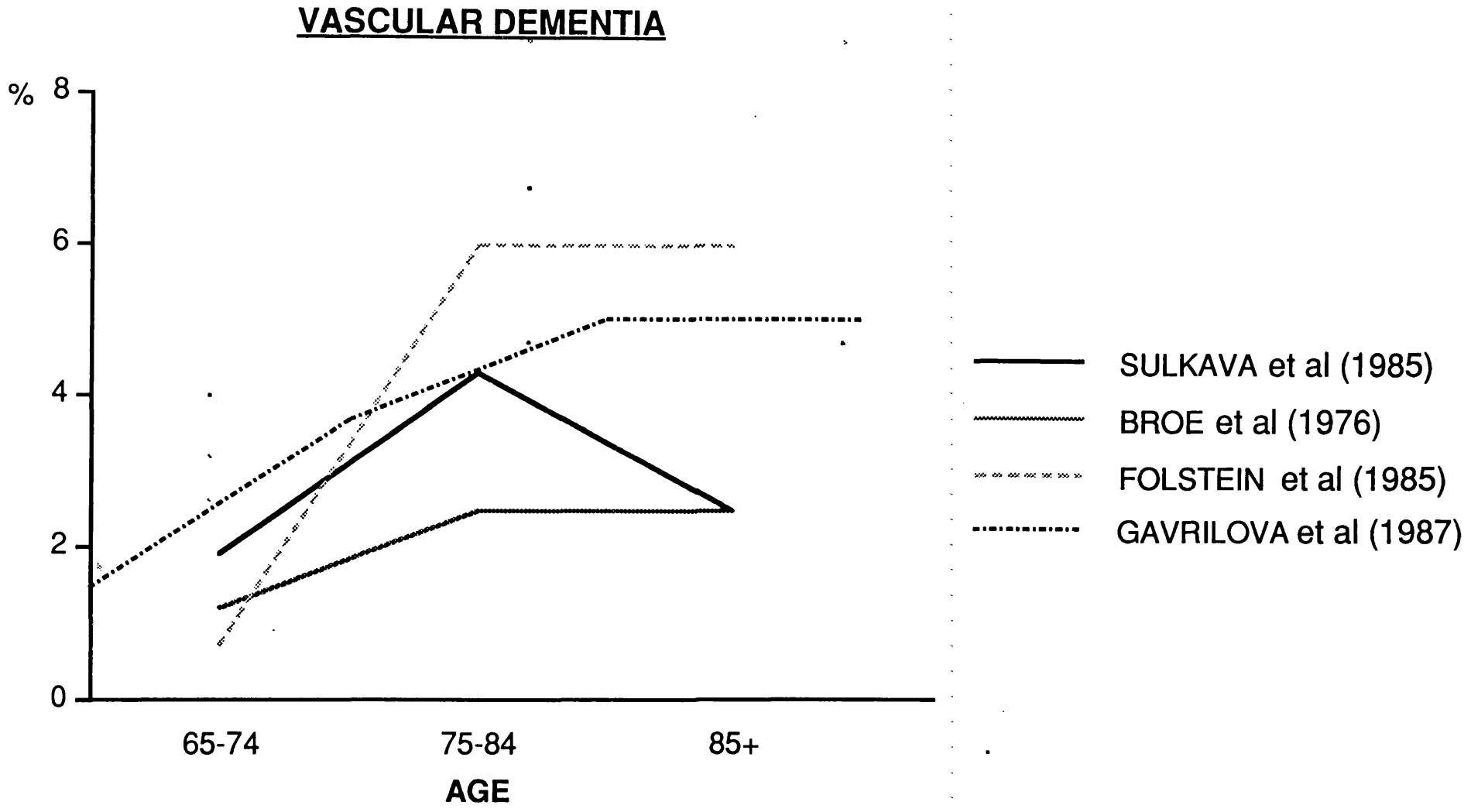

VASCULAR DEMENTIA
%
8
6
4
2
0
65-74
75-84
85+
AGE
SULKAVA et al (1985)
BROE et al (1976)
FOLSTEIN et al (1985)
GAVRILOVA et al (1987)

FIGURE 4

TABLE 10 RATIO OF ALZHEIMER'S DISEASE TO MULTI-INFARCT DEMENTIA
(PREVALENCE STUDIES)

FIRST AUTHOR	ALL	MALE	FEMALE
Broe (1976)			
<75	2.0		
75+	4.4		
Molsa (1982)	1.4		
Folstein (1985)			
65-74	0.4		
75+	0.7		
Sulkava (1985)			
65-74	0.9	0.4	0.8
75-84	1.5	1.6	1.2
85+	5.9	10.1	2.0
Gavrilova (1987)			
60-69	0.3		
70-79	1.4		
80+	3.6		

RATIO OF ALZHEIMER'S DISEASE TO MULTI-INFARCT DEMENTIA
(INCIDENCE)

FIRST AUTHOR	BOTH SEXES
Bergmann (1971)	1.1
Bickel (1989)	1.5

Comparison of large cities

The GMS AGECAT algorithm was applied to a comparative study of the community elderly in New York and London (the US:UK study, Gurland et al 1983 and Copeland et al 1987b). Sampling was based on general practice lists in London and a State household list in New York. The response rate was lower in New York than London (71% and 81% respectively). About 400 subjects were seen in each centre. There were relatively fewer older men in the London sample, and more people from ethnic minorities in New York. Organicity level 03 and higher rates were found to be 2.2% for men and 5.7% for women in London, and 5.4% for men and 10.1% for women in New York. The rate rose to 20% in those aged over 80 years. The difference between the cities was not explained by differences in rates of institutionalisation, but could possibly be accounted for by an increased level of difficulty in conducting such a study in New York. In New York communication problems were noted three times more commonly than in London, inappropriate answers were noted twice as often, with four times the number of probable response set biases (Gurland et al 1983). In New York 12% of interviews were conducted with an interpreter. The ethnic background was predominantly white in the Londoners, of whom 90% had been born in London itself. In New York 10% were black, 10% were of other ethnic groupings, and only half had been born in New York. Interestingly, in New York dementia was associated with physical illness, with the association greater in non-whites than whites. Education showed a negative correlation with dementia. In the face of such huge differences in cultural background and interviewer difficulties, it is difficult to conclude that the observed difference reflects a true finding.

Institutions

There are large differences between the patterns of institutionalisation in different parts of the world and different sections of the population. There are also changes in fashions of institutionalisation over time. In the early epidemiological studies in the UK only a fifth of demented individuals were found to be cared for in institutions (Kay et al 1964). More recent studies have been reported in which considerable numbers of demented individuals in

institutions have been found (see Table 11); some prevalence rates are adjusted for these. For example, in a Japanese study Shibayama et al (1986) found that when the institutionalised population was taken into account the rates of moderate to severe dementia rose from 2.2% to 2.7%, and the rates of mild dementia from 3.6% to 4.2%. Not all researchers have felt it worthwhile to sample institutions, an example of this approach being the Mannheim study in which those in old people's or geriatric homes, or in psychiatric institutions, were excluded from the sample. This made up only about 4% of the city's elderly population and their absence from the analysis was felt unlikely to make any significant difference to the statistical findings (Bickel 1987). Whether this approach is accepted depends on whether the difference of a maximum of 4% to prevalence rates is of importance to the study in question.

It is likely that there has been some change in the pattern of institutionalisation over time. The impact of this on prevalence rates remains debatable, but is probably not insignificant and therefore differences in sampling methods between studies does make comparison difficult. The only method for valid comparison is to sample from the institutionalised population relevant to the community under study, with correction of the estimates found.

Table 11 The prevalence of dementia in institutions

First author	% demented*	Comment
Copeland (1981)	29	geriatric services (75+)
Clarke (1981)	51	general medical ward (75+)
Mann (1984)	36	GMS used for diagnosis
Sulkava (1985)	57	Severe dementia only
Spagnoli (1986)	30	GMS
Serby (1987)	46	
Ames (1988)	49	GMS

* includes severe cognitive impairment

Refusal and non contact

There are many different ways of reporting the stages in sample construction. These include errors in the original sample, loss through death after sample definition, non contact for reasons of

migration or non-response on the doorstep as well as refusal. The numbers in these groups will depend on the period of data collection. Noncontact rates will depend on the accuracy of sample lists; urban general practitioner lists have been found to be extremely unreliable (Livingston et al 1990). Urban populations tend to be mobile, and it is likely that rural general practitioner lists are a more accurate reflection of the resident population of an area. Response rates often refer to available or effective samples, which can hide the lost sample. The Nottingham study reported a response rate of 80.3%, but only 65% of the original target sample was seen (Morgan et al 1987).

Refusal rates vary widely between studies. The population's perception of the research will affect response rates, and location, length and type of interview will influence this. If the study is identified with the general practitioner response rates will be influenced by the opinion of the individual doctor and the patient's opinion of him or her. Clarke et al (1984) had an extremely high response rate at 95%, with a long interview containing much personal information, but a very short section on cognition. Copeland et al (1987) achieved a lower rate of 70%, with an interview that consists mainly of questions about mental health. These response rates were probably also influenced by the locations - market town and inner city. Non-responders are traditionally thought to be sicker and older than responders, but in the elderly it is possible that this assumption no longer holds. It is possible to argue that moderately demented subjects would be more likely to comply with research projects than the normal elderly and also that minimally or mildly demented are less likely to comply. Investigators comparing responders and non-responders in a sample in Edinburgh found that non-responders required significantly less hospital care than responders, and that there was no difference in the rates of dementia and depression reported by the general practitioners for the different groups (Milne et al 1971). An unknown possible bias is therefore introduced when dealing with a condition where refusal rates exceed prevalence estimates.

Racial differences

Despite interest in comparison of populations from different ethnic backgrounds for aetiological purposes, few comparative studies have been done. These present particular methodological difficulties since it is recognised that many of the methods of measurement in dementia are culture and education bound. In the Epidemiologic Catchment Area study higher rates of cognitive impairment were found in blacks compared to whites (Weissman et al 1985), but this was thought to be related to educational differences. In a study of the area of Copiah, Mississipi, the rates for Alzheimer's disease were found to be higher in blacks than whites (Schoenberg et al 1985), but again bias in case ascertainment is possible. No allowance for educational or social class differences was made. A study from Israel found that the age and sex adjusted incidence rates of treated cases of Alzheimer's disease (ie known to hospitals) was higher in Jews born in Europe or America than Africa or Asia (Treves et al 1986). Thus there may be racial differences but confounding factors have not been adequately controlled.

Social class and educational differences

A striking difference in morbidity from almost all conditions between socioeconomic groups has been found in England, Wales and Scotland (Blaxter 1987) and some differences in the occurrence of dementia, particularly in multi-infarct dementia, might be expected. Various studies have examined this, both for the diagnosis of dementia and the estimation of rates of cognitive impairment.

Many types of study have reported an absence of relationship between social class, educational level and dementia. These have included population studies, case series and case control studies (Larsson et al 1963, Kasniak et al 1979, Soininen and Hoinonen 1982, Filley et al 1985, Sulkava et al 1985 and Shalat et al 1987). In Germany in a community study of the elderly higher rates of organic psychiatric disorder were noted in "lower" social classes than "higher". 5.3% of the "upper" classes had such a disorder, 9.7% in the "middle" classes and 23.7% in the "lower" (Cooper and Sosna 1983). One clinical series based on subjects from a psychogeriatric hospital reported that more subjects than expected had low educational levels (Coquoz 1984). In a

study of presenile dementia the opposite was found, with more subjects than expected having had a university education (Gaillard 1984). The finding of higher educational level in cases than controls has also been noted in two case control studies (Heymann et al 1984, French et al 1985). The same finding was reported in a study which involved a three stage procedure to identify subjects with Alzheimer's disease from the community, although the number of cases was only 12 and the response rate at the third stage was under 40% (Folstein et al 1985). These study designs are not equivalent in terms of the quality of the data and the only type of study which can really examine these associations is one with samples which are unbiased.

An association between educational level, social class and measures of cognitive function is well established. A negative gradient with lower education has been found with most widely used scales including the MMSE (Gurland 1981, Weissman et al 1985, Kramer et al 1985). Anthony et al (1982) advised caution in interpretation of MMSE results because of these marked educational effects on score. There is, therefore, conflicting evidence on the relationship of dementia and cognitive decline to education, although there is a clear relationship between cognitive impairment and education.

Marital status

In community studies widows and those who are separated and divorced have been shown to have higher rates of dementia than married women or spinsters (Schoenberg 1985, Weyerer 1983). This finding is likely to be confounded by other factors such as age and differential institutionalisation.

Physical health, drug therapy, retirement and other factors

Most studies of age related conditions do not take account of the clinical and social phenomena associated with age which might have a profound effect on cognition (Avorn 1983). A comparison of a small number of non-demented subjects with non-insulin dependent diabetes found lower mean scores on Mini Mental State Examination and other measures of cognition when compared with matched controls (Ciotti et al 1986). It has been suggested that elevated blood pressure is

related to impairment of cognitive function (Hertzog 1978), and one community study reported an negative association of free recall with increasing diastolic blood pressure in the over 65 age group (Wallace et al 1985). The Gothenburg cohort demonstrated no difference in IQ and memory according to cardiovascular disorders on a cross sectional basis, but those with such disorders showed significant decline over time in verbal reasoning and spatial ability. No blood pressure effect was found (Berg 1980). Disability measured on simple scales was found to be related to a short dementia scale in a small study of the community elderly, but this was confounded by the relationship of age and sex to these variables (Griffiths et al 1987). A further community study of 60 selected subjects found no relationship between focal neurological signs, developmental reflexes, physical health and drug use with cognitive level (Eastwood et al 1983).

Sensory impairment

In a community study of 253 subjects aged over 70 using the CARE interview and a formal hearing assessment, 60% were found to have some degree of hearing impairment (Herbst and Humphrey 1980) An apparent association of hearing impairment with cognitive impairment was accounted for by the confounding factor of age. There was, however, a significant relationship between hearing impairment and depression independent of age and socioeconomic status. In contrast to these findings, it has been reported anecdotally that auditory loss appeared to precede the onset of dementia in a community study of the elderly in San Marino (D'Alessandro et al 1988). Considerable variation in rates according to sensory impairment was reported from another community study in Germany, but no significant differences were found because of small sample size (Cooper and Sosna 1983).

Acute confusional state

Although acute confusional states are noted in hospital samples, they are usually reported as rare in community studies. This is expected since they are transient episodes with either recovery or death as an outcome. There have been only few studies in which a valid attempt has been made to differentiate between dementia and acute confusional states by means of investigations. Several community studies report a substantial minority of individuals diagnosed in one phase of a

prevalence study is no longer found to be "demented" at follow up (Bergmann et al 1971, Copeland et al 1986, O'Connor et al 1990). Whether this apparent change in diagnosis reflected acute confusional states, alcohol ingestion, chronic physical illness, depression or error at first interview is speculative. It is unlikely, however, that acute confusional states would lead to significant variation between different prevalence estimates.

Depression

Different approaches to dementia and depression lead to different reported rates. An example of this is the fact that in the CAMDEX clinical criteria for the diagnosis of dementia and depression, an organic diagnosis always takes precedence over a functional diagnosis, whereas in the GMS algorithm AGECAT the condition which reaches at least the confidence level 03, whether organic or functional is taken as the primary diagnosis. Rates of depression in community studies vary according to the definition of the disorder (Weissman and Myers 1978). If there is a group of individuals in the community with coexistent depression and cognitive impairment prevalence rates could be biased by whether depressed individuals with cognitive deficits are counted as demented or not. Few studies have examined the relationship between depression and dementia in the community or corrected for it.

Levels of severity of diagnosis

Not only do the methods of case identification vary from short cognitive scale to full psychiatric interview and investigation such as computerised tomography, magnetic resonance imaging and evoked potentials, but definition of levels of severity also vary. Some studies have reported severe dementia, others moderate and severe, others mild and still others minimal. Sometimes all this information has been collected, but in other studies only enough information to identify moderate and more severe dementia has been identified. The levels of dementia included for identification could influence the way the diagnostic process operates. If there was a minimal category, those who might otherwise have been classified as mild could have been allocated to minimal, and so on. The description of levels of severity in the diagnostic criteria are vague and difficult to

operationalise. Some investigators have constructed their own definitions of severity, and inevitably these have varied. Even where guidelines for severity are laid down, such as in CAMDEX, interpretation of the same guidelines can be different. These factors could account for a large amount of the variation in rates between those studies where a clinical diagnosis of dementia has been made. Level of severity included in different studies was found to be important in influencing the rates reported in the meta-analysis by Jorm et al (1987).

Effect of diagnostic criteria

Few studies have examined how different case identification and diagnostic methods compare in the same population. In a systematic sample in Hobart in which 158 individuals aged 70-79 years and 116 aged 80 years and over were seen (80% and 68% response rates respectively), trained lay interviewers administered the Canberra version of the GMS together with the MMSE (Kay et al 1985, 1987). Different standardised diagnostic criteria included DSM-III, "pervasive cognitive disturbance", the "rational dementia scale" (Gurland 1983) and AGECAT. Although the overall prevalence rates were similar, different systems identified different subjects.

A comparison of cognitive assessments of various lengths including the abbreviated mental test score (AMTS), the Inglis paired associate learning test and the psychogeriatric assessment schedule (PAS) in community residents with a 2 year follow up (Little et al 1987) showed that the PAS identified 18% of the population and the AMTS 14%, but that these were not the same individuals. The AMTS was the best predictor of decline over 2 years. However, the measure of outcome was also the AMTS.

A study of mild dementia in 100 individuals aged over 70 years from a community in Australia (Mowry and Burvill 1988), using the DSM-III, Gurland's "pervasive dementia", the "rational scale for dementia", the MMSE and Pfeffer's mental function index showed that 25 were classified as mildly demented by one criterion or another. Only 20 of the 25 completed the mental function index (of whom 17 were positive), and 47 out of the 75 not classified as mildly demented by

other criteria were positive on this scale. An informant history was also taken, and the results were as follows:

Diagnostic measure	70-79	80+	All
DSM-III mild			
+ social performance	3	4	3
- social performance	12	22	15
MMSE 18-23	5	19	9
Gurland rational scale	7	15	9
Gurland pervasive scale	8	30	14
Gurland limited scale	19	41	24
Mental function index	63	67	64

Cohort effects

In the psychological literature it has been questioned whether the changes noted in cognitive function between age groups should be attributed to cohort effects alone. There is often a genuine difference in educational attainment between cohorts, such as in the Gothenberg study of 70 and 75 year olds where cognitive tests were less well performed by the older cohort at 76/77 than the new cohort originally studied at the age of 71/72 (Berg 1980). However, it has also been found that within each educational level age effects are found, which are stronger in the less educated groups (Holzer et al 1984). No correlation of years of education and change in score has been found on a longitudinal basis in the Gothenburg cohorts (Berg 1980). It appears that cohort effects do exist, but that there is age associated decrement also.

Incidence studies

Prevalence is a function of incidence, death and migration. Since this is a cross-sectional study, this section is limited to a resume of the incidence studies to date. There have been fewer incidence than prevalence studies and results from these are summarised in Tables 12a and b according to country. The variation in methodology has been at least as great as for prevalence studies with extra differences in the conduct of the longitudinal component. Some incidence rates are based on admission figures for dementia to institutions or contact with services, which seriously underestimates

the rates (Bickel and Cooper 1989) with estimates of 1 to 2/1000 per year for men and 2 to 4/1000 for women aged over 60. Field studies have reported rates up to ten-fold higher (Bergmann and Cooper 1986), although, on average, they are four times higher (Cooper 1989). No consistent patterns have emerged to suggest differences between populations.

TABLE 12a DEMENTIA INCIDENCE/100,000/YEAR

COMMUNITY STUDIES/COHORT STUDIES

FIRST AUTHOR	RATES					COMMENTS
UK						
Bergmann (1971)	1500					2.5-4 year follow up 737 subjects. 5% missing.
EUROPE						
Hagnell (1981, 1983, 1986 Lundby, Sweden) Rorsman (1986)						psychiatric interview multiple sources 1947-72 high response rates n=2550.
	1947-57					
	60-69	70-79	80-89	90-99		
MALE	0	470	1740	---	severe	1053 added in 1957
FEMALE	80	460	3300	---		
	1957-72					
MALE	0	420	1350	---	severe	
FEMALE	13	480	1640	---		
	1947-57					
MALE	190	1100	2880	---	severe & moderate	
FEMALE	250	750	3760	6090		
	1957-72					
MALE	50	720	2150	---	severe & moderate	
FEMALE	170	590	2220	---		
Nilsson (1984) Norway		70-74	75-79			70 year olds (385) 9 year follow up
MALE		500	2530			disorientation severe
FEMALE		1770	3230			memory difficulty response 85.2%
Bickel (1989) Mannheim		65-74	75-84	85+		community 7-9 year follow up
MALE	1410	1510	1230	1900		(343/418 followed)
FEMALE	1970	7700	2380			
		65+				Institutions (146/167 followed)
MALE		13,100				
FEMALE		71,600				
USA						
Sayetta (1986) Baltimore	60	70	80	90		Baltimore Longitudual Study. 519 white men 1958-78. Diagnosis by algorithm.
	83	222	1337	5371		
Katzmann (1988) New York	80					400 80 year old volunteers.
	300					

TABLE 12b

DEMENTIA INCIDENCE/100,000/YEAR

CASE RECORD/INSTITUTIONALISED SUBJECTS

FIRST AUTHOR		RATES				COMMENT (no)
UK						
Adelstein (1968)		60+	60-69	70-79	80+	Senile & organic psychosis in
Salford						
	MALE		109	243	687	psychiatric care
	FEMALE		78	281	674	1959-1963
Wing (1972)						dementia, any
Camberwell	MALE	150				cause 1964-1971
	FEMALE	300				(19,860)
EUROPE						
Akesson (1969)		60+	60-69	70-79	80+	Roth's criteria
Rural Sweden						1964-7
	MALE	260	28	480	860	(4198)
	FEMALE	340	120	360	1370	
Reimann (1972)	MALE	198				First consultation
Germany	FEMALE	117				
Helgason (1973,1977)		60-69	70-74	75-79	80+	1966-1967
Iceland rural, urban						(47336)
	MALE	80	210	340	940	
	FEMALE	70	210	400	830	
Magnusson (1981)		75-81				senile syndrome
Iceland						1971-1977
	MALE	1420				(2649)
	FEMALE	1320				

Nielsen (1981,1982)	60+	60-64	65-69	70-74	75-79	80+	mod./severe dementia
Danish rural	1200	380	170	1500	3310	3460	1972-1977

Moisa (1982)	65+	case records &
Urban Finland		interview
	447	1966-76

US					
Schoenberg (1987)	60-69	70-79	80+		medical records: AD in case record.
MALE	169	770	1582		30% had autopsy
FEMALE	104	725	2406		results. 1960-64.
Kokmen (1988)	30-59	60-69	70-79	80+	Case records
Rochester					1960-1975
MALE	3	171	528	2060	(AD differentiatial)
FEMALE	2	114	700	2042	1970-74 figures

ISRAEL		
Treves (1986)	40-60	Presenile dementia
		National neurologic
	2.6	Register-all poss.,
African/Asian origin	1.4	prob. and definitely
European origin	2.9	demented viewed.

Causation

"If the incidence of Alzheimer's type in black males and white females is the same, it suggests that events occurring under the age of 70 have little important influence on the development of the disorder" (Brody 1982a,b).

There is great interest in the identification of risk factors for dementia, in particular Alzheimer's disease. Risk factors suggested have included aluminium toxicity, heavy metal intoxication, immunological deficiencies, enzyme deficiencies, viral infections and vascular incompetence (Glenner 1985, Masters 1984). Others have considered that other variables such as low social class, low premorbid IQ, urban environment, western life styles, affective disorders and other degenerative disorders could be important risk factors in their own right (Henderson 1986, 1988). The other associations which have been examined include allergies, arthritis, asthma, tonsillectomy, lymphoma, leukaemia, eating brain and raw meat, raw seafood, animal contact, travel, previous disease, surgery, anaesthesia, specific disease in relatives, extreme temperatures, X rays, smoking, drinking, stressful life events, fertility, previous history of psychiatric disorder, calcium deficit and malnutrition. Some of the associations reported are likely to be accounted for by case and control selection bias, and methods of measurement of risk.

The main type of study used to examine levels of risk for these possible factors has been the case control design, particularly in studies of Alzheimer's disease. Different protocols for these studies are described below and the evidence for some of the risk factors mentioned above is summarised in the following section. The methodologies of a group of studies is shown in Table 13. This shows that the recent case-control studies have begun to use broadly comparable methodology, allowing some comparison of risks.

COUNTRY	NUMBER Cases	NUMBER Controls	ORIGIN Cases	ORIGIN Controls	DX CRIT	ELIGIBLE CASES	EXCLUSION	RESPONSE RATE	INFORMANT Q		MATCHING	ELIGIBILITY CRITERIA	RR	INFORMANT QUESTION.
Soininen (Finland)	63	91	popn	nursing home popn	N	>65	oligophrenia, chronic abn. ,MID, other 2° dem.	61	next of kin	i/v	Sex, Age	Age >65 no dem	50%	same
Amaducci (Italy)	116	213	hosp	hosp 116 neighbour/friend 97	N	40-80	next of kin available residence out of area	79	next of kin	i/v	Sex, Age± 3, Res, hosp	no dem (Blessed)	?	same
Hofman (The Netherlands)	198	198	popn	popn	N	<65	MID(HIS>7) P.D. 2°dem.	98.5	next of kin	i/v	Sex, Age±5, Res	No dem (SPMSQ)	61	same
Shalat (USA - Bedford)	106	214	hosp/reg	neighbour	N	Male All ages	Alcohol hx, Head Injury Resident out of area	77	next of kin	self admin mail questionnaire & phone calls	Sex, Age	–	31	same
Chandra (USA - Denver)	64	64	hosp	hosp	N	>70	No informant	100	next of kin	i/v	Sex, Age±3, Rel, Race	No dem	100	same
Heyman (USA - Durham)	40	80	hosp	popn. (random digit dialling)	N	<67	CVA , Alcohol, P.D.	100	next of kin	i/v	Sex, Age ±5, Race, Res. area	MMSE >21	100	same
Schuman (USA - Minneapolis)	76	126	hosp	hosp 75 neighbour 51	N	Male All ages	2°dem	97.5	informant lived with pt >5 yrs	i/v	Sex, Age±3, Race	No dem	hosp 83.5 neighbour 64	same
Kokmen (USA - Rochester)	392	392	register	register	N	All	Resident outside Rochester. Other dementia	–	medical records	–	Sex, Age±3	No dem in index yr	–	same
Graves (USA - Seattle)	130	130	hosp	friend. non blood rel.	N	All	MMSE>26. P.D. Affective disorder Hypothyroidism, CVA No suitable informant	69.2	next of kin	telep. i/v	S, A (10 years)	No memory loss	?	same

TABLE 13

N = Similar or NINCDS ADRDA criteria (mainly possible or probable levels)
HIS = Hachinski Ischaemic Scale
MID = Multi-infarct dementia
P.D. = Parkinson's disease
2° dem = Dementia secondary to other condition
CVA = Cerebrovascular accident

Case control studies

Choice of subject. Patients have been selected from multiple sources such as registers, specialised centres, community studies. Examples include use of a clinical series (Larsson et al 1963, Huff et al 1988), an autopsy group of confirmed cases of Alzheimer's disease (Whalley et al 1982) and use of the Alzheimer's disease societies (Fitch et al 1988).

Age. Several of the case control studies have considered presenile dementia only, but more recently these have extended to examine those with senile dementia also.

Definition of disease. Although almost all case control studies have been of Alzheimer's disease, there has been wide variation in the criteria used. This includes both exclusion and inclusion criteria. With time, the conditions have become increasingly stringent and the cases "purer". Most recent studies have used the NINCDS-ADRDA criteria (eg Fitch et al 1988).

Depression. Because of the possible confounding effect of depression on dementia and cognitive measures, many studies have excluded those subjects with any symptoms of depression. The exclusion has often been based on the result of scores on scales such as the Hamilton depression rating scale (eg Amaducci et al 1986).

Multi-infarct dementia. Many studies have as exclusion criteria a score on the Hachinski scale of more than 4 or 5. As described earlier, this probably excludes subjects who do have Alzheimer's disease, but does allow confidence that a group of patients with high probability of Alzheimer's disease has been selected.

Source of controls. Controls have been selected in many ways. These have ranged from choosing the patient after the case from neuropathological records (Whalley et al 1982), to volunteers and biologically unrelated relatives such as spouses (Silverman et al 1986, Mohs et al 1987). Not all studies have described the source of controls (Huff et al 1988).

Matching. There has been considerable variability in matching procedures. Matching has usually been carried out for age and sex. Neighbourhood, social class and education matching has also been carried out in some studies. Some would argue that this is overmatching on the basis that these may be risk factors themselves (Henderson 1986, Berkman 1986).

Exclusion and inclusion criteria. The controls have rarely been tested as rigorously as the cases and the same criteria for selection have not always been adopted. Some studies have administered short cognitive tests to the controls.

