

**THE PREVALENCE OF DEMENTIA AND ITS SUBTYPES IN AN ELDER
COMMUNITY POPULATION**

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ABSTRACT

Background Epidemiological studies of dementia subtypes have revealed widely varying distribution rates. There are almost no published community prevalence data for dementia with Lewy bodies (DLB) or the frontal lobe dementias (FLD).

Aims To identify the distribution of dementia subtypes in a representative community population of older people.

Method People aged 65 years and older in randomised enumeration districts in Islington, north London, were screened using a reliable and valid questionnaire. People screened as having dementia were assessed in detail and diagnoses were made according to standard diagnostic criteria. Associations were examined between demographic variables and type of dementia.

Results Of 1085 people interviewed, 107 (9.86%) met screening criteria for dementia. Diagnoses were made for 72 people (67.3%). Distribution of subtypes varied according to the criteria used, the best-validated criteria yielding: Alzheimer's disease 31.3%; vascular dementia 21.9%; DLB 10.9%; and FLD 7.8%. Dementia, and particularly the vascular subtype, was over-represented in people born in Africa or the Caribbean.

Conclusions Alzheimer's disease is confirmed as the most common cause of dementia in older people, followed by vascular dementia. However, DLB and FLD occur sufficiently often to be seen frequently in clinical practice and should be

incorporated into future editions of standard diagnostic criteria. Given the differing rates of subtypes according to the diagnostic system used, it is desirable that a degree of consensus be reached on the diagnostic criteria to be employed in future epidemiological research. The excess of dementia in older adults from non-UK countries needs to be addressed.

OUTLINE OF THESIS

This thesis is divided into six chapters. The first three chapters provide the context for the research project which formed the basis for the thesis. In chapter 1, I discuss in detail the demographics of ageing and the impact of increasing age in health, social and personal terms. I also define and describe the key concepts of classification, diagnosis and epidemiology and their historical as well as current uses in psychiatry, specifically psychiatry of older people. Finally, I provide a critique of current methods of classification.

Chapter 2 is concerned with the concept of dementia, including definitions, historical changes in the concept, and prevalence data. I address each of the most widely diagnosed subtypes of dementia – Alzheimer's type, vascular, dementia with Lewy bodies and frontal dementias – and discuss what is currently known about the relative distributions of the subtypes. Chapter 3 draws together elements of the first two chapters and focuses on the existing methods of diagnosing individual subtypes of dementia.

Chapters 4 to 6 describe the epidemiological study forming the basis of the thesis. In chapter 4 I report the methods, including the identification of the study population, case definition, the evaluation tools used and the various diagnostic criteria employed in each case to arrive at a diagnosis. Chapter 5 reports results from stages 1 and 2, incorporating the prevalence of dementia overall and the distribution of subtypes according to different diagnostic systems, as well as associations between diagnoses and such variables as age, gender, country of

birth and place of residence. In chapter 6 I discuss the implications of the results, both for diagnostic systems and for future research and clinical policies.

The study was part of the Islington Study of older people in the community. My supervisors for the thesis were Dr Gill Livingston, Reader in Psychiatry of Older People, and Professor Cornelius Katona, Professor of Psychiatry for the Elderly, both in the Department of Psychiatry and Behavioural Sciences at University College London. I wrote the protocol for stage 2 of the study and obtained ethical approval from the local Ethics Committee. I assisted with the screening of the population in stage 1 and performed all the evaluations of cases in stage 2. Dr Livingston and I made diagnoses jointly by reviewing each case and applying diagnostic criteria. I performed all the statistical analysis and wrote the initial paper reporting the results (Stevens et al, 2002) and this thesis.

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Chapter 1

Ageing, disease and diagnosis

Before describing the study which forms the basis for this thesis, I regard it as necessary to 'set the scene' by outlining the context in which the study was conducted. Changes in population demographics over the years, evolving concepts of disease and illness, and refinements of the methods by which diagnostic entities are defined and classified, all necessarily influence the type of research which is done and the manner in which it is conducted. I propose in this chapter to discuss the nature and impact of the changes in human life expectancy, the purpose of epidemiological research and classification, the historical basis for concepts of health and illness, and types of classification previously and currently in use.

1.1 The ageing population

The mean life expectancy for human beings has been increasing in irregular leaps for the last one hundred thousand years. In 1600, for example, women of the aristocracy could expect to live into their early thirties, and this had increased to the early fifties by 1900. At present, women reaching the age of 50 years can expect to live another 30 years, men another 26 (Kendrick & Warnes, 1997). The average age of the world's population is increasing owing to a combination of increasing life expectancy and falling birth rates. The proportion of the population aged 65 and older currently stands at 15% for the developed world and 5% for

less developed countries. These figures are projected to rise to 25% and 15% respectively by 2050 (United Nations, 1997). In the United Kingdom, the proportion of the population aged over 60 is expected to reach 29.1% by 2031 (OPCS, 1991). Over the last 20 years, population projections in the United Kingdom and United States are thought to have underestimated the number of survivors to advanced old age (Olshansky, 1988), and the proportion of people aged 80 and over is anticipated to rise to 32% of the over-65 population by 2050, as compared with 13% in 1950 (Kendrick & Warnes, 1997). Even with regard to the next ten years, there is a predicted increase of 14% in the number of people in the UK aged 80 and older, to 2.3 million people (Audit Commission, 2000).

1.2 The impact of increasing age

One result of an increase in absolute numbers and proportion of older people is that those disorders of health which increase in prevalence with age are becoming relatively more important and represent a significant public health problem (Jorm, 2000). These disorders may be physical or mental, or combinations of both. For example, there is an association between increasing age and physical disability (OPCS, 1988), and depression has been shown to be associated with physical disability in old age (Griffiths et al, 1987), as in other age groups. Consultation rates with a general practitioner have been found to increase with advancing age, with visits to patients aged 75 and older constituting over 40 per cent of general practitioners' home visits (Mann, 1997). Similarly, demands on social services are likely to rise with increasing numbers

of people living to older age. For example, Livingston et al (1990a) found that people who were very old, living alone or limited in activity were most likely to be provided with home help, meals-on-wheels or community nurses, and Mann et al (1984) reported an increasing trend towards residential care for older adults with dementia, depression and physical disability.

1.3 Epidemiology

Epidemiology can be defined as the population-based, quantitative study of distribution, determinants and control of disease, and may be considered to be the basic science of public health medicine (Lewis & Mann, 1992). It has three main functions:

- a) the description of the amount and distribution of disease in a population;
- b) the investigation of specific aetiological hypotheses (analytical epidemiology);
- c) the determination of public health policy and the distribution of resources, according to cost-benefit calculations.

Epidemiological studies of mental health problems in older people have usually been carried out using either case-control or descriptive studies. The latter have included cross-sectional surveys and longitudinal studies. The boundaries of the population at risk, or denominator (Mann, 1997), have varied, and even within community populations the sub-populations under investigation may differ according to such factors as age range, whether or not residential and nursing homes are included, and method of identification of the population. Examples of the latter factor include census lists, the electoral roll (Lindesay et al, 1989) and

lists obtained from service providers. These methods have their limitations, as the census does not provide names and addresses for people, not everyone is registered on the electoral roll and it does not provide information about age groups, and lists from providers such as social services will necessarily yield an unrepresentative population. As approximately 95% of people in the United Kingdom are registered with general practitioners (GPs), primary care practices can also be used for recruitment (Brayne & Calloway, 1989; Copeland et al, 1987), although the patient lists from these practises may often be out of date (Livingston et al, 1990b). Perhaps the best method of defining a representative population is through direct house-to-house contact within clearly defined enumeration districts, which in the United Kingdom represent the smallest unit of the national census data publicly available (Craig & Boardman, 1991). An example of a study employing this approach is the Gospel Oak Study (Livingston et al, 1990b). Disadvantages of this method include the amount of manpower required, the time needed and the necessity of informing and obtaining consent from local agencies.

Once the study population has been defined, standardised, reliable psychiatric interview instruments such as the Geriatric Mental State Schedule (GMS; Copeland, 1976) are used to allow reproducibility. The time required to complete interviews using such instruments can, however, limit their effectiveness for assessing the large numbers of people required for epidemiological research, and efficiency may be improved by means of a two-stage approach (Cochran, 1977). This involves employing a brief, cost-effective screening instrument to

detect depression and anxiety caseness (for example, the General Health Questionnaire; Goldberg & Williams, 1988) to interview the population under investigation (stage one), followed by longer interviews with individuals identified as positive 'cases' (stage two). In a paper investigating the efficiency of the two-phase design, Newman et al (1990) suggested that under certain conditions, this approach has the potential to increase the efficiency of an epidemiological study with regard to case detection and point prevalence estimation. The authors concluded that the ideal circumstances were those in which the disorder under investigation was rare, the screening test had high sensitivity and specificity, and the costs of recruitment and screening were relatively low compared to that of diagnosis. The last factor was viewed as potentially the most significant. Deming (1977), however, has pointed out the increased complexity of data analysis, in particular the estimation of the standard error of the prevalence rate, as a result of the more elaborate sampling method.

'Caseness' has been defined by Copeland (1990) as 'a collection of symptoms which a psychiatrist would recognise as a characteristic and abnormal mental state for which intervention would be appropriate if it were available'. This definition, however, implies a degree of subjective judgement on the part of the researcher, and clarification of the concept of case definition is required.

1.4 Principles of case definition and classification

Classification has been viewed as a fundamental human cognitive activity underlying concept formation, a 'cutting up of the environment... [so that] non-

identical stimuli can be treated as equivalent' (Rosch et al, 1976). Jablensky (1988) defines classification as 'the process of creation of categories', and identifies three ways of classifying systems of classification themselves:

1. According to taxonomic strategy

This may be *phyletic*, grouping together members of a category according to a shared primary essence (such as the species concept in Darwinian evolutionary theory), or *phenetic*, in which groups are defined according to the maximum number of shared characteristics, chiefly physical.

2. According to the type of cognitive operation involved

This includes the *empirical* approach, which is limited to observable facts, and the *inferential* approach, which hypothesizes about underlying mechanisms.

3. According to the result of the classificatory strategy

The classification may be *monothetic*, in which categories differ from each other on the basis of a value assigned to a single variable, or *polythetic*, in which members of a category share a large proportion of their properties but are not necessarily identical in a single one.

Most classificatory systems in medicine employ the empirical approach, and assign cases to categories according to polythetic standards. This is especially true for classification systems in psychiatry, a specialty in which histopathological

abnormalities are seldom detectable ante-mortem, if at all.

1.5 Diagnosis

Feinstein (1972) has identified three main purposes of classification in medicine:

- a) denomination (the giving of a name to a phenomenon);
- b) qualification (the associating of qualifying and descriptive features to that phenomenon);
- c) prediction (making statements about outcome).

The concept of 'diagnosis' may be seen as the assigning of an individual to a category which has been identified through the processes of denomination and qualification, and possibly, though not necessarily, prediction. The word 'diagnosis' itself arises from the Greek root meaning 'to recognise', which emphasises the importance of grouping individuals according to recognisably shared features. The consensus required for consistency in such grouping has resulted in an innate conservatism in diagnostic systems, so that the diagnostic categories formulated by the Greek physician Galen in the first century AD persisted until well into the eighteenth century. The Swedish taxonomist Carl von Linné was one of the first to suggest an alternative system of diagnosis and classification, and his *Genera Morborum* (1742) included psychiatric as well as physical diagnoses.

Pinel's *Nosographie Philosophique* (1803) proposed a classification system for mental disorders which was based on the naturalistic description of observable symptoms. This employed empirical and polythetic approaches as defined in

section 1.4., although there were inferential elements in that the symptoms were equated with disease species. Following this, the inferential method rose to prominence in the systems of Heinroth (1818) and Meynert (1884), which were based on speculations about the aetiology of psychiatric disorders and favoured psychological and organic bases respectively. It was the work of Griesinger (1861), however, which laid the foundation for modern psychiatric diagnostic classification by emphasising the importance of the evolution of symptoms over time, and by referring to syndromes rather than diseases, the former term describing a constellation of signs and symptoms, the latter aetiologically defined entities.

The first truly international disease classification system appeared in 1855 and was promoted as a nomenclature of the causes of death. It was adopted in a revised form by the newly-created World Health Organisation (WHO) in 1948 and renamed the International Classification of Diseases (ICD). This was published in successively modified editions, culminating in the tenth (ICD 10; WHO, 1992) which is currently in use. Simultaneously, in the United States, the Diagnostic and Statistical Manual (DSM), while employing an inferential approach to classification influenced by psychodynamic theory in its first two editions, adopted in its third and subsequent editions the principle of 'operationalised' criteria for diagnosis, based on the St Louis/Feighner criteria (Feighner et al, 1972) and the Research Diagnostic Criteria (Spitzer et al, 1978).

Both ICD and DSM in their current forms employ operationalised criteria, according to which syndromes are described in terms of their phenomenological

manifestations independently of the putative aetiologies (the so-called 'atheoretical' approach). Strict inclusion and exclusion criteria are used to assign individuals to discrete categories. Both systems eschew the use of the term disease and refer to *disorder*, which is defined in ICD as 'a clinically recognisable set of symptoms or behaviour associated in most cases with distress and with interference with personal functions' (WHO, 1993), and in DSM as 'a clinically significant behavioural or psychological syndrome or pattern that occurs in an individual and that is associated with present distress or disability' (American Psychiatric Association, 1994).

1.6 Advantages and disadvantages of operationalised criteria

Operationalised diagnostic systems define categorical entities by means of their unambiguous format. This enables them to be used easily by clinicians, to be incorporated into structured interview schedules which can be applied even by lay interviewers (Robins et al, 1988), and to improve inter-rater reliability and communication between researchers (Regier et al, 1994). The absence in these systems of dogmatic assertions about aetiology, based on theoretical models, means that they allow hypotheses to be generated which are falsifiable, in keeping with Popper's (1968) requirement for scientific hypotheses.

The rigidity of the boundaries of each category may, on the other hand, lead to a reduction in the validity of the entities described (Farmer, 1997). Given that categorical definitions correspond to the degree of severity of disorder seen in specialist psychiatric practice, it is likely that a range of symptoms found in the

population are not adequately described by these systems. This problem may be seen in the context of the ancient debate on the nature of disease between the Hippocratic and Platonic schools of thought. The Platonic view was that diseases should be divided into distinct, ideal types (using phyletic taxonomy as described in section 1.4), whereas the Hippocratic approach regarded disease states as existing on a continuum with premorbid characteristics. The latter model implies that the disease cannot be separated from the person suffering from it, and by extension from his or her life experiences and social circumstances. This idea has led to the introduction of dimensional or multi-axial elements into diagnosis; for example, in DSM III and its successors, DSM III-R and DSM IV, individuals are classified according to five axes: axis I, the main psychiatric disorder; axis II, personality disorders; axis III, concurrent physical health problems; axis IV, psychosocial stressors; and axis V, the highest level of functioning in the previous year. This multi-axial approach does not, however, significantly alter the nature of DSM, since operationalised criteria are still used to identify the disorders in axes I and II.

1.7 Conclusion

In summary, the projected rise in both the absolute and relative numbers of people living to old age is likely to place an increased burden on both health and social services. The effective planning of these services is dependent on representative epidemiological data about disease prevalence in this age group. The generation of these data in turn requires the accurate diagnosis and

classification of disorders. At present, the diagnostic systems in common use employ operationalised criteria to assign cases to discrete categories. While this approach shows advantages in the form of ease of use and reliability, its relative inflexibility may result in a loss of validity. The validation of the existing classification systems with regard specifically to the diagnosis of dementia, will be discussed in chapter 3.

Chapter 2

Dementia: definitions, prevalence and subtypes

2.1 Definitions of dementia

The word 'dementia' has historically been used in two contexts: to label a group of specific disease entities, and to refer to the concept of a clinical syndrome with numerous different causes (Lishman, 1997). Several attempts have been made to reach a consensus on the use of the word. For example, Schulte (1989) recommends restricting the term to denote a characteristic clinical syndrome, without presumption of an underlying organic cause (in keeping with the atheoretical approach discussed in section 1.6), and as such rejects the use of neuropathological criteria to define it.

The Royal College of Physicians has defined it as:

'the acquired global impairment of higher cortical functions including memory, the capacity to solve the problems of day-to-day living, the performance of learned perceptuo-motor skills, the correct use of social skills and the control of emotional reactions, in the absence of gross clouding of consciousness. The condition is often progressive though not necessarily irreversible' (Royal College of Physicians, 1982).

DSM IV states that 'the essential feature of a dementia is the development of multiple cognitive deficits that include memory impairment and at least one of the following cognitive disturbances: aphasia, apraxia, agnosia, or a disturbance in executive functioning. The cognitive deficits must be sufficiently severe to cause

impairment in occupational or social functioning and must represent a decline from a previously higher level of functioning' (APA, 1994). (The last clause is superfluous as the *development* of cognitive deficits has already been specified as a requirement.) Both of these definitions assign the status of a *syndrome* to the concept, defining it in terms of a collection of symptoms and signs, with no speculation as to aetiology.

ICD 10 defines dementia as 'a syndrome due to disease of the brain, usually of a chronic or progressive nature, in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language and judgement. Consciousness is not clouded. Impairments of cognitive function are commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behaviour, or motivation' (WHO, 1992). Although the concept of syndrome is again invoked, the statement that it is 'due to disease of the brain' reveals an assumption about aetiology, distinguishing this definition from the preceding two. The ICD and DSM systems differ further in that the former requires the symptoms to have been present for at least six months, whereas the latter does not specify a minimum duration.

The DSM definition goes further than those of the Royal College and ICD 10 in emphasizing the importance of the impact of the disorder on social or occupational functioning, bringing to mind the Hippocratic idea of the inseparability of a disease from the person it affects (section 1.6). However, in DSM IV, memory disturbance is an essential element of the definition whereas in

the other two, it is only one of several possible examples of impaired cognitive function. This narrowness has implications for the diagnosis of disorders in which memory impairment may be absent but which nonetheless fulfill the other criteria, such as frontal lobe dementia (section 2.5.4).

2.2 History of the dementia concept

The word 'dementia' is derived from the Indo-European root *MN, which is also the source of 'mind' and 'memory'. The historical roots of the modern concept of dementia have been reviewed by Berrios and Freeman (1991). The first recorded appearance of the word in the English language was in the Oxford English Dictionary in 1644. However, the Latin poet Lucretius in the first century BC described a condition of being 'out of one's mind', the name of which may be translated as dementia (Berrios & Freeman, 1991). A chapter on dementia (though the condition was not named as such) entitled 'De Memoriae Detrimento' appeared in the first textbook of neurology, *De Cerebri Morbis*, by Jaso de Pratis (1549).

Descriptions of conditions recognisable as dementia appear throughout Western literature. In *As You Like It* (act II scene VII), Shakespeare describes seven stages of man's life, the final stage ending 'In a second childishness and mere oblivion, sans teeth, sans eyes, sans taste, sans everything.' Shakespeare's most famous portrayal of madness is in *King Lear*, whose ageing king makes increasingly unwise judgements and is prone to episodes of disorientation and

mood disturbance. Furthermore, he acknowledges his own failures of recall and recognition: 'I fear that I am not in my perfect mind;/ Methinks I should know you, and know this man;/Yet I am doubtful; for I am mainly ignorant/ What place this is; and all the skills I have/ Remembers not these garments; nor I know not/ Where I did lodge last night. Do not laugh at me.' (Act IV, scene VII). It must be noted that there is disagreement about the nature of Lear's madness, and acute confusion and depression have been proposed as alternative explanations.

In Jonathan Swift's *Gulliver's Travels*, first published in 1726, the protagonist says of the 'Immortals' of Luggnagg: 'When they (come) to fourscore years ... they have no Remembrance of anything but what they learned and observ'd in their Youth and middle Age, and even that is very imperfect ... In talking they forget the common Appellation of things, and the names of Persons, even of those who are their nearest Friends and Relations. For the same reason they can never amuse themselves with Reading, because their Memory will not serve to carry them from the beginning of a Sentence to the end ... neither are they able ... to hold any Conversation (farther than a few general Words)...'. Ironically, Swift himself appears to have suffered from dementia (Lewis, 1993): in 1738 he wrote, 'I have entirely lost my memory', and four years later he was declared incompetent, his caretakers reporting that '[He] hath for these nine months past, been gradually failing in his memory and understanding and is of such unsound mind and memory that he is incapable of transacting any business, or managing, conducting, or taking care either of his estate or person.'

