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Risk Factors for Dementia and Cognitive Decline

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A Literature Review by

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EXECUTIVE SUMMARY

BACKGROUND TO THE REPORT

This literature review of risk factors for dementia and cognitive decline was carried out between January and November 2002. It has been written by research staff at the University of Paisley. The project was commissioned and funded by the Public Health Institute of Scotland (now NHS Health Scotland) in the light of concerns about the expected dramatic increase in the numbers of older people in Scotland (as elsewhere) living with dementia. The effects of the syndrome can cause considerable problems for those affected and for others. At one time, dementia and cognitive decline were seen as inevitable consequences of ageing. Now, however, as more is known about ageing and about the brain, possible means of prevention and treatment are being investigated, with a view to reducing the prevalence of dementia. However, although treatment may slow the progress of dementia in some cases, the condition cannot be reversed or cured, and there has been growing interest in the possibilities for averting or delaying the occurrence of the condition. Although little is known about the causal processes that result in dementia, epidemiological studies examining some of the factors which appear to increase or decrease risk are being carried out around the world.

It was hoped that a review of this research literature would suggest answers to the following questions: Are there any prospects of preventing dementia in Scotland? What are the prospects? How far away are we? And what are the implications for public health practice in Scotland? The review was later extended to include 'risk factors' for cognitive decline. There is a debate about whether dementia should best be seen as an extension of 'normal' age-related cognitive decline or as a qualitatively different disorder, and answers to this question could have important implications for approaches to prevention.

The timescale of the project precluded a comprehensive and systematic review. The literature is vast, and commentators on empirical work have drawn attention to the difficulties of summarising the findings from existing research or making comparisons. Because of these problems, this report draws largely on existing reviews of the literature, book chapters, editorials and commentaries, although recently published studies have also been included. It is acknowledged that the report might be partial or incomplete, although steps have been taken to ensure factual accuracy.

The report is intended for health professionals and policy makers in Scotland. It is hoped that it might also be useful to academics, since references have been included wherever possible.

PART I - BACKGROUND TO EMPIRICAL WORK

Demography and trends
- Because of the general increase in life expectancy and the ageing of the 'baby boomer' generation, the number of older people in Scotland is projected to rise substantially, with the oldest groups experiencing the largest relative increase.
- The number of people with age-related conditions such as dementia is rising, and will continue to rise, particularly in the oldest age group.
- Applying recognised prevalence figures to projected population statistics, the number of people living with dementia in 2040 could be over 100,000, i.e. one in fifty of the population.

Implications for public health, and primary prevention strategies
- The increasing prevalence of dementia is an important public health issue, because of the impact on individuals and on service provision.
- While the progress of dementia can sometimes be slowed, no cure is available.
- There would be immense benefits to public health if ways of reducing the incidence (as well as the prevalence) of dementia and cognitive decline could be found. Since the rates of incidence of dementia rise exponentially with age, raising the mean age of onset could significantly reduce the prevalence.
- A primary prevention approach rests on a knowledge of causal factors and appropriate means of intervention.
- The processes underlying the development of dementia and cognitive decline are not fully understood. At the same time as more is known about changes in the brain, epidemiological studies of potential risk and protective factors are being carried out.

Cognitive decline, dementia and types of dementia
- Dementia can broadly be divided into vascular dementia and dementia of the Alzheimer type, but dementia with Lewy bodies and fronto-temporal dementia are now thought to have been under-diagnosed in the past.
- There is increasing knowledge of types and sub-types of dementia, but also of the overlap between types or categories. With increasing knowledge, terminology is evolving.
- Cognitive decline has been sub-divided into 'age-associated cognitive decline' (AAMI) and 'cognitive impairment no dementia' (CIND).
- Diagnosis of both cognitive decline and dementia is difficult, but there are now internationally agreed standards.
- A number of hypotheses and models of dementia of the Alzheimer type have been proposed, based on pathological and clinical criteria.
- There is interest in whether cognitive decline and Alzheimer's disease should be seen as a continuum, or as qualitatively different conditions. This issue could have important implications for approaches to prevention.

EXECUTIVE SUMMARY

Methodological issues

- In assessing the findings from epidemiological work, a number of methodological issues concerned with definition and measurement, and the design of the study, have to be taken into account.
- The presence of the disorder or type of disorder must be capable of being reliably assessed, as must the strength of exposure to risk factors.
- The design of the study can strongly influence the findings. Early empirical research was based on case-control studies of prevalence, but large longitudinal studies of incidence are needed to distinguish between association and causality, and to examine interactions between risk factors.
- There may be various explanations for some of the findings of epidemiological studies.

PART II - RISK FACTORS FOR DEMENTIA AND COGNITIVE DECLINE

Age, gender, ethnic and national factors

- Cognitive function declines with age, although there are wide individual differences, and also differences between domains in the rate of decline.
- Both the prevalence and incidence of dementia increase exponentially with age. Key issues are the size (or relative importance) of 'age' as a risk factor, and explanations for the effect of ageing.
- Age has generally been seen as the main risk factor for dementia, but there is debate about whether the 'cause' should be seen in terms of ageing per se (in which case everyone would develop dementia if they lived for long enough), or the ageing-related increasing incidence of disease.
- There are gender differences in the prevalence of dementia, but whether these reflect differences in incidence is still unclear.
- By contrast with other chronic disorders, cross-cultural studies have thrown little light on causal factors. The difficulty of separating biological and environmental factors has been widely acknowledged.

Genetic factors

- Early onset Alzheimer's disease is strongly related to family history, and three genetic mutations associated with this disorder have been identified. Although cases of early-onset Alzheimer's disease account for a small proportion of cases of dementia overall, a high proportion of such cases are thought to be associated with these genes.
- One genetic mutation has been linked with some forms of late onset dementia including Alzheimer's disease. This is the APOE 4 allele. However, the presence of APOE 4 is neither necessary nor sufficient to cause Alzheimer's disease; only about half of affected individuals carry the allele.
- Other genetic factors are being investigated.
- At the moment, research findings have not suggested any means of prevention.
- An increased knowledge of genetic factors has been seen as useful in gaining a better understanding of the mechanisms underlying the development of dementia.

Pre-existing conditions

- A number of conditions can predispose to dementia of the Alzheimer type. These include

Down's syndrome and Parkinson's disease. Some studies have found an association with thyroid disease but others have not.

- Pathological and genetic associations between Down's syndrome and Alzheimer's disease have been found. The incidence of dementia of this type occurs 30 – 40 years earlier in the population of people with Down's syndrome than in the general population.
- The prevalence of dementia in people with Parkinson's disease is thought to be between 28 – 40%, i.e. considerably higher than in the general population.

Physical injury, illness and medication
- There is some evidence that brain injury increases the risk of cognitive decline.
- There is evidence to support a link between head trauma and loss of consciousness and an increased risk of Alzheimer's disease, although not all studies show this.
- There is some evidence to suggest that herpes simplex type 1 virus (HSV1) may be a risk factor in individuals who carry the APOE 4 allele. If this is the case, it is possible that some cases of Alzheimer's disease could be prevented by vaccination.
- The link with aluminium suggested by some early studies has not been proved.
- A few studies have examined exposure to other toxins and pollutants, but the findings are inconclusive.
- There is some evidence of a link between non-steroidal anti-inflammatory drugs (NSAIDs) and a reduced risk of Alzheimer's disease, although this protective effect remains to be confirmed by clinical trials. NSAIDs have a number of side effects that preclude their widespread use.

Risk factors for vascular disease
- The risk factors for vascular dementia are relatively well understood. These include cerebro-vascular disease, and risk factors for vascular disease, such as hypertension, diabetes and obesity.
- An association has recently been found between vascular factors found in mid-life (e.g. hypertension) and Alzheimer's disease. At the same time, low blood pressure has sometimes been found among people with the disorder.
- Findings from recent large studies have indicated that high blood pressure measured in mid-life is also a significant predictor of poorer cognitive function in later life.
- The long-term cognitive decline experienced by a minority of heart bypass patients is being investigated.

Smoking, alcohol and drug use
- Smoking is a known risk factor for vascular dementia.
- Findings from studies examining smoking and the risk of Alzheimer's disease have varied. It has been concluded that any effect, in either direction, is likely to be small.
- High alcohol intake is linked with cognitive impairment, although the effects may be reversible. It is also the commonest cause of Wernicke-Korsakoff syndrome, the main feature of which is memory impairment.
- Alcohol use is thought to contribute to a significant proportion (10%) of cases of dementia. A high intake of alcohol is associated with vascular disease and, hence, with vascular dementia. Also, although alcohol per se might not cause dementia, it has been seen as a contributory factor in conjunction with other factors, particularly nutritional deficiencies.

- Although there is interest in the long term effect of recreational drug use on the brain, drug use has not been examined as a risk factor.

Diet, nutrition and hormones

- Weight loss is commonly associated with Alzheimer's disease, and a number of possible explanations have been suggested.
- Nutritional deficiency has been found to affect cognition, and associations with dementia are being investigated.
- A deficiency of B vitamins (B12, B6 and folate) has been found to be correlated with increased serum homocysteine (tHcy) concentrations. Low levels of B vitamins have been associated with lower levels of cognitive function. Similarly, a high concentration of homocysteine (or folate deficiency) has been associated with an increased risk of dementia, particularly Alzheimer's disease.
- Clinical trials of vitamin B supplements for people with Alzheimer's disease are planned, and these may be extended to people with mild memory impairment.
- High cholesterol levels are associated with an increased risk of vascular disease and hence vascular dementia. There is evidence of an association between high levels of dietary saturated fat, or high cholesterol level, in mid-life and an increased risk of cognitive decline and dementia.
- There is some evidence to suggest that regular consumption of foods rich in N-3 polyunsaturated fatty acids may decrease the risk of Alzheimer's disease.
- Statins (one type of lipid-lowering agent) have been found to lower the risk of vascular disease and mortality from all causes. There is also some evidence that they reduce the risk of developing Alzheimer's disease. Clinical trials are under way.
- Clinical intervention studies are examining whether anti-oxidant vitamins might reduce the risk of dementia. Findings have been contradictory, but tend to suggest that vitamins from food sources are more effective than supplements.
- Some observational studies have suggested that oestrogen use in post-menopausal women can have a beneficial effect on cognitive function. However, the evidence for a protective role against the development of dementia is weak. The effects of oestrogen and HRT use are being investigated, although long term trials have been halted.
- Reviewers of the literature have emphasised that nutritional factors should be considered in conjunction with others, and that there may be a number of possible explanations.

To what extent, if any, might interventions currently targeted at vascular disease have helpful impacts on dementia or cognitive decline?

- The fact that some dementia and cognitive decline is linked with vascular factors, particularly hypertension, suggests that there is some scope for intervention. Treatment of hypertension has been established, and has been found to be effective in reducing the risk of vascular events. Thus, vascular dementia may be preventable, to an extent, by medication and/or lifestyle change.
- However, little is known about whether interventions targeted at vascular disease have any impact on the incidence of dementia or cognitive decline.
- The identification of those whose age, sex, smoking and blood pressure indicate a high risk of vascular disease is felt to be worthwhile in relation to vascular risk, and may be worthwhile in relation to dementia.

Factors related to social context: Social class, occupation and education

- Factors relating to social context or class have a significant effect on health and on the incidence of a number of disorders.
- Lower socio-economic status (as measured by income or occupation) has been linked to lower cognitive function in later life.
- Lower socio-economic status is known to be associated with an increased risk of vascular disease, and, hence, potentially with an increased risk of vascular dementia.
- Little is known, however, about the relationship between lower socio-economic status and the risk of cognitive decline or dementia. Few longitudinal studies examining social class or poverty as a factor have been carried out. In the US, education has been taken as a proxy measure of social class, but education can have a number of meanings.
- Occupation can be a marker for a number of factors, in addition to social class (e.g. exposure to toxic substances).
- Lower educational level is known to be associated with lower cognitive function later in life, but there has been little examination of the nature of this association, or of links with cognitive decline.
- There is evidence that lower educational level is associated with an increased risk of vascular dementia.
- The findings from studies examining links between lower educational level and an increased risk of dementia of all types or Alzheimer's disease are mixed. Some studies have found evidence of an association, but others have not.
- Education has often been taken as a measure of innate intelligence or mental stimulation, either or both of which have been viewed as serving to enhance 'brain reserve'. It has been suggested that brain reserve might protect the brain from degeneration, or might mitigate against the effects, hence delaying a diagnosis of dementia or cognitive decline.
- Because of the many meanings of education, implications for prevention are unclear.

Physical, mental and social activity

- Research is beginning to examine relationships between physical, mental and social activity – in mid-life and in old age – and the incidence of cognitive decline and dementia. If associations are found, there may be implications for social policy, e.g. in relation to retirement.
- The findings from some studies have indicated that the maintenance of cognitive function in old age is associated with good physical health. Other research has not found this, however.
- There is some evidence that pulmonary function (FEV1) in mid-life predicts cognitive function in old age, although the mechanisms are unknown.
- Physical exercise has been linked with a reduced risk of vascular disease. However, links with the incidence of cognitive decline and dementia have been little examined by research.
- There is some evidence that mental activity can enhance or maintain cognitive function, or protect against a degree of decline, although there are wide variations. Further research is felt to be needed to establish whether cognitive activity could protect against long-term cognitive decline or dementia.
- There is also some evidence that social activity, involvement and support can help to maintain cognitive function. Preliminary findings which suggest a reduced susceptibility to dementia are felt to warrant further investigation.
- Although there is some evidence that some forms of 'activity' seem to have a preventive

effect on cognitive decline, caution has been expressed about ascribing a protective role to 'activity', since those experiencing cognitive decline might be less likely to be active.

• There is felt to be enough evidence to take seriously the possibility that depression is a risk factor for dementia and cognitive decline.

• There has been increasing interest in the role of stress in cognitive functioning, because of the link with stroke, because prolonged exposure to a stress hormone (cortisol) is known to affect mental performance, and because ageing can be viewed in terms of a loss of adaptive capacity.

PART III - DISCUSSION AND CONCLUSION

Discussion

• Cognitive function declines with age, although such decline is not inevitable and not always progressive. A 'healthy lifestyle', and measures to maximise mental and social, as well as physical health, have been recommended as potentially protective against cognitive decline.

• The risk factors for vascular dementia are relatively well understood; these include cerebro-vascular disease and risk factors for vascular disorders. The risk of vascular dementia may be reduced by lowering the risk of vascular disease, e.g. through the control of hypertension.

• At the moment, the only risk factors for Alzheimer's disease confirmed beyond reasonable doubt are old age, a family history of dementia (particularly for early onset dementia), Down's syndrome and the APOE 4 genotype. The evidence for other risk factors is inconclusive. None of the known risk factors for Alzheimer's disease is felt to give scope for preventive action. Also, because of the links with age and – perhaps - genetic factors, the potential for primary prevention may always be relatively limited. However, an association with vascular factors suggested by recent research has caused the dichotomy between vascular dementia and ('degenerative') Alzheimer's disease to be questioned, and has indicated that there may be some scope for prevention.

• Although the causal mechanisms underlying the development of dementia and cognitive decline are not fully understood, with increasing knowledge about the brain and the findings from epidemiological studies of risk factors, progress is being made. There is felt to be considerable potential for further research.

• Evidence suggests that there is often no single cause of dementia or cognitive decline, and hence no single solution, but that there may be some limited scope for intervention. Clinical trials of potentially benefical interventions are felt to be worthwhile.

• One key issue may be the relationship between age-related cognitive decline and dementia. Some commentators (although not others) have suggested that the evidence from risk factor research tends to support the view that cognitive decline and dementia of the Alzheimer type should be seen as a continuum rather than as qualitatively different conditions. If this is the case, then changes associated with ageing are of interest.

• Reviewers of the literature have noted a number of limitations of current research. It has been emphasised that the evidence base must be adequate before considering strategies of prevention.

• Some environmental risk factors, particularly social class, have been little examined by research.

- A focus on primary prevention has been criticised for an over-emphasis on individual and biological 'risk factors', for promoting the view that such prevention strategies are feasible and ignoring the role of age, and for increasing anxiety and pathologising mild cognitive impairment. A focus on primary prevention has also been seen as shifting priorities and diverting attention from solutions of care and the needs of those affected.
- One approach to a public health goal of 'healthy ageing' is to consider the extent to which 'compression of morbidity' is achievable, by delaying the onset of certain conditions or preventing their occurrence.
- In moving from knowledge about risk factors to strategies of intervention, there are a number of practical and philosophical issues to be taken into account. These include questions of ethics, responsibility, feasibility and acceptability.
- At the moment, targeted strategies (based on 'high-risk' groups) seem to offer more potential than those based on populations, with the further investigation of potential protective measures felt to be worthwhile. Questions remain about screening as a method of identifying those at high risk.
- An important issue is when strategies of intervention might be most effective or beneficial. Some evidence that 'mid-life' risk factors may predict later cognitive decline, and that initial neurodegenerative changes of Alzheimer's disease may occur up to 40 years before the first clinical symptoms, suggests that mid-life preventive measures might be worthwhile.

Conclusion

The report concludes that at present there are very few immediate prospects for effective action to reduce the incidence of dementia in Scotland, particularly dementia of the Alzheimer type. However, prospects may be beginning to improve. Research into risk factors and potential interventions is ongoing, and there is much that remains to be investigated. Progress is being made. More factors may be found, and much more will be learned about – for example - the relative importance of different factors, the ways in which and the extent to which these factors interact, and the extent to which they can be modified. The hope is that new knowledge, together with the increased understanding about ageing and the brain, will contribute to a better understanding about the nature and the causes of cognitive decline and dementia. This in turn may suggest possible methods of primary prevention. Research findings tend to suggest that there is no one single 'cause' of dementia, and hence no single solution. Although age is an important contributory factor for dementia and cognitive decline, there may be some scope for preventive action, particularly for the latter, perhaps in mid-life.

CHAPTER ONE
INTRODUCTION

Given the increasing numbers of older people in most western populations, there is concern about the anticipated rise in the prevalence of ageing-related disorders such as dementia. It has been predicted, for example, that by 2040 one in every fifty people in Scotland could be living with this disorder. The effects of the syndrome can cause considerable problems for those affected and for others. At one time, dementia and cognitive decline were seen as inevitable consequences of ageing. Now, however, as more is known about ageing and about the brain, possible means of prevention are being investigated, with a view to reducing the prevalence of dementia.

One approach to 'prevention' involves the early detection of a condition and intervention to halt or delay its progress (secondary prevention). Another approach – primary prevention - aims to avert or delay the occurrence of a condition by reducing exposure to causative factors, i.e. by reducing risk. Although little is known at the moment about the mechanisms or causal processes which result in dementia, or about when the degenerative processes begin, progress is being made, and considerable research efforts are being expended in investigating both primary and secondary approaches to dementia.

However, although treatment may slow the progress of dementia in some cases, the condition cannot be reversed or cured. There has been growing interest, therefore, in the possibilities for primary prevention, since even delaying the onset of dementia could dramatically reduce the numbers of people affected. Epidemiological studies across the world are investigating some of the factors which appear to increase or decrease the risk of dementia (especially Alzheimer's disease). The findings from large longitudinal studies and clinical trials are beginning to emerge, and some intervention trials have been instigated.

A review of this epidemiological literature was commissioned by the Public Health Institute of Scotland (now NHS Health Scotland). It was hoped that the review might suggest answers to the following research questions: Are there any prospects of preventing dementia in Scotland? What are the prospects? How far away are we? And what are the implications for public health practice in Scotland? It was decided that the review would focus on primary prevention, and on the results of studies investigating the evidence for
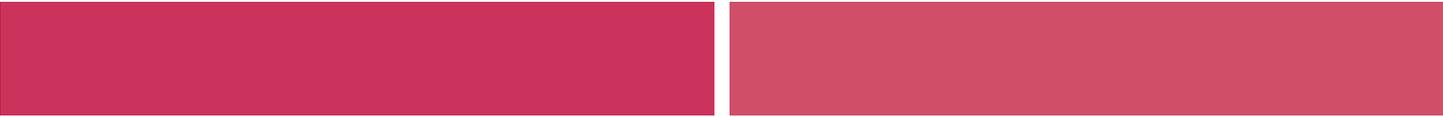
'risk factors'. Literature detailing the findings from treatment studies would be excluded, except where such interventions were felt to prevent (rather than slow) the development of dementia. The review was later extended to include evidence about 'risk factors' for cognitive decline. There is a debate about whether dementia should best be seen as an extension of 'normal' age-related cognitive decline or as a qualitatively different disorder, and answers to this question could have important implications for approaches to prevention.

The timescale of the project precluded a comprehensive and systematic review. The literature is vast, and commentators on empirical work have drawn attention to the difficulties of summarising the findings or making comparisons. Various methods have been used, and a range of factors examined. In addition, studies examining cognitive decline have been carried out by psychologists, interested in differences between domains, rather than by epidemiologists. Diagnosing and defining dementia and cognitive decline is problematic, and the terms 'cognitive decline' and 'dementia' have been used in writing up some of the research. Because of these problems, this report draws largely on existing reviews of the literature, book chapters, editorials and commentaries. However, the findings from recently published studies have been included. It is acknowledged that the report might be partial or incomplete, although steps have been taken to ensure factual accuracy. The report is intended for health professionals and policy makers in Scotland. It is hoped that it might also be useful to academics, since references have been included wherever possible.

The first four chapters in Part I provide the background to current empirical work. They cover: demography and trends, implications for public health and primary prevention strategies, definitions of cognitive decline and dementia, hypotheses and models, and methodological issues. Part II, the body of the report, reports on the evidence from empirical work which has examined risk (or protective) factors for dementia or cognitive decline, and intervention studies. This section is structured according to risk factors under the following headings:

• Age, gender and ethnicity
• Genetic factors
• Pre-existing conditions
• Physical injury, illness and medication
• Classical [personal and lifestyle] risk factors:
  • risk factors for vascular disease
  • smoking, alcohol and drug use
  • diet, nutrition and hormones
  • interventions targeted at vascular disease
• Factors related to social context: social class, occupation and education
• Physical, mental and social activity

In Part III, the discussion chapter summarises the findings from research. It also considers what the evidence suggests about the nature of dementia and cognitive decline and the relationship between the two. The limitations of existing empirical work are discussed, as well as some critiques of a focus on primary prevention. Starting from the concept of 'healthy ageing', the chapter considers the feasibility of 'compression of morbidity'. It concludes by outlining the conclusions that can be drawn about public health strategies for preventing dementia and cognitive decline.

The report concludes that at present there are very few immediate prospects for effective action to reduce the incidence of dementia in Scotland, particularly dementia of the Alzheimer type. However, prospects may be beginning to improve. Research into risk factors and potential interventions is ongoing, and there is much that remains to be investigated. Progress is being made. Much is being learned about risk factors, ageing and the brain, and about the nature and causes of dementia and cognitive decline. The hope is that this new knowledge will indicate possibilities for methods of prevention.

PART ONE
BACKGROUND TO EMPIRICAL WORK

CHAPTER TWO
DEMOGRAPHY AND TRENDS

The populations of most developed countries are ageing, leading to an increase in the prevalence of age-related disorders such as cognitive decline and dementia. This chapter gives the predicted increase in the numbers of older people in Scotland. Prevalence ratios derived from a meta-analyses of European studies have been used to derive estimates of the number of people in Scotland with dementia in 2002, and until 2040.

The populations of most developed countries are ageing. In Scotland, the older population has been growing in absolute and relative terms throughout the 20th century, and this trend is predicted to continue. Whereas in 2000, people aged 65 and over made up just over 15% of the population, NHS Scotland (Information and Statistics Division) estimates that this group will account for 24% of the population by 2031.[1] (At the moment, women outnumber men in the older age groups, but male and female life expectancies are predicted to become more similar.[1]) The main reasons for the absolute increase in numbers are the ageing of the 'baby boomer' cohort, and a general increase in life expectancy or ongoing decline in mortality at older ages. Declining birth rates contribute towards the relative growth in numbers of older age groups.

In 2000, there were approximately 787,000 people aged 65 and over in Scotland. Of these, approximately 347,000 were aged 75 and over and 84,000 aged 85 and over.[1] Substantial increases are predicted to occur over the coming 30 years, with the oldest age group experiencing the largest relative increase.[1] Government Actuaries Department figures based on the Registrar General's estimates suggest that the number of people aged over 65 in Scotland is expected to grow from 787,000 in 2000 to 1,238,000 in 2040, an increase of 57%.[2]

As the number of older people in the population increases, the prevalence of impairment is also expected to increase, since rates of limiting longstanding illness and disability increase dramatically with age.[1,3] A number of age-related disorders relate to mental health and cognitive function. Hence, the increase in life expectancy observed over the last decade has particular relevance for conditions such as cognitive decline and dementia.[4] These conditions can detract from an individual's quality of life, and reduce their ability to live independently, with consequences for others, particularly family members, and for health and social services.

THE PREVALENCE OF DEMENTIA

Knowledge of the prevalence (number of cases) of given conditions within a population is important for the provision of services. It has been estimated that, in the UK, about 600,000 people have dementia, and that over 300,000 of these have Alzheimer's disease.[5] No large-scale studies of the prevalence of dementia have been carried out in Scotland, although Gordon and Spicker have estimated that, in 1994, 6.9% of the population aged 65+ in Scotland had dementia, and that 55% of these people were resident in the community, rather than in care homes or hospitals.[6] Numbers can be estimated by applying prevalence ratios to local populations.

Prevalence ratios depend on the definition of terms, criteria for diagnosis and methods of measurement, as well as on the study population. The most satisfactory overall prevalence ratios for dementia are felt to be those which were derived from the European Community Concerted Action on the Epidemiology and Prevention of Dementia (EURODEM), which re-analysed original data from 12 prevalence studies of dementia conducted in eight countries in Europe between 1980 and 1990.[7-9] Although the EURODEM estimates of prevalence could now be seen as dated, they have been seen as the most useful available for people aged 65+ for three reasons:[6]

- they only included data from studies with rigorous inclusion criteria - those studies which had used a DSM III or equivalent definition of dementia and had ascertained a dementing illness by individual examination;
- they are based on studies which included institutionalised populations; and
- they provide details of prevalence ratios according to age group and gender.

Although widely differing prevalence ratios for dementia have been reported for different countries, these variations have generally been considered to be due to methodological differences in study design, the diagnostic criteria employed, or differences in mortality.[7;10-12] The EURODEM collaborative analyses found that, among European studies using similar methodologies and diagnostic criteria, there were only trivial differences in the age-specific prevalence of dementia[7] and Alzheimer's disease.[8] Similarly, a recent UK study (MRC CFAS) employing the same methodology in multiple centres (with sufficient sample size to detect differences large enough to be of public health or epidemiological interest) has found no regional differences in the prevalence of dementia across five centres in England, despite known differences in vascular risk and cardiovascular mortality.[3;10]

The EURODEM estimates indicated gender differences in prevalence, as have a number of other studies.[1;7;10;13] In addition, studies throughout the world have shown that the prevalence of dementia increases dramatically with age,[7;11;14-16] although the condition is uncommon before the age of 65 years.[1] The EURODEM estimates have suggested that prevalence nearly doubles with every five years of increase in age.[7]

There are relatively few studies on the prevalence of dementia which include people below the age of 65 years. Many of the studies combined in EURODEM omitted young onset dementia.[17] A more recent study by Harvey (see Table 2.1 below) is felt to provide the most satisfactory prevalence ratios for younger people with dementia (those aged between 30 – 64 years).[17] Table 2.1 shows the prevalence ratios for dementia by age group and gender, derived from both the EURODEM analysis and the Harvey study.

TABLE 2.1 Prevalence ratio (%) of dementia by age group & gender

AGE GROUP	BOTH SEXES	WOMEN	MEN
30-64	0.067		
65-69	1.4	1.1	2.2
70-74	4.1	3.9	4.6
75-79	5.7	6.7	5.0
80-84	13.0	13.5	12.1
85-89	21.6	22.8	18.5
90-94	32.2	32.2	32.1
95-99	34.7	36.0	31.6

Source for rate 30-64: Harvey R (1998) Young onset dementia: epidemiology, clinical symptoms, family burden, support and outcome. London: Dementia Research Group, Imperial College School of Medicine. Source for rates 65+: Hofman A, Rocca WA, Brayne C, Breteler MMB et al (1991) The prevalence of dementia in Europe: A collaborative study of 1980-1990 findings. Int. J. Epidemiology, 20(3), 736-48. (EURODEM) Reproduced with permission from 'Needs Assessment Report on Dementia', NHS Health Scotland, 2003.[18]

Applying the above prevalence figures to the population of Scotland gives the following estimates of the number of people with dementia, by age group and gender. It is emphasised that the numbers in Table 2.2 below are estimates only.

TABLE 2.2 Estimate of the number of people with dementia in Scotland in 2002, by age group and gender

ESTIMATED POPULATION WITH DEMENTIA - 2002			
AGE GROUP	BOTH SEXES	WOMEN	MEN
30-64	1,321		
65-69	3,732	1,395	2,337
70-74	8,587	4,486	4,101
75-79	9,892	6,600	3,292
80-84	12,950	8,852	4,098
85-89	12,540	9,466	3,074
90+	8,299	6,512	1,786
Total	57,321		

Source: EURODEM and Harvey prevalence figures applied to Government Actuaries Department (GAD) projections based on the Registrar General's estimate of the population at mid-2000. Reproduced, with permission, from 'Needs Assessment Report on Dementia', NHS Health Scotland, 2003.[18]

Little is known about the prevalence of age-related cognitive decline,[19] although there is known to be a range of individual differences and a wide variation among older people.[20] The UK study mentioned above (MRC CFAS) has been designed to estimate and compare the prevalence and incidence of dementia in five centres, to examine the natural history of cognitive decline and dementia in the population and to evaluate the degree of disability associated with any decline.[21]

STUDIES OF INCIDENT CASES

Another way of examining the rates at which disorders develop and the pattern of their development is to study incidence rates, i.e. the rate of new cases developing in a population over a specified period. Investigating the incidence rates for cognitive decline and dementia is problematic because of the gradual onset and the difficulty of diagnosis, and because of the need for large studies. (For example, in Scotland, GP consultations have been proved to be unsatisfactory as a marker for incidence.[1]) Existing studies of incidence have not presented a consistent picture.[14;17] Alzheimer Scotland - Action on Dementia has stated that the results of existing research support a cautious assumption that there might be 200 new cases of dementia per year per 100,000 people.[17] Rates of incidence of a dementing disorder rise exponentially with age.[16] Launer and colleagues have suggested that about 2.5 new cases per 1000 person-years develop at age 65; and about 85.6 new cases per 1000 person years after age 90 years.[22]

THE PREDICTED INCREASE IN THE PREVALENCE OF DEMENTIA

Given the demographic trends of increasing numbers of older people (since more people are living into old age, and life expectancy is increasing), the number of people with dementia is rising and is expected to continue to rise. Some have argued that the prevalence of Alzheimer's disease will double over the next 50 years.[23] Also, because the rates of incidence of dementia rise exponentially with age, people in older age groups are increasingly likely to be living with this condition.