Methods of gathering information. Not all case control studies have been consistent in the method of gathering information about cases and controls. In some studies the controls provided information on risk about themselves (Silverman et al 1986, Huff et al 1988). Most of the more recent studies have, however, used an informant to gather information for both groups. The quality of informant information is difficult to check, and where this has been done it has been found to be of variable quality. The informants of cases and controls have not always been matched. Thus some studies report that the informant was usually a spouse for cases, whereas for the controls it was not (Amaducci et al 1986). A few studies have used more than one informant for some of the cases (Silverman et al 1986, Mohs et al 1987, Huff et al 1988). The actual questions asked to establish exposure to a question such as family history vary also. Fitch et al (1988) report a "typical clinical history" in relatives. Others asked standardised questions (Mohs et al 1987) such as "was he/she forgetful or confused in his/her later years" and "did he/she have a medical condition which could have caused or contributed to the forgetfulness" (Huff et al 1988). Postal questionnaires have also been used for informants, in which control over the source and quality of information is poor (Shalat et al 1987). Possible bias introduced by the use of different type of informant is not known.

Medical records. Other studies have relied on searches of available medical records for information about the particular risk factor of interest (Whalley et al 1982, Spence et al 1986). This approach is used mainly for comparing medical histories. This assumes reporting to be unbiased by the disease process.

Missing data. Not all studies report on the missing data. If there is a difference in the amount of missing data between cases and controls bias could be introduced.

Risks for dementia

Virtually no case control study has been based on a truly representative population sample. Akesson (1969) performed the first comparison based on a community sample to examine the effect of maternal age and birth order and found no effect. The Framingham study in later phases has examined dementia and it is reported that in this study diabetes mellitus, inactivity, heart failure and less than one bowel action per day have been associated with subsequent development of dementia (Henderson 1988). In the Liverpool study of Continuing Health in the Community 56 AGECAT cases of organic level 03 and above were compared using logistic regression with 435 AGECAT 00 on any diagnoses on a cross sectional basis (Dewey et al 1988). It is not stated from whom the information was collected. There were no differences in stroke in parents, high blood pressure, paternal age or maternal age at birth, pet ownership, smoking history, chest pains or kidney disease. Significantly lower odds ratios were found when dizziness (0.44), headpains (0.49) and headaches (0.44) were reported. It is difficult to interpret these findings since the information was probably collected from the subjects themselves.

Risks for Alzheimer's disease identified by studies

The risks for Alzheimer's disease have been extensively reviewed by Henderson (1988).

Fertility. An increase in fertility has been reported in one community study (Kay et al 1964), but found to be reduced in other studies (Whalley et al 1982, Coquoz 1984, Gaillard 1984) and no different in two others (Soinenen and Hoinonen 1983, White et al 1986).

Parental age. Maternal age was found to be higher in one case control study (Amaducci et al 1986). Most other case control studies have examined this and not confirmed the finding. It has also been suggested that this question is unreliably answered (Chandra et al 1987). A Japanese study found a significant difference between the maternal age at the time of the subject's birth for Alzheimer's disease and multi-infarct dementia from a study of community registers. There were no controls in this study (Urakami et al 1988).

Down's Syndrome. The relationship between Down's syndrome and Alzheimer's disease has been noted for some time (Cutler et al 1985). It is thought that the changes of Alzheimer's disease in the brain are almost inevitable in patients with Down's syndrome if they live long enough (Ellis et al 1974). Similar areas of the brain are damaged in both disorders although some differences have been noted in the degree and distribution of abnormalities (Mann et al 1987). Senile plaques and neurofibrillary tangles are noted in Down's syndrome subjects aged over 40 years, whether dementing or not (Wisniewski and Rabe 1986, Mann and Esiri 1988) and are at their most abundant in the over 50 year age group (Wisniewski et al 1985). This led to a search for increased prevalence of Alzheimer's disease in the family trees of subjects with Down's syndrome. An increase was found in two case control studies (Heston et al 1981, Heymann et al 1984, Marazita et al 1987). Conversely two studies failed to find an increase in Down's syndrome in the relatives of subjects with Alzheimer's disease (Whalley et al 1982, Huff et al 1988, Yatham et al 1988).

Finger prints. The finger prints of 50 patient with Alzheimer's disease were compared with controls and with Scotland Yard population norms. A significant increase in ulnar loops and decreased whorls were found in cases, thought to be due to multiple additive genetic factors (Weinreb et al 1985).

Blood group and histocompatability leucocyte antigens. In a study of Alzheimer's disease in 37 subjects with presenile onset and 87 with senile onset significant differences were found in blood groups (Renvoize 1985). It is reported that b15, A2, CW3, C4*B2, Chromosome 6 and 14 are all associated with Alzheimer's disease (Kay 1989).

Handedness. In a study of 3 different populations, 217 normals, 73 depressed and 114 diagnosed subjects with Alzheimer's disease, 11% of the normals, 14% of the depressed and 3% of the subjects with Alzheimer's disease were found to be left handed. Although there was increased right handedness with age, the differences remained significant when this was taken into account (de Leon et al 1986). Another observational study of presenile and senile dementia found that there was more left handedness in presenile subjects than in senile (Seltzer et al 1984).

Lymphomas. An increased risk of lymphomas in subjects was found by one case control study (Heston et al 1981), but not confirmed by others, one in an autopsy series of 74 subjects (Whalley et al 1982) and the other in a case control series (Huff et al 1988).

Thyroid disorder. In one case control any previous history of thyroid disorder was examined and, where positive, was found to be significantly higher in cases (Heyman et al 1984). This finding has not been replicated in subsequent case control studies (eg Lopez et al 1989).

Head injury. There are theoretical grounds for suspecting that head injury may be a risk factor for Alzheimer's disease since there is some resemblance between the changes found in the brain in Alzheimer's disease and those in Dementia Pugilistica, for instance

abundant neurofibrillary tangles in the cortex. It has also been found that these tangles show evidence of common antigenicity. Head injury has been found to be associated with Alzheimer's disease in several case control studies (Heymann et al 1984, Mortimer et al 1985, Shalat et al 1986). It has been suggested that this could be a reporting bias, since the same finding has been reported in other neurological disorders such as Parkinson's disease, brain tumours, multiple sclerosis, epilepsy and mental retardation (Rimm 1986, Kurtzke and Kurland 1985). Attributable risk in the population would be low, highlighted by one study of 66 consecutive subjects with probable Alzheimer's disease, and 152 with multi-infarct dementia diagnosed using DSM-III in whom no history of brain contusion was found (Sulkava et al 1985).

Blood brain barrier. It has been suggested that the blood-brain barrier may be important in the pathogenesis of Alzheimer's disease and that impairment might account for a specific sub-group of the disorder (Lal et al 1985, Masters and Beyreuther 1988), but the blood brain barrier is poorly understood in normal ageing also (Davies and Hardy 1988). Abnormal permeability in both Alzheimer's disease and multi-infarct dementia was reported in one study (Elovaara et al 1987). The methods of measuring the permeabilitiy of the blood-brain barrier have varied.

Fractures and Falls. These have been found to be more common in subjects with Alzheimer's disease than in the general population of comparable age (Buchner and Larson 1987). There may be an aetiological link but some falls are undoubtedly secondary to the dementing process.

Psychiatric history. There is often underreporting of psychiatric history, particularly in normal subjects and there are problems of recall bias in asking informants for such information (Andreasen et al 1977). Increased risk of previous depression in cases was found in one study (French et al 1985). In another study of the case records of 188 subjects diagnosed as having Alzheimer's disease and 80 age and sex matched controls, 34 out of the demented group had a history of psychiatric illness, mainly unipolar depression whereas only 3 out

of 80 of the controls had such a history (Agbeyawa et al 1986). However, in a more recent study no association of previous psychiatric history with Alzheimer's disease was found (Huff et al 1988). There could be bias according to the source of the cases, such as those identified through long stay geriatric hospitals compared to those identified through neurological services.

Vibratory tools. One study has reported that cerebral atrophy is associated with exposure to vibratory tools (Ivanaineen 1975), but this has not been confirmed by other studies and has not been identified as a risk factor for Alzheimer's disease.

Solvents. In a case control study of Swedish workers an odds ratio for mental and neuropsychiatric disorders of 5.1 for exposure to paint, varnish and carpet laying was reported. However, there is some question about the validity of diagnosis, and this risk would not necessarily apply to Alzheimer's disease (Axelson et al 1976).

Smoking. It has been suggested that there is a theoretical reason why smoking and Alzheimer's disease might have a special relationship. Loss of nicotinic receptors in the cerebral cortex of patients with Alzheimer's disease has been demonstrated (Jones et al 1987). A positive dose response relationship between cigarette smoking and Alzheimer's disease was reported in one study (Shalat et al 1987), but no other studies have found this.

Analgesics. It has been reported that the changes of Alzheimer's disease are seen in subjects who have been chronically exposed to phenacetin (Murray et al 1970). The study was based on psychiatric patients, a large proportion of whom consumed large quantities of analgesics. This observation has not been replicated.

Calcium. A positive relationship has been found between calcium levels in serum and MMSE scale of 0.488. It has been reported also that calcium blood levels are lower in moderate to severely demented subjects than mildly affected (Deary and Hendrikson 1986, Deary et al 1987). A mechanism is suggested whereby disruption of the

microtubules by low calcium would occur. However, serum calcium may not reflect intraneuronal calcium levels.

Aluminium. Aluminium is the third most common element in the earth's crust, and there are traces in every body tissue examined. It is absorbed in the gut and accumulates in bone, parathyroid and brain. It is eliminated via the kidney. A variety of foodstuffs contain aluminium (Lione 1985). It is added to water in some areas as a flocculant (Martyn et al 1989), and it has been suggested that increasing acidification of rainwater will increase bioavailable aluminium in the water supply (Perl 1985). Exposure in animals such as cats and rabbits leads to neurofibrillary degeneration which differs from paired helical filaments found in humans with Alzheimer's disease. Such changes are also not found in the brains of subjects with dialysis dementia, known to be due to the large quantities of aluminium which used to be present in dialysis fluids. Study of brains from subjects with Alzheimer's disease has led to the observation that there is an accumulation of aluminium in paired helical filaments (Crapper et al 1976). Aluminosilicates have been found in senile plaques (Edwardson et al 1986, Candy et al 1986), but some have argued that the plaques examined have only been mature plaques and therefore an increase in aluminium concentration may merely be a secondary association (Perl et al 1984, Yates and Mann 1986).

Many conditions increase brain aluminium content without producing the changes of Alzheimer's disease. Aluminium has not been found to be increased in the serum, cerebrospinal fluid or hair of subjects (Shore and Wyatt 1983). In 180 subjects with Alzheimer's disease no correlation of spinal fluid aluminium levels with dementia severity was found (Delaney 1979). Some have argued that, although there may be a special vulnerability to aluminium in Alzheimer's disease, the observation that increase in aluminium concentrations in the brain simply reflects a function of ageing, and that this has been inadequately corrected for (Shore and Wyatt 1983).

Because of the difficulties of examining exposure to aluminium, epidemiological studies have been limited. No case control study has found aluminium exposure to be a risk factor, the most common exposure examined being antacid ingestion. In one more

ambitious study the concentration of aluminium in water supplies in various areas of the United Kingdom was examined in relation to the rates of presenile dementia, measured by the rates of computerised scans in people aged 40 to 69 years with a diagnosis suggestive of Alzheimer's disease on the request form. A small but significantly positive relationship was found with higher exposure in the water supply over the previous ten years (Martyn et al 1989). If aluminium is a risk factor for Alzheimer's disease, even a small relative risk could lead to a large population excess attributable risk because of the numbers of people in the population exposed to the element.

Other elements. There has been a search for differences in elements between subjects with Alzheimer's disease and controls in brain regions, cerebrospinal fluid, serum and hair. No differences have been reported for copper, zinc, calcium, silver, cobalt, chromium, iron, potassium, selenium and magnesium (Kenn and Gibb 1986, Shore et al 1984, Ehmann et al 1986). Significant differences were found in ribidium between cases and controls (Ehmann et al 1986). Bromide, chlorine, caesium, mercury, nitrogen, sodium and phosphorus were also examined. Some of these elements such as magnesium show some positive correlation with age alone (Shore et al 1984).

Viruses. It has been suggested that repeated reactivation of the latent herpes virus might be a mechanism for the causation of Alzheimer's disease. The virus is often found in the trigeminal ganglion which could allow the virus to migrate to the mesial temporal lobe (Ball 1986, Roberts 1987). However no difference in herpes simplex activity was found in one study of senile dementia and schizophrenia (Libikova et al 1981); herpes simplex sequences have not been found in brains from subjects with Alzheimer's disease in other studies (Taylor et al 1984, Pogo et al 1987); similarly antibody titres have not been found to be different in a further study of cases and controls (Molsa 1980). The measles virus and adenovirus have been examined in the same studies and no increased antibody levels nor brain sequences were found (Molsa 1980, Pogo et al 1987). Pogo et al (1987) also examined brains from subjects with Alzheimer's disease for sequences of vaccinia, hepatitis B,

cytomegalovirus, SV40, polio and influenza A and B, and no positive results were found.

Prions. Some similarity between AD and Creutzfeld Jakob disease has been noted. Creutzfeld Jakob disease is thought to be cause by prions - subviral particles which act as infective agents. It has also been found that in mice a "prion clock gene" appears to play an important part in the metabolism of healthy cells. Prions may, therefore, play a part in the control of ageing (Prusiner 1987). Up to now, however, any link between Creutzfeld Jakob disease and Alzheimer's disease remains theoretical, although interest in Creutzfeld Jakob disease itself has increased due to Bovine Spongiform Encephalopathy and the claim that many spongiform or prion dementias pass undetected during life (Collinge et al 1990).

Susceptibility and protective factors

In the more recent literature there has been debate and interest in the possible protective effects of some variables. The main suggestion has been initial brain capacity with larger capacity associated with an ability to survive intact despite neuropathological indices of dementia (Katzmann et al 1988).

Family history and Genetic studies

There is a considerable literature surrounding family history and Alzheimer's disease (eg. Larsson et al 1963, Whalley et al 1982, Silverman et al 1986, Spence et al 1986, Mohs et al 1987, Fitch et al 1988, Huff et al 1988). The major problems of these studies are similar to those noted in earlier sections. These include differences in diagnostic criteria, pathological confirmation, duration of follow up, age at onset, methods of ascertainment of family history, whether multiple informants were used and whether controls were included. These methodological difficulties have been well reviewed (Wright and Whalley 1984, Silverman et al 1986, Rocca and Amaducci 1988).

Twins. The biggest twin series of Alzheimer's disease is that of Kallman and Jarvik, but each follow up wave of this group reports widely differing rates of AD risk in relatives (Nee et al 1987). Many of the twin studies are based on single case reports such as that of

a discordant pair where one monozygotic twin died aged 64 with AD, and the other had no sign of the disorder at 65 (Renzoive 1986). A larger series reported that out of 22 pairs where 1 or both twins had AD, 7 were concordant, 10 were discordant in the monozygotic twins and in the dizygotic group 2 were concordant and 3 discordant. There was no difference in the concordance but the numbers are very small (Nee et al 1987). Rocca and Amaducci (1988) point out that these studies are not population based and are subject to ascertainment bias, that the other twin may die before developing AD, large samples are needed for any statistical confidence in the data and that twins are unlike singletons for other reasons than genetic.

First degree relatives. The cumulative risk in first degree relatives of someone with Alzheimer's disease has been estimated as 2-5% at age 70, 5-10% at age 75, 10-17% at age 80, 15-21% at age 85. It is interesting to note that these risks are similar to the prevalence in the general population reported from community studies. It therefore appears that a consistent bias may be introduced in the choice of controls, who always appear to have lower rates than the general population (Kay 1986). Mohs et al (1987) estimated that the risk of developing Alzheimer's disease by the age of 90 would be 50% in relatives and other studies agree broadly with this finding (Fitch et al 1988, Huff et al 1988). Others disagreed with Mohs et al's findings highlighting the difficulty of control selection for these studies, and suggesting that the risk was overestimated for cases and underestimated for controls (Heston 1988). Further studies have found a variation in family history according to age of onset, and more have found positive family history for presenile onset dementia than senile dementia (Constantinidis 1986).

There has been a suggestion that 3 types of Alzheimer's disease should be considered. The first would be an autosomal dominant pattern with a single gene identified, the second would be familial with a polygenic pattern of inheritance, and the third would be sporadic with an interaction of genes and environment (Rocca and Amaducci 1988). Alternatively, it has been suggested that all Alzheimer's disease conforms to a simple polygenic model (Whalley et al 1982). This emphasis on the genetic basis is still contested, and

others argue that the genetic theories can be explained by environmental factors (Bergmann and Cooper 1986). The mechanism of this association may be that there is a genetic modifier of the ageing process (Nee et al 1987), as it is known that genes are implicated in longevity. Several thousand genetic loci may influence the ageing phenotype, but fewer than 100 exert major efects. Premature ageing is seen in Down's syndrome which has been closely linked to Alzheimer's disease. Some of these manifestations are increased chromosomal aberrations, malignancy, premature greying or hair loss, lipofuscin deposition, hypogonadism, diabetes mellitus, autoimmunity, degenerative vascular disease, cataract, skin and adipose tissue changes. Some of these have been reported as altered in Alzheimer's disease, supporting the view that ageing and the neuropathological of Alzheimer's disease are closely related (Wright and Whalley 1984).

CONCLUSIONS

Dementia is an area in which knowledge has burgeoned in the past decade. Alzheimer's disease, in particular, has been the focus of considerable research activity. Despite advances in many areas, the nature of the relationship between dementia, usual ageing and successful ageing is not clear. The diagnosis of dementia is fraught with difficulties as is the differential diagnosis during life. Possible risk factors for Alzheimer's disease have been identified but findings tend to be inconsistent between studies. Possible reasons for the lack of findings are the methodological difficulties of these studies, including uncertainty about diagnosis. Despite the neuropathological findings reported above, in most studies of dementia there has been the assumption that dementia fits a dichotomous disease model. There is a need to study true population samples in detail to gain a better understanding of the changes throughout the range from successful to unsuccessful ageing.

The Department of Health and Human Services Task Force on Alzheimer's disease (1985) recommended that there was a need for the development of reliable diagnostic research criteria with standardised screening measurements, structured interviews and psychometric assessment. Case control studies, incidence studies, and longitudinal follow up to describe natural history were all identified as being urgently needed. Research in epidemiology should establish demographic trends, life expectancy, methodological research and aetiological research. Khachaturian's comments following a concensus conference are pertinent here - "only by obtaining better data for the normal biological, neurologic and psychologic mechanisms can the abnormal be differentiated" (1985). This study attempts to address these problems.

PRESENT STUDY

AIMS

1. To estimate the prevalence of dementia and cognitive impairment in a female elderly rural population.

2. To examine the distribution of the features of dementia in a homogeneous population of elderly women.

3. To investigate factors which are associated with these features.

METHOD

The sample

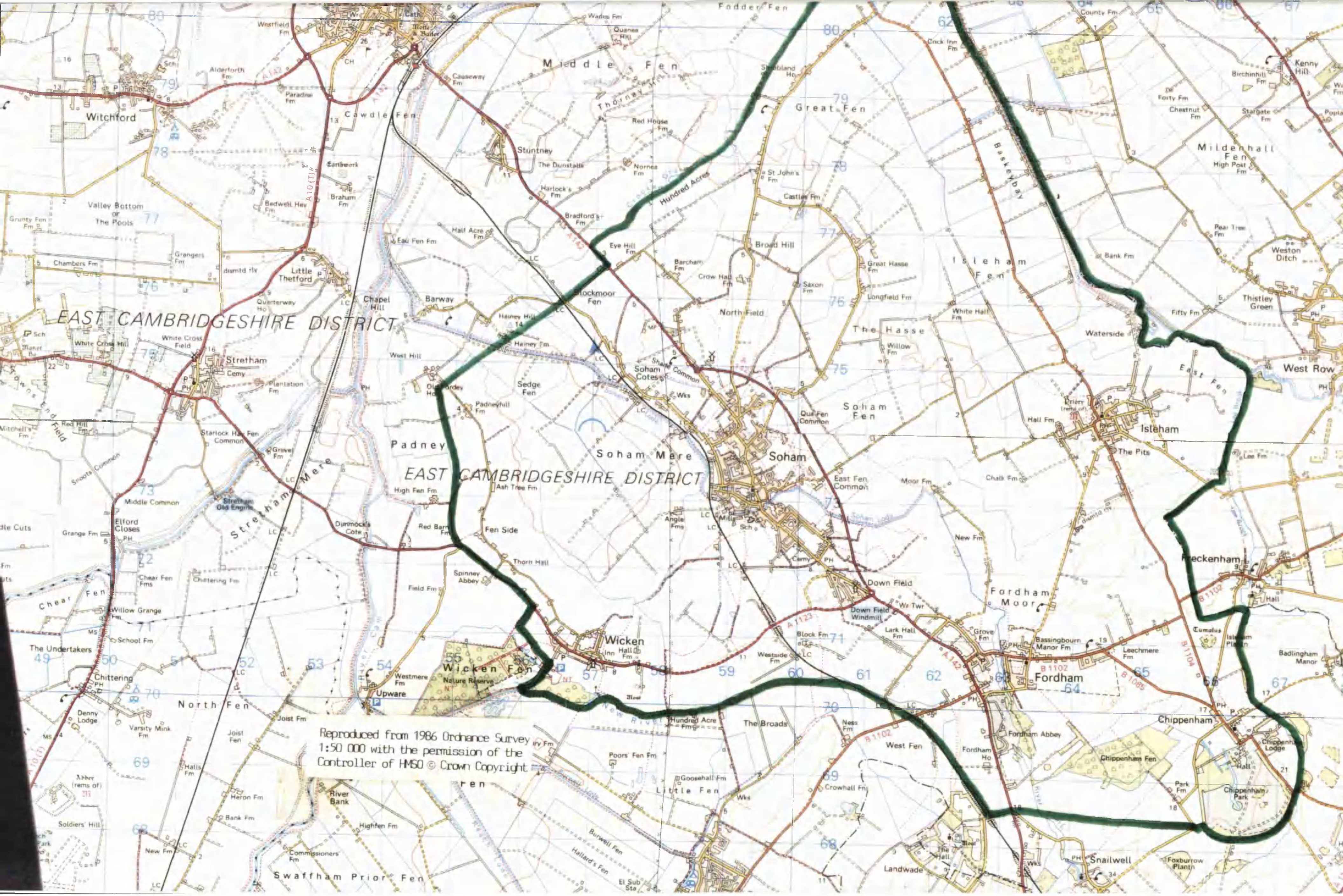
Geographical location

"The whole country was as level as the table on which I am now writing...The land is covered with beautiful grass, with sheep lying upon it as fat as hogs...Everything grows well here" wrote William Cobbett on a visit to the Fens in the 1820s. From the eighteenth century when the Fens were drained to the present this area has been a vast agricultural area. The towns and villages are situated on ancient islands which were the few dry areas in earlier centuries. The towns and villages remain clearly circumscribed even today, and the area is relatively sparsely populated.

The area chosen for study was a stable rural area on the edge of the Fens, 15 miles north east of Cambridge. The geographical boundaries incorporated one small town and four villages (see Figure 5). There has been relatively little migration in and out of this area over many generations. The population is, therefore, relatively homogeneous. Most immigration has been very recent, during periods when house prices were rising and pensioners moved to areas with cheaper prices.

Sampling frame

The sampling frame was the computerised age sex register of the health centre in Soham, which serves the geographical area outlined in Figure 5. There were 6 general practitioners in the health centre, 4 full time and 2 part time. The coverage of the local population is complete such that in the last five years at least no long term residents have been discovered who were not registered with the practice. There is virtually no overlap of coverage with other health centres outside the area, and it is therefore possible to define the area covered by the health centre.


EAST CAMBRIDGESHIRE DISTRICT
Soham
Isleham
Fordham
Wicken
Chippenham
Freckenham
Snailwell
Stretham
Witchford
Upware
Wicken Fen
Soham Mere
Middle Fen
Great Fen
Isleham Fen
Soham Fen
Fordham Moor
North Fen
West Row
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Sampling procedure

Since the number of interviews possible in this study was limited, it was decided, with the advice of Dr D. Ashby and Dr D. Cooke, Biostatisticians at the Royal Free Hospital to the Regional Heart Study in 1985, that the sample should be limited by age and sex. Age was known to be associated with cognitive function; it was possible that sex was also associated with cognitive function in community samples, since dementia had been reported as more common in women than men in some epidemiological research (Jorm et al 1987). It would not have been possible to examine other factors with any power if the age range were unlimited or if both sexes were represented. Using the practice register, a sample was drawn of all women aged 70 to 79 inclusive on 1.10.85. This sample was then stratified by age 70-74 years and 75-79 years. Within each age group random numbers were allocated. The first random 200 out of 272 of those aged 70-74 were chosen, and all those aged 75-79 were included. The remainder of the younger age group were used as reserves where there was loss through death and migration before the sample definition (see Table 15).

Method of approach

Within each age group individuals were assigned a random number. Each age group was then approached in parallel in order, that is, one person from the younger stratum would be invited to participate followed by one from the older stratum. Individuals received a letter from their general practitioner inviting them to participate. An interview time and date were given. Those not wishing to take part or who found the time inconvenient made contact with the general practice reception staff. On the allocated date the subjects were visited at home and the study was explained in detail. If the person was willing to take part, a consent form was signed and the interview continued. All home visits and main interviews were undertaken by the investigator.

The standard interview with the subject was conducted in private since the answers could be influenced by the presence of a third person.

The interview

The interview obtained the following information:

Sociodemographic and general information

The major sociodemographic variables collected were education, living accommodation, social class and socioeconomic group of subject, father and husband (Clarke et al 1984), living accommodation, current and past interests, social activities and intimacy (modified from Brown and Harris 1978). The coding for occupation was performed according to the Registrar General's system of social class as well as socioeconomic group, using a simplifed version of the Classification of Occupations 1980 (OPCS). Contact was made with the Office of Population Censuses and Surveys to clarify any queries which could not be resolved from the manual.

Psychiatric profile

There were two possibilities for the standardised psychiatric assessment. Other instruments, such as the Diagnostic Interview Schedule, were not considered because they were not developed for the elderly. This study required an interview which was directed towards dementia, but was also appropriate for the general and mildly impaired population. Despite its widespread use and extensive validation in the field of geriatric psychiatry, the Geriatric Mental State (GMS) was not chosen for the following reasons. At the time that this choice was made, the interview did not contain all the information necessary to satisfy full criteria for the diagnosis and differential diagnosis of dementia. It did not incorporate more than a few questions on cognition and was designed to be sensitive to case level dementia. It collected detailed information on psychiatric morbidity which was not of direct relevance to this study. The CAMDEX was chosen as the core of the interview for the whole sample because it was designed to include all aspects of the diagnosis of dementia and was capable of examining the full spectrum of performance of cognitive function in the community. Because of the importance of the GMS interview, a small comparative study was conducted on a random 10% of the sample in order to examine the relationship between CAMDEX clinical diagnoses and AGECAT diagnoses.

Additional items to CAMDEX

In addition to the neuropsychological section of CAMDEX, CAMCOG, the information/orientation scale and MMSE were included to facilitate comparison of this study with some of the other studies in this country and abroad. It is possible to calculate the total MMSE score in several ways: including serial sevens or WORLD only, or adding the best score of these two items. Spelling WORLD backwards was asked during the interview. The shortened information-memory-concentration scale was included because it has been correlated with neuropathological measures of Alzheimer's disease. The Medical Research Council has recommended a core set of data to be collected in studies of Alzheimer's disease (MRC 1987, Wilcock et al 1989). It was agreed that additional items to MMSE should be recommended in order to fulfill diagnostic criteria. The Workshop took place after the data collection had been completed, but all, or equivalent items had been included in the present study. Results are therefore presented on an intermediate length of cognitive scale which is shorter than CAMCOG and longer than MMSE. Additional items to MMSE were a complex instruction, a read instruction, abstract thought, two questions on remote memory, and two naming items. The equivalent items contained in the scale in this study are described in Appendix 2. Extra items were added for praxis (copying) and language (fluency). In addition to subscales of CAMCOG which measure orientation, language, memory, attention, praxis, abstract thinking and perception, tentative scales were constructed according to items purported to measure function of specific brain areas (Taylor et al 1980). These areas were frontal, dominant temporal, dominant parietal, temporal and contralateral parietal (Appendix 2). The National Adult Reading Test (NART - Appendix 2).

In the present study, in addition to the informant section of CAMDEX, corroboration for most of the items except cognitive questions was obtained by asking the informant the same or similarly worded questions. This interview was conducted either in person or on the telephone. Additional codes were constructed for phenomena such as a history of visual and auditory hallucinations, hypnagogic phenomena and also for oversensitivity about being watched, and strongly held beliefs about premonitions.

The physical examination included observations on the following systems :

general - impression of obesity, height, posture, mobility, vision (using standard charts) and hearing;

neurological - pupillary inequality, eye movements, tone, tremor, tendon reflexes for briskness and symmetry, primitive reflexes including pout, grasp, palmomental and rooting reflexes, fine finger movement, limb weakness (plantar response was not included in the examination);

cardiovascular - pulse rate and regularity, blood pressure, jugular venous pressure, ejection systolic murmurs and carotid bruits, ankle oedema, crackles and wheezes at lung bases, shortness of breath on exertion allowing an assessment of left, right or congestive cardiac failure, blood pressure was measured twice after the physical examination, before venepuncture, using a random zero sphygmomanometer;

dentition - false teeth or number of fillings.

Laboratory tests

Venepuncture was performed in willing individuals (96%). Routine laboratory services performed haemoglobin, urea and electrolyte, glucose and calcium analyses. Total T4, thyroid stimulating hormone, thyroid antibodies, antinuclear antibody and creatine kinase isoenzymes levels were measured in batches by the Departments of Biochemistry and Immunology at Addenbrooke's Hospital. The CKBB analysis was performed using a two site monoclonal antibody assay (Thompson et al 1980).

