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Prevalence and projections of dementia

Blossom Stephan and Carol Brayne

Learning objectives

By the end of this chapter you will be able to:

+ explain the implications of the ageing of our population for the prevalence and incidence of dementia
+ describe the different types of dementia and the difficulty in distinguishing between them
+ summarize the incidence and prevalence of dementia, regionally and worldwide
+ identify risk factors for the development of dementia
+ explain that dementia is associated with both disability and mortality

Introduction

In the next decades large numbers of people will enter the ages when the incidence rates of dementing diseases are the highest. People 60 years and over make up the most rapidly expanding segment of the population: in 2000, there were over 600 million persons aged 60 years or over worldwide, comprising just over 10% of the world population and by 2050 it is estimated that this figure will have tripled to nearly two billion older persons, comprising 22% of the world population (United Nations 2007).

This ageing epidemic, while once limited to developed countries, is expected to become more marked in developing countries (see Figure 1.1: Population pyramids high income countries). Population ageing poses the greatest threat to Japan and Continental Europe, where falling birth rates and increases in life expectancy are expected to have wide-ranging economic and social consequences especially with regard to health and long-term care. Yet in light of this, population ageing also has positive consequences. The elderly population make a valuable contribution to the society through volunteer work, providing informal care to grandchildren, families and communities, in addition to an accumulation of wisdom, experience and skills that can be passed to younger generations.

The change in population age structures will influence both the prevalence and incidence of age-related conditions such as dementia. In the United Kingdom alone, the percentage of older people (aged 65 and over) increased from 13% of the total population in 1971, to 16% in 2003 (Office for National Statistics 2003). It is estimated that of those individuals aged 65 and over, 6% will be suffering from dementia, with those in their eighties having...
more than a 30% chance (Peters 2001). Worldwide the proportion of very elderly people (85 years and above) is also projected to grow (Table 1.1). Developing regions, particularly China, India and Latin America, which are set to dominate world ageing, will show the greatest increase in disease burden (Prince 2000). It is predicted that by 2040 there will be as many people with dementia in China as combined in the developed world (Ferri et al. 2005). The consequences of this ageing, epidemic will depend on how ageing is viewed in each culture and the mechanisms in place to anticipate and cope with demographic change.

The identification of modifiable risk factors that prevent or delay dementia onset is a major public health priority. It was concluded from a systematic review on dementia, cognitive impairment and mortality in persons aged 65 and over living in the community that there is an increased risk of mortality for
even moderate levels of cognitive impairment and that at more severe levels the risk increases two-fold (Dewey and Saz 2001). In addition to increased mortality is increased dependence. The high dependency of patients with dementia means that any new information on aetiology would be an important addition to public health services not only for the potential sufferers and carers but also, financially, for future service planning. Indeed, the economic cost of dementia is already higher than that of heart disease and cancer together.

Table 1.1 Estimated changes in the world population age structure of the elderly (over 65 and over 80)

<table>
<thead>
<tr>
<th>Population</th>
<th>2000</th>
<th>2025</th>
<th>2050</th>
</tr>
</thead>
<tbody>
<tr>
<td>65 and over (%)</td>
<td>6.9</td>
<td>10.5</td>
<td>16.2</td>
</tr>
<tr>
<td>80 and over (%)</td>
<td>1.1</td>
<td>1.9</td>
<td>4.4</td>
</tr>
<tr>
<td>TOTAL (millions)</td>
<td>6055</td>
<td>7823</td>
<td>8900</td>
</tr>
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In the past twenty years there has been a large advance in our understanding of the epidemiology of dementia and its subtypes. Epidemiological studies have been carried out with three principal aims. The first is to describe the frequency and distribution of disease. This informs health services planning and public health priorities. The second is to identify risk factors responsible for disease in order to guide treatment and ultimately prevention. These, along with evidence of change, feed a third aim which is to assess the possible impact of protective action in future populations. It is assumed that the clinical expression of dementia is to some extent environmentally modifiable so that its clinical manifestations can be delayed or prevented and its signs and symptoms alleviated.