Until the end of the seventeenth century, conditions of cognitive and behavioural

deterioration were referred to using terms such as amentia, imbecility, morosis, fatuitas, simplicity, carus, idiocy, dotage and senility (Berrios, 1994). Thomas Willis (1684) described an affliction called 'Stupidity or Foolishness' which entailed 'a defect of the intellect and judgement', was 'a disease of the head or brain', and resulted either from hereditary transmission or from ageing. Throughout the early part of the eighteenth century, the term dementia was in common use, and appeared in Blanchard's *Physical Dictionary* (1726), where it was considered equivalent to 'anoea' meaning 'extinction of the imagination or judgement'. Pinel (1801) recognised the term, as did Esquirol (1814), who distinguished acute and chronic types, the former including what is now called delirium and resulting from fever, haemorrhage and metastasis, the latter being caused by melancholia, mania, epilepsy and masturbation, among other factors. Until the early 1800s, dementia was not defined in terms of cognitive deficit, nor was it associated with a particular age group (Berrios, 1987). By the mid-nineteenth century, however, the clinical boundaries of the concept were defined sufficiently rigorously to separate it from other psychiatric disorders (Kendrick & Warnes, 1997).

After 1898 it became possible to visualise the microscopic structure of the post-mortem brain following the development of the silver impregnation technique by Cajal (Adams, 2000). This resulted in the diversification of diagnoses based on neuropathological findings, as discussed in section 2.4. The idea persisted that senile dementia (i.e. dementia occurring in old age) was a severe form of normal ageing (Simkowitz, 1924), but the findings of Sjogren (1956) and others, that

similar histopathology appeared in the brains of older people with dementia to that in younger patients, led to the gradual abandonment of the senile-presenile dichotomy.

2.3 Prevalence of dementia

There have been over one hundred published studies on the community prevalence of dementia (Ineichen, 2000). Reported prevalence rates in people aged 65 and over derived from community studies show wide variation. Kay et al (1964) identified a rate of 5.6% in the first study of its kind; rates of 2.3% (Gurland et al, 1981) to 9.5% (Woo et al, 1998) have subsequently been reported. A meta-analysis of 47 studies reported prevalence rates varying between 0.5-16.3% for mild dementia and 1.1-7.4% for moderate to severe dementia (Jorm et al, 1987). Lobo et al (2000), in a recent comparison of European prevalence studies, found an age-standardized prevalence of 6.4%.

Of the numerous possible factors which may influence the reported prevalence rates in individual studies, the following five are particularly salient:

1. The age of the study population

Dementia is more prevalent the older the age of the population under investigation. Three age-specific meta-analyses of prevalence have been published to date (Jorm et al, 1987; Hofmann et al, 1991; Ritchie et al, 1992).

The findings of these meta-analyses are shown in table 2.1.

Age groups	Prevalence rates from Jorm et al (1987)	Prevalence rates from Hofman et al (1991)	Prevalence rates from Ritchie et al (1992)
60-64	0.7	1.0	0.9
65-69	1.4	1.4	1.6
70-74	2.8	4.1	2.8
75-79	5.6	5.7	4.9
80-84	11.1	13.0	8.7
85+	23.6	24.5	16.4

Table 2.1 Prevalence rates from age-specific prevalence meta-analyses (source: Henderson & Jorm, 1998)

Ritchie & Kildea (1995) found a levelling-off of dementia prevalence at the age of 95, and have suggested that the increase in the prevalence of dementia may be 'age-related rather than ageing-related', i.e. that dementia is a disorder occurring within a specific age range and not an inevitable consequence of the ageing process itself. More recently, however, von Strauss et al (1999) reported a 90% increase in dementia prevalence every five years in nonagenarians, and Forsell & Winblad (1997) identified dementia in 46.7% of people aged between 90 and 102 years. Blansjaar et al (2000) reported a dementia prevalence of 88.2% in a sample of 17 people aged between 100 and 104. A widely-accepted rule of thumb is that the age-specific prevalence rate of dementia doubles with each additional five years of age (Cooper, 1997).

2. Ethnicity

Lower rates of dementia compared to those seen in Western European populations have been identified in Chinese (Liu et al, 1998; Wang et al, 2000), Nigerian (Hendrie et al, 1995) and Indian (10/66 Dementia Research Group, 2000) people. In contrast, higher rates have been reported among African-American and Hispanic (Perkins et al, 1997) and Korean (Park et al, 1994) populations. As will be discussed later in this chapter, the relative distribution of subtypes of dementia has been found to differ among different ethnic groups. The relative importance of genetic and socio-cultural factors in accounting for these different findings is unclear, although there is some evidence that, for

example, the gradual adoption by Japan of Western culture has resulted in a corresponding change in the rate of dementia as well as its subtypes (Hatada et al, 1999).

3. The definition of 'community'

Studies investigating the prevalence of dementia in 24-hour care settings (residential and nursing homes) have reported rates of 66% for all such settings (Mann et al, 1984), 17.1% for residential homes (Adolfsson et al, 1981) and 67.4% for nursing homes (Rovner et al, 1990). Study samples which include people in 24-hour care are therefore likely to yield higher dementia prevalence rates than those confined to a more narrowly-defined concept of community comprising people living at home.

4. Gender

There has been conflicting evidence for the relative prevalence of dementia in women and men. A collaborative study re-analysing data obtained in European studies between 1980 and 1990 found that the prevalence of dementia was slightly higher in men than in women before the age of 75, and this was reversed in people over age 75 (Hofman et al, 1991). A similar review of studies carried out in the 1990s reported a higher prevalence in women (Lobo et al, 2000). After adjusting for age, Jorm et al (1987) found no overall gender difference in dementia prevalence, and it is likely that the more common finding of an increased prevalence among women is a result of the greater longevity of women

compared to men.

5. The diagnostic methods used

These will be discussed in chapter 3.

2.4 Impact of dementia

Dementia places a significant burden on not only the person suffering from it, but also his or her caregivers and society as a whole. Mortality has been calculated to be increased in people with dementia compared with the age-matched population as a whole, by a factor of 2.1 in men and 2.3 in women (Witthaus et al, 1999), and this may be an underestimate as mortality figures are often drawn from death certificate data, which seldom list dementia as a cause of death (Lanska, 1998). Indeed, it is only in recent years that dementia has been recognised as a cause of death in its own right. The emotional and financial burden on caregivers of people with dementia has been well-documented, with an increase in psychiatric morbidity in this group (Burns & Rabins, 2000), particularly with regard to depression. Dementia has been revealed as the most expensive psychiatric disorder per sufferer in older people, in terms of formal community care costs (Livingston et al, 1997). The annual net economic cost of dementia has been estimated at \$3.9 billion in Canada (Ostbye & Crosse, 1994) and \$58 billion, including informal costs, in the United States (Max, 1993).

In recent years, the introduction of cholinesterase-inhibiting drugs for the treatment of Alzheimer-type dementia has been a hopeful development, a

number needed to treat analysis indicating that only a small number of patients (3 to 7) need to be treated with these drugs to effect an improvement in symptoms or postpone deterioration in one of them (Livingston & Katona, 2000). Although these medications remain expensive at present, there is some evidence of their cost-effectiveness when compared to standard treatment plans (Neumann et al, 1999; O'Brien et al, 1999). Accurate identification of patient groups which are likely to benefit from these treatments is clearly essential, and in light of the growing evidence that certain non-Alzheimer-type dementias such as dementia with Lewy bodies (DLB) may respond to cholinesterase inhibitors (McKeith et al, 2000), the accurate definition of dementia subtypes and establishment of their prevalences is a priority in dementia research.

2.5 Subtypes of dementia

2.5.1 Alzheimer's disease

2.5.1.1 History

In 1906, the psychiatrist and histopathologist Alois Alzheimer described the case of a 51-year-old woman with progressive cognitive impairment, hallucinations, delusions of jealousy and 'psychosocial incompetence' (Alzheimer, 1907). At post-mortem, she was found to have cortical atrophy, arteriosclerotic changes, plaques and neurofibrillary tangles. Kraepelin (1911) subsequently called this condition 'the presenile dementia of Alzheimer'. Initially there were doubts as to whether the condition was anything other than a variety of 'senile' dementia (Lugaro, 1916). In the ensuing decades, the name Alzheimer's disease was

restricted to a disorder occurring in younger people who developed dementia in the absence of other known aetiology, and although a clinically identical picture was seen in older patients, this was generally attributed either to arteriosclerotic causes (section 2.4.3) or to an ill-defined process of 'senility'. The notion of diagnostically distinct senile and presenile (Alzheimer-type) dementias persisted until the 1970s, although post-mortem studies had begun to reveal identical neuropathology in the brains of older demented people to that seen in 'true' Alzheimer's disease (Tomlinson et al, 1970).

2.5.1.2 Classification

DSM IV names the condition 'dementia of the Alzheimer's type' and includes sub-coding categories specifying whether the disorder is early onset (before age 65), late onset, or accompanied by behavioural disturbance. ICD 10 refers to 'dementia in Alzheimer's disease', a term that assumes a specific aetiology, and includes four types: early onset (before age 65), late onset, atypical or mixed, and unspecified.

2.5.1.3 Prevalence

Alzheimer-type dementia (AD) is the most frequently identified type of dementia in the majority of clinical studies, with reported prevalence rates of 53% (Wang et al, 2000) to 69% (Lobo et al, 2000) in demented patients aged 65 and older and 75% in patients aged 75 and over (O'Connor et al, 1989). In a review of 47 studies conducted over a 40-year period, Jorm et al (1987) noted considerable

differences in the reported prevalence rates and attributed these to methodological variables such as the definition of the disorder, the study design, the characteristics of the sample and methods of assessment and diagnosis. As is the case for dementia overall, there appear to be ethnic differences in the prevalence of AD, and it has been found to represent only 21% of dementia in one Japanese sample (Kiyohara, 1999). Mixed pathology (AD coexisting with another type of dementia) has been identified in 2.5% (O'Connor et al, 1989) to 33.8% (Holmes et al, 1999). AD is consistently found to be more common in women than in men, even after allowing for gender differences in life expectancy, with reported female:male ratios ranging from 1.9:1 (Yamada et al, 1999) to 2.6:1 (Bachman et al, 1992).

2.5.2 Vascular dementia (VD)

2.5.2.1 History

In 1881, Ball and Chambard described 'apoplexies' of organic origin caused by haemorrhage, softening or tumour, usually followed by cognitive impairment (Dening, 1992). Binswanger (Blass et al, 1991) gave the name 'encephalitis subcorticalis chronica progressiva' to a condition in which deterioration in cognitive performance and behaviour was accompanied by diffuse white matter changes with sparing of the cortical parenchyma. Alzheimer (1895) reported cases of dementia with arteriosclerotic brain lesions and Kraepelin included in the sixth edition of his textbook the category of arteriosclerotic dementia. By the second decade of the twentieth century, dementias occurring in the senium were

all considered to be due to cerebral arteriosclerosis (Barrett, 1913) and it was not until as late as the 1970s, with the recognition that the distinction between senile and presenile dementia was an arbitrary and untenable one (section 2.4.1.1), that dementia due to vascular causes became accepted as one of a number of possible explanations for cognitive impairment in patients of any age, rather than the default diagnosis in older adults with intellectual deterioration.

2.5.2.2 Classification

Until the 1970s, the broad term 'arteriosclerotic dementia' was used to describe a deterioration in cognitive function which was, by implication, due to 'hardening' of the cerebral arteries (Adams, 1997). Following the recognition that dementia may be associated with a variety of patterns of cerebrovascular pathology, three broad types of vascular cognitive impairment have been identified (Erkinjuntti, 2000):

1. *Strategic infarct dementia*, in which one or more cerebrovascular accidents occur in clearly identifiable areas of the brain which are known to be involved in specific cognitive mechanisms, and which has a relatively rapid onset.
2. *Multi-infarct dementia*, resulting from a succession of minor ischaemic episodes producing an accumulation of cerebral infarcts.
3. *Subcortical dementia*, in which the white matter of the brain shows multiple small areas of infarction (lacunes) and sometimes diffuse demyelination. When the latter feature is present, the condition is also known as Binswanger's disease or chronic subcortical leucoencephalopathy.

DSM IV does not distinguish between these different types, recognising only the category of 'vascular dementia' and including further coding categories specifying the presence of delirium, delusions, depressed mood or no complications. ICD 10 permits diagnoses of vascular dementia of acute onset (corresponding to the 'strategic infarct' type described above), multi-infarct dementia, subcortical vascular dementia, mixed cortical and subcortical vascular dementia, other vascular dementia, and vascular dementia, unspecified. Both classification systems require similar clinical features including a relatively abrupt onset and step-wise progression of cognitive impairment, a deficit which may be patchy rather than diffuse, relative preservation of insight initially, frequent associated depression, slowing of thought, and physical evidence of stroke disease such as unilateral motor signs.

2.5.2.2 Prevalence

Estimated prevalence rates of vascular dementia have shown wide variation. For example, Kase (1991) reviewed eight studies of dementia subtypes published between 1982 and 1990 and found the prevalence of VD to be 4.5% to 39% of dementias. Most studies have found VD to be less common than AD (Erkinjuntti, 1997), but higher rates of VD than AD have been identified in large community populations in Japan, for example, 48% as opposed to 41% (Shibayama et al, 1986) and, more recently, 43% versus 21% (Kiyohara, 1999). A recent comparison of European studies reported a prevalence for VD of 25%, compared with 69% for AD (Lobo et al, 2000). Gender differences in prevalence are less

clear than for AD, and although a tendency has been demonstrated for higher VD rates in men (Jorm et al, 1987; Rocca & Kokmen, 1999), no significant difference was noted in a large recent study (Yamada et al, 1999).

2.5.3 Dementia with Lewy bodies

2.5.3.1 History

In 1912, the German neuropathologist Friedrich Lewy described spherical intraneuronal inclusions in the brain stems of patients with Parkinson's disease (Lewy, 1912), and these so-called Lewy bodies became one of the hallmarks of the brain stem pathology in Parkinson's disease (Mindham, 2000). Almost half a century after Lewy's report, Lewy bodies were noted in the cerebral cortex of two older New York men, who had presented with dementia and died shortly afterwards with severe extrapyramidal rigidity (Okazaki et al, 1961). Over the next 20 years, 34 similar cases were reported from Japan (McKeith, 2000). The term 'diffuse Lewy body disease' (DLBD) was coined in the late 1980s to describe demented patients whose brains showed widespread Lewy bodies in the neocortex and hippocampus, in supposed contrast to patients with idiopathic Parkinson's disease in which Lewy bodies were thought to be confined to subcortical areas (Dickson et al, 1989; Byrne, 1992). However, cortical Lewy bodies have since been demonstrated in most patients with Parkinson's disease (McKeith et al, 1995). The frequent presence of Alzheimer-type pathology, especially neurofibrillary tangles, in patients with diffuse cortical Lewy bodies (Hansen et al, 1989) led other researchers to use the term 'Lewy body variant of

Alzheimer's disease' (Hansen et al, 1990; Forstl et al, 1993).

Regardless of the terminology, there was growing recognition in the early 1990s of the clinical syndrome observed in patients who would later be shown to have cortical Lewy bodies. This syndrome consisted of a progressive dementia which often showed fluctuation, transient episodes of delirium, well-formed visual hallucinations, spontaneous motor features of parkinsonism, and exquisite sensitivity to the extrapyramidal side effects of neuroleptic drugs (McKeith et al, 1995). Later work has identified further characteristics such as pronounced and early visuospatial impairment (Walker et al, 1997; Gnanalingham et al, 1998). Attempts were made to establish operationalised criteria for the disorder (Byrne et al, 1991; McKeith et al, 1992), and in 1996 the Consortium on Dementia with Lewy Bodies International Workshop adopted consensus criteria for diagnosis (McKeith et al, 1996). These will be discussed in detail in section 3.3.2. At the same workshop, the term 'dementia with Lewy bodies' (DLB) was adopted as the preferred one, describing a clinical syndrome and associated pathology without assuming a causal link between the two.

2.5.3.2 Classification

Neither DSM IV nor ICD 10 include separate categories for DLB or its variant terms. A recent text revision of DSM IV stipulated that cases of DLB should be classified under 'dementia due to other medical diseases specified elsewhere' (APA, 2001).

2.5.3.3 Prevalence

Several studies have been carried out on the prevalence rate of DLB in cases of dementia referred to specialist centres for autopsy. The results are summarised in table 2.2.

Reference	Sample	% with DLB
Forno & Langston (1988)	Consecutive autopsies	4.6
Joachim et al (1988)	Ante-mortem diagnosis of dementia	17.3
Dickson et al (1989)	Ante-mortem diagnosis of degenerative brain disease	12.5
Lennox et al (1989)	Consecutive autopsies	6.9
Burns et al (1990)	Patients fulfilling diagnostic criteria for Alzheimer's disease	12.0
Galasko et al (1990)	Ante-mortem diagnosis of possible/probable Alzheimer's disease	24.7
Perry et al (1990)	Psychiatric hospital patients with dementia	21.5

Table 2.2 The prevalence of DLB in post-mortem studies (source: McKeith et al, 1995)

Ballard et al (1993) diagnosed DLB in 14 of 60 patients with dementia (23.3%) attending a day hospital for older people with psychiatric disorder. A retrospective study of the medical casenotes of 200 patients with dementia by Londos et al (2000) found a clinical prevalence of 24% for DLB. It has been claimed that DLB is the second commonest type of dementia (for example, Robes (2000)). The above studies were, however, carried out on specialised and unrepresentative samples. In 2001, Yamada et al reported on a prevalence study of dementia and its subtypes in 3,715 people aged 65 and older living in a rural town in Japan. This study was the only one published prior to the paper which reported my results (Stevens et al, 2002) which had examined the prevalence of DLB in a community sample. The prevalence rate in the Yamada study was 0.1%, giving a distribution rate for DLB of 2.63% of dementias.

Subsequent to Stevens et al's 2002 paper, two community studies have reported on the distribution of DLB. Shaji et al (2002) examined a population of 1979 people aged 60 and older in Kerala in southern India. Thirty three cases of dementia were identified, of whom three (9%) fulfilled consensus criteria for probable DLB and one (3%) met criteria for possible DLB. Rahkonen et al (2003) examined a population of adults aged 75 and older in an urban area of Finland and found a dementia prevalence of 22.8%. Of these, 22% fulfilled consensus criteria for either possible or probable DLB.

2.5.4 Frontal lobe dementia

2.5.4.1 History

Arnold Pick published in 1892 a description of a series of patients with aphasia, dementia, and localised cortical atrophy in the frontal and temporal lobes at post-mortem (Pick, 1892). Alzheimer (1911) described inflated neurones (Pick cells) and argentophilic inclusions (Pick bodies) in patients with a similar clinicopathological picture, and Schneider (1927) named the condition Pick's disease, which was considered to be one of two major neurodegenerative disorder (the other being Alzheimer's disease). The clinical picture differed from that of Alzheimer's disease in that memory impairment was less prominent than a profound change in behaviour and personality, manifesting as disinhibition, apathy, reduction in empathy, hyperorality, facetiousness and poor judgement, together with cognitive features characteristic of frontal lobe damage such as impaired executive functioning (Lishman, 1996).

In the late 1980s, Brun (1987) and Gustafson (1987) in Sweden presented evidence of patients with similar clinical features to those seen in Pick's disease, and with frontal cortical atrophy at post-mortem but lacking Pick cells and Pick bodies. Neary et al (1988) reported on a series of patients drawn from clinical practice, who displayed a Pick-type clinical picture and showed anterior frontal dysfunction on SPECT scanning. The authors suggested that a degenerative disorder of the frontal lobes existed which was distinct from, and more common than, classical Pick's disease. Brun (1987) proposed the term 'frontal lobe degeneration of non-Alzheimer type' for this condition. The terminology was

subsequently altered to 'frontotemporal dementia', in recognition both of the importance of referring to a clinical syndrome rather than a disease process, and of the frequent occurrence of cognitive impairment related to temporal lobe pathology and the identification of such pathology at post-mortem. Clinical and pathological criteria were proposed jointly by the Lund and Manchester groups (Brun et al, 1994), and were subsequently updated and extended (Neary et al, 1998). The latter authors further viewed frontotemporal dementia as one of three possible clinical manifestations of so-called 'frontotemporal lobar degeneration', the others being progressive non-fluent aphasia and semantic dementia.

The nosological status of this group of disorders remains highly controversial, with some authors (for example, Gregory et al (1998)) disputing the validity of the notion 'frontotemporal dementia' and claiming that it includes disparate conditions, preferring a more restrictive concept confined to abnormalities of the frontal lobes. To this end, Gregory & Hodges (1993) have recommended the term 'dementia of frontal type' and have proposed clinical diagnostic criteria. These and the other criteria mentioned above will be discussed in section 3.4.

2.5.4.2 Classification

DSM IV includes the category 'dementia due to Pick's disease' and ICD 10 includes 'dementia in Pick's disease'. Neither classification system has a category for frontal or frontotemporal dementia. As is the case for DLB (section 2.5.3.2), the text revision of DSM IV (APA, 2001) stipulates that such dementias be classified under 'dementia due to other medical diseases specified

elsewhere’.