CAMDEX Diagnosis

At the end of the subject interview a preliminary diagnosis was made, which was reviewed after the informant interview. When all results from blood tests were received the final diagnosis was made. The CAMDEX criteria used are given in Appendix 1. The possibilities were as follows: Primary diagnosis: None, Alzheimer's disease, multi-infarct dementia, mixed Alzheimer's disease and multi-infarct dementia, dementia secondary to other causes, clouded state, clouded state + Alzheimer's disease, clouded state + multi-infarct dementia, depression, paranoid illness. A clinical estimate of severity of dementia was made in the following categories: none, mild, mild/moderate, moderate, moderate/severe, severe. There was also an assessment of depression which followed the same schema. The mild category of this version of CAMDEX includes cases that would be classified as minimal under the revised published version of CAMDEX. The mild category of depression in this study would not be considered as case level and would be more compatible with the dysphoric mood of DMS-III-R.

Medical information

Each subject was rated by her own general practitioner for the presence of dementia and depression, and, if present, to what degree. This information was requested without providing criteria, in order to be able to compare the general practitioners' concepts of these disorders applied to subjects they have known for years with those arrived at by standardised methods over a short time period, but including informant history. The general practitioners were blind to refusal to participate in the study at the time of completing these diagnoses.

Information on medical, psychiatric and surgical history was extracted from practice notes. Current medication was also recorded. Medical conditions were coded according to the WHO Classification of Diseases, Ninth Edition. Surgical conditions were coded according to the Office of Population and Censuses coding method used in the Hospital Activity Analysis. Medication was coded according to the Drugs section of the Ninth Edition of the International Classification of Diseases.

Risk factors

Embedded in the full study interview above were most of the risk factors for AD identified from previous case control studies, risk factors for vascular disease and factors postulated as influences on cognitive function as described in the Introduction. The method of collection of information is shown in Table 14. The variables were as follows:-

Risk factors for AD: family history of AD or dementia, Down's syndrome, lymphoma, handedness, thyroid disorder, head injury, integrity of blood brain barrier as measured by CKBB, presence of neurotropic viruses such as herpes simplex and zoster, educational level and socioeconomic group, depression and psychiatric history, antacid ingestion and medical history of peptic ulcer (for aluminium ingestion).

Risk factors for vascular disease: hypertension, stroke, transient ischaemic attack, alcohol and smoking histories.

Associations with cognition not included above: physical health, medication and social engagement.

Risk factors not included were fertility (data collected but not coded), parental age (too unreliable), finger prints (socially unacceptable), blood group and HLA typing (evidence too weak to justify expense), exposure to vibratory tools and solvents (not relevant) and brain capacity (not possible practically).

Table 14

Risk factors for dementia and cognitive impairment

	Position in interview			
Risk factor	Subject	Informant	Examination	Records
Diabetes	+	+	glucose	+
Inactivity	+	+	-	-
Constipation	+	+	-	+
Heart failure	+	+	+	+
Dizziness	+	-	-	+
Headaches	+	-	-	+
Handedness	+	-	-	-
Thyroid disorder	+	+	T4,TSH	+
Head injury	+	+	-	+
BBB integrity	-	-	CKBB	-
Fractures	+	+	-	+
Falls	+	+	-	-
Mental illness	+	+	-	+
Peptic ulcer	+	+	-	+
Stroke	+	+	+	+
Hypertension	+	+	+	+
Autoimmunity	+	+	+	+
Transient ischaemia	+	+	-	+
Herpes simplex	+	-	+	+
Herpes zoster	+	+	-	+
Alcohol	+	+	-	-
Cigarettes	+	+	-	-
Analgesics	+	-	-	+
Aluminium	Antacids	-	-	+
Mercury fillings	-	-	+	-
Family history				
dementia	+	+	-	-
Down's	+	+	-	-
lymphoma	+	+	-	-

List of variables

General: age at interview, marital status, social class and socioeconomic group for self, husband and father, interests in the past, interests at present, activities of daily living, religious beliefs, social contacts, sleep, smoking, alcohol.

Psychiatric: anxiety, depression, other mental disorder.

Past History: myocardial infarction, cerebrovascular accident, transient ischaemic attack, thyroid disease, latent central nervous system viral infection -herpes zoster and simplex, medical history including operations,
psychiatric history.

Medication: current medication, previous barbiturates and psychoactive drugs.

Laterality: handedness and footedness.

Cognitive function subscales: orientation, memory- recent and remote, language- comprehension, expression, reading, praxis, writing, calculation, abstract thinking, perception- tactile and visual.

Derived cognitive scales: CAMCOG, Mini Mental State Examination, information/orientation test of the Clifton Assessment Procedure for the Elderly, modified version of the information-memory-concentration (Roth and Hopkins 1953).

Other scales: Hachinski and CAMDEX ischaemia scales, CAMDEX depression scale.

Physical Examination: teeth- false, own and number of fillings, pupillary abnormalities, reflexes - tendon and primitive, hemiparesis, cardiac failure, breathlessness on minor exertion, visual and hearing difficulties, obesity, visual reaction time - simple, choice.

From both subject and informant: basic demographic features (as in first section above), family history, longevity, change in memory.

From informant only: Blessed dementia rating scale
CAMDEX organicity scale.

Blood tests: haemoglobin, urea and electrolytes, glucose, total thyroxine, thyroid stimulating hormone, creatine kinase isoenzymes.

General practice notes: illnesses, operations, prescribed medication.

Timetable and approach

Field work began in October 1985, shortly after sample definition. Most of the interviews were conducted in the first seven months, and all were completed within 12 months of sample definition. The full interview took from one and a half hours to two hours. On three occasions the interview was conducted over two time periods, the same or next day. After the interview permission was requested to approach an informant. A specific request was made that this person should be aged under 70 years since in the pilot study it was noted that spouses or those of similar age tended to dismiss change as "the same" or "no worse than me". This also avoided the questioning of informants who were themselves subjects in the study. The subjects themselves were asked to let the informant know that permission had been given to approach them for interview. This method was mostly satisfactory. Informants were usually available at the time of interview where a subject was demented but not institutionalised. After completion of the interview the subject was given a note thanking her again for taking part. Any major abnormalities found were reported to the general practitioner with the permission of the subject.

Data Protection

All identifiable information apart from subject number was removed from the questionnaires after completion of the schedules. The storage of data complied with the Data Protection Act.

Quality Control

Intra-interviewer bias was assessed by examining for trends in scores on cognitive scales over the 12 month interviewing period. Drift in interviewing methods could be identified in this way. Neither the general practitioners' diagnoses nor any information from the notes was obtained before interview to avoid bias. There was a single exception where the general practitioner felt obliged to inform me that a subject was suffering from terminal carcinoma of the bronchus. Nearly all interviews with the subject were audiotaped. Four interviews were randomly chosen and were recoded. Each individual item code was checked. Nine tapes were chosen randomly, rated and diagnoses allocated for comparison with the original field diagnoses.

Since there was a single interviewer for this study inter-interviewer bias could not appear within the study. However, for comparison with other studies I took part in a small inter-rater study with Dr Daniel O'Connor from the Hughes Hall Project for Later Life.

Sample bias due to loss of institutionalised subjects from the practice lists was checked. The three subjects in this sample who were in long-stay hospital beds were seen in the same way as those living at home. In order to establish the completeness of the practice register, a search of records for the psychiatric hospital, geriatric hospital and Part III homes serving the area was made for the previous three to five years. The number of patients of the correct age and sex who came from the study area per year was recorded.

In order to establish how much bias was introduced into the results by refusal, those people who had not participated at the first invitation were visited after the period of main data collection, between one and 10 months following their initial refusal. No further approach was made to those who refused at this visit. It was possible to meet almost the entire sample. The medical notes of the refusers were perused in exactly the same way as the interviewed sample, and the general practitioners were asked for their diagnoses without knowledge of refusal.

The validity of diagnoses was examined by selecting a random 10% of those seen, and reinterviewing them with the GMS. The subject was asked if she was willing to be seen again, explaining that this was for quality control. Those who agreed were seen within ten days by a consultant psychiatrist (Dr Paul Calloway) using the hospital version of GMS, but without the History and Aetiology Schedule or Social Status Schedule. These were not carried out because it would have been unacceptable in this study to approach an informant twice. It was then possible to derive the computerised algorithm AGECAT diagnoses on this small group.

Data handling

Data Preparation

Most of the coding was carried out at the time of the interview ready for data entry. Some questions required postcoding. These were the social activity, migration, social class and socioeconomic group, medications, surgical operations and medical history. Diagnosis was completed after subject and informant interviews and results of investigations. After the interviews were completed the schedules were checked for completeness. All the blood results were coded at this stage. The coding for occupation was performed according to the Registrar General's system of social class I to V as described. The interviews were checked twice for completeness and accuracy of coding.

Data Entry

The data were entered onto the mainframe IBM Pheonix system of the University of Cambridge. Data entry was verified (100%) and errors corrected. Once this was completed, further checks on the completeness of the data were carried out. All gaps were checked and cross checked with the interviews to see whether the data were genuinely missing. A random 5% of printouts were checked against the schedules; very few errors were found. Once the data had been defined using SPSS-X, simple frequency checks were performed to identify values outside accepted ranges.

Statistical Analysis

Because one of the purposes of this study was to examine distributions of variables associated with dementia in the community, statistical techniques included the following:

i) simple examination of the data in categories such as educational levels and age groups. Where appropriate, differences were examined by means of t-tests or chi squared tests, using both the SPSS-X package or hand-held calculator;

ii) tests for bimodality using the standard normal test suggested by Haldane (Spiegelhalter personal communication);

iii) nonparametric correlations, using Spearman rank rho (SPSSX);

iv) logistic regression was performed on selected data using the package GLIM (Aitkin et al 1989) to calculate odds ratio estimates of relative risk and confidence intervals on these;

v) Comparison of diagnoses was carried out using the kappa statistic, which is more stringent than the other methods available, taking into account chance agreement (Cohen 1960).

RESULTS

The sample

Response rates

365 women were interviewed fully out of 400 alive at the time of contact. The final response rate of the available sample, excluding those who died before being interviewed, was 91% (Table 15). The response was slightly higher in the 70 to 74 age group (185/200) than in the 75 to 79 age group (180/200). A small number of individuals were included incorrectly on the age sex register, either because they moved out of the area or died before sample definition. In order to balance the age groups, losses from the younger group were replaced by adding a new name from the randomly ordered reserve list. 10 individuals died after sample definition, but before they were due to be interviewed. In the younger age group these were also replaced with individuals from the reserve. This left 200 available women in each age group.

The refusal rate fluctuated during the study, with higher numbers refusing at the beginning of the study, fewer in the middle and more at the end. All those who had cancelled appointments were re-contacted at the end of the interviewing period, and an attempt was made to meet all these individuals to explain the study and invite them to participate. At this second approach, 15 out of a total of 50 individuals agreed to take part, 9 from the younger age group and 6 from the older. The 15 who participated at this later stage did not differ in diagnosis or level of cognitive function from those who took part at the first contact contact and are included the main analyses presented here.

All but 4 individuals from the available sample were seen. Two husbands and one son acted as proxy refusers, not allowing me to meet their wives or mother, the fourth had moved out of the area and refused on the telephone. Some refusers were persuaded to refuse by their families (e.g. three husbands who insisted on remaining present during the interview and prompted abandonment of the interview by negative remarks and one subject who was dissuaded by a daughter-in-

law who felt it was "immoral to bother old folk in this way"). Fear of discovery of disease was a reason for refusal. Mental and physical illness appeared to be rare in this group, from the brief general impression I obtained and from examining their medical records. Other reasons given by the population were similar to those of another study (Akhtar 1972). Examples of these were "I dont need a check up", "Waste of tax payers money","I don't want people poking their noses into my business","I'm too busy". Only one person who was in the terminal stage of pancreatic cancer was felt by the GP to be too sick to be interviewed. There was no obvious difference in the refuser group and the main sample in dementia on the basis of my brief observation and information from the general practitioners and reception staff.

The interview was found to be reasonably acceptable to the population despite its length and content. Most objections were to the cognitive testing, particularly the pencil and paper items. Only 3 individuals abandoned the interview.

Informant interview

96% (350/365) of the women agreed to allow an informant to be approached (Table 15) and there were no differences by age group in the availability of informants. Very small numbers of people refused to allow me to approach an informant, and only one informant refused on approach when the subject had given permission. Only 4 women were unable to give me the name of someone who knew them reasonably well. The age range of the informants was 22 to 77 years, with only 9 aged above 70 years. 70% were women. Most (78%) had known the subjects for many years, 13% for several years and 5% recently only. Most informants were children (64%). Other close members of the family provided information on a further 19%. Friends were chosen as informants by 6%. The remainder (11%) was a miscellaneous group including more distant relatives, warders and nurses. Most of these interviews (76%) were conducted on the telephone.

Table 15 The sample

	Age on 1.10.85	
	70-74	75-79
Total sample	272	214
Outside area	0	2
Random sample	200	212
Reserve	72	0
Moved/ghosts	2	5
Replacements	+2	0
Death	3	7
Available sample	200	200
Not seen	2	2
Seen briefly	6	14
Partial interview	7	4
Incomplete/refusal	15	20
Full interview	185	180
	(92.5%)	(90%)
Informant	178	172
Not available	2	2
Refusal	5	5

Description of sample

Age

The distribution of age at interview is shown in Table 16. A few women passed their 75th and 80th birthdays after the sample was drawn and before interview. Because of possible cohort effects, they were retained in their original age group for most analyses. In those analyses where age is treated as a continuous variable, age at interview was used.

Table 16 Age at interview

Age	Number (%)
70	24 (6.6)
71	26 (7.1)
72	42 (11.5)
73	45 (12.3)
74	34 (9.3)
75	39 (10.7)
76	30 (8.2)
77	44 (12.1)
78	37 (10.1)
79	25 (6.8)
80	19 (5.2)
All	365 (100)

Marital status

Table 17 shows the marital status of the main sample in comparison with the refuser group (including those who had completed only partial interviews). More of the refusers were married than the interviewed sample. Since the refusers tended to be older, more of them would be expected to be widowed. There is therefore a difference in the response pattern by marital status. More women in the younger age group were married than widowed (53% and 42% respectively) whereas more women in the older age group were widowed than married (58% and 36% respectively). Few were single or divorced in either age group.

Table 17 Marital Status (%)

Status	Main sample (n=365)	Refusers (n=35)
Single	4.4	0
Married	44.8	60.0
Divorced/sep	1.1	0
Widowed	49.7	37.1
Unknown	0	2.9
Total	100	100

Accommodation and mobility

Most of the women lived in independent accommodation, either with their spouse (41%), with family or other (11%), or on their own (38%). Only two lived in long stay hospitals, and two in residential homes. 14% of the women of the 75 to 79 year age group and 5% of the 70 to 74 year age group lived in sheltered accommodation.

Specific questions were asked about mobility and how long subjects had lived at their present residence. One in five subjects had moved house in the previous 4 years, and 1 in 3 had been in their current house for 30 years.

Social class

Those who had ever been married were allocated to their last or current husband's social class. Those who never had been married were allocated their own social class. There was sufficient information to categorise most subjects: of those unclassified two were housewives married to retired military officers; 2 had never been married and had spent their adult lives looking after their parents; the only possible informant (a neice) of one demented subject did not know her occupational history.

There was no difference in the social class distributions (I to V) between the age groups. 44% and 45% of the younger and older groups respectively were in social class III, with 23% and 22% in social class IV, 17% of each group were in social class II, with just over 2% in social class I. Those in social class II and IV were mainly associated with agricultural occupations. The social class distributions of the subjects, their fathers and their husbands is shown in Table 18. There was insufficient information from the refuser group for examination of social class to be useful.

Table 18 Social class

	Subject	Father	Husband
I	0.3	0.3	2.5
II	7.7	21.1	17.3
III	13.2	32.3	44.4
IV	37.5	32.9	22.7
V	0.5	5.5	0.3
Unclass.	40.3	7.9	5.8
Total	100	100	100

Unclass.=unclassified

Educational level

Educational level was similar for the two groups. 79% of the younger and 73% of the older group left school at the statutory leaving ages of 13 or 14 years.

When social class was dichotomised into non-manual and manual, and educational level into those leaving school at 14 years or below and 15 years or above, the pattern of educational level by social class was as expected. 38% of those in the non-manual category and 14% of those in the manual category left school at 15 or above ($p<0.001$).

Activities and interests

10% of subjects and 6.5% of their informants reported that subjects had difficulty in handling money. 11% reported difficulty with simple household chores. 18% of subjects reported stress or urge incontinence, with only 11% of informants reporting knowledge of this. 10% subjects used a stick or other aid for mobility. All these proportions were lower for the younger than the older age groups. In contrast to this no differences were found by age in how much women got out of the house. Half of the women reported getting out of the house at least every week, with 40% getting out every day, a small proportion (4%) managed to get out once a month and only 6% even less often.

A large proportion reported watching at least an hour of television every day (82%). Over half (55%) gave knitting as an important hobby, with half reporting club membership as a hobby also. Just under half (47%) reported reading as a hobby, including regular reading of magazines. 40% reported gardening and 30% church membership as important recreation. Only 18% reported hobbies which involved active mental activities such as regular crosswords, word games and bridge, and only 15% reported active physical hobbies such as cycling, swimming and yoga.

Contact with family and friends

A quarter of subjects did not see any close friend regularly and 10% saw family infrequently. A quarter of subjects did not have any confidante. According to informants 36% had suffered what they considered to be an important life event, such as a serious illness, bereavement or moving house, in the previous 2 to 3 years.

General mental function

Approximately 30% to 60% of the women reported deterioration in such functions as coping, energy, maintenance of attention (see Table 19) but these reports bore no relationship to current cognitive level as measured by the cognitive scales. Only 1% of women reported that they had lost their way in the neighbourhood. On each of these items the older age groups reported more change than the younger group.

Table 19 General mental function

Function	Positive response (%)
Difficulty with coping	29
Less energy than in past	63
Attention difficulty	44
Difficulty remembering	53
Forgets where puts things	47
Forgets names	22

General health

On the whole the women reported reasonable health, although 40% felt that they were limited in some way by their health. Specific problems reported are shown below in Table 20.

Table 20 Problems with health

Problem	Positive response(%)
Dizziness	22
Eyesight	32
Hearing	30
Current hypertension	31
Past hypertension	8
Myocardial infarction	4
Stroke	4
Transient ischaemia	4
Thyroid disease	10
Herpes zoster	25

The numbers of disorders reported are shown in Table 21 according to subject and informant and are compared with those recorded from the general practitioners' notes. The distributions are very similar.

Table 21 Disorders past and present

(% including joint aches)

Number	Subject/informant	GP notes
0	2	5
1	11	12
2-3	31	22
4-5	22	37
6+	31	17

Medication

The interview included questions on sleep disturbance and whether medication was taken for this. 29% reported taking sleeping tablets regularly. 32% reported medication for hypertension. This figure was very close to the 31% recorded in the general practitioners' notes as hypertensive. At the end of the interview each subject was asked

their entire medication and usually this resulted in all the bottles being shown to the interviewer. The total number of drugs taken regularly was compared with the number prescribed by the general practitioner (Table 22). The proportions were almost identical suggesting that self-prescribed medication was either uncommon or that there was a consistent relationship between noncompliance and self prescribing habits.

Table 22 Current medication

	Practice notes	Self report
Numbers	%	%
None	20	20
1	12	13
2	18	16
3	22	19
4	12	14
5+	16	18
ALL	100	100

Clinical diagnoses

In the women aged 70 to 74 the prevalence of all levels of dementia was 4.3%, and for those aged 75 to 79 11.7%. The prevalence estimates for levels of severity by age group are shown in Table 23. These diagnoses were based on the CAMDEX clinical criteria, made by the interviewer at the end of all data collection using CAMDEX clinical guidelines (see Appendix 1). Only one individual who had no available informant was diagnosed as mildly demented on CAMDEX clinical criteria (multi-infarct dementia). There was an increase from the younger age group to the older for both the mild category and the mild/moderate and more severe category ($p<0.01$).

Table 23 Prevalence of organic brain syndrome (%)

	Age group (n)	
Severity	70-74 (185)	75-79(180)
Mild	4.3 (8)	8.9 (16)
Mild/moderate	0 (0)	2.8 (5)
All	4.3 (8)	11.7 (21)

Table 24 sets out the differential diagnosis using CAMDEX guidelines for the age groups. A large increase is seen between the age groups for senile dementia of the Alzheimer's type (SDAT) but not for multi-infarct dementia (MID). The individuals with dementia secondary to other causes were all graded as mildly affected. One individual, although not fulfilling the criteria for dementia, was performing under her normal level secondary to gross hypothyroidism. When she was treated by the general practitioner marked improvement was reported by both the subject and her informant. One subject had suffered from an acute confusional state shortly before being seen, and one woman whose family refused the interview was in a terminal confusional state due to cancer of the pancreas. Minimal and patchy cognitive impairment was found in a further woman, whose informant reported mild changes in personality and memory, but these were insufficient to fulfill CAMDEX dementia criteria. This individual was found to be markedly hyperglycaemic, although not previously known to be diabetic.

Table 24 Differential diagnosis of dementia:

CAMDEX clinical diagnoses

	70-74		75-79	
Diagnosis	% popn (n)	% dementia	% popn (n)	% dementia
SDAT	1.6 (3)	37.5	6.7 (12)	57
MID	2.2 (4)	50	2.8 (5)	24
Mixed	0 (0)	0	0.6 (1)	5
Other	0.6 (1)	12.5	1.6 (3)	14
Confusion	0 (0)	0	0 (0)	0

Death, institutionalisation and refusal

One individual out of the 10 in the sample who died before being seen was definitely demented according to the general practitioner's and the hospital case records. There was no evidence available to the health centre that any of the others were demented. The search of local institutions for individuals of the correct age and area identified only 2 demented individuals not known to the study. One of these, who died during the study, had been given a tentative diagnosis of multi-infarct dementia. The other, who was definitely demented with possible Alzheimer's disease, had died shortly before sample definition. A marked finding during this search was that a small number of demented and depressed individuals had been admitted repeatedly to the same and different insitutions. I was able to meet all but 4 of the 35 individuals who refused to participate. There was partial information on a considerable number of these. In 7 my conversation with them was too short to exclude mild dementia, but they were clearly not moderately or severely demented. Two individuals appeared to have a somewhat dysphoric mood. In the other 22 there were no obvious features of dementia or of manifest mental illness.

To correct the prevalence estimate for loss through death, institutionalisation and refusal, two additional demented subjects would be added to the numerator. These two died during the study, one known to the sample but not interviewed. The other was found from the search of institutions records and was missed from the sample because she was not on the general practitioners' lists. The denominator for the total sample therefore becomes 411. The total prevalence (unweighted) remains just under 8% for both uncorrected and corrected estimates. The estimates for the individual age groups also alter little, although one of the cases was under 75 years increasing the numerator in this age group for mild/moderate dementia from none to one.

CAMDEX Diagnosis by Age, Education and Social class

Table 25 shows the distribution of diagnoses by educational level and Table 26 by social class (I to V). There were no significant differences in the distributions. Social class IV appeared to have a higher proportion of subjects diagnosed as demented than the other classes grouped together (14% and 6% respectively, $p<0.01$). If the prevalence of dementia was examined by manual and nonmanual groups there were no significant differences, although 4% of the non-manual and 8% of the manual group were categorised as mildly demented.

Table 25 Dementia severity and level of education

	Age on leaving school	
Severity	<15 (%)	>14 (%)
None	264 (92)	72 (92)
Mild	19 (7)	5 (6)
Mild/moderate+	4 (1)	1 (1)
All	287 (100)	78 (100)

Table 26 Dementia severity and Social Class

	Social Class					
Severity	I	II	III	IV	V	Unclass.
None	10	62	158	77	25	4
Mild	0	3	9	10	2	0
Mild/moderate+	0	0	1	3	0	1
All	10	65	168	90	27	5

Unclass.=unclassifed

General practitioners' diagnoses

The general practitioners diagnosed 6.7% subjects as mildly demented in the 70 to 74 year age group, and 7.3% in the 75 to 79 year age group. 0.5% were identified as more demented in the 70-74 age group and 1.7% were identified in the older. There were 6 individuals where the general practitioner did not feel confident in making a tentative diagnosis, because the individuals never consulted.

Alternative operational CAMDEX diagnosis

In the published CAMDEX (Roth et al 1988) a suggested schema for alternative operational guidelines is given. This involves the use of scores on the CAMCOG, Blessed dementia rating scale, and ischaemia scale in addition to clinical diagnosis. Cutpoints are given: for CAMCOG 79/80 and for the Blessed dementia rating scale (4/5). Using this method 6.0% of the entire sample were identified as possibly demented, 3.0% identified as probable dementia and 1.4% as definitely demented.

A comparison of diagnoses

Ten subjects were rated as demented by both the general practitioners and clinical CAMDEX. 19 subjects were rated as demented by the general practitioner and 19 by CAMDEX alone. In 311 both agreed that dementia was not present.

A logistic regression analysis was conducted to examine the relationship of age, housing tenure, social class, educational attainment and subjects' history of psychiatric illness on CAMDEX clinical diagnoses and general practitioners' diagnoses. In this analysis the diagnosis of dementia (any level of severity) was entered as the dependent variable, first according to the CAMDEX clinical diagnosis and then according to the general practitioners' diagnosis. The independent variables entered into the model were age (continuous), housing tenure (categories), social class (1 to 5), age at leaving full time education (continuous), and previous history of treatment for psychiatric illness (0/1). These were entered individually into the model. None of these variables was identified as significantly related to the risk of clinical diagnosis of dementia using CAMDEX criteria. Previous psychiatric history was selected out by the modelling procedure for general practitioners' diagnosis with an odds ratio of 2.9 (95% confidence limits 1.3-6.6) for those with a positive history compared to those without. No other factors were identified and no interactions were found.

Subsample diagnoses

For the random subsample of 36 women where GMS was administered, two further diagnoses were available. The psychiatrist who administered the GMS made a diagnosis based on the single interview without an informant history. The data were sent to Liverpool University where Dr. M. Dewey processed them through the AGECAT diagnostic algorithm and sent back AGECAT diagnoses. The agreement between AGECAT (03 and above) and the psychiatrist's assessment following GMS was high, as expected. Most agreement was in the non-cases.

When CAMDEX diagnosis, general practitioner diagnosis, AGECAT algorithm diagnosis and psychiatrist's diagnosis of dementia and depression in this 10% subsample are considered, all were agreed that 17 individuals were not demented. All were agreed that 2 were cases (one of dementia and one of depression). Overall agreement was therefore 54%. Results on individuals is shown in Table 27 with a summary of comparison of different diagnoses in Table 28. Cohen's kappa (1960) is used here, which takes chance agreement into account. The kappa for CAMDEX clinical diagnosis when compared with AGECAT diagnosis of dementia (03 and above) was 0.65; for CAMDEX clinical diagnosis and psychiatrist's clinical diagnosis of dementia it was 0.79.

Table 27 Comparison of diagnoses

Subject	CAMDEX	GP	Psychiatrist	GMS
a	Dm	Dm/Dp	Dp	Dm
b	Dp	Dm/Dp	Dp	Dp
c	Dp	Dp	Dp	Dp
d	Dm	Dp	Dm	Dm
e	Dp	Dp	-	Dp
f	-	Dp	Dp	Dp
g	-	Dm	-	Dm
h	-	-	Dp	Dp
i	-	-	Dp	-
j	-	-	Dp	-
k	Dp	-	-	-
l	-	Dm	-	-
m	-	Dp	-	-
n	-	Dp	-	-
o	-	Dp	-	-
p	-	Dp	-	-
q	-	D/K	-	-
r	-	Dm/Dp	-	-
s	-	-	-	Dp

Dm=dementia Dp=depression D/K=don't know

Table 28 Comparison of three methods

Method	Case	Non-case	Disagree	% agreed
CAMDEX:GMS:Psych	3	18	15	58
GP:Psych:GMS	3	18	14	60
CAMDEX:Psych:GP	4	19	12	66
CAMDEX:GMS:GP	2	18	15	52
Comparison of two methods				
GMS:Psych	6	25	5	86
GMS:CAMDEX	3	26	7	81
GMS:GP	4	19	12	66
CAMDEX:Psych	5	25	6	83
CAMDEX:GP	4	21	10	71

Cognitive and other scales

The distributions of four cognitive scales of varying length were continuous, highly skewed and unimodal (Figure 6). The distribution of the information-memory-concentration scale was the most skewed showing a ceiling effect, that is, most individuals scored at the highest level. The MMSE did not have such a marked ceiling effect and the distribution was more attenuated. The extended version of the MMSE and CAMCOG were similar with maximum scores of 64 and 107 points. These did not demonstrate ceiling effects. The derived variables reflecting brain areas are shown in Figure 7, and showed the same pattern, according to length of scale rather than area of the brain represented. The items contained in these scales are given in Appendix 2. The distribution of predicted IQ measures is shown in Figure 8. Unlike the other measures of cognitive function this was a normal distribution with a mode of around 100 points.

The distributions of the Blessed dementia rating scale, the ischaemic scale and the depression scale are shown in Figure 9. All these distributions were unimodal, skewed, continous distributions in the opposite direction to the cognitive scales.

The distributions of CAMCOG, MMSE, Blessed dementia scale, depression and ischaemia scales were tested for bimodality, using the statistic $z_i = \frac{|n_i - n_{i+1}| - 1}{\sqrt{n_i + n_{i+1}}}$. This tests whether adjacent pairs of counts are significantly different from each other other. If a significant rise is followed by a significant drop this suggests bimodality. No evidence of bimodality was found in any of these distributions in this population.