**Defining dementia and its subtypes**

The term dementia defines a group of syndromes characterized by progressive decline in cognition of sufficient severity to interfere with social and/or occupational functioning, caused by disease or trauma, and often associated with increasing age. To date, over 200 subtypes have been defined, each characterized by differences in course and subtle variations in pattern of expression and neuropathology. The main subtypes include Alzheimer’s disease (AD), vascular dementia (VaD), dementia with Lewy bodies (DLB), frontal lobe dementia, Pick’s disease and alcohol-related dementia. Each is briefly described in Table 1.2.
### Table 1.2 Summary of the main dementia types

<table>
<thead>
<tr>
<th>Dementia Type</th>
<th>Primary impairments/disability/symptoms</th>
<th>Pathology/causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer's disease</td>
<td>Memory, language and functional disability</td>
<td>Neuritic plaques (proteinaceous extra-cellular deposits consisting mainly of amyloid-beta peptide fragments) and neurofibrillary tangles (twisted fibres of a protein called tau)</td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>Poor concentration and communication and physical symptoms such as paralysis or weakness in limbs</td>
<td>Problems of circulation of blood to the brain – related to stroke, high blood pressure (hypertension), diabetes and heart problems</td>
</tr>
<tr>
<td>Dementia with Lewy bodies</td>
<td>Hallucinations, spatial disorientation, impaired recent memory and fluctuations in mental performance</td>
<td>Presence of Lewy bodies which refer to abnormal structures within nerve cells of the brain</td>
</tr>
<tr>
<td>Frontal lobe dementia</td>
<td>Changes in personality and behaviour, and emotional and language dysfunction. No dysfunction in memory</td>
<td>Frontal lobe degeneration</td>
</tr>
<tr>
<td>Pick's disease</td>
<td>Impairment in emotional and social functioning</td>
<td>Abnormalities in Pick's bodies. Focal damage in the frontal and temporal lobes</td>
</tr>
<tr>
<td>Alcohol related dementia – Korsakoff's syndrome</td>
<td>Impaired memory, planning, organizing, judgement, social skills and balance</td>
<td>Chronic/excessive alcohol intake</td>
</tr>
</tbody>
</table>

AD is the most prevalent subtype, accounting for approximately 70% of all cases (Barberge-Gateau and Fabrigoule 1997; Cowan et al. 2000; Nourhashemi et al. 2000). AD is characterized by a steady and progressive loss of memory and cognitive faculties including language deterioration, impaired visuospatial skills, poor judgement and an attitude of indifference. AD has a distinct neuropathological pattern of amyloid plaques and neurofibrillary tangles predominately in the neocortex, but becoming more widespread with disease progression. The second most common cause of dementia is VaD, accounting for 10–20% of all cases (Barberge-Gateau and Fabrigoule 1997; Ladislas 2000). VaD represents a heterogeneous group of conditions that includes all dementia syndromes that result from ischaemic, anoxic or hypoxic
brain damage. Similar to AD, onset is progressive and life expectancy poor although for VaD the disease course can be highly variable. The exact prevalence of DLB is not known although some estimates suggest that it may be as common as VaD.

The risk of developing dementia increases with age. Indeed, results from the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS) found that for those individuals aged 65–69 years at death, 6% had dementia while for those aged 95 years and above at death, 58% had dementia. This pronounced increase in dementia with age has been interpreted as an increase in the rates of AD, as shown in Figure 1.2. In contrast, rates for clinically diagnosed VaD remain relatively constant across age. This has implications for the optimum health care strategy for different age groups, and raises the question of whether the effect of dementia risk manipulation on the prevalence estimates of dementia and its subtypes is constant across age groups.

The distinction between subtypes has been questioned. Considerable overlap in pathology suggests that mixed forms may be more common (Peters 2001). Increased levels of amyloid plaques and neurofibrillary tangles characteristic of AD pathology have been found in hypertensive subjects post-mortem and it has been suggested that vascular pathology may play a role in the development of amyloid plaques (Peters 2001). Furthermore, both AD and VaD share similar risk factors (e.g. advancing age and poor cardiovascular health), overlapping clinical symptoms and cerebro-microvascular pathology (Skoog 1998). Yet, a steady progressive decline is still considered characteristic of AD while a stepwise deterioration characterized by periods of sharp decline alternating with plateaus or periods of minimal decline is characteristic of VaD (Peters 2001). Novel neuroimaging strategies coupled with careful clinical and

![Figure 1.2 Prevalence of dementia subtypes](image)

**Figure 1.2** Prevalence of dementia subtypes
Data from the Cambridge City Over-75s Cohort Study (CC75C).
pathologic examinations may provide the answers needed to determine whether VaD is really mixed dementia or AD alone.