2.5.4.3 Prevalence

Accurate identification of the frequency of these disorders has been made difficult by the lack of consensus about the boundaries of the concept. The majority of prevalence studies have been carried out on post-mortem samples (Gustafson, 2000). Pick’s disease has been found to represent 1-2% of cases of dementia at post-mortem (Jellinger, 1990). The Lund study in Sweden (Brun, 1987; Gustafson, 1987) investigated 158 cases of dementia clinically and neuropathologically, and found 10% to have frontal degeneration, non-Alzheimer type, and 2.5% to have Pick’s disease. Pasquier et al (1995) diagnosed frontotemporal dementia in 4.8% of 1015 consecutive patients examined in a memory clinic. As with DLB (section 2.5.3.3), existing prevalence data is derived from unrepresentative samples, and the only published community study is that of Yamada et al (2001), which found no cases of frontotemporal lobar degeneration (as the authors defined the disorder) in a Japanese community population.

2.6 Conclusion

The concept of dementia is an old one but it is only in the last hundred years that the various pathological mechanisms underlying it have begun to be understood and differentiated. In addition to the considerable suffering it causes the person afflicted with the disorder, there are significant health and economic costs

affecting caregivers and society as a whole, and these are likely to increase as the longevity of the world population rises. The development of new treatments for specific subtypes of dementia means that the accurate differentiation of the subtypes and estimation of their prevalence is a priority. Variation in reported prevalence rates is largely attributable to differences in diagnostic methods. Little information is available on the prevalence of two newly identified types, dementia with Lewy bodies and frontal lobe dementia. The next chapter will review the commonly used methods of identifying individual dementia subtypes.

Chapter 3

Clinical and pathological diagnosis of dementia subtypes

3.1 Diagnosis of Alzheimer's disease

3.1.1 Neuropathological diagnosis

Until the mid-1980s, clinical systems for diagnosing AD depended for their validation on the shifting sands of diverse and unstandardised sets of neuropathological criteria. A workshop held in the United States attempted to standardise the neuropathological diagnosis of Alzheimer's disease by proposing post-mortem criteria (Khachaturian, 1985). These criteria specify requisite numbers of plaques and neurofibrillary tangles per square millimetre of cerebral neocortex, and discriminate according to age such that younger people require fewer changes than older people for a diagnosis to be made. The use of this 'sliding scale' has been criticised by Jorm (1990) as being based on unjustified assumptions about the normality of plaques and tangles in older brains. The Khachaturian criteria have also been criticised for being unspecific about the areas of the brain to be examined and about the type of staining technique to be used, as well as for disregarding the question of whether or not there were clinical signs of dementia ante-mortem (Esiri et al, 1997). In addition, neuropathologists have been shown to vary strikingly in their counting of the number of plaques from identical sets of slides (Mirra et al, 1993).

By definition, the validation of neuropathological criteria is difficult, as they are expected to represent a 'gold standard' against which clinical diagnostic systems

themselves can be validated. However, the Khachaturian criteria were applied in one study to 150 cases diagnosed by over 100 clinicians as having Alzheimer-type dementia, using various sets of clinical criteria (Joachim et al, 1988), and the agreement between clinical and pathological diagnoses was 87%.

In an attempt to overcome the problems of inter-rater differences in counting of pathological features and variability in staining techniques between different laboratories, in 1990 the Neuropathology Task Force of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) developed a neuropathology protocol based on a semi-quantitative assessment of plaque frequency in three defined areas of the cerebral neocortex (the superior temporal gyrus, prefrontal cortex and inferior parietal lobule). The protocol also recommends (but does not require) the use of specific staining techniques, namely the modified Bielschowsky technique or thioflavine S stain (Heyman et al, 1990). As with the Khachaturian criteria, the CERAD system records an age-related plaque score, but it differs in taking into account clinical history and examination, which in combination with the neuropathological findings can yield a diagnosis of possible, probable or definite Alzheimer's disease. In a pre-test of the protocol, 142 patients with clinical diagnoses of probable Alzheimer's disease and eight non-demented people were examined at post-mortem, and 84% met CERAD neuropathological criteria for definite dementia (Mirra et al, 1991).

Despite the widespread use of both of these sets of criteria, there remains disagreement about the pathological diagnosis of Alzheimer's disease. In a questionnaire survey of 169 European neuropathologists, 59% regarded

neuropathological diagnosis as a problem, with 29% believing that the diagnosis of Alzheimer's disease cannot be made without knowledge of clinical data (Baner et al, 1997). Only 43% of those surveyed had exact knowledge of the Khachaturian criteria and this fell to 29% for the CERAD criteria.

In 1996, a consensus conference on Alzheimer's disease in the United States discussed the difficulty of establishing a 'gold standard' for diagnosis. The consensus view was that the CERAD guidelines were to be preferred at present (Wisniewski & Silverman, 1997). As a result of this conference, new criteria have been proposed by the National Institute on Aging in collaboration with the Reagan Institute (Geddes et al, 1997). These NIA-RI criteria place more emphasis on the presence of neurofibrillary tangles than do the earlier two systems, and assign cases to one of three categories, high, intermediate and low, based on the likelihood that the dementia is due to Alzheimer's disease. Geddes et al (1997) acknowledge, however, that these new criteria have yet to pass into common use, and emphasize that a definitive gold standard does not yet exist.

3.1.2 Clinical diagnosis

3.1.2.1 NINCDS-ADRDA criteria

The absence of standardised clinical criteria for the diagnosis of AD led to the formation of a working group by the National Institute of Neurology and Communicative Diseases and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA). The group developed criteria to be

used for identifying a homogenous group of sufferers for research purposes (McKhann et al, 1984). Patients whose brains at post-mortem are found to conform to standard pathological criteria are diagnosed as having 'definite' Alzheimer's disease. In the absence of post-mortem confirmation, a combination of inclusionary and exclusionary clinical criteria, based on information obtained from a wide range of sources including history and mental state/physical examination, blood tests and neuroimaging, allows a diagnosis of 'probable' or 'possible' Alzheimer's disease to be made. Rates of 86% to 100% accuracy for the clinical diagnosis of probable Alzheimer's disease, as validated at biopsy or autopsy, have been reported for these criteria (Martin et al, 1987; Morris et al, 1988; Tierney et al, 1988; Burns et al, 1990; Morris & Rubin, 1991). Galasko et al (1994), in a prospective cohort autopsy study, found NINCDS-ADRDA clinical criteria to be 90% accurate in diagnosing possible or probable Alzheimer's disease. However, these results must be viewed with caution as the neuropathological Alzheimer's disease cases included cases where infarcts or Lewy bodies were present. Including only pure cases of Alzheimer's disease, the clinical-pathological agreement rate dropped to 58% (60% for probable and 50% for possible Alzheimer's disease). Similarly, Boller et al (1989) found the criteria to have high sensitivity but low specificity, with frequent overdiagnosis of probable or possible Alzheimer's disease in cases where another cause of dementia was identified at subsequent post-mortem. The most recently-published comparison of NINCDS-ADRDA diagnoses with neuropathological diagnosis confirmed a high sensitivity (95%) but a relatively low specificity (79%)

for the clinical criteria, with most of the false-positive cases having cerebrovascular disease (Lopez et al, 1999).

Converse findings were reported by Tierney et al (1988), who found a specificity of 89-91% but a relatively low sensitivity of 64-86%. The fact that this variable sensitivity depended on the neuropathological criteria used, highlights the potential problem of circularity which may arise from any attempt to decide whether the disease should be ultimately defined by either neuropathological or clinical criteria.

Henderson and Jorm (1987) have pointed out that the reliance of the McKhann criteria on detailed neuropsychological and physical examination, as well as neuroimaging, makes them better suited for use in clinic-based research than in field studies. Two recent population-based post-mortem studies have been carried out using the criteria, the first (Holmes et al, 1999) reporting a sensitivity of 66% and a specificity of 75% for 'probable' AD, the second (Lim et al, 1999) reporting sensitivity as 83% and specificity as only 36%.

In a review of validation studies, Blacker et al (1994) suggest that the NINCDS-ADRDA criteria can be used with fair reliability and good validity across multiple sites. The authors recommend modifications to the criteria such that cases with early prominent behavioural changes should not receive a diagnosis of AD, and also suggest that at some point, a limit will be reached in the ability of researchers and clinicians to improve diagnostic criteria, but that finer gradations than 'probable' or 'possible' AD may need to be developed as understanding of the disease increases.

3.1.2.2 DSM IV and ICD 10 criteria

Despite the existence of the DSM IV criteria since 1994, and that of the ICD 10 criteria since 1992, there have been no studies specifically examining the reliability and validity of these criteria in the diagnosis of AD, as research has mainly focused on the use of the two systems in diagnosing functional psychiatric illnesses such as schizophrenia and the affective disorders. This is somewhat surprising, given that both sets of criteria are widely used in research into AD. A study of the validity of DSM III criteria for AD showed sensitivity of 76% and specificity of 80% (Kukull et al, 1990), with the Khachaturian criteria as the neuropathological standard, and these results compared with sensitivity and specificity of the NINCDS-ADRDA criteria of 92% and 65% respectively. However, the differences between DSM III and DSM IV are such that validity findings for the former system cannot be assumed to apply to its successor.

3.2 Diagnosis of vascular dementia

3.2.1 Neuropathological diagnosis

As noted in section 3.1.1, the neuropathological diagnosis of Alzheimer's disease is confounded by the question of whether the presence of typical 'Alzheimer-type' changes in the brain, chiefly plaques and tangles, is sufficient for diagnosis or whether clinical signs and symptoms of dementia must also be present. The neuropathological diagnosis of VD is potentially even more difficult, as it has long been recognised that cerebrovascular abnormalities may be found in people who show no clinical features of dementia (Tomlinson et al, 1970). The very term

'vascular dementia' assumes the presence of a clinical dementia syndrome. Accordingly, there exist no standardised post-mortem criteria for VD, as the diagnosis must be made on a 'best estimate of probability' which relates the clinical picture to accompanying cerebrovascular changes (Roman et al, 1993).

A neuropathological classification of VD proposed by Brun et al (1988) includes cases of dementia which result from ischaemic and haemorrhagic brain lesions, whether manifesting as single large infarcts or multiple insults to cortical or subcortical areas. The identification of these cases depends ultimately, however, on the confidence of the clinician that the dementia is in fact due to the cerebrovascular events confirmed at post-mortem, rather than to other causes, and so this classification system may better be regarded as a classification of cerebrovascular disease, to which the clinical syndrome may be related.

3.2.2 Clinical diagnosis

3.2.1.1 Hachinski ischaemic score

The realisation in the early 1970s that the dementia due to Alzheimer's disease and that due to vascular causes were separate entities, led to the understanding that the latter condition was potentially treatable. This prompted the development of the Hachinski Ischaemic Score (HIS) (Hachinski et al, 1975), a scale aimed at distinguishing vascular dementias from those due to degenerative causes (Devasenapathy & Hachinski, 1997) in cases where dementia had already been identified, rather than diagnosing VD *per se* in a population. Prospective clinicopathological correlation studies have shown this score to be sensitive in

differentiating pure AD and VD (70-80%) but not in separating pure cases of AD from mixed dementias (17-50%) (Chui, 1989). People with cerebrovascular disease tend to score highly on the HIS regardless of whether or not this disease is related to their dementia (Fischer et al, 1991).

3.2.2.2 NINDS-AIREN diagnosis

In recognition of the fact that difficulties in classification and terminology have hindered the development of research studies on VD (Devasenapathy & Hachinski, 1997), the Neuroepidemiology Branch of the National Institute of Neurological Disorders and Stroke (NINDS) convened an international workshop on VD at the National Institutes of Health in the USA in 1991, with support from the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (AIREN), with a view to defining VD for research purposes and developing diagnostic criteria for the condition. These criteria, as elucidated by Roman et al (1993), permit the diagnosis of 'definite', 'probable' or 'possible' VD. The diagnosis of 'probable' VD requires the presence of dementia, defined as impairment in memory and in two or more other cognitive domains, clinical *and* radiological evidence of cerebrovascular disease, and a temporal relationship between the onset of the two disorders. 'Definite' VD can be diagnosed when there is histopathological evidence of cerebrovascular disease in the absence of neuritic plaques and neurofibrillary tangles exceeding those expected for age. 'Possible' VD is diagnosed in the absence of a temporal link between the respective onset of dementia and neurological signs/symptoms, or of

pathological findings.

Two problems with these criteria can be identified immediately. Firstly, mere histopathological evidence of cerebrovascular changes is sufficient for the diagnosis of 'definite' VD, overriding any clinical opinion as to the degree of relatedness of the pathological findings to the clinical picture. Secondly, the histopathological abnormalities specified as exclusionary criteria for a diagnosis of 'definite' VD include only those seen in Alzheimer's disease. Findings of, for example, cortical Lewy bodies or Pick cells would not rule out the diagnosis of definite VD.

By definition, the validity of the NINDS-AIREN criteria must be 100% with regard to the diagnosis of definite VD. In the absence of standardised neuropathological criteria for VD, validation studies for the NINDS-AIREN criteria are necessarily few, and comparison with other diagnostic systems is the most frequent means of judging their reliability. Two recent studies have compared NINDS-AIREN clinical criteria with post-mortem diagnosis. Gold et al (1997) reported a sensitivity of 58% and a specificity of 80% for the criteria, while Holmes et al (1999) found sensitivity to be 43% and specificity to be 95%.

Two more studies, neither of which included post-mortem confirmation, have compared the NINDS-AIREN criteria with other systems. Pohjasvaara et al (1997) assessed cognitive function in 486 patients three months after an ischaemic stroke, and found that dementia was diagnosed in 21.1% by NINDS-AIREN criteria, compared with 18.4% using DSM IV and 6% with ICD 10. Chui et al (2000) prepared 25 case vignettes representing a spectrum of severity and

subtypes of dementia and asked clinicians from seven centres to make diagnoses using NINDS-AIREN, HIS and DSM IV criteria. The frequency of a diagnosis of VD was highest using HIS and DSM IV criteria, and lowest using NINDS-AIREN criteria.

3.2.1.3 DSM IV and ICD 10 criteria

As noted in section 3.2.1.2, the DSM IV criteria for VD have been compared with those of the NINDS-AIREN system, and found to have similar rates of diagnosis of VD (Pohjasvaara, 1997). The ICD 10 system was shown to diagnose VD significantly less frequently. Neither set of criteria has been compared with neuropathological diagnosis, and as mentioned previously, this is in part due to the absence of a standardised pathological definition of the condition.

3.3 Diagnosis of dementia with Lewy bodies

3.3.1 Neuropathological diagnosis

Lewy bodies, intraneuronal inclusions composed of abnormally truncated and phosphorylated neurofilament proteins, were first described in patients with paralysis agitans or Parkinson's disease by Lewy (1912), and have been identified as coincidental pathology in a wide range of conditions (Ince et al, 1998). Initially they were thought to be confined to subcortical areas, but growing recognition of their presence in limbic areas and the neocortex (Perry et al, 1990) in the late 1980s led to the development of the concept of a spectrum of Lewy body disorders, as discussed in section 2.5.3.1.

The Consortium on DLB International Workshop made recommendations about the areas of the brain to be examined for Lewy bodies, and devised a semiquantitative scoring system for the generation of pathological categories (McKeith et al, 1996). These categories are: brainstem-predominant DLB; limbic (transitional) DLB; and neocortical DLB. As is the case for the neuropathological classification systems for Alzheimer's disease, the DLB pathological criteria suffer from the drawback of being able to identify neuropathology without necessarily being able to link specific pathology with clinical signs and symptoms, and indeed people may fall into one of the above categories without having shown evidence of dementia in life. In recognition of this, Ince et al (1998) have emphasized that a diagnosis of DLB can only be made in the presence of a history of dementia, regardless of the pathological picture.

Debate exists about the interpretation of coexistent Alzheimer-type pathology in brains which show characteristic DLB changes. Eighty to 90% of DLB cases show neuritic plaque counts in similar proportions to those of pure Alzheimer's disease, with an equal percentage showing no significant tau pathology (McKeith, 2000). This has led Hansen et al (1990) to suggest that in cases with high plaque density, the term 'the Lewy body variant of Alzheimer's disease' should be used. This is only applicable if Alzheimer's disease is defined according to plaque density, however, and as noted in section 3.1.1, more recent neuropathological criteria for AD have placed more emphasis on the presence of neurofibrillary tangles.

The consensus criteria for the neuropathological diagnosis of DLB have become

widely accepted as the current standard. Recent research has led to recommendations for modifying the way in which Lewy bodies are detected, as alpha-synuclein immunostaining has been shown to be more specific and slightly more sensitive in detecting Lewy bodies than the earlier ubiquitin immunostaining (Gomez-Tortosa, 2000). This has not, however, affected the basic classification of pathology.

3.3.2 Clinical consensus criteria

As described in section 2.5.3.1, two sets of criteria for the clinical diagnosis of DLB were proposed in the early 1990s, and in 1995 the Consortium on DLB International Workshop developed consensus criteria which have subsequently been widely adopted. These criteria require progressive cognitive decline and specify the following core features: fluctuating cognition, recurrent well-formed visual hallucinations, and spontaneous motor features of parkinsonism. Two of these features must be present for a diagnosis of 'probable' DLB, and one for 'possible' DLB. There are no exclusion criteria, although the diagnosis is said to be 'less likely' in the presence of stroke disease or evidence of physical illness or brain disorder sufficient to account for the clinical picture.

Five studies have assessed the validity of the DLB consensus criteria. In the first, Mega et al (1996) investigated 18 people fulfilling NINCDS-ADRDA criteria for AD and obtained post-mortem confirmation. The sensitivity of the consensus criteria for probable or possible DLB was 40% and the specificity 100%. However, the post-mortem criteria used in this study were considerably more

inclusive than is usual, requiring the presence of only one cortical Lewy body for the diagnosis to be made. Holmes et al (1999) clinically diagnosed 80 people with dementia recruited from referrals to psychiatric, medical and social services, and confirmed diagnoses at post-mortem. The sensitivity of the criteria for probable DLB was 22% and the specificity, 100%. In a third post-mortem study of 40 demented patients, Lopez et al (1999) found a sensitivity for the combined probable and possible categories of 34% and a specificity of 94%. The interrater reliability was, however, low, with a generalised kappa of 0.37, and this was comparable to the reliability ($k = 0.38$) reported by Litvan et al (1998).

Recently, 50 cases were evaluated at post-mortem from a cohort to which NINCDS-ADRDA, NINDS-AIREN and DLB consensus criteria had been applied (McKeith et al, 2000). The sensitivity and specificity of a clinical diagnosis of probable DLB were 83% and 95% respectively. Of the false-negative cases, visual hallucinations and spontaneous motor features of parkinsonism were absent, and the diagnosis was made on the basis of fluctuations.

In contrast to the uniformly high values for specificity reported in the above studies, Hohl et al (2000) examined at post-mortem ten patients with a clinical diagnosis of probable DLB according to consensus criteria. The clinical diagnostic accuracy was found to be 50%. Of the five misdiagnosed cases, four had AD, and there were fewer hallucinations in this group and more spontaneous extrapyramidal signs. The authors concluded that the distinction between DLB and AD would better be made by emphasizing hallucinations rather than parkinsonian signs.

3.4 Diagnosis of frontal lobe dementias

3.4.1 Neuropathological diagnosis

Since the seminal reports by Brun (1987) and Neary et al (1988) (section 2.5.4.1), standard neuropathological criteria for the diagnosis of frontotemporal dementia have been in use and virtually unchallenged. These are described by Mann et al (1993) and require gross brain atrophy which is most marked within the frontoparietal cortex and cingulate gyrus, and which produces a characteristic 'knife-edge' narrowing of the temporal pole. The histopathological picture is one of two types: primarily gliotic, with or without balloon cells and inclusion bodies (Pick type), or predominantly microvacuolar without specific histological features (frontal lobe degeneration type).

3.4.2 Clinical diagnosis

3.4.2.1 Lund and Manchester criteria for frontotemporal dementia

In 1994, a joint conference of the Lund and Manchester groups published clinical criteria for the diagnosis of frontotemporal dementia (Brun et al, 1994). These included a list of core features, divided into the categories of behavioural disorder, affective symptoms, speech disorders, and characteristic findings on neuropsychological tests and neuroimaging. Supportive diagnostic features were also suggested, including onset before 65 years of age, positive family history, and signs of motor neurone disease. These criteria differ significantly in character from those previously mentioned for other disorders, in that they are not operationalised, i.e. do not specify inclusion and exclusion criteria, and they do

not grade diagnoses into 'probable' and 'possible' categories. It is unclear, for example, how many features are required to be present before the diagnosis can be made with any confidence.