The influence of sociodemographic variables on cognitive scales

The results for MMSE are reported in detail, since this is the most frequently used scale in community studies. The extended version of MMSE and CAMCOG demonstrate the same patterns.

Age. MMSE distributions, stratified by age 70 to 74 and 75 to 79 (Figure 10), show that the older age group tended to score less well (t-test, p=0.002). The median is the same and this significant difference was brought about by the longer tail in the distribution.

Tests for Bimodality

There are several methods of testing distributions for bimodality. Haldane's method, recommended for this study, is appropriate because it tests for significant differences between adjacent frequencies. As always with significance tests lack of significance may be due to small numbers. In its application to data here lack of significance may be due to small numbers in the tails of the distribution.

The power of the test varies according to the scale examined and whether there is grouping of data. For example, CAMCOG cannot be examined as individual points, but in decile or quintile values. Furthermore the point at which bimodality would occur is where power must be examined and this varies according to the scale. For these reasons there is no single power, but examples of how power might be examined are given below (*).

Since Haldane's test is essentially the same as McNemar's test, with the null hypotheses that neighbouring frequencies are identical (ie $n_i = n_{i+1}$) the power can be calculated using the following formula:

$$u = \frac{\sqrt{n}\ (\pi_1 - \pi_0) - v\sqrt{\pi_0(1-\pi_0)}}{\sqrt{\pi_1(1-\pi_1)}}$$

Where v and u are points corresponding to the percentages of normal distribution, v relates to the significance required and u to the power. n is the total of the two frequencies to be examined. π_0 refers to the null hypothesis ie n is split 50:50 in the adjacent scores, and π_1 to the split to be demonstrated. With significance level set at 0.05 (two tailed), the graph on the page 121c demonstrates the effect on power of different numbers and different values of π_1.

There is no power to detect a 60:40 split in this study. A 70:30 split could be detected on the MMSE at cut point 21/22 or with more power at 23/24. There is no power to detect bimodality at lower scores, such as at 17/18, but this is not where the recommended cutpoint for mild dementia falls. The short scales such as the information/orientation subscale of CAPE do not have power to detect bimodality at their recommended cutpoints, but short scales do not detect mild dementia.

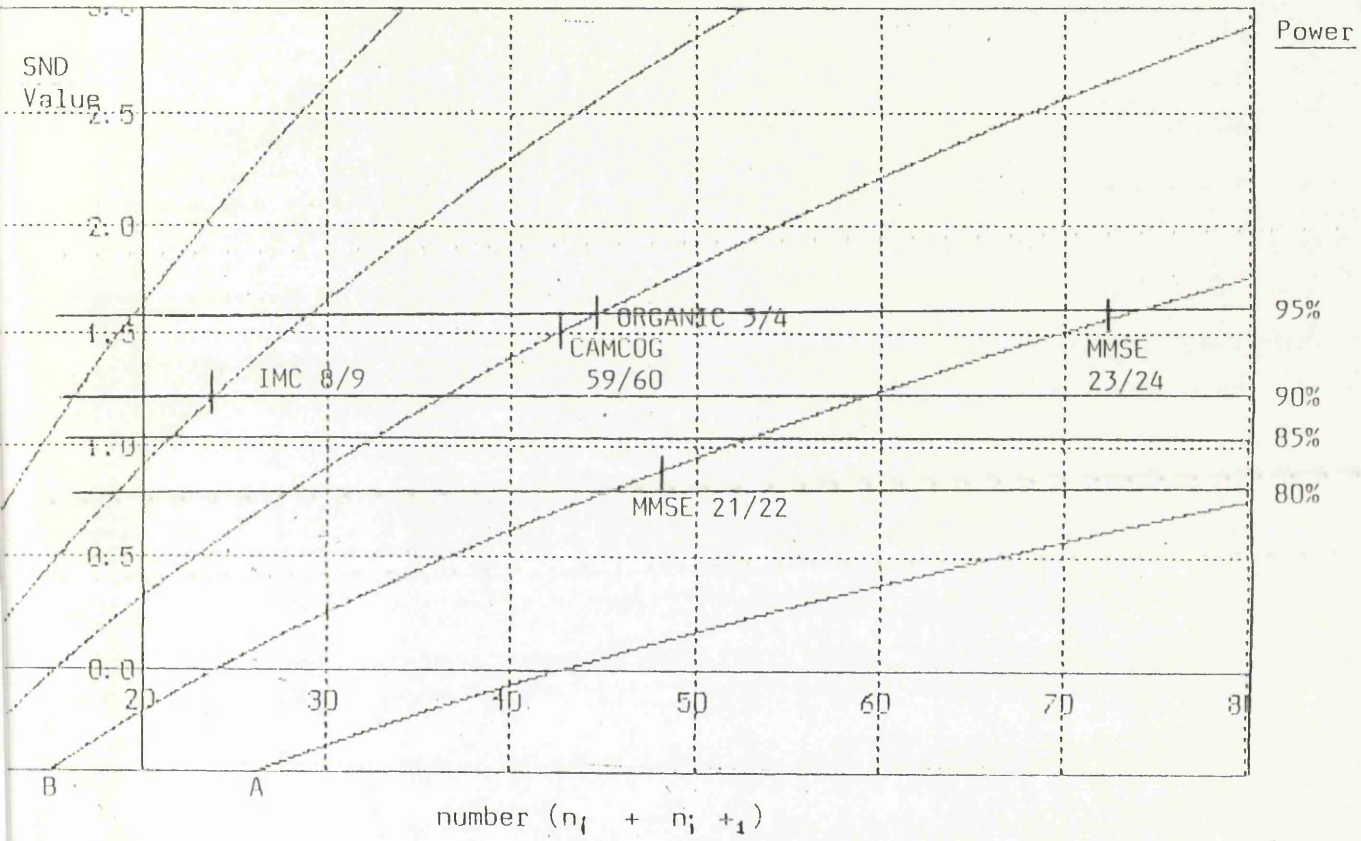
A few power levels for different scales are given below to demonstrate the range for different scales, taking n +n + from around the cutpoints, as shown (see also 121c).

	Cutpoint	Power	$\pi_1 : 1 - \pi_1$
MMSE	21/22	80%	70:30
MMSE	23/24	90%	70:30
CAMCOG	50-59/60-69	90%	75:25
BDRS	3/4	90%	75:25
I-M-C	8/9	90%	80:20
I/O	7/8	-	-

To detect bimodality on the larger scales such as CAMCOG using ungrouped data would require much larger numbers.

(* I am grateful to Dr L. Carpenter, Dr D. Spiegelhalter and Ms C. Gill for their advice on this).

Haldane's test for bimodality - power



A - π_1 = 65 ie 65:35

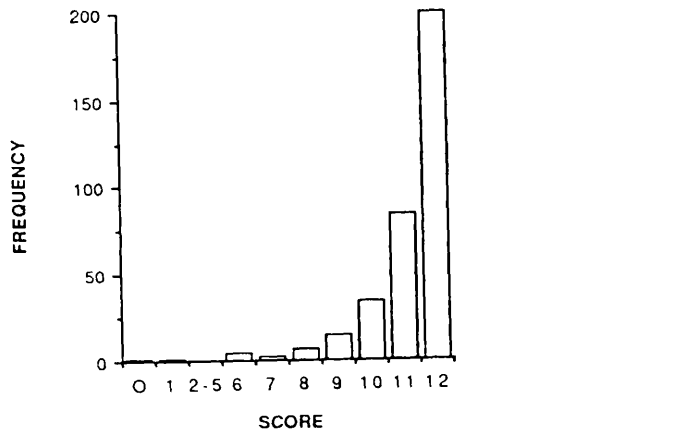
B - π_1 = 70 ie 70:30

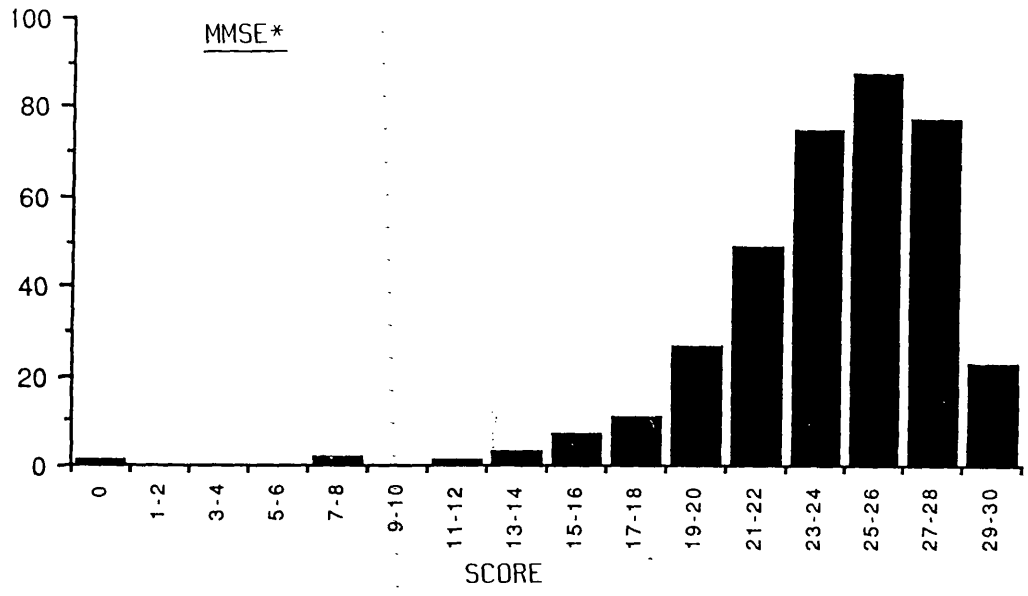
C - π_1 = 75 ie 75:25

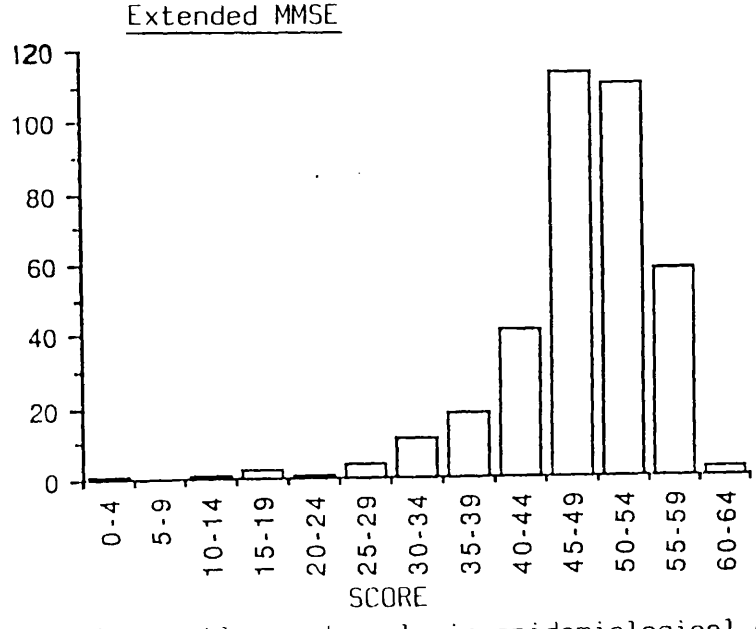
D - π_1 = 80 ie 80:20

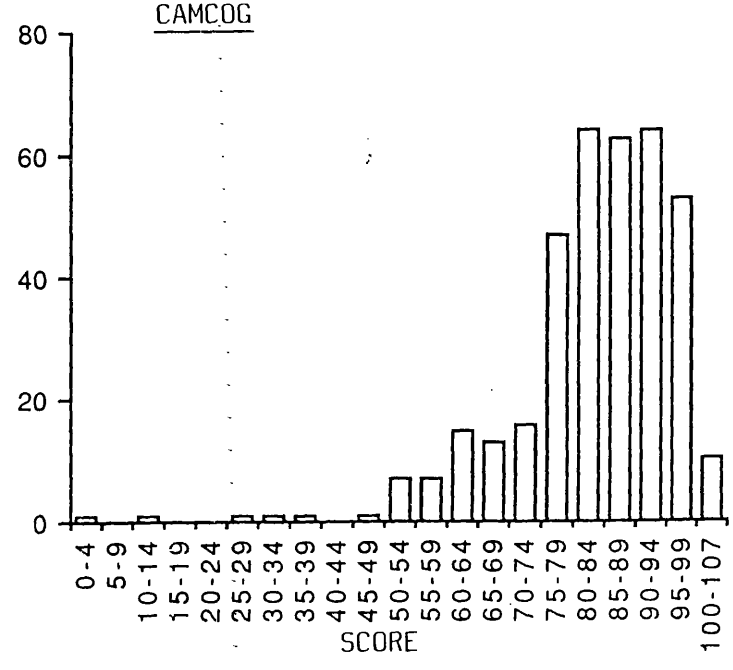
E - π_1 = 85 ie 85:15 (see text)

Figure 6 Frequency distributions for four cognitive scales (total sample)



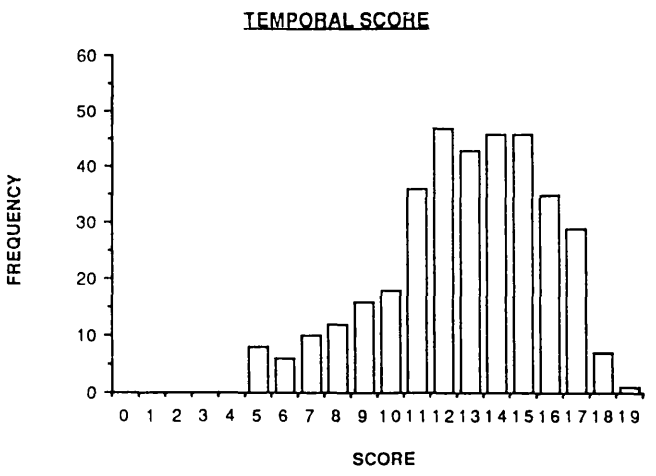


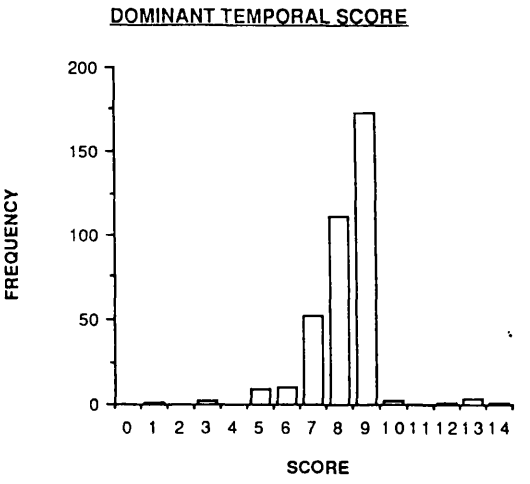


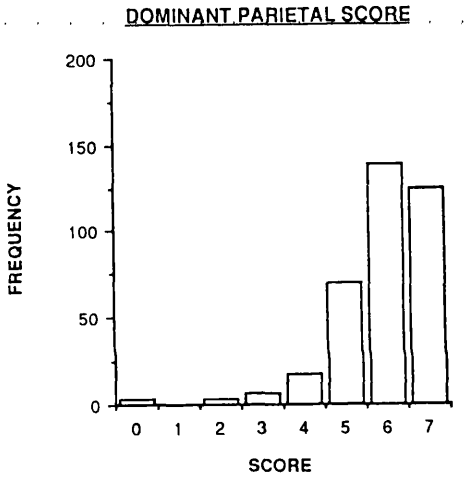


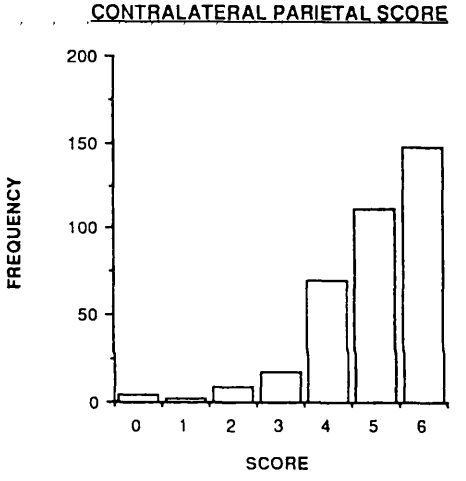
Most frequently used scale in epidemiological studies

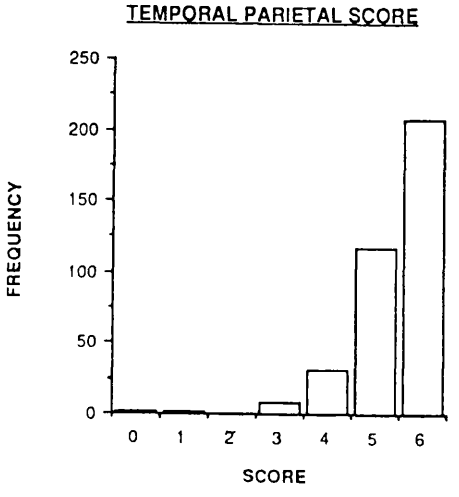
Figure 7 Frequency of derived neurological scales (total sample)

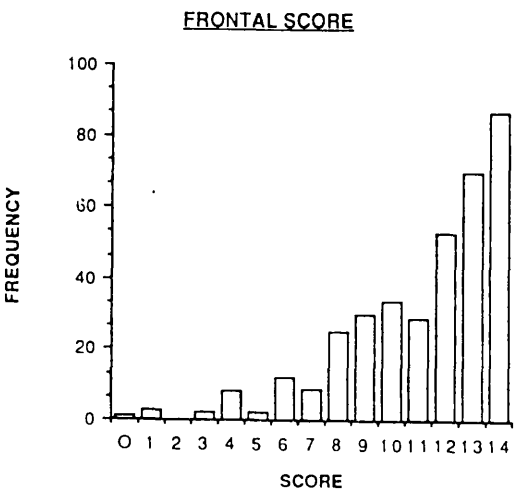












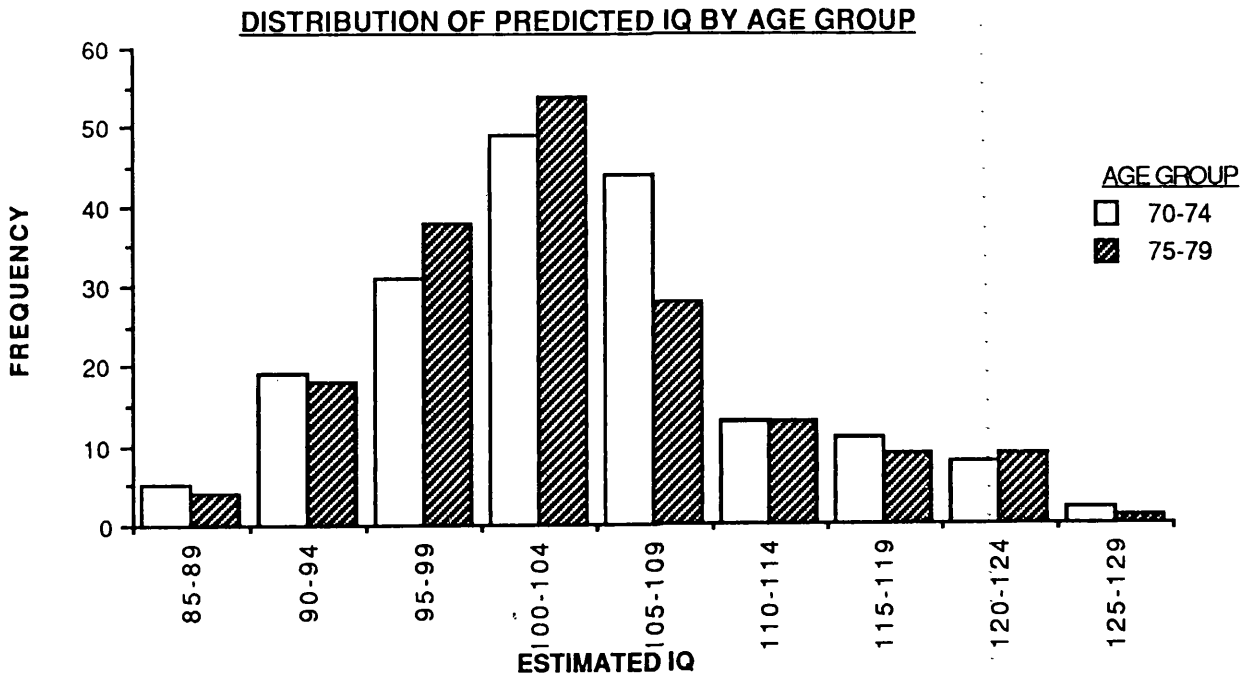
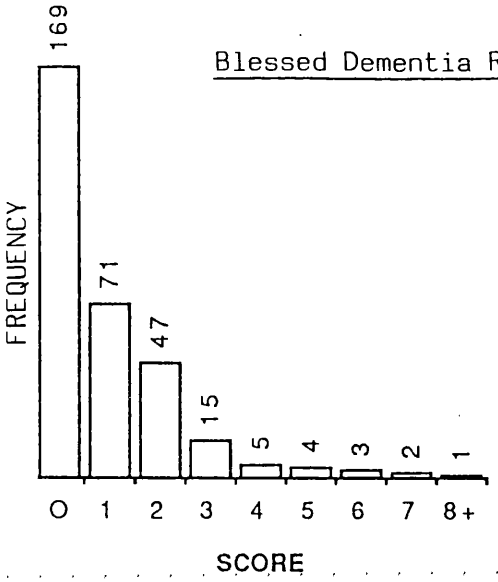
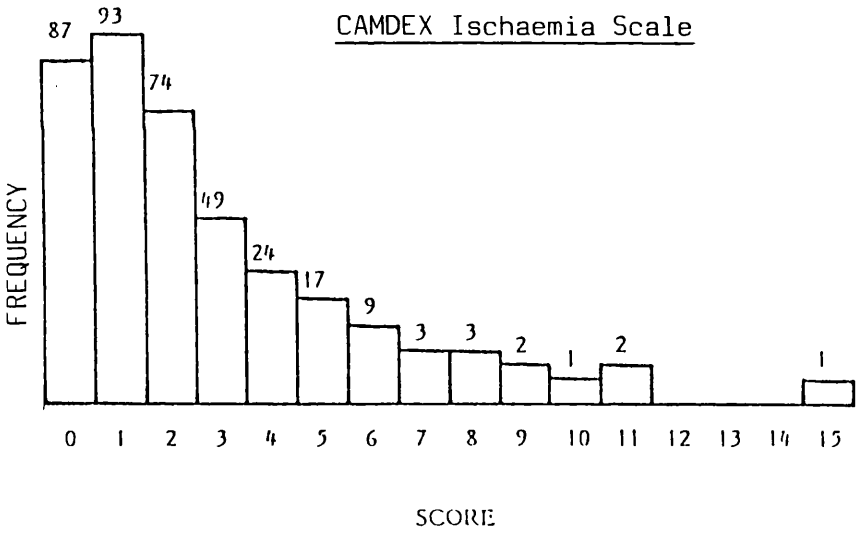
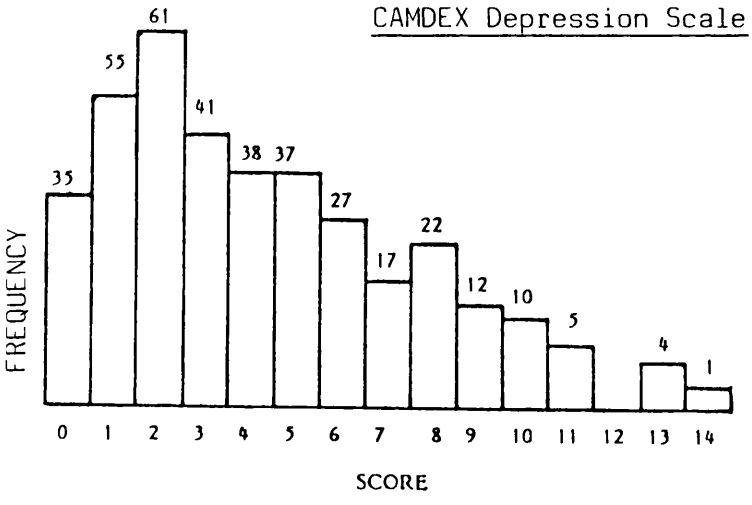

DISTRIBUTION OF PREDICTED IQ BY AGE GROUP
FREQUENCY
60
50
40
30
20
10
0
85-89
90-94
95-99
100-104
105-109
110-114
115-119
120-124
125-129
ESTIMATED IQ
AGE GROUP
70-74
75-79

FIGURE 8

Figure 9 Distributions of other scales (total sample)







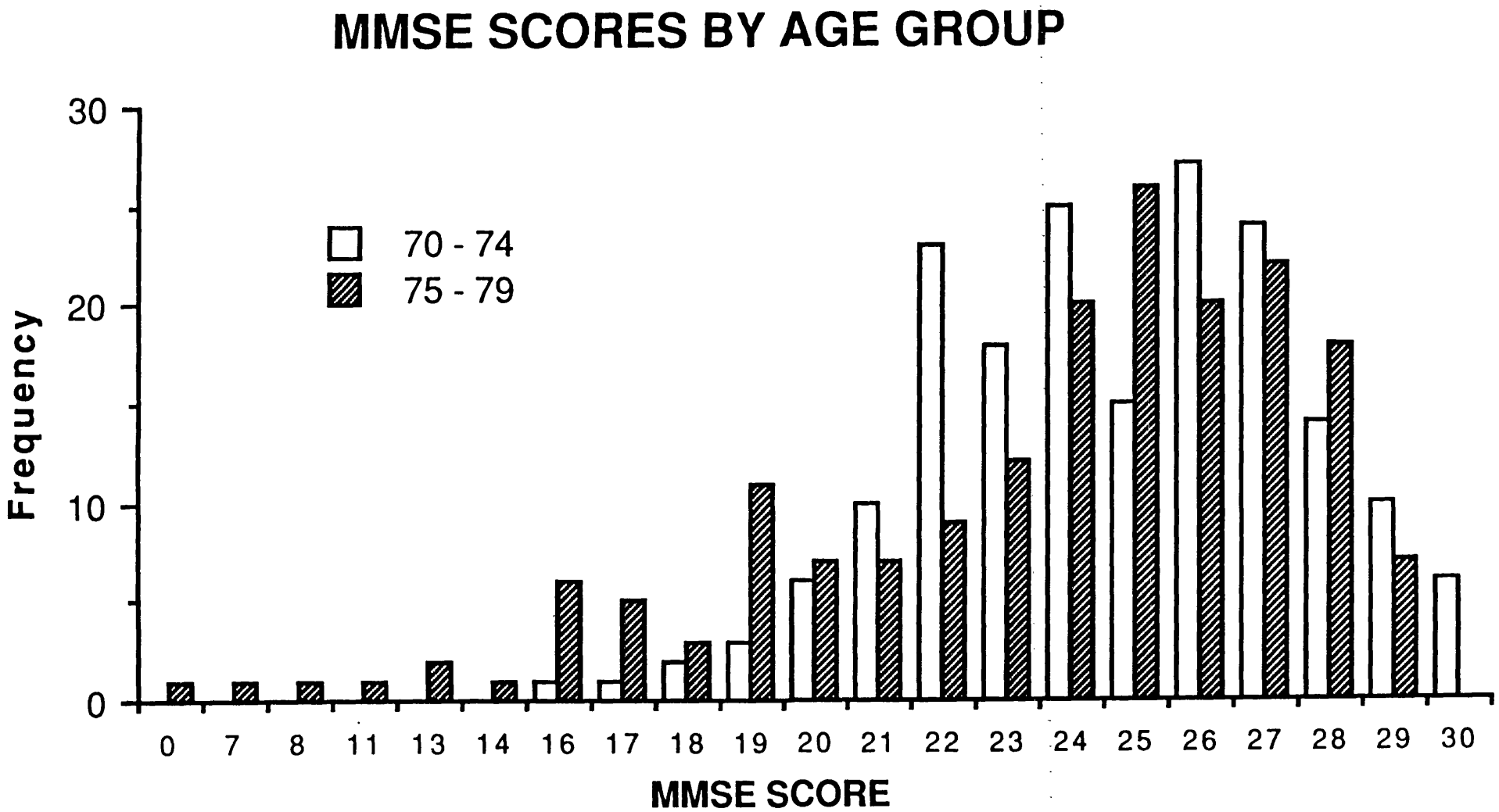

MMSE SCORES BY AGE GROUP
Frequency
30
20
10
0
70 - 74
75 - 79
0 7 8 11 13 14 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
MMSE SCORE

FIGURE 10

The individuals with the lowest scores were all diagnosed as demented.

In Figure 11 CAMCOG distributions by age group are shown, with the same shift in distribution as seen in MMSE. Unlike MMSE, the median was slightly lower in the 75 to 79 year age group than the 70 to 74 year age group, suggesting a shift in the whole distribution, as well as an increased skew. In Figure 12 the distribution of a shorter scale, the information-memory-concentration scale, also shows a change in shape with more people tending to score lower in the older 75 to 79 year age group. Table 29 shows the means and standard deviations for CAMCOG by age in years. This shows a tendency for lower scores in the older age groups (chi-squared trend, $p<0.01$), with an increase in standard deviation with age. This reflects similar changes in shape of distribution to that noted above for MMSE.