The results of applying prevalence figures (Table 2.1) to the projected population of Scotland at intervals until 2040 are given in Table 2.3 opposite. This table shows the projected estimates of the numbers of people in Scotland expected to have dementia. The most rapid growth in the expected numbers of people with dementia is predicted to be in the 75+ age group.

TABLE 2.3 Projected estimates of numbers of people in Scotland with dementia by age group and gender

POPULATION PROJECTIONS FOR PEOPLE WITH DEMENTIA IN SCOTLAND						
	2000	**2005**	**2010**	**2020**	**2031**	**2040**
Persons						
30-64	1,321	1,408	1,492	1,616	1,438	1,284
Males						
65+	18,688	20,461	22,602	28,623	36,319	41,749
75+	12,250	13,845	15,687	20,137	26,426	32,186
Females						
65+	37,311	38,028	39,241	44,437	54,160	62,992
75+	31,430	32,221	33,330	37,334	45,988	55,011
Persons						
65+	55,999	58,489	61,843	73,060	90,479	104,741
75+	43,680	46,066	49,017	57,471	72,414	87,197

Source: EURODEM and Harvey prevalence figures applied to Government Actuaries Department (GAD) projections based on the Registrar General's estimate of the population at mid-2000. Reproduced, with permission, from 'Needs Assessment Report on Dementia', NHS Health Scotland, 2003.[18]

From these figures, the number of people with dementia in Scotland is expected to almost double over the next forty years. Even though they are estimates, these statistics suggest that, by 2040, there could be more than 100,000 people with dementia in Scotland. The numbers are high. The population of Scotland is currently around 5 million (and is predicted to fall to around 4.5 million by 2040).[2] 100,000 people represents over one in fifty of the population. In a street of 100 people, for example, two could be living with dementia.
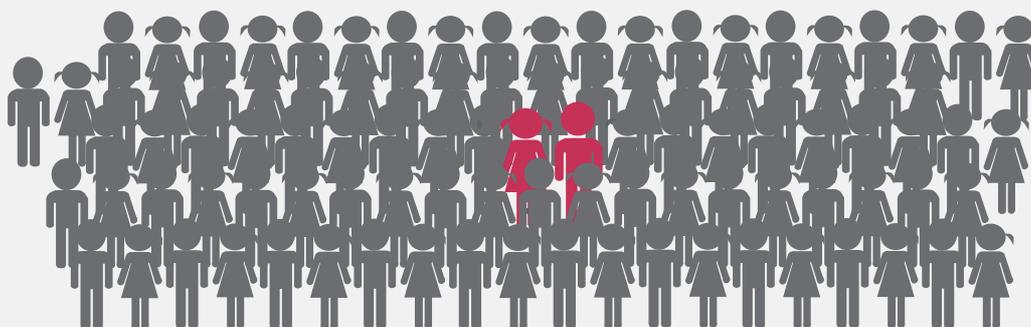
However, predicting trends in the overall numbers of people with dementia is a complex matter, and others have recommended caution, since such projections are based on assumptions, and these may turn out to be wrong. In addition, a number of unknown factors, particularly environmental, might influence the development of dementia over the next few decades. (Two long-term population studies found no significant change in the prevalence ratios, over time, of dementia or types of dementia.[12] These were not recent studies, however.)

SUMMARY
- Because of the general increase in life expectancy and the ageing of the 'baby boomer' generation, the number of older people in Scotland is projected to rise substantially, with the oldest groups experiencing the largest relative increase.
- The number of people with age-related conditions such as dementia is rising, and will continue to rise, particularly in the oldest age group.
- Applying recognised prevalence figures to projected population statistics, the number of people living with dementia in 2040 could be over 100,000, i.e. one in fifty of the population.

CHAPTER THREE
IMPLICATIONS FOR PUBLIC HEALTH, AND PRIMARY PREVENTION STRATEGIES

The anticipated rise in the prevalence of dementia and cognitive decline is an important public health issue. Although progress has been made in assessing the needs of people with dementia, and although treatment may slow the progress of dementia in some cases, nevertheless, the costs of dementia for individuals and for services are high. There has been increasing interest in investigating primary methods of prevention. An epidemiological approach can throw light on 'risk factors' for dementia.

The anticipated rise in the prevalence of age-related conditions such as dementia and cognitive decline is an important public health issue. Cognitive function is a key determinant of quality of life, and underlies nearly all daily living activities;[24] it is linked with the capacity for self-care, and the ability to take part in social activities, to exercise self-determination and to maintain independence at older ages.[25-27] Many people are frightened of a decline in cognitive function, and particularly of developing a dementing disorder.[28] The effects of dementia can cause significant problems, both for those affected and for those caring for them. Hence, a predicted increase in the prevalence of dementia is an issue of concern for public health, because of the numbers involved, and because of the implications for individuals and for service providers.

Caring for people with dementia is enormously costly in terms of resources, and these costs are likely to rise with an ageing population.[29] The care required for those with moderate to severe dementia is proportionately much greater than that required by the majority of older people.[30;31] Caring for people with dementia is highly labour-intensive, whether in the formal or informal sector. Studies have shown the heavy burden on informal caregivers in terms of stress and strain.[29;30] For example, one Scottish study which compared the needs of the supporters of demented and non-demented elderly people found that among the dementia group there was significantly greater use of mainstream day care services, and a significantly higher level of unmet need, as well as some extra household expense.[32]

Dementia also causes significant costs for social care services and the health care system in terms of the provision and financing of services and residential accommodation.[30;31] Cognitive impairment is the main reason for long term institutional care in old age,[33] and it has been estimated that dementia accounts for 14% of the bed occupancy in psychiatric

hospitals.[34] Also, the number of people with cognitive impairment in institutional care is predicted to increase considerably, because of the rising numbers of cognitively impaired people aged 85 and over, the age group which is most likely to need residential or nursing care.[33] Estimates for the cost of care (which may be contingent on government policy) vary.[30] One recent review by the Audit Commission has estimated that dementia costs the United Kingdom £6.1bn a year (at 1998-1999 prices), with £3.3bn of this direct spending by health and social services.[35] There would be immense benefits to public health, therefore, if ways of reducing the prevalence of dementia could be found.

PUBLIC HEALTH APPROACHES TO 'PREVENTION'

The goals of public health are broadly those of 'health improvement'. At the moment, public health management is based on a 'needs assessment' approach.[36] There may be a number of conflicting priorities within public health, with fundamental questions about how benefit should be measured. Costs and benefits are relative, and can be seen either in terms of health outcomes (which can have a number of aspects) or in terms of resources (human and financial). In addition, although populations include individuals, there are questions about whether the recipients of health care are populations or individuals,[36] how to balance individual and more general 'good', and whether healthcare measures are to be aimed at those at high risk or at populations.

There are three approaches towards 'health improvement', all of which may be encompassed by a 'needs assessment' approach to public health.

- The aim of **primary prevention** is to reduce the prevalence of disease in a population by averting or delaying the occurrence of conditions by reducing the risk of a condition developing, e.g. by the avoidance of causative exposure. Primary prevention measures require an understanding of the factors which cause a condition to develop, or which increase risk, and about the means by which 'risk factors' may be modified.
- The aim of **secondary prevention** is to limit the progression and recurrence of disease in people who already have it, by effecting a change in the natural history at an early stage. Secondary prevention measures involve early detection, diagnosis and intervention, either by treatment or lifestyle change, and they rely on an understanding of the mechanisms underlying the progress of the condition.
- The aim of **tertiary prevention** is amelioration of the effects of disease, by containing disability and dependency, and maintaining an acceptable quality of life.[37] Tertiary prevention measures mainly involve the provision of services and support, and are based on ways in which the needs (including socio-psychological needs) of those affected might be met.

In relation to dementia, these approaches to 'prevention' tend to overlap.[37] Until recently, the emphasis – rightly - has been on tertiary prevention; considering the needs of those affected, the ways in which the effects of the disorder might be ameliorated by increased support or by treatment, and the quality of life for those affected and their carers improved. The NHS Health Scotland report, 'Needs Assessment Report on Dementia and Older People' (2003)[18] gives a comprehensive outline of the main issues.

Now, however, as more is known about the central nervous system and about age-related changes to the brain,[28] and as neurodegenerative disorders are no longer assumed to be

inevitable and natural accompaniments of ageing, there is considerable public health and research interest in finding out more about the nature and the causes of dementia and cognitive decline,[10;28] and in considering ways in which the prevalence of these conditions might be reduced.

An enormous amount of effort is being expended on the development of treatment (secondary prevention) which might halt or delay the progression of disease in people with mild dementia.[37] Dementia (of the Alzheimer type) might seem to be a good candidate for secondary prevention approaches because of its natural history – an extended pre-clinical phase after which the severity increases gradually over a period of years. Drugs such as antidepressants, anti-psychotics and cholinesterase inhibitors have been found to alleviate or stabilise some symptoms for a limited period of time. However, although the progress of dementia can sometimes be slowed, and although a small proportion of cases of dementia are treatable, in general the condition cannot be reversed or cured.[18;37] The difficulty of detecting dementia at an early or 'preclinical' phase creates further problems for secondary prevention measures.

Because of these difficulties, another approach has been to consider whether there are ways of preventing or delaying the onset of dementia (i.e. reducing the age-specific incidence rates) by primary prevention measures. Since the rates of incidence of dementia (especially Alzheimer's disease) rise exponentially with age,[16] raising the mean age of onset could significantly reduce the numbers affected.[38] It has been suggested, for example, that delaying the onset by 5 years could halve the prevalence,[39] or reduce it by at least a third.[38]

PRIMARY PREVENTION: AN EPIDEMIOLOGICAL APPROACH

A primary prevention approach to health improvement has been seen as appropriate, especially where the possibilities for treatment or cure are limited. Primary prevention has also been seen positively, as having general, as well as individual, benefit.10 Primary methods of prevention require some knowledge about the factors involved in causing a condition to develop, or increasing individuals' susceptibility, and about the means by which these factors may be modified, or risk reduced.

Strategies for primary prevention to reduce risk are limited; they include lifestyle change, reduction in exposure to risk, 'treatment' (e.g. medical and dietary supplements), vaccination and family planning. There are two main approaches to primary prevention; those based on risk reduction in the general population (e.g. health promotion measures) and those based on risk reduction in 'high-risk' groups.[19;37] (The distinction between individuals at high risk and those with pre-clinical disease - and hence between primary and secondary prevention - is not always clear-cut.) Approaches targeted at the whole population aim to lower general levels of exposure, whereas those targeted at high-risk groups aim to protect individuals by reducing their vulnerability.[37] The anticipated benefit of any intervention should outweigh possible harm, so that there are issues of ethics and human rights, and about responsibility, as well as feasibility, to be taken into account, when considering potential 'strategies'.[19]

Even if the processes leading to the development of a condition are not fully understood, a knowledge of risk factors might suggest possible strategies of prevention. A variety of

factors – individual or social, biological or environmental, innate or acquired - can be involved in the pathophysiological processes underlying the development of any disorder.[20] Such 'risk factors' can interact in a variety of ways. Causal processes and risk (or protective) factors can be suggested by hypotheses, theory or knowledge about the mechanisms underlying the development of any disorder, or – in the case of age-related disorders – the processes related to ageing. They can also be derived inductively, perhaps from observation of treatment which has been found to slow the progress of a disorder, but particularly from the evidence provided by epidemiological work.[19]

An epidemiological approach is based on statistical comparisons. For example, case-control studies of populations with and without dementia (studies of prevalence) might suggest characteristics or factors (either current or at earlier stages of life) associated more frequently with the 'case' group. A preferable approach, however, which – although expensive - can throw more light on causality, is to carry out large longitudinal studies of incidence (new cases) over time.

Within public health, the main focus of a primary prevention approach has been on physical conditions, such as heart attack, stroke and cancer. Recently, however, there has been an interest in investigating risk factors for non-fatal disorders, because of the potential to reduce healthcare costs and improve public health.[40] Maintaining mental health has been little examined in epidemiological work. However, with the establishment of a European Network for the Calculation of Health Expectancies (one of whose aims is the development and promotion of mental health expectancies),[4] and in the context that older people may work for longer,[41] commentators have noted an increasing interest in monitoring the mental health of populations.

Strategies to prevent or delay the onset of symptoms of dementia, as well as to prevent decline into the advanced stage, have been viewed as urgently needed.[10;37;42;43] Because the causes of dementia and cognitive decline, and the processes underlying their development are not fully understood, possible preventive interventions are unclear. However, at the same time as more is becoming known about about age-related and 'dementia-related' changes in the brain, epidemiological studies of potential risk and protective factors are being carried out. As Cooper has noted, the public health challenge of dementia is beginning to be confronted.[37]

SUMMARY
- The increasing prevalence of dementia is an important public health issue, because of the impact on individuals and on service provision.
- While the progress of dementia can sometimes be slowed, no cure is available.
- There would be immense benefits to public health if ways of reducing the incidence (as well as the prevalence) of dementia and cognitive decline could be found. Since the rates of incidence of dementia rise exponentially with age, raising the mean age of onset could significantly reduce the prevalence.
- A primary prevention approach rests on a knowledge of causal factors and appropriate means of intervention.
- The processes underlying the development of dementia and cognitive decline are not fully understood. At the same time as more is known about changes in the brain, epidemiological studies of potential risk and protective factors are being carried out.

CHAPTER FOUR
COGNITIVE DECLINE, DEMENTIA AND TYPES OF DEMENTIA

An epidemiological approach rests on the ability to define and diagnose the conditions being investigated, as well as on some understanding of causal processes. This chapter considers what is meant by cognitive decline and dementia. Dementia has been classified into types and sub-types, and the diagnostic criteria are outlined, although there is increasing recognition of the overlap between classifications. The chapter concludes by outlining some of the explanatory models for Alzheimer's disease, some of which relate to debates about the nature of ageing

Potential risk and protective factors can be investigated by epidemiological studies of disease cohorts, but the condition must be capable of being well defined and diagnosed.[41] The decline of certain aspects of cognitive function with age has generally been distinguished from dementia. Defining and diagnosing cognitive decline and dementia (and 'types' of dementia) is problematic although, with increasing knowledge and improvements in technology, standardised diagnostic criteria have been developed.

Cognitive function is multi-dimensional, encompassing both memory and intelligence, both of which have been seen as reflecting a number of cognitive domains. Memory is commonly divided into short term (STM) and long term (LTM), with LTM further subdivided into declarative and procedural memory. The former refers to conscious recollection and recall whereas the latter includes priming, conditioning and skill-based learning.[44] Two types of intelligence are often distinguished – crystallised and fluid.[45] Fluid intelligence, which can be seen in terms of mechanisms or processing resources,[46] reflects the ability to acquire or use new information. Crystallised intelligence, or the knowledge base, is taken to be the cumulative end product of information acquired by the activity of fluid intelligence processes.[47] Cognitive function is seen, therefore, as comprising crystallised intelligence, fluid intelligence, declarative memory and procedural memory,[44] and as also including strategies, which are related to the concept of executive function.[46]

WHAT IS COGNITIVE DECLINE?
Cognitive performance declines with age,[48] although there is known to be a range of individual differences and a wide variation among older people.[20] By the age of 70, most people have a significant, although manageable, decline in cognitive abilities compared

with their mid-life level.[49] Studies indicate that many changes in cognitive function are gradual and develop from early adulthood, the extent of decline depending on the type of cognitive domain.[44;48] There is general agreement that with age comes the increasing likelihood of developing memory loss,[27;50] although some abilities are more affected by age than others, and fluid intelligence is more likely than crystallised intelligence to decline.[27]

The decline of certain aspects of cognitive function with age has generally been seen as distinct from 'pathological' conditions such as dementia, in which there are disorders of personality, memory, and other cognitive functions.[51] Three broad states have generally been distinguished (although various classificatory terms have been used): normal age-related decline or age associated memory impairment (AAMI), cognitive impairment no dementia (CIND) or mild cognitive impairment (MCI), and dementia.[13;19;44;50;52] It has been pointed out that - in common with other psychiatric diagnoses - there is no clear distinction between 'normal' and 'low' cognitive function,[20] and also that none of the classificatory terms fulfils satisfactory criteria for clinical validity.[44]

Normal age-related decline in memory is often described as 'benign senescent forgetfulness'. It is 'benign' because it is not considered to be a harbinger of dementia. AAMI is basically the same as 'benign senescent forgetfulness', except that it quantifies the degree of memory loss required for the diagnosis, namely, performance at or below the minus one standard deviation level for young adults on any standardised test of recent memory for which adequate norms have been established.[26] Some criteria also include self-perception of memory loss.[50] In addition, individuals should exhibit adequate performance on dementia screening instruments and tests designed to assess intellectual function, and they should be free of medical, psychiatric, or pharmacological factors that might confound memory performance.[26] Some have further sub-divided 'normal age-related decline' into 'normal' and 'successful'.[44] Little is known about the prevalence of age-related cognitive decline,[19] although some studies have suggested that, in the US, about 40% of people aged 65 and over have AAMI.[50] Only a minority will develop progressive cognitive failure and dementia;[49] research has suggested figures between 1% per year[50] and 9.1% over a 3.6 year period.[49] Attempts have been made to distinguish markers which might distinguish those who are at risk of subsequent dementia from those whose cognitive impairments will remain stable.[49] Mild cognitive impairment (or CIND) defines a transitional stage between normal age-related decline and dementia. The diagnosis is important (and can be described as 'transitional') for two reasons. It helps clinicians to recognise – and take seriously - a pathological (i.e. more than normal) degree of memory loss in older people, and it also identifies a group of people who are at high risk of developing dementia. It is however a heterogeneous condition, which suffers from heterogeneous definitions. It can be mild, moderate or severe, and although it is not necessarily progressive,[53] the annualised conversion to dementia is quite high in most follow-up studies - between 10% and 15%.[50;52] The condition is characterised by important memory deficits, similar to those in people with very mild Alzheimer's disease, without functional impairment.[50] Studies have suggested that about 10% of people aged 65 years and over have this condition.[50] In one recent longitudinal study examining the evolution of CIND among subjects aged 75 years and over, between baseline and a 6-year follow-up, 34% of subjects died, 35% progressed to dementia, 11% remained stable and 25% showed cognitive improvement.[53] Similar rates of progession to dementia – which represent a threefold increase in risk over people without

MCI - were found in the Religious Orders Study.[54] Findings from other empirical work have indicated that decline in specific cognitive domains might indicate reversible cognitive impairment.[55] The absence of a subjective memory complaint has been found to be associated with improvement.[53]

WHAT IS DEMENTIA?

Dementia is a term used to refer to a variety of illnesses and conditions which affect the brain. These conditions result in impairment of brain function and a multi-faceted decline in cognitive functioning, including memory problems, personality changes and behaviour, severe enough to cause impaired function in, and severe disruption to, everyday life.[50] The effects of the condition change over time, but the cognitive performance of people with dementia is substantially worse than that of the normal elderly on crystallised and fluid intelligence and declarative memory tasks.[44] Dementia can be associated with a number of conditions,[56] and can occur as the result of a number of pathological processes.

Dementia can be classified in a number of ways. One important distinction is between progressive and treatable dementia. A small but significant proportion of those with a dementing illness have a potentially treatable condition, such as Vitamin B12 deficiency, normal pressure hydrocephalus or depression. Other possible ways of classifying dementia are according to the effect on a person's ability to function and their need for care (mild, moderate or severe), according to underlying pathology, or according to the age of onset. Different classifications may stem from the reasons for classification. (While there may be concerns about stigmatisation, a diagnosis of dementia, or type of dementia, can be helpful in enabling needs to be addressed.) For service provision, a broad definition in terms of the needs of the person or the severity of the condition may be most appropriate. When considering possibilities for treatment, a more specific diagnosis and prognosis can be helpful for patients and their families.[57] For research, or in considering the potential for prevention, dementia has been classified in terms of types and sub-types, often based on pathology.

Types and sub-types of dementia

There has been considerable progress in the ability to diagnose dementia and to distinguish between types and sub-types.[39] The most common types of progressive dementia are Alzheimer's disease, vascular dementia, and dementia with Lewy bodies. Rarer types include fronto-temporal dementia (including Pick's disease) and Korsakoff's syndrome. In addition, a number of conditions, which include Down's syndrome, Parkinson's disease, Huntingdon's disease, Creutzfeld-Jacob disease, HIV /AIDS can predispose to dementia.

At the same time, there is an increasing understanding of the heterogeneity of dementia, and of the overlap between classifications.[58] For example, although vascular dementia and Alzheimer's disease are normally seen as characterised by different types of brain pathology, it has recently been suggested that the evidence from empirical work makes the idea of a dichotomy no longer tenable.[19] It has also been noted that, with the increasing knowledge about neurodegenerative disorders and improved diagnostic techniques, terminology is evolving, and that in the future such disorders may be defined by the rogue proteins responsible (and ultimately by their solutions).[59]

Alzheimer's disease

Alzheimer's disease is associated with progressively worsening memory, and a decline in other intellectual functions including language, motor skills and perception.[18] Frequently there are changes in behaviour. The clinical diagnosis is based on the exclusion of other causes of dementia, including vascular dementia.[56;60] Alzheimer's disease mostly affects the hippocampal area of the brain, and is characterised by the presence of neouropathological features, including neuritic plaques, amyloid angiopathy, neuronal loss and neurofibrillary tangles.[43;56] A definite diagnosis can only be made after death. Evidence indicates that the pathophysiology is very complex,[61] and it has been suggested that there may yet be different types of Alzheimer's disease.[62] The causes of the condition are largely unknown. Although Alzheimer's disease has always been seen as a degenerative disorder, there is recent evidence to suggest an association with vascular disease.[62;63]

In the UK, the majority of people with dementia are thought to have Alzheimer's disease. Large studies such as the EURODEM analysis[8;9] and the MRC CFAS study[3;10] have investigated the relative prevalence of the various types of dementia, but there is no consensus on a definitive breakdown of types. Research findings suggest that, of the cases of dementia in those aged 65 and over, 55% will be Alzheimer's disease; 20% vascular dementia, 20% Lewy body disease; and 5% other types.[17] The prevalence of Alzheimer's disease increases markedly with age,[14] and a number of studies have suggested that the prevalence is higher in women than in men.[56]

Vascular dementia

Vascular dementia is a complex disorder, characterised by intellectual impairment as a result of cerebrovascular disease and ischaemic-hypoxic brain injuries.[56;64] The symptoms are similar to those of Alzheimer's disease, although periods of relative stability and sudden decline occur more frequently in vascular dementia, frontal lobe damage appears earlier,[18] and survival rates are lower.[56] Again, diagnosis is difficult and can only be confirmed at post-mortem.[65] Diagnostic criteria rely on both clinical and radiographic criteria,[26] i.e. the presence of dementia and cerebrovascular disease or ischaemic white matter lesions (evidenced by neuroimaging) and a temporal relation.[56;57;65;66] The criteria for vascular dementia allow for the possibility of sub-types,[57] and clinical sub-types, including Binswanger's disease, have been recognised.[56;65] The concept of vascular dementia as resulting from 'mini-strokes' in the brain (hence multi-infarct dementia) has been replaced by more sophisticated models, suggesting a spectrum of vascular causes,[58;66;67] although the causes are not easy to establish.[66] Some have argued, therefore, that the term 'vascular dementia' is now obsolete, and that a broader category, vascular cognitive impairment (VCI) should be substituted.[68]

The prevalence of vascular dementia has been difficult to estimate, since different diagnostic and pathological criteria have been used.[65] Before about 1970, vascular dementia was thought to be the most common form of dementia,[67] but it is now felt that the condition may have been over-diagnosed in the past.[65] There is some evidence that vascular dementia is more common in men than in women.[56]

Mixed dementing illness

It is possible to have a 'mixed dementing illness', i.e. Alzheimer's disease and vascular

dementia, although the traditional separation between 'senile dementia' and 'arteriosclerotic dementia' is now being questioned.[58;67;69] Magnetic resonance imaging and neuropathological studies have shown that many individuals with dementia in old age have more than one type of pathology.[43] Indeed, a recent review of this topic argued that mixed states are probably more common than 'pure' dementia syndromes.[70]

Dementia with Lewy bodies

Dementia with Lewy bodies (DLB) is now the preferred term for a variety of clinical diagnoses used over the last decade, and current thinking suggests that there is a spectrum of disease.[71] The condition is associated with tremor, rigidity and slowness of movement, delusions and hallucinations and unexplained falls.[18] The pathology is that of a primary degenerative dementia with features resembling both Alzheimer's and Parkinson's diseases.[72] There are microscopic changes, called Lewy bodies, in the nerve cells of the brain, similar to those in the brains of people with Parkinson's disease.[73] A diagnosis of possible DLB can be made when other causes of dementia or Parkinsonism have been excluded.[71] Initially thought to be uncommon, DLB is now thought to be the second most common pathological cause of dementia, accounting for up to 20% of all elderly cases reaching autopsy.[71] There could, therefore, be approximately 11,000 people with DLB in Scotland.[73]

Fronto-temporal dementia

Fronto-temporal dementia (FTD) is the commonest clinical syndrome arising from frontotemporal lobar degeneration (FTLD), a non-Alzheimer degeneration of the frontal and temporal lobes.[74] At first, personality and behaviour are more affected than memory; symptoms include behavioural and emotional problems, disinhibition, apathy, inertia and loss of speech.[18] The disease progression is usually slow. Clinical diagnostic criteria for FTLD syndromes have been the subject of an international consensus,[75] and the types of histology classified into three main sub-types, including Pick type and motor neurone type. FTD is strongly familial, and in some families the disorder mutations have been identified in tau sequencing on chromosome 17.[76] FTD is thought to account for up to a quarter of patients presenting before the age of 65 with dementia due to primary cerebral atrophy. However, in other parts of the world the condition is more widespread, and it is now felt that FTD has been underdiagnosed.[74]

Subcortical dementias

Subcortical dementias include dementia stemming from progressive supranuclear palsy, motor neurone disease, Parkinson's disease, Huntingdon's disease and multiple sclerosis.[18] Each is associated with specific neurological changes. These dementias feature diminished initiative, increased irritability, and difficulty processing and manipulating information, a pattern of intellectual decline which is seen in multi-infarct dementia.[26] The prevalence ratio for Parkinson-related dementia has been estimated as 41.1 cases per 100,000 in those up to 50 years old, and 787.1 cases per 100,000 in those 80 years or older.[77] Progressive supranuclear palsy (PSP) is clinically similar to Parkinson's disease and tends to emerge in older populations. Up to 80% of those who develop this disorder will ultimately show signs of moderate to severe dementia.[26]

Alcohol associated dementia

It has been estimated that alcohol may contribute to dementia of all types in about 10% of cases.[78] Alcohol-related brain disorders include a widespread impairment of mental function, which has been termed 'alcohol associated dementia'. There are severe problems with

memory, and also with attention, despite retention of language.[18] A heavy alcohol intake can be associated with vascular disease, and with an increased risk of vascular dementia. In addition, alcohol intoxication and withdrawal accompanied by thiamine deficiency is also associated with the more specific disorder, Wernicke-Korsakoff's syndrome, or Korsakoff's syndrome. There is contention about whether alcohol ingestion per se can cause dementia.[79]

Early onset dementia

While dementia is largely a condition of old age, people aged under 65 years can develop the condition. Common causes of dementia which occurs below the age of 65 include Down's syndrome and alcohol-related dementia, as well the more prevalent forms.[17;18] Further information about early onset dementia can be found in Cox and McLennan (1994)[80] and the SNAP report, 'Huntingdon's disease, Acquired Brain Injury and Early Onset Dementia'.[81]

DIAGNOSIS

In order to examine risk factors for dementia and cognitive decline, the presence of the condition must be capable of being reliably assessed.[41] However, diagnosis may be difficult for a number of reasons. A certain threshold of severity has to be reached to justify a definite, rather than probable, diagnosis, and in some cases of dementia, an accurate diagnosis can only be made months or years after the first symptoms.[39] Key problems have been seen as a lack of consensus about the definition of 'significant' impairment, or the boundary between dementia and cognitive impairment.[11] A number of difficulties relate to psychological testing of mental performance, since 'normal' scores of cognitive function vary widely and it may be difficult to distinguish between impairment and decline without repeated re-examination, and because testing methods may be unsophisticated.[41]

A number of concerns relate to the suitability and reliability of clinical tests of cognitive function. Some have drawn attention to ethical considerations in administering such tests, which can cause anxiety and distress, especially in people with dementia.[11] (There is a view that some older people might perform less well on certain tests of cognitive function because of anxiety,[41] and there is some evidence that practical problem-solving performance does not show the same decline with age as traditional measures of intelligence.[82]) The most widely used test world wide for global cognitive function or ability is the Mini-Mental State Examination (MMSE)[83] which tests a range of cognitive abilities and provides a total score of cognitive function. An alternative is the Cambridge Cognitive Examination (CAMCOG).[84] Other tests are used to examine memory and intelligence. Questions have been raised, however, about the extent to which measures of cognitive function are able to measure cognitive decline, and whether they are sensitive to changes to a neuro-pathological grading.[19] It has been noted, for example, that the MMSE cannot be used to measure domain-specific change, since most domains are represented by only one or two items, resulting in floor and ceiling effects and insensitivity to change.[55] The MMSE has also been seen as limited because it will not detect subtle memory losses, particularly in those with more education.[50] Although others have argued that the MMSE has been shown to be sensitive to change in cognition over time,[85] and has been used to derive a tentative probability of dementia,[10] the best tests of cognitive decline are felt to be those with a range of measures.[41]

The diagnosis of dementia is notoriously difficult during life, partly because of the gradual onset of the condition and because the early signs can be indicators of other diseases or life

changes.[60;62] Differentiating between different types of dementia can also be difficult because the processes which result in dementia can be difficult to distinguish from one another clinically, particularly at the early stages.[57;65] Neuro-pathological confirmation of a diagnosis is problematic, since changes in the brain can only examined after death. Identification methods have varied considerably, but there are now sets of standardised clinical and neuropathological diagnostic criteria,[10;29;58;65] and improvements in diagnostic tools.[17] A tentative probability of dementia can be derived from the total MMSE score,[10] but ICD-10 criteria for the dementia syndrome require a decline in memory and in cognitive abilities, retained awareness of the environment, and a decline in emotional or social behaviour, all present for at least six months.[10;66] Diagnostic methods include clinical tests, and biological markers in the fields of neuropsychology, genetics and neuro-imaging,[86] in particular magnetic resonance imaging (MRI),[57] and also measurement of brain electrical activity.[41]

The detection of dementia might not occur until the disease is quite advanced and there is irreparable brain damage. Because of the possibilities for treating the symptoms of some types of dementia in the early stages, and because those affected are entitled to information about their condition, early detection and diagnosis is becoming more important.[17;41;57] As a consequence, ways of identifying dementia – in particular Alzheimer's disease - at the 'pre-clinical phase' are being developed. At present, predictive testing is based on memory tests. The findings from a number of studies have indicated that low scores in tests assessing delayed recall are a better predictor of dementia than atrophy of the medial temporal lobe,[86;87] and can best discriminate between those with presymptomatic Alzheimer's disease and those who remain non-demented.[88] On the other hand, some have suggested that the changes in the brain observed at autopsy in some older people without dementia represent a 'pre-clinical phase' of Alzheimer's disease.[39] Since brain changes can be detected by structural imaging, and changes in brain activity by positron emission tomography (PET),[89] it has been suggested that these techniques will increasingly be used to aid the identification of Alzheimer's disease early in its course.[41;50;57] Other methods of evaluation are being investigated.