Only one published study (Lopez et al, 1999) has examined the reliability and validity of the Lund and Manchester criteria. Four experienced clinicians applied the criteria retrospectively to 40 patients who were pathologically diagnosed with dementia, using data from medical records. There was considerable interrater reliability for the criteria, with a generalised kappa of 0.75. The mean sensitivity and specificity of the criteria was 95% in each case.

3.4.2.2 Gregory & Hodges criteria for dementia of frontal type

Gregory and Hodges (1993) questioned the grouping-together of frontal and temporal pathology under the term 'frontotemporal dementia' and proposed a separate entity, 'dementia of frontal type' (DFT), in contrast to 'semantic dementia' which presents with characteristic pathological changes in the temporal lobes. The authors devised clinical diagnostic criteria for DFT, which are operationalised and require the presence of a) an insidious disorder of personality and behaviour of at least six months' duration; b) five or more features from a list of 15 abnormalities of speech and behaviour; c) frontal dysfunction on neuropsychological assessment; d) relative preservation of memory. In addition, an exclusion criterion is a history of head injury, stroke or long-term alcohol abuse. These criteria are more restrictive than the Lund and Manchester system, both in specifying inclusion and exclusion criteria and in

being confined to frontal lobe abnormalities rather than encompassing temporal lobe dysfunction.

3.4.2.3 Consensus criteria for frontotemporal dementia

An international conference on frontotemporal dementia convened to update the Lund and Manchester criteria and specifically to alter them for use in research (Neary et al, 1998). The symptoms specified in the new criteria do not differ substantially from those present in the Lund and Manchester system, but significantly, only five are listed as core features (insidious onset and gradual progression, early decline in social interpersonal conduct, early impairment in regulation of personal conduct, early emotional blunting, and early loss of insight), and all are required to be present for a diagnosis to be made. The remainder of the features, including all abnormalities of speech, physical signs and investigations, are considered to be supportive of the diagnosis. The use of these criteria relies heavily on the availability of a detailed history as none of the five core features can be elicited purely from examination of the individual. As yet, there have been no published data on the reliability or validity of these criteria.

3.5 Conclusion

There exist no Platonic ideal forms against which the diagnostic criteria for the different forms of dementia can be measured for accuracy. On the whole, neuropathological diagnosis is considered the gold standard, but cannot be

accepted on its own without reference to clinical findings. Validation of pathological diagnostic criteria has sometimes been attempted using recognised clinical criteria as a yardstick, but this raises the problem of circularity as the clinical criteria themselves have often been validated against post-mortem diagnoses.

The NINCDS-ADRDA criteria are the best-validated clinical criteria for the diagnosis of AD, although there is disagreement about their sensitivity and specificity. For the diagnosis of VD, the NINDS-AIREN criteria are the best-validated, although they appear to be relatively insensitive. The consensus criteria for the diagnosis of probable or possible DLB have been repeatedly shown to be highly specific and relatively insensitive; validation studies have, however, been carried out on selected samples rather than naturalistic populations. With regard to FLD, two sets of criteria, the consensus criteria for frontotemporal dementia and the Gregory & Hodges criteria for dementia of frontal type, are in use, although they are intended to diagnose slightly different conditions. Neither has been subject to tests of reliability or validity.

Chapter 4

Methods

4.1 Epidemiology

As was discussed in section 1.3, epidemiological studies into mental disorders of older people may be divided into two main types: the case-control and the descriptive. In the former type, people with the condition under investigation, for example dementia, are defined as 'cases' and are compared with people in whom the condition is absent, or 'controls'. This design is well suited to studies of aetiological factors contributing towards a condition.

The frequency of dementia and its subtypes, on the other hand, is best determined using a descriptive method. This in turn may investigate either the incidence or the prevalence of the condition.

4.1.1 Incidence studies

The incidence of a disease is the number of new cases arising in a population over a specified period of time. If the incidence is regarded as the numerator, and is divided by the population at risk of the disease (the denominator), an incidence rate is derived. The advantages of incidence studies are that they can potentially be used to identify risk factors, as well as differences between populations with regard to disease onset. The predictive validity of current classification and diagnostic systems can also be assessed. For these reasons, incidence studies

have been regarded as having greater theoretical importance than prevalence studies (Jorm, 1990; Mann, 1996).

Several factors limit the usefulness of this method. The longitudinal nature of this research has implications regarding cost and staff resources (Freeman and Tyrer, 1989). Also, the study of the incidence of conditions which are relatively rare, such as dementia, requires large sample sizes or long periods of follow-up to estimate rates accurately. As discussed in chapter 1, accurate identification of cases of dementia is often difficult, and this is even more so when the onset of illness is to be determined.

Unsurprisingly, there have been relatively few incidence studies of dementia in the community, and fewer than twenty have met acceptable standards of case definition (Ineichen et al, 2000). One problem with the usefulness of published incidence studies has been the failure of some of them to distinguish between the cumulative incidence rate, in which an individual is included in the denominator even after developing the disorder, and the person-time incidence rate, which excludes a person from the population once they have become a 'case'.

4.1.2 Prevalence studies

The prevalence of a disease is the number of cases in a population at a specified time. As with incidence, the prevalence rate is derived by dividing the prevalence by the population at risk. In this thesis, the common practice of shortening 'prevalence rate' to 'prevalence' is employed. The prevalence at a particular

instant in time is the 'point prevalence'; less frequently, studies report the 'period prevalence', which is the prevalence rate over a defined time period.

The point prevalence study is the most common type of method used in research into the epidemiology of dementia, and as noted in section 2.3, there have been over one hundred studies published on the point prevalence of dementia in community samples alone. The first such published study was that by Sheldon (1948), although the earliest study considered to meet acceptable standards in terms of recruitment and case ascertainment was by Kay et al (1964).

The problems of attempting to characterise alternatives of 'disease' and 'non-disease' as binary variables have been discussed in section 1.6. Different methods of identifying cases make comparisons between prevalence studies difficult. Nonetheless, if criteria for case identification are applied consistently throughout a particular study, the study may be expected to yield a reliable figure for the prevalence of dementia so defined. Clearly, in the absence of an unequivocal gold standard for diagnosis, reliability between prevalence rates in studies using similar methods of case definition is important.

4.1.2.1 Design of prevalence studies

The ideal method of locating every case in a prevalence study is to interview each individual in the population, a strategy which is usually highly impractical, as financial and manpower considerations will inevitably result in a limitation of the population's parameters. The alternatives are to assess cases who are on a register as a result of contact with professional services, or to examine a

representative sample of the whole population. The case register approach has the advantage of being relatively inexpensive and quick to carry out, but is most effective when the population is small and the condition under investigation is unusual and easily detected (Jorm, 1990). The type of service used also has a bearing on the effectiveness of this method, with highly specialised services such as psychiatric outpatient clinics, for example, tending to underestimate case numbers, and registers involving general practice surgeries yielding greater numbers but possibly also false positives.

Several recognised methods have been used to generate representative samples. General practitioners' and social services' lists suffer from the drawbacks that they are likely to overinclude people with dementia, and may rapidly become out of date. For example, in the North London Gospel Oak Study (Livingston et al, 1990), the names of 1,231 pensioners living in Gospel Oak ward were obtained from local general practitioners, social services and community workers. Subsequently, door-knocking yielded 1,151 names of pensioners, and this new list was 50% different from the original one. Conversely, the electoral roll and the census will tend to under-represent the mentally ill (Mann, 1997), although Lindesay et al (1989) have employed a technique to correct for inaccuracy in the electoral roll.

Direct house-to-house contact to ascertain numbers of older people within a defined area has the potential to avoid the above pitfalls, and is being used increasingly frequently (for example, Livingston et al, 1990; Lobo et al, 1995; Boersma et al, 1997). In this method, each household within the defined area is

approached, either through a letter or in person, in order to establish whether or not a member of the population under investigation is resident. Cases are subsequently identified from the members of the population who agree to further assessment. This method has the advantage of potentially identifying both the population size and the prevalence of the disorder, unlike one which relies on an external source for population data, such as the electoral roll.

The means by which the geographical area is defined are clearly important in order for a representative area to be selected. It must be sufficiently large to ensure representativeness, but small enough to take into account practical considerations. In Britain, enumeration districts, which represent the smallest unit into which the UK population is divided for the census (Craig & Boardman, 1991), may be selected randomly in order to yield a sampling frame.

Disadvantages of direct house-to-house contact include the invasion of privacy or even threat which residents, particular older ones, may perceive. The relatively large number of people interviewed will usually require several interviewers, and in addition to placing a burden on cost and training requirements, this raises the possibility of discrepancies in information gathering by different people. The latter problem can be addressed, at least in part, by adequate training of staff in interviewing techniques, and by the use of instruments with high inter-rater reliability (section 4.2.3.1). During the study, differences between case identification rates between individual interviewers should be monitored (Mann, 1997).

4.1.2.2 Single-stage versus two-stage design

One method of interviewing members of the population who have been identified in their homes is to gather all information required in a single visit, as in, for example, the study by O'Connor et al (1989). This technique would work best if the purpose of the study was solely to identify the 'screening-positive' prevalence of dementia. Such a study would, however, have limited value, and all of the diagnostic systems described in chapter 1 require comprehensive assessment of history, mental and physical state in order for their various sets of operationalised criteria to be employed. This entails the gathering of a large amount of information over considerable time, and also requires an experienced clinician to conduct each interview.

An alternative is to use a two-stage design, as described in section 1.3. This entails screening for the condition under investigation (stage 1) followed by a detailed assessment of all screening-positive cases (stage 2). Such an approach parallels the division of health care services into primary and secondary, and allows for rapid and relatively inexpensive identification of cases followed by efficient use of time and manpower at stage 2. It also enables the accuracy of the screening instrument to be assessed, by determining at clinical assessment whether or not cases actually have the condition in question. As dementia is a relatively rare condition and the costs of diagnosing it are relatively high (Zhou and Higgs, 2000), its prevalence lends itself to investigation using the two-stage method (section 3.3.1.1), and it has been used extensively in recent years (Livingston et al, 1990; Lobo et al, 1995; Liu et al, 1996; Boersma et al, 1997).

4.2 The epidemiological study

As discussed in sections 2.4 and 2.5, very little is known about the community prevalence rates of dementia with Lewy bodies and the frontal lobe dementias, and accordingly the appropriate deployment of health and social services resources for these conditions is difficult to plan. Distribution figures for even the more commonly recognised and extensively studied causes of dementia, such as Alzheimer-type and vascular, vary considerably depending on the diagnostic criteria used, and this makes interpretation of the prevalence data problematic. The study reported in this thesis was intended to address this deficiency.

For the reasons given in section 4.1, a descriptive design was chosen. The pattern of epidemiological research on dementia has historically been for prevalence studies to be performed before incidence studies, and in keeping with this, as well as in accordance with financial and time limitations, a prevalence study was chosen over an incidence study.

4.2.1 Aims

The aims of the present study were as follows:

4.2.1.1 To determine the distributions of subtypes of dementia in a representative community population aged 65 and older

While the intention was to examine all subtypes of dementia, a particular aim was to identify the distributions of DLB and FLD, given the scarcity of data currently

available. The community was chosen as the population, as opposed to outpatient, hospital or post-mortem groups, to increase the representativeness of the figures. As noted in chapter 1, dementia has been shown unequivocally to be over-represented in older people. Focusing on an older population was thus seen as more appropriate for the purposes of this study, as this population is the one most likely to benefit from dementia research. Previous prevalence studies have differed in the cut-off age defining the 'elderly' population. A minimum age of 65 was chosen in this study for two reasons. Firstly, the majority of studies to date have used 65 as a cut-off (Ritchie et al, 1992), and continuing with this practice allows comparisons to be made more easily between studies. Secondly, mental health and social services for older people in the United Kingdom also employ 65 as a watershed age, and research aimed at influencing health and social policy is best advised to use the same parameters.

4.2.1.2 To compare the particular distributions of subtypes according to different standardised diagnostic clinical criteria

Although certain diagnostic systems have been validated to a greater degree than others in their ability to define particular subtypes of dementia (for example, NINCDS-ADRDA in AD and NINDS-AIREN in VD), no published study to date has compared the distributions of the subtypes according to the major systems. This was seen as a worthwhile aim as, depending on the results, the different criteria may either be shown to diagnose subtypes with similar frequency, suggesting similar reliability, or may yield significantly different distribution rates,

which would indicate the need for caution in interpreting past and future results of prevalence research.

4.2.1.3 To examine associations between diagnostic subtypes and demographic variables

This was not a case-control or cohort study, and therefore the aim was not primarily to investigate possible aetiological factors. Nonetheless, it was decided to gather data on such demographic variables as age, gender and country of birth, in order to examine whether significant associations exist between the particular subtype of dementia and these variables.

4.2.2 Ethical approval

Ethical approval was obtained from Camden & Islington Community Health Services NHS Trust Local Research Ethics Committee. Separate approval was obtained for the two stages of the study. One of the Committee's conditions of approval was the inclusion of an information sheet and a consent form which met certain standards.

4.2.3 Design

A two-stage design was chosen for this study, for the reasons discussed in section 4.2.1.1., namely that this method permits the cost-effective identification of a relatively rare condition through the screening of a large sample of the population, and the subsequent detailed assessment of the relatively few

screening-positive cases thus identified. The methods of stage 1 and stage 2 are described below.

4.2.3.1 Stage 1

Sample selection

Participants were recruited from the borough of Islington, North London. Figures from the 1991 census indicate a population of 164,686 in this borough, of whom between 13.8% and 15.3% are of pensionable age (Wenzel, 1991). The Jarman Underprivileged Area Score (UAS) is commonly used in National Health Service epidemiological research, and is based on eight variables selected following a nation-wide survey of general practitioners, which asked them to list the most common factors which were perceived to increase their workloads (Jarman, 1983). Islington has a UAS of 49, making it the sixth most deprived area in England and Wales.

In this study, the sampling frame was generated by random selection of enumeration districts (section 4.1.2.1). It must be noted that a single population, that of Islington, was examined. This strategy imposes limits from the outset on the generalisability of the results; for example, the prevalence of dementia and distribution of subtypes may be a function of the high UAS of the area in which the population resides, and this relationship would only become noticeable if these results were compared with those from a prevalence study in a less deprived area.

Identification of interviewees

For the purposes of stage 1, the term 'researcher' refers to one of the two research nurses, two research doctors and two psychiatrists who undertook the work. One of the psychiatrists was the author of this thesis. Each researcher assumed responsibility for a specified region of the enumeration districts chosen for the sample. An introductory letter was posted through each door in the designated area. This included a brief outline of the purpose of the study. It informed the resident or residents that the purpose of the research was to interview people aged 65 and older in order to gather information about the state of their health and about any help they were receiving from health or social services, so as to plan services in the future. The letter stated that a researcher would be attempting to make face-to-face contact within a few days. It also stated that ethical approval had been obtained from the appropriate Ethics Committee, and gave the name and telephone number of the researcher. To save time, recipients of the letter were encouraged to telephone the researcher to inform them whether or not there was anyone aged 65 or older in the home, and whether he or she was willing to be approached face to face for an interview. At the time of posting the letters, the researcher asked any available members of the public who were obviously neighbours, whether they knew of any people in the area whose ages were above the required minimum. This approach was also used for blocks of flats, where a superintendent or caretaker was available.

Following the posting of the letters, a researcher visited each residence to ask if a person aged 65 or over was present. Two attempts were generally made to

make verbal contact with the occupants. The researcher wore photographic identification, and checked to ensure that the resident had received and read a copy of the letter. Each person over 65 years thus identified was asked to take part in an interview, after the purpose of the interview had been explained in more detail. If the person agreed, verbal consent was recorded in writing by the researcher.

The screening interview

The duration of this interview depended on the experience of the researcher and interviewee factors, such as hearing ability. The interview was intended to be completed in an average of approximately forty minutes.

The shortened version of the Comprehensive Assessment and Referral Evaluation Short-CARE; Gurland et al, 1984) was used to elicit psychiatric symptoms and diagnoses. The Short-CARE is a 143-item screening instrument derived from the Comprehensive Assessment and Referral Evaluation (CARE; Gurland et al, 1977), which was itself adapted from the Geriatric Mental State (GMS) Schedule (section 1.3), but was considered too lengthy for use as a screening tool. The Short-CARE can be used to generate diagnoses using indicator scales, such that interviewees scoring above a specified cut-off point on these scales are said to have, for example, dementia or depression, depending on the scale (Jorm, 1990). The indicator scales relevant to the detection of cognitive abnormalities include the organic brain syndrome scale (OBS), designed as a sensitive scale for cognitive impairment and including only

cognitive items, and the dementia diagnostic scale (DDS), to detect cases of dementia severe enough for clinical intervention (Kay et al, 1985), and including both cognitive items and items indicating impairment in activities of daily living. The interrater reliability correlations for the depression, dementia and disability scales have been shown to be high (0.94, 0.76 and 0.91 respectively), and internal consistency coefficients have been calculated as 0.75, 0.64 and 0.84 (Gurland et al, 1984). Although the Short-CARE DDS has been claimed to diagnose dementia while not identifying the particular subtype (Blessed et al, 1991), its failure to incorporate a clinical history means that it is suitable only as a screening tool identifying probable dementia (Livingston, 1994).

Demographic data were collected about each participant. These included details of age, gender, ethnicity, input from formal or informal caregivers, and use of social and health services.

Follow-up

Interviewees were informed at the beginning of the interview that routine follow-up visits were not part of the study. However, if it became apparent during the interview that the person had cognitive impairment, the researcher asked whether a second and more detailed assessment would be acceptable.

4.2.3.2 Stage 2

Identification of screening-positive cases

The author, an experienced psychiatrist, performed a follow-up assessment. Those interviewees who scored seven or greater on the dementia sub-scale of the Short-CARE were identified as screen positive for dementia. Their general practitioners, if identified at stage 1, were sent a letter informing them of their patient's having screened positive for dementia, and of the researcher's intention to approach them and their carers for participation in stage 2. The general practitioners were asked to telephone the researcher if they objected to their patient's being thus approached. This letter was followed up by a telephone call within a week to confirm that the letter had been received and that there were no objections. The general practitioners were also asked to provide telephone numbers for their patients if these had not been obtained in stage 1.

The author of this thesis carried out all the stage 2 assessments, and is henceforth referred to as the researcher. He attempted initially to contact the potential cases or their carers by telephone, and explained the purpose of the study, and that at screening the findings had suggested that the person had memory problems. If the person did not have a telephone or did not answer after repeated attempts, the researcher attempted to visit them at their home in person. Those people who agreed over the telephone to take part, were visited at home, and given a copy of the information sheet about the study.

If the person agreed to further assessment, he or she was asked to provide written consent to undergo more detailed evaluation. If the participant was unable to provide written consent, a family member was asked to provide written assent

instead. If a family member could not be located, the principal carer, who may have been a professional caregiver, was asked to provide assent.

The assessment typically lasted two-and-a-half hours, and the person was informed at the outset that this would be the likely duration. This varied considerably, however, depending on the ability of the person to communicate and the availability of history at the time of assessment.

As much of the assessment was performed as the person would allow. As many people were tired towards the end of the evaluation, several refused physical examination and/or blood tests. These individuals were asked if they would agree to be revisited for the purposes of completing the evaluation.

Evaluation

Clinical history

This was obtained from the participants and any carers, general practitioners (GPs), other health care professionals involved in the participants' care, and medical and psychiatric notes. Wherever possible, this was gathered in the course of a single day, but it was often necessary to interview carers or family members at a different date, and medical notes were not always easily obtainable.

The history focused on the onset and duration of the illness, the rapidity of deterioration, the nature of progression including the presence or absence of fluctuation, as well as the extent of impairment of the participant's functioning. Both the person's own impression of his or her problems and the views of family

and carers were taken into account in each case. Information was sought on past medical or psychiatric history, medication, use of alcohol or nicotine, occupational history, brain imaging and family history of dementia or other psychiatric illness.

Mental state examination

A detailed, standard mental state examination was carried out, with particular emphasis on affective and psychotic symptoms and cognitive performance. This was obtained using both a semi-structured clinical interview and the Geriatric Mental State (GMS) schedule (Copeland et al, 1976), which was discussed in section 1.3.