Table 29 CAMCOG and age at interview (by stratum)

Age	Mean CAMCOG (s.d.)	Number
70	86.6 (9.9)	24
71	87.1 (11.3)	26
72	86.6 (8.7)	42
73	85.2 (9.9)	45
74	84.4 (9.6)	34
75	84.1 (11.2)	14
75	80.6 (17.5)	25
76	82.7 (12.9)	30
77	79.4 (18.1)	44
78	78.7 (15.6)	37
79	75.6 (16.0)	25
80	84.3 (10.3)	19

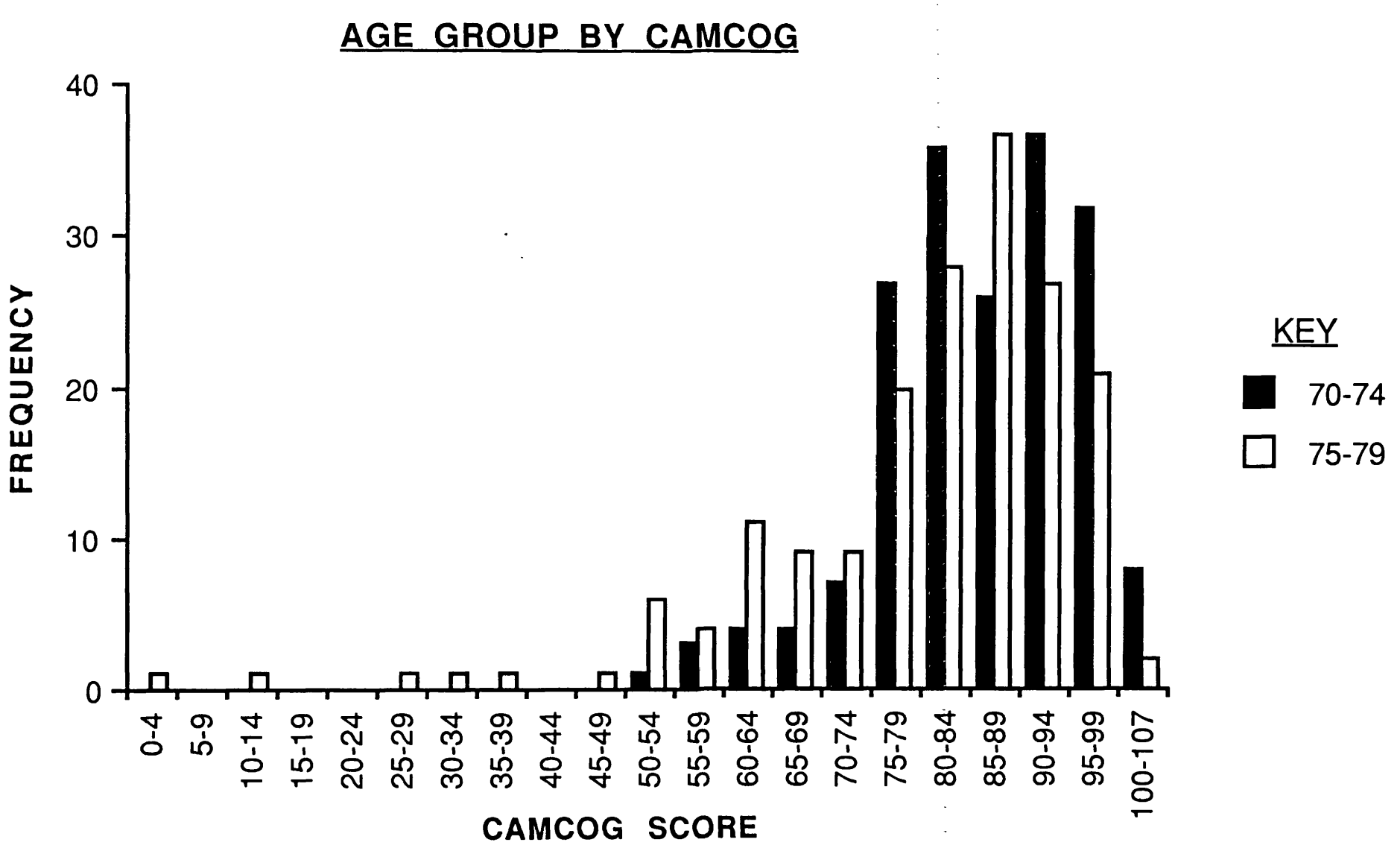
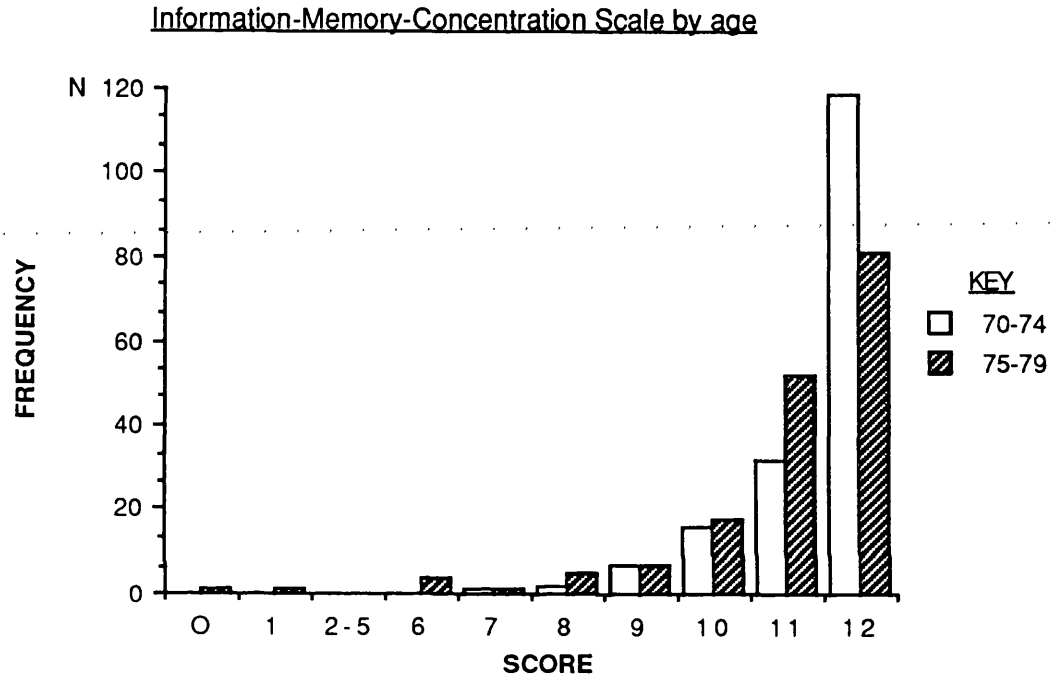

AGE GROUP BY CAMCOG
FREQUENCY
40
30
20
10
0
0-4
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70-74
75-79
80-84
85-89
90-94
95-99
100-107
CAMCOG SCORE
KEY
70-74
75-79

FIGURE 11

FIGURE 12


Information-Memory-Concentration Scale by age
N 120
100
80
60
40
20
0
FREQUENCY
0
1
2-5
6
7
8
9
10
11
12
SCORE
KEY
70-74
75-79

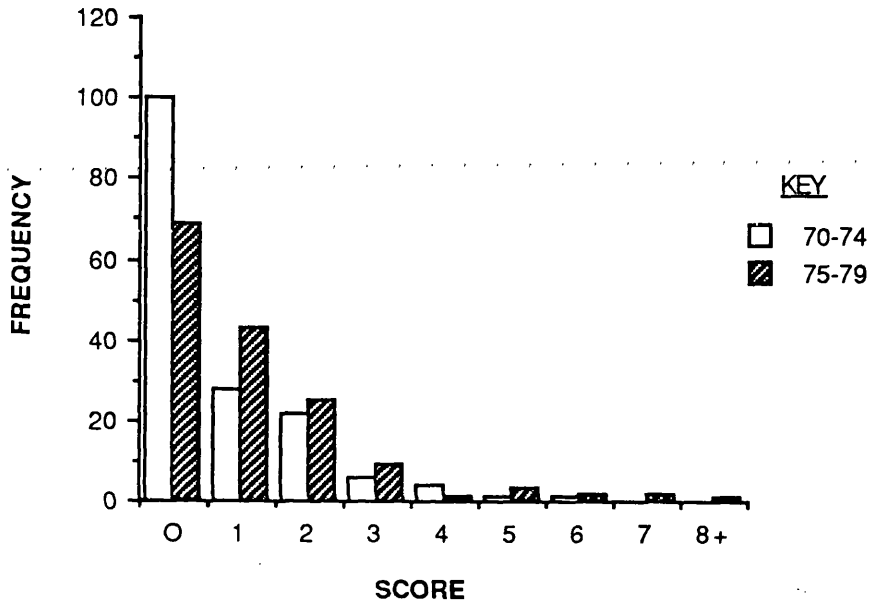
Since the data collection was carried out over 12 months (although 96% of interviews were carried out in the first 7 months of this time), the two age strata were ageing during the study. Although there were no downward trends in cognitive scales for the whole sample, it was possible to compare those who attained the age 75 years during the study, and were therefore retained with their cohort for the age group analyses with those who were 75 at the outset and therefore in the older age group. The 75 year olds from the younger age group performed better than the older 75 year olds on CAMCOG (84.1 and 80.6 respectively, $p<0.05$), but the same as the 74 year olds (84.4). More striking was the difference between the 79 year olds and the 80 year olds (75.6 and 84.3 respectively, $p<0.01$).

Social class and education. Similar differences in distribution were found in the Blessed dementia rating scale (Figure 13), with a tendency to higher scores in the older age group.

Since the numbers in some of the social class groupings I to V were small, these were regrouped into non-manual and manual categories, shown for MMSE in Figure 14. Those individuals in the non-manual group achieved significantly higher scores than those in the manual (t-test, $p<0.001$). The shapes of the distributions were similar. The distributions of scores according to educational level are shown in Figure 15. Educational level was divided into 3 categories: those leaving school before the age of 13 years, those leaving at 13 or 14 years, and those leaving at 15 years or above. There was a clear relationship between educational attainment and score with similarly shaped distributions for each educational level. The difference in performance between those leaving school before the age of 15 years, and those leaving school at 15 years or above was highly significant (t-test, $p<0.001$).

Social class and educational level are closely associated and were entered into a multiple regression to assess their independent effects. Social class (I to V) and age on finishing full-time education were normally distributed and were entered as continuous variables.

Blessed Dementia Scale by age



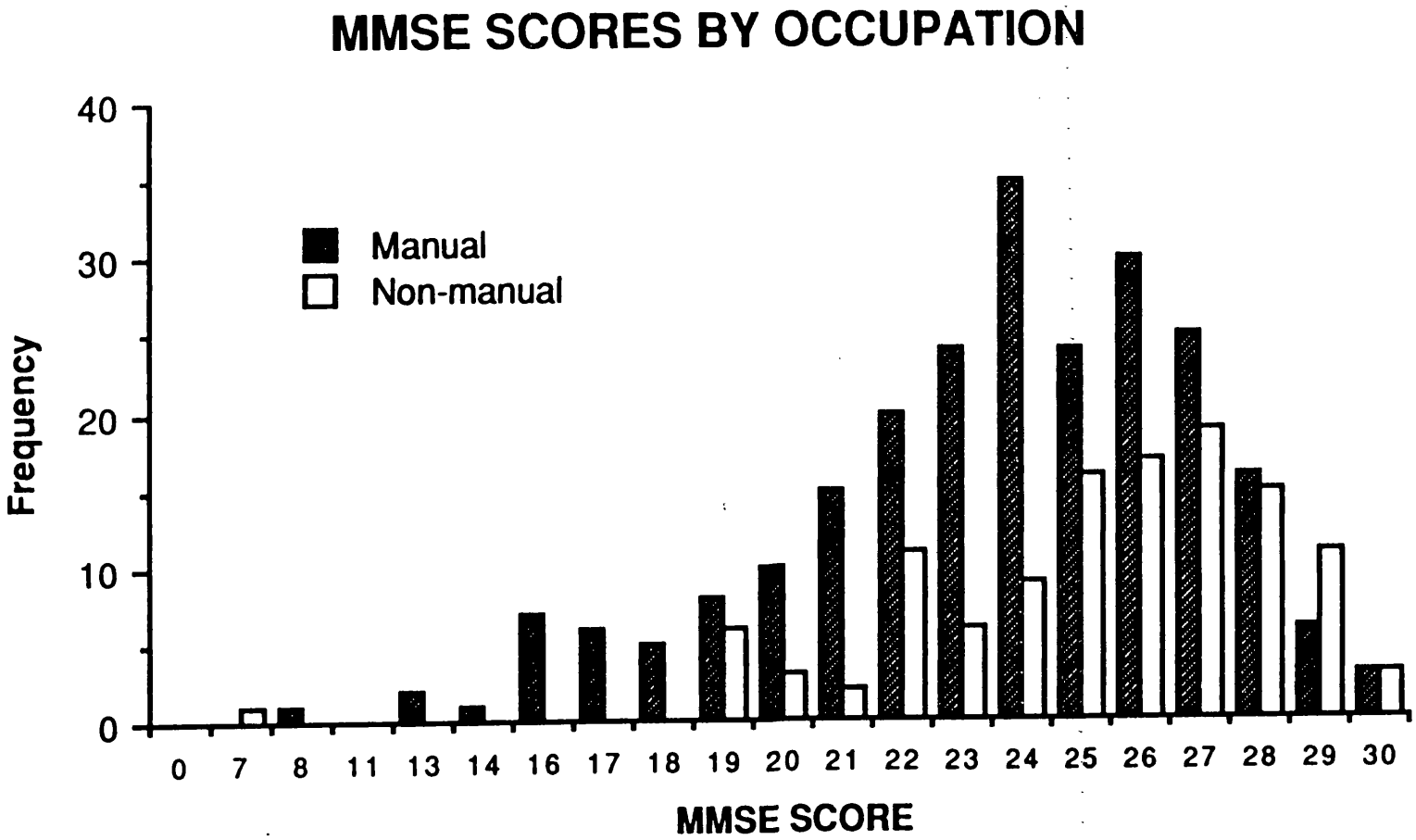

MMSE SCORES BY OCCUPATION
Frequency
40
30
20
10
0
Manual
Non-manual
0 7 8 11 13 14 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
MMSE SCORE

FIGURE 14

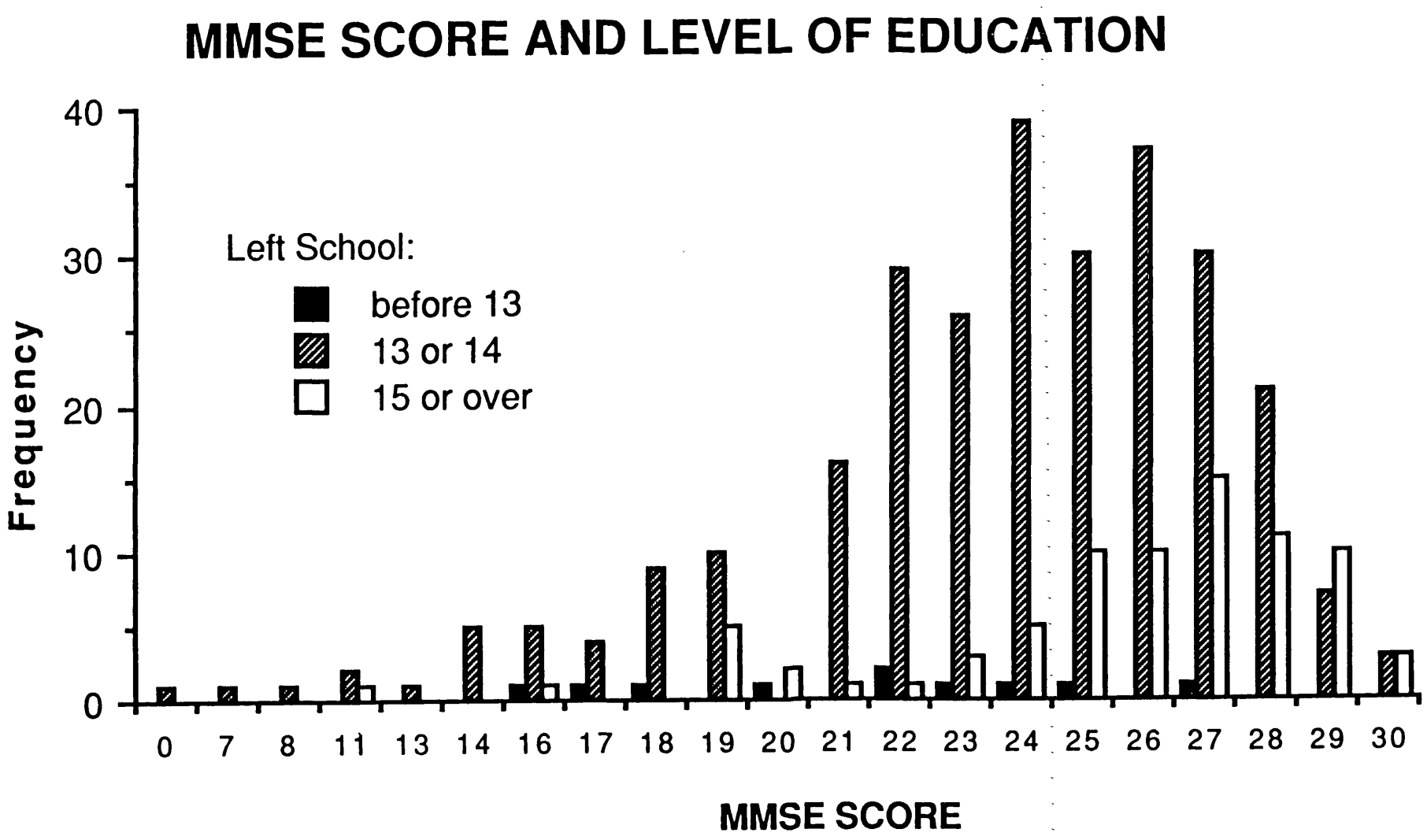

MMSE SCORE AND LEVEL OF EDUCATION
Frequency
40
30
20
10
0
Left School:
before 13
13 or 14
15 or over
0 7 8 11 13 14 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
MMSE SCORE

FIGURE 15

These variables and age at interview were entered as independent variables into a stepwise multiple regression (SPSS-X) with MMSE score as the dependent variable. Educational level accounted for 10% of the variance ($p<0.001$), with age and social class contributing a further 2.5% each ($p<0.001$). The information/orientation scale and Blessed dementia rating scale scores were not associated with educational level or social class.

There was no age effect within educational levels for predicted IQ, but a considerable and significant increase is seen in those with more education ($t=-9.07$, df 356, $p<0.001$). A multiple regression for the whole sample of age at interview, educational level (actual age at which finished full time education) and social class (I to V) on predicted IQ showed that educational level and social class contributed significantly and independently to the model ($r^2=.28$ $p<0.0001$ and $r^2=.30$ $p<0.001$ respectively), whereas age did not. Together they accounted for 55% of the variance.

The influence of sociodemographic variables on single cognitive items

Single items were examined for the MMSE because this is the most widely used cognitive scale in community studies.

Age. The 75 to 79 year age group was not significantly different from the 70 to 74 year age group in reponse to the basic orientation items, writing a sentence and reading. In most of these items the older group had slightly, but consistently higher failure rates. Only a small proportion of the population failed most of these items (0.5% to 7%). A higher proportion (27%) failed to give the correct date. 21% in each age group was one day out, and 4% of the younger compared to 8% of the older were two or more days out. There were significant differences (chi squared $P<0.025$ or less) comparing the numbers failing the following items by age group: year, streets nearby, repetition of "no ifs, ands, or buts", registration of 3 items, folding paper, spelling WORLD backwards and serial sevens.

Social class and education. The numbers failing individual MMSE items were examined by the dichotomised grouping of social class and educational level to see which were most influenced by these

variables. There were no differences in the proportions failing on the individual orientation items, repetition of 3 items and reading aloud for either social class or education. The proportion of those failing to copy a pentagon correctly was similar in the non-manual and manual groups (26% and 32% respectively), but not for the less and more educated (34% and 16% respectively, $p<0.01$). Recall of the 3 items from the registration question was not significantly different for either social class or educational level, with only a small proportion scoring the maximum (7%). Nearly half the population in each group failed the repetition item of "no ifs, ands, or buts". There were significant differences by both social class and educational level in the distributions of scores for serial sevens, spelling WORLD backwards, recall of 3 items and the complex instruction (dichotomised, chi-squared, 1 d.f. $p<0.005$).

The relationship between scales

The correlations between all cognitive scales were higher in the older age group than the younger (Table 30), using Spearman rank correlation (rho), ranging from 0.32 in the age group 70 to 74 for the information/orientation scale and MMSE to 0.84 for CAMCOG and MMSE in the age group 75 to 79. The high correlation between MMSE and CAMCOG was mainly accounted for by the overlap of items in the two scales. There was no association between the Blessed dementia rating scale and the cognitive scales in the younger age group; in the older age group the relationship between the Blessed dementia rating scale and cognitive scales became significant, although small at -0.25 to -0.38, the highest association being most associated with the more detailed cognitive scale.

Table 30 Correlation Matrix for cognitive scales and the BDRS (Spearman rank rho correlation)

	CAMCOG	MMSE	I/O	I-M-C	BDRS	Organicity
CAMCOG	-	.77	.36	.51	n.s.	-.28
CAMCOG	-	**.84**	**.53**	**.60**	**-.38**	**-.33**
MMSE	-	-	.32	.39	n.s.	-.23
MMSE	-	-	**.53**	**.54**	**-.30**	**-.27**
I/O	-	-	-	.42	n.s.	n.s.
I/O	-	-	-	**.67**	**-.31**	**-.40**
I-M-C	-	-	-	-	n.s.	n.s.
I-M-C	-	-	-	-	**-.25**	**-.35**
BDRS	-	-	-	-	-	.59
BDRS	-	-	-	-	-	**.70**

Light figures = age group 70-74

Bold figures = age group 75-79

All correlations $p<0.01$

I/O = information/orientation subscale of CAPE

I-M-C = information-memory-concentration scale

BDRS = Blessed dementia rating scale

Scales and cutpoints

Varying proportions of the population were identified as possibly demented when different scales and different cutpoints on the scales were used (Table 31). On all scales more in the older age groups were identified. Recommended cutpoints for the shorter scales identified smaller proportions than those for the longer scales. The women identified by the different scales overlapped to some extent. This applied particularly to those with the lowest scores. Applying recommended cutpoints to the scales CAMCOG and the organicity scale, 27 individuals were identified as impaired by both and 194 as not impaired (66% agreement). A further 98 were identified as abnormal by CAMCOG, but not by the organicity scale and 18 by the organicity scale but not by CAMCOG.

Table 31 The proportion of each age group identified as possible cases by various cutpoints (%)

Scale cutpoint	70-74 (n=185)	75-79 (n=180)
I/O scale 7/8	0	3.3
MMSE		
17/18	1.1	10.0
21/22	12.4	25.6
23/24	34.6	37.2
CAMCOG		
69/70	6.5	22.2
79/80	24.9	36.1
Organcity		
3/4	13.3	23.7
4/5	10.4	16.5

Scales and Diagnoses

In this section the relationship between the clinical diagnosis of dementia and the embedded scales of the interview are provided. Table 32 shows mean scores on the information-memory-concentration scale, information-orientation sub-scale, MMSE, CAMCOG and the organicity scale of CAMDEX according to the level of severity diagnosed by CAMDEX and the general practitioner. The total numbers were different in each group because for some individuals informants were not available (n=15) or the general practitioner was unable to provide a tentative diagnosis (n=6). There were differences in the mean value of all cognitive scale scores between those with and without a CAMDEX clinical diagnosis of dementia. This constrasts with the finding that those rated as mildly demented by the general practitioners scored nearly the same on all cognitive scales as those rated normal. On the organicity scale there was an increase in mean scores from those diagnosed as normal to those diagnosed as mildly demented for both CAMDEX clinical diagnosis and general practitioner diagnosis.

Table 32 Cognitive and organicity scales and diagnosis

Scale (max)	No dementia	Mild+	Mild/Mod+
I-M-C (11)			
CAMDEX dx	10.3(1.0)[336]	7.7(2.6)(24)	2.4(2.1)[5]
GP dx	10.1(1.5)[330]	10.0(1.3)[25]	8.1(4.3)[4]
I/O (12)			
CAMDEX dx	11.7(0.6)	9.7(2.2)	4.2(2.9)
GP dx	11.5(1.0)	11.1(1.1)	5.3(4.8)
MMSE (30)			
CAMDEX dx	24.7(2.9)	18.3(4.0)	9.6(6.1)
GP dx	24.3(3.5)	22.9(3.4)	14.0(11.2)
CAMCOG (107)			
CAMDEX dx	85.4(9.3)	58.8(13.5)	29.6(18.5)
GP dx	83.6(12.1)	79.0(13.8)	40.8(34.6)
ORGANICITY			
CAMDEX dx	1.7(2.2)[322]	5.6(3.0)[23]	18.4(5.5)[5]
GP dx	1.9(2.6)[319]	4.0(3.6)[24]	16.3(7.8)[4]

(s.d)[numbers]

CAMCOG, MMSE and predicted IQ are shown by age group, and levels of severity of dementia in Table 33. This shows that, within each age group, there was a large mean difference between those without a diagnosis and those with a diagnosis of dementia, with considerable variability and overlap between groups. The differences were less marked for predicted IQ, but remained significant.

The major diagnoses of Alzheimer's disease, multi-infarct dementia and depression have the expected relationships with the relevant CAMDEX scales, as shown in Table 34. Depression is the only diagnosis with a marked increase
in mean scores on the depression scale, although the small number of individuals with a diagnosis of secondary dementia also scored more. All the dementias had high mean scores on the organicity and Blessed dementia rating scale, and low mean scores on CAMCOG. Multi-infarct dementia was the only diagnosis with raised CAMDEX ischaemic scale score means, although there was no significant increase in the mean scores on the Hachinski ischaemia scale.

The severity of dementia showed a consistent relationship with higher mean scores on the Blessed dementia rating scale. There was no change in mean ischaemia scale scores or depression scale scores with severity. The severity of depression showed no relationship to mean CAMCOG scores, and, as expected, a positive relationship to the mean scores on the depression scale. A non-significant tendency to an increase in mean scores with severity of depression was also noted in the organicity and ischaemia scales.

CAMCOG subscales

The relationship of differential diagnosis and dementia severity to the CAMCOG subscales, and also to the MMSE items WORLD and serial sevens is shown in Table 35. There was a consistent relationship between any diagnosis of dementia and mean subscale scores, but none with depression. There was no difference in the subscale profile between those with a diagnosis of Alzheimer's disease and multi-infarct dementia. There was also a consistent relationship between mean subscale scores and severity. Abstract thinking was the only item in which this trend was not marked, the difference being between

TABLE 33

CAMCOG, MMSE, and Predicted IQ according to age group, together with diagnosis and level of severity

	70-74 years old			75-79 years old		
CAMCOG	**Mean**	**(sd)**	**(n)**	**Mean**	**(sd)**	**(n)**
All	85.7	(9.8)	(185)	80.0	(15.7)	(180)
Normal	86.6	(8.7)	(177)	84.1	(9.8)	(159)
Mild dementia	66.1	(12.3)	(8)	55.1	(12.9)	(16)
Mild/moderate+ dementia	---			29.6	(18.2)	(5)
MMSE						
All	24.7	(2.9)	(185)	23.5	(4.5)	(180)
Normal	24.8	(2.8)	(177)	24.6	(3.0)	(159)
Mild dementia	21.3	(3.2)	(8)	16.8	(3.5)	(16)
Mild/moderate+ dementia	---			9.6	(6.1)	(5)
PREDICTED IQ						
All	104	(8.0)	(183)	103	(8.0)	(175)
Normal	104	(8.2)	(176)	104	(8.2)	(156)
Mild dementia	97	(7.5)	(7)	97	(4.6)	(15)
Mild/moderate+ dementia	---			99	(2.9)	(4)

TABLE 34

MAJOR DIAGNOSES AND SCALES - MEAN VALUES

	No diagnosis	SDAT	MID	Secondary Dementia	Depression
Depression	3.0	3.8	2.7	5.3	8.4
Organicity	1.5	**7.9**	**7.6**	**9.0**	2.5
MID Scale	1.8	2.6	**6.1**	1.8	2.3
Ischaemia	2.3	3.5	4.3	3.5	3.0
Blessed	1.2	**7.1**	**6.2**	**4.8**	1.6
Camcog	85.3	**51.0**	**58.1**	**56.3**	85.5

DEMENTIA SEVERITY AND SCALES - MEAN VALUES

	None	Mild	Mild/Moderate	Moderate
Depression	3.9	4.3	3.7	0.5
Organicity	1.7	5.8	16.7	21.0
MID Scale	1.9	3.9	2.7	2.5
Ischaemia	2.6	3.9	4.3	2.0
Blessed	1.3	3.8	16.0	23.0
Camcog	85.4	58.8	38.7	16.0

DEPRESSION SEVERITY AND SCALES - MEAN VALUES

	None	Mild	Mild/Moderate	Moderate
Depression	3.0	7.4	9.3	10.3
Organicity	2.0	3.0	3.1	3.7
MID Scale	1.9	2.5	2.3	3.7
Ischaemia	2.5	3.7	3.7	4.0
Blessed	1.6	2.2	2.0	2.2
Camcog	83.0	80.7	84.9	90.1

TABLE 35

DIAGNOSIS

	No diagnosis (278)	SDAT (15)	MID (9)	Depression (56)
Orientation	9.6	7.1	7.5	9.5
Language	24.5	17.1	18.1	24.9
Memory	20.3	11.3	11.4	20.1
Attention	5.0	1.7	2.4	5.0
Praxis	10.5	6.3	7.3	10.5
Calculation	1.7	1.0	0.6	1.7
Abstract thinking	4.8	0.5	3.7	4.6
Perception	8.9	5.9	7.0	9.2
World	4.5	2.5	2.4	4.4
Serial sevens	3.2	0.6	1.2	3.3

DEMENTIA SEVERITY

	None (336)	Mild (24)	Mild/Moderate (3)	Moderate+ (2)
Orientation	9.6	7.9	5.0	2.0
Language	24.6	18.5	16.0	8.0
Memory	20.3	12.8	5.3	2.5
Attention	5.0	2.4	0.7	0
Praxis	10.5	7.7	5.0	0.5
Calculation	1.7	1.0	0.3	0
Abstract thinking	4.8	1.5	1.3	1.5
Perception	8.9	7.0	5.0	1.5
World	4.5	3.0	1.3	0
Serial sevens	3.2	1.0	0	0

those without a diagnosis of dementia to those with a diagnosis of mild dementia. Mean scores for the MMSE item WORLD are higher for the nondemented than serial sevens, and the difference in score for both items was similar for any diagnosis of dementia. WORLD shows a trend to lower scores for increasing severity, whereas serial sevens demonstrates a floor effect for those with greater than mild severity. However, the numbers in all these diagnostic groups were small.