A number of ethical issues arise in relation to predictive or pre-symptomatic testing, which can be seen as risk assessment or screening. These concern the accuracy of the test results, and the degree of certainty of the eventual diagnosis, which may be expressed in terms of probability or risk. For example, only half of those with 'Alzheimer-like' changes in the brain detected by a PET scan will go on to develop Alzheimer's disease.[90] Another concerns the extent to which it might be felt beneficial or helpful to know of an early diagnosis of dementia. Hence, the role of routine cranial imaging in the evaluation of dementia in older people continues to be debated.[26]

HYPOTHESES, THEORIES AND MODELS

Despite the existence of criteria for diagnosis and classification, relatively little is known about the nature of cognitive impairment and dementia, why and how these conditions develop, i.e. what are the causal mechanisms or processes, or the factors associated with their occurrence.[19;20;61;66] This is particularly the case for Alzheimer's disease, the causes of which are generally seen as being multi-factorial.[91] Understanding the mechanisms might suggest possible means of prevention, such as drugs, but the causes (and effects) are far from clear.[41] A further reason for the difficulty of modelling a late-onset condition like Alzheimer's disease is the uncertainty of the lag periods between putative exposure, disease onset and dementia

presentation.[92] Nevertheless, a number of hypotheses to explain the development of Alzheimer's disease have been proposed, based on theories about the nature of ageing and observed clinical and pathological changes.

There are a number of theories of 'ageing'.[27;93] Ageing has been seen as due primarily to the accumulation of defects.[93] First, as the body ages, there is a limit to replication of cells, and systems break down; these changes have been seen as genetically programmed to an extent.[27;94] From the 'immune' theory of ageing, the ageing body becomes more vulnerable to damage. The work of Hayflick has suggested that the human organism appears less able to maintain its own viability with increasing age.[95] At the same time, damage to the cells or organs of the body can occur by 'insults', injury, disease processes or chemical reactions. Figure 4.1 below shows a model of the factors thought to contribute to disorders, such as dementia, which have been seen as 'ageing-dependent' (see also the discussion on page 45).

Figure 4.1 A model showing the sequence of events resulting in ageing-dependent disorders.
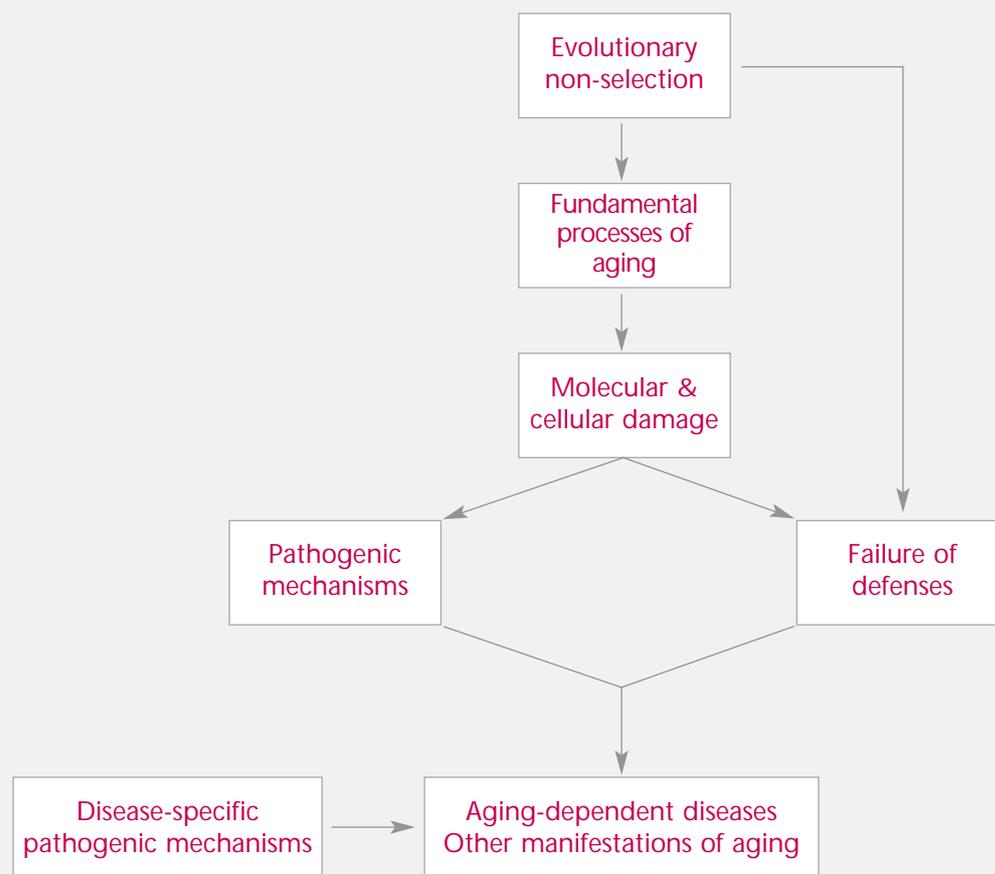
Source: Adapted from D.H. Solomon, "The role of aging processes in aging-dependent diseases", figure 81, page 135, in Bengston and Schaie (eds), Handbook of Theories of Aging, 1999. New York, Springer Publishing. Reproduced with permission from Springer Publishing Company.

Recently, much more has been learned about the brain, both at the general and the molecular level,[28] and about what happens to the brain in old age.[41] Some hypotheses about the processes causing dementia or cognitive decline are based on known changes to the brain. For example, the brain of a 90-year-old weighs about 10% less than previously, largely because of loss of neurons.[26;27] There is some evidence that growing older, in itself, leads to impaired cognition, and some have linked this cognitive decline with 'age-related' atrophy of the brain,[26;27] and with a deterioration in the efficiency of important neurotransmitter systems.[27] In addition, the amyloid plaques and neurofibrillary tangles, which have been seen as characteristic of Alzheimer's disease, have been found to occur with greater frequency with age, even in otherwise normal older people.[26;88]

On the other hand, although age has been seen as the 'cause' of cognitive decline and dementia, there is now increasingly a view that age is not the only cause. From the assumption that dementia occurs in older people only in the presence of specific disease,[26] the term 'senile dementia', suggesting dementia as a natural consequence of ageing, has been abandoned. It has been pointed out that older people are at greater risk of illness or disease, so that the effects of age itself might not be separable from those of age-related disease.[26;27] It has also been noted that the hippocampus – the area of the brain thought to be responsible for cognitive function – is vulnerable to insults such as head trauma, stroke, epilepsy and chronic stress, as well as changes due to increasing age.[96] From the view that Alzheimer's disease is an extreme variant of brain ageing, one suggestion is that age-related changes in the brain could upset the glucocorticoid balance and lead to hippocampal neuronal death.[41]

Some hypotheses about the causes of Alzheimer's disease are based on explanations for the pathological changes to the brain. Brain damage may result from inflammation,[97] injury or disease (e.g. viruses)[14] as well as from cerebro-vascular events. Also, although it is not known whether amyloid plaques and neuro-fibrillary tangles should be seen as causes or effects,[41] there has been interest in the role of biological mechanisms, particularly protein production, in their formation.[98;99] Various mechanisms for the interaction of proteins, pathological features, inflammation and neurons have been suggested.[88] There has been debate between those who have argued for a key role for **ß**-amyloid **p**rotein ('**bap**-tists') and others ('**tau**-ists') who have offered explanations based on **tau** protein.[88]

Amyloid plaques are clumps of cellular debris containing amyloid protein, and are one of the main – and earliest - changes in the brains of people with Alzheimer's disease.[41;100] Amyloid deposits have been seen by some as a primary (necessary but not sufficient) cause of Alzheimer's disease,[38] the 'amyloid hypothesis' positing that these deposits result from abnormal amyloid clearance.[38] An increased synthesis of Aß (or ß-amyloid) protein, which precedes symptoms of Alzheimer's disease, and which may be associated particularly with the genes for early onset AD, has given support to this hypothesis.[38;101] The 'amyloid cascade hypothesis' proposes that the ß-amyloid plaques resulting from abnormal protein production are toxic to neurons and also stimulate inflammation leading to tangles.[88] It has been pointed out that if amyloid plaques are present before the onset of Alzheimer's disease symptoms, then treatment might usefully target plaque formation. However, if amyloid itself impairs brain function or is cytotoxic, then such treatment would be ineffective at best and could magnify brain damage.[41]

The neuropathology of Alzheimer's disease also includes the formation of neurofibrillary tangles. These tangles contain tau protein of various types in a phosphorylated state.[41] Tau protein is now known to be toxic,[99] and some have argued that the key step in the pathogenesis of Alzheimer's disease lies with tau protein and the breakdown of systems preventing the formation of tangles.[41;88]

Another view is that brain ageing, or brain damage, is associated with free radical action.[98] From the 'oxidative stress hypothesis', damage can be caused by the action of free radicals or exposure to toxins. Free radicals, or oxidative stress, can be produced by (for example) infection, smoking, a high intake of saturated acids, or a low intake of antioxidants.[27;51;91] The observation that non-steroidal anti-inflammatory drugs (NSAIDs) can reduce the rates of dementia has lent support to this hypothesis.[41] The brain is thought to be low in anti-oxidant substances (which can stop the free radical chain reactions).[43] It has been suggested that the free radical reactions generated by oxidation might contribute to both vascular and Alzheimer's disease pathology;[43] for example, the Aß protein of 'senile plaques' has been seen as evidence of an oxidative reaction.[102] As knowledge about the pathways of neuronal cell death that occur during oxidative challenges is increasing,[102] one view is that oxidative damage to lipid membranes can disrupt normal neuronal cell functioning, leading to the formation of amyloid plaques and to neuronal cell death.[103]

However, research has shown that the occurrence of dementia is not always associated with pathological changes in the brain.[104] From a clinical perspective, explanations have focused on neuronal changes, which have been seen as largely independent of amyloid deposition,[105] and particularly on the concept of 'brain reserve'. It has been proposed that individuals can vary in their 'reserve capacity' (a hypothetical concept related to the 'amount' of functioning brain tissue)[62] because of genetic differences and exposure to environmental factors. The reserve capacity is seen as being capable of being depleted by injury, but also of being enhanced (or maintained) by intellectual stimulation.[98] A clinical diagnosis, therefore, might result from a combination of factors, including both physiological and psychosocial processes.[39] From this view, one hypothesis is that low pre-morbid intelligence hastens the clinical diagnosis of dementia of the Alzheimer type.[39] Another is that psychosocial factors might act to reduce the margin of intellectual reserve to a level which results in a diagnosable dementia.[39]

Several authors have speculated that the brain has a form of neuronal 'reserve', such that it can lose some of its functional capacity without degenerating dramatically.[98] From this view, the brain will start to demonstrate clinical degeneration if this reserve capacity is depleted, with the onset of dementia once a 'threshold' (corresponding to the critical amount of brain tissue at which normal cognitive function cannot be sustained) has been crossed.[62;98] Figure 4.2 on page 38 illustrates the threshold model of dementia.

(A) indicates normal brain aging, where the threshold for dementia is not reached until after normal life expectancy. (B) indicates attainment of the dementia threshold in middle age because of an increased rate of loss of reserve capacity over the life course. (C) indicates attainment of the dementia threshold in middle age because of a decreased reserve capacity present at birth.

Figure 4.2 Threshold model of dementia
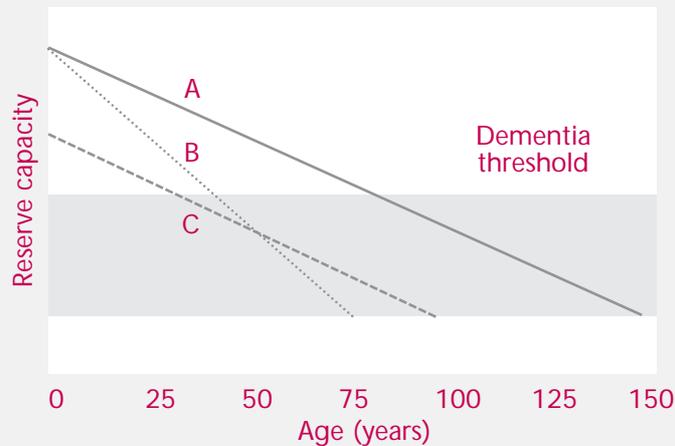
Source: J A Mortimer, "What are the risks for dementia?" figure 10.1, page 209 in Huppert, Brayne and O'Connor (eds) Dementia and Normal Ageing, 1994. Cambridge: Cambridge University Press. Reproduced with permission from Cambridge University Press.

There is continuing debate about the nature of cognitive decline and dementia, and the relationship between the two, which relate to wider questions about the nature of ageing.[44] One issue concerns whether cognitive decline should be seen as occurring as part of 'normal ageing'.[26;106] Keefover and Rankin have argued that the cognitive changes seen in older people cannot be assumed to be benign just because they are common, and have noted that severe cognitive decline, including significant memory loss and dementia, almost always occurs only in the context of specific disease.[26]

A related unresolved question concerns the relationship between age-related cognitive impairment and dementia,[42;44] something which has been very little investigated by research.[49] One view is that the processes leading to dementia can be seen as similar to – although more severe than - those resulting in cognitive decline.[55] An alternative view is that the deficits in dementia should be seen as qualitatively, as well as quantitatively, distinct from those in normal ageing.[44] This issue may have important implications for approaches to prevention. If cognitive decline and dementia are seen as a continuum, with Alzheimer's disease as an extreme variant of ageing, then, as Whalley has pointed out (p125), "its proper study will rest firmly on the account of the neurobiology and neuropsychology of the ageing process", rather than on the study of disease cohorts.[41]

SUMMARY
- Dementia can broadly be divided into vascular dementia and dementia of the Alzheimer type, but dementia with Lewy bodies and fronto-temporal dementia are now thought to have been under-diagnosed in the past.
- There is increasing knowledge of types and sub-types of dementia, but also of the overlap between types or categories. With increasing knowledge, terminology is evolving.
- Cognitive decline has been sub-divided into 'age-associated cognitive decline' (AAMI) and 'cognitive impairment no dementia' (CIND).
- Diagnosis of both cognitive decline and dementia is difficult, but there are now internationally agreed standards.
- A number of hypotheses and models of dementia of the Alzheimer type have been proposed, based on pathological and clinical criteria.
- There is interest in whether cognitive decline and Alzheimer's disease should be seen as a continuum, or as qualitatively different conditions. This issue could have important implications for approaches to prevention.

CHAPTER FIVE
METHODOLOGICAL ISSUES

This chapter outlines the main methodological issues which need to be taken into account in reviewing empirical work examining risk factors. These concern issues of definition and measurement, the design of the study and interpretation of the findings.

Empirical work examining risk factors for dementia, particularly Alzheimer's disease, is being carried out in a number of countries. Those reviewing empirical work have drawn attention to a number of important methodological issues which need to be taken into account in drawing conclusions from the findings or making comparisons between studies.[10;11;107] It has been emphasised that the data must be adequate for drawing conclusions about risk factors,[11] and that issues of bias should be acknowledged and addressed as far as possible.[56] The main methodological difficulties can be seen in terms of:

- issues of definition and measurement
- the design of the study
- interpretation of findings.

ISSUES OF DEFINITION AND MEASUREMENT

It has been pointed out that measurement error is an often unacknowledged but important source of bias in epidemiological work examining risk factors.[19] Both the presence of the disorder and the exposure to risk factors have to be assessed.

Some reviewers have noted that estimates of the prevalence and incidence of dementia (or type of dementia) are heavily influenced by the methods used to identify the syndrome.[10] Certain criteria have been seen as unsatisfactory, either because the data would be incomplete (e.g. only moderate to severe dementia is normally mentioned on death certificates[60]) or because of the possibility of bias (e.g. carers' diagnoses are subjective, certain groups might be more likely to be admitted to hospital). It has also been claimed that the rates reported can be affected by the efforts made to detect or identify cases,[107] particularly in incidence studies,[17] or that there might be tension between researchers and clinicians about diagnostic categories.[19]

With different diagnostic criteria being used in different countries,[11] and in different settings, methods of identification of dementia have varied widely across existing studies.[10] Early work was hampered by the variety of definitions of dementia, assessment strategies and population samples, but the introduction of reliable, internationally agreed clinical and neuropathological diagnostic criteria has now made it more feasible for population-based comparative studies to be carried out,[64] or for the literature to be critically reviewed.[108] Nevertheless, difficulties in diagnosing the presence of dementia continue to be noted. For example, Whalley and colleagues have commented that the most important limitation of their large study lay in the difficulty of reliably distinguishing between Alzheimer's disease and vascular or 'mixed' dementias.[92] Those reporting the recent MRC CFAS study have drawn attention to the difficulties of collecting the complex information required for a diagnosis of dementia over a long period of time and for very large population samples.[10] There are also a number of difficulties in defining and measuring 'risk factors' or 'protective factors'.[56] For example, how should the strength or level of exposure to the risk factor be measured? By whom? How long ago did the exposure occur? For how long? It has been suggested that some of these issues can cause particular difficulties for case-control studies, in which the assessment of exposure to the risk factor of cases (but not controls) may be based on information from surrogates, or in which informants of patients (rather than controls) might be better at recalling exposures such as head injuries.[56]

THE DESIGN OF THE STUDY

Reviewers of the epidemiological literature have drawn attention to the range of methods used. Many have pointed out that that methodological differences between studies have caused difficulties in interpreting the results and in making comparisons between studies.[10;11;107] Important issues relate to whether studies examine prevalence or incidence, the power of the study to test for risk factors, and the characteristics of the sample.

Prevalence or incidence studies

Early empirical work examining risk factors for dementia were case-control studies based on prevalence. These studies, which were often small, compared the presence or absence of certain 'risk factors' in the population with dementia and the population without.[11;56] In some studies, e.g. the Canadian Study of Health and Ageing,[109] the samples were matched for factors such as age, gender, residence, although in others the populations were unmatched.[110]

Prevalence figures (the number of individuals living with the condition) reflect survival as well as new cases. One limitation of prevalence or case-control studies is that rates can be biased by differences in survival, since differences in occurrence (incidence) and survival of disease in a population cannot be distinguished.[56] Hence, they cannot be used to investigate either temporal effects or the complex interactions between risk factors.[19] Epidemiologists have argued that research examining causal factors should be based on large longitudinal studies of incident cases, ideally prospective (to examine variables before the onset of disease) and preferably with a number of measurements over time,[20;41] to provide more reliable evidence, and to avoid the influence of variations in mortality, i.e. to distinguish between association and causality.[10;56]

The confounding effect of survival is particularly important in considering risk factors for

cognitive decline and dementia. In the UK, cognitive function is strongly related to survival, and has been seen as a marker for capacity for survival.[111] Hence, the survival of people with dementia for longer periods has enormous implications for prevalence studies.[112] Studies examining risk factors for dementia conducted before 1991, which were mostly based on the comparison of prevalent cases of Alzheimer's disease with control subjects, have been reviewed and re-analysed by the EURODEM Risk Factors Research Group.[7]

Longitudinal or cohort studies, as well as being expensive and time-consuming to carry out, are prone to potential problems of non-response, competing mortality and co-morbidity.[56] Prospective studies, in which the exposure state is measured before the onset of the disease, have been seen as preferable to retrospective studies,[11;56] since, in the latter, assessment of exposure to the risk factor may be prone to various kinds of bias. For example, historical items may be based on recall measures, and data are more likely to be influenced by selective memory.[113] In the case of dementia or cognitive decline, longitudinal studies may be hampered by difficulties with diagnosis, since the onset is hard to define. Also, since the course of these disorders is gradual and slow, observation has to cover a number of years.

The power of the study to test for risk factors
Reviewers of the literature have noted that many early studies examining risk factors for dementia have been small, and that risk factors can be rare.[11;56] The point has been made that one of the most important determinants of the identification of risk factors might be the power of the study to confirm or deny a hypothesis.[62] Large cohort studies are now under way.

Characteristics of the sample
A major concern of any population study is the representativeness of the sample studied, since the characteristics of the sample can profoundly affect the rates of prevalence or incidence.[10] The point has been made that, among the study population, there might be sub-populations with – for example - high rates of illness or high frequencies of genetic variants.[11;107] It has been argued, therefore, that studies based on institutions, such as nursing homes or hospitals, will indicate higher rates of dementia,[11] although they will also fail to identify a substantial proportion of those affected.[107] Ideally, studies would be based on institutional and community samples, but where this is not feasible, it has been suggested that community studies are preferable.[107]

The method of sampling might also affect the numbers or characteristics of those who take part. Jorm and colleagues found that rates were lower when all of a community, rather than a random sample, were studied.[107] Sampling methods can be particularly important in comparative studies, since there might be variations between groups in the proportion who decline to take part.[113]

INTERPRETATION OF FINDINGS
Commentators on empirical work have stressed that, while studies can demonstrate the consistency, or otherwise, of associations between the prevalence or incidence of dementia and given risk factors, care must be taken in suggesting explanations. This is

particularly important since the findings can be used to consider possible interventions.[11] It has been noted that an effect might not necessarily be causal, and that there could be a number of explanations, e.g. the apparent variable might be a marker for another, or the apparent association might be a measurement artefact.[11] For example, the effects of cardiovascular disease on cognitive maintenance might simply represent the results of lifestyles that are unfavourable for both cardiovascular health and maintenance of cognitive function.[48] Many commentators have also emphasised the possible confounding effects of pre-morbid cognitive ability on a diagnosis of dementia, especially when examining education as a risk factor.[108;114]

SUMMARY

- In assessing the findings from epidemiological work, a number of methodological issues concerned with definition and measurement, and the design of the study, have to be taken into account.
- The presence of the disorder or type of disorder must be capable of being reliably assessed, as must the strength of exposure to risk factors.
- The design of the study can strongly influence the findings. Early empirical research was based on case-control studies of prevalence, but large longitudinal studies of incidence are needed to distinguish between association and causality, and to examine interactions between risk factors.
- There may be various explanations for some of the findings of epidemiological studies.

PART TWO
RISK FACTORS FOR DEMENTIA AND COGNITIVE DECLINE

Empirical research examining risk factors for dementia, or cognitive decline, is being carried out in many countries across the world. Because of the number and range of studies, this review draws largely on recent reviews of empirical work, on book chapters, and on editorials and commentaries. Details of recent empirical work have been included, among them some of the findings from papers presented at the 8th International Conference on Alzheimer's disease and related disorders, held in Stockholm, Sweden, between 20-25 July 2002.

The review is structured according to 'risk factors', under the following headings:

• Age, gender and ethnicity
• Genetic factors
• Pre-existing conditions
• Physical injury, illness and medication
• Classical [personal and lifestyle] risk factors:
    • risk factors for vascular disease
    • smoking, alcohol and drug use
    • diet, nutrition and hormones
    • interventions targeted at vascular disease
• Factors related to social context: social class, occupation and education
• Physical, mental and social activity

Each section outlines the strength of the evidence for seeing the variable as a risk factor for dementia and cognitive decline, possible interpretations of the findings and implications for prevention.

CHAPTER SIX
AGE, GENDER, ETHNIC AND NATIONAL FACTORS

Studies examining risk factors have conventionally been corrected for socio-demographic factors, such as age, gender and ethnicity, education and occupation. However, there is increasing interest in the extent to which these variables should be seen as 'risk factors'. This chapter outlines the evidence for risk due to age, gender and ethnic and national differences, and considers the extent to which age should be seen as the main risk factor for dementia or cognitive decline. Since these factors cannot be modified, the implications for strategies of prevention rest on the relative importance of these risk factors.

AGE

Age and the risk of cognitive decline

Numerous psychological cross-sectional studies have shown age differences in cognitive function,[10;115;116] and in a recent two-wave study carried out in Cambridge, the incidence of cognitive impairment at various cut-off points showed that age was a major influence on MMSE score.[10] There are also differences with age in the rate of cognitive decline. Findings from longitudinal aspects of the Cambridge study showed that, with increasing age, the mean drop in score increased.[10;85]

Schaie has made the point that cross-sectional studies do not take account of cohort differences in experience, so that longitudinal studies are needed to examine cognitive decline, both generally and in different domains.[116] He has reported that the data from the 40-year Seattle Longitudinal Study does indicate age-related cognitive decline, although not as great as that suggested by cross-sectional studies. The evidence from this study suggests that cognitive decline below the age of 60 is not characteristic of normal ageing, but neither is intact functioning at age 80. In a review of the literature, Fillit has observed that the nature and extent of changes in cognitive function associated with ageing have now been reasonably well defined.[49] Cognitive decline is not universal nor are all aspects of intellectual functioning equally affected.[116] There is also some evidence that inter-individual differences increase in old age.[44;116] It has been suggested that older people may develop coping strategies in order to maximise function and compensate for the loss of abilities in specific areas.[49]

There is general agreement, however, that with age comes the increasing likelihood of developing memory loss, although some abilities (episodic memory, especially recall) are more affected by age than others.[27;50] Fluid intelligence is more likely than crystallised intelligence to decline (although there is some evidence from longitudinal studies that such decline may be cohort-related and may be decreasing over time).[27] One recent study which found significant decline in total CAMCOG score and all of the subscales over a 4-year period in a 75+ age cohort found that greater decline in the perception subscale was associated with older age.[55] Certain cognitive domains, on the other hand, appear to be particularly resistant to age-related deterioration.[26] Schaie has found that decline is least in magnitude and occurs later on verbal ability.[116]

Age and the risk of dementia

Studies throughout the world have shown that the prevalence of dementia increases dramatically with age.[11] While the condition is uncommon before the age of 65 years, the prevalence of dementia, particularly Alzheimer's disease, increases exponentially with age, at least up to age 90.[7;14-16] Hofman and colleagues, reporting the estimates from the EURODEM collaborative analysis, have noted that rates of prevalence nearly double with every five years of increase in age,[7] and the findings from the recent MRC CFAS study in the UK show the same relationship.[10]

The incidence of dementia, particularly Alzheimer's disease, also rises dramatically with age. The annual incidence of Alzheimer's disease has been estimated as approximately 1.4 per 1000 in the seventh decade, 6.4 per 1000 in the eighth decade and 20.5 per 1000 in those aged 80 years of age or over.[16] This describes a Gompertzian exponential (a linear relationship between the log of age-specific incidence and chronological age) with a doubling time of only 5 or 6 years from age 60 to age 90.[16] There is some dispute about what happens in very old age;[14] some studies have suggested some levelling-off in the rise of incidence in very old age.[117] Others, however - the MRC CRAS study for example - have found no levelling-off in the rise of prevalence in the 85 years and over age group.[10]

Interpretation of findings

Reviewers of the epidemiological evidence have concluded that 'age' (i.e. increasing age or ageing) is the most important risk factor for dementia,[15] at least on the basis of current knowledge. However, there are debates about the reasons for the rise in incidence of dementia (and cognitive decline) with age, and about the shape of the rise. These concern the question of what it is about ageing that might explain the increased incidence of cognitive decline and dementia, and whether increasing age, or ageing per se, can be considered the most important risk factor.[16;118]

Solomon has suggested that a condition may be described as 'age-related' if a specific age-range (e.g. 65-90) is most at risk, but that an 'ageing-related' disorder is one associated with increasing age.[41] He makes a further distinction between ageing-related and ageing-dependent conditions,[41] arguing that those such as cognitive decline and dementia, which occur with increasing frequency as individuals age, i.e. the rates of incidence show an exponential rise with increasing age, should be seen as 'ageing-dependent'.[16] (See also Figure 4.1, page 35). A linear rise would be expected if disease were the main cause. For Solomon, the definition 'ageing-dependent' does not preclude the existence of other causal

factors, but indicates that ageing seems to be more important than environmental factors.[16]

However, as many commentators have pointed out, neither the mechanisms of ageing nor the mechanisms underlying the development of dementia or cognitive decline are understood.[93] It has often been suggested that 'ageing' should be seen as the accumulation of changes that accompany age, whether these stem from the environment or from disease, or from inborn processes of ageing.[27;119] From this view, genetic and environmental factors which influence ageing of the brain are thought to play a part in the development of dementia or cognitive decline, i.e. the 'causes' may be several and may be interlinked.[26;27;44;56] Starr and colleagues have concluded, for example, that cognitive decline should be attributed to the effects of the interaction between age and disease on cognitive function.[106] However, while many commentators have noted the difficulty of separating the effects of increasing age from the effects of disease, some have argued that it is important to distinguish between the two.[26;106]

From the view (held by Solomon) that the effects of ageing should be seen as the most important factor increasing the risk of cognitive decline and dementia, Christensen and O'Brien have suggested that the culmination of a biological ageing process might be an acceleration of the rate of cell death, producing the characteristic neurological and cognitive deficits of dementia.[44]

Others, on the other hand, have pointed to the fact that older people are at greater risk of illness or disease, and have seen this increased vulnerability to certain risk factors, physical events or age-associated disease as a more important factor.[26;27] Keefover and Rankin have noted, for example, that whereas cognitive decline has traditionally been attributed to 'normal ageing', EEG literature shows that cognitive slowing virtually always indicates an underlying pathological process.[26] Similarly, in a study of healthy old people, Starr and colleagues found that the mean decline in cognitive function over 4 years was non-significant.[106]

It has been noted that, if the incidence of dementia continues to rise exponentially in very old age, then logically, everybody will develop the disorder if they live for long enough.[14;16;44;118] If the incidence levels off, some individuals will never develop the disease over a feasible life span, i.e. the disorder is not inevitable with increasing age.[14;26] McGee and Brayne have argued that a falling-off in the rise in prevalence with advanced age (as found in some studies) gives support to the theory that age is one of several 'risk factors' for dementia, rather than the condition being ageing-dependent.[118] Other explanations, such as slower rates of decline in capacity among a survival elite, have also been suggested.[62] The point has been made, however, that because so few people live beyond 85 years, it might never be possible to prove or disprove the invariability of a relationship between old age and cognitive impairment.[26]

Implications for prevention
Strategies of prevention depend on the extent to which risk factors can be modified. Where disorders are strongly age-related, as is the case with cognitive decline and dementia, the feasibility of prevention will be limited,[118] unless ageing itself can be slowed. From the alternative theories of ageing, ageing-related decline might be delayed either by the

avoidance or mitigation of damage, or by the boosting of capacity. In rats, caloric restrictions have been found to increase longevity, delay many of the signs of ageing, and reduce the incidence of a variety of disorders.[16] The possibility of preventing or even reversing the damage to human brain cells implicated in mental decline has been discussed, in particular by Whalley.[41]

A key issue is the strength, or relative importance, of age as a risk factor. While there is a view that age is the most important risk factor for dementia (and perhaps cognitive decline), the evidence about variation in the age of onset of both conditions, together with views about the influence of disease, warrants the investigation of other factors, those which are modifiable and those which are not.