Further assessment of cognitive performance

The Mini-Mental State Examination (MMSE; Folstein et al, 1975) was used. This is the most frequently employed structured screening tool for dementia (Oppenheimer & Jacoby, 1997) and was developed at Johns Hopkins University specifically for use in older people. The validity of the MMSE has been established by obtaining significant correlations with clinical diagnosis; for example, Folstein et al (1985) found 97% sensitivity and 56% specificity in a field study, and O'Connor et al (1989) reported sensitivity and specificity of 86% and 92% respectively. Correlation with in vivo structural neuroimaging and electrophysiological indices has also been found to be high (Cockrell & Folstein, 1988). As regards reliability, test-retest correlation has been found to be

acceptable, at 0.84 over eight weeks (O'Connor et al, 1989). Nonetheless, some controversy remains as to the optimal cut-off score, with the original author favouring a score of 23 or less out of 30 for the diagnosis of dementia (Folstein et al, 1975) but a Beijing group recommending a score of 17 or less (Li et al, 1989). A significant correlation with education has also been found, with more false positive cases of dementia being identified in less-well educated people (Anthony et al, 1982; Escobar et al, 1986). For the purposes of this study, 23 was regarded as the cut-off score for dementia.

The MMSE assesses the cognitive domains of orientation, memory, attention, naming, comprehension, and constructional praxis, and as such is insufficient in cases of frontal lobe dementia. For this reason, in this study a series of tests of frontal lobe function was performed, namely the Trail Making Test, cognitive estimates and verbal fluency. The latter included both category and letter fluency ('FAS') tasks. As there is no standard validated bedside battery of tests for frontal lobe impairment, the tests used were chosen as providing a relatively broad, although by no means comprehensive, assessment of the various frontal lobe functions.

Physical examination

A comprehensive and systematic physical examination was conducted on all people who agreed to it. It comprised a detailed examination of all systems with an emphasis on the central and peripheral nervous systems. The latter included an assessment of frontal lobe release signs, and of parkinsonian signs, using the

motor section of the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn, 1987), a standard assessment instrument for Parkinson's disease which also includes sections for the evaluation of mentation and behaviour, and activities of daily living. The latter two sections were not employed in this study. The UPDRS has been validated against neuropathological diagnosis (Fahn & Elton, 1994). The researcher carrying out the assessment was trained in the use of the motor section of the UPDRS.

Based on the collated information from the physical examination and other sources including history, medical notes and neuroimaging, the Modified Hachinski Score (Hachinski et al, 1975; section 3.2.1.1) was calculated.

Further investigations

Venepuncture was carried out in all people who permitted it, and blood samples were obtained for standard 'dementia screen' investigations, including full blood count, serum urea and electrolytes, liver function tests, serum folate and vitamin B12, thyroid function tests and syphilis serology. Other investigations such as brain imaging were not performed, although the results of previous such tests, carried out as part of clinical investigations, were taken into account when diagnoses were made later.

Diagnostic criteria for classification of dementia

Once the researcher was satisfied that all sources of information about a person had been consulted, he recorded a diagnosis based on his clinical impression,

without recourse to classificatory systems. In particular, the diagnosis of DLB was made in the presence of progressive dementia with prominent well-formed visual hallucinations, if one or both of the following features were present: (i) spontaneous motor features of parkinsonism; (ii) pronounced fluctuation in cognitive performance. Evidence of cerebrovascular disease on history, physical examination or neuroimaging did *not* rule out the diagnosis unless there was a clear temporal relationship between a cerebrovascular accident and the onset of symptoms. Similarly, no restriction was imposed on the duration of parkinsonian symptoms prior to the onset of dementia, in contrast to the recommendation by the First International Workshop on Dementia with Lewy Bodies that motor features of parkinsonism should not be considered a 'core' criterion for the diagnosis of DLB if they have been present for more than one year before the onset of cognitive symptoms. These separate 'clinical' diagnostic criteria were influenced by a post-mortem study by Hohl et al (2000), who reported a clinical diagnostic accuracy of 50% for DLB and found fewer hallucinations in the false-positive clinical cases, suggesting that hallucinations are an important diagnostic marker. This clinical approach to the diagnosis of DLB therefore differed from that taken by the consensus criteria in requiring the presence of visual hallucinations, and allowing a longer duration of motor features of parkinsonism before the onset of cognitive impairment.

Thereafter, the researcher and a second rater, an experienced psychiatrist, made diagnoses jointly in accordance with the DSM IV and ICD 10 criteria, as described in section 1.5. Alzheimer-type dementia, vascular dementia, dementia

in Parkinson's disease and other or unspecified dementias were diagnosed using these criteria. Two raters were used to improve the reliability of the diagnoses made.

In addition, diagnoses were made using criteria specific to certain subtypes of dementia, as follows:

Alzheimer's disease

National Institute of Neurological and Communicative Diseases and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann et al, 1984; section 3.1.2.1).

Vascular dementia

National Institute for Neurological Diseases and Stroke/ Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria (Roman et al, 1993; section 3.2.2.2).

Dementia with Lewy bodies

The consensus criteria for the diagnosis of DLB (McKeith et al, 1996; section 3.3.1).

Frontal lobe dementias

The Gregory and Hodges criteria (Gregory and Hodges, 1993) for dementia of frontal type (section 3.4.2.2), and the consensus criteria for frontotemporal

dementia proposed by Neary et al (1998) and based on the Lund and Manchester criteria (Brun et al, 1994; section 3.4.2.1).

For each case, both raters read through the criteria of each diagnostic system together and decided whether or not the person fulfilled each criterion. If the person fulfilled criteria for a diagnosis which was strongly at odds with the assessor's clinical impression, the process was repeated with especial emphasis on the relative prominence of the various symptoms.

The diagnostic criteria are reproduced in the Appendix.

4.3 Conclusion

Of the different varieties of epidemiological study, the descriptive type lends itself best to the determination of the frequency of dementia and its subtypes. Studies of incidence allow aetiological factors to be identified and can be used to demonstrate different rates of onset in different populations, but are time-consuming and require large numbers of cases to be identified. Prevalence studies are simpler to carry out in practical terms, and are a suitable starting point for research into the frequencies of conditions about which relatively little is known, such as dementia with Lewy bodies and the frontal lobe dementias.

The study reported in this thesis aims to identify the distribution of subtypes of dementia, including DLB and FLD, in a representative community sample. It has been conducted using a two-stage design, in which the initial screening of large numbers of a representative sample of people aged 65 and older in Islington

yields dementia 'cases', who are then evaluated in more detail in order to make diagnoses. The results using different diagnostic systems are compared in order to determine the reliability of the systems in making a given diagnosis.

Chapter 5

Results

5.1 Stage 1

The first stage was carried out between December 1996 and October 1999. A total of 1,282 people aged 65 or older were identified and approached for interview. The districts identified for the sampling frame included two residential homes and one nursing home.

5.1.1 Response rate

One thousand and eighty-five of those approached were interviewed, giving a response rate of 84.6%. Of the 197 people not interviewed, 127 (64.3%) were female. The reasons for non-participation were: 153 (77.7%) refused an interview, 16 (8.1%) could not be contacted, 15 (7.6%) did not speak English, two (1.0%) had other communication problems, and relatives refused on behalf of 11 (5.6%).

5.1.2 Participants: demographic data

5.1.2.1 Age

The ages of those interviewed ranged from 65 to 102, with a mean of 75 years and a median of 74 years. The age distribution was as follows: 23.4% were aged

65 to 69, 27.8% 70 to 74, 22.5% 75 to 79, 13% 80 to 84, 10.2% 85 to 89 and the remaining 3.1% aged 90 or older.

5.1.2.2 Gender

Six hundred and forty-four participants (59.4%) were female.

5.1.2.3 Country of birth

Fifty countries were represented among participants. Six hundred and sixty-seven people (61.5%) were born in Britain, 139 (12.8%) in Ireland, 71 (6.5%) in Cyprus, Greece or Turkey, 98 (9.1%) in Africa or the Caribbean, 60 (5.5%) in Continental Europe and 50 (4.6%) in other countries. By comparison, the ethnic breakdown of the borough of Islington as a whole, including people under 65 years of age, was found at the 1991 census to be 81.1% white, 8.7% African-Caribbean and 1.9% black others (OPCS, 1991).

5.1.2.4 Accommodation

One thousand and thirty-one participants (95%) lived at home in privately-owned, rented or sheltered accommodation with the remaining 54 (5%) occupying residential or nursing care facilities. A significantly higher proportion of women (6.53%) than men (2.71%) lived in the latter form of accommodation (Chi-square 8.07; $p=0.005$). Five hundred and seven of the non-residential home and non-nursing home participants (46.7%) lived alone, and again a significantly higher

proportion of women (54.9%) than men (41.2%) lived on their own (Chi-square 18.9; $p < 0.005$).

5.1.3 Participants: screening results for dementia

5.1.3.1 Prevalence rates

Of the 1,085 people screened, one hundred and seven (9.86%) scored as screening-positive on the dementia scale (DDS) of the Short-CARE. One hundred and twelve people (10.3%) scored above the cut-off on the organic brain syndrome (OBS) scale.

5.1.3.2 Age and sex effects on prevalence rate

Seventy-one participants (66.4%) screening positive on DDS for dementia were female. This difference between female and male participants was not significant. The age range was 65 to 102 years (mean and median 80 years). Table 5.1 indicates the prevalence of DDS screening-positive dementia cases by gender and age range.

Age range (years)	Screening-positive dementia prevalence in women N(%)	Screening-positive dementia prevalence in men N(%)
65-69	9 (6.57)	3 (2.56)
70-74	11 (6.51)	9 (6.82)
75-79	10 (7.04)	9 (8.74)
80-84	14 (14.3)	7 (16.3)
85-89	20 (27.8)	6 (15.8)
90 and older	7 (28.0)	2 (22.2)

Table 5.1 Distribution of screening-positive dementia prevalence by gender and age

With regard to the OBS scale, 77 people (68.8%) scoring above the cut-off on the OBS were women. Again, this finding was not significant. Table 5.2 shows the prevalences by age and sex of the 'OBS positive' participants.

Age range (years)	Screening-positive OBS prevalence in women N(%)	Screening-positive OBS prevalence in men N(%)
65-69	8 (5.84)	4 (3.42)
70-74	9 (5.33)	10 (7.58)
75-79	16 (11.3)	9 (8.74)
80-84	15 (15.3)	4 (9.30)
85-89	20 (27.8)	6 (15.8)
90 and older	9 (36.0)	2 (22.2)

Table 5.2 Distribution of prevalence rates of people scoring above cut-off point on Organic Brain Syndrome (OBS) scale of the Short-CARE, by gender and age

Ninety-six participants scored above the cut-off points on both the DDS and OBS. Women comprised 65 (67.7%) of these. The implications of the differences between the OBS and DDS positive rates will be discussed in section 6.1.

5.1.3.3 Effects of type of accommodation on prevalence rates

Of the 107 participants who screened positive for dementia on the DDS, 69 (64.5%) lived in rented, sheltered or owner-occupied accommodation. Thus the screening prevalence rate of dementia for those who lived in the community without 24-hour care was 6.7%. In this group, 24 (34.8%) lived alone, 16 of whom were women (38.1% of all female screening-positive cases) and eight of whom were men (29.6% of male screening-positive cases). The differences in the rates of men and women living alone was not statistically significant.

Thirty-eight people (35.5%) lived in residential or nursing care, 29 of whom were women (40.8%) and 9 of whom were men (25.0%). The screening prevalence rate for dementia among those living in 24 hour care was therefore 70.4%. All but one of the participants who screened positive on the DDS and lived in a 24-hour care facility, also scored positive on the OBS scale.

5.1.3.4 Effects of country of birth on prevalence rates

Sixty-seven people screened as having dementia (62.6%) were born in the United Kingdom, 17 (15.9%) in Africa or the Caribbean, eight (7.5%) in Cyprus,

Greece or Turkey, five (4.7%) in Ireland, five (4.7%) in other European countries and five (4.7%) in other countries outside Europe. Rates were similar for people who scored positive on the OBS, as follows: United Kingdom 67 (59.8%), Africa/Caribbean 18 (16.1%), Cyprus/Greece/Turkey eight (7.1%), Ireland eight (7.1%), Europe five (4.5%) and other countries six (5.4%).

The numbers and proportions of people interviewed who screened positive for dementia, by country of birth, are shown in table 5.3.

Country of birth	Number interviewed	Number screening positive for dementia	% screening positive for dementia
United Kingdom	667	67	10.0
Ireland	139	5	3.60
Africa/Caribbean	98	17	17.3
Cyprus/Greece/Turkey	71	8	11.3
Europe (non-UK)	60	5	8.33
Other	50	5	10.0

Table 5.3 Distribution of screening-positive dementia prevalence rates by country of birth

5.2 Stage 2

The number of people who screened positive for dementia in stage 1 was 107. Contact was made with 74 (69.2%) of these people or their carers. A total of 64 (59.8%) were assessed in person. Hospital case notes were obtained for 84 (78.5%) of the screening-positive cases, including 55 who were subsequently assessed in person and 33 who were not.

5.2.1 Demographic features of non-assessed group

Ten of the 74 people with whom contact was made, were not assessed owing to refusal. In three cases the people themselves refused, saying they did not want to answer any more questions. In each of the other seven cases a family member refused to allow their relative to be interviewed, the most common reason given being that the relative was unlikely to benefit from further assessment. The mean age of people refusing assessment was 78.9 years, and eight were female. Eight lived in rented or their own accommodation and one each in nursing and residential care.

Of the 33 people who screened positive but were not contacted, 16 had died. This information was obtained in most cases from the general practitioner, although in two cases the person had been resident in a 24-hour care facility and staff there informed me of their death. In two cases, the spouse of the deceased person gave this information. Fourteen (87.5%) of people who were dead at the time of attempted follow-up had lived at home when first seen, compared with

two (12.5%) in residential care. The mean age for people who had died was 82.3 years.

The remaining 17 screening-positive cases were not traceable, either because repeated attempts to contact them by telephone and by personal visits to their home addresses were unsuccessful, or because they had moved out of the area following screening and were either living too far away for an assessment to be carried out, or were living in an unknown location. The mean age of people who were not contactable was 81.6 years.

In each case where an assessment in person was not made, whether because the individual refused, was not traceable or had died, attempts were made to obtain information sufficient for a diagnosis to be made. This information derived from hospital and community case notes, general practitioners, and family and carers. As a result, although 64 people were assessed in person, sufficient information was obtained for diagnoses to be made for 72 people (67.3% of screening-positive cases).

5.2.2 Demographic features of assessed group

The mean age of those further evaluated was 80.0 years, and 40 (62.5%) were female. Thirty-nine (60.9%) lived in rented or owner-occupied accommodation, two (3.2%) in a nursing home and 23 (35.9%) in part III residential care. The mean time between the interviews for stage 1 and stage 2 was 8.8 months.

With regard to country of birth, 43 (67.2%) of those assessed were from the United Kingdom, nine (14.1%) from Africa or the Caribbean, six (9.4%) from

Ireland, three (4.7%) from European countries other than the UK or Ireland, two (3.1%) from Cyprus, Greece or Turkey, and one (1.6%) from another country (Israel).

5.2.3 Data collected from assessed group

For all of the 64 people assessed, sufficient information was obtained from either history, examination or both, for diagnoses to be made as to whether or not the person had dementia, although as noted below, the diagnosis was sometimes not able to be further specified if the information was limited.

5.2.3.1 Neuropsychological testing

A Mini-Mental State Examination (MMSE) score was recorded for all but one of the 64 people assessed, the single exception being a man who refused to attempt the test. In seven cases, the MMSE score was zero as the interviewee was unable to answer any questions correctly. The range of scores was zero to 28, with a median of 17 and a mean of 15.5. A total of 55 people (85.9%) scored below the usual cut-off of 24.

Interviewees were, on the whole, reluctant or unable to carry out the tests of frontal lobe function (appendix 3). Ten attempted the trail-making test, 18 the cognitive estimates task and 19 the category and letter fluency tests. There was no significant correlation between MMSE score and willingness or ability to attempt the frontal lobe tests.

5.2.3.2 Physical examination

Fifty-five people (85.9%) were able to be physically examined. Of the remaining nine, four declined and five, while unable to refuse verbally owing to severe dementia, indicated that they did not want to be examined.

The majority of the people examined physically (50; 90.9%) scored positively on at least one item of the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS). As this scale refers to certain signs which are not specifically parkinsonian, for example, an inability to rise from a chair unassisted, I regarded the the Hoehn and Yahr (H&Y) score as the more accurate determinant of the presence or absence of parkinsonism. Thirty-one people (56.3% of those examined) scored at least one on the H&Y scale, indicating clear motor signs of parkinsonism. Twenty-five of these 31 (80.6%) were either currently taking neuroleptic medication or had done so in the previous six months, and it was therefore difficult to establish whether the parkinsonian signs were primary, or the result of medication.

5.2.4 Data collected on both assessed and non-assessed groups

As noted in section 5.2.1, sufficient information for clinical diagnoses to be made was obtained from the medical case notes, social services' reports, general practitioners and relatives of eight of the screening-positive people who were not interviewed. The rest of the results section refers accordingly to the 72 people for whom diagnoses were made.

5.2.4.2 Demographic data

The mean age was 80.3 years (81.3 years for women and 77.9 years for men). Forty-five (62.5%) of the sample were female. Forty-seven (65.3%) were born in the UK, 10 (13.9%) in Africa or the Caribbean, six (8.3%) in Ireland, two (2.8%) in Cyprus, Greece or Turkey, four (5.6%) elsewhere in Europe, and three (4.2%) in other countries.

5.2.4.3 Clinical features

Nineteen people (26.4%) had a history of a single fall in the previous year, while four (5.6%) had had recurrent falls. Eight (11.1%) were either currently experiencing delusions or had experienced delusions in the previous year. Ten (13.9%) had experienced or were currently experiencing hallucinations, all of which were reported to be visual in type.

5.2.4.4 Investigations

Evidence in the medical notes of brain imaging was found for 14 people (19.4%). For 64 people there was sufficient data to derive the Hachinski Ischaemic Score (HIS), which was equal to or greater than the cut-off point of six in 10 people (13.9%).

5.3 Diagnoses

I present hereunder the distributions of diagnoses of dementia subtypes using the respective classification systems listed in chapter 4, namely my own clinical

diagnoses, DSM IV and ICD 10, as well as the distribution of AD using NINCDS-ADRDA criteria, VD according to NINDS-AIREN, DLB according to the consensus criteria, and FLD using the Gregory and Hodges criteria for frontal dementia and the consensus criteria for frontotemporal dementia. In each case, the number and percentage of cases is followed by 95% confidence intervals.

The distribution of diagnoses according to country of origin is also noted for people born in the United Kingdom (n=47) and Africa or the Caribbean (n=10). The numbers of people from each of the other categories of country are small, and consequently the distributions of diagnoses are not shown here. Sex differences in distributions were not significant, except for diagnoses of AD made using NINCDS-ADRDA criteria (section 5.3.4).

5.3.1 Clinical diagnoses

Sixty-seven (93.1%; CI 85-97) of the 72 people for whom diagnoses were made, were judged actually to be suffering from dementia. Twenty-six (36.1%; CI 26-48) had Alzheimer-type dementia, 20 (27.8%; CI 19-39) had vascular dementia, five (6.9%; CI 3-15) had dementia with Lewy bodies, four (5.6%; CI 2-14) had frontal lobe dementia, two (2.8%; CI 1-10) had dementia in Parkinson's disease, five (6.9%; 3-15) were judged to have 'mixed' dementia with features suggestive of both Alzheimer-type and vascular dementia, and in three (4.2%; CI 1-11) the aetiology could not be established with any confidence. The last three people were not assessed in person, and such information as was available was obtained solely from medical casenotes. One of the interviewees who was

diagnosed with dementia in Parkinson's disease had a clear history of having developed parkinsonian features several years before the onset of cognitive impairment or other psychiatric symptoms. In the other case, the time of onset of parkinsonian symptoms was not clear, but in the absence of other features suggestive of DLB, such as fluctuating cognition and visual hallucinations, a diagnosis of dementia in Parkinson's disease rather than DLB was made. As noted in chapter 4, for the purposes of the initial clinical diagnosis, visual hallucinations were a necessary (though not a sufficient) requirement for the diagnosis of DLB to be made.

5.3.1.1 Comparison by country of birth

For UK-born people, the distribution rates of diagnoses were: no dementia 8.5%; AD 38.3%; VD 21.3%; DLB 6.4%; mixed dementia 10.7%; FLD 6.4%; dementia in Parkinson's disease 4.3%; unspecified dementia 4.3%. With regard to those born in Africa or the Caribbean, 40% were considered to have AD, 50% VD and 10% mixed dementia.

5.3.2 Diagnoses according to DSM IV criteria

Sixty-four (88.9%; 80-94) people met criteria for dementia. Twenty-five (34.7%; CI 25-47) were diagnosed with AD, 19 (26.4%; CI 17-37) with VD, two (2.8%; 1-10) with dementia in Parkinson's disease, five (6.9%; 3-15) with mixed dementia and 13 (18.1%; 11-28) with unspecified dementia. Eight people (11.1%) did not meet DSM IV criteria for dementia. One did not have memory impairment, and

was given a clinical diagnosis of frontal lobe dementia. One had English as her second language and was judged insufficiently to have understand the screening questions. Three were depressed and three had cognitive dysfunction but no significant impairment in social or occupational function due to cognitive deficit.