Scales and diagnoses

In Table 36 the performance of some of the scales used is examined in relation to CAMDEX clinical diagnoses of mild and more severe dementia. In the second column the mild group have been re-classified as normal. The numbers of subjects with a diagnosis of dementia of any severity was small and these results are tentative. Ideally the performance of a scale should be examined in relation to longitudinally validated diagnoses. The results for MMSE are shown for both methods of calculating a total; either including serial sevens only, or taking the better score of spelling WORLD backwards and serial sevens. All sensitivities and specificities were higher when the mildly demented were re-classified in this way. Examining the sensitivities and specificities of the scales by age group revealed considerable differences. The cutpoint 7/8 on the information/orientation scale appeared unable to detect those with a clinical diagnosis of mild dementia in the younger age group, but had a sensitivity of 75% and a specificity of 99% for all dementia in the 75-79 age group. In the younger age group CAMCOG had the following sensitivities and specificities: for the cutpoint 59/60 50% and 100%; for the cutpoint 69/70 63% and 96%; and for the cutpoint 79/80 75% and 77%. For the older age group the results were as follows: for the cutpoint 59/60 71% and 99%; for the cutpoint 69/70 95% and 90%; for the cutpoint 79/80 100% and 72%. Sensitivity was therefore higher in the older age groups for a given cutpoint reflecting the shift in distributions, and possibly a difference in the diagnostic process at different ages.

For the MMSE the optimal cutpoint for identifying all levels of dementia in the older age group was 21/22 giving a sensitivity of 95% and specificity of 84%. If the mild group were re-classified as normal, the optimal cutpoint became 17/18 with a sensitivity of 100% and specificity of 99%.

Table 36 Selected sensitivities and specificities according to level of dementia

	Mild +		Mild/Moderate+	
	Sensitivity	Specificity	Sensitivity	Specificity
I/O				
7/8	21	100	80	99
MMSE (total including serial sevens)				
17/18	52	99	100	96
21/22	**83**	**87**	100	82
23/24	93	68	100	65
MMSE(total including better of WORLD and serial sevens)				
17/18	28	99	**100**	**99**
21/22	66	95	100	91
23/24	79	88	100	84
CAMCOG				
69/70	86	93	100	87
79/80	93	75	100	63

(Bold figures indicate the cutpoint with the highest simultaneous sensitivity and specificity for level of dementia in this population. For CAMCOG only the decile values were considered.)

Quality Control

Influence of time of year on cognitive tests

Most of the testing in this study was performed between October 1985 and May 1986, with small numbers over the summer of 1986. It was possible therefore to compare the means on cognitive tests for autumn, winter and spring. There was no significant difference in the means on CAMCOG of the whole sample broken down in this way.

Influence of diurnal variation on cognitive tests

There were no sigificant differences when CAMCOG score means were compared for interviews conducted in the early morning (8.00 till 10.59), late morning (11.00 till 12.59), early afternoon (2.00 till 3.59) and late afternoon (4.00 till 6.00).

Intra-interviewer study

As mentioned in the section on cognitive function, there were no significant differences in scores for the periods during which the study was conducted. Since the sample was ordered randomly this suggests that there was no consistent interviewer drift during the field study.

Four tapes of subject interviews were randomly chosen and rated at the end of the study. The coding was compared with the original coding. 96% of codes were entered identically to the first occasion. Of the 4% differences found, 67% were on items such as frequency of attending meetings per month, frequency of contact with family and friends. These codes were single numbers different from the original coding. 1.5% of the cognitive items were coded differently from the original. Several of these differences were in the coding of the National Adult Reading Test, where the differences were again single integer differences in a range of 50. There was no evidence of consistent differences which would have led to bias in the results.

Re-rating 9 subject interviews selected at random and listening to the tapes blind for rating clinical diagnosis led to the results shown in Table 37. This shows that there was some small variation in allocation of level of severity, but in this small sample there was 100% agreement on diagnosis. There were, however, no demented subjects in this random group.

Table 37 Rerating interview tapes for diagnosis

Subject number	Field diagnosis	Tape diagnosis
016	-	-
017	-	-
134	-	-
189	-	-
194	-	-
297	mild/mod depression	mod depression
324	-	-
329	-	-
349	mild depression	mild depression

Inter-interviewer study

The comparison between AGECAT diagnosis from the Geriatric Mental State Examination interview conducted on a separate occasion by Dr Paul Calloway and CAMDEX clinical diagnosis has been presented earlier. There was agreement mainly on the non-cases, Cohen's kappa was 0.7.

The results of the joint interviewing conducted with Dr D. O'Connor (DO'C) are shown in Table 38. These interviews were conducted in 1987 and 1988. All these subjects were in the Hughes Hall Project for Later Life (O'Connor et al 1989). The cross tabulation of the primary diagnosis in Table 39 shows disagreement in only one case who was rated as normal by CB and as minimally demented by DO'C, although there is more variation in the interpretation of the severity of the dementia or depression. The numbers are very small in this study, but Dr O'Connor has found similar results from a larger inter-rater study (O'Connor et al 1990).

Table 38 Interviewer/Observer Study

Diagnosis

	CB				DO'C			
	diag1	diag2	sev	depsev	diag1	diag2	sev	depsev
A	10	1	1	3	10	0	0	4
B	0	0	0	0	0	0	0	0
C	1	0	2	0	1	0	2	0
D	0	0	0	0	0	0	0	0
E	0	0	0	0	1	0	1	0
F	1	0	2	0	1	0	2	0
G	0	0	0	0	0	0	0	0
H	1	0	1	0	1	0	2	0
I	0	0	0	0	0	0	0	0

diag1=primary diagnosis diag2=secondary diagnosis

1=Alzheimer's disease 10=Depression

sev=severity of dementia (1=minimal, 2=mild, 3=moderate, 4=severe)

depsev=severity of depression (1=minimal, 2=mild, 3=moderate, 4=severe)

Table 39 Cross tabulation of interviewer/observer diagnoses

		DO'C		
		None	Dem	Dep
CB	None	4	1(sev1)	0
	Dem	0	3	
	Dep	0	0	1

Risk factors for dementia and cognitive impairment

Risk factors which have been put forward in the literature for AD, MID and impairment of cognitive function were examined. These are presented in the following section. Information was available from several sources, the subjects themselves, the informant and the general practitioners' notes.

Quality of the information

Table 40 shows the degree to which subject and informant histories concurred on social class and risk factors for dementia. The subjects with any diagnosis of organic disorder have been removed from this analysis. Agreement is high, but usually because of the high proportion of non-exposure. The proportion of informants reporting positive exposure is noted since this is almost always the method of measuring exposure in case control studies of Alzheimer's disease. There is wide variation in the degree to which subjects and informants agree, from 26% on the amount smoked currently to 98% on history of cerebrovascular accident (CVA); for many of the exposures the proportion of the population exposed is very small, such that only 2% of informants report history of myocardial infarction in subjects and 3% for CVA and family history of leukaemia.

Table 40 Subject/Informant agreement on exposure in non demented subjects

Variable	% agreement	% informant positive
Social class		
subject	70	-
husband	84	-
TIA		
memory	94	6
vision	94	1
Stroke	98	3
Myocardial infarct	97	2
Hypertension	83	41
Head injury	92	5
Smoking	96	12
Cigarettes p.d.	26	9
Alcohol quantity	87	51

Family history	%agreement	%informant pos.
Stroke	73	33
Diabetes	85	16
Leukaemia	96	3
Dementia	72	28
Down's	96	4

The relationship of possible risk factors to the diagnosis of dementia and cognitive function are summarised in Table 41. These were examined in a formal manner using linear regression, with CAMCOG dichotomised between 79 and 80, the cut-point suggested by the authors.

Table 41 Risk factors, cognition and dementia

	CAMCOG	Dementia	Alzheimer's
Age	-	+	+
Social class	+	-	-
Diabetes	+	+	-
Mental interests	+	+	-
Heart failure	-	-	-
Bowel problems	-	-	-
Dizziness	-	-	-
Falls	-	+	-
Headache	-	-	-
Alzheimer's (FH)	-	-	-
Down's (FH)	-	-	-
Lymphoma (FH)	-	-	-
Thyroid disorder	-	+	-
Thyroid function	-	-	-
Handedness	-	-	-
Fractures	-	-	-
Psychiatric history	-	-	-
Hearing problems	-	-	-
Cigarettes	+	-	-
Analgesics	-	-	+
Antacids	-	-	+
Amalgam fillings	+	+	-
Herpes simplex	-	-	-

	CAMCOG	Dementia	Alzheimer's
Herpes zoster	-	-	-
Herpes simplex (Ab)	higher titres in non-demented		
Stroke	-	+	-
TIA	+	-	-
Hypertension	-	-	-
Alcohol	-	-	-
Thyroid autoab.	-	-	-

+=positive relationship -=no relationship
FH=family history, TIA=transient ischaemic attack
autoab.=autoantibodies

Final models

CAMCOG. For the CAMCOG dichotomised with all the positive variables from above, the final model was as follows:

	Odds Ratio (95% limits)
No teeth or no fillings	1.0
A few fillings	3.8 (1.8-8.2)
Many fillings	3.1 (1.1-8.4)
Active mental interests	3.4 (1.3-9.1)
[Diabetes mellitus	0.34 (0.15-0.75)]
[TIAs	3.8 (0.8-17.50)]

Thus many of the associations noted above were no longer in the model once independent effects were sought. There were no interaction effects.

Dementia. For the diagnosis of dementia the following model was constructed:

	Odds ratio (95% limits)
Stroke	16.2 (3.5-75.5)
Diabetes	24.8 (4.1-150.0)
[Mental interests	$3.3*10^{-4}(10^{-6}-10^{8})$]
Age group	5.8 (1.5-22.6)
[Amalgam fillings-few	0.19 (0.02-1.5)]
[-many	0.25 (0.03-2.3)]

Because of the importance of cognitive function in the diagnosis of dementia, there is overlap with the findings on CAMCOG, although the only major associations are diabetes and stroke. These were associated with the diagnosis of vascular dementia, rather than Alzheimer's disease.

Alzheimer's disease. The final model for Alzheimer's disease was as follows:

		Odds ratio (95% limits)
Age		2.7 (0.7-10.5)
Neurological abnormality		
	1	3.0 (0.8-10.9)
	2	3.2 (0.3-29.9)
	3	49.6 (3.4-587)

The number of individuals in this category was small, and hence the confidence limits on these odds ratios are wide. It is of interest that only age and neurological abnormalities appear in this model in contrast to the mixed associations of the other two categories.

Most of these factors were unrelated to measures of cognitive function. There were some variables where the relationship observed was the opposite to that postulated, for example those with dental fillings had higher scores. This relationship is spurious, confounded by the relationship of better dental care to social class, although it remains signficant, since it appears that this is a better measure of the underlying latent variable than social class itself. Other positive features reported by the informant were examined in relation to CAMCOG scores. No decrease in mean level on CAMCOG was found for those whose informant reported hearing loss, recent life event, lack of confidante or personality type (whether out-going or introverted).

On the general question, not contained in CAMDEX "has there been any change in her mental or physical function over the last few years" there was an association with informant reported decline in mental function (n=37), with mean difference of CAMCOG scores of 15 points. When slowing mentally and physically of the subject (n=93) was reported by informant the difference in CAMCOG mean scores compared

to those without such slowing was 9 points (103 reported slowing). Some estimate of the informant's grasp of the interview was made with the interviewers impression of comprehension of questions and accuracy of replies (5 and 6 informants were rated as poor respectively). For these two groups the mean CAMCOG of the subject was 10 points less than for the rest of the group. Thus the quality of information from an informant for those subjects with lower cognitive scores was perceived as poorer by the interviewer than for those with high cognitive scores. The informant interviews were not performed blind to knowledge of the subject interview, since the same interviewer performed both.

The diagnosis of dementia did not appear to be related to any of the exposures examined, although the numbers with a diagnosis of dementia were small. 3 out of 9 individuals with a diagnosis of multi-infarct dementia were reported to have diabetes mellitus. A similar pattern was seen among those with a positive history of diabetes from the medical notes (4 out of 9 for multi-infarct dementia). A medical note of transient ischaemic attack was also noted to be higher in those with a diagnosis of multi-infarct dementia (3 out of 9). 17% of those without any diagnosis had had a psychiatric illness recorded in the general practitioners' notes, 27% of those with a diagnosis of AD, and 32% of those with a diagnosis of depression. Where the subjects reported a family history of any dementia in first and second degree relatives there was no association with dementia. When first degree relatives only were included who had a more definite history of dementia, there was still no relationship with dementia or with the differential diagnosis of Alzheimer's disease.

To test the hypothesis that cognitive function is related to blood brain barrier function and whether this is the mechanism for the observation in other studies of a relationship between head injury and Alzheimer's disease in more detail, the relationship between a measure of blood brain barrier permeability, creatine kinase BB isoenzyme, and age group, diagnosis and history of head injury were examined (Table 42). There was no relationship with age, diagnosis or history of head injury, whether reported by subject or informant. The relationship between creatine kinase BB and cognitive scores was also

examined. Non-parametric correlations were calculated (Spearman rank rho) for CAMCOG, MMSE and information-memory-concentration scores with creatine kinase BB isoenzyme levels. There was a weak positive rho correlation in each case (0.18, p=.01, 0.21, p=.003, 0.20, p=.005 respectively). There was, however, no correlation with the behavioural scale, the Blessed dementia rating scale (-0.09, non significant).

Table 42 Creatine kinase BB levels by diagnosis and history of head injury

	Mean CKBB level (ug/l) [s.d.]	Number
Dementia severity		
None	1.5 [0.7]	153
Mild	1.2 [0.6]	14
Mild/Mod	1.6 [0.2]	2
Dementia subtypes and depression		
Alzheimer's	1.4 [0.6]	8
MID	1.2 [0.6]	6
Depression	1.7 [0.7]	28
Head injury with loss of consciousness		
Self reported - none	1.5 (0.7)	157
- 1+	1.5 (0.4)	11
Informant report - none	1.5 (0.7)	159
- 1+	1.5 (0.3)	7

DISCUSSION

The results of this study have shown that in a true population sample there is no evidence of discontinuity between those individuals with a diagnosis of dementia and those without, or those with poor cognitive function and those without. None of the distributions on cognitive and other scales showed evidence of bimodality. Prevalence estimates for moderate and severe dementia using CAMDEX clinical criteria were lower than urban studies in the United Kingdom, but similar if mild dementia was included.

The prevalence of cognitive impairment using suggested cutpoints for cognitive scales provided similar figures to recent UK studies. This study provided further evidence to support the relationship of cognitive function with social class and education. In this study putative risk factors for dementia and Alzheimer's disease were not associated with level of cognitive function or diagnoses of dementia, with the exception of age, cerebrovascular events and diabetes mellitus. The latter two were associated with the diagnosis of mult-infarct dementia.

The possibility of error arising from the methodology in the study leading to bias in these findings must first be considered. The findings of this study in relation to previous work will then be discussed.

METHODOLOGY

Bias could have been introduced into the study from each of the following: a) design error b) limitations of the instruments used c) error in procedure. These will be considered in turn.

Design error

A geographically delimited sampling frame was chosen for its completeness and homogeneity. Evidence is available from other epidemiological studies of wide differences in performance on cognitive scales, related to cultural and socioeconomic differences within studies (e.g. Holzer et al 1984). In this study, where the

primary aim was to examine the underlying distributions of variables associated with dementia, it was important to reduce the number of confounding variables.

Although there are reports on considerable inaccuracy in general practice age-sex registers (Silman 1984), in the rural area chosen this problem did not arise. Relatively few ghosts were found, and most subjects were well known to the doctors and their reception staff.

It could be argued that to choose such a restricted sample, both of sex and age group would lead to results of limited value. Most studies of dementia and cognitive function to date have examined the whole range of ages using limited instruments. By choosing a limited sample, it has been possible to examine in detail the influences of variables of interest, unaffected by the potential major confounding variables. Furthermore, in the meta-analysis of Jorm et al (1987), it was found that the consistent association of age with prevalence estimates allowed prediction of all rates of dementia from the rates of one age band.

The method of interviewing in the home setting was successful, both for response rate and full assessment of the individual. The informant histories were mostly collected on the telephone. Despite reservations about possible loss of information, the method appeared to be satisfactory; a finding noted by recent reviews of the method (McCann et al 1984, Groves and Kahn 1979).

Bias in the informant interview could have been introduced since one clinician performed the CAMDEX interviews. The diagnostic system required for CAMDEX clinical criteria was a review of all the available information, made by the clinician rather than a concensus diagnosis. There have been few, if any, studies where the informant history has not been collected by the same interviewer and thus the potential biases introduced have not been assessed. However, the GMS interview was conducted blind to the CAMDEX clinical diagnosis, and the agreement between the two clinicians was reasonable.

The risk section of this study is powerful only when the entire population is examined, for example for associations with cognitive function. For the examination of risk for dementia, there are rather few cases. It was for this reason that logistic regression was used to examine potential risk factors, and that some results are likely to be chance findings, reflected in wide confidence limits.

Limitations of methods used

CAMDEX was chosen above other instruments because it was the only one available at the time which incorporated all the criteria necessary for making the diagnosis of dementia according to internationally accepted criteria. It included current mental state to identify depression, and other psychiatric disorders, full cognitive assessment, physical examination and investigations and informant history. It was also chosen because it examines function over a range, allowing differentiation of high function from average to minimal and more severe dementia. It had been validated on hospital samples and had not been applied to population samples. There was difficulty in applying the diagnostic criteria in the community sample, since there are no fixed responses which identify fulfilment of criteria. The levels of severity used in this study were those available on the first version of CAMDEX. This caused the current minimal category to be classified in with the mild dementia group. Like all standardised interviews at present, validity studies have been based on comparison with psychiatrists' views. This is to some extent tautology, since it was from these views that the need for standardised instruments arose. Ideally the validation would be based on continuing follow-up of the population to observe progression, with post-mortem examination of brain tissue. Previous studies which have examined this issue have found that high mortality precludes the follow up of many individuals, but that in survivors most diagnoses of dementia are confirmed, with the level of severity unchanged or worse (O'Connor et al 1990). It seems, therefore, that it is reasonable to have some confidence in the diagnoses if rigorous criteria have been applied.

The accuracy of differential diagnosis is likely to be low. In this study it was not feasible to investigate all possible cases. The

hospital was perceived as far away, and many subjects stated that it "was only because it had nothing to do with the hospital" that they took part. Therefore only a brief physical examination and venepuncture were possible. This allowed a little more confidence about the exclusion of confusional states, but did not allow examination for uncommon causes of dementia. The main differential diagnoses were Alzheimer's disease and multi-infarct dementia. It is known from pathological studies that the two co-exist fairly often (Todorov et al 1975), but the clinical criteria are such that it is rarely diagnosed.

Whether it is correct to assume that Alzheimer's disease and multi-infarct dementia are the major contenders in the differential diagnosis of dementia has been recently challenged, with the publication of post-mortem studies of Lewy body disease (Perry et al 1989a and b, Lennox et al 1989) and prion dementias (Collinge et al 1990). Only epidemiological studies with post-mortem follow-up can address these new issues. The rates provided by this study must be interpreted with caution for two reasons: the small number of individuals assigned a diagnosis of dementia of any type and the inaccuracy of in vivo diagnoses.

Errors in procedure

Bias could have been introduced into the study by poor response rates, where the non-responders were those at different risk for the condition of interest. In order to maximise response rates the approach to subjects was made through the subject's own general practitioner. The second approach of all those women who did not take part on first invitation was successful, and these individuals were not more likely to be demented than those already seen. Information from briefly meeting the true refusers, and from the health centre did not suggest that serious bias was introduced by the refusal rate of around 10%. This is in contrast to the finding of Livingston et al (1990) in the Gospel Oak study who found that the more approaches to the subject necessary, the more likely they were to be cognitively impaired. The subjects in this study were not approached through the general practitioners and this could affect reasons for refusal. It seems likely, however, that some of this difference is due to differences in urban and rural communities. Lower refusal rates have

been achieved in other studies, mainly in those employing less sensitive interviews (e.g. 5% in Clarke et al 1984, O'Connor et al 1989). Most comparable studies have higher refusal rates (e.g. 20% in Kay et al 1985, 24% for appropriate age group in Copeland et al 1987a).

Further bias could be introduced into the study by death after sampling, but before interview. Correction for this using information from the health centre and hospital notes did not increase the prevalence by more than a marginal amount. Only 10 individuals died out of 410, although other studies report higher rates (e.g. 6% in Milne et al 1971). The additional demented subjects would have been more severely affected, and it is possible that the results have been slightly biased towards overestimating the mild category and underestimating the severe category.

Loss of individuals to institutions could have occurred leading to bias in prevalence estimates downwards, and in distributions of cognitive function towards higher function. There were few severely demented individuals and these were found in institutions. High rates of cognitive impairment have been reported in institutional settings, particularly more recently, and it is possible that there are different rates and criteria for institutionalisation between rural and urban areas. The age group examined in this study from a small geographical area is unlikely to provide large numbers for institutions, but it is also possible that a lower rate of institutionalisation might be expected due to the stability of the population, and large support networks. The prevalence of mild/moderate dementia was low in this study, but similar to the low prevalence of severe cognitive impairment found in Melton Mowbray (Clarke et al 1984). This finding was challenged by local psychogeriatricians, but on review of all the demented people known to services and those known to the study, it was found that these were almost identical. Similarly, in this study, there was no evidence of bias in rates downwards due to loss to institutions.

It has often been suggested that the greatest proportion of patients with severe dementia are to be found in the community, referring to studies conducted in previous decades. Recent studies suggest that there is a more equal balance between institutions and community in the care of severe cognitive impairment (Clarke et al 1984). With recent studies which are sensitive to milder levels of impairment, it is likely that more community individuals will be identified. The impact of these milder levels of severity, where dementia has not necessarily been recognised, on services is not known.

In this study, it has been possible to examine different methods of identification of dementia. The cognitive tests compared with clinical diagnosis were within the same interview. The two are not truly independent. However, the MMSE has shown reasonable test-retest repeatability (Folstein et al 1985) and it is unlikely that performance would have deviated significantly from one examination to another spaced soon after. In the assessment of all information for diagnosis, no attempt was made to add up scores on any of the scales within CAMDEX.

The quality control in this study showed good agreement on item recoding from tapes and on rediagnosis from tapes, with no evidence of seasonal effects on cognitive tests. There was also reasonable agreement between the two interviewers in the inter-rater study, with kappa values similar to those reported in previous studies. The agreement between the CAMDEX interviewer, GMS interviewer and AGECAT was less good, but these were rated from different interviews. This type of inter-rater study always leads to relatively low agreement. A difficulty here was the small number in the random 10% of the sample who had a diagnosis of dementia. Future studies should select out those with a diagnosis and match with individuals without a diagnosis. This would have been difficult in the present study, since in order to achieve randomisation, the interview schedules were marked and at the end of the interview the interviewer looked at the mark to see if further interview should be requested. To ask all subjects about a potential further interview could have adversely affected response rates.

There was no test-retest study for quality control. This was largely because the interview was long, and subjects would not have been willing to repeat the same interview twice. Those who agreed would have been a biased group. There would have been practice effects in some sections of the interview such as cognitive function and reaction time. Other learning effects might have been found as in the Epidemiologic Catchment Area Study at one year follow-up, where lower life-time prevalence rates were reported than at initial interview. It seemed that people had learnt that a positive response to a symptom question lead to probing questions and a longer interview (Mortimer, personal communication).

It seems unlikely that any of the areas above would have introduced serious bias into the results presented.

DISCUSSION OF RESULTS

Having discussed the potential sources of error inherent in the methodology of this study, the results will now be discussed in relation to previous studies and literature.

Case identification

Different case identification methods were found to identify different individuals, both on cognitive scales, behavioural scales and by different diagnostic methods. Poor agreement with general practitioners' diagnoses has been previously reported, and this was not an unexpected finding (Weyerer 1983, O'Connor et al 1989). It seems likely that the general practitioners are identifying individuals based on knowlege over time and that they are influenced by knowledge of previous psychiatric history, whereas the CAMDEX clinical diagnosis of mild dementia is not. The CAMDEX clinical diagnosis of mild dementia may be subject to other biases. Although diagnosis is based on the whole of CAMDEX, including examination, investigation and informant history, it is possible that levels of cognitive performance influenced the diagnosis, not least because cognitive function is the key part of the clinical criteria. The demented subjects were found to have significantly lower estimated permorbid IQ scores than those without any such diagnosis, although

only by a few points. This could point to bias, drift in the instrument NART with dementia (also noted by O'Carroll et al 1987), low IQ as a risk factor for dementia or to chance. The best agreement between the diagnostic methods in the random subsample interviewed with GMS was between the psychiatrist administering the GMS and the AGECAT program. This was expected since these diagnoses are not independent. The agreement between CAMDEX clinical rating and GMS was less good, although the two clinicians agreed reasonably well. The numbers of demented individuals were very small in this sample, and further studies to examine the relationship of these widely used standardised instruments are necessary. In a single phase study without longitudinal confirmation of progression, the predictive accuracy of these different methods cannot be compared.

The variability noted here is in agreement with other comparisons of methods. In the Hobart study it was found that similar prevalence rates were found with different methods, but that different individuals were identified by the different systems (Kay et al 1985). Other studies have now reported similar findings (Mowry and Burvill 1988). These findings suggest that until instruments are truly validated by study of progression and post-mortem valiation careful scrutiny of the possible biases of different methods should be made, and where possible multiple methods used in diagnosis.

If the CAMDEX clinical diagnosis is used as a standard, CAMCOG is the most sensitive of the cognitive scales in identifying mild dementia including minimal cases. The MMSE, although considerably shorter, also performs well. The CAPE information-orientation scale could not identify these individuals in this population, but performed well in identifying the mild/moderate and severe cases. In the context of low prevalence these scales would still have relatively low positive predictive values. If it is necessary to identify mild/moderate and more severe dementias a short scale, such as the information-orientation scale, is appropriate, perhaps in conjunction with an activities of daily living scale. For minimal to mild dementia CAMCOG is the most sensitive instrument, but will identify a high proportion of false positives (depending on the cut-point chosen). MMSE performs at a level in between these two, and, where brevity is essential, may

be the instrument of choice. Before applying the cut-points identified in this study, these would need to be validated on an independent sample. No single scale is likely to fulfill the requirements of all research studies.

An important possible bias in the use of cognitive scales is the strong association of education and social class with performance. This replicates the findings of Anthony et al (1982) for a UK population. Entire scales, in particular MMSE and CAMCOG, and individual items, such as orientation in time, serial sevens, WORLD, recall and copying a design, showed relationships with education. Higher educational level and social class were associated with better scores for all of the more complex questions such as drawing a pentagon, following a 3 stage command, serial sevens and WORLD. All items in cognitive scales were affected by age except the orientation times and registration, also shown in the Epidemiologic Catchment Area study (Holzer et al 1984, Kramer et al 1985). Only the demented failed the orientation items consistently, as expected. Significantly greater numbers of the older group failed the complex items WORLD and serial sevens, but not copying a pentagon. More older individuals failed on those items which could be associated with impaired hearing, such as repetition of "no ifs ands or buts" and the accurate registration of three items at first hearing. Although the complex items were associated with education and social class, they also helped in the identification of dementia. The value of these derived cognitive scales did not rest on the performance of the individual items, but on the composite score. Increased sensitivity to dementia, and milder levels of dementia, is gained by adding complex items. This adds the disadvantage of introducing apparent educational and social class bias. It is unlikely that an instrument based purely on cognitive function can escape this possible bias, unless it is accepted that there is no need to examine minimal and mild levels of impairment. It appears there is a complex set of influences on the distribution of cognitive scale scores which include education, social class and age. This applies even within a limited and relatively homogeneous sample, and is likely to be much more important in more heterogeneous populations.

Different suggestions have been put forward to explain the association of education and social class with cognitive scales. Better education could delay or minimise cognitive decline; social class might influence both education and those aspects of personal and medical care which could delay the onset of mental deterioration; education-age interaction with MMSE scores are an artefact of different initial abilities and are due to ceiling effects (Jorm et al 1988). This latter would be consistent with Mortimer's hypothesis that factors such as poor education and low social status "primarily reduce the margin of intellectual reserve to a level where a more modest level of brain pathology results in a diagnosable dementia" (Ferry 1988).