GENDER

The findings from a number of studies, including the Canadian Study of Health and Aging[13] and the MRC CFAS study[10] have indicated gender differences in the prevalence of dementia in men and women, with higher prevalence estimates in women.[1] (The MRC CFAS study also found gender differences associated with MMSE scores of cognitive function, with men scoring higher than women.[10]) The EURODEM collaborative reanalysis of individual studies suggested that there were gender differences in the prevalence of dementia in different age groups, with a slightly higher prevalence in men than in women among subjects aged under 75 years, but a higher prevalence in women among those aged 75 or over.[7] There is also some evidence that the major subtypes of dementia, Alzheimer's disease and vascular dementia, might occur in different proportions in men and women, with Alzheimer's disease more common in women and vascular dementia more common in men.[56]

The gender difference in the prevalence ratios of dementia and Alzheimer's disease has been the subject of discussion.[107] There are important implications of a higher prevalence in women, since the majority of the very elderly population at the moment are women (although this could change).[10] Most commentators have speculated that the higher prevalence in women is more likely to result from differential survival (i.e. women's longer life-expectancy and the larger number of women still alive at ages when Alzheimer's disease is common), rather than from a higher incidence in women.[10;14;107;120] Lower rates in men have been suggested as being due to a healthy survivor effect,[10] or to the fact that diagnostic criteria for Alzheimer's disease rest on the absence of cerebro-vascular disease, a condition more common in men.[41] The reasons for the difference in prevalence remain to be confirmed by large studies.[10]

Findings from incidence studies vary. In relation to vascular dementia, although EURODEM pooled analyses found no gender differences in rates or risk,[121] a number of studies have found a higher incidence in men.[56] Unusually, one US study indicated that men had a higher incidence rate of 'all-cause' dementia than women.[122] Regarding Alzheimer's disease, some meta-analyses, including EURODEM, have found that female gender increases the risk of Alzheimer's disease significantly,[22;117] and that women tend to have a higher incidence rate than men in very old age.[22;123] However, one longitudinal study (the PAQUID project) indicated that the incidence of Alzheimer's disease was higher in men than women before the age of 80, although higher in women after this age.[124] Other recent studies, however, have found that the age-specific incidence of Alzheimer's disease did not differ significantly

by sex,[120;125] and – in a review of the literature - van Duijn has concluded that most studies have shown a similar incidence in men and women.[56]

Any increased vulnerability to cognitive decline or dementia on the basis of gender is only of relevance in relation to other potentially modifiable factors, e.g. vascular factors, alcohol consumption. Any such evidence will be noted.

ETHNIC AND NATIONAL FACTORS

If national and ethnic differences in the incidence of dementia could be found, they might indicate important genetic or environmental differences in risk factors, or those endemic in a given culture which might not be revealed by single-group studies.[10;12;14;19] There might also be different implications for 'prevention' among different cultural groups, and between countries (e.g. developing, rather than developed, countries).[12;126] There is increasing interest in assessing the prevalence and the incidence of dementia or types of dementia among different communities and groups, or in different locations or types of location.[12;127;128] Studies examining risk factors for dementia are also now being carried out in many countries,[129;130] and, with standardised diagnostic criteria and improved techniques, cross-national and multi-centre studies are under way.[14]

All commentators have drawn attention to the difficulties of comparing the findings from different populations or carrying out cross-cultural work.[131] Cultural background is a complex matter, and the difficulty of distinguishing between environmental and biological, national and ethnic, factors is well understood. People from different ethnic groups might differ in their exposure to certain risk factors for a variety of reasons, such as diet, behaviour, or the social context of their lives.

Early research suggested the possibility of wide variations in the prevalence of dementia or types of dementia between countries and between ethnic groups.[15;56;107] However, it has generally been felt that these differences were explainable by differences in study design, the diagnostic criteria employed, or differences in mortality.[7;10-12] The consensus until recently, from the results of European studies, was that there were no important regional differences in the frequency of dementia or Alzheimer's disease which could not be explained by differences in methodology.[12] Commentators have called for longitudinal studies of incidence to provide a better means of comparing rates.[12;113]

Recent studies have indicated some differences. One compilation of studies examining dementia and cognitive decline has indicated some variations within and between ethnic groups.[126] There is some evidence, for example, that the highest proportion of dementia cases among black individuals is attributable to vascular dementia.[126] Also, a recent longitudinal study in Manhattan, US, has found that the incidence rate for Alzheimer's disease was significantly higher among African-American and Caribbean Hispanic elderly individuals compared with white individuals.[132] A trend for the age-related dementia prevalence estimates to be lower in developing than in developed countries has also been noted.[12;133] For example, one recent study found significant lower age-adjusted prevalence ratios for Alzheimer's disease and dementia among Nigerian Africans in Ibadan than in African Americans in Indianapolis, using the same methodology.[113] It has been pointed out, however, that there could be several possible explanations for such differences, including differences in survival.[12]

Findings from the existing studies of incident cases support the possibility that incidence rates of dementia might be higher in some countries than others,[14] although commentators have highlighted the importance of making direct comparisons between countries or between ethnic groups using standardised methodology, especially in relation to the methods used to identify the syndrome.[10;14] In a review of the literature, van Duijn has concluded that there is some evidence of differences in the risk of vascular dementia between populations, but that comparative studies are difficult to interpret because of the lack of biological markers and unique clinical features for the subtypes of dementia.[56] Cross-cultural comparison of studies of Alzheimer's disease have suggested no evidence for the existence of risk factors that are to be found predominantly in some populations but not in others. Van Duijn has concluded that, by contrast with other chronic disorders, cross-cultural research has not led to important clues about the causes of dementia or any of its subtypes.[56]

SUMMARY

- Cognitive function declines with age, although there are wide individual differences, and also differences between domains in the rate of decline.
- Both the prevalence and incidence of dementia increase exponentially with age. Key issues are the size (or relative importance) of 'age' as a risk factor, and explanations for the effect of ageing.
- Age has generally been seen as the main risk factor for dementia, but there is debate about whether the 'cause' should be seen in terms of ageing per se (in which case everyone would develop dementia if they lived for long enough), or the ageing-related increasing incidence of disease.
- There are gender differences in the prevalence of dementia, but whether these reflect differences in incidence is still unclear.
- By contrast with other chronic disorders, cross-cultural studies have thrown little light on causal factors. The difficulty of separating biological and environmental factors has been widely acknowledged.

CHAPTER SEVEN
GENETIC FACTORS

This chapter outlines the genetic factors which are thought to be associated with Alzheimer's disease, both early onset and late onset. Although genetic factors cannot be modified, increasing knowledge about the mechanisms associated with genetic mutations might suggest possibilities for intervention

Epidemiological studies have shown that about 30% of people with Alzheimer's disease have a family history of the disorder, in that at least one first-degree relative is affected.[38] It has also been suggested that the association with various conditions, such as Down's syndrome and Parkinson's disease might indicate a common genetic component or shared susceptibility, in at least a sub-group of those affected.[56] As knowledge about the human genome is increasing, there has been interest in examining genetic factors. Since genes are thought to be associated with protein production, the hope is that a greater understanding of genetics might throw light on some of the mechanisms or processes underlying the development of dementia, and might suggest possible methods of prevention, such as drugs.

GENETICS AND THE RISK OF EARLY ONSET ALZHEIMER'S DISEASE

Family history is an important risk factor for Alzheimer's disease, particularly early onset. The occurrence of dementia of the Alzheimer type in specific families is well documented, and the pattern of inheritance is consistent with autosomal dominant transmission with age-dependent penetrance.[62] Single gene mutations in three genes are known to be associated with certain forms of early onset Alzheimer's disease. These are the amyloid precursor protein (APP) located on chromosome 21, and genes for presenilin 1 and presenilin 2 located on chromosomes 14 and 1 respectively.[101] The mutations of the presenilin genes are thought to disrupt the breakdown of APP.[39]

Although cases of early-onset Alzheimer's disease account for a small proportion of cases of the syndrome overall, a high proportion of such cases are thought to be associated with these genes.[12;44] Mutations associated with APP are extremely rare, but the 50 or so mutations associated with presenilin 1 are thought to explain up to half of all cases of early onset Alzheimer's disease.[101]

GENETICS, APOE, AND THE RISK OF LATE ONSET ALZHEIMER'S DISEASE

Most cases of late onset dementia are sporadic, rather than familial.[38] A family history of dementia has been associated with a higher risk in some studies,[13;134-136] but not in others.[22] At the moment, only one genetic factor has been indisputably linked with late-onset forms of Alzheimer's disease; this is the 4 allele of the APOE gene on chromosome 19, which codes for apolipoprotein E (ApoE),[101] a lipoprotein thought to be involved in the development of vascular dementia.[41]

Three common allelic variants of apolipoprotein E exist – 2, 3 and 4 - encoded on a single locus on chromosome 19.[101] A number of large cohort studies have provided evidence that the presence of the APOE _ allele is associated with a higher risk of Alzheimer's disease.[125;137;138] The finding that the frequency of the APOE 4 allele among 'cases' was around 45-50% compared with around 16% among controls has been replicated in other studies.[41] Research results have suggested an apparent 'dose-response' relationship, with individuals who are homozygous for this allele (4/4) having a significantly higher risk of developing Alzheimer's disease than those who are heterozygous for the allele, and higher again than those without the gene.[99] Recently, the APOE 4 allele has been shown to be associated with other forms of dementia including vascular dementia, Lewy body disease and Creutzfeldt-Jacob disease.[56]

However, the presence of APOE 4 is neither necessary nor sufficient to cause Alzheimer's disease.[12;101] Low concordance rates among monozygotic twins suggest a substantial environmental influence.[12] It is thought that, at most, only half of individuals with late onset Alzheimer's disease carry the allele.[12;41] Findings from one large study have suggested that the presence of the apoliprotein E genotype predicts when – rather than whether – individuals are predisposed to develop Alzheimer's disease.[139] While most studies have indicated that the APOE genotype is second only to age as a risk factor for dementia of the Alzheimer type,[41;140] questions remain about the importance (or size) of the effect of the 4 allele relative to other factors. Commentators have called for large, population-based epidemiological studies to evaluate the risk of developing cognitive decline and dementia.[56;141]

Several recent studies have investigated the extent to which other risk factors, such as smoking,[142] coronary artery surgery,[143] gender, education or vascular risk factors might be modified by the presence or absence of the APOE 4 allele. There is some evidence that women who possess the APOE 4 allele appear to be at significantly greater risk of Alzheimer's disease than men who are APOE 4 allele carriers.[11] One recent longitudinal study in a biracial community sample found that interactions with gender (being female) and with baseline functional status predicted functional decline, although no relationship was found between the APOE 4 allele and a decline in functional status overall.[144] Findings from the Zutphen elderly study in the Netherlands showed a significantly increased risk of cognitive decline associated with a lower level of education in subjects without the APOE 4 allele. By contrast there was no association between education and cognitive decline in subjects with the allele.[145] APOE 4 has also been shown to increase the risk of athero-sclerosis, which – it is thought - might explain its association with vascular dementia.[56;99] The findings from one twin study showed greater vascular or degenerative damage among subjects with the APOE 4 allele.[146]

There is some evidence that the APOE 2 allele may be associated with lower relative risk of Alzheimer's disease and later onset.[38;98] Additionally, it may well be that further polymorphisms are associated with an increased risk of dementia of the Alzheimer type. Other genetic risk factors have been and are being investigated.[14]

INTERPRETATION OF FINDINGS

The mechanisms by which proteins associated with genetic mutations are involved in the development of Alzheimer's disease (and whether they are causes or effects) are not known,[41;88] but there are a number of hypotheses.[98] Proteins are thought to be implicated in the production of amyloid plaques and neurofibrillary tangles. They may also have a role in neuronal damage and interaction with other mechanisms such as viruses.

ApoE is a plasma protein thought to be involved in cholesterol transport and neuronal repair (e.g. after head injury).[14;41;98] A number of mechanisms by which the APOE 4 allele might influence the development of dementia have been proposed.[98] It has been associated with higher levels of oxidative insults in Alzheimer's disease brains.[147] The possibility of interaction with the herpes simplex virus to increase risk has also been suggested.[99] The genes for early onset AD have been associated with the synthesis of Aß (or ß-amyloid) protein, involved in the formation of amyloid plaques. Also, an inherited form of fronto-temporal dementia, which is characterised by tau tangles, in the absence of amyloid plaques, is thought to be associated with mutations of the tau gene.[99] It has been suggested that APOE 3 prevents tangles from forming, but that APOE 4 provides no such protection.[88]

IMPLICATIONS FOR PREVENTION

Because genetic make-up is not modifiable, if genetic mutations are important risk factors for early onset Alzheimer's disease, then opportunities for prevention of this condition may be limited. The mutations in APP, presenilin 1 and presenilin 2 allow for screening in suspected cases of familial Alzheimer's disease with early onset, and for appropriate genetic counselling and support.[99] The point has been made that the numbers are far too small for family planning to be considered as a method of prevention; in addition, family planning is only effective when the pattern of occurrence indicates an autosomal dominant transmission.[37]

In the case of late onset Alzheimer's disease, there is less evidence, at the moment, for genetic risk factors. The view has been expressed that, in the absence of disease-slowing treatments, there is little justification for predictive testing.[101] Also, using APOE genotyping for this purpose has been seen as inappropriate;[41] Eastwood and colleages have noted that the current position on the place of APOE genotyping – which 'may' be used to assist an already suspected diagnosis of Alzheimer's disease, but which may not be used to screen healthy individuals for future risk – has been summarised in a consensus statement.[19] Key evidence on the scope for primary prevention, taking genetic factors into account, will come from twin studies (which show low concordance), and from the incidence or prevalence of Alzheimer's disease in different populations or sub-populations.

Although genetic makeup is not modifiable, attempts are being made to develop a vaccine, whose purpose would be to interfere with protein production in order to prevent, slow or reverse the deposition of amyloid plaques in the brain (although amyloid plaques are not necessarily a feature of Alzheimer's disease,[88] nor has it been established that interfering with

protein production would prevent dementia.) The findings from studies of mice have been encouraging;[41] transgenic mice that were given such a vaccine performed better on a memory test than did unvaccinated mice.[100] A vaccine has been developed for use with humans, although the trial was abandoned in March 2002 after several patients developed symptoms of brain inflammation.[148]

At the moment research findings have not suggested any means of prevention. There are many unanswered questions about the relative importance of genetic factors and their related effects. Most commentators have concluded that that there is much still to be learned about the genetics of Alzheimer's disease (e.g. what gene products do, the correlates with brain changes, and the interactions of APOE genotype and drug response) and that more genetic factors will probably be found.[19] It has been suggested by some that the importance of genetic findings could be in throwing light on biological mechanisms of Alzheimer's disease, and hence on therapeutic targets,[19] and on aiding the search for non-genetic factors.[11] More work is felt to be needed to quantify genetic risk,[19;56] and to investigate possible interaction between genetic and other risk factors.[11;19;56]

SUMMARY
- Early onset Alzheimer's disease is strongly related to family history, and three genetic mutations associated with this disorder have been identified. Although cases of early-onset Alzheimer's disease account for a small proportion of cases of dementia overall, a high proportion of such cases are thought to be associated with these genes.
- One genetic mutation has been linked with some forms of late onset dementia including Alzheimer's disease. This is the APOE 4 allele. However, the presence of APOE 4 is neither necessary nor sufficient to cause Alzheimer's disease; only about half of affected individuals carry the allele.
- Other genetic factors are being investigated.
- At the moment, research findings have not suggested any means of prevention.
- An increased knowledge of genetic factors has been seen as useful in gaining a better understanding of the mechanisms underlying the development of dementia.

CHAPTER EIGHT
PRE-EXISTING CONDITIONS

A number of conditions are known to predispose towards dementia. Vascular disease, as a risk factor for dementia of various types, is discussed in Chapters 10 and 13. This chapter outlines the evidence for considering Down's syndrome, Parkinson's disease and thyroid disease, as risk factors for dementia of the Alzheimer type.

DOWN'S SYNDROME

Cognitive and functional decline has long been recognised as a feature of ageing in people with Down's syndrome.[149] One recent project found significant differences in cognitive function between younger (30-44 years) and older (45+ years) subjects with Down's syndrome.[150] Since the decline in function has usually been accompanied by changes in personality and behaviour, links have been suggested with Alzheimer's disease. The findings from one study have indicated that age-specific prevalence and incidence rates of 'Alzheimer's disease' and the pattern of cognitive decline were similar, although appearing approximately 30-40 years earlier in life in the Down's syndrome population.[150] The dramatic increase in life expectancy for people with Down's syndrome - now about 50 years - has implications for the ageing of people with this condition, and there is interest in finding out the prevalence of dementia among people with Down's syndrome, and in establishing whether such dementia should be seen as Alzheimer's disease.[149]

Numerous studies have found that there are ageing-related increases in plaque and tangle formation in the brains of people with Down's syndrome,[151;152] and recent studies show that virtually all people with Down's syndrome have the neuropathological features of AD by the age of 40 years.[14] However, the prevalence of dementia in people with Down's syndrome is much less than 100% even by age 50.[153] The reasons for the discrepancy between pathology and function are not understood.[14]

Findings from a number of studies have suggested a shared genetic susceptibility to Down's syndrome and Alzheimer's disease.[14] Links have now been found with the presence of trisomy 21 (a genetic modification associated with Down's syndrome),[149] and it is thought that the similar pathology is due to people with Down's syndrome having an extra copy of the amyloid precursor gene (APP) on chromosome 21.[14] There is also some evidence that

the presence of the APOE 4 allele increases the risk of Alzheimer's disease (in people with Down's syndrome),[14;149] and one recent study has suggested that, after chronological age, the APOE 4 genotype is the most important risk factor.[150] It has been concluded that the influences on the risk of developing Alzheimer's disease for people with Down's syndrome may be similar to those for people without Down's syndrome, although whether or not the mechanisms are similar is unclear.[149]

PARKINSON'S DISEASE

Parkinson's disease (PD) is an ageing-related progressive neurodegenerative disorder, which has been seen as essentially a profound disturbance of motor function.[26] The condition typically begins between the ages of 50 and 65 and exhibits a prolonged course of deterioration, so that more than half of those with symptoms are aged over the age of 70.[26] The condition is associated with cognitive changes,[26;154] particularly bradyphenia or 'slow thought',[26] but there is controversy about the prevalence and incidence of dementia within Parkinson's disease.[154]

Like Parkinson's disease itself, Parkinson-related dementia is strongly ageing-related; the prevalence ratio increasing from 41.1 cases per 100,000 in those up to 50 years old to 787.1 cases per 100,000 in those 80 years or older.[77] A review of cross-sectional studies carried out since 1990 indicates that the prevalence of dementia in PD is in the range of 28 – 40%,[154] i.e. well above the figures expected if the association between dementia and Parkinson's disease were coincidental. The authors of the review have noted an association with older age of onset, rather than with illness duration.[154]

There is some evidence of higher rates of Parkinson's disease among farmers. One study carried out in France over 10 years found that, in a small sample of 'dementia with parkinsonism' among women, eight cases were found among farmers.[155] The authors have recommended exploring this possible link further, suggesting that one possible explanation could relate to exposure to environmental factors.

THYROID DISEASE AND NEURO-ENDOCRINE CONDITIONS

Thyroid disease is a hormonal disturbance widely recognised for its capacity to disrupt brain function.[26] Thyroid metabolism is complex, and a number of changes can increase or decrease the production and utilisation of the active form of thyroid hormone.[26] The presence of thyroid disease appears to be relatively high in older people, with hypothyroidism five to six times more common than hyperthyroidism. Both high and low levels of thyroid hormone can produce cognitive or psychiatric behavioural change. In addition, older people appear to be prone to a form of thyroid dysfunction (apathetic thyrotoxicosis) which may account for a number of cases of dementia in older people.[26] Some empirical studies have indicated an association between Alzheimer's disease and hypothyroidism,[156] but others have not.[135] Findings from one recent longitudinal study have indicated a link between sub-clinical hyperthyroidism and Alzheimer's disease.[157] An association between Alzheimer's disease and autoimmune thyroid disease has been reported in Down's syndrome and familial Alzheimer's disease.[56]

It has also been suggested that, since there are two-way links between the brain and the endocrine system, other neuro-endocrine mechanisms, for example those related to hormones or to stress, may be relevant to cognitive function.[96]

SUMMARY

- A number of conditions can predispose to dementia of the Alzheimer type. These include Down's syndrome and Parkinson's disease. Some studies have found an association with thyroid disease but others have not.
- Pathological and genetic associations between Down's syndrome and Alzheimer's disease have been found. The incidence of dementia of this type occurs 30 – 40 years earlier in the population of people with Down's syndrome than in the general population.
- The prevalence of dementia in people with Parkinson's disease is thought to be between 28 – 40%, i.e. considerably higher than in the general population.

CHAPTER NINE
PHYSICAL INJURY, ILLNESS AND MEDICATION

As the pathological features of Alzheimer's disease are increasingly understood, there is interest in the role of brain damage, injury and inflammation. This chapter summarises the evidence for seeing brain injury, or exposure to viruses and pollutants, as risk factors. It also considers the extent to which non-steroidal inflammatory drugs might protect against dementia.

The pathological features of Alzheimer's disease are increasingly well understood.[102] There has been interest in the role of brain damage, whether caused by biological or environmental factors, i.e. trauma, inflammation or illness. Brain tumours represent one cause of dementia. The incidence of aggressive tumours is rising in older populations, but since the individuals affected seldom survive into very old age, less aggressive tumours account for more cases of dementia in older people.[26] Chronic inflammation is also thought to have a key role in the abnormal processes related to ageing, possibly including dementia,[158] and a number of lines of evidence suggest that inflammatory mechanisms play a significant role in the pathogenesis of Alzheimer's disease.[159] Research has investigated possible links between head injury, exposure to infection or toxins, and medications such as non-steroidal anti-inflammatory drugs (NSAIDs) and the occurrence of dementia of the Alzheimer type.

BRAIN INJURY

Head injury causing identifiable brain injury is thought to affect tens of thousands of individuals in the UK per year,[98] and is a major cause of disability.[160] While most of those injured are young people, and there are low rates in midlife, the risk of traumatic brain injury rises again after age 60,[161] and significantly after age 70, the most likely causes being falls and road accidents.[162] Postural instability is a physical characteristic of old age that increases an individual's tendency to falls.[26] Although many of the effects of head injury are temporary, there may be longer-term consequences.[98] There is some evidence that traumatic brain injury increases the risk of cognitive decline,[163] although a review of the literature indicates that older adults do not have a uniformly poor functional and cognitive outcome.[164]

Neuropathological signs similar to those found in Alzheimer's disease have been found in the 'punch drunk' dementia pugilistica, which is associated with repeated blows to the

head, but the extent to which the two conditions share a common pathogenesis is unknown.[56;98] Because of these links, there has been interest in the extent to which traumatic head injury could be a risk factor for Alzheimer's disease.[98]

Reviewers of the literature have suggested that there is evidence to support a link between a history of head trauma with loss of consciousness and an increased risk of Alzheimer's disease.[12;14;56;98] A 1991 meta-analysis, which included seven case control studies, found that head injury with loss of consciousness increased the risk of Alzheimer's - though the results were significant only for males.[165] A more recent meta-analysis of 15 case control studies conducted since 1991 confirmed this finding.[166] There is also some evidence from prospective studies that individuals with a history of head injury with loss of consciousness are more likely to develop dementia over a 2-year period.[98] Greater severity of head injury has been associated with greater risk of Alzheimer's disease,[98] and Mortimer's 1991 meta-analysis suggested that head trauma in the decade before onset of Alzheimer's disease was more important than head trauma earlier in life.[165] Also, Aß (or ß-amyloid) protein – one of the hallmarks of Alzheimer's disease – has been found in the brains of head injury fatalities,[14;98] and there is some evidence that the presence of the APOE 4 allele may be associated with a poorer recovery from brain injury.[98] Several studies have found that the association between head injury and Alzheimer's disease is stronger in males.[98]

However, not all studies have found a significant risk of Alzheimer's disease after head injury, and some reviewers have concluded that the relationship remains uncertain.[56;164] Many have commented on the possibility of bias in the studies. One reason is because of the use of retrospective reporting of head injury, often by relatives, with consequent biases of recall;[56;98] another is because of the subjective definitions of head injury.[14;98] Jorm has reported that the findings from studies which used objective medical records of head injury did not support an association.[14] (One study indicated that head trauma was only a risk factor for individuals who carried the APOE 4 allele.[167]) On the other hand, Morris[98] has drawn attention to a recent US study which verified the occurrence and severity of head injury using medical records, and which found a clear relationship between severity of injury and risk of Alzheimer's disease.[168]

EXPOSURE TO ILLNESS, INFECTION OR VIRUSES

Herpes simplex type 1 virus (HSV1)

It has been suggested that dementia may be associated with the presence of the herpes simplex type 1 virus (HSV1) in the brain. HSV1 is harboured in latent form in the peripheral nervous system of nearly all adults,[5] and in the brains of elderly people with and without Alzheimer's disease.[5;169] When the virus is reactivated, it causes an acute infection which – in some people – causes cold sores.

Neuro-pathological studies have found that Alzheimer's disease patients who harbour the virus are far more likely than those who do not to possess the APOE 4 allele.[5] Results have shown that those with the APOE 4 allele are not more susceptible than others to HSV1 infection. Itzhaki and colleagues have concluded, therefore, that HSV1 in the brain together with the possession of the APOE 4 allele confers a high risk of developing Alzheimer's disease, whereas neither factor on its own does so,[5] i.e. that HSV1 is a risk factor in

individuals who carry the APOE 4 allele.[170] Evidence that a higher proportion of cold sore sufferers than non-sufferers possess the APOE 4 allele lends support to this view.[5] These findings have been replicated in one study,[171] but not in another, and the authors of the latter have recommended the use of larger studies with attention to potential sampling bias to investigate the reasons for discrepancies.[172]

Itzhaki and colleagues have postulated that the virus is present in the brain in latent form and re-activates under certain conditions,[14] and that limited reactivation of the virus causes more damage in Alzheimer's disease patients than in other older people because of differences between individuals.[170] They have speculated about possible causal mechanisms, suggesting a link with genetic factors. They have also noted, however, that, whatever the mechanisms involved, if HSV1 is a risk factor for Alzheimer's disease, then some cases might be preventable by vaccination, and anti-viral drugs might slow the course of the disorder in those already affected.[5]

Human immunodeficiency virus type 1 (HIV)
Dementia has been associated with the human immunodeficiency virus type 1 (HIV).[173] The point has been made that little knowledge is available about HIV/AIDS in the elderly population, although it has been estimated that 10% of all diagnosed cases in the US are in people age 50 and over.[174]

Illness: delirium
Adults over age 75 years are particularly vulnerable to developing delirium during acute illness and hospitalization.[175] Dementia has been seen as an important risk factor in the development of this multi-factorial syndrome. Delirium has traditionally been seen as reversible, but Inouye has argued that an examination of the literature suggests that delirium poses substantial risks for cognitive decline and dementia.[175] The condition could serve to unmask unrecognised dementia, but it might also lead to irreversible cognitive decline and dementia, particularly in people with an underlying degree of cognitive impairment. Inouye has suggested that any strategy to prevent cognitive decline in later life should include efforts to prevent delirium in hospitalised older people.