5.3.2.1 Diagnoses by country of birth

Among people born in the UK, 12.8% had no dementia, 38.3% had AD, 23.4% VD, 4.26% dementia in Parkinson's disease, 14.9% mixed dementia and 6.38% unspecified dementia. For those born in Africa or the Caribbean, 30% had AD, 40% VD, 20% mixed dementia and 10% unspecified dementia.

5.3.3 Diagnoses according to ICD 10 criteria

Sixty (86.1%; CI 76-92) people met criteria for dementia, of whom 33 (45.8%; CI 35-57) were diagnosed with AD, 16 (22.2%; CI 14-33) with VD, two (2.8%; 1-10) with dementia due to Parkinson's disease, and 11 (15.3%; 9-25) with dementia not otherwise specified. Of the 12 people who did not meet criteria sufficient for the diagnosis of dementia, eight had not clearly been suffering from the disorder for at least six months, one was thought to have misunderstood the screening questions owing to a language barrier, and three were judged to be depressed rather than demented.

5.3.3.1 Diagnoses by country of birth

For the UK, distribution rates were as follows: no dementia 12.8%; AD 48.9%; VD 19.1%; dementia in Parkinson's disease 4.26%; unspecified dementia 14.9%.

For people from Africa or the Caribbean, 10% had no dementia, 40% AD, 40% VD and 10% unspecified dementia.

5.3.4 Diagnoses according to NINCDS-ADRDA criteria

Twenty people (27.8%; CI 19-39) fulfilled criteria for probable Alzheimer's disease, while 37 (51.4%; CI 40-62) were diagnosed as either probable or possible AD. 48.9% of people from the UK had no AD, 25.5% possible AD and 25.5% probable AD. Among people from Africa or the Caribbean, 40% had no AD, 30% possible AD and 30% probable AD.

These criteria were the only ones which yielded a significant difference in sex distribution of diagnosis. Eighteen women (25% of the 72 people) had no AD compared with 17 men (24%). Ten women (13.9%) had possible and 17 (23.4%) probable AD, compared with seven men (9.72%) for possible and three (4.17%) for probable AD. The chi-square value was 6.25 and the p-value was 0.04.

5.3.5 Diagnoses according to NINDS-AIREN criteria

Fourteen people (19.4%; CI 12-30) were diagnosed as having probable VD, 24 (33.3%; CI 23-44) as having either probable or possible VD. By country of birth, 72.3% of people from the UK had no VD, 10.6% possible VD and 17.0%

probable VD, while 40% of those from Africa or the Caribbean had no VD, 40% possible VD and 20% probable VD.

5.3.6 Diagnoses according to DLB consensus criteria

Seven people (9.7%; CI 5-19) met criteria for probable DLB. Twenty-two (30.5%; 22-42) were diagnosed with either probable or possible DLB. All 15 people who fulfilled criteria for possible DLB had spontaneous motor features of parkinsonism but no visual hallucinations. By contrast, all those who were diagnosed with probable DLB had both parkinsonism and visual hallucinations. 63.8% of people from the UK had no DLB, 25.5% possible DLB and 10.6% probable DLB. No DLB was diagnosed in 80% of people from Africa and the Caribbean, with the remaining 20% having possible DLB.

5.3.7 Diagnoses according to Gregory and Hodges criteria

These criteria yielded four people (5.6%; CI 2-14) with frontal dementia. All were from the UK (8.51% of UK-born people assessed).

5.3.8 Diagnoses according to consensus criteria for frontotemporal dementia

Six people (8.3%; CI 4-17) were diagnosed with frontotemporal dementia. As with the Gregory and Hodges criteria, all were from the UK (12.8% of UK-born people on whom diagnoses were made).

Table 5.4 summarizes the numbers and proportions of people fulfilling the different diagnostic criteria. 'Alzheimer's disease' includes all formulations for 'dementia of the Alzheimer's type' in DSM IV and 'dementia in Alzheimer's disease' in ICD 10. Similarly, 'vascular dementia' includes all subcategories under this heading in DSM and ICD. 'Mixed dementia' includes cases fulfilling DSM IV criteria for 'dementia due to multiple aetiologies', and 'other/unspecified dementia', cases of 'dementia in other medical conditions specified elsewhere' and 'dementia not otherwise specified' in DSM IV.

Diagnosis by criteria	Dementia <i>N</i> (%; CI)	AD <i>N</i> (%; CI)	VD <i>N</i> (%; CI)	DLB <i>N</i> (%; CI)	FLD <i>N</i> (%; CI)	PD <i>N</i> (%; CI)	Mixed dementia <i>N</i> (%; CI)	Other/ unspecified dementia <i>N</i> (%; CI)
DSM IV	64 (88.9; 80-94)	25 (34.7; 25-47)	19 (26.4; 17-37)			2 (2.8; 1- 10)	5 (6.9; 3-15)	13 (18.1; 11-28)
ICD 10	60 (86.1; 76-92)	33 (45.8; 35-57)	16 (22.2; 14-33)			2 (2.8; 1- 10)	0	11 (15.3; 9- 25)
NINCDS								
<i>Possible and probable</i>		37 (51.4; 40-62)						
<i>Probable</i>		20 (27.8; 19-39)						
AIREN								
<i>Possible and probable</i>			24 (33.3; 23-44)					
<i>Probable</i>			14 (19.4; 12-30)					
DLB consensus				22 (30.5; 22-42)				
<i>Possible and probable</i>				7 (9.7; 5-19)				
<i>Probable</i>								
Gregory & Hodges					4 (5.6; 2-14)			
FTD consensus					6 (8.3; 4-17)			
Clinical	67 (93.1; 85-97)	26 (36.1; 26-48)	20 (27.8; 19-39)	5 (6.9; 3-15)	4 (5.6; 2-14)	2 (2.8; 1- 10)	5 (6.9; 3-15)	3 (4.2; 1-11)

Table 5.4 Diagnoses by criteria (CI, 95% confidence interval; DSM, Diagnostic and Statistical Manual; ICD, International Classification of Diseases; AD, Alzheimer-type dementia; VD, vascular dementia; DLB, dementia with Lewy bodies; FLD, frontal lobe dementia; FTD, frontotemporal dementia; PD, dementia in Parkinson's disease)

(If the diagnosis cannot be made according to the specific clinical criteria the relevant box has been left blank)

5.3.9 Comparison of diagnoses of DLB and FLD with other diagnostic criteria

All five people who were diagnosed 'clinically' (i.e. before application of diagnostic criteria by the two clinicians) met consensus criteria for probable DLB. The two other people who fulfilled consensus criteria for probable DLB, were diagnosed clinically as having dementia in Parkinson's disease and Alzheimer-type dementia respectively. All seven consensus criteria 'probable DLB' cases met DSM IV criteria for dementia, four fulfilling criteria for AD, one for VD, one for dementia due to Parkinson's disease and one for unspecified dementia.

With regard to the diagnosis of FLD, all four people diagnosed clinically with FLD met both Gregory and Hodges criteria for frontal dementia and consensus criteria for frontotemporal dementia. The two additional people who fulfilled consensus criteria for FTD, received clinical diagnoses of Alzheimer-type dementia. One person who was both Gregory and Hodges and consensus-positive, was diagnosed according to DSM IV as having no dementia. The majority of the others met DSM IV criteria for AD. Table 5.5 compares diagnoses made using the DLB criteria and the two frontal lobe dementia criteria with those of DSM IV.

DSM IV diagnosis

	No dementia <i>N</i> (%)	Alzheimer's disease <i>N</i> (%)	Vascular dementia <i>N</i> (%)	Dementia due to Parkinson's disease <i>N</i> (%)	Unspecified dementia <i>N</i> (%)
DLB consensus criteria (probable DLB)	0	4 (57.1)	1 (14.3)	1 (14.3)	1 (14.3)
Gregory and Hodges DFT	1 (25)	2 (50)	1 (25)	0	0
Consensus criteria for FTD	1 (16.7)	3 (50)	1 (16.7)	0	1 (16.7)

Table 5.5 DSM IV diagnoses of cases of DLB and FLD (DSM, Diagnostic and Statistical Manual; DLB, dementia with Lewy bodies; FLD, frontal lobe dementia; DFT, dementia of frontal type; FTD, fronto-temporal dementia)

5.4 Non-demented cases

As indicated above, a sizeable proportion of the sample was not found to be demented using clinical, DSM IV and ICD 10 criteria. The ICD 10 system is more restrictive than DSM IV in that it requires both the presence of memory impairment and a duration of at least six months for a diagnosis of dementia to be made with confidence, thereby potentially excluding people with dementia that does not have memory impairment as a prominent feature (such as FLD) and those with newly diagnosed dementia. DSM similarly specifies memory impairment as a *sine qua non* for diagnosis, but does not impose a minimum limit on the duration of symptoms. However, it does specify that there must be impairment in social and/or occupational functioning, failure to fulfil which criterion excluded three of the sample.

The presence of non-demented people has an impact on the determination of the distribution of subtypes, as the denominator is artificially large. A more accurate method of determining distribution would therefore require the exclusion of non-demented people from the denominator. This raises the question of which people to exclude, as in this study ICD 10 and DSM IV yielded different numbers of non-demented. As discussed in chapter 3, there exists no 'gold standard' for the clinical diagnosis of dementia. Nonetheless, the DSM IV system is widely used and there is more evidence for its validity than there is for ICD 10. For this reason, those people who did not meet DSM IV (rather than ICD 10) criteria for dementia were considered 'truly' non-demented, and distribution rates were re-examined after these people had been excluded.

Table 5.6 shows the numbers and proportions of people fulfilling the different diagnostic criteria once those not meeting DSM dementia criteria have been excluded. No DLB consensus cases of probable or possible DLB have been excluded, i.e. all of these cases met DSM criteria for dementia. The proportions of people with probable DLB and probable plus possible DLB are, accordingly, higher, namely 10.9% and 34.4% respectively. One person fulfilling both sets of criteria for FLD was excluded.

Diagnosis by criteria	Dementia <i>N</i> (%; CI)	AD <i>N</i> (%; CI)	VD <i>N</i> (%; CI)	DLB <i>N</i> (%; CI)	FLD <i>N</i> (%; CI)	PD <i>N</i> (%; CI)	Mixed dementia <i>N</i> (%; CI)	Other/ unspecified dementia <i>N</i> (%; CI)
DSM IV	64 (100; 94-100)	25 (39.1; 28-51)	19 (29.7; 20-42)			2 (3.1; 0-9)	5 (7.8; 3-17)	13 (20.3; 12-31)
ICD 10	61 (95.3; 87-98)	32 (50.0; 38-62)	16 (25.0; 16-37)			2 (3.1; 0-9)	0	11 (17.2; 10-28)
NINCDS								
<i>Possible and probable</i>		36 (56.3; 44-67)						
<i>Probable</i>		20 (31.3; 21-43)						
AIREN								
<i>Possible and probable</i>			23 (35.9; 25-48)					
<i>Probable</i>			14 (21.9; 14-34)					
DLB consensus								
<i>Possible and probable</i>				22 (34.4; 24-46)				
<i>Probable</i>				7 (10.9; 5-21)				
Gregory & Hodges						3 (4.7; 2-13)		
FTD consensus						5 (7.8; 3-17)		
Clinical	63 (98.4; 91-100)	26 (40.6; 30-53)	20 (31.3; 21-43)	5 (7.8; 3-17)	2 (3.1; 0-9)	2 (3.1; 0-9)	4 (6.3; 2-15)	3 (4.7; 2-13)

Table 5.6 Diagnoses by clinical criteria (DSM non-demented cases excluded)

5.5 Summary of results

The results reveal Alzheimer's disease as the most common cause of dementia by both DSM IV and ICD 10 criteria. In addition, the majority of the sample fulfilled NINCDS-ADRDA criteria for either possible or probable Alzheimer's disease. The second most common diagnosis, again by both DSM and ICD criteria, was vascular dementia, with one-third meeting NINDS-AIREN criteria for possible or probable vascular dementia. The majority of people diagnosed with unspecified dementia were those with severe dementia on whom insufficient collateral information was available, with regard to onset and course of the illness, for a probable aetiology to be identified.

Almost ten per cent of the sample fulfilled consensus criteria for probable DLB, 30.5% fulfilling criteria for either probable or possible DLB. Of the cases of probable DLB, four (57.1%) met DSM IV criteria for Alzheimer's disease and one (14.3%) each met DSM criteria for vascular dementia, dementia due to Parkinson's disease and unspecified dementia. Identical results were seen when probable DLB cases were compared with their ICD 10 diagnoses.

Figure 5.1 indicates the degree of diagnostic overlap for cases meeting DSM criteria for dementia. For example, a person fulfilling consensus criteria for probable DLB but also NINCDS-ADRDA, DSM and/or ICD criteria for Alzheimer's disease would fall in the area of overlap between DLB and AD. The category 'unspecified dementia' has been excluded as this does not represent a diagnostic entity. The single cases of 'pure' DLB and FLD, i.e. those not lying in an area of overlap, had been diagnosed as unspecified dementia by DSM and/or ICD.

Cases of mixed dementia have been included in the area of overlap between AD and VD, as these were judged to be the combined aetiologies in each instance.

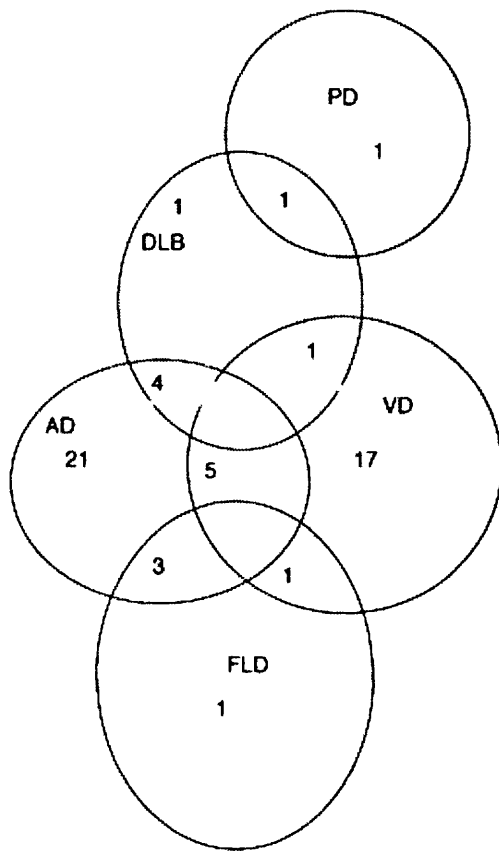


Figure 5.1 Overlap of diagnoses (AD, Alzheimer-type dementia; VD, vascular dementia; DLB, dementia with Lewy bodies; FLD, frontal lobe dementia)

5.6 Summary of chapter

Of 1,085 people who underwent the screening interview, 107 (9.86%) screened positive for dementia. Sixty-four of these (59.8%) were assessed at stage 2, and detailed information was obtained on a further eight, so that diagnoses were made on a total of 72 people. Different distribution rates for the subtypes were obtained depending on the diagnostic criteria used, and a number of people did not meet criteria for dementia. The implications of the differing distribution rates, and the high false-positive rate at screening, will be discussed in chapter six.

Chapter 6

Discussion

In this chapter I will focus on three main results found and the areas they highlight. Firstly, I shall concentrate on the prevalence rate of dementia as a whole in the light of previous reported findings, and examine the possible influence of the demographic factors of the population under study. Next, I will discuss the relationship between factors including country of birth and gender, and diagnosis of dementia and its subtypes. Finally, I will look at the distribution rates of the subtypes of dementia and how these are influenced by the diagnostic criteria used, and will comment on the implications for the future use of diagnostic criteria.

6.1 The prevalence of dementia

The community prevalence of screening-positive dementia was found in this study to be 9.9%. This figure fell to 6.7% when people living in residential or nursing homes were excluded. Lobo et al (2000), in a recent comparison of European prevalence studies, reported a dementia prevalence of 6.4%. It is not clear from the paper by Lobo et al whether people in institutional care were included or not. The prevalence of dementia in residential and nursing homes has been reported as 66% (Mann et al, 1984), and this study found a screen-positive prevalence of 70.4%. As noted in chapter 2, therefore, the prevalence

rate of dementia is unsurprisingly higher in a sample which includes participants living in 24-hour care facilities.

As described in chapter 5, not all of the screen-positive cases were found to have dementia according to clinical, DSM IV and ICD 10 criteria. To recapitulate: 93.1% were judged to have dementia on clinical examination prior to the application of standardised criteria, 88.9% fulfilled DSM IV criteria and 86.1% met ICD 10 criteria. There are two main possible explanations for the discrepancy between positivity on screening and no evidence of dementia on more detailed assessment.

6.1.1 Stringency of classification systems

6.1.1.1 DSM IV

Of the eight people who did not meet DSM IV criteria for dementia, one failed to show evidence of memory impairment despite fulfilling the other inclusion criteria, and was clinically diagnosed as having a frontal lobe dementia. Three people similarly met all criteria except one, namely that stipulating impairment in social or occupational function. One person was considered to have screened positively as a result of a misunderstanding of the Short-CARE questions, as her first language was not English, and when interviewed with an interpreter, was found not to be demented. The remaining three people were diagnosed as having depressive pseudodementia rather than dementia.

The failure of the last four of these people to fulfill DSM IV criteria for dementia may be attributed to the administration of the Short-CARE and arguably to the

nature of the instrument itself. This will be discussed in the next section. The clinical features of the first four of these people highlight characteristics of the DSM criteria themselves. By specifying memory loss as a fundamental inclusion criterion, DSM automatically excludes any case in which memory loss is not present, which can occur in frontal lobe dementia. The tendency to specify memory deficit is present in most current definitions of the word 'dementia', and whether or not a loss of memory is an essential feature or merely a typical one is often ambiguous at best. For example, the definition by the Royal College of Physicians, which begins with the words 'the acquired global impairment of higher cortical functions including memory...' (Royal College of Physicians, 1982), leaves open to interpretation whether or not 'including' is intended to mean 'invariably including'.

As regards the failure of three people to demonstrate impairment in social or occupational functioning, the DSM IV criteria are in my opinion less vulnerable to criticism here. The consideration of the impact of physical and psychiatric symptoms on the social and/or occupational milieu of the sufferer is increasingly recognised as an important aspect of psychiatric classification, if not medical classification as a whole. On the face of it, it is difficult to conceive of a person suffering from the cognitive losses of dementia, even in the early stages, who does *not* experience impairment in their relations with other people or in their ability to support themselves in daily living. The criteria could perhaps be improved by including a specification about *usual* functioning being impaired, rather than specifically occupational or social functioning. The absence of such

impairment in the three people in this study is probably illusory. In one case, the person's wife appeared to be minimizing the extent of her husband's impairment, and in each of the other two, the person had been a long-term resident of a nursing home since before the onset of cognitive impairment, and their reduction in self-sustaining activities could not be attributed to the dementing process. This underlines the difference between the use of classification systems for research and for clinical diagnosis: in the former case, criteria must be adhered to strictly to ensure reliability, while in the latter, they may be used as guidelines to direct and complement clinical judgement. I submit that no classification system, however reliable or valid, can ever make rules which encompass every eventuality, and that it is crucial to bear this in mind when interpreting the results of epidemiological research and attempting to apply them to clinical practice.

6.1.1.2 ICD 10

Twelve people did not meet ICD 10 criteria for dementia. In one case, as noted above, the person did not have English as her first language, and in three others depression was considered to have caused them to screen positively. The remaining eight people had not clearly been suffering from the disorder for at least six months. I do not regard this criterion of ICD 10 as an unreasonable one, as it is presumably intended to exclude temporary conditions such as acute confusional states which have shorter durations. Nonetheless, the comments about the difference in emphasis when using diagnostic criteria in research and clinical settings, apply to ICD 10 as well as DSM IV.

6.1.1.3 'Clinical' diagnoses

Five people were judged not to have dementia clinically, before the application of diagnostic criteria. One of these was not assessed in person but with reference to the medical case notes, which gave no indication of dementia, although as there was no reference at all to cognitive functioning it is possible that this was not tested and dementia was missed. The other four corresponded to the three depressed and one non-English-speaking people mentioned earlier.