A correlation of 0.78 has been reported between MMSE and verbal IQ in one study (Folstein et al 1975), which compares with 0.58 between MMSE and predicted IQ using NART in this study. Correlations of a similar order between cognitive scales and estimated IQ have been reported in other studies (Kokmen et al 1987). Social class and educational level were shown to be as strongly associated with estimated IQ as in the non-random samples of wider age groups in the literature. The estimates appeared to be unaffected by the age group, which is consistent with other reports from healthy normals (Crawford et al 1988). The lack of difference beteen the mean NART predicted IQ and age group contrasts with the mean scores of cognitive scales for the two age groups suggesting that the difference in cognitive performance is not due to underlying IQ differences, and is not a cohort effect. It is more likely to be due to cognitive decline and the increasing prevalence of dementia in the older group.

A possible use of this type of measurement is to predict an individual's performance on cognitive scales and measure it against that observed. This could improve the sensitivity and specificity of cognitive scales by adjusting for the individual. This is in contrast to the suggestion that an adjustment be made according to social class and educational level (eg Kittner et al 1986).

Education and social class were not found to be associated with the Blessed dementia rating scale, based on questions from an informant. This supports the suggestion of Jorm et al (1988) that informant questionnaires could be used more widely as unbiased tests to identify demented subjects. This technique would not necessarily be acceptable in the community setting, where it could present problems to identify informants before subjects. A combined approach, similar to that used in this study, would partially resolve the possible bias, as well as allowing the investigators to examine the possibility that education and social class are themselves risk factors for cognitive decline.

A further possible methodological problem which has not been fully addressed in the literature is depression. The relationship between depression and dementia is well researched in clinical settings, but the relationship between the two in epidemiological studies is relatively poorly understood. If depression has a high prevalence, the approach to diagnosis of dementia in the presence of depression is very important. In CAMDEX the organic diagnosis takes precedence, even in the case of mild dementia, in the presence of moderate depression. Other diagnostic systems deal with this differently. This could lead to different rates of dementia when the underlying rates are the same. In this study there was no relationship between dementia and depression and rates would not have been altered by the different approaches. There was no relationship between levels of depression and cognitive function, and no individuals with a diagnosis of pseudodementia were seen. It is possible that such individuals were missed, and this can only be checked by a longitudinal study of the population.

Risk measurement

In order to examine the accuracy of reporting of putative risk factor exposure the agreement between subject and informant in women without a diagnosis of dementia was calculated. Reasonable agreement was found between informant and subject report for many variables but this was mainly due to the small proportion of positive responses. Agreement was best on marked events such as stroke, as has been

reported in other studies (Murphy 1982, Thompson et al 1982). Very few items were missing, as most informants made a guess where they were not certain. The agreement is, on the whole, similar to those reported by Rocca et al (1986) where agreement in 52 non-demented subjects was compared with next of kin. This is of interest since most of the informants in Rocca's study were spouses, whereas in the present study they were children. For some of the exposures there was considerable disagreement in reporting. With inaccuracies in the differential diagnosis and difficulties in obtaining accurate measures of exposure, considerable error is incorporated into case control studies. In view of these findings it is, perhaps, not surprising that few risk factors have been found. A further problem is the choice of controls. Using a continuous model of the disorder, the best controls would be those without any evidence of neuropathology. The population attributable risk of many factors would be very low. An example of this is family history of Down's syndrome. Despite the high relative risk found in some studies for this factor, it would not account for much of the dementia in the population.

It has been estimated that with a misclassification rate of 20% and an exposure of 10% the sample size of a study of Alzheimer's disease needs to be increased by 50% to show a relative risk of 3 (Henderson and Jorm 1987). However, in studies examining causation such issues are rarely mentioned. Those studies which have given power calculations rend to be larger and based on hospital medical records (Bharucha et al 1983). Relative risk is mentioned often, but very little mention is made of attributable risk (Schoenberg 1986). In this study the number of cases did not allow formal case-control analysis, but the nested case-control study within a population sample is the ideal design, because of difficulties of bias in case and control selection. Even on a cross-sectional basis this design would present problems because of the necessity to ask for information from informants. The most powerful design recommended would be a case-control study of the different types of dementia in an incidence study, where risk factors have been assessed in the future cases and controls at the outset. This requires large longitudinal population surveys.

Prevalence of dementia in a rural area

Prevalence rates of dementia were estimated in this study, and it is possible to compare these rates, and rates of cognitive impairment with other studies from this country and abroad where methodology is similar. There have been no similar rural studies in the United Kingdom which allow direct comparison of rural rates from one area and another. The comparison is, therefore, limited to urban studies. The prevalence rates of dementia of all severities found in this study were similar to those reported from Liverpool (Copeland et al 1987a) in which the prevalence of AGECAT level 03 organicity scale or case level for the age group 70 to 74 was 4.1% (cf 4.3%), and for the age group 75 to 79 8.5% (cf 11.7%). In the Hughes Hall Project for Later Life the rate for 75 to 79 in women was mild and greater severity was 2.0% (cf 2.8%). Although these rates are similar, it is difficult to make formal comparisons because of the different methodologies and the small numbers of cases in all studies once age specific rates are calculated.

The numbers of women with cognitive impairment identified by the study varied widely according to different scales and cut-points. In the 75 to 79 age group 3.3% scored below the cut-point suggested for the information/ orientation scale of CAPE. This lies between the proportion in both sexes identified in Melton Mowbray (Clarke et al 1984) and Nottingham for the over 75 age group (Morgan et al 1987), which were 1.6% and 5.6% respectively. A possible reason for the lower figure in Melton is the fact that 40 subjects remained unclassifed. If these latter were all classified as impaired the proportion would rise to 5.4%. A higher figure would be expected because of the unlimited upper age. MMSE results are available from the Baltimore section of the Epidemiologic Catchment Area study (Folstein et al 1985). For the 17/18 cut-point in the 65-74 and 75-84 age groups 1.1% and 4% were identified respectively, and for the 23/24 cut-point 3% and 21.4%. For the present study using the entire age group the proportion identified by the 17/18 cut-point was 3%, and the 23/24 cut-point 19.2%. The proportions are similar for the lower cut-point, but the higher cutpoint is higher than would be expected from the ECA findings. The mean scores for mild/moderate and more severe dementia were similar

in the original study of MMSE and the current study, at 9.6 and 9.7 respectively (Folstein et al 1975).

Without further investigation of progression and post-mortem validation, the differential diagnosis made in this study can only be seen as tentative. In this study using the differential diagnostic list from CAMDEX the majority of diagnoses were Alzheimer's disease (58%) and a smaller proportion with multi-infarct dementia (24%). These figures are similar to those for the Hughes Hall Project for women in the 75 to 79 age group (63% and 31%). The proportion of the population with Alzheimer's disease over the whole age group 70 to 79 (reweighted) was 3.8%. In a European meta-analysis of all comparable studies of dementia the figure was 2.8% (Rocca et al, submitted for publication). The proportion of those diagnosed with multi-infarct dementia was similar in the younger and the older age group. If this finding reflects underlying neuropathological change, the lack of increase with age may be due to the different lengths of survival of subjects with multi-infarct dementia and Alzheimer's disease.

There were no women with transient impairment secondary to known conditions allowing a diagnosis of acute confusional state. This group is known to have a high mortality and it is likely that this is the reason for this finding. The rates would probably increase in older age groups where chronic illness is more prevalent. Dementias secondary to other conditions formed only a small proportion of all dementias. It is likely that this also is due to high mortality.

Jorm et al (1987) found that there was a tendency to report lower rates for moderate and severe levels of dementia in studies where mild categories were included, than in those in which there was no mild category.
This study appears to conform to this pattern. It is likely that the same is observed in studies with a minimal category, such as the Hughes Hall Project for Later Life (O'Connor et al 1989). The study described in this thesis has higher rates of dementia of all levels for the 75 to 79 age group compared to the Hughes Hall Project (8.9% and 3.3% respectively, O'Connor personal communication). These differences could be partly due to the differences in age of the

sample. The age groups in the current study were defined by the age at sample definition, rather than age at interview, in order to retain the cohort. The numbers of affected individuals in both studies within age bands is small. In the Hughes Hall Project age at interview was recorded. The differences in these two studies are not in line with Jorm's further observation that lower rates tend to be reported when complete populations are examined. The rates given as a hypothetical baseline for moderate and severe dementia by Jorm are similar to those found in the Hughes Hall study, and for mild/moderate and more severe in this study. Since the levels of dementia are different in the each case, it may be that there are different underlying trends in dementia rates. However, the consistency may point more to the fact that whatever level of severity is used similar proportions of the population tend to be identified as abnormal.

Distributions: dementia as disease or continuum?

One of the main aims of this study was to examine distributions of indices of dementia in a representative population. The prevalence results presented in this thesis assume an underlying bimodal distribution of the features of dementia in a population. The distributions of the indices of dementia in this homogeneous age and sex limited population showed no evidence of bimodality. Measures of cognitive function, brain area function, behavioural measures, depression scales and ischaemia scales all demonstrated the same properties.

It has been suggested that case definition and case identification in psychiatry are still poorly developed and rooted in concepts derived from hospital psychiatry (Williams 1980). This applies to virtually all areas of medicine, but in particular in the elderly age group. Many authors have warned against using categorical models of disorders of the senium, arguing for dimensional models instead (Cluff 1981, Shepherd 1984, Evans 1984, Jorm and Henderson 1986). It has been suggested that "to draw a distinction between disease and normal ageing is to attempt to separate the undefined from the undefinable" (Evans 1988).

The studies which have led to the definition of dementia, particularly Alzheimer's disease as distinct from normal ageing have been based on highly selected samples. Also the medical research into distinct disorders and causes has tended to foster this division (Holliday 1984). Despite these selection procedures a middle ground has been noted, and labelled according to the underlying dichotomous model. Benign senescent forgetfulness was said to be a form of forgetfulness, more extreme than that seen in normal ageing, but not progressing on to dementia (Kral 1962). The lack of specific criteria have been criticised and the name altered to age associated memory impairment, but the term has become part of the literature. It has been suggested that there is no evidence that the processes are different, merely milder (LaRue 1982). The current study would support this latter view, although longitudinal follow-up would be required to confirm it.

The lack of bimodality in behavioural and cognitive measures is also reflected in the literature by grey areas in all the formal clinical studies of ageing and dementia. In the investigation of normal ageing it is clear that all biological theories of ageing refer to deterioration or decline in levels of capacity. Until recent centuries the marked decline in mental function of some individuals, and the slight decline of most, was regarded as a natural occurrence. Decline is noted in many systems with age and is often not viewed as pathological.

Age related decline is found in the few laboratory animals which can be studied for long enough. Age related impairment in tests of cognitive function such as learning mazes have been demonstrated in more than one strain, sex and species of laboratory rat (Ingram 1985). In animals it has not proved possible to separate out the benign senescent type animal from the models of senile dementia (Campbell et al 1984). There are single case reports of neurofibrillary tangles occurring in aged primates and plaqes have been found in the cerebral cortex of aged monkeys and dogs (Selkoe et al 1987). Cross reactivity was found between antibodies against amyloid filaments and constitutional proteins from Alzheimer's disease with neuritic plaques and cerebrovascular deposits in monkeys, orang utans, polar bears and dogs. These authors observed that development of cortical foci of dystrophic neurites, often if not always associated with amyloid in the centre, is an age related process shown in several mammalian species including humans.

There are changes in the nervous system in ageing populations, with more abnormal signs such as developmental reflexes appearing over the age of 70 years (Jenkyn et al 1985). Some of these changes are those noted to be increased in patients with Alzheimer's disease, and highlight the difficulties of interpretation of studies with no comparable age matched populations.

Changes in cognitive function with age have been noted over centuries. William Salmon, a Professor of Physick 200 years ago described certain defects of imagination, reason and memory..."in a man superannuated.."decayed in his intellectuals". Hodge in 1894

noted the changes in ganglion cells from birth to senility "life starts with a superabundance of cells which furnish the animal with all the energy it needs..as the work of life is being done the cells, one by one, are worn out" (Corsellis 1977). The approach to formal examination of changes in cognition with age has been to perform cross-sectional studies of different age groups, or to examine selected cohorts. On the whole these approaches have not provided results which are relevant to the whole population. Despite this, decline in cognitive function has been consistently noted over the age of 80 (Benton et al 1981). But it has also been noted that subjects with superior ability without time pressure showed little or no deterioration in many cognitive tests (Busse and Pfeiffer 1977). The normal elderly tend to do worse than younger people on tests of recent memory, but perform well on tests of vocabulary and general information. Many of the tests used have little relevance to day to day living and motivation to perform well has been questionned (Avorn 1983). Furthermore many cognitive tests are culture bound, and, as described in the methodology section above, appear to introduce potential bias in different groups within the same culture.

The longitudinal studies which have been conducted on the normal elderly include the Duke Longitudinal study (Siegler 1983) in which 59% of the cohort eventually received a rating of organic brain syndrome. This is despite the fact that those subjects who remain in longitudinal studies tend to be of higher intelligence and more stable generally than drop-outs (Palmore 1974, Schaie and Labouvie-Vief 1974). In the Duke Study the older subjects demonstrated more decrement in verbal and total cognitive scores than younger survivors, although IQ remained relatively stable over time. This was also found in the Seattle Longitudinal study (Yesavage 1985). Higher socioeconomic status has been associated with maintenance of higher function in later life in several of these studies (Yesavage 1985). These studies tend to be flawed because of lack of representative populations and lack of information on those who dropped out or died.

In this study, where there was a cross-sectional examination of cognitive function in two age groups, cohort differences in education and life experience were minimal due to the type of sample selected.

The difference observed in cognitive function is likely to be truly associated with the age difference. A shift in distribution of cognitive scores downwards was demonstrated for the older age, which was largely accounted for by the increased number in this age group diagnosed as demented. There was a shift in the whole distribution, however, which was reflected by the small shift in the median score on CAMCOG downwards.

The decline observed in longitudinal studies and in the current cross-sectional study is reflected in the increasing pathology found post-mortem in the brains of elderly people. In Alzheimer's disease brain atrophy, ventricular enlargement and loss of cortical neurones are found (Hubbard and Anderson 1981a and b), but these changes are also observed to a lesser extent in aged individuals without dementia (Hubbard and Anderson 1981a and b, Mountjoy et al 1983). The histopathognomic changes of Alzheimer's disease are found in the brains of those who were not noted to be demented during life. There is considerable debate about what constitutes the diagnosis of Alzheimer's disease pathologically, and this changes according to the age of the subject. In extreme old age the demented may have many plaques, but no tangles. The young demented have many tangles but no plaques (Terry et al 1987). A review of autopsy records and clinical records of 32 patients and 68 non-demented demented from a clinical service of a defined geographical area revealed that a large number of the demented had the same pattern of plaque and tangle distribution as the non-demented (Kokmen et al 1987). These studies were not based on population samples, but those which have been carried out on unselected autopsy series support the finding of a lack of specific changes with very good concordance with in vivo findings. A consistent rise in the numbers of plaques and tangles with age has been observed (Miller et al 1987).

There is, therefore considerable overlap in the pathological changes of Alzheimer's disease between non-demented and demented in those brains studied (Gellerstedt 1933, Tomlinson et al 1968, White et al 1977, Berg 1985, Creasey and Rapoport 1985). Despite this acknowledged difficulty in differentiating between disease and normality the conclusion of many of these reviews has been that there

are different processes operating (e.g. Creasey and Rapoport 1985). The arguments set out against Alzheimer's disease as being the extreme end of a continuum are as follows (Berg 1985):
a) fibroblasts from demented individuals do not show limited doubling capacity compared to age-matched controls (as demonstrated by Hayflick 1984), which would be expected in accelerated ageing; b) there is not accumulation of the ageing pigment lipofuscin in the Alzheimer's brain compared to normals; c) that the severity of changes in Alzheimer's disease related to age appears to have an inverse relationship with age (Mann et al 1984, Rossor et al 1984, Alafuzoff et al 1987, Terry et al 1987). The arguments to put forward against these points are as follows: a) the first suggests that ageing is a unitary phenomenon throughout the whole body, whereas the indicators of ageing in the brain are all found to a greater extent in Alzheimer brains; b) the second has been disputed by a careful examination of Alzheimer's disease which shows that accumulation does occur (Dowson 1982); c) the third is most likely due to a survival effect, such that the old with neuropathology die at an earlier stage in the pathological process than the young.

The lack of division noted between pathology and normality in the current study corresponds to the neuropathological observations, and also to the fact that in vivo tests show similar results. Although some groups have reported an association between computerised tomography appearances of atrophy, ventricular enlargement and dementia, non-specificity is always noted (Jacoby and Levy 1980, Jacoby et al 1980, Jacoby 1981, Bigler et al 1985, Creasey et al 1986). Electro-encephalogram (EEG) tracings are noted to show increase in theta activity, decrease in beta activity and decrease in overall mean frequency (McIntyre 1985), but the EEG has been shown to change in longitudinal studies of the healthy elderly, with similar changes, although less marked (Fenton 1986). Evoked potentials also show more change in the demented than in the normal elderly, but the finding has been criticised as neither specific nor sensitive to the dementing process (Goodin and Aminoff 1986, Gordon 1986). The distributions of non-Alzheimer's disease neuropathological abnormalities, such as vascular lesions and Lewy bodies, in fully representative populations is not known. Computerised tomography has

been used to examine for vascular lesions and white matter lesions have been found in a high proportion of the elderly generally, but is non-specific in dementia (Rezek et al 1987, Inzitari et al 1987, Steingart et al 1987, Johnson et al 1987, Fazekas et al 1987).

One interpretation of these findings has been the threshold effect. There are different threshold models, such as the hypothesis that there is a reserve of cells in life and that with nerve cells loss leading to increased susceptibility to dementia (Henderson et al 1980). This was developed further by Arendt and Bigl (1987) who suggested that the threshold for neuron loss would be 140,000 neurons in one hemisphere. The more accepted model is that until a certain number of plaques and tangles are present, no clinical dementia is present (Roth 1986). Actual numbers have been suggested in the literature, but it seems unlikely given that there are a number of different influences on the appearance and recognition of the dementia syndrome. A threshold of sorts has to exist given that diagnostic criteria have to be fulfilled, and an individual has to fail extra critical functions to be diagnosed. It seems more likely that there is a general association of function with underlying neuropathology, but that there are many modifying factors which are both related to an individual's previous capacity and to society's expectations of that individual with ageing.

The review of the literature suggests that, as yet, there is no test for dementia, in particular Alzheimer's disease, which clearly separates those without a diagnosis from those with a diagnosis. The current study supports this observation for a variety of cognitive and behavioural scales in a population sample. It may be that the finding in this study is due to small

numbers, although the same distribution patterns have been reported from the Hughes Hall Project for Later Life and the Epidemiologic Catchment Area study for much larger studies using the Mini-Mental State examination. If there is a unimodal distribution the imposition of thresholds may be more a function of the requirement for services than a reflection of underlying neuropathological abnormality. If dementia, in particular Alzheimer's disease, is on a continuum with normal ageing, the research programme elucidating the mechanisms of neuropathological lesions and risks may yield results which can eventually delay or reduce the cognitive decline noted in many elderly people.

Risk

There appears to be little biological advantage to members of a species living much beyond the age of reproductive ability and the rearing of offspring. It has been suggested that the increase in risk factors with ageing is rooted not in the pathology itself but in normal age associated decrements. The underlying genetic basis for developmental sequences could be the same mechanism that produces ageing changes (Hayflick 1981, 1984). Many of the suggested mechanisms suggested for Alzheimer's disease are the same as those suggested for the ageing process, such as damage by oxygen free radicals (Henderson 1988). This study has investigated the possibility that some of these variables can be associated with cognitive function in a population or with those identified as demented.

Age was the most consistent risk factor for dementia in this study. This was accounted for by the increase in the prevalence of diagnoses of Alzheimer's disease, rather than multi-infarct dementia. The suggestion that social class and low education are risk factors for dementia (Henderson 1987) was not supported by the findings from this study, although there may have been a tendency for higher rates in social class IV. These findings are limited by the small numbers who were diagnosed as suffering from dementia.

In order to use the data most efficiently logistic regression was used so that all the "controls" could be compared with the "cases", identified either by diagnosis or cognitive score. The only finding of interest in the risk for diagnosis was the consistent finding that those with a history of diabetes mellitus were at higher risk for both cognitive impairment and the diagnosis of dementia. This was accounted for by the high proportion of people with diabetes in the multi-infarct dementia. This finding needs further investigation as it has important preventive potential if control in younger groups leads to less cardiovascular and cerebrovascular disease.

The factors which have been identified by previous case control studies were not supported by this study, in particular family history of Down's syndrome, or Down's syndrome itself, family history

of dementia and head injury. The rational for examining association with level of cognitive function was that if the factor was an important risk factor for dementia an association with the key component of the diagnosis would be expected. This comparison allowed the use of the entire sample, rather than selected groups.

One of the a priori hypotheses to be tested in this study was that cognitive function, dementia or Alzheimer's disease would show relationships with a measure of the integrity of the blood brain barrier, creatine kinase BB isoenzyme (CKBB). Within this homogeneous sample no relationship between age and levels of CKBB was found, nor was there any significant difference between the levels found in the distribution of previously reported large samples and this one. There was no relationship between the severity of dementia and the level of CKBB. Since Alzheimer's disease is probably the most common form of dementia some relationship would be expected if the hypothesis was correct. Although differental diagnosis in this sample must be seen as tentative the findings reported here have been supported by two recent studies, where no relationship was found (Court et al 1987, Schlageter et al 1987). There was no sub-group of demented individuals who had higher levels.

It is possible that raised levels of CKBB are only seen when the level of dementia is severe. Since this was a community study of relatively young elderly, only two individuals were more than mildly demented. Their levels were not raised. If the levels rise only in more severely demented individuals it is clear that peripheral measures of blood brain permeability would not be of great diagnostic use early in the disorder.

There was a consistent and puzzling positive relationship between the cognitive scales and CKBB levels. The significance of this finding is unclear. The absence of a relationship with the Blessed dementia scale and CKBB levels supports the absence of a relationship with dementia itself. The finding could be a chance ocurrence because of multiple comparisons, but this was tested as an a priori hypothesis. These findings do not support the suggestion that impairment of the blood brain barrier is important in the dementing process.

It has been suggested that selective hormonal changes might provide a useful diagnostic tool in Alzheimer's disease (Christie et al 1987). However, others have observed the relative normality of neuroendocrine function (Thomas et al 1987). Conflicting findings have been reported for thyroid function, with increase in total thyroxine (T4) in one (Newhouse et al 1986), low liothyronine (T3) in another (Thomas et al 1987) and no differences in others (Sunderland et al 1986, Tappy et al 1987, Christie et al 1987). In this study no association was found for either the diagnosis of dementia or for the level of cognitive function. Other hormones were not measured in this study. No association was noted for history of thyroid disorder, in contrast to one case-control study (Heyman et al 1984) but in agreement with others (Small et al 1985, Lawlor et al 1988). The clinical studies tend to be flawed by choice of control groups, lack of drug free subjects, small numbers and multiple comparisons. The current study provides no supporting evidence of a relationship between the function of the hypopituitary thyroid axis and the level of cognitive function or the dementing process. Longitudinal studies and more detailed study of neuroendocrine function would be needed to confirm this.

Demented subjects have been found to have higher antinuclear antibody levels than age matched controls (Smith and Powell 1985). In this study levels of the nuclear and thyroid autoantibodies were not found to be related to cognitive function or dementia.

It has been stated that "population based studies have as yet added little, if anything, to our scanty knowledge of the causal factors of dementia" (Bergman and Cooper 1986). The findings of this study agree, to some extent, with this comment. Age was the only risk factor found for dementia. Age, education and social class were the most important variables associated with cognitive function. The view must be challenged, however, since few studies of adequate design and power have been conducted to examine causation. The optimum design of a large nested case control study on incident, validated diagnoses within a longitudinal study has not yet been carried out. Furthermore, with this sort of design the predictors of change in

cognitive function, and subsequent neuropathological appearances, can be investigated which may yield other clues to the risks for accelerated decline of cognitive function in old age.

IMPLICATIONS FOR FUTURE RESEARCH

The prevalence estimates for dementia in this study, excluding the mild group, were low. This was not accounted for by loss of individuals into institutions, but could be due to the levels of severity employed. Comparison between studies is extremely difficult unless exactly the same methodology is used. Future studies need to address these issues as well as differences in survival, migration patterns and rates of institutionalisation before valid comparisons can be made and aetiological hypotheses developed and tested.

Several of the scales measured in this study have been correlated with underlying neuropathology, such as tangles, plaques and cell loss (Blessed dementia scale, information-memory-concentration scale and MMSE). To prove a continuous distribution of neuropathological lesions, such as plaques, tangles, Lewy bodies in the population it would be necessary to examine the representative sample of brains from communities where subjects have been examined during life. This has not been possible up to the present. In this study proxies for underlying neuropathology have been measured. From the distributions of these, and from the literature on unselected autopsy series there seems to be evidence that neuropathological lesions are continuously distributed in populations. Given the known correlation with in vivo measures, it seems probable that there would be some association between the occurrence of different pathologies and the level of cognitive function in populations also. Figure 16 shows the hypothetical average frequency of brain lesions associated with dementias. There is considerable variation about this average, as there is during life. Figure 17 shows the average function in such variables as cognition with age, with decline noted particularly after the age of 75. It is likely that the diagnostic threshold alters with age, and that more impairment is necessary before a diagnosis is made because of an adjustment in expectations. Various risks shift an individual away from the mean. Few have been identified with certainty, although family history and head injury have been identified in case control studies. In this study they have not been found to be associated with differences in cognitive level, but the possibility that they affect the course of cognitive decline over time remains to be examined.

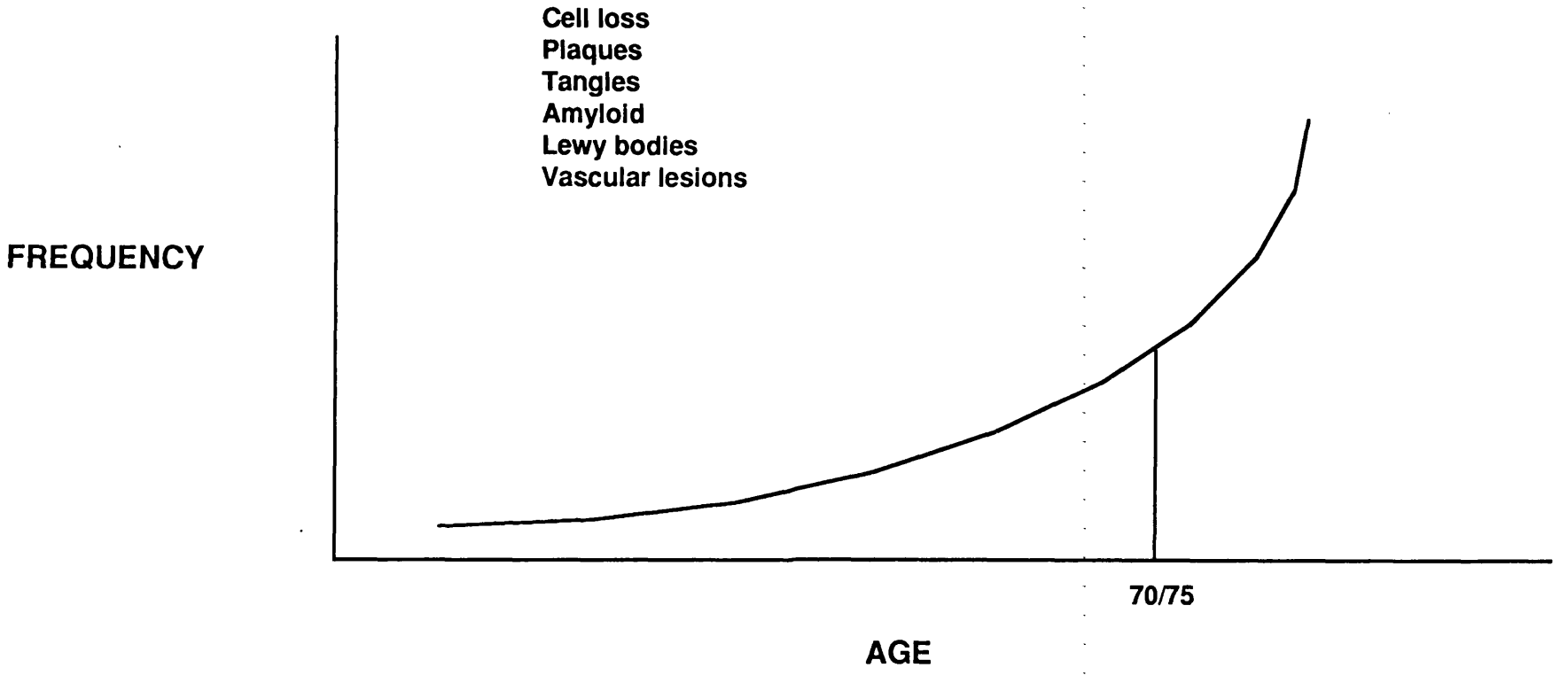
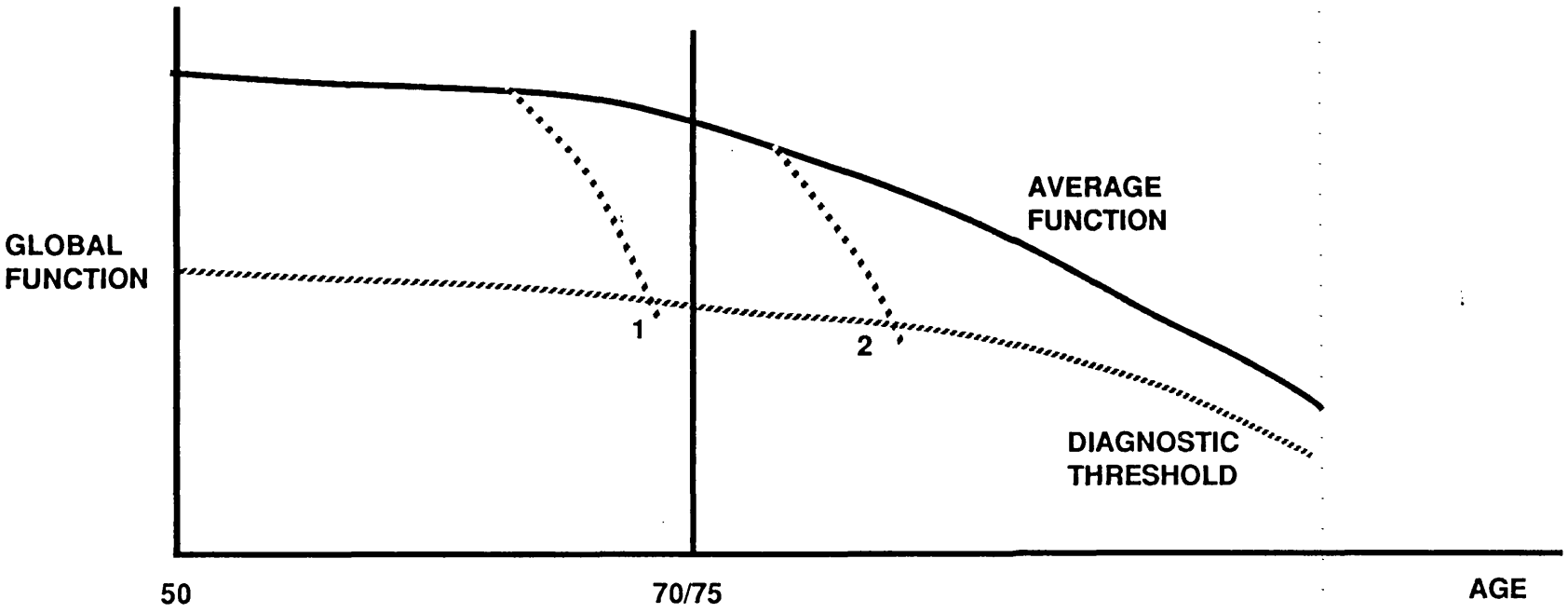

Cell loss
Plaques
Tangles
Amyloid
Lewy bodies
Vascular lesions
FREQUENCY
70/75
AGE

FIGURE 16

A MODEL FOR AGEING/ALZHEIMER'S DISEASE



1. POWERFUL INFLUENCES (D.S., F.H.)
2. MINOR PUTATIVE RISK FACTORS (e.g, HEAD INJURY, ALUMINIUM EXPOSURE)

FIGURE 17

It is suggested that successful ageing would be associated with minimal neuropathological change, that statistically normal ageing with some decline would be associated with some occurrence of one or more of the lesions and that abnormal ageing would be associated with substantial occurrence of one or more of the lesions.