EXPOSURE TO TOXINS OR POLLUTANTS

Aluminium
There is some circumstantial evidence, which has accumulated over a period of decades, linking aluminium with Alzheimer's disease.[176] Early pathological research found increased concentrations of aluminium in the brains of Alzheimer cases.[14;62] In addition, aluminium has been linked with the presence of plaques in the hippocampus, although not the plaques and tangles characteristic of Alzheimer's disease.[176] Aluminium has also been identified as the cause of 'dialysis dementia', although people with this condition do not appear to develop plaques and tangles in the brain.[176] Some empirical research has suggested a possible relationship between aluminium in drinking water and the occurrence of Alzheimer's disease.[14;56;62] However, reviewers have drawn attention to methodological weaknesses in the studies and the strong possibility of bias,[56;62] as well as to the small size of the increased risk.[176] They have concluded that there is no evidence that aluminium plays a causative role in the development of the condition,[176] and that more research is needed.[62;177]

Other toxins and pollutants

Findings on occupational exposure to other toxins and pollutants have been controversial.[14;56] One case-control study has indicated an association with Alzheimer's disease for men exposed to certain solvents,[178] and another has found a similar association with exposure to pesticides and fertilisers,[179] and glues.[109] However, reviewing the evidence, van Duijn has argued that overall, the results are inconclusive, partly because of the low frequency of exposure and the imprecise definition.[56] Jorm has concluded that the findings relating to other occupational hazards have generally been negative, although an exception might be exposure to electro-magnetic fields.[14]

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

Inflammation has been seen as a response triggered by the interplay of a range of factors.[180] It has been hypothesised that Alzheimer's disease involves inflammation of the brain,[97] although the role of inflammation in the pathogenesis of the disease has been debated.[159] Non-steroidal anti-inflammatory drugs (NSAIDs) are often prescribed for arthritis, and it has been estimated that at least 10 –15% of people over the age of 65 years in the US take these medications.[181] It is known that high NSAID use may be associated with a reversible impairment of cognition in the elderly,[181] and a number of other adverse effects of the drugs have also been noted.[158;182]

Some research has indicated, however, that the use of NSAIDs might slow the rate of cognitive decline in patients with Alzheimer's disease.[182] In addition, there is now evidence from large longitudinal population-based studies, as well as from earlier observational and small interventional studies, that the prolonged use of NSAIDs might prevent - to an extent - the decline in cognition associated with ageing,[181] and that the past use (i.e. before the onset of disease) of such medications is associated with a reduced risk of developing Alzheimer's disease.[14;56;158;159;181-183] A recent meta-analysis of observational studies has concluded that NSAID use does appear to lower the risk of Alzheimer's disease – though the appropriate dosage and duration of use are still unclear.[184]

The possible protective effects of NSAIDs remain to be clarified by clinical trials.[56;185] Commentators have pointed out that the side effects of the drug make it difficult for randomised controlled trials to be carried out,[56] and that not all elderly patients are candidates for NSAIDs.[182] NSAIDs are currently being tested in clinical trials of patients with Alzheimer's disease and cognitive impairment,[11] but in the US a major prevention trial (ADAPT) is now recruiting healthy participants who have a family history of Alzheimer's disease.[186] It has been stressed that the risks of NSAIDs must be shown to be outweighed by the benefits before their use to reduce the risk of cognitive decline and dementia is indicated,[181;182] and that determining the definitive mechanism of action of NSAIDs in the development of Alzheimer's disease might suggest alternative agents which have similar pharmacological activity but which are associated with fewer side effects.[182] The point has also been made that, although the benefits of NSAIDs have been seen from a patho-physiological perspective, it is not known whether the protection comes from an anti-inflammatory effect that modifies pathways involved in Alzheimer's disease, or is mediated by a platelet effect that decreases the risk of cerebro-vascular disease.[181]

SUMMARY

- There is some evidence that brain injury increases the risk of cognitive decline.
- There is evidence to support a link between head trauma and loss of consciousness and an increased risk of Alzheimer's disease, although not all studies show this.
- There is some evidence to suggest that herpes simplex type 1 virus (HSV1) may be a risk factor in individuals who carry the APOE 4 allele. If this is the case, it is possible that some cases of Alzheimer's disease could be prevented by vaccination.
- The link with aluminium suggested by some early studies has not been proved.
- A few studies have examined exposure to other toxins and pollutants, but the findings are inconclusive.
- There is some evidence of a link between non-steroidal anti-inflammatory drugs (NSAIDs) and a reduced risk of Alzheimer's disease, although this protective effect remains to be confirmed by clinical trials. NSAIDs have a number of side effects that preclude their widespread use.

CHAPTER TEN
CLASSICAL (PERSONAL AND LIFESTYLE) RISK FACTORS I: RISK FACTORS FOR VASCULAR DISEASE

A number of factors are traditionally seen as increasing the risk of a wide variety of conditions. These 'classical' factors, which can also be seen as 'personal' or 'lifestyle' factors, include vascular factors, smoking, alcohol, diet, nutrition and hormones. This chapter examines the evidence for seeing risk factors for vascular disease as also risk factors for dementia or cognitive decline. Possible strategies for intervention are outlined in Chapter 13.

There is interest in vascular causes of dementia since, to the extent to which vascular disease is preventable or treatable, the incidence rates of dementia might be reduced.[12;20;56] Vascular risk factors for dementia include vascular disease, and risk factors for vascular disease. Hypertension (high systolic blood pressure) is a main risk factor for vascular disease, but there are many others, such as diabetes and atrial fibrillation. One important issue is whether vascular risk factors measured in old age or in mid-life have a more significant effect on the risk of cognitive decline or dementia.

VASCULAR FACTORS AND THE RISK OF VASCULAR DEMENTIA
Vascular dementia is thought to be caused by a disruption of the blood supply to the brain. However, the concept of 'mini-strokes' in the brain (hence multi-infarct dementia) has been replaced by more sophisticated models suggesting a spectrum of vascular causes.[67] The risk factors for vascular dementia (or vascular cognitive impairment [VCI]) are relatively well understood, and are thought to be very similar to those for stroke and coronary artery disease.[68] They include cardio-vascular disease and risk factors for vascular disease, which in turn include cerebro-vascular disorders (CVDs) and vascular risk factors such as hypertension and diabetes.[56;64-67] Erkinjuntti has listed the risk factors for vascular dementia (see Table 10.1 on page 66).[67] He has noted, however, that the individual roles that these factors play in causation have not been identified in detail, nor is it clear which mechanisms are of primary importance.

Table 10.1 Different Aetiologies of Vascular Dementia

Cerebrovascular disorders
Large artery disease
       Artery to artery embolism
       Occlusion of an extra- or intracranial artery
Cardiac embolic events
Small vessel disease
       Lacunar infarcts
       Ischaemic white matter lesions
Haemodynamic mechanisms
Specific arteriopathies
Haemorrhages
       Intercranial haemorrhage
       Subarachnoid haemorrhage
Haematological factors
Venous diseases
Hereditary entities

Risk factors
Vascular
       Arterial hypertension
       Atrial fibrillation
       Cardiac abnormalities
           Myocardial infarction
           Coronary heart disease
       Diabetes
       Generalised atherosclerosis
       Lipid abnormalities
       Smoking
Other
High age
Low education

Source: T. Erkinjuntti, "Vascular dementia: an overview", table 48.1, page 624 in O'Brien, Ames and Burns (eds) Dementia, 2nd edition, 2000. London: Hodder Arnold. Reproduced with permission from Hodder Arnold.

Hypertension

Hypertension or elevated blood pressure reportedly affects at least 50% of older people in the US.[26] It is well known that, if untreated, hypertension can contribute to the development of cerebrovascular disease,[20;187] and hence to conditions such as vascular dementia which can occur as a consequence of stroke. Hypertension is one of the leading causes of vascular dementia.[188] (Much less frequently, severe hypertension has been associated with characteristic changes in the brain, called white matter hyperintensities,[189] and with acute or subacute global cerebral disturbance.[26]) Systolic blood pressure has been found to be far more important than diastolic blood pressure in predicting the risk of cardiovascular disease in those aged 50 and over.[190]

Diabetes

The link between diabetes and cognitive impairment among older people is well documented,[191;192] and a recent BMJ editorial has noted that there is now evidence from prospective longitudinal studies of an association between diabetes and cognitive decline.[191] The majority of these cohort studies have found that diabetes is associated with an approximate doubling of the risk of dementia, more often with 'stroke mediated dementia' than Alzheimer's disease.[191] A recent Swedish study looking specifically at Type2 diabetes found no association between diabetes and Alzheimer's disease, though the risk of vascular dementia increased twofold.[193] It has been pointed out that there are numerous mechanisms by which the complications of diabetes can alter mental status; for example, vascular complications can contribute to the development of stroke and cardiac disease, and renal failure can affect brain function.[26]

Obesity

There is increasing interest in obesity as a risk factor for cerebro-vascular conditions,[194] since people with excess body fat have a greater risk of illnesses such as diabetes and hypertension.[50] One recent US study which followed participants in the Framingham heart study found that, even when hypertension was controlled, obesity was still a risk factor for heart failure.[194] A similar finding has recently been reported for the association between obesity and cognitive decline in the same cohort,[195] though the link was found only in men. Results from a recent 18-year Swedish study have also indicated that overweight and obesity at high ages could be risk factors for the development of late-onset dementia, particularly Alzheimer's disease. In this case, however, the association was found only in women.[196] Suggested mechanisms include a thickening of the wall of the heart, or a cluster of symptoms known as the metabolic syndrome and characterised by insulin resistance and dyslipidaemia.[194]

VASCULAR FACTORS AND THE RISK OF DEMENTIA OF THE ALZHEIMER TYPE

There is evidence from a number of recent studies of an association between vascular disorders and risk factors (e.g. raised systolic blood pressure) and Alzheimer's disease.[12;63;197-203] Skoog lists as evidence: the frequency of APOE 4 allele in middle aged individuals with coronary heart disease and atherosclerosis; the increase in neurofibrillary tangles and senile plaques in the brains of non-demented individuals with hypertension, and the increased systolic and diastolic blood pressure before the onset of Alzheimer's disease.[63;204] A recent prospective, population-based study has suggested that raised systolic blood pressure and high serum cholesterol concentration, and in particular, the combination of these risks, in midlife, increased the risk of Alzheimer's disease in later life.[188] Also, a recent large population-based study has found that features of the insulin resistance syndrome were associated with an increased risk of Alzheimer's disease independent of APOE 4 phenotype.[205] Skoog has noted, however, that the mechanisms for the association between vascular risk factors and dementia are unclear.[63] He has suggested that they could include shared pathogenic pathways of various sorts, environmental as well as individual. It has also been pointed out that, although an increased risk of stroke or transient ischaemic attacks has been implicated in inducing Alzheimer–type degenerative changes, the converse has been suggested; i.e. that individuals with Alzheimer's disease may be at increased risk for stroke and cerebral infarction, the main diagnostic features in vascular dementia.[199]

Low blood pressure and Alzheimer's disease
A number of studies have found low blood pressure among people with dementia, including Alzheimer's disease,[197;206-210] and in the years just preceding its onset.[204] Some commentators have concluded that low blood pressure might be a complication of the disease process,[197;200;206] or that low blood pressure might predispose a subpopulation to developing dementia.[197] Others, on the other hand, have suggested that the decrease in blood pressure in the very elderly might stem from age-related changes in brain structure, with low blood pressure in dementia disorders being a secondary phenomenon.[208]

There is some concern, therefore, about the safety of treatment for hypertension.[211] However, the more general view, drawing on studies which suggest that treatment of hypertension has no effect on cognitive function,[212] is that low blood pressure is more likely to be the result of dementia or the healthy survivor effect than its cause.[213] More longitudinal studies are felt to be needed to investigate cause and effect.[206]

VASCULAR FACTORS AND THE RISK OF COGNITIVE DECLINE
There was some early evidence that the cognitive function of individuals at risk of cardiovascular disease tended to decline earlier than that of those not so affected.[214] One recent small cross-sectional study has found that cardiovascular risk factors are important predictors of cognitive function among middle-aged and older African Americans.[215] Reviewers of the literature[20;189] have noted that a number of recent studies, including the Rotterdam study, have shown evidence of a link between vascular risk factors and cognitive impairment (and dementia).[204;216-219]

Some research has found that blood pressure values are related to cognitive performance scores,[220] and it has been suggested that blood pressure and hypertension might account for variance in performance that might otherwise be attributed to ageing.[220] Findings from a number of studies have suggested that individuals with elevated blood pressure during midlife exhibit lowered cognitive functioning in old age.[221-223] Results from the Framingham longitudinal community study of vascular risk factors have demonstrated that blood pressure measured about 20 years prior to cognitive function testing was associated with recent poorer function.[209] These findings have been confirmed in the Honolulu-Asia Aging Study (HAAS), in which midlife systolic blood pressure (SBP) was found to be a significant predictor of reduced cognitive function in later life,[216] even after controlling for a number of factors and even when people with dementia were excluded from the analysis.[189] The authors have recommended that early control of SBP levels may reduce the risk of cognitive impairment.[189;216] In another longitudinal study of healthy old people in Edinburgh (the HOPE study), Deary and colleagues found that blood pressure was related prospectively to fluid intelligence but not to memory differences.[224] A somewhat puzzling note has, however, been struck by a Swedish longitudinal study which found the association between hypertension and cognitive decline did not exhibit the expected dose-response relationship.[225] Individuals with blood pressure in the highest ranges showed a smaller decline in cognitive performance than people with moderate hypertension.

White and colleagues have noted that, in the HAAS, diastolic blood pressure measured during the same earlier time period did not predict later poor cognitive function.[189] Neither was current systolic or diastolic blood pressure related to cognitive function.[189;226] In fact, it

appeared that a relatively low systolic blood pressure was associated with the highest risk of poor cognitive function.[189] The authors have concluded that relationships between base variables and outcomes are complex, but that it is possible that the identification of a risk factor in mid-life might be a better indicator of exposure than identification of the same factor in later life.[189]

Cerebral hypoxia and sleep apnoea

Some research has suggested that chronic disorders of blood gas regulation (e.g. sleep apnea or breathing cessation during sleep) are associated with long-term cognitive deficits,[26] perhaps because of low levels of blood oxygen or high levels of carbon dioxide. Sleep apnoea is a common medical disorder exhibiting an increased incidence with age, and affected individuals can develop chronic cardio-vascular disorders, such as hypertension and heart failure.[26]

Heart bypass surgery and cognitive decline

There are clear signs of cognitive dysfunction immediately after coronary artery bypass surgery (CABG) in about 75% of patients, although in the majority of cases the problems are temporary. There is interest in whether there are more subtle, long-term, cognitive deficits in a sub-set of patients, whether the effects of CABG can be separated from any subtle cognitive effects that were present before surgery, and whether any cognitive deficits seen before surgery in people with heart disease might be pre-clinical Alzheimer's disease.[227] The findings from one recent study have indicated that a significant predictor of cognitive decline after 5 years was cognitive function at discharge, and the authors have argued that interventions to prevent or reduce short- and long-term cognitive decline after cardiac surgery are warranted.[228]

SUMMARY

- The risk factors for vascular dementia are relatively well understood. These include cerebro-vascular disease, and risk factors for vascular disease, such as hypertension, diabetes and obesity.
- An association has recently been found between vascular factors found in mid-life (e.g. hypertension) and Alzheimer's disease. At the same time, low blood pressure has sometimes been found among people with the disorder.
- Findings from recent large studies have indicated that high blood pressure measured in mid-life is also a significant predictor of poorer cognitive function in later life.
- The long-term cognitive decline experienced by a minority of heart bypass patients is being investigated.

CHAPTER ELEVEN
CLASSICAL (PERSONAL AND LIFESTYLE) RISK FACTORS II: SMOKING, ALCOHOL AND DRUG USE

This chapter summarises the strength of the evidence for seeing smoking and alcohol consumption as risk factors for dementia or cognitive decline. These factors have been linked with vascular disease and with other disorders. Recreational drug use has not been examined by research.

SMOKING

Smoking is a known risk factor for vascular disease, and the risk of vascular dementia has been found to be increased for subjects who smoked.[229] If smoking were found also to increase or decrease the risk of cognitive decline or Alzheimer's disease, there would be implications for public health campaigns, since smoking habits are potentially changeable. Research investigating smoking and Alzheimer's disease has appeared to produce contradictory findings.[14;56;60;230] Early case-control studies[110] and meta-analyses[231] suggested that smoking might be associated with a decreased risk of Alzheimer's disease. There is also some evidence of a protective effect of smoking on early onset Alzheimer's disease, although strongly modified by genetic factors.[142] It has been suggested that smoking could have a short term therapeutic effect on cognition, attention and reaction time.[60] A protective effect on Alzheimer's disease has also been seen as biologically plausible, since smoking increases the density of nicotinic receptors in the cortex, and Alzheimer's disease involves a loss of these receptors.[14;60] Various alternative explanations have been offered, however, including elderly smokers being a survival elite,[232] and classification of demented smokers as having vascular or mixed dementia rather than Alzheimer's disease.[233] It has also been pointed out that the diagnostic criteria for Alzheimer's disease exclude those with vascular disorders and hence those more likely to have smoked early in life.[60]

Recent studies examining links between smoking and Alzheimer's disease have yielded more equivocal results. Findings from longitudinal studies - the Rotterdam study,[232] a community-based study in Manhattan,[234] the Kungsholmen project in Sweden[235] and the Honolulu-Asia Aging Study[236] - have suggested that smoking is associated with an increased risk of Alzheimer's disease, thus tending to confirm the findings from EURODEM pooled analyses which showed that current smoking (more strongly in men), increased the risk of Alzheimer's disease significantly.[24] Doll and colleagues have concluded that the findings from a long-term study of smoking and dementia in British doctors, taken together with other longitudinal studies, suggest that persistent smoking does not substantially reduce

the age-specific rate of dementia, but that any net effect on severe dementia – in either direction – must be small.[233] Others, however, have called for long-term prospective studies to clarify the direction of any association.[14;60] Commentators have noted that the findings from within the Swedish study,[235] and from a number of other studies, have highlighted differences between cross-sectional and longitudinal analyses, perhaps due to the effect of survival in the former.[60;230]

There are a number of difficulties in examining smoking as a risk factor, especially in retrospective studies. Comparing current smokers, ex-smokers and non-smokers is problematic, since the first two categories can cover a range of experience.[60;233] Also, since the presence of disease might change smoking habits, earlier smoking patterns have to be examined, and a brief period of smoking might be more likely to be overlooked in cases than controls.[233] It has also been pointed out that, in any study carried out among hospital patients, the prevalence of smoking among the controls is likely to be high.[230;233]

ALCOHOL

The lifetime incidence of alcoholism exhibits a bi-modal pattern, with the second peak representing people in their 60s and 70s.[26] It has been argued, therefore, that the prevalence and the consequences – which can be cumulative - of alcohol abuse can be seen as age-related.[26]

One reviewer of the literature has suggested that alcohol may make a contribution to dementia of all types in roughly 10% of cases.[78] Alcohol is known to affect the brain in a variety of ways. There is some evidence that a significant proportion of heavy drinkers have a degree of mental impairment on some tests, although an improvement has been found with abstinence.[237] There are also thought to be long-term effects of alcohol abuse on the brain, since a proportion of chronic alcoholics develop dementia,[79] and since scanning evidence suggests that 50-70% have shrinkage of and damage to the brain.[26;237] The consequences of alcohol abuse were at one time included under the general term 'Alcohol related brain disorder' (ARBD), but it is now felt that the effects should be seen as separate conditions, rather than as a specific syndrome.[26] These conditions include Korsakoff's syndrome (or Wernicke-Korsakoff syndrome) and a widespread impairment of mental function, which has been termed 'alcohol-associated dementia'.

Alcohol abuse is the commonest cause of Wernicke's encephalopathy, an acute syndrome consequent on thiamine deficiency, whose features include memory impairment. A longer-term consequence is Korsakoff's syndrome, the main feature of which is amnesia, or impaired recent memory. (For further details, see 'Korsakoff's syndrome and other chronic alcohol related brain damage' (2002).[237]) One post-mortem study of Korsakoff's syndrome patients indicated that some dementia was present in 34% of cases.[238] It has been pointed out, however, that many cases of pathologically proven Wernicke's encephalopathy are clinically aysymptomatic before death.[79]

The term 'alcohol-associated dementia' or 'dementia associated with alcohol' has been used to describe the development of a dementia following prolonged and heavy ingestion of alcohol, for which all other causes of dementia have been excluded. This definition acknowledges that (although there is convincing evidence that alcohol is directly

neurotoxic) the causal role of alcohol per se in dementia is controversial, and that some of the medical effects of alcoholism are potentially reversible.[79] Although some have seen 'alcohol associated dementia' as a more severe form of Korsakoff's syndrome, there is no recognised microscopic pathology,[239] and no direct evidence linking the cognitive deficits of alcoholics with subsequent findings at post-mortem.[79] Much of the evidence for the existence of the condition is based on neuropsychological tests and scanning.[237]

A high intake of alcohol is associated with vascular disease, and hence with an increased risk of vascular dementia.[18] On the other hand, there is also some evidence that light to moderate alcohol intake is associated with a lower risk of coronary heart disease and stroke,[240] and the findings from two recent prospective studies have indicated that light to moderate alcohol consumption might be associated with a lower risk of developing dementia, including Alzheimer's disease,[241] and vascular dementia.[240] A slightly more complex picture is suggested by results from the Copenhagen City Heart Study, which found that the association between alcohol intake and risk of dementia depended on the type of alcohol that was being consumed.[242] Although alcohol intake (irrespective of the type of alcohol) was not associated with reduced risk of dementia, regular consumption of wine was associated with a lower risk. The authors have suggested that one explanation for these results may lie in the antioxidant effects of the flavonoids in wine (absent in other forms of alcohol). However, the results of studies linking light or moderate alcohol consumption with a lower risk of dementia have been questioned. One commentator has argued that, in the light of strong evidence associating alcohol with a significantly increased risk of dementia and Alzheimer's disease, the findings from studies which do not find this should, perhaps, be treated with caution, since cases with high alcohol intake might have been excluded.[56] There might also be other explanations for the effect, such as moderate drinking being associated with a healthier lifestyle.

In reviewing the literature, Joyce has concluded that there are several possible routes to brain damage in alcoholics, that these are interlinked, and that a combination of malnutritional and alcohol intake can give rise to a range of cognitive deficits from mild cognitive impairment to severe dementia.[79]

RECREATIONAL DRUG USE
Some forms of dementia have been seen as drug-induced.[59] There is increasing interest in the long term effect of recreational drug use on the brain. At the moment, however, epidemiological research has not examined recreational drug use as a risk factor.

SUMMARY
- Smoking is a known risk factor for vascular dementia.
- Findings from studies examining smoking and the risk of Alzheimer's disease have varied. It has been concluded that any effect, in either direction, is likely to be small.
- High alcohol intake is linked with cognitive impairment, although the effects may be reversible. It is also the commonest cause of Wernicke-Korsakoff syndrome, the main feature of which is memory impairment.
- Alcohol use is thought to contribute to a significant proportion (10%) of cases of dementia. A high intake of alcohol is associated with vascular disease and, hence, with vascular dementia. Also, although alcohol per se might not cause dementia, it has

been seen as a contributory factor in conjunction with other factors, particularly nutritional deficiencies.

- Although there is interest in the long term effect of recreational drug use on the brain, drug use has not been examined as a risk factor.

CHAPTER TWELVE
CLASSICAL (PERSONAL AND LIFESTYLE) RISK FACTORS III: DIET, NUTRITION AND HORMONES

Until recently, research on nutrition and cognitive function in older people has been limited. However, there has been increasing interest in examining the extent to which nutritional factors can be considered as risk factors for dementia or cognitive decline, and at the recent 8th International Conference in Sweden, a number of papers reported the results of studies of this type. Diet and nutrition has a number of aspects. This chapter examines the strength of the evidence for regarding weight loss, nutritional deficiency, B vitamins, cholesterol and anti-oxidants – whether in midlife or old age - as risk or protective factors for cognitive decline and dementia. The role of hormones such as oestrogen is also examined.

WEIGHT LOSS
Weight loss is commonly associated with Alzheimer's disease, and a number of possible explanations have been suggested.[91] The evidence is equivocal. However, although one study found no association with malnutrition in early life,[243] two recent long-term prospective studies, including the Honolulu-Asia Aging study,[244] have found a significant correlation between previous weight loss and the subsequent development of Alzheimer's disease, not explainable substantially by co-morbid disease.[244;245]

NUTRITIONAL DEFICIENCY
Older people might be at risk of nutritional deficiency for a number of reasons. The effects of nutritional factors have been seen as important in the risk of heart disease, and there has been increasing interest in investigating whether aspects of nutrition might have long-term effects on cognitive function or might be implicated in the development of dementia. Food deprivation of varying degrees has been found to affect cognition, although the size of the effects can be small.[26;51] The central nervous system is known to depend on glucose and almost all of the essential nutrients for effective functioning.[246] Vitamins and minerals are thought to be crucially involved in the formation of certain neurotransmitters, suggesting an explanation for links between deficiency and impaired cognitive functioning.[247]

B VITAMINS: FOLATE, VITAMIN B12 AND LEVELS OF HOMOCYSTEINE
Deficiencies in B vitamins (folate, vitamin B12 and vitamin B6) are thought to be relatively

common in the general population and in older adults in particular.[26;246;248] Folate deficiency at a cellular level can occur even with 'normal' serum folate values.[249] Low levels of B vitamins have been found to correlate with increased serum levels of homocysteine, an amino acid.[61;249;250] It has been has suggested that folate concentrations in serum and cerebrospinal fluid fall (and plasma homocysteine rises) with age, perhaps contributing to the ageing process.[251]

There is evidence from a number of cross-sectional studies that folate intake and/or status, either alone or in combination with vitamin B12, appears to be associated with cognitive functioning,[26;51;61;246;249] especially memory performance and measures of abstract reasoning.[246] Elevated plasma homocysteine levels have also been found to be associated with poor cognition.[252-254] However, the links between B vitamins and the incidence of cognitive decline and dementia have been little examined.[255]

Low folate levels have been associated with an increased likelihood of vascular disease including stroke.[249] Similarly, a high concentration of plasma total homocysteine (tHcy) has been identified as a major cardiovascular risk factor,[61;91;250;252;255;256] (although recent studies indicate that the risk might not be as high as was once thought[257]), as well as being associated with some cancers and possibly multiple sclerosis.[258]

There is clinical and epidemiological evidence linking low (serum) levels of vitamin B12 and folate to dementia,[26;91;249] and to Alzheimer's disease in particular.[61;258;259] For example, the Canadian Study of Health and Aging found that low folate levels were common in all types of dementia and were associated with a history of weight loss, lower body mass index and lower serum albumin concentrations.[249] In the Nun study, serum folate deficiency correlated significantly with neocortical atrophy found at postmortem.[260] In addition, a number of cross-sectional studies, including those carried out by Clarke and colleagues[261] and McCaddon and colleagues[253] in the UK, have found evidence of raised homocysteine levels in people with Alzheimer's disease.[14;61;91;258;262] In the OPTIMA Project (Oxford Project to Investigate Memory and Ageing), Clarke and colleagues found that low blood levels of folate and vitamin B12, and elevated tHcy levels, were associated with Alzheimer's disease, as diagnosed at autopsy.[261]

Some commentators have pointed out that it is unclear whether the observed levels of homocysteine or folate are cause or effect of dementia or cognitive decline, since they could reflect the reduced ability of people with dementia or cognitive decline to eat properly.[91;249;258] On the other hand, Clarke and colleagues have argued that the findings do suggest homocysteine levels as a cause of disease and warrant further investigation. There have been other calls for longitudinal studies.[252] The findings from two recently reported longitudinal studies have tended to confirm the associations found in early work.[251] Results from the Kungsholmen project have indicated an association with Alzheimer's disease, especially among cognitively intact subjects, when both vitamin B12 and folate were taken into account,[259] and those from the larger Framingham Study have suggested that an increased plasma homocysteine level is a strong, independent risk factor for dementia and Alzheimer's disease.[252]

Various theories have been put forward about possible mechanisms by which hyperhomocysteinemia (or elevated tHcy) might be related to cognitive decline, dementia

and Alzheimer's disease.[91;263] Since there is strong evidence that elevated tHcy is associated with an increased risk of vascular, cardiac and cerebral pathologies, it has been suggested that the cognitive impairment that occurs in older subjects might be mediated by homocysteine-related cerebrovascular lesions.[61] (With the recent evidence that cerebrovascular disease might contribute to the risk of Alzheimer's disease, tHcy may again be relevant.[91;261]) It has also been suggested that folic acid deficiency and homocysteine might impair DNA repair in hippocampal neurons and sensitise them to amyloid toxicity, something which has been demonstrated in mice.[264]

Implications for prevention

In considering strategies for intervention, there are issues of feasibility and ethics to be considered. Interventions should be effective (and perhaps cost-effective), but should also not cause harm. There are particular concerns about safety where people do not suffer from a recognised disease, as is the case with cognitive impairment. B vitamins are found in low concentrations in certain foods, such as broccoli, fruit and beans.[258] They can also be taken as supplements. Alzheimer Scotland – Action on Dementia (ASAD) has pointed out that, at the doses found in commercially available supplements, taking B vitamins is not normally harmful, although at high doses all vitamins can be dangerous and toxic.[258]

High levels of homocysteine in people with dementia can be reduced, relatively inexpensively, by taking folic acid or vitamin B12 supplements.[250;258] There have been suggestions that vitamin B12 treatment might improve frontal lobe and language function in patients with cognitive impairment,[265] or might even offer a means of protection against cognitive decline or dementia. There is as yet no consensus about screening for hyperhomocsyteinaeima, with some reviewers arguing that tHcy levels should be monitored – with a view to treatment - in all older people,[259] and others recommending that only high-risk individuals (i.e older people with cognitive impairment) be investigated.[265;266] Another suggestion has been that flour should be fortified with folic acid as a general population measure.[248]

One UK study in which baseline vitamin level correlated with cognitive function found that vitamin supplements, while increasing blood vitamin levels, had very little effect on performance.[247] On the other hand, although few longitudinal studies have been carried out,[246] there is evidence that treatment with vitamin B12 has a positive (improving) effect among patients presenting with cognitive impairment,[265] and that supplementation can enhance cognitive performance in older adults.[246] Intervention studies with vitamin B supplement are felt to be warranted.[61;246] Clinical trials of homocysteine-lowering vitamins for people with Alzheimer's disease are planned, and it has been suggested that these should be extended to people with mild memory impairment.[148] As to whether taking such supplements might offer any protection against developing dementia, ASAD has noted that longitudinal studies with a large number of participants, carried out over many years, would be needed to determine this.[258]

CHOLESTEROL

There has been increasing interest in the role of dietary fat (saturated or unsaturated) in dementia, and in the relationship between blood cholesterol levels and cognitive decline and Alzheimer's disease. Cholesterol levels might be modifiable, either by changes in the diet, or by medication.