6.1.2 The Short-CARE

The Short-CARE was described in section 4.2.3.1. It consists of six indicator scales which are each intended to identify problems in the particular area of functioning under study, such as depression or sleep disorder, for further assessment. The dementia indicator scale is one of two which have been refined to become diagnostic scales (the other is the depression indicator scale). By means of the dementia diagnostic scale, probable cases of so-called 'pervasive dementia' can be identified. Gurland et al (1984) point out that 'pervasive dementia' is not intended to represent a specific condition, but rather to refer to a syndrome of cognitive impairment severe enough for clinical intervention. The dementia diagnostic scale has an inter-rater reliability of 0.76, and follow-up data indicate that a correct prediction can be made for 84% of cases of pervasive dementia and 91% of non-cases (Gurland et al, 1984).

When the Short-CARE is used for health screening, the result of the depression diagnostic scale is used in conjunction with that of the dementia diagnostic scale to decide whether the apparent cognitive impairment or functional disability of an individual is in fact caused by depression rather than dementia. In the context of this study, no such interpretation was made, and all people who screened positive for pervasive dementia were automatically regarded as dementia cases. The fact that three screen-positive people were subsequently judged to have depression and not dementia, is more a reflection on the way the Short-CARE findings were interpreted than evidence of an intrinsic flaw in the screening instrument itself. Indeed, the purpose of using a screening instrument was to avoid false negatives as far as possible rather than false positives.

6.2 Sociodemographic characteristics of the study population

6.2.1 Socioeconomic status

In section 4.2.3.1 I noted that the geographical region chosen for this study, namely the London borough of Islington, is the sixth most deprived area in England and Wales. Several studies have examined the relationship between social class and risk of cognitive impairment and dementia. O'Connor et al (1989) administered the Mini-Mental State Examination (MMSE) to 1,865 general practice attenders and found a significant association between low social class and MMSE scores below the cut-off point for cognitive impairment. Similarly, Brayne & Calloway (1990) found low MMSE scores to be associated with lower socio-economic group among women aged 70 to 79 years in rural

Cambridgeshire. This study did not, however, find an association between socio-economic group and diagnosis of dementia, and the authors cautioned against the use of the MMSE score as a proxy measure of dementia, a notion which is relevant to the present study. These findings are not confined to Western studies, as Woo et al (1994) identified lower social class as a significant risk factor for cognitive impairment in Hong Kong Chinese people aged 70 and older.

More recently, Hobson & Meara (1999) reported a significant association between low scores on the Cambridge Cognitive Examination (CAMCOG) and lower social class, and Cullum et al (2000) found a significant association between decline in the attention/calculation subscale of the CAMCOG and manual social class. By contrast, Paykel et al (1994) found no difference in incidence rates of dementia by social class, and in a study of autopsy-confirmed cases of AD by Munoz et al (2000), no evidence was found that education, income or socio-economic levels had an effect on the risk of developing AD. There was no effect of social class on general practice consultation rates for psychiatric disorders, including dementia, in an investigation of 60 GP practices in England and Wales carried out by Shah et al (2001).

Meta-analyses of prevalence studies for dementia such as that by Lobo et al (2000) do not provide detailed information about the socio-economic characteristics of the populations under investigation, and so it is difficult to draw firm conclusions about the relationship, if any, of such characteristics to dementia prevalence. This in turn makes it impossible to state confidently whether the

present study, with its relatively socially deprived population, yields unusually high or low prevalence rates.

6.2.2 Age distribution

The age-specific prevalence rates for dementia in the present study are shown in table 6.1, and the results of the three meta-analyses by Jorm et al (1987), Hofman et al (1991) and Ritchie et al (1992), previously shown in table 2.1, are reproduced for the purpose of comparison.

Age groups	Prevalence rates from present study (residential/nursing homes included)	Prevalence rates from present study (residential/nursing homes excluded)	Prevalence rates from Jorm et al (1987)	Prevalence rates from Hofman et al (1991)	Prevalence rates from Ritchie et al (1992)
65-69	4.7	3.5	1.4	1.4	1.6
70-74	6.6	5.3	2.8	4.1	2.8
75-79	7.8	4.5	5.6	5.7	4.9
80-84	14.9	9.9	11.1	13.0	8.7
85+	24.1	13.8	23.6	24.5	16.4

Table 6.1 Age-specific prevalence rates from current study compared with meta-analyses

The trend in the present study towards increasing dementia prevalence with increasing age, matches that of the three meta-analyses and indeed most reported studies, but there appear to be more people with dementia at younger ages. The number of people interviewed who were aged 90 and over was comparatively small and so a detailed analysis of subgroups within this range is not possible. The prevalence of dementia within the 85 to 89 year age group was, however, 23.4% (13.5% excluding those in residential or nursing care), and that in the 90 and older group was 26.5% (14.7% outside institutional care), suggesting that the trend towards increased rates of dementia continues with ageing and does not level off, as found by Ritchie & Kildea (1995). The above rates in the 90 and older group are notably lower than, for example, the prevalence of 46.7% reported by Forsell & Winblad (1997).

A striking feature of the comparison in the above table is the relatively high prevalence of dementia in the 65-69 age group in our study. Even when people in institutional care are excluded, the prevalence rate is almost twice that of the highest rate found among the meta-analyses (namely that of Ritchie et al). Unlike in the Jorm meta-analysis, which illustrates elegantly the widely-quoted principle that the age-specific prevalence ratio for dementia doubles with each additional five years of age (Cooper, 1997), the prevalence rates in our study show a relatively small increase with every additional five years between ages 65 and 80, after which they begin to conform to the recognised model. It is difficult to account for this unusual finding, particularly as the numbers of people screened

who were aged 65 to 69, 70 to 74 and 75 to 79, namely 254, 302 and 244 people respectively, were large when compared to the number of people screened who were aged 80 and older (286 people in total), and therefore the prevalence values in the younger age groups are likely to have more statistical power. A possible explanation is the disproportionate number of younger people with dementia who were of African/Caribbean origin. If African/Caribbean participants in the study aged under 70 are excluded from the analysis, the prevalence rate for dementia in the 65 to 69 age group drops to 3.2%.

6.2.3 Gender distribution

Women constituted 66.4% of people screening positive for dementia. As was discussed in section 2.3, individual prevalence studies as well as meta-analyses have drawn conflicting conclusions about the relative preponderance of dementia in women compared with men. Jorm (1987) found no overall gender difference in prevalence after adjusting for age, and a two-phase door-to-door population survey carried out in rural Italy revealed prevalence rates for dementia of 8.2% and 7.9% respectively for women and men, a difference which was not significant (Prencipe et al, 1996). By contrast, the meta-analysis of European studies by Lobo et al (2000) found a higher prevalence in women, and two large studies in Canada and Korea respectively each reported a female to male dementia prevalence ratio of 2:1 (Anonymous, 1994; Park et al, 1994).

6.2.4 Country of birth

Table 5.3 indicated the prevalence of dementia by country of birth, as follows:

United Kingdom 10%, Ireland 3.6%, Africa/Caribbean 17.3%, Cyprus/Greece/Turkey 11.3%, continental Europe 8.33% and other countries 10%. As was discussed in section 2.3, the study of dementia prevalence in relation to ethnic or national background is difficult, as the two designations do not necessarily correspond, and the relative influence of genetic and environmental factors is difficult to determine. Hatada et al (1999) and more recently Yamada et al (2001) have reported Japanese rates of both dementia as a whole and its subtypes which have more closely matched Western figures than those of previous studies, and have postulated that the 'Westernisation' of global culture in the form of lifestyle, industrialisation and diet may account for this change.

The number of UK-born people interviewed in this study (667) was greater than the combined total from all other countries (418), and the prevalence rate in the former group may therefore be more representative. Nonetheless, there is a significant difference between the overall dementia prevalence rate and the rates in the second- and third-largest groups, namely people born in Ireland and Africa/Caribbean respectively. No published studies have examined the prevalence of dementia specifically in people born in Ireland. A possible explanation for the small prevalence of dementia among Irish-born people is that few of these people lived in the residential and nursing homes included in our study, which may reflect the fact that people tend to cluster in particular homes

according to ethnic background. It has been suggested that dementia is a 'First-World' condition as low prevalence has been found in Nigerian and Indian populations (Hendrie et al, 1995; 10/66 Dementia Research Group, 2000). The difference in rates has not been clearly attributable to genetic factors, as conversely high rates have been reported in African-Americans (Perkins et al, 1997). The significance of the high prevalence of dementia in people from Africa and the Caribbean in this study will be discussed in section 6.3, when the relation to subtype is examined.

The largest body of data regarding differences in dementia prevalence between different ethnic or national groups, concerns the comparison of Western and Asian populations, particularly Japanese. Such a comparison cannot be made in this study as none of the people screened was from the Far East.

6.3 Subtypes of dementia

In section 5.3, the diagnoses arrived at were grouped sequentially by the different diagnostic criteria employed in the study. In this section I will present the data differently, considering each diagnostic category in turn and examining the use of the various sets of criteria. My purpose in doing this is to highlight the differences in prevalence rates when using different classification systems, and to provide a context in which to make a case for the relative merits of each system in diagnosing the particular condition.

6.3.1 Alzheimer's disease

Table 6.2 shows the distribution of AD as a proportion of total dementia cases, according to DSM IV, ICD 10, NINCDS-ADRDA and 'clinical' criteria.

Diagnostic system	Distribution of AD cases (%)
DSM IV	34.7
ICD 10	45.8
NINCDS-ADRDA (possible)	13.6
NINCDS-ADRDA (probable)	27.8
NINCDS-ADRDA (possible + probable)	51.4
Clinical	36.1

Table 6.2 Distribution of cases of Alzheimer's disease (AD) by diagnostic system

Using both DSM IV and ICD 10 criteria, a relatively large proportion of cases were diagnosed as having unspecified dementia (18.1% and 15.3% respectively). In the majority of cases these diagnoses were made when there was insufficient evidence on history to indicate with certainty an insidious onset and gradual progression of the disorder, which is a defining characteristic of the syndrome in both classification systems. For this reason, it is feasible that several of the 'unspecified' cases may have received a diagnosis of AD under both systems, if a clearer history had been available. The above distributions for DSM IV and ICD 10 may therefore be artificially low. Nonetheless, both sets of criteria are designed for use in a naturalistic setting, in which a complete and accurate history is not always available, and so it is perhaps inappropriate to speculate about 'ideal' circumstances.

The high proportion of cases fulfilling NINCDS-ADRDA criteria for probable plus possible AD may reflect the criticism of Blacker et al (1994), that the criteria allocate disproportionate prominence to relatively early behavioural symptoms. While validation studies of these criteria have produced conflicting results (section 3.1.2.1), they are the most extensively-studied clinical criteria for the diagnosis and can justifiably be regarded as the clinical 'gold standard' for this diagnosis. The majority of studies (e.g. Holmes et al, 1999; Lim et al, 1999; Lopez et al, 1999) have found the criteria to have high sensitivity but relatively low specificity. Given this apparent tendency towards over inclusiveness, it is probably reasonable to regard the cases of 'probable' AD as more representative

of the actual prevalence. If these last two points are accepted, the distribution of AD in this study population is 27.8%.

The figures in table 6.2 have been calculated using a denominator of 72, i.e. on the assumption that all 72 people in the study for whom diagnoses were made, actually had dementia. As was noted in section 5.4, however, both classification systems which were able to distinguish between dementia and non-dementia (as opposed to those systems which are only designed to identify a particular subtype, such as NINCDS-ADRDA), namely, DSM IV and ICD 10, diagnosed dementia in only 88.9% and 86.1% respectively of the 72 people. The greater evidence for the clinical validity of the DSM IV system suggests that it is more deserving of the title 'gold standard', at least with regard to distinguishing dementia from non-dementia. Accordingly, if all the 'DSM non-demented' cases are excluded from the denominator, the distribution of AD changes as follows: DSM IV 39.1%; ICD 10 50%; NINCDS-ADRDA probable 31.3%; clinical 40.6%. The revised figure for the distribution of AD, using the best-validated criteria available (namely NINCDS-ADRDA), is therefore 31.3%.

The only significant difference in gender distribution of diagnosis in the entire study was demonstrated with regard to the NINCDS-ADRDA diagnosis of probable AD. 23.4% of women with dementia had probable AD, compared with 4.17% of men ($p=0.04$). This yields a female to male ratio of 5.6:1, which is more than double the highest ratio hitherto reported, namely 2.6:1 (Bachman et al, 1992).

6.3.2 Vascular dementia

Table 6.3 shows distribution rates for vascular dementia (VD) according to DSM IV, ICD 10, NINDS-AIREN and clinical diagnoses.

Diagnostic system	Distribution of VD cases (%)
DSM IV	26.4
ICD 10	22.2
NINDS-AIREN (possible)	13.9
NINDS-AIREN (probable)	19.4
NINDS-AIREN (possible + probable)	33.3
Clinical	27.8

Table 6.3 Distribution of cases of vascular dementia (VD) by diagnostic system

The distributions according to the different criteria are more uniform than was the case for AD. This is unsurprising given that the inclusion criteria are similar across the systems, and are more clearly identifiable than many of those required for the diagnosis of AD. For example, a sudden decline in cognitive ability following an event such as a stroke is more likely to be revealed in a history than a gradual, insidious onset of symptoms. Similarly, exclusion criteria for VD are fewer in all three systems than those for AD, and there is therefore less likelihood of a case being excluded by one system but not another.

A relatively high figure was obtained for NINDS-AIREN 'possible' dementia. This was owing to the fact that radiological evidence of cerebrovascular disease was frequently not available, and in the absence of such evidence a diagnosis of 'probable' VD cannot be made.

As with the NINCDS-ADRDA criteria for AD, the NINDS-AIREN system has been the most extensively validated against post-mortem diagnosis of VD, with Gold et al (1997) reporting a sensitivity of 58% and a specificity of 80%, and Holmes et al (1999) finding sensitivity to be 43% and specificity to be 95%. Once again, if people who did not fulfill DSM IV criteria for dementia are excluded, the distribution of NINDS-AIREN cases of probable VD rises to 21.9%, and this represents the most accurate estimate of the distribution of VD in this population.

The absence of a significant gender difference in VD distribution mirrors the findings of Yamada et al (1999). By country of birth, there were no significant differences in distribution rates of NINDS-AIREN probable VD, with 17% of

demented people from the UK fulfilling criteria for probable VD versus 20% of people from Africa or the Caribbean. Forty percent of the latter group, however, had possible VD compared with 10.6% of the former, and in each case of possible VD among African/Caribbeans, the person fulfilled all criteria for probable VD except for evidence on neuroimaging of cerebrovascular disease, which was unavailable in each case rather than negative. With regard to less well-validated criteria for VD, 40% of people with dementia from Africa or the Caribbean were diagnosed with VD using both DSM IV and ICD 10 systems, compared with 23.4% (DSM IV) and 19.1% (ICD 10) of UK-born people. Although the number of African/Caribbean participants was comparatively small, these findings nevertheless provide compelling evidence that VD is overrepresented among people born in Africa or the Caribbean. Given that all other diagnoses were made less frequently in this group than in the UK-born group, it is reasonable to assume that VD accounts for the increased prevalence of dementia as a whole in people from Africa and the Caribbean.

6.3.3 Dementia with Lewy bodies

The only criteria for the diagnosis of DLB for which validation studies have been carried out are the DLB consensus criteria. 9.7% of demented people in this study met consensus criteria for probable DLB, 20.8% fulfilling criteria for possible DLB. My 'clinical' diagnosis of DLB, which required the presence of visual hallucinations, was made in 6.9% of demented people. The two people who met consensus criteria for DLB but not 'clinical' criteria, each had two of the

three requirements for probable DLB, namely fluctuating cognition and spontaneous motor features of Parkinson's, but not the third, visual hallucinations. With the exclusion of DSM IV- negative dementia cases, the consensus criteria distribution figures rise to 10.9% for probable and 23.5% for possible DLB. The 'clinical' figure increases to 7.8%.

As the consensus criteria are the only ones for which there is evidence, if conflicting, of reliability and validity, they represent the best existing method of diagnosing this disease, and the conclusion from this study is therefore that the distribution of probable DLB in the community is 10.9% of cases of dementia. It is possible that this figure is an overestimate of the true distribution of the disease.

As reported by Hohl et al (2000), post-mortem confirmation of DLB correlates with the presence of visual hallucinations before death, although admittedly the number of cases in the study was small, namely ten. Excluding participants without visual hallucinations would reduce the distribution rate of DLB in my study to 7.8%.

Conversely, the figure of 10.9% may be an *underestimate*. Given that a history of fluctuation in cognitive performance was not always clearly obtainable, and that participants were assessed only once rather than on serial occasions, one of the core features of DLB as defined by consensus criteria may have been missed in many cases. As reported in section 5.2.3.2, 56.3% of those assessed showed clear motor signs of parkinsonism, and the combination of this sign with cognitive fluctuation would have qualified the individual for a diagnosis of probable DLB, provided that no exclusion criteria were present and the person suffered from a

progressive dementia. An emphasis on visual hallucinations as a relatively more significant criterion than parkinsonism would reduce the risk of missed cases, as only 13.9% of people assessed had a clear history of visual hallucinations. It is of course possible that this history may in some cases be inaccurate itself.

The high figure for possible DLB cases, namely 23.5% of dementias, raises questions about the usefulness of the 'possible' category, particularly as it is currently defined so as to fit any person with progressive dementia, no exclusion criteria and a single one of the core criteria. This means, for example, that a person with advanced AD who has parkinsonian signs, a not uncommon occurrence, would be classified as having possible DLB under consensus criteria. Inclusiveness of this kind does serve the function of raising the index of suspicion about DLB and encouraging the clinician to consider differential diagnoses, but as a nosological category, the merits of currently constituted 'possible DLB' are unclear.

All people who met consensus criteria for probable DLB were judged to be demented according to both DSM IV and ICD 10 systems. The majority of probable DLB cases were diagnosed as AD by DSM IV and ICD 10. This suggests that both systems are sensitive at identifying DLB as a dementia, but unable to distinguish it from other aetiologies such as AD.

There were no significant gender differences with regard to the diagnosis of probable DLB, and all people so diagnosed were born in the UK. The relatively small number of probable DLB cases makes it difficult to draw firm conclusions

about the association of the disease with variables such as gender and country of birth.

The distribution of DLB in our study contrasts markedly with the findings of the only other previously published study of this type, by Yamada et al (2001), in which the prevalence of DLB in a Japanese population was 0.1%. Given that the prevalence of dementia in the Japanese study was 3.8%, the distribution of DLB as a subtype may be calculated as 2.63%. The reason for the difference in distribution between these two populations is uncertain, and a further study comparing the two populations may help highlight aetiological and preventative factors. Subsequent studies by Shaji et al (2002) and Rahkonen et al (2003), while carried out in populations of different age parameters (60 and older in the former study, 75 and older in the latter) have found distribution rates for probable DLB which are similar to our own: 9% and 14.6% respectively.

6.3.4 Frontal lobe dementias

Neither the consensus criteria for frontotemporal dementia (FTD) nor the Gregory & Hodges criteria for frontal dementia have been subjected to validity or reliability studies. The former criteria, however, are closely based on the Lund and Manchester criteria, which have been validated in a single study by Lopez et al (1999) (section 3.4.2). For the purposes of this discussion, the FTD consensus criteria are thus regarded as the 'gold standard' for diagnosis. Accordingly, the distribution of FTD in this study is 7.8%. In accordance with the distribution figures for the other dementias, all DSM IV non-demented cases have been

excluded. This, however, presents a problem, because as was noted in section 6.1.1.1, frontal lobe dementias are excluded from the DSM IV dementia category almost by definition, as they do not characteristically present with memory loss in the early stages.

The distribution of Gregory & Hodges frontal dementias is 4.7% (5.6% if DSM IV non-demented cases are not excluded). All people with this diagnosis also fulfilled consensus criteria for FTD. The two people who fulfilled consensus FTD criteria but not Gregory & Hodges criteria were diagnosed according to other systems as having AD, and showed evidence of AD-like features including memory impairment. These findings support the assertion of Gregory and Hodges (1993) that 'frontotemporal dementia' is a broader category than their own 'frontal dementia'. The authors' further contention that 'frontotemporal dementia' is indefensible as a disease category, and groups together disparate conditions artificially, cannot be supported or refuted by the findings in my study.

As is the case for DLB, the only previously published community prevalence study of FLD is that by Yamada et al (2001). This study revealed no cases of FLD. Again, as with DLB, no significant gender difference existed for FLD, and all people with diagnoses according to both sets of criteria were born in the UK.