Standardised measures made during life remain problematic. Cognitive measures are influenced by education and social class. It has not been demonstrated in this study that either of these has an important association with the diagnosis of dementia. Education and social class as risk factors for cognitive decline must be investigated longitudinally. It would be premature to correct for these variables until they have been discounted as predictors of decline. Cutpoints and screening procedures remain relatively arbritrary and subject to error, as do levels of diagnostic severity. This study confirms that a dimensional approach is essential to the examination of dementia in the community.

This study highlights the complex relationship between scales and diagnostic methods for different age groups, even within such a homogeneous age group. This further supports the recent move away from viewing the elderly as a single group. They are a heterogeneous group, diverse in age, cohort, education, social class and other cultural biased influences.

CONCLUSIONS

It is hoped that this study has contributed to the field of dementia research in the way which Henderson and Jorm suggested when proposing a moratorium on prevalence and incidence studies (1987). They saw the real priority at that time as the exploration of methodological problems of diagnosing Alzheimer's disease in the field. Longitudinal study will remain the true validation of these different methods and eventually provide a "gold standard" against which to improve diagnostic methods. In order to understand unsuccessful ageing, we also need to understand usual and successful ageing (Rowe and Kahn 1987). Therefore future approaches to research into dementia and cognitive function with age must be population based, and incorporate investigation of the determinants of successful ageing (Katzmann 1987). This study has highlighted the continuity between normal and abnormal mental ageing.

The underlying model for dementia in the population for future studies should be flexible, allowing examination of multiple possible aetiological factors as reflected by, for instance, plaques, tangles, Lewy bodies, vascular pathology, cell loss, reduced dendritic extent (Coleman and Flood 1987). Longitudinal study is necessary with full neuropathological examination wherever possible, including techniques developed in molecular biology. In this way it will be possible to examine the influences of the different pathological indices on grades of function. At the same time more understanding is needed of the influences on the diagnosis of dementia, such as cultural expectations of ageing. Cross cultural studies with carefully designed equivalent methodology are needed to investigate the risk factors of specific neuropathologies. The immediate potential for prevention of dementia is likely to lie with disorders associated with vascular lesions. Until more is known about the actual impact of various lesions in the brain upon cognitive ability the full preventive potential of any intervention cannot be estimated. This area of research continues to be urgent as the population ages. "Any condition which debilitates a fifth or more of the population if they succeed in reaching the age of 85 years and eliminates the essence of humanness deserves every bit of scientific energy we can muster" (Plum 1986).

APPENDICES

APPENDIX 1

Criteria for dementia, Alzheimer's disease and multi-infarct dementia are given in this section for DSM-III-R, CAMDEX and NINCDS-ADRDRA. Depression criteria for CAMDEX are also given.

Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R) of the American Psychiatric Association (1987)

Dementia

The subject must fulfill each of the major criteria below:

A Loss of intellectual abilites severe enough to interfere with social functioning

B Memory impairment

C At least one of the following:

1) impaired abstract thinking

2) impaired judgement

3) other disturbance of higher cortical functions- eg aphasia, apraxia, agnosia.

4) personality change ie alteration or accentuation of premorbid traits

D State of consciousness not clouded ie does not meet the criteria for delirium or intoxication although these may be superimposed

E Either 1 or 2

1) evidence from the history, physical examination or laboratory tests, of a specific organic factor that is judged to be aetiologically related to the disturbance

2) in the absence of such evidence, an organic factor necessary for the development of the syndrome can be presumed if conditions other than organic mental disorders have been reasonably excluded and if the behavioural change represents cognitive impairment in a variety of areas.

Primary degenerative dementia (Alzheimer's disease)

A Dementia

B Insidious onset with uniformly progressive deteriorating course.

C Exclusion of all other specific causes of dementia by the history, physical examination, and laboratory tests.

Multi-infarct dementia

A Dementia

B Stepwise deteriorating course ie not uniformly progressive, with patchy distribution of deficit i.e. affecting some functions, but not others, early in the course.

C Focal neurological signs and symptoms e.g. exaggeration of deep tendon reflexes, pseudobulbar palsy, gait abnormalities, weakness of an extremity etc.

D Evidence from the history, physical examination or laboratory tests of significant cerebrovascular disease that is judged to be aetiologically related to the disturbance.

Cambridge Examination for Mental Disorders in the Elderly

Operational diagnostic criteria for dementia and depression

Dementia

Global deterioration of the patient's intellectual and (usually) emotional and motivational behaviour in a state of unimpaired consciousness over a period of at least 6 months.

Inclusion criteria

(Criteria A,B and C need to be satisfied.)

A Progressive failure in performance at work and in the common activities of everyday life not due to impairment in health or physical handicap. There is general confusion of mental processes manifest as impairment or loss of occupational skills, ability to use household utensils and equipment, to handle money, and to find the way along familiar routes in the patients own neighbourhood or at home.

B Impairment of memory with particular difficulty in recalling recent personal experiences and current happenings. The decline in memory is sufficiently severe to impair functioning in daily life. There is difficulty in registering, storing and recalling recent events in daily life, frequent loss of belongings, persistent forgetfulness regarding information, recently acquired and social arrangements, and in the recall of names of familiar persons and of past events previously recollected with ease. At an advanced stage, there is inability to recall the address where the patient lives, and failure to recognise the identity of spouse, children and close relatives.

C At least one of the following:

1. Deterioration in general intellectual ability with impaired capacity for reasoning and inference, and impairment of abstract thinking, e.g. inability to discern simple similarities and differences between related objects, or difficulty in defining words and concepts, or following instructions or an ordinary conversation. Objective verification of deterioration in intellectual ability should be sought by obtaining a history from an informant and from neuropsychological tests administered as part of the examination of the present mental state.

2. Progressive impairment of judgement reflected by an inability to take decisions, to discharge personal, familial and social responsibilities, and by general incompetence in management of affairs. The failures are clearly evident to relatives and friends and there is partial or complete dependence on help from others.

3. Disturbance of specific higher cortical function such as language disorder manifest in failures in comprehension and/or expression, defective execution of motor tasks despite adequate comprehension and physical function, impaired recognition or identification of objects despite intact senory function, constructional difficulty manifest in copying three-dimensional figures, or the assembly of objects such as blocks or sticks in specific designs.

4. Deterioration of personality or general behaviour manifest in two or more of the following features: fading or disappearance of characteristic personality traits, blunting of emotion, deterioration of the finer aspects of social adaptation, deterioration in self-care, coarsening of habits, growing apathy and progressive decline in interest and curiosity, and incontinence of sphincters.

Exclusion criteria

Clouding of consciousness most of the time. Episodes of delirium may be superimposed upon a dementing illness. In the presence of a clouded or delirious state or stupor the diagnosis of dementia should be deferred until clouding of consciousness or stupor has subsided.

Diagnostic note

The presence of a concomitant depressive, anxiety or psychotic syndrome no matter how severe or incapacitating should not be allowed to preclude a diagnosis of dementia. The organic syndrome takes precedence in diagnosis over affective and paranoid-schizophrenic disorders and over anxiety and other neurotic syndromes.

Senile and presenile dementia of Alzheimer type (SDAT)

Inclusion criteria

In addition to the inclusion criteria for the diagnosis of dementia, the following must be satisfied:

A Gradual onset and slow but irreversible progression of the dementia. The degree of impairment and effectiveness of social functioning may remain stationary over periods ranging from 3 to 12 months.

B Absence of evidence from the history, physical examination and/or special investigations that dementia is not attributable to metabolic or sytemic disease, or deficiencies and intocixications liable to give rise to interference with cerebral function. The commoner causes of such secondary dementias are hypothyroidism, vitamin B12 deficiency, cranial arteritis, primary or secondary cerebral tumour (particularly affecting frontal and temporal lobes), subacute bacterial endocarditis, and chronic alcoholism. Other causes comprise syphilis, hypercalcaemia, and other brain disorders associated with dementia such as Huntington's disease, Parkinson's disease, normal pressure hydrocephalus or viral infections such as Creutzfeldt-Jakob disease or AIDS.

C The following features provide support for a clinical diagnosis but are not essential inclusion criteria:

1. Early appearance of psychological deficits such as dysphasia, agnosia or some form of apraxia.
2. Evidence on imaging studies that there is indubitable cerebral atrophy, particularly where this can be shown to have increased over a period.
3. A conclusive pathological diagnosis which can be obtained only with the aid of neuropathological studies which show the presence of abundant senile plaques containing amyloid, abundant neurofibrillary tangles with paired helical filaments on electron-microscopic examination and granulovacuolar degeneration.

Exclusion criteria

The dementia is not associated with hemiparesis, visual field deficits, cerebellar symptoms, other focal neurological physical signs, epileptic seizures, severe gait disturbance in the early stages of illness or clear evidence of cerebral infarction. (Such findings are suggestive of multi-infarct dementia.)

Vascular (multi-infarct) dementia

In addition to the inclusion criteria for dementia, the following must be satisfied:

Any three of the following:

A Relatively sudden onset.

B Step-like deteriorating course.

C History suggestive of one or more strokes manifest in sudden attacks of loss of consciousness associated with focal neurological deficits of a transient or lasting character.

D Focal neurological signs and symptoms, such as exaggeration of deep tendon reflexes, extensor plantars, gait abnormalities, or focal disturbances of higher cortical function such as aphasia or apraxia in the presence of relatively good general intellectual preservation.

E Any two of the following:

1. Patchiness of psychological deficits: for example, severe intellectual impairment with relatively well-preserved personality or perservation of some intellectual skills, such as abstract thinking, in the presence of severe memory impairment or failure in simple arithmetical tasks.

2. Emotional lability or paroxysms of inappropriate weeping, laughter or both.

3. Preservation of insight in the presence of indubitable deterioration of intellect.

4. Conspicuous depression or anxiety or both, of fluctuating character.

5. Epileptic fits.

6. Hypertension with diastolic pressure above 100mm Hg.

7. Frequent severe headache and/or dizziness.

8. Broad-based unsteady gait, often with falls in the early stages of the disease.

Secondary dementia

In addition to the inclusion criteria for dementia, one of the following must be satisfied:

A Presence of metabolic or systemic disease, deficiencies or intoxications liable to give rise to interference with cerebral function. The commoner causes of such secondary dementias are hypothyroidism, vitamin B12 deficiency, cranial arteritis, subacute bacterial endocarditis, chronic alcoholism, normal pressure hydrocephalus, hypoparathyroidism, non-metastatic effects of malignant tumours.

B Any cerebral disease such as: Parkinson's disease, normal pressure hydrocephalus, space-occupying lesions (particularly in frontal or temporal lobes), progressive supranuclear palsy, Down's syndrome, cerebral syphilis, chronic traumatic encephalopathy (dementia pugilistica).

C Any form of cerebral viral infection such as: Creutzfeldt-Jakob disease, AIDS, progressive multi-focal leucoencephalitis (commonly associated with Hodgkin's disease or lymphatic leukaemia), subacute sclerosing panencephalitis (due to measles or rubella virus).

D Does not satisfy criteria for vascular (multi-infarct) dementia.

Clouded/delirious state

Any two of the following:

A Change in level of awareness manifest in any three of the following:

1. Slowness and vagueness in thought.
2. Markedly impaired ability to focus and sustain attention and concentration.
3. Faulty comprehension with misinterpretation of surroundings.
4. Periodic excitement or stupor.
5. Incomplete arousal with periodic drowsiness.

B Rapid onset of change in level of consciousness and cognitive function present for less than 6 months.

C Disorientation in two of the following:

1. Time.
2. Place of abode.
3. Place at present time.

D Impairment of recent memory (defects in the recording and recall of recent events.)

E Visual (more rarely auditory) perceptual distortion in the form of illusions or hallucinations of a fearful quality and often delusions of an anxiety-laden or other persecutory nature.

F Marked fluctuation in level of consciousness and cognitive performance.

Note: If a diagnosis clouded/delirious state plus dementia is to be made then the criteria for dementia have also to be satisfied, and the type of dementia specified.

Depressive illness

Criteria A, B and C must be satisfied.

A Depression of mood (feelings of sadness, gloom, hopelessness) described by the patient or inferred by others from the patient's speech, facial expression and general behaviour.

B Loss of pleasure and interest in most activities and pastimes.

C In addition, four of the following features should be present:

1. Loss of self-esteem and confidence.
2. Sustained fatigue, loss of drive, energy.
3. Remorse over minor or imaginary misdeeds and mistakes in the past.
4. Groundless or disproportionate pessimism about the future.
5. Marked decrease in effectiveness and productivity at work and/or at home (observable by others).
6. Loss of libido after relatively normal sexual functioning for age.
7. Social withdrawal, self-isolation.
8. Frequent attacks of tearfulness and crying.
9. Marked weight loss (when not dieting) or marked decrease in appetite. (More rarely increase in weight and appetite.)
10. Insomnia nearly every night (more rarely hypersomnia).
11. Sustained impairment in ability to think, concentrate or make decisions.
12. Feelings of worthlessness or guilt or remorse (nearly every day) without objective foundation.
13. Recurrent ideas about suicide and centring on potentially dangerous or lethal forms of self-injury.
14. Depression at peak intensity in mornings.
15. Early morning awakening (2 or more hours before normal time).
16. Marked psychomotor retardation or agitation (manifest at clinical examination or observed by others).
17. Stable and effective personality prior to and between attacks of illness.
18. One or more previous attacks of depression followed by complete recovery or good remission.
19. Good response to somatic antidepressant treatment (tricyclic components, MAOIs or ECT) in previous attacks.
20. Delusions of guilt or of serious or incurable physical disease.

21. Delusions of persecution, pubishment or deserved retribution.

22. Auditory hallucinations (more rarely visual) with depressive content.

Exclusion criteria

A Not associated with psychiatric features of an organic nature (clouding/delirium, consistent memory impairment, dementia).

B Not associated with symptoms diagnostic of a schizophrenic or paranoid psychosis.

CAMDEX severity guidelines

The four syndromes described are intended as guidelines for the gradation of dementia. As there is considerable variation in the range of features manifest, the criteria have to be used for the present in a flexible manner.

Minimal

Limited and variable impairment in acquisition of new information and in recalling recent events.
An increased tendency to misplace and lose possessions.
Minor and variable errors in orientation.
Some blunting in the capacity to follow or pursue a reasoned argument and to solve problems.
Occasional errors (but of slowly advancing frequency) in occupational tasks and/or housework. Errors of judgement on occasion in professional or highly skilled tasks or socially responsible roles requiring difficult decisions or choices.
Self care unimpaired.
Emotional life and responses well preserved.
Clinical examination usually yields negative results except for manifest anxiety when asked to carry out demanding tasks.

Mild (early) dementia

Difficulty in acquiring new information and recalling recent events. Belongings are therefore lost or misplaced and information recently imparted intermittently forgotten or totally lost.
Orientation as regards the date, day of the week, time and place is impaired to a limited extent or in a patchy and inconsistent manner.
Impairment is evident in activities demanding problem-solving or reasoning.
Speech shows mild defect in respect of clarity of meaning
Defects in knowledge or names of prominent figures important events, simple geographical information
Impairment of skills in daily living, errors and confusion of tasks in everday work, mistakes in housework, cooking (inappropriate ingredients or other errors). More conspicuous errors of judgement

and inappropriate conduct in those in professional, highly skilled or socially responsible activities.

Self care mildly impaired or not at all. There may be occasional errors in dress, and a limited decline from usual standards of tidiness and cleanliness.

Emotional responsiveness may be well retained or mildly impaired according to the type of dementia. There may be blunting or lability of emotion or both.

Clinical examination at this stage shows the social facade well preserved, but systematic enquiry reveals indubitable cognitive deficits and emotional or personality changes.

Moderate dementia

Severe impairment in the retention and the retrieval of new information and recently experienced events and activities. Recent events are rarely remembered and then usually in a transient manner. Well learned or very familiar material may be better retained but also defective.

Amnesia for recent events which may be associated with confabulation.

Impairment for most or all indices of orientation.

Capacity for reasoning and problem-solving severely impaired.

Language unclear or incoherent but not invariably to a marked extent.

Competence at work and in daily living severely affected. Unable to function independently as regards work, housework, shopiing, handling money.

Inability to dress or eat meals unaided partly or intermittently affected.

Marked impairment in self-care, severe deterioration in personal standards of cleanliness and methods of eating and intermittent incontinence of sphincters.

Clinical examination reveals indubitable dementia though limited aspects of "cognitive function" (personality and also language and certain well established skills such as musical ability) may be relatively intact.

Severe dementia

Severe impairment of memory. No new information or learning or recent experiences retained. Evidence for islands of memory may be manifest. Capacity for recalling or retrieving remote memories also severely impaired. Confabulation to amnestic gaps rare at this stage but may be manifest at times in gifted and intelligent subjects.

All indices of orientation severely impaired.
Capacity for reasoning and problem-solving is lost.
Speech markedly incoherent and comprehension grossly impaired or absent.
Incapable of independent existence. Cannot undertake tasks requiring any measure of skill and coordination. Unable to dress, wash, feed or look after self.
Information regarding prominent political and other figures, current events and simple geographical knowledge largely or completely obliterated.
Fleeting or variable delsional beliefs may be present.
Failure to recognise close relatives; may be unable to identify own mirror images.
Incontinence of urine and faeces almost invariable at this stage.
Emotional poverty, apathy and inertia.
Clinical examination confirms global and advanced dementia.

The criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association - NINCDS-ADRDA (McKhann et al 1984)

Dementia syndrome

Dementia is the decline of memory and other cognitive functions in comparison with the patient's previous level of function as determined by a history of decline in performance and by abnormalities noted from clinical examination and neuropsychological tests. A diagnosis of dementia cannot be made when consciousness is impaired by delirium, drowsiness, stupor, or coma or when other clinical abnormalites prevent adequate evaluation of mental status. Dementia is a diagnosis based on behaviour and cannot be determined by computerised tomography, electro-encephalography, or other laboratory instruments, although specific causes of dementia may be identified by these means.

Criteria for Alzheimer's disease

Alzheimer's disease is a progressive, dementing disorder, usually of middle or late life.

1. The criteria for the clinical diagnosis of PROBABLE Alzheimer's disease include:

dementia established by clinical examination and documented by the Mini-Mental State test, Blessed dementia scale, or some similar examination, and confirmed by neuropsychological tests;

deficits in two or more areas of cognition;

progressive worsening of memory and other cognitive functions;

no disturbance of consciousness;

onset between ages 40 and 90, most often after age 65; and

absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition

II. The diagnosis of PROBABLE Alzheimer's disease is supported by:

progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia);

impaired activities of daily living and altered patterns of behaviour;

family history of similar disorders, particularly if confirmed neuropathologically; and laboratory results of:

normal lumbar puncture as evaluated by standard techniques,

normal pattern or nonspecific changes in EEG, such as increased slow wave activity, and

evidence of cerebral atrophy on computerised tomography with progression documented by serial observation.

III. Other clinical features consistent with the diagnosis of PROBABLE Alzheimer's disease, after exclusion of causes of dementia other than Alzheimer's disease, include:

plateaus in the course of progression of the illness;

associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional or physical outbursts, sexual disorders, and weight loss;

other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder;

seizures in advanced disease; and computerised tomography normal for age.

IV. Features that make the diagnosis of PROBABLE Alzheimer's disease uncertain or unlikely include:

sudden apopleptic onset;

focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and

seizures or gait disturbances at the onset or very early in the course of the illness.

V. Clinical diagnosis of POSSIBLE Alzheimer's disease:

may be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course;

may be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia; and

should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

VI. Criteria for diagnosis of DEFINITE Alzheimer's disease are:

the clinical criteria for probable Alzheimer's disease and histopathologic evidence obtained from a biopsy or autopsy.

VII. Classification of Alzheimer's disease for research purposes should specify features that may differentiate subtypes of the disorder, such as:

familial occurrence;

onset before age of 65

presence of trisomy 21

coexistence of other relevant conditions such as Parkinson's disease.

APPENDIX 2

Cognitive scales

Mini Mental State Examination

Day, date, month, year, season, county, town, streets, floor, place, name objects (2)*, ifs, registration (3)*, serial sevens (5), recall objects (3)*, read: close eyes, pentagon, write sentence*, paper folding (3)*.

* items are those not included in CAMCOG

Information-Memory-Concentration scale

Items corresponding to the 10 most discriminating items of Roth and Hopkins (1953) Information-Memory-Concentration task, which is equivalent to the Abbreviated Mental Test (Hodkinson 1972)

Age, time now, recall address, year, place, recognition of two persons, date of birth, year of world war 1, name of present monarch, count backwards (20 to 1).

1 score per item for the Abbreviated Mental Test, count backwards scores 2 in CAMDEX.

Information/Orientation subscale of CAPE

age, date of birth, address, town, prime minister, president of the US, colours of the union jack, day, month, year, name, place.

Extended MMSE

(Cognitive scale complying with MRC guidelines)
Complex instruction - look at ceiling and then at floor.
Read instruction - If you are older than 50, put your hands above your head.
Abstract thought - In what way are a plant and an animal alike.
Remote memory - Who was Mae West.
Remote memory - Who was the famous flier whose son was kidnapped.

CAMCOG

Orientation = day, date, month, year, season, county, town, streets, floor, place.

Language

Comprehension= nod, touch, ceiling, tap, hotel, village, radio, 2 read items.

Expression= hammer, chemist, bridge, opinion, naming objects, fluency, ifs, address.

Memory

Remote= world war 1, world war 2, leader germans, russians, Mae West, Lindbergh.

Recent= queen, heir, prime minister, recent news.

Learning= recall pictures, recognise pictures, recall address.

Attention = count backwards, serial sevens.

Praxis = copying pentagon, spiral, house, clock, envelope, wave demonstrating cutting and brushing teeth.

Abstract thinking = 4 similarity questions.

Perception = identifying coins, recognising faces, recognising familiar objects from unusual angles recognising types of people.

60 items, score of 107.

Items corresponding to the Blessed Dementia Scale (1968)

Changes in performance of everyday activities.

1. Inability to perform household tasks.
2. Inability to cope with small sums of money.
3. Inability to remember short list of items.
4. Inability to find way about indoors.
5. Inability to find way about familiar streets.
6. Inability to interpret surroundings.
7. Inability to recall recent events.
8. Tendency to dwell in past.

Changes in habits

9. Eating.
10. Dressing.

11. Sphincter control.

Items relevant to the Hachinski score (1975)

Abrupt onset.

Stepwise deterioration.

Fluctuating course.

Nocturnal confusion.

Relative preservation of personality.

Depression.

Somatic complaints.

Emotional incontinence.

History of hypertension.

History of strokes.

Evidence of associated atherosclerosis.

Focal neurological symptoms.

Focal neurological signs.

The National Adult Reading Test (Nelson and McKenna 1975)

Chord, ache, depot, aisle, bouquet, psalm, capon, deny, nausea, debt, courteous, rarefy, equivocal, naive, catacomb, gaoled, thyme, heir, radix, assignate, hiatus, procreate, subtle, gouge, gist, superfluous, simile, banal, cellist, quadruped, facade, zealot, drachm, aeon, placebo, idyll, abstemious, detente, puerperal, aver, gauche, topiary, leviathan, beatify, prelate, sidereal, demesne, syncope, labile, campanile.

Derived scales for tentative localised areas of the brain (after Taylor et al 1980)

Frontal = WORLD backwards, serial sevens, day, month, year, place.
Temporal = registration, recall 6 items, recall of 3 items, World War 1, World War 2, leader of germans, leader of Russia, Mae West, Lindbergh, copying spiral, house and pentagon.
Temporoparietal = Complex instruction with paper and envelope, carry out written instructions.
Dominant frontal = no ifs ands or buts.
Dominant temporal = name 6 items, name watch, pencil, winder, observation of peculiar use of terms.
Contralateral parietal = copying hand figures, calculation items, writing a sentence.
Dominant parietal = carrying out instructions, nod head, touch right ear with left hand, tap shoulders.

APPENDIX 3

Resume of the report from the Medical Research Alzheimer's Disease Workshop (Wilcock et al 1989)

This workshop was held in New college Oxford on the 16th and 17th September 1986. The aim of the workshop was to "see whether workers in Britain in the field of dementia research could agree on guidelines for the minimum data which should be collected in clinical and pathological studies on patients with presumed Alzheimer's disease and dementia:

1. to allow data collected from different reserach projects to be more readily compared and pooled; and,

2. where data collected in different research projects apparently conflict, to allow the testing of basic hypotheses to account for such conflict.

It was emphasised the the recommendations did not form criteria to derive the clinical diagnosis of dementia or Alzheimer's disease.

Clinical information

Basic demographic information such as age, last occupation, current residence, educational level and handedness.

Historical information from informant including data and place of interview; family history, first degree relatives affected by dementia; past medical history - epilepsy, meningitis, mental handicap, head injury, stroke, transient lateral weakness, treated hypertension; past psychiatric history - treatment by psychiatrist, treatment for depressive illness or chronic schizophrenia; evidence of cognitive impairment and personality change - this includes a series of questions from the CAMDEX; delusions; onset of problems, duration and course; depression; alcohol; drugs.

Examination of subject. Cognitive assessment - much of this section is from CAMCOG, but there are several items which are different, although equivalent items are included in CAMCOG.

Psychiatric assesment of mental state to establish presence and degree of any depression or paranoid ideas.

Physical examination - pulse rate and rhythm, systolic and diastolic blood pressure, hemiparesis with reflex changes, gait abnormality, deafness, visual handicap, hemianopia, abnormal involuntary movements, rigidity, dysarthria, physical disability interfering with motor ability. Current medical diagnoses.

Neuropathological assessment should include :

sections of temporal lobe containing three temporal gyri, hippocampus, parahippocampal gyrus at level of lateral geniculate body;

sections of representative frontal lobe eg superior frontal gyrus;

sections of representative parietal lobe eg superior parietal lobule.

Quantification of neurofibrillary tables in the neocortex and/or hippocampus and assessment of senile plaques in neocortex recommended for series of random fields from the above. Details of stains are given.

APPENDIX 4

International Classification of Diseases (Ninth Edition)

Codes which might contain demented individuals

290 senile and presenile organic psychotic conditions

290.1 senile dementia simple

290.4 arteriosclerotic dementia

294 other organic psychotic conditions

330 other cerebral degeneration

331 Alzheimer's Disease

331.2 senile degeneration of the brain

430-438 cerebrovascular disease

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