High blood cholesterol levels are associated with an increased risk of cardiovascular disease. Low-density lipoproteins (LDLs) are the part of cholesterol that enables fats to attach to the walls of arteries, narrowing and eventually blocking them. High-density lipoproteins (HDLs) in contrast help to keep the arteries clear, so that blood can flow freely. If left untreated, elevated LDL and cholesterol levels can increase the risk of stroke, heart attack and death. There is some evidence that – for women – after the menopause, cholesterol and LDL levels may rise and HDL levels may fall slightly.[267]

There is also accumulating evidence from epidemiological studies pointing towards a link between cholesterol and Alzheimer's disease,[91;268] and indicating that lower fat diets in mid-life might reduce the risk for Alzheimer's disease decades later.[50] Findings from the Rotterdam study have provided some evidence that dietary saturated fat and cholesterol measured at baseline increased the risk of cognitive impairment and dementia a few years later,[269;270] and those from a 21-year Finnish study have indicated that raised systolic blood pressure and high serum cholesterol, and in particular the combination of these risks, in midlife, increased the risk of Alzheimer's disease in later life.188 Another Finnish study has found an association between blood lipid levels in mid-life and the amount of ß-amyloid protein (Aß) seen in the brain at post-mortem, although the issue appears to be complex.[271]

Several recent studies have indicated similar links between cholesterol and cognitive decline more generally.[272-275] Longitudinal or prospective studies are felt to be needed to further investigate these findings.[276] It has also been argued that, since the risk from these treatable factors appears to be relatively high, in relation to genetic factors for example, intervention may be worthwhile.[277]

The fats that are strongly associated with vascular damage and may also be associated with damage to the brain are rich in monosaturated fatty acids. Fats that are rich in polyunsaturated fatty acids appear by contrast to offer a significant degree of protection from cardiovascular disease, and there is now also some evidence to suggest that they might benefit brain health (independently of their effect on vascular disease). In both the Rotterdam Study and the Zutphen Elderly Study, moderate fish consumption (as a marker of n-3 fatty acid intake) appeared to decrease the risk of Alzheimer's disease.[269;270;278] More recent reports from the longer PAQUID project, though here linked with the higher education of regular consumers,[279] and from a Chicago-based study[280] have confirmed these findings.

Interpretation of findings
It is thought increasingly likely that cholesterol might play a role in the pathophysiology of Alzheimer's disease,[91;268;281;282] although the mechanisms are unclear. It has been pointed out that the epidemiological evidence linking dietary cholesterol intake to Alzheimer's disease is stronger than the epidemiological evidence linking levels of serum cholesterol and Alzheimer's disease.[91] So, for example, a recent follow-up of subjects in the long-running Framingham Heart Study found no association between serum cholesterol (measured at various ages) and risk of Alzheimer's disease.[283] It has also been suggested that the associations with cholesterol found by research could reflect differences or disturbances in endogenous fatty acid metabolism.[275]

Fatty acids could be involved in dementia through several mechanisms, including atherosclerosis, thrombosis and inflammation,[279] and various hypotheses have been proposed. One suggestion is that the ApoE protein is involved in the transport of cholesterol and other lipids between neurons.[91] There is also growing evidence from studies with animal models of a link between cholesterol and the accumulation of ß-amyloid in specific regions of the brain (the common pathogenic event that occurs in all forms of Alzheimer's disease).[268;281;284] In addition, it has been suggested that a high intake of saturated acids, or a low intake of antioxidants, can increase oxidative stress,[51;91] causing oxidative damage to the brain, changes which may contribute to both vascular and Alzheimer's disease pathology.[43] N-3 polyunsaturated fatty acids, on the other hand, might reduce inflammation in the brain. Saturated fatty acids are associated with increased atherosclerosis, and both inflammation and atherosclerosis are thought to be involved in dementia pathogenesis.[272] One view is that dietary fats might interact with genetic factors to accelerate Alzheimer's disease pathology.[285] Hence, lower fat diets during mid-life might substantially reduce risk of Alzheimer's disease for those with the APOE 4 allele.[276]

Implications for prevention

Possible protective mechanisms related to cholesterol include (1) changes in diet, i.e. reducing the intake of saturated fats, or replacing with unsaturated fats, (2) treatment with lipid-lowering agents, or 'cholesterol-busters', and (3) increased intake of anti-oxidants. Prospective clinical trials have been recommended, to evaluate the impact of specific macronutrient intakes on age-related changes in cognitive function.[273]

Lipid-lowering agents

It has been suggested that large reductions in cholesterol concentrations might be easily and safely achievable with the discovery of statins.[286] (Early trials of cholesterol-lowering agents were not found to be convincingly effective, because the available interventions - drugs or diet - lowered cholesterol to only a modest degree, the interventions were not well-tolerated, or the studies lacked statistical power.[286]) Statins are a group of cholesterol-lowering drugs, the HmG-CoA reductase inhibitors, which are currently available clinically and which are thought to have few side effects.[268] The discovery of statins has led to a series of trials, which have demonstrated benefits in selected populations.[286] The results of a recent 5-year randomised control trial (the MRC/BHF Heart Protection Study) have shown that, for the group of patients taking a statin (simvastin), there were significant reductions in the incidence of vascular disease and in mortality from all causes, and that there were clear benefits, even from those high-risk patients considered to have 'normal' or 'low' blood cholesterol concentrations.[287] Because of the possibility that treatment with statins might reduce the incidence of cognitive decline, the study included a test of cognitive status at the final follow-up, but no significant differences were observed between groups. However, the results of two other observational studies have indicated that statin therapy can reduce the risk of developing Alzheimer's disease among patients with hypertension and cardiac disease.[288;289] Reviewers have commented that randomised controlled trials are needed, but that statins appear to have other beneficial effects in addition to that on cholesterol.[282;290] Preliminary findings from one large study in Boston US, which includes a large number of African Americans (a group known to have a higher risk of developing Alzheimer's disease) have confirmed earlier indications of a reduction in risk.[291]

Anti-oxidants

A high intake of saturated acids has been seen as increasing oxidative stress, and hence the risk of brain damage.[51;91] Evidence of oxidative reactions (e.g. Aß protein of plaques) has come from neuropathologic studies of Alzheimer's disease.[43;102] Conversely, it has been argued that high plasma levels of anti-oxidants might correlate with cognitive performance in healthy older individuals,[51] or might mitigate against oxidative damage. Anti-oxidants, or 'free radical scavengers' include vitamins A, E, C, ß-carotene and minerals such as zinc, as well as ginkgo biloba, red wine flavonoids and oestrogen.

Research has indicated that high levels of cognitive function are associated with higher levels of vitamins A, C and E (as well as B1, B2 and B3),[51] and that, conversely, a decrease in cognitive test results is associated with sub-deficiencies of various vitamins and minerals, including vitamins C and E.[61] One case-control study, for example, found that lower vitamin C plasma concentrations were found in Alzheimer's disease patients than in control subjects.[292] In a review of the literature, Launer has concluded that, although there are a number of methodological limitations in the existing studies and larger, better designed trials are needed, there is increasing experimental data from observational studies and randomised trials to implicate oxidative damage as a mechanism contributing to brain disease.[43]

There has been speculation that dietary vitamins with anti-oxidant properties might have a role in the prevention or slowing of cognitive decline in patients with Alzheimer's disease,[91] or that such lipophilic free radical scavengers might play a protective role against oxidative toxicity.[102] Launer has pointed out that trials can help in clarifying a role, if any, for anti-oxidant therapy to reduce the risk of dementia, noting that many of the hypotheses regarding the role of oxidation in neurodegeneration must remain speculative in the absence of knowledge about the pathophysiology of neurodegenerative diseases. Ideally, trials would be used to test a model or hypothesis, but the problem of finding possible ways to prevent severe cognitive decline is such that trials have been instituted already.[43]

Anti-oxidants: intervention studies

Findings from empirical studies examining the relationship between anti-oxidants and vascular disease have been seen as contradictory.[158] The recent UK MRC/BHF Heart Protection Study of antioxidant vitamin supplementation found that allocation of high-risk patients to the vitamin regime markedly increased their plasma concentrations of a-tocopherol, vitamin C and b-carotene, but no significant differences in mortality, nor in the occurrence of major vascular events were found.[293] These findings agree with those from three other major trials.[286]

In relation to cognitive decline and dementia, one small cohort study in Australia found that consumption of vitamin C supplements was associated with a lower prevalence of more severe cognitive impairment, and the authors have concluded that vitamin C might have a protective function.[294] On the other hand, a small UK study found that, although multivitamin supplementation increased blood vitamin levels, it had little effect on cognitive function or mood.[247]

Some studies have found that anti-oxidant (e.g. vitamin E) supplements have a beneficial effect on the cognitive function of people who have been diagnosed with early dementia.[91]

Longitudinal studies and trials of putative protective agents among people with Alzheimer's disease and people with cognitive impairment are now under way,[11] and, in the US, a clinical trial examining the prevention of Alzheimer's disease by vitamin E and selenium (PREADVISE) is recruiting men aged 60 living in the community.[295] Reviewers of intervention studies have found that, overall, the evidence for a protective role of anti-oxidants on the incidence of dementia is inconclusive.[14;61;296] There is some evidence from the Honolulu-Asian study that supplementary vitamin E might be protective against developing vascular dementia.[297] Also, findings from the recent US Cache County Study have suggested that the use of vitamin E supplements is associated with a reduced prevalence and incidence of Alzheimer's disease (and that the combination of vitamin E and C supplements might be particularly advantageous).[298] Interestingly, two recently reported longitudinal studies have found that high dietary intake of antioxidants, especially vitamin E, from food sources may reduce the risk of developing Alzheimer's disease.[103;299] Findings from the Rotterdam study have indicated that vitamins C and E may both be beneficial,[300] while those from a study in Chicago have suggested the protective nature of dietary vitamin E, an association only observed among individuals without the APOE 4 allele.[301] Neither study found a benefit from consuming the supplement sources of vitamins, even though a higher dose was available in the supplements.[103;299]

Again, any medical intervention has to be proved to be both safe and effective. Yusuf has argued that the data from the MRC/BHF study indicates that prolonged use of antioxidant vitamins in Western populations without vitamin deficiencies could potentially lead to some increase in vascular disease.[286] Vitamin E is soluble in fat, and can accumulate in the liver and cause poisoning. There has been interest, therefore, in other supplements with an anti-oxidant effect. Certain fruits have a relatively high antioxidant capacity.[50]

Oestrogen

Another putative protective factor is oestrogen. There is some evidence that, for women, after the menopause cholesterol and LDL levels might rise.[267] Animal and in-vivo cell studies have suggested that oestrogens can protect brain structures, including those related to memory,[302] and there has been interest in whether this might be the case in humans. A number of women in Western countries take either synthetic oestrogen or hormone replacement therapy (HRT – oestrogen combined with progesterone) to treat menopausal symptoms or to guard against osteoporosis. While oestrogen therapy has been found not to slow the progress of Alzheimer's disease significantly in patients who already have the disease,[303] there has been interest in finding out whether oestrogen supplements might have beneficial effects for women in delaying or averting cognitive or memory decline, or the incidence of dementia.[304] A higher prevalence of Alzheimer's disease in women than in men suggests a possible link with gonadal hormone levels. There is also increasing evidence to support the view that oestrogen has a role in brain regions involved in learning and memory, and in the protection and regulation of cholinergic neurons which degenerate in Alzheimer's disease.[305] At the same time, there have been concerns about the safety of taking oestrogen or HRT for long periods, since there are several known side effects. A number of studies have been carried out, particularly in the U.S.

Reviewers of the literature have concluded that evidence (from observational studies) for the beneficial effect of oestrogen on cognitive function is inconclusive.[267;296;303] There is

clearly quite a lot of data supporting the view that HRT has a positive effect on certain aspects of cognitive performance in women with menopausal symptoms,[303-307] but there appears to be no evidence of benefit in asymptomatic women.[296;303] There are, however, a number of substantial methodological problems in some of these studies, most notably the failure to control for the fact that women who take oestrogen tend to be better educated and healthier than non-users.[56;296;303] Although the findings from one large study in New York, as well as the Cache County Study, have suggested that oestrogen use in postmenopausal women might delay the onset and decrease the risk of Alzheimer's disease,[308;309] overall the evidence for a protective role against the development of dementia has been seen as weak.[56;61;296;310] A large UK case-control study based on the General Practice Research Database found no reduction in risk even in patients who had taken oestrogen for 5 years or longer,[311] and another recent study has indicated that oestrogen does not prevent dementia in women with APOE 4.[312] Results from the Cache County Study do, however, suggest one possible explanation for this apparent weakness, namely that oestrogen use within 10 years of the onset of disease yields little, if any, apparent benefit.[309] In other words, oestrogen therapy may only have a protective effect if taken well in advance of the onset of symptoms.

Two large clinical trials which were examining the long term effects of HRT and oestrogen on healthy post-menopausal women were halted during 2002. The international WISDOM trial was investigating the incidence of dementia (among other diseases), but it was felt that the results, ten years hence, would be unlikely to affect clinical practice.[313] Part of the Women's Health Initiative Study (WHI)[314] was stopped early because of small increases in the rates of breast cancer, coronary heart disease, stroke and pulmonary embolism among the case group compared with controls.[315] Further analysis of the results of the WHI study found in fact that prolonged HRT use was associated with a small increased risk of clinically significant cognitive decline.[316] Another recent study has found that women who used oestrogen-only replacement therapy, particularly for 10 or more years, are at significantly increased risk of ovarian cancer.[294] It seems clear that further trials, as well as much longer follow-up of the women in studies like the WHI study, are needed in order to evaluate fully the real long term risks and benefits of HRT.[14;56;61;303]

CONCLUSION: DIET, NUTRITION AND HORMONES

Reviewers of the literature have concluded that there is evidence to suggest that nutritional factors can play a part in reducing the risk of dementia or cognitive decline.[51;61;91] It has been argued that eating a healthy diet – or changing to a healthier diet – can reduce the risk of conditions such as diabetes and cerebrovascular disease, and hence the risk of dementia.[50] Nevertheless, more research is felt to be needed,[91] and it has been noted that, since nutritional effects are liable to be subtle, samples must be large enough to provide adequate power.[246] It has also been emphasised that nutritional factors should be seen as interacting with other factors.[61]

Commentators have urged caution in suggesting explanations for empirical findings, or in recommending interventions. For example, it has been stressed that research should ascertain that the problem is not that people with declining cognitive function might not eat properly.[51] Also, in ascribing causality, the effect of body metabolism, and the possibility that the ability to process foods might be at least as important as diet, should be taken into

consideration.[26;275] Reviewers of the literature have also emphasised the importance of controlling for extraneous variables that might affect the absorption of vitamins (e.g. smoking), and of identifying other background and demographic factors that should be used as co-variates (e.g. way of life).[246;318] At the same time, it has been noted that, although low socio-economic status is often cited as a major cause of nutritional deterioration in older people, other factors such as age-related physiological changes may be more important.[26]

Some commentators have made the point that the interest in nutritional factors rests on the assumption that nutrition can be modified, relatively cheaply and safely, by supplementing (for those at high risk) or by changing the diet, perhaps in mid-life.[51;246] It has been noted, however, that, even where there is evidence linking nutritional deficiency with an increased risk of dementia or cognitive decline, supplements might not necessarily be beneficial.[319] Also, although high intakes of folic acid are known to reduce plasma homocysteine, there is no evidence from clinical trials that fortification of cereals reduces cardiovascular disease.[319] Riedel and Jorissen have discussed the fact that different interventions (dietary enhancement, treatment with supplements, and treatment - of patients - with drugs) may be more or less appropriate for different groups.[51] There are safety issues, in that drugs – and to a lesser extent supplements – can have side effects. They have noted that, since cognitive decline is not a disease, medication would be inappropriate, but that in fact anti-oxidant supplements appear to be equally beneficial. These authors have concluded that a proper dietary composition with regard to the ratio of carbohydrates to proteins, as well as the inclusion of micronutrients, seems to help in maintaining cognitive function in the elderly.[51]

SUMMARY
- Weight loss is commonly associated with Alzheimer's disease, and a number of possible explanations have been suggested.
- Nutritional deficiency has been found to affect cognition, and associations with dementia are being investigated.
- A deficiency of B vitamins (B12, B6 and folate) has been found to be correlated with increased serum homocysteine (tHcy) concentrations. Low levels of B vitamins have been associated with lower levels of cognitive function. Similarly, a high concentration of homocysteine (or folate deficiency) has been associated with an increased risk of dementia, particularly Alzheimer's disease.
- Clinical trials of vitamin B supplements for people with Alzheimer's disease are planned, and these may be extended to people with mild memory impairment.
- High cholesterol levels are associated with an increased risk of vascular disease and hence vascular dementia. There is evidence of an association between high levels of dietary saturated fat, or high cholesterol level, in mid-life and an increased risk of cognitive decline and dementia.
- There is some evidence to suggest that regular consumption of foods rich in N-3 polyunsaturated fatty acids may decrease the risk of Alzheimer's disease.
- Statins (one type of lipid-lowering agent) have been found to lower the risk of vascular disease and mortality from all causes. There is also some evidence that they reduce the risk of developing Alzheimer's disease. Clinical trials are under way.
- Clinical intervention studies are examining whether anti-oxidant vitamins might reduce

the risk of dementia. Findings have been contradictory, but tend to suggest that vitamins from food sources are more effective than supplements.

- Some observational studies have suggested that oestrogen use in post-menopausal women can have a beneficial effect on cognitive function. However, the evidence for a protective role against the development of dementia is weak. The effects of oestrogen and HRT use are being investigated, although long term trials have been halted.

- Reviewers of the literature have emphasised that nutritional factors should be considered in conjunction with others, and that there may be a number of possible explanations.

CHAPTER THIRTEEN
CLASSICAL (PERSONAL AND LIFESTYLE) RISK FACTORS IV: TO WHAT EXTENT, IF ANY, MIGHT INTERVENTIONS CURRENTLY TARGETED AT VASCULAR DISEASE HAVE HELPFUL IMPACTS ON DEMENTIA OR COGNITIVE DECLINE?

A number of the 'classical' risk factors described in the previous three chapters (e.g. vascular factors, smoking, cholesterol levels) have been associated with an increased risk of vascular disease. This chapter outlines the interventions currently targeted at vascular disease, and considers whether there is any evidence that they lower the risk of dementia or cognitive decline.

There have been calls for more emphasis to be placed on the identification and appropriate treatment of risk factors for cerebrovascular disease, with a view to reducing the incidence of vascular dementia or 'vascular cognitive impairment' (VCI), as well as vascular disease.[68;320] The results from the Systolic Hypertension in the Elderly Program (SHEP)[321] have been seen as confirming the need for active treatment of isolated systolic hypertension, and as indicating measures which might help to reduce stroke and other complications of high blood pressure including dementia.[28] Along with control of hypertension (a major cause of vascular dementia), it has been suggested that the control of hyperlipidaemia (raised blood fat levels) and diabetes mellitus might have a stabilising effect, although evidence is lacking.[66] Other modifiable factors include cigarette smoking, excessive alcohol consumption, obesity and lack of exercise,[66] although the interaction between social and behavioural factors (e.g. between lower socioeconomic status and an increased likelihood of smoking and high alcohol consumption) has also been pointed out.[322]

Several commentators have seen the potential for the effective treatment of vascular disease or the control of vascular risk factors as very promising.[68;286] Others, however, have argued that in spite of the known association between high blood pressure and stroke, effective means of prevention of stroke have not yet been identified.[187] It has also been noted that the adverse effects of antihypertensive medication use can negatively affect mental state.[189]

Management of the risk of vascular disease relates to appropriate treatment, but also to the promotion of potential protective factors and behaviour. Interventions currently targeted at vascular disease include measures aimed at individuals at high risk, and those aimed at the population as a whole. These have been seen as worthwhile in relation to vascular events, and may be worthwhile in relation to dementia.

CHAPTER THIRTEEN CLASSICAL (PERSONAL AND LIFESTYLE) RISK FACTORS IV: TO WHAT EXTENT, IF ANY, MIGHT INTERVENTIONS CURRENTLY TARGETED AT VASCULAR DISEASE HAVE HELPFUL IMPACTS ON DEMENTIA OR COGNITIVE DECLINE?

HOW EFFECTIVE ARE CURRENT INTERVENTIONS IN REDUCING THE RISK OF VASCULAR DISEASE?
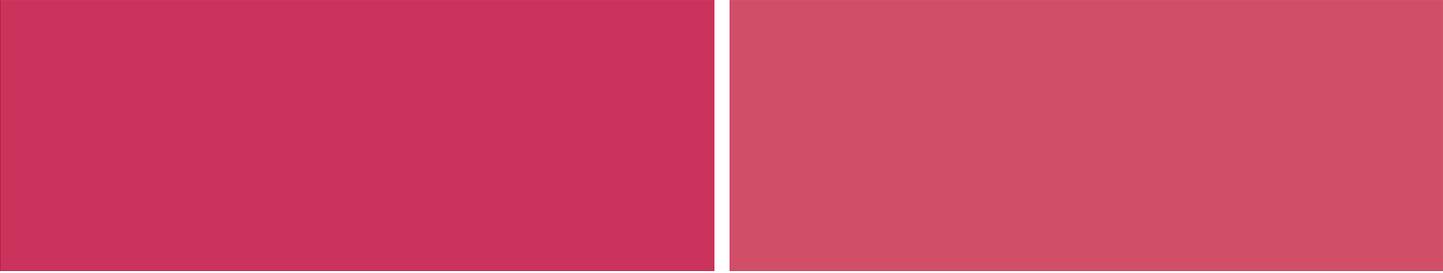
The treatment of systolic hypertension (either by medication or by weight loss, decreased salt intake and exercise) as a preventative approach has been established,[66;321] and this has been shown to be effective in the primary prevention of cerebrovascular disease among hypertensive patients.[158;189;286;323] It has been noted that there is evidence to suggest that aspirin, b-blockers, ACE-inhibitors and lipid-lowering agents can lower the risk of future vascular events (coronary heart disease and strokes) to a moderate but important degree, in high-risk patients, the benefits of each intervention appearing to be largely independent.[286] Medication measures have usually been combined with recommendations for lifestyle change. Smoking cessation is thought to lower the risk of myocardial infarction by a half after about two years.[286] However, in general, the evidence for lifestyle or non-pharmacological measures has been seen as inadequate at present, with large-scale trials of long duration thought to be needed.[324]

Other approaches to prevention involve population-based strategies, either by means of screening programmes or risk assessment, or by health promotion measures. Population screening for individuals at high risk of coronary heart disease is an explicit objective in primary care.[325] The national service framework for coronary heart disease,[326] and the joint British recommendations on prevention of coronary heart disease,[327] propose that all patients with a 10 year absolute risk of a coronary event of over 30% should be identified (by general practitioners and primary healthcare teams) and should be offered appropriate advice and treatment to reduce their risk.[325] Some questions have been raised about the feasibility and ethics of the proposed screening, and a recent BMJ editorial has argued that a scientific evaluation of effectiveness and benefit should be carried out.[325] The authors have suggested that a more practicable approach might be to restrict cholesterol measurements to those whose age, sex, smoking and blood pressure would indicate high risk. Concerns have also been raised about how benefit should be assessed (given that individual and public health values and goals might differ and given the consequences of being classed as 'high risk'),[328] how information is presented, and how decisions about interventions are arrived at, particularly when there is little evidence to suggest the extent to which risk might be reducible.[325]

Health promotion measures aim to reduce the risk of vascular disease by encouraging a moderate reduction in blood pressure among the population as a whole, through lifestyle change. Health education campaigns have emphasised the importance of exercise, diet and weight control, smoking cessation and stress reduction. However, there are concerns about the effectiveness of this approach, and one review has suggested that, although weight reduction is potentially useful in controlling blood pressure, multiple risk factor interventions may be ineffective in reducing mortality from cerebrovascular disease in the general population of middle aged adults (as opposed to among hypertensive patients).[329]

IS THERE ANY EVIDENCE THAT INTERVENTIONS CURRENTLY TARGETED AT VASCULAR DISEASE HAVE HELPFUL IMPACTS ON DEMENTIA OR COGNITIVE DECLINE?

There is some evidence that control of blood pressure in hypertensive patients and cessation of smoking may improve cognitive function.[330] Also, in one large double-blind

placebo-controlled European study, treatment of mild systolic hypertension decreased the incidence of dementia.[331]

However, findings from the UK Medical Council trial have suggested that treating moderate hypertension in older people had no effect on subsequent cognitive function.[212] Those reviewing the literature have concluded that the evidence for any effect of either anti-hypertensive treatment,[37;67;158] or other interventions to modify cardiovascular factors,[20] on the incidence of dementia remains scanty and unclear, and that little is known, as yet, about whether and how the general (or cohort) effects of cardiovascular and cerebrovascular reduction will influence future rates of cognitive impairment.[19] There have been calls for further clinical trials.[201;211]

SUMMARY

- The fact that some dementia and cognitive decline is linked with vascular factors, particularly hypertension, suggests that there is some scope for intervention. Treatment of hypertension has been established, and has been found to be effective in reducing the risk of vascular events. Thus, vascular dementia may be preventable, to an extent, by medication and / or lifestyle change.
- However, little is known about whether interventions targeted at vascular disease have any impact on the incidence of dementia or cognitive decline.
- The identification of those whose age, sex, smoking and blood pressure indicate a high risk of vascular disease is felt to be worthwhile in relation to vascular risk, and may be worthwhile in relation to dementia.

CHAPTER FOURTEEN
FACTORS RELATED TO SOCIAL CONTEXT: SOCIAL CLASS, OCCUPATION AND EDUCATION

Findings from empirical work examining the prevalence and incidence of dementia have conventionally been corrected for socio-demographic factors such as education and occupation. Factors related to social context have been found to be a major influence on the incidence of many other disorders. A number of studies have investigated the extent to which the risk of cognitive decline and dementia might be affected by social class, occupation and education. However, while education has been taken as a proxy measure of social class, it has also been seen as a marker for 'brain reserve'.

Factors related to social context may have a significant effect on health. There is a view that more attention should be paid to these potentially important environmental factors in the development of dementia and cognitive decline, and some recent studies are examining social class as a risk factor.[112;332] In the UK, occupation has often been taken as a marker for social class, and research has generally distinguished between social class and educational level.[10] In the US, the number of years of education has often been used as a proxy measure for social class. However, educational level has sometimes also been seen as a marker for 'brain reserve'.

SOCIO-ECONOMIC STATUS
Numerous studies, including some in Scotland,[333] have found that social class is related to health differentials, with lower socio-economic status (both in childhood and in adult life) being associated with higher levels of mortality and with a higher incidence of certain diseases.[334-337] Lower socio-economic status is known to be associated with an increased risk of cardiovascular disease,[338] and is an established risk factor for cerebro-vascular disease.[92;322] It might be expected, therefore, that lower social class or socio-economic status might be associated with a higher risk or incidence of dementia and of cognitive decline. Any evidence of such a relationship would have important implications for policy, since this would suggest that the rates might be lowered if deprivation or poverty could be reduced.[332]

There are a number of possible ways of measuring social class, and it has been noted that the choice of index of deprivation can influence the findings of research.[31] Deprivation can be seen in either absolute or relative terms, and can be measured in terms of individual or

area characteristics. Individual deprivation – which can relate either to the individual or to the head of the household - can be assessed in terms of income or employment status (or sometimes education). Other measures of deprivation are provided by local area (e.g. the social deprivation index,[339] or Scottish Area Deprivation Index), or by the housing council tax band.

Where subjects are retired, using income or occupation may be problematic, but when social class is examined as a risk factor for late-onset conditions, there are additional questions about the stage in life at which it should be measured (even though there is little upward mobility). There are also particular difficulties in using educational level as a proxy measure of social class when examining differences between age-groups (since the age of leaving school might be cohort-specific)[108] and when examining cognitive function late in life (since there is a known association with that in early life).[48] The point has also been made that occupation can be a surrogate marker for a number of factors, such as premorbid intelligence, cognitive stimulation, but also level of medical care and attitude to health, psychosocial characteristics, or exposure to chemicals or other environmental factors.[155]

Lower socio-economic status and the risk of cognitive decline
A number of studies have found that lower socio-economic status – whether measured currently, in mid-life or in childhood – is associated with lower cognitive function in later life.[10;92;115;340-342] The same relationship has been found using occupation as the variable; there is evidence from a number of cross-sectional studies to indicate that cognitive impairment in old age varies across occupational groups.[343] In one Australian study, these differences held even when age, education and language fluency were statistically controlled.[343]

The findings from one recent UK study (the Cambridge City Over-75 Cohort Study) have suggested that a greater decline in the Attention /Calculation sub-scale is associated with manual social class.[55] Other longitudinal studies, however, have found no association between socio-economic status and cognitive decline,[343] although this relationship has in fact been little examined.