6.4 Limitations of the study

The results of this study are restricted by the numbers of people identified at screening as having dementia on whom a diagnosis could not be made. Several factors accounted for this. First, there was a relatively high attrition rate between the first and second stages: contact was made with 69.2% of screening-positive cases and 59.8% were assessed in person. Of those people not contacted, almost identical numbers (16 and 17 respectively) had died and moved out of area. Given the age and poor health of the population under study, a high mortality rate is unsurprising. What is more unexpected is the number of people who had moved away, especially as the mean time between screening and attempts to contact for stage two was only 8.8 months. This may reflect institutionalisation and the attempt to find less expensive accommodation outside central London. Second, 39.1% of people interviewed at stage two were in residential or nursing care, and in many cases had been institutionalised for several years. Information about onset and progression of cognitive problems was frequently scanty for these participants, especially as it was often obtained from staff who had not known the person for long. Third, although hospital case notes were obtained for 78.5% of the screening-positive cases, the notes frequently made little or no reference to the patient's mental condition, focusing rather on physical disorders.

The Short-CARE has not been validated as an instrument on people who have dementia without significant memory impairment, and we do not know to what extent this may have influenced our findings, although we did detect some

people with this syndrome (those with frontal lobe dementia). In addition, it is a limitation of the study that post-mortem diagnoses were not available, against which clinical diagnoses could be verified.

A relatively high proportion (11.1%) of people identified by initial Short-CARE screening did not have dementia according to DSM IV. For three of these eight people there was insufficient evidence of impairment in social or occupational functioning for dementia to be diagnosed, despite clear evidence of cognitive impairment in multiple domains. As this was an epidemiological study, we employed a screening instrument and, subsequently, diagnostic criteria which produced categorical outcomes. Caution, however, clearly needs to be exercised in the use of these criteria in clinical practice, to avoid excessively strict adherence to the inclusion and exclusion requirements at the expense of common sense.

Another shortcoming of this study is that a single assessment of cognitive function at stage 2 was carried out. Given that one of the core characteristics of dementia with Lewy bodies is fluctuating cognitive performance, it is possible that this feature was missed even though every effort was made to elicit a history of fluctuation from informants. The use of validated scales of fluctuation in dementia, such as The Clinician Assessment of Fluctuation and the One Day Fluctuation Assessment Scale (Walker et al, 2000), is important in future studies of this kind.

6.5 Conclusions

The prevalence of dementia in the Islington community aged 65 and older is 9.9%, as defined by positivity on the dementia diagnostic scale of the Short-CARE screening instrument. The prevalence rate for people living outside institutional care is 6.7%, which is similar to that identified in a recent meta-analysis of European studies. For people in residential and nursing care, the prevalence is 70.4%. Women comprise two-thirds of dementia cases. Dementia is significantly more prevalent in people born in Africa or the Caribbean and occurs at a younger age in this group, and significantly less prevalent in people from Ireland.

With regard to subtypes of dementia, distribution rates varied according to the diagnostic system used. The most uniformity between diagnostic systems was seen for vascular dementia, which was over-represented in people from Africa and the Caribbean. The only significant gender difference was identified for the NINCDS-ADRDA diagnosis of probable AD, which was found in five times as many women as men.

If those cases not meeting DSM IV criteria for dementia are excluded, and the best-validated diagnostic criteria for each subtype of dementia are taken as the clinical 'gold standard' (NINCDS-ADRDA for AD, NINDS-AIREN for VD, consensus criteria for DLB and consensus criteria for FTD) then the distribution of the subtypes is as follows: probable AD 31.3% (95% CI 21-43), probable VD 21.9% (95% CI 14-34), probable DLB 10.9% (95% CI 5-21) and FLD 7.8% (95% CI 3-17).

6.5.1 Clinical implications

This study confirms dementia as a condition likely to be seen frequently in clinical practice, and especially among people who live in 24-hour residential care. An unexpected finding was the comparatively high prevalence of dementia, and particularly the vascular subtype, in people from Africa and the Caribbean. This finding requires replication in similar populations, and points towards a need for research into the reasons for this discrepancy, especially with regard to the known risk factors for VD such as hypertension.

Alzheimer's disease is confirmed as the most common subtype, in keeping with the majority of prevalence and distribution studies, but there exist several other subtypes, namely VD, DLB and FLD, which are likely to be encountered by the clinician.

Previous studies of the frequency of DLB have concentrated on hospital inpatient or outpatient populations and in particular on the epidemiologically unrepresentative cohorts that come to post-mortem. It is highly likely that many of the figures from published studies on the distribution of other dementia subtypes are contaminated by DLB cases, particularly as neither of the two major classification systems currently in use, DSM IV and ICD 10, includes the diagnosis of DLB. This is the first study in the Western world to report on the community prevalence of DLB. Most cases of 'probable' DLB in this study were diagnosed as having Alzheimer's disease using DSM IV and ICD 10. Almost one third of the sample fulfilled DLB consensus criteria for either 'probable' or

'possible' DLB. This suggests that the consensus criteria are broad, at least in regard to the diagnosis of 'possible' DLB. The 'clinical' criteria used to diagnose DLB, which were simultaneously more restrictive in requiring the presence of visual hallucinations and more flexible in leaving unspecified the time relationship between onset of parkinsonism and that of dementia, yielded a lower rate for this disorder.

As with DLB, neither DSM IV nor ICD 10 permit the diagnosis of FLD, though both include Pick's disease as a possible aetiology. As other aspects of cognition and activities of daily living are relatively preserved in early FLD, our rates may be conservative as some cases may have been missed using a screening test which relies on orientation, memory and independence in activities of daily living (Gregory and Hodges, 1996). There are suggested ways of overcoming this problem using additional bedside tests (Gregory et al, 1997). In my study, FLD was diagnosed more often using consensus criteria than Gregory and Hodges criteria. This may be due to disagreement about the terminology used to describe these dementias, with some groups preferring 'frontotemporal dementia' (Brun et al, 1994) while others regard this term as including disparate conditions and prefer 'dementia of frontal type' (Gregory et al, 1998). Both sets of criteria used in our study are weighted towards a purely degenerative aetiology of FLD and exclude the possibility of a vascular contribution to symptoms.

Our results indicate that it is possible to determine a probable aetiology in most cases of dementia. The relatively small degree of overlap of the AD and VD categories, as shown in figure 5.1, indicates that the diagnostic systems in current use lead to the same diagnostic conclusions for most individuals. This, however, is only true for AD and VD.

The ability to distinguish particular subtypes of dementia is important for several reasons. It enables clinicians to identify associated risk factors, to implement specific treatment strategies, to inform patients and relatives more accurately of the prognosis of each one, and to provide relevant services. This is particularly pertinent in the light of the development of treatments such as the cholinesterase-inhibiting drugs for Alzheimer's disease. The demand for these drugs, together with their high cost, requires accuracy of diagnosis and standardisation of diagnostic criteria. Further validation of current criteria needs to be carried out against post-mortem diagnosis, in particular for those systems which attempt to diagnose VD, DLB and FLD, as there is relatively little validity data in these areas compared to that available for the NINCDS-ADRDA criteria for AD, for example. The inability of DSM and ICD to identify DLB and FLD, which are relatively common forms of dementia, means that they do not suffice to categorise these conditions. Both DLB and FLD should be incorporated in future editions of standard diagnostic criteria.

APPENDIX: DIAGNOSTIC CRITERIA

DSM-IV criteria for dementia (APA, 1994)

I Demonstrable evidence of impairment in short- and long-term memory. Impairment in short-term memory may be indicated by inability to remember three objects after five minutes. Long-term memory impairment may be indicated by inability to remember past personal information or facts of common knowledge

II At least one of the following:

- **impairment in abstract thinking, as indicated by inability to find similarities and differences between related words, difficulty in defining words and concepts, and other similar tasks**
- **impaired judgement, as indicated by inability to make reasonable plans to deal with interpersonal, family and job-related problems and issues**
- **other disturbances of higher cortical function such as aphasia, apraxia, agnosia and constructional difficulty**
- **personality change, ie. alteration or accentuation of premorbid traits**

III The disturbance in I and II significantly interferes with work or usual social activities or relationships with others

IV Not occurring exclusively during the course of delirium

V Either:

- **there is evidence from the history, physical examination or laboratory tests of a specific organic factor judged to be aetiologically related to the disturbance**
- **in the absence of such evidence, an aetiologic organic factor can be presumed if the disturbance cannot be accounted for by any non-organic mental disorder eg. major depression**

DSM-IV criteria for dementia of the Alzheimer's type (APA, 1994)

I The development of multiple cognitive deficits manifested by both

- memory impairment (impaired ability to learn new information or to recall previously learned information)
- one (or more) of the following cognitive disturbances: aphasia (language disturbance), apraxia (impaired ability to carry out motor activities despite intact motor function), agnosia (failure to recognize or identify objects despite intact sensory function), disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)

II The cognitive deficits in criterion I each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

III The course is characterized by gradual onset and continuing cognitive decline.

IV The cognitive deficits in criteria I and II are not due to any of the following:

- other central nervous system conditions that cause progressive deficits in memory and cognition (e.g., cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor)
- systemic conditions known to cause dementia (e.g., hypothyroidism, vitamin B12 and folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV infection)

V The deficits do not occur exclusively during the course of a delirium.

VI The disturbance is not better accounted for by another Axis I disorder (e.g., Major Depressive Disorder, Schizophrenia).

DSM-IV criteria for the diagnosis of vascular dementia (APA, 1994)

I The development of multiple cognitive deficits manifested by both:

- memory impairment (impaired ability to learn new information or to recall previously learned information)
- one or more of the following cognitive disturbances: aphasia (language disturbance), apraxia (impaired ability to carry out motor activities despite intact motor function), agnosia (failure to recognize or identify objects despite intact sensory function), disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)

II The cognitive deficits in criterion I each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning

III Focal neurological signs and symptoms (e.g., exaggeration of deep tendon reflexes, extensor plantar response, pseudobulbar palsy, gait abnormalities, weakness of an extremity) or laboratory evidence indicative of cerebrovascular disease (e.g., multiple infarctions involving cortex and underlying white matter) that are judged to be etiologically related to the disturbance

IV The deficits do not occur exclusively during the course of a delirium

ICD 10 criteria for the diagnosis of dementia (WHO, 1992)

- The primary requirement for diagnosis is evidence of a decline in both memory and thinking which is sufficient to impair personal activities of daily living
- The impairment of memory typically affects the registration, storage and retrieval of new information, but previously learned and familiar material may also be lost, particularly in the later stages
- The above symptoms and impairments should have been evident for at least six months for a confident clinical diagnosis of dementia to be made

ICD 10 criteria for the diagnosis of dementia in Alzheimer's disease (WHO, 1992)

The following features are essential for a definite diagnosis:

- presence of a dementia as described above
- insidious onset with slow progression. An apparent plateau may occur in the progression
- absence of clinical evidence, or findings from special investigations, to suggest that the mental state may be due to other systemic or brain disease which can induce a dementia (eg. hypothyroidism, hypercalcaemia, vitamin B12 deficiency, niacin deficiency, neurosyphilis, normal pressure hydrocephalus or subdural haematoma)
- absence of a sudden, apoplectic onset, or of neurological signs of focal damage such as hemiparesis, sensory loss, visual field defects, and incoordination occurring early in the illness

ICD 10 criteria for the diagnosis of vascular dementia (WHO, 1992)

- The diagnosis presupposes the presence of a dementia as described above
- Impairment of cognitive function is commonly uneven, so that there may be memory loss, intellectual impairment, and focal neurological signs
- Insight and judgement may be relatively well preserved
- An abrupt onset or a stepwise deterioration, as well as the presence of focal neurological signs and symptoms, increases the probability of the diagnosis

**NINCDS-ADRDA criteria for clinical diagnosis of Alzheimer's disease
(McKhann et al, 1984)**

I The criteria for the clinical diagnosis of *probable* Alzheimer's disease include:

- dementia established by clinical examination and documented by the mini-mental test, Blessed dementia scale, or some similar examination, and confirmed by neuropsychological tests
- deficits in two or more areas of cognition
- no disturbance of consciousness
- onset between ages 40 and 90
- absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in cognition

II Other clinical features consistent with the diagnosis of probable Alzheimer's disease, after exclusion of other causes of dementia, include:

- progressive deterioration of specific cognitive functions such as language, motor skills and perception
- impaired activities of daily living and altered patterns of behaviour
- family history of similar disorders, particularly if confirmed neuropathologically
- laboratory results of normal lumbar puncture, normal pattern or non-specific changes in EEG, evidence of cerebral atrophy on CT with progression documented by serial observation

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

- plateaus in the course of progression of disease
- other neurological 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
- CT normal for age

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

- sudden, apoplectic onset
- focal neurological findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness
- seizures or gait disturbance 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 neurological, 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
- 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 histopathological evidence obtained from a biopsy or autopsy

NINDS-AIREN criteria for the diagnosis of vascular dementia (Roman et al, 1993)

I The criteria for the clinical diagnosis of *probable* vascular dementia include *all* of the following:

Dementia defined by cognitive decline from a previously higher level of functioning and manifested by impairment of memory and of two or more cognitive domains (orientation, attention, language, visuospatial functions, executive functions, motor control, and praxis), preferably established by clinical examination and documented by neuropsychological testing; deficits should be severe enough to interfere with activities of daily living not due to physical effects of stroke alone.

Exclusion criteria: cases with disturbance of consciousness, delirium, psychosis, severe aphasia, or major sensorimotor impairment precluding neuropsychological testing. Also excluded are systemic disorders or other brain diseases (such as AD) that in and of themselves could account for deficits in memory and cognition.

Cerebrovascular disease, defined by the presence of focal signs on neurologic examination, such as hemiparesis, lower facial weakness, Babinski sign, sensory deficit, hemianopia, and dysarthria consistent with stroke (with or without history of stroke), and evidence of no relevant CVD by brain imaging (CT or MRI) including multiple large vessel infarcts *or* a single strategically placed infarct (angular gyrus, thalamus, basal forebrain, or PCA or ACA territories), as well as multiple basal ganglia and white matter lacunes, *or* extensive periventricular white matter lesions, *or* combinations thereof.

A relationship between the above two disorders, manifested or inferred by the presence of one or more of the following: (a) onset of dementia within 3 months following a recognized stroke; (b) abrupt deterioration in cognitive functions; or fluctuating, stepwise progression of cognitive deficits.

II Clinical features consistent with the diagnosis of *probable* vascular dementia include the following:

- early presence of gait disturbance (small-step gait or marche a petits pas, or magnetic, apraxic-ataxic or parkinsonian gait)
- history of unsteadiness and frequent, unprovoked falls
- early urinary frequency, urgency, and other urinary symptoms not explained by urologic disease
- pseudobulbar palsy
- personality and mood changes, abulia, depression, emotional incontinence, or other subcortical deficits including psychomotor retardation and abnormal executive function.

III Features that make the diagnosis of vascular dementia uncertain or unlikely include:

- early onset of memory deficit and progressive worsening of memory deficit and progressive worsening of memory and other cognitive functions such as language (transcortical sensory aphasia), motor skills (apraxia), and perception (agnosia), in the absence of corresponding focal lesions on brain imaging
- absence of focal neurological signs, other than cognitive disturbance
- absence of cerebrovascular lesions on brain CT or MRI

IV Clinical diagnosis of *possible* vascular dementia may be made in the presence of dementia with focal neurologic signs in patients in whom brain imaging studies to confirm definite CVD are missing; or in the absence of clear temporal relationship between dementia and stroke; or in patients with subtle onset and variable course (plateau or improvement) of cognitive deficits and evidence of relevant CVD

V Criteria for diagnosis of *definite* vascular dementia are:

- clinical criteria for *probable* vascular dementia
- histopathologic evidence of CVD obtained from biopsy or autopsy
- absence of neurofibrillary tangles and neuritic plaques exceeding those expected for age
- absence of other clinical or pathological disorder capable of producing dementia

VI Classification of vascular dementia for research purposes may be made on the basis of clinical, radiologic, and neuropathologic features, for subcategories or defined conditions such as cortical vascular dementia, subcortical vascular dementia, BD, and thalamic dementia.

Consensus criteria for the clinical diagnosis of probable and possible dementia with Lewy bodies (DLB) (McKeith et al, 1996)

I The central feature required for a diagnosis of DLB is progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention and of frontal subcortical skills and visuospatial ability may be especially prominent.

II Two of the following core features are essential for a diagnosis of probable DLB; one is essential for a diagnosis of possible DLB:

- fluctuating cognition with pronounced variations in attention and alertness
- recurrent visual hallucinations which are typically well formed and detailed
- spontaneous motor features of parkinsonism

III Features supportive of the diagnosis are:

- repeated falls
- syncope
- transient disturbances of consciousness
- neuroleptic sensitivity
- systematised delusions
- hallucinations in other modalities

IV A diagnosis of DLB is less likely in the presence of:

stroke disease, evident as local neurological signs or on brain imaging
evidence on physical examination and investigation of any physical illness, or
other brain disorder, sufficient to account for the clinical picture

Provisional criteria for the diagnosis of dementia of frontal type (Gregory & Hodges, 1993)

I Presentation with an insidious disorder of personality and behaviour of at least six months' duration

II The presence of five or more of the following features:

- loss of insight
- disinhibition
- restlessness
- distractibility
- emotional lability
- reduced empathy or unconcern for others
- lack of foresight, poor planning or judgement
- impulsivity
- social withdrawal
- apathy or lack of spontaneity
- poor self-care
- reduced verbal output
- verbal stereotypes or echolalia
- perseveration (verbal or motor)
- features of Kluver-Bucy syndrome (gluttony, pica, sexual hyperactivity)

III Evidence of frontal dysfunction on neuropsychological assessment

IV Relative preservation of memory

V Psychiatric phenomena may be present (usually mild mood disorder or paranoia)

VI Absence of past history of head injury, stroke, long-term alcohol abuse

Consensus clinical diagnostic features of frontotemporal dementia (Neary et al, 1998)

I Core features (all required to be present)

- Insidious onset and gradual progression
- Early decline in social interpersonal conduct
- Early impairment in regulation of personal conduct
- Early emotional blunting
- Early loss of insight

II Supportive features

Behavioural disorder

- Decline in personal hygiene and grooming
- Mental rigidity and inflexibility
- Distractibility and impersistence
- Hyperorality and dietary changes
- Perseverative and stereotyped behaviour
- Utilisation behaviour

Speech and language

- Altered speech output:
 1. asponaneity and economy of speech
 2. press of speech
- Stereotypy of speech
- Echolalia
- Perseveration
- Mutism

Physical signs

- Primitive reflexes
- Incontinence
- Akinesia, rigidity and tremor
- Low and labile blood pressure

Investigations

- Neuropsychology: significant impairment on frontal lobe tests in the absence of severe amnesia, aphasia or perceptuospatial disorder
- Electroencephalography: normal on conventional electroencephalography despite clinically evident dementia
- Brain imaging (structural and/or functional): predominant frontal and/or temporal abnormality

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POSTSCRIPT TO MD THESIS: THE PREVALENCE OF DEMENTIA AND ITS SUBTYPES IN AN ELDER COMMUNITY POPULATION

The following are amendments to the thesis.

Chapter 4, section 4.2.3.2, page 78

My original intention was to regard 23 as the cut-off score for dementia in the Mini-Mental State Examination. In practice, a more flexible approach was adopted: where a participant scored 23 or less but the score was regarded to have been influenced by educational level, dysphasia or poor English, for example, the assessors used their discretion in deciding whether or not a diagnosis of dementia should be made.

Chapter 6, section 6.4, pages 136-137

‘Screen-negative’ participants were not sampled, and this is likely to have predisposed to further limitations. It is probable that some people who did not screen positively for dementia were nonetheless demented, and the prevalence figures derived should therefore be considered to represent a minimum prevalence of dementia rather than an unbiased estimate. Similarly, certain subtypes of dementia, such as frontal lobe dementia, are likely to have been missed because of the nature of the screening tool and its emphasis on such cognitive domains as memory and orientation, and this would have an effect on

the relative distributions of the subtypes. The validity of the Short-CARE as a screening instrument is potentially problematic when people from different ethnic groups are being screened, as cultural factors such as mother language and education are not taken into account. Consequently, the numbers of people from ethnic minorities who screened positive in this study may have been either too high or too low, and the associations between dementia subtype and country of birth may therefore be inaccurate.

Two further limitations of the study were:

- a) The variable quality and quantity of information available case by case; frequently there was little clinical history especially for those participants in residential or nursing care settings, and a minority of participants had had optimal investigations such as blood tests and neuroimaging.
- b) Diagnoses were made by two raters who reached a consensus having reviewed each case and applied the different diagnostic criteria sets. A more valid method would have been to employ three raters, one of whom could have acted as an arbitrator in cases of diagnostic disagreement between the other two.

Abstract, page 3; and chapter 6, section 6.3.2, page 131

There are no statistical grounds for the assertion that dementia and vascular dementia in particular are overrepresented among people born in Africa or the

Caribbean. The small numbers involved indicate that the differences between this group and the others fall within the limits of sampling error.