Lower socio-economic status and the risk of dementia
The findings from the few studies which have investigated lower socio-economic status as a risk factor for dementia are inconclusive. Where an association has been found, it has usually been with vascular dementia. For example, one small longitudinal study in Germany found significant associations between socio-economic status (as measured by former occupation) and vascular dementia, whereas Alzheimer's disease was evenly distributed.[344] Similarly, a study in Iceland found no significant association between education and occupation before old age and the incidence of Alzheimer's disease.[345] A study carried out in Central Scotland indicated that, using records from mental hospitals, vascular dementia was associated with deprivation, although early onset Alzheimer's disease was not. Using death certificate records, however, there was a clear trend towards a higher incidence of dementia (from all causes, and in all age groups) among those in the most deprived categories.[346] Similarly, a US study has found that people who had been in low status jobs had a higher risk of dementia, even where education was controlled.[347] Rather different findings have emerged from another US study which found that three markers of low socio-economic status, including education, predicted the risk of developing incident Alzheimer's disease.[332]

Others studies, however, have found no relationship between lower socio-economic status or occupation and the incidence of dementia.[343] One UK study found no difference in risk of dementia between high and low status occupations,[348] and a Greater Glasgow Health Board (GGHB) report has stated that, whereas for most mental health problems there is a strong link with deprivation, dementia appears to be the exception, since no link is apparent.[349] Similarly, a large 10-year longitudinal study in France found that occupational category had no major impact on the risk of Alzheimer's disease, findings which contrasted with the strong relation found at the baseline screening phase of the cohort between cognitive performance and principal lifetime occupation.[155] The authors have commented that the findings seem unusual at first sight, given that an association is often found between cognitive ability and education, but they have suggested that the results could be explained by the fact that occupational category can be a marker for a number of factors. Jorm and colleagues, however, have concluded that cross-sectional differences on cognitive tests and dementia prevalence are due to differences in pre-morbid ability, rather than to differences in the rate of cognitive decline.[343]

It should be stressed, however, that these conclusions are based as much on a lack of information, as on research findings showing no relationship. The results of research have been inconclusive, as well as difficult to interpret because of the different types of study, variety of measures of social class and different types of dementia examined. Also, importantly, associations between socio-economic status and the incidence of cognitive decline or dementia have been little examined. The literature in this area is limited, with few longitudinal studies specifically examining social class having been carried out. Studies in the US have taken education as a proxy measure of social class, but the meaning of education has been interpreted in a number of ways.

EDUCATION

A number of studies have examined associations between educational level (years of education or age of leaving education) and the prevalence or incidence of cognitive decline and dementia. Gilleard has commented (p33) that, "if findings do indeed reflect a real and substantial relationship between learning in early life and mental decline in later life, the social and medical implications are profound".[108] As he points out, since future cohorts of older people in Western countries are likely to have had a higher level of education than older people now have had, a lower incidence of cognitive impairment and dementia might be predicted in the future (by contrast with increasing numbers in developing countries).

Education and the risk of cognitive decline

There is considerable evidence linking educational level with the level of cognitive function in later life. A number of studies, including the recent MRC Cognitive Function and Ageing Study (MRC CFAS)[10] have found that lower cognitive function in old age is clearly associated cross-sectionally with lower educational level.[350-353] Similarly, findings from the Nun study have shown that that nuns who were poorly educated had higher rates of severe cognitive impairment (as well as reduced motor function, greater impairment in activities of daily living, and higher mortality rates).[354-356] The relationship between educational level and cognitive impairment in later life has been widely debated.[10] Mortality has been suggested

as a possible confounding factor, since both current cognitive function,[110] and childhood IQ,[357] have been shown to be related to survival.

The relationship between educational level and cognitive decline has been little examined, but the Cambridge City Over-75 Cohort Study data has found that a greater decline in the memory subscale was associated with less education.[55] The findings from a recent Finnish study have suggested that any association between education and cognitive decline might be modified by the presence or absence of the APOE 4 allele, although larger studies are felt to be needed.[145]

Education and the risk of dementia

Since 1990, studies from a number of countries have indicated potential associations between lower educational level and the prevalence or incidence of dementia of various types.[22;347;358] Some longitudinal studies, particularly the Framingham study,[353] have shown a relationship between lower educational level and the risk of vascular dementia. In a review of the literature, Gilleard has noted that it is reasonably well established that limited education, low paid occupation and lower socio-economic status all contribute to the risk of vascular disease, and by implication to the risk of vascular dementia.[108] Commentators have concluded that any increased risk of vascular dementia associated with low education can be seen as occurring indirectly.[56;108;359]

In addition, a number of studies, including the EURODEM pooled analyses,[22] the Canadian Study of Health and Aging,[13] and the work of Stern,[347] have found an association between limited educational experience and Alzheimer's disease,[124;205;360] or dementia generally.[122;361] Recent findings from large longitudinal studies such as the Rotterdam study,[362;363] and the PAQUID project[124] have supported these conclusions. The results of the EURODEM pooled analyses have also suggested that low levels of education might increase the risk of Alzheimer's disease, more strongly in women.[22]

Not all empirical work has shown an association between education and dementia, however, and those reviewing the literature have expressed various views about the strength of the evidence. Although some have claimed that the strength and consistency of the association, as well as the partly established dose-response relationship, indicates that higher education is associated with a lower risk of developing dementia,[364] others have been more cautious.[56;108] Van Duijn has argued that the finding that highly educated subjects had a lower risk for all types of dementia (for example the work of Katzman[358]) was based on prevalence studies, so that the results might be explainable by survival and selection bias.[56] The findings from incidence studies examining Alzheimer's disease or dementia have been seen as inconsistent.[56;108] Gilleard has concluded that, while educational background has been found consistently to influence mental state performance (and hence the probability of a diagnosis of dementia), the evidence for an aetiological link between educational background and dementia is ambiguous at best, and in many studies non-existent.[108]

Interpretation of findings

Reviewers of the literature have noted a number of issues which need to be taken into

consideration in interpreting research evidence examining links between education and dementia. First, the inclusion of a large institutional population (who might be significantly less well educated) could introduce serious problems of bias. If this were the case, any finding of links with education would have to be questioned.[108] Gilleard has also argued that it is essential to control for age, since older people have inevitably received less education than younger generations. The confounding effects of age might lead to the effects of education being exaggerated.[108] Gilleard has observed that, in some studies,[353] although not in others,[365] the relative risk of dementia in less educated people declined when age was controlled for.

Many commentators have also drawn attention to the nature of the diagnostic tools for identifying cognitive decline and dementia, pointing out that it can be difficult to distinguish between low and declining cognitive function,[41] and that it is well known that scores in cognitive assessments are highly correlated with education.[108;114;366] They have noted that the relationship between education and dementia appears to be strongest when the diagnostic criteria emphasise 'cognitive impairment', and to be least evident in long-term studies based on clinically verified cases.[108;366] Some commentators have pointed out that educated people might perform more competently on neuropsychological and mental state tests for Alzheimer's disease (as well as on those for cognitive function)[114] leading to a possible over-diagnosis of dementia in poorly educated populations, and an under-diagnosis in well-educated populations.[108;366] Stern has made the point that the use of cognitive tests makes it difficult to establish whether educational experience is a risk factor for Alzheimer's disease, because educational attainment can influence performance on diagnostic tests.[347]

Not only does 'education' have a number of meanings, but educational level might be associated with a number of factors, biological and environmental; e.g. level of income, level of stress or depression, adequacy of nutrition or tendency to physical illness. The findings of a possible relationship between low educational level and dementia have been interpreted in various ways.

Environmental interpretation: socio-economic status
Some commentators have argued that any association between lower educational level and the incidence of dementia might be explained by other factors associated with low socio-economic status such as peri-natal nutritional difficulties,[62] or by lifestyle factors such as alcohol consumption and occupational exposures,[354] rather than by education itself. Mortimer has made the point that low education has been found to be a risk factor for other signs of 'accelerated ageing'.[62] Evidence from one small study has suggested that lower education and / or poverty might diminish cognitive reserve or resistance to Alzheimer's disease, rather than higher education providing a 'protective effect'.[367]

Biological interpretations: the 'brain reserve' hypothesis
The data suggesting that less well educated individuals appear to be more susceptible to late-onset dementia has often been interpreted environmentally, but recently the link with education has tended to be explained in terms of the protective or compensatory effects of 'brain reserve'.[14] There is a view that individuals will exhibit dementia only if their cognitive

or neurological reserve capacity falls below a specific threshold, i.e. a critical volume of brain tissue.[354] From the 'brain reserve hypothesis', the brains of individuals vary in their resistance to cognitive decline or dementia. A higher capacity can provide a 'buffer', hence delaying (rather than preventing) the manifestation of dementia or Alzheimer's disease.[10;26;364]

Katzman has proposed that the protective effects of education could be seen as related to neuronal reserve, such that those with higher levels of education may be more resistant to the effects of dementia.[358] Orrell and Sahakian have noted that education can be seen either as protecting against neurodegeneration (by delaying the pathological process of decline) or as delaying the onset of clinical symptoms.[359] 'Brain reserve' has been explained in terms of early or innate capacity or intelligence, enhancement by mental stimulation or training, or a combination of the two.[14]

Education as a marker for innate intelligence
Some studies have tried to examine whether premorbid intelligence, rather than education, reduces the risk of dementia or cognitive decline. Higher cognitive function in early life is known to predict higher cognitive function in later life.[50;368;369] One UK study has indicated that those with higher baseline ability and more education (but also higher social class) are relatively protected from age-related decline in certain verbal abilities.[370]

Jorm has noted that there is some evidence that brain size might be a protective factor for Alzheimer's disease.[14] The findings from one study have suggested that larger brain or head size appears to be associated with a reduced risk of Alzheimer's disease.[371] Another neuropathological study found that individuals who had Alzheimer's disease changes at autopsy, but were not demented during life, had bigger brains.[372] These findings have been replicated in the Nun study.[373]

There is also some evidence that premorbid, early life or childhood intelligence, as measured by a single test, is a better predictor of subsequent dementia than education.[343;374;375] Whalley and colleagues have reported that, in a large study which examined the records of intelligence test scores for children born in Scotland and tested in 1932, an association with poor mental ability in childhood was found with late onset dementia, which became significant by age 72 years.[92] (The authors have interpreted their data as support for the role of childhood mental ability in modifying the link between age-related brain changes and late-onset dementia. They have noted, however, that explanatory mechanisms are unknown, and that other factors, including environmental factors, which contribute to individual differences in mental abilities at age 11 years might also contribute to late-life differences in susceptibility.)

Education as acquired protection
Others have seen education as providing mental stimulation or an enriching experience.[26] Intellectual stimulation promotes brain growth in animals,[376] and it has been suggested that mental activity might modulate the natural history of neurodegenerative disease in humans, hence delaying the onset of dementia.[377] Education has been considered as building or enhancing a potential functional reserve, and suggested mechanisms include improved

neuronal networking,[359] or 'enhanced synaptic complexity',[358] and improved cerebral blood flow.[14] From this view, because of improved neuronal networks, people might continue to benefit from cognitive abilities, even when the neuronal networks begin to deteriorate due to the biological processes of dementia or decline.[359;366]

Support for the 'brain reserve' hypothesis
The findings from some neuropathological studies appear to support the 'education hypothesis'. The long term Nun study has found that lower idea density in early adulthood was associated with poorer cognitive functioning in old age, and was also related to Alzheimer's disease pathology in nuns who had died, findings which might support the role of premorbid intelligence, or cognitive ability and neurological development in early life.[354] Other findings from the same study have indicated that formal education seems to be associated with a delay in the expression of dementia, even in individuals with clear evidence of the pathology of Alzheimer's disease.[373] Another study has found an association between lower education and age-related cortical atrophy.[378] However, further longitudinal studies are felt to be needed.[354;378]

In addition, findings from the Seattle Longitudinal Study have indicated that the higher the base levels on a given ability, the more likely it is that significant decline will occur, (and that this inverse relationship appears to be strongest in the oldest age-group).[48] The more rapid decline in memory in Alzheimer's disease patients with higher educational (and occupational) attainment has been seen as lending support to the view that the discontinuity between the degree of pathology and the observed clinical severity is mediated through some form of protective 'reserve'.[379]

Implications for prevention
Protective interventions require an understanding of the processes underlying any possible association between lower educational level and late-onset dementia, and commentators have noted that such mechanisms are unclear.[347;359] The point has been made that the findings of an association between higher education in early life and a reduced risk of dementia or cognitive decline in later life might indicate that increased neuronal branching and connectivity related to learning are protective, or might mean that individuals with early higher intellect have 'further to fall'.[380] It has also been noted that people with a higher premorbid intellect might tend to seek more stimulating environments, which in turn might help to prevent a decline in cognitive skills.[381] Gatz, in reporting the problems in carrying out a twin study, has gone further, noting the difficulties in resolving a variety of alternative explanations of the meaning of 'low education'.[382] Gatz has concluded that any support for a 'cognitive reserve' hypothesis can only be equivocal. The point has been made, therefore, even if there is evidence for an inverse correlation between educational attainment and an increased risk of dementia, there is no clear lead to preventive action. One reason for this conclusion is that poverty – for which education may be a marker – may be associated with a number of potential 'risk factors'.[37]

SUMMARY

- Factors relating to social context or class have a significant effect on health and on the incidence of a number of disorders.
- Lower socio-economic status (as measured by income or occupation) has been linked to lower cognitive function in later life.
- Lower socio-economic status is known to be associated with an increased risk of vascular disease, and, hence, potentially with an increased risk of vascular dementia.
- Little is known, however, about the relationship between lower socio-economic status and the risk of cognitive decline or dementia. Few longitudinal studies examining social class or poverty as a factor have been carried out. In the US, education has been taken as a proxy measure of social class, but education can have a number of meanings.
- Occupation can be a marker for a number of factors, in addition to social class (e.g. exposure to toxic substances).
- Lower educational level is known to be associated with lower cognitive function later in life, but there has been little examination of the nature of this association, or of links with cognitive decline.
- There is evidence that lower educational level is associated with an increased risk of vascular dementia.
- The findings from studies examining links between lower educational level and an increased risk of dementia of all types or Alzheimer's disease are mixed. Some studies have found evidence of an association, but others have not.
- Education has often been taken as a measure of innate intelligence or mental stimulation, either or both of which have been viewed as serving to enhance 'brain reserve'. It has been suggested that brain reserve might protect the brain from degeneration, or might mitigate against the effects, hence delaying a diagnosis of dementia or cognitive decline.
- Because of the many meanings of education, implications for prevention are unclear.

CHAPTER FIFTEEN
PHYSICAL, MENTAL AND SOCIAL ACTIVITY

There has been increasing interest in the effect of personal and lifestyle factors on the development of age-related cognitive decline and dementia. This chapter examines the evidence for seeing physical activity, mental activity, social involvement and support, depression and stress, as risk factors or protective factors for cognitive decline and dementia.

It has been suggested that personal and lifestyle differences, as well as individual and cohort differences in adaptation, might explain some of the differences in the maintenance of cognitive function in old age.[48] The point has also been made that the effect on cognitive function of factors connected with retirement, for example, is unknown.[189] Keefover and Rankin have argued that a shift to a less demanding or stimulating environment with expectations of a less challenging role, as well as the loss of friends who can share activities, could represent a threat to cognitive vitality in old age.[26]

Factors such as physical, mental and social activity may be potentially modifiable to an extent,[50] although not necessarily by the individual. For example, if associations with the incidence of cognitive decline or dementia are confirmed, there might be important implications for social policy, relating to work-family relations and housing, as well as to retirement.[26;383] In investigating these risk factors, however, there can be particular difficulties in quantifying the 'strength of exposure', as well as in examining at what stage of life the factor might have most impact. Drawing conclusions about the relative importance can therefore be problematic.

PHYSICAL HEALTH, PHYSICAL ACTIVITY, AND PULMONARY FUNCTION

Physical health
The evidence for seeing certain disorders as 'risk factors' for dementia and cognitive decline has been outlined in previous chapters of this report. The effects of various factors classically associated with 'ill health' (and particularly those linked with vascular disease) have also been discussed. Some studies have taken a rather different approach, and have tried to examine whether 'physical health' itself, or fitness, might have a protective effect, particularly in relation to cognitive decline in later life.[384]

Reviewing the literature in 1991, Salthouse concluded that (contrary to intuition and popular opinion) there was little evidence that declines in cognitive performance associated with increased age were mediated by declines in health status.[385] Findings from an Australian cross-sectional study which examined a variety of subjective and objective health measures and a number of measures of intelligence and memory, have lent support to this view.[384] The authors have concluded that cognitive decline can be seen as largely due to neuropathology rather than to the secondary effect of other medical conditions.

On the other hand, Schaie, reporting the findings from the Seattle Longitudinal Study, has stressed that the absence of chronic disease is positively associated with the maintenance of intellectual abilities with age.[116] Similarly, the HOPE study in Edinburgh found that the decline in cognitive function over four years in healthy old people was non-significant.[106] The findings from another small study have indicated that, in the healthiest group, although lifetime risks of cognitive impairment are similar to the general population, onset is later.[386]

Ventilatory capacity or pulmonary function
Pulmonary function, as measured by the rate of forced expiratory volume in litres in one second (FEV1) has received considerable examination as an influence on cognitive function.[189] The Honolulu-Asia Aging Study (HAAS), which examined over 8000 Japanese-American men, found a significant positive association between FEV1 performance at baseline and cognitive performance 25 years later (i.e. better pulmonary function predicted better cognitive function).[387] White and colleagues have concluded that that low FEV1 should be seen as a potential risk factor for cognitive impairment.[189] They have noted that behaviour such as smoking and exercise can affect pulmonary function considerably, as can air quality, and have suggested that it is possible that accelerated ageing of the lung might predict accelerated ageing of the brain.

Physical exercise
Participation in physical activity has been associated with reduced risk of mortality, as well as with maintenance of functional ability among older people.[388] Since physical exercise minimises the risk of cardio-vascular incidents, high blood pressure and coronary heart disease,[388;389] such activity might be expected to reduce the risk of vascular dementia. It has also been suggested that, insofar as physical health influences cognitive function, physical exercise can be expected to contribute to this influence.[390] Conversely, a relatively sedentary lifestyle might contribute to a deterioration in cognitive proficiency.[26] It is thought that physical exercise can increase the blood flow to the brain, and that this might promote nerve cell growth.[50] Some studies of animals have shown that those which are physically active develop new neurones in the hippocampus, compared with inactive animals.[50]

The relationship between physical activity and cognitive decline in later life, in the long term, has been little examined.[26] However, some recent research, mainly in the US, has examined the effects on cognitive function or performance (in the short term) of current physical activity (mainly vigorous exercise), often in conjunction with mental activity,[391] or social activity.[392;393] One recent study, for example, found that mental tasks in executive control improved in a group of healthy older adults taking aerobic exercise compared with a control group.[394] Reviewers of the literature have noted that there is some evidence that,

in relatively healthy older people, sustained regular exercise might confer at least some protection against an age-related deterioration in reaction time (or the processing speed component of cognitive function),[26;390] but that there is insufficient evidence to base conclusions about the impact of physical activity on other cognitive processes.[26] Large, well-controlled longitudinal studies directed at identifying effective behavioural change for older adults have been called for.[390]

MENTAL STIMULATION AND ACTIVITY

Mental activity has been found to have an effect on cognitive function. Older adults living in the community have shown significant improvement in performance on a number of mental abilities, including various aspects of memory, inductive reasoning, spatial orientation and perceptual speed, as a result of relatively brief behavioural interventions.[395] It has been found also that older people who participate in activities that use cognitive skills, such as working memory and reasoning, are better able than non-participants to perform other tasks using similar skills.[26] These observations have lent credence to the view that you 'use it or lose it'.[26] Some commentators have argued that links between dementia and education (when seen in terms of mental stimulation) lend support to this view.[359]

The goals of intervention (mental stimulation or training) can be seen in terms of remediation (correcting a problem), enrichment or prevention of problems,[396] and there is interest in whether mental exercise in mid-life or in old age might protect against cognitive decline or even dementia. Reviewers of the literature have concluded that there is evidence that mental stimulation can help to improve memory performance, so that it is possible that such stimulation might help to preserve cognitive function or stave off decline in old age.[50;359] Orrell and Sahakian[359] cite the work of Yesavage,[397] which indicates that stimulation programmes may be effective in reducing memory problems associated with normal ageing. In addition, Schaie has reported that the findings from the Seattle Longitudinal Study (SLS) have suggested that high levels of motor-cognitive and attitudinal flexibility appear to be conducive to the maintenance of function in early old age.[48]

There is also some evidence from case-control studies of links between lower levels of mental activity in the recent and more distant past, and an increased risk of Alzheimer's disease.[136;391] Two longitudinal studies have reported similar results. Findings from the Nun study have suggested that frequent participation in cognitively stimulating activities was associated with a reduced risk of Alzheimer's disease,[398] and data from the Kungsholmen Project have indicated that physical activity, emotional/structural support and intellectual stimulation seemed to decrease the risk of dementia.[399]

Some commentators have argued, however, that caution should be exercised in ascribing causality, since people in the early stages of developing dementia might be less likely than others to be cognitively active or to take part in stimulating activities.[400] A recent report from the Einstein Aging Study went some way towards clarifying this issue by excluding individuals with possible preclinical dementia at the study baseline from their analyses.[401] The association between participation in 'cognitive leisure' activities and reduced risk of dementia persisted after these individuals had been excluded. Although further research

(e.g. controlled trials) is felt to be needed to establish whether increased cognitive activity can protect against Alzheimer's disease,[400] the point has been made that - while there might be much variation in the capacity to benefit - if mental stimulation could delay the onset of the clinical symptoms of dementia to any extent, it would be worthwhile.[359] It has been emphasised, however, that, in considering the feasibility of intervention, the reasons for the problem – such as memory loss – have to be established.[396] Hence, although training might offer remediation when older people have experienced decline, and enhancement when there was no decline, training might be ineffective where people have preclinical or mild dementia, since the condition is associated with a markedly reduced ability to acquire and recall new information.[395] (This difference in responsiveness to training interventions has been suggested as a way of differentiating between normal ageing and dementia.[402])

PSYCHOSOCIAL FACTORS

Until recently, the relationship between psychosocial factors and the development of cognitive decline and dementia had been little examined,[392] but as interest in risk factors has widened, these factors are receiving increasing attention.[25] In one early study in Sweden, Persson and Skoog investigated a number of 'psychosocial risk factors'.[403] Although the findings were preliminary, the authors have suggested that greater exposure to such risk factors in early life might contribute to the development of dementia in old age. There are questions about how psycho-social factors should be defined and measured, and which potential factors should be examined. Some studies have investigated social activity and support; others have examined psychological factors such as depression and stress.

Social activity, involvement and support

There is a wealth of data indicating that engagement in meaningful and productive activities, within the context of socially supportive networks, can have a protective effect on morbidity and mortality from many causes in later life.[383;404] Those reporting associations between mental activity and a reduced risk of cognitive decline and dementia have often speculated on the protective role of social activity or involvement. The association has been seen as biologically plausible, since interactions between mother and infant rodents have been found to influence cognitive decline and hippocampal cell loss in later life.[383] In humans, early work on enriched environments showed that increasing social interactions, as well as dealing with a complex physical environment, can lead to improved cognition, and more recent work on neuronal recovery has similarly indicated the critical role of social environment.[383] A number of recent studies have extended findings about marital status and living arrangements to examine the putative role of social activity, social involvement, networks and support in reducing the incidence of cognitive decline and dementia.[383]

Findings from the MacArthur Study of Successful Aging in the US have indicated that staying in close touch with people and remaining involved in meaningful activities predicted 'successful ageing',[404] a large part of the definition of which was in terms of cognitive success.[50] Greater baseline emotional support was a significant predictor of better cognitive functioning at a 7.5 year follow-up, controlling for baseline cognitive function and known sociodemographic, behavioural, psychological and health status predictors of cognitive ageing.[25] In a review of the literature on cognitive decline, Keefover and Rankin

have concluded that the complexity of the environment appears to have a proportionately invigorating influence on intellectual proficiency, even in later life.[26]

Findings from some recent longitudinal studies have suggested that social involvement might also protect against dementia. Data from the PAQUID study in France indicated that regular participation in social or leisure activities was associated with a lower risk of subsequent dementia.[393] Similarly, findings from the Kungsholmen project in Sweden have suggested that a poor or limited social network might increase the risk of dementia, though the authors have noted that risks rose substantially only where there were no close ties across several domains.[405] Diversity of relations appeared to be critical.[383] A US study also found that the risk of dementia was decreased in subjects with high leisure activities.[392]

Berkman has concluded that the recent findings are consistent and potentially important, although causal mechanisms may be unclear.[383] One view is that it might be plausible that social engagement could promote cognitive health, since the challenge of participating in complex personal exchanges might contribute to a protective 'reserve'.[383;392] Reviewing the literature, Jorm has concluded that there is some evidence, from both psychological and physiological studies, that activity in general - during old age rather than over the life span - may have some preventative effects on both cognitive decline and dementia.[343] A lack of physical, mental and social activity could have a negative impact on mental health.

Nevertheless, commentators have noted that questions remain unanswered, and that longer follow-up periods are needed for several reasons: to confirm the findings, to investigate at what point in life the effect of social interaction is important, to clarify protective mechanisms, and also to ensure that social withdrawal is not influenced by cognitive decline.[383] It has been demonstrated, for example, that people with dementia have less contact with friends, neighbours and community groups than do non-sufferers,[406] and it has been noted that this group may also be more likely to exhibit symptoms of depression.

Psychological factors: depression and stress

Some studies have examined the links between dementia or cognitive decline, and depression, psychiatric history more generally, and stress. Snowdon has explained that research carried out at the Mayo clinic, Minnesota (US) has found that an optimistic or positive outlook is associated with longevity. Findings from the Nun study, although the data is limited, have appeared to confirm this association.[88]

Depression

Depression may be associated with significant cognitive deficits, and may be a feature of, or an early sign of Alzheimer's disease.[407] There has been interest, however, in whether depression earlier in life could be a risk factor for subsequent dementia or cognitive decline.[14;56;408]

Cognitive impairment often co-exists with depression. One view is that mood exerts an effect on cognitive proficiency,[26] but there are contradictory views about which condition should be seen as primary.[407] Both conditions are generally seen as reversible. Although some commentators have stated that neither depression, nor the cognitive conditions

sometimes associated with depression, are age related,[26] others have argued that vulnerability to depression, like cognitive impairment, increases with age.[51]

There is some evidence that previous psychiatric history can be associated with an increased risk of late life dementia,[409-412] although not all studies have found this.[413] A recent study of twins has suggested that a history of psychiatric illness, especially depression, may be associated with an increased risk of Alzheimer's disease,[414] and a meta-analysis of early case-control studies found that people with late-onset Alzheimer's disease were more likely to have had a history of medically treated depression (although no association was found with either anti-depressant treatment or adverse life events).[415] The findings from prospective studies have been mixed, with some finding that depression pre-dates dementia or cognitive decline and others not.[14] One meta-analysis, however, found that depression was associated with an increased risk of subsequent dementia and cognitive decline in both case-control and prospective studies.[408] Jorm has noted that, in general, the duration of follow-up has not been long enough to rule out depression as a clinical feature of the disease, but has concluded that there is sufficient evidence to take seriously the possibility that depression is a risk factor for dementia and cognitive decline.[408]

A number of possible explanations have been suggested, including a common biological basis of vulnerability to depression and cognitive disorders,[51] links with dietary factors,[51] overlapping neuropathology,[14] or mild cognitive deficits with depression lowering the threshold for the clinical manifestation of Alzheimer's disease.[14] In a comprehensive review of the epidemiological evidence from case-control and prospective studies, Jorm has considered six hypotheses: (1) depression treatments are a risk factor for dementia, (2) dementia and depression share common risk factors, (3) depression is a prodrome of dementia, (4) depression is an early reaction to cognitive decline, (5) depression affects the threshold for manifesting dementia, and (6) depression is a causal factor in dementia.[408] He has concluded that there is limited support for hypotheses 3, 4, 5 and 6, which warrant further research.

Stress

Stress and key hormones secreted during stress are now viewed as being relevant to many aspects of health. For example, in old age, the stress response may be directly linked to heart attack or stroke.[41] The work of Sapolsky has shown that glucocorticoids (the adrenal steroids secreted during stress) can have adverse effects on the nervous system, if secreted in excess.[416;417] This evidence mostly relates to rodents, but there is evidence that, in humans, chronic stress can impair mental performance, and that prolonged exposure to stress hormones (e.g. cortisol) has an adverse effect on the hippocampus.[50;416] Chronic stress is known to contribute to depression and anxiety disorders, conditions which interfere with normal memory processing, particularly – perhaps - as people age.[50] Stress has also been associated with factors such as high blood pressure.[112] Another suggested mechanism is that high levels of cortisol could damage the immune system, which may be involved in brain ageing. There is a view that ageing is best seen in terms of a loss of adaptive capacity, and that the responses of older individuals to stress are greater than those of younger people.[41] Persson and Skoog have suggested that observed associations between psychosocial risk

factors and the development of late onset dementia found in a Swedish study could be explained by stress as a possible link (although they have acknowledged that other interpretations are possible).[403] On the other hand, a study of former World War II prisoners-of-war found no evidence that they were at increased risk of Alzheimer's disease, despite their higher prevalence of anxiety and depressive disorders decades after the war.[243]

SUMMARY

- Research is beginning to examine relationships between physical, mental and social activity – in mid-life and in old age – and the incidence of cognitive decline and dementia. If associations are found, there may be implications for social policy, e.g. in relation to retirement.
- The findings from some studies have indicated that the maintenance of cognitive function in old age is associated with good physical health. Other research has not found this, however.
- There is some evidence that pulmonary function (FEV1) in mid-life predicts cognitive function in old age, although the mechanisms are unknown.
- Physical exercise has been linked with a reduced risk of vascular disease. However, links with the incidence of cognitive decline and dementia have been little examined by research.
- There is some evidence that mental activity can enhance or maintain cognitive function, or protect against a degree of decline, although there are wide variations. Further research is felt to be needed to establish whether cognitive activity could protect against long-term cognitive decline or dementia.
- There is also some evidence that social activity, involvement and support can help to maintain cognitive function. Preliminary findings which suggest a reduced susceptibility to dementia are felt to warrant further investigation.
- Although there is some evidence that some forms of 'activity' seem to have a preventive effect on cognitive decline, caution has been expressed about ascribing a protective role to 'activity', since those experiencing cognitive decline might be less likely to be active.
- There is felt to be enough evidence to take seriously the possibility that depression is a risk factor for dementia and cognitive decline.
- There has been increasing interest in the role of stress in cognitive functioning, because of the link with stroke, because prolonged exposure to a stress hormone (cortisol) is known to affect mental performance, and because ageing can be viewed in terms of a loss of adaptive capacity.

PART THREE
DISCUSSION AND CONCLUSION

CHAPTER SIXTEEN
DISCUSSION

This chapter summarises the findings from research examining risk factors for dementia and cognitive decline. It considers what the evidence suggests about the nature of dementia and cognitive decline and the relationship between the two. The limitations of existing research are discussed, as well as some limitations and critiques of the focus on primary prevention. Starting from the concept of 'healthy ageing', the chapter considers the feasibility of 'compression of morbidity'. It concludes by outlining the conclusions that can be drawn about public health strategies for preventing dementia and cognitive decline.

Research examining risk factors for dementia, particularly Alzheimer's disease, is being carried out in a number of countries. Early work consisted of case-control studies, but large longitudinal studies, some multi-centre, are now ongoing, and results are beginning to emerge. Risk factors are generally seen in terms of possibility or probability, since it is recognised that they do not operate in isolation. There may often be no single cause of dementia or cognitive decline, therefore, and no single 'solution'. Where epidemiological and other research has indicated the putative protective role of certain interventions (e.g. reduction of hypertension, vitamin supplements, NSAIDs), clinical trials are beginning to examine whether there are benefits for people with mild cognitive impairment, or who are asymptomatic. There is an increasing interest in examining risk factors for cognitive decline.

In considering what the findings from research indicates about possible strategies of 'prevention', a number of key questions have still to be answered. These include: What weight should be given to specific factors, such as age? How do the findings from research relate to, or add to, hypotheses about causal mechanisms or processes? What does research evidence suggest about the nature of cognitive decline and dementia and the relationship between the two? To what extent is modification of specific risk factors feasible or ethical? When might intervention measures be appropriate? This chapter addresses these questions, after summarising the findings from existing research.

SUMMARY OF RESEARCH EVIDENCE: RISK FACTORS FOR DEMENTIA AND COGNITIVE DECLINE

Risk factors for cognitive decline

Cognitive function declines with age, although such decline is not inevitable and not always progressive. A range of risk and protective factors has been examined by research. There are differing views about the extent to which physical health should be seen as protective, with some studies finding that the absence of chronic disease is associated with the maintenance of intellectual abilities with age,[116;404] but others not.[385] Small has summarised the risk factors identified by recent research as follows: genetic factors, female sex, APOE 4 genotype, medical co-morbidities, hypertension, heart disease, diabetes, elevated low-density lipoprotein cholesterol level, elevated homocysteine level, transient ischaemic attacks, head trauma, environmental exposure to toxins (particularly lead), lifestyle choices, smoking, substance abuse including alcohol and illicit drugs, psychological /psychosocial factors, low educational achievement, lack of physical activity, lack of social interaction / leisure activities, excessive response to stress (elevated cortisol levels).[50] From a psychological perspective, findings from the Seattle Longitudinal Study have suggested that protective factors include: living in favourable economic circumstances, involvement in complex or intellectually stimulating activities, higher levels of education, a flexible personality in middle age, having a spouse functioning at a high level of cognitive abilities, maintenance of high levels of perceptual processing speed, above average success in life, high satisfaction with accomplishments and a perception of intellectual competence.[116]

In relation to strategies of prevention, lifestyle measures, such as stress reduction, physical activity, healthy diet, mental activity and psychosocial activity, have been recommended, rather than unproven treatments or large doses of supplements, since age associated cognitive decline is not seen as a disease.[50;51;376;418] Small has concluded that, 'what is healthy for the body is healthy for the brain',[50] and the Institute for the Study of Ageing and the International Longevity Center, USA have offered the following recommendations:[376;418]

- Pursue lifelong learning and memory training
- Engage in physical activity
- Keep working at a job and/or participating in social activities
- Practice stress reduction techniques
- Get help for sleeping disorders
- Seek treatment for depression
- Maintain a nutritious, low fat diet
- Effectively control medical problems such as high blood pressure, diabetes and high cholesterol.

Risk factors for vascular dementia

Some vascular dementia might be preventable to the extent that susceptibility to cerebrovascular disease can be modified, whether by public health measures or by management of putative risk factors and the promotion of potential protective factors. The control of hypertension (above certain limits, and taking care to avoid hypotension) by

medication is now accepted, and has been shown to be effective in the primary prevention of cerebrovascular disease for those at high risk.[20;28;66] At the same time, lifestyle changes which lower blood pressure have been seen as advisable at all levels of blood pressure, across the population as a whole.[66]

Risk factors for dementia of the Alzheimer type

Dementia of the Alzheimer type is generally seen as a multi-factorial syndrome, whose risk factors are ubiquitous.[56] Reviewers of the epidemiological literature have concluded that, at the moment, the only risk factors for Alzheimer's disease confirmed beyond reasonable doubt are old age, a family history of dementia (particularly for early onset dementia), Down's syndrome and the APOE 4 genotype.[14] There is recent evidence of an association between vascular disease and its factors and the risk of Alzheimer's disease.[12] The evidence for other risk or protective factors is felt to be inconclusive and to need further investigation,[37;56;133] and it has been suggested that other causal factors may remain to be identified.[62] Cross-cultural studies and trends over time have yielded few clues.[56] The mechanisms underlying the development of dementia of the Alzheimer type are not yet understood,[61] and some commentators have argued that examining interactions between factors (e.g. genetic and environmental) might offer the best hope of understanding the aetiology.[56]

None of the known risk factors for Alzheimer's disease is felt to give scope for preventive action.[14] Also, because of the links with age and – perhaps - genetic factors, the potential for primary prevention may always be relatively limited. Research suggests that it would be prudent to avoid - where possible - head injury, a deficiency of folate or vitamin 12 (which can result from a high alcohol intake or from malnutrition), and an excess of cholesterol, although the nature of the connection between these and other candidate 'risk factors' and Alzheimer's disease remains unclear. However, the association with vascular factors suggests that some dementia of the Alzheimer type might be preventable to an extent. Clinical trials of potentially beneficial interventions are felt to be worthwhile.

THE NATURE OF DEMENTIA AND COGNITIVE DECLINE

The causal mechanisms underlying the development of dementia and cognitive decline are not fully understood, but there is increasing knowledge about changes in the brain associated with ageing,[41] or with biological mechanisms. Cognitive research examining decline, and epidemiological studies of risk factors, have been seen as usefully adding to knowledge about what is 'normal' and 'pathological' ageing,[26;395] and about the nature of cognitive decline and dementia. The point has been made, for example, that evidence from empirical work shows that the idea of a dichotomy between vascular dementia and Alzheimer's disease is no longer tenable.[19]

There is a continuing debate about the nature of cognitive decline, and about the relationship with dementia. One question concerns whether cognitive decline and dementia should be seen as part of a continuum or as different conditions; i.e. to what extent are there similar or distinct processes involved – one leading to slow decline and the other to severe decline?[42;44;49;395] It has been suggested that, if Alzheimer's disease can be seen as an extreme variant of normal ageing, then the focus of study should be on the ageing process, rather than on disease.[41]

One view is that dementia is a disorder distinct from cognitive decline. Christensen and O'Brien have noted that there is evidence, although it is not conclusive, to suggest that the deficits in dementia might be qualitatively, as well as quantitatively, distinct from those in normal ageing.[44] Age-related cognitive decline takes place across various domains, whereas in Alzheimer's disease there is a sequential decline across specific cognitive domains.[55] Some cognitive decline can be avoided or remedied with training, but dementia is not amenable to these measures.[395]

On the other hand, a number of commentators have claimed that the processes leading to dementia can be seen as similar to, although more severe than, those resulting in cognitive decline.[19;44;55] Brayne and colleagues have suggested that the evidence which shows that cognitive decline, like dementia, becomes increasingly common with advancing age, indicates that dementia may be regarded as one extreme of the continuum of cognitive decline.[85] In a similar way, Willis has argued that, since the earliest decline in both normal age-related decline and pathological ageing occurs with respect to the higher-order executive level abilities (fluid and crystallised intelligence), and since the proportion of older adults experiencing decline in these abilities increases with age (even though there is evidence of wide individual differences),[402] the relationship can be seen as hierarchical.[395] Christensen and O'Brien have concluded that the findings from risk factor research have suggested that, except for rare, early-onset cases of dementia (involving specific single genes) there is no clear evidence that the risk factors associated with Alzheimer's disease are not also predictors of normal ageing.[44] In their view, dementia could, therefore, be seen as the final stage of 'normal' biological ageing.

LIMITATIONS OF RESEARCH

A number of commentators have drawn attention to some limitations of epidemiological research examining risk factors. Since the findings are not just of academic interest, but might suggest ways in which the onset of dementia or cognitive decline might be delayed or even prevented, it has been emphasised that the evidence must be adequate.[11;19] Methodological shortcomings of early case-control studies, such as the low statistical power and the possibility of bias,[56;62] have been noted earlier in this report. Large longitudinal studies are now ongoing, and the point has been made that early suggestions about factors could be superseded as more understanding is gained.[11]

Reviewers of the literature have stressed that findings from empirical work so far have tended to highlight how much remains to be understood. Hence, there is felt to be considerable scope for further research, both in the sense of 'factors' that might be examined, and in research questions. Dementia is often seen as having multiple causes, and it has been suggested that possible interactions between risk factors, including genetic, environmental and vascular factors, should be investigated.[11;19;56] More work is also felt to be needed in quantifying risk, particularly genetic risk.[19;56] Commentators have pointed out that the findings from research, together with new technological possibilities, raise a number of new questions, such as – for example - how much of the risk of Alzheimer's disease is due to genetics, age or other factors, and hence how much risk is modifiable.

Existing empirical work has largely been carried out from medical and epidemiological perspectives, and there has been little examination so far of environmental factors such as social class or poverty. There may be links between socio-economic status and other factors, such as diet or education. If social factors were found to be important, then the implication is that approaches to 'prevention' should include social or structural change.

The findings from current research are also limited in the sense that few conclusions can be drawn about causality, or about methods of prevention. Several commentators have emphasised that, since there might be various ways in which the findings from epidemiological research could be interpreted, and since the processes underlying the development of dementia and cognitive decline are not fully understood, care should be taken in ascribing causality.[43;61] There continue to be many gaps in knowledge and unanswered questions. Little is known about the nature of dementia and cognitive decline, and the nature of ageing, about causal mechanisms of decline, or about the effectiveness of interventions.

LIMITATIONS AND CRITIQUES OF A FOCUS ON PRIMARY PREVENTION

There have also been critiques of a focus on 'risk factors' and primary prevention strategies, although from a number of perspectives. Some commentators have criticised an over-emphasis on individual, or biological 'risk factors'. There are concerns, for example, about an over-emphasis on genetic explanations for the causes of disease (or 'genetic determinism'). One BMJ editorial has emphasised that the main contributors to disease or impairment - malnutrition, poor water and sanitation systems, unsafe sex, tobacco and alcohol, physical inactivity, occupation, drug misuse, and air pollution – are unlikely to be affected by knowledge of genetics.[419] From this view, a recourse to 'simplistic' genetic explanations can marginalise more difficult – often political – questions, which are relevant to public health.[419] Others, on the other hand, have argued that the growing evidence that genetic factors are involved in disease expression has served to strengthen support for a specific biological aetiology, hence focusing attention on individual, biological factors, rather than those which are social or environmental.[420] Gilleard and Higgs have contended that a focus on 'types' of dementia, and on the family history of Alzheimer's disease, has provided the beginnings of a notion that there are people 'at risk' of the condition.[420] Individual risk factors can imply individual blame, and Katzman, for example, has argued that a discussion of risk factors should focus on populations, rather than on individuals.[39]

A search for risk factors associated with dementia has also been criticised for promoting the view that a primary prevention strategy (i.e. by modifying risk) is realisable, whether by lifestyle management or by medical intervention, thus omitting any consideration of the role of age in disease causation.[94;420] Some have seen dementia as an almost inevitable corollary of ageing. For example, Blumenthal has noted that the production of amyloid (which is implicated in dementia, diabetes and myocardial fibrillation) is a phenomenon prevalent in old age.[94] He has argued that strategies based on risk factors will not eliminate the diseases of senescence, since the same or other diseases will later emerge.

Another argument is that the very laudable attempts to publicise the risk of dementia, and to investigate risk factors, may have the effect of creating anxiety and fear of dementia

among older people and informal care-givers.[421] It has also been suggested that the increasing interest in links between cognitive decline and dementia may result in the stigmatisation of those with mild cognitive impairment, and the pathologising of this condition (which is not necessarily progressive).[422]

Finally, some have argued that a focus on primary prevention involves a shift in priorities away from those affected and from service provision.[94;420] An epidemiological approach has been seen as diverting attention from the fact that an increasing prevalence of age-related disorders might imply a greater provision of care, whether in terms of treatment (secondary prevention) or improved support to ameliorate social and psychological as well as biological effects (tertiary prevention).

PUBLIC HEALTH, HEALTHY AGEING AND THE COMPRESSION OF MORBIDITY

With increasing longevity and a predicted rise in the numbers of older people, there is concern to find ways in which the health of older people might be maintained for longer, both for their own sake and for more general benefit. Questions about the extent to which the goal of 'healthy ageing' is possible and – if so - how this might be achieved, have raised wider questions about how and why individuals age, and about the relationship between ageing and disease. Healthy ageing might come about or be achieved 'naturally' or through 'strategies', and by various means, such as by changes to the environment or to behaviour, or by interventions such as treatment.

There has been interest in whether ageing itself might be slowed,[16;41;423] but also in the extent to which ageing might be separated from disease. If the rate of disease progression could be slowed and/or the onset of disease occurrence delayed or prevented, this could result in 'healthy ageing' or 'compression of morbidity'.[424] Individuals would have the same life expectancy, but they would remain healthier for longer. On the other hand, it has been pointed out that measures to improve health might, instead, extend life expectancy, leaving the period of morbidity unchanged,[16] or even lengthened.[37] A more pessimistic scenario is that other current trends, such as increasing alcohol consumption or obesity, might serve to increase the risk of disorders, resulting in a lengthened period of morbidity. At the moment, the potential for the 'compression of morbidity' is largely unknown.

PUBLIC HEALTH STRATEGIES FOR PRIMARY PREVENTION

'Healthy ageing' can have a number of dimensions. Fillitt and Butler have argued that, in line with the current emphasis on preventive medicine and health maintenance, one goal (which would be reflected in health programmes) ought to be the promotion of robust cognitive health in later life.[425] There is general agreement that – despite concerns about priorities, about raising anxiety, and about feasibility - it is right and important to try to delay the onset, or prevent the occurrence, of dementia and also cognitive decline, by primary precention methods, and to allocate resources to investigate risk factors.[42;386] If there are risk factors that are modifiable, and if the means of modification are known, then some prevention of dementia, by primary prevention measures, may be feasible.

In moving from a knowledge of risk factors to considering primary prevention strategies, however, there are important practical and philosophical issues to be taken into

account.[11;19;36] These include: How certain is it that an intervention will lower risk? To what degree? To all equally? To whom might intervention be beneficial, rather than harmful? When might intervention be most beneficial? To be beneficial, any intervention should be effective in modifying risk and – perhaps – cost-effective. Interventions should also be feasible and acceptable. How might benefit, feasibility and acceptability be measured? Whose responsibility is it to reduce risk – since there may be implications for individuals, for policy-makers and public health, or for both?[19] (For example, what is the best way to lower vascular risk?) What are the implications for ethics and human rights?[19]

Since the anticipated benefit of any intervention, or prevention strategy, must outweigh possible harm, there are a number of ethical issues to be considered.[11] First, the evidence base must be adequate. There are also issues of safety. Any intervention may have consequences or side effects and hence may carry a risk. In relation to primary prevention measures, there are concerns about prescribing – or offering - medication for people who are healthy or asymptomatic.[11] In addition, knowledge of increased risk might be of questionable benefit, especially if information is uncertain or not easily understood, or if no effective treatment is available. Screening can provoke anxiety. Concerns have also been expressed about confidentiality, especially about the way that genetic information could be used.

Views about the importance of 'prevention', about priorities, or about definitions of a problem, can differ between individuals or groups, and can conflict even within individuals. Interventions must be voluntary, and different individuals might judge benefit, risk and harm in different ways. The point has also been made that ideas about what is important can be cultural, as well as individual; they can be specific to a generation and can change.[396] For example, as noted earlier, there are questions about the effectiveness of health promotion campaigns in changing behaviour, and about the acceptability of screening, e.g. for vascular risk factors.

Strategies for primary prevention are based on either 'population' or 'high-risk' approaches.[37] They include lifestyle change, reduction in exposure to risk, 'treatment' (e.g. medical and dietary supplements), vaccination and family planning. What does the evidence from studies of risk factors suggest about the scope for reducing the incidence of dementia or cognitive decline by primary prevention methods?

WHAT IS THE SCOPE FOR THE PRIMARY PREVENTION OF DEMENTIA AND COGNITIVE DECLINE?

Population-based strategies

There is little evidence of differences in risk between different populations, which might suggest environmental factors or protective measures. In relation to limiting exposure to hazards in the physical environment, evidence does suggest that any workable measures to reduce brain injury or head trauma could be useful, although the numbers affected are small.[37] There is no evidence to support measures to limit exposure to toxins in the environment. Findings of studies examining education do not lead to any suggestions for prevention, partly because of the different meanings of 'education'. Although socio-economic status has been linked with health status, as yet there has been little examination of links with dementia and cognitive decline.

There is a body of research connecting a 'healthy lifestyle' (stress reduction, avoidance of harmful stimulants, exercise, a diet low in cholesterol and high in vitamins, maintenance of social activity) with protection against chronic disabling disease generally.[50] Such a lifestyle is being promoted for everyone, and has been advocated for older people.[376;418] (Older people may be seen as a 'population'.) There is some evidence that elements of a 'healthy lifestyle' might offer some protection against age associated cognitive decline. Also, to the extent that elements of a healthy lifestyle protect against vascular disease, there is evidence to suggest some lowering of the risk of vascular dementia, and perhaps dementia generally. There is also some evidence to link low alcohol consumption, and a diet adequate in vitimanins and (perhaps) rich in fish oil with a reduced risk of dementia. However, there is a general problem with suggesting protective measures such as dietary changes or supplements (and of course medication or vaccination) because of the possibility of harm. Hence measures such as oestrogen and NSAIDs cannot be recommended. Debates about individual versus social responsibility are particularly relevant in considering population-based measures of prevention.

Strategies targeted at 'high-risk' groups

Research examining risk factors has suggested the possible benefit of certain protective measures targeted towards specific 'high-risk' groups. For example, dietary supplements may be beneficial for those with hyperhomocysteinaemia, statins may be beneficial for those with high cholesterol, and anti-hypertensive medication may be beneficial for those with high blood pressure. Although at the moment, the evidence about whether, and if so to what extent, such 'protective' measures reduce the risk of dementia (or long-term cognitive decline) is limited, all of the above interventions (along with NSAIDs) have been felt to be worth further investigation by clinical trials.

Cooper (p898) has suggested that high-risk measures might focus on "a strongly positive family history and the presence of medical conditions known to be associated with brain pathology".[37] Individuals with certain genetic mutations constitute 'high-risk' groups, although - because genetic make-up is not modifiable - the only potential preventive strategy at the moment rests on the possibilities presented by vaccination. However, if in the future genetic polymorphisms are found to interact with other modifiable (biological or environmental) risk factors, there may be possibilities for targeted intervention measures. Other high-risk groups, and appropriate interventions, may be indicated by further research (e.g. into links between depression and dementia). People experiencing cognitive decline may also be at higher risk of dementia, although in this case, interventions have been in terms of secondary prevention.[37] The issue of whether 'older people' should be seen as a 'high-risk' group raises a number of questions; for example, at what age might 'risk' be felt to be increased, or might intervention be appropriate.

Questions have also been raised about how those at 'high-risk' might be identified, and about the feasibiloity and acceptability of screening, which might form part of the preventive method. These concerns about screening (e.g. for vascular risk) have been noted earlier in this report. At the moment, APOE genotyping may not be used for screening for Alzheimer's disease,[19;41] although some commentators have predicted that, despite ethical concerns, there will eventually be susceptibility testing (of people who are asymptomatic).[42]

Regarding the prospects intervention (either for drug therapy or for the modification of risk of dementia), Eastwood and colleagues have argued that, in considering what can be learned from clinical trials, there are a number of difficulties in study design to be resolved.[19] For example: Should the primary outcome measures to judge efficacy be in terms of function or imaging? How should the likely size effect of a given treatment be estimated? How should the study population be stratified? How should the issue of informed consent be addressed? These authors have suggested that there should be a first stage of smaller exploratory trials to gather data on efficacy, driven by hypotheses generated from longitudinal surveys, followed by larger, more pragmatic trials, which will have wide inclusion criteria and which will look at effectiveness, acceptability, compliance and cost. Their view is that the latter might not be warranted for some time.[19]

When might intervention measures be appropriate?

Any intervention measure to prevent the occurrence of a condition or delay its onset can only be effective when there is the potential for change, whether this is in terms of modifying risk or arresting the disease (or ageing) process. In the case of dementia, it is widely felt that, by the time clinical symptoms are apparent, it may be too late for any measures of prevention to be effective.[41] They will be more likely to succeed when the process of neurological deterioration is in its early stages.[61] However, the 'early stages' at which it might be felt right or beneficial to intervene have not yet been identified, since the mechanisms by which dementia develops, and when risk factors operate, are still largely unknown.[42;61]

There is some evidence that certain risk factors, measured in mid-life, predict later cognitive decline, and some have suggested that the degenerative processes may begin in mid-life.[426] For example, the 1998 Alzheimer's Association Research Grants Program has noted evidence that initial neurodegenerative changes of Alzheimer's disease can occur up to 40 years before the first clinical symptoms appear.[42] (The focus of their research programme is on early detection, with the purpose of delaying the onset of symptoms for those at high risk.) With the 'baby-boomer' generation approaching retirement, interest has focused on whether there are interventions in mid-life which might avert or delay the onset of dementia and cognitive decline. It has been suggested that the prevention of Alzheimer's disease ought to be a concern of middle-aged people.[42]

SUMMARY

- Cognitive function declines with age, although such decline is not inevitable and not always progressive. A 'healthy lifestyle', and measures to mental and social, as well as physical health, have been recommended as potentially protective against cognitive decline.
- The risk factors for vascular dementia are relatively well understood; these include cerebro-vascular disease and risk factors for vascular disorders. The risk of vascular dementia may be reduced by lowering the risk of vascular disease, e.g. through the control of hypertension.
- At the moment, the only risk factors for Alzheimer's disease confirmed beyond reasonable doubt are old age, a family history of dementia (particularly for early onset dementia), Down's syndrome and the APOE 4 genotype. The evidence for other risk factors is

inconclusive. None of the known risk factors for Alzheimer's disease is felt to give scope for preventive action. Also, because of the links with age and – perhaps –- genetic factors, the potential for primary prevention may always be relatively limited. However, an association with vascular factors suggested by recent research has caused the dichotomy between vascular dementia and ('degenerative') Alzheimer's disease to be questioned, and has indicated that there may be some scope for prevention.

• Although the causal mechanisms underlying the development of dementia and cognitive decline are not fully understood, with increasing knowledge about the brain and the findings from epidemiological studies of risk factors, progress is being made. There is felt to be considerable potential for further research.

• Evidence suggests that there is often no single cause of dementia or cognitive decline, and hence no single solution, but that there may be some limited scope for intervention. Clinical trials of potentially benefical interventions are felt to be worthwhile.

• One key issue may be the relationship between age-related cognitive decline and dementia. Some commentators (although not others) have suggested that the evidence from risk factor research tends to support the view that cognitive decline and dementia of the Alzheimer type should be seen as a continuum rather than as qualitatively different conditions. If this is the case, then changes associated with ageing are of interest.

• Reviewers of the literature have noted a number of limitations of current research. It has been emphasised that the evidence base must be adequate before considering strategies of prevention.

• Some environmental risk factors, particularly social class, have been little examined by research.

• A focus on primary prevention has been criticised for an over-emphasis on individual and biological 'risk factors', for promoting the view that such prevention strategies are feasible and ignoring the role of age, and for increasing anxiety and pathologising mild cognitive impairment. A focus on primary prevention has also been seen as shifting priorities and diverting attention from solutions of care and the needs of those affected.

• One approach to a public health goal of 'healthy ageing' is to consider the extent to which 'compression of morbidity' is achievable, by delaying the onset of certain conditions or preventing their occurrence.

• In moving from knowledge about risk factors to strategies of intervention, there are a number of practical and philosophical issues to be taken into account. These include questions of ethics, responsibility, feasibility and acceptability.

• At the moment, targeted strategies (based on 'high-risk' groups) seem to offer more potential than those based on populations, with the further investigation of potential protective measures felt to be worthwhile. Questions remain about screening as a method of identifying those at high risk.

• An important issue is when strategies of intervention might be most effective or beneficial. Some evidence that 'mid-life' risk factors may predict later cognitive decline, and that initial neurodegenerative changes of Alzheimer's disease may occur up to 40 years before the first clinical symptoms, suggests that mid-life preventive measures might be worthwhile.

CHAPTER SEVENTEEN
CONCLUSION

Given the increasing numbers of older people in most western populations, there is concern about the anticipated rise in the prevalence of ageing-related disorders such as dementia. It has been predicted, for example, that by 2040 one in every fifty people in Scotland could be living with this disorder. At one time, dementia and cognitive decline were seen as inevitable consequences of ageing. Now, however, as more is known about ageing and about the brain, possible means of prevention are being investigated. Although treatment may slow the progress of dementia some cases, the condition cannot be reversed or cured. There has been growing interest, therefore, in finding out whether there are ways in which the incidence (as well as the prevalence) of dementia might be reduced, since delaying the onset could dramatically reduce the numbers affected.

Although little is known at the moment about the mechanisms which result in cognitive decline and dementia, or about when the degenerative processes begin, progress is being made. Considerable research efforts are being expended in investigating possible methods of prevention. Epidemiological studies across the world are investigating possible risk and protective factors for dementia (especially Alzheimer's disease), and more recently cognitive decline. The findings from large longitudinal studies and clinical trials are beginning to emerge, although many of the conclusions are tentative. Some intervention trials have been instigated.

Cognitive decline is not always progressive, and some research findings have indicated that a 'healthy lifestyle', and measures to maintain physical, mental and social health might be beneficial in maintaining cognitive function in later life, at least in the short term. Risk factors for vascular dementia are relatively well understood, and some dementia with vascular causes may be preventable by reducing the risk of vascular disease by the control of hypertension. At the moment, the only risk factors for Alzheimer's disease confirmed beyond reasonable doubt are old age, a family history of dementia, Down's syndrome and the APOE 4 genotype. The evidence for other risk factors is inconclusive. However, an association with vascular factors has been suggested by recent research, suggesting that there might be some scope for prevention. At the moment, none of the known risk factors

for dementia of the Alzheimer type is felt to give scope for preventative action. Also, because of the relative importance (it seems at the moment) of age and – perhaps – genetic factors, it may be that the possibilities for primary prevention of Alzheimer's disease by reducing risk will always be limited (compared with cardio-vascular disease, for example). Nevertheless, clinical trials of potentially beneficial interventions are felt to be worthwhile.

The conclusion to be drawn from a review of the literature, therefore, is that at present there are very few immediate prospects for effective action to reduce the incidence of dementia in Scotland, particularly dementia of the Alzheimer type. However, prospects may be beginning to improve. Research into risk factors and potential interventions is ongoing, and there is much that remains to be investigated. For example, a number of environmental factors, such as social class or poverty, have been little examined as yet. More factors may be found, and much more will be learned about – for example - the relative importance of different factors, the ways in which and the extent to which these factors interact, and the extent to which they can be modified. Progress is being made. The hope is that new knowledge, together with the increased understanding about ageing and the brain, will contribute to a better understanding about the nature and the causes of cognitive decline and dementia. This in turn may suggest possible methods of primary prevention.

Research findings tend to suggest that there is no one single 'cause' of dementia or cognitive decline and, hence, that there is no one single 'solution'. Age is an important contributory factor, so that – unless ageing itself can be slowed – there is a limit to the extent to which dementia and cognitive decline can be prevented altogether. At the same time, the findings from research suggest that there are ways in which some risk might be reduced; there is some scope for action. Measures to reduce the risk of vascular disease and stroke, such as management of hypertension, avoiding excess cholesterol, stopping smoking, taking moderate exercise, as well as reducing poverty, can help to reduce the risk of dementia of vascular origin. It would also be prudent to avoid, where possible, severe head injury and nutritional deficiency (which can occur with eating disorders or alcoholism). Eating a healthy diet, staying socially involved and keeping mentally alert may also be beneficial. The main message, therefore, is that 'every little helps' and may be worthwhile.

APPENDIX

USEFUL REFERENCES AND WEBSITES

Alzheimer's Scotland – Action on dementia
www.alzscot.org

The **Dementia Services Development Centre**, which is part of the Applied Social Science Department, Faculty of Human Sciences at the University of Stirling, assists in the development and improvement of services for people with dementia and their carers (but not directly to carers).
www.stir.ac.uk/Departments/HumanSciences/AppSocSci/DS

Scottish statistics: see ISD webpage
http://www.show.scot.nhs.uk/isd/joint_futures/mental_health/mental_health_dem.htm

The **Alzheimer's Association** is the largest national voluntary health organization supporting Alzheimer research and care.
http://www.alz.org

Alzheimer's Research Forum gives details of research
http://www.alzforum.org

KEY TEXTS

Cooper B. Thinking preventively about dementia: a review. *International Journal of Geriatric Psychiatry* 2002;17:895-906.

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