Diagnosis of dementia depends on the defining criteria and sampling method. Different diagnostic criteria can produce up to a ten-fold variation in prevalence (O’Connor et al. 1996). For example, the WHO International Classification of Diseases, 10th revision (ICD-10) sets a higher threshold for dementia diagnosis compared to the widely used Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria. Dementia variation can also be related to culture or diagnostic applicability (e.g. views of ageing and validity of instruments). When applying criteria it is also necessary to distinguish dementia from other disorders such as poor physical health, depression, anxiety, sensory difficulties, language barriers and education level, all of which can reduce cognitive scores.

### Prevalence and incidence of dementia

<table>
<thead>
<tr>
<th>Description</th>
<th>Prevalence: The total number of individuals with a disease in the population at a particular time point</th>
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<tbody>
<tr>
<td>Description</td>
<td>Incidence: The rate of occurrence of new cases with a given disease during a specific time period</td>
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</table>

Variation in the incidence and prevalence of dementia across populations may provide insight into the aetiology and prevention of the disease. Although there have been few large population-based studies of dementia internationally or in multiethnic communities, a consistent pattern has emerged of decreased incidence and prevalence: (1) Asian nations compared to Europe and North America; (2) rural compared to urban areas; and (3) developing rather than developed countries (White 1992; White et al. 1996). These differences have been linked to various factors including diet, genetics, mortality and criteria for case selection. We will first look at the challenges inherent in conducting research of this kind.

### Methodological issues when studying prevalence and projections

For no other disorder associated with old age are the methodological issues of conducting community-based studies so complex. The lack of a unique pattern of clinical symptoms for dementia and its subtypes, for example, only reflects a mixture of underlying aetiologies and pathogenetic mechanisms. Population-based studies of incident disease where risk factors are identified before disease onset and individuals followed up longitudinally to document change are powerful tools for the identification of risk factors and modifiable strategies. However, these studies are expensive, time-consuming and are only now being conducted. Furthermore, differences in methodology and sample population lead to inconsistencies in findings, making comparative research difficult.
All epidemiological research depends on the definition of a ‘case’, that is, who is identified as having that particular condition. When evaluating dementia research, the following must be considered:

- **Observation bias** as individuals with dementia often are unable to provide their own past medical and social histories and the information has to be supplied by surrogate informants who may have variable amounts of knowledge about these factors.

- **Selection bias** through the choice of population source as the percentage of persons with AD, for example, living in institutions varies widely from place to place but may exceed half of all cases with severe AD. Exclusion of institutionalized persons would result in an underestimation of prevalence rates.

- **Response rate** as it is likely that response is affected by cognitive status so that more impaired individuals are less likely to have complete data and typically refuse further testing. This affects prevalence estimates and it is hard to guess in what direction they may have been biased because non-response can cause over- as well as under-estimation.

### Exercise 1.1 Identifying the number of people with dementia in a given geographic area

Steve is a new commissioner of services for people with dementia in Edinburgh. In order to understand the extent of need for services, he is interested in finding out the number of people with dementia in the city. He has decided to send a survey to all day centres in the area asking them to tell him the number of people with dementia they serve. Based on replies to this survey he feels he will have a good sense of the number of people with dementia in the city.

Consider the above information and complete the following:

- List three reasons that Steve may be misled by his findings.
- Suggest an alternative approach to finding out the number of people with dementia in Edinburgh.

### Prevalence of dementia

It is currently estimated that there are 24 million people with dementia worldwide and if mortality, prevention and treatment strategies remain unchanged this number will double every 20 years to an estimated 42 million by 2020 and 81.1 million by 2040 (Ferri et al. 2005). However, increases are not uniform across the world. A 100% increase is predicted in developed countries from 2001 to 2040, while more rapid changes in life expectancy in developing countries is estimated to result in a more marked effect, with the number of people with dementia in China and India likely to rise over 300% over this time period. In Latin America and Africa, depending on region, prevalence is
estimated to either double or triple (Ferri et al. 2005). Projected increases across the 17 sub-regions of the world as defined by the World Health Organization (WHO) are shown in Figure 1.3.

![Figure 1.3 Dementia prevalence 2001, 2020, 2040 by WHO Region Source: Ferri et al. (2005).](image)

Where available, cross-national comparisons using similar methodology have highlighted this variation: lower prevalence of AD in rural India (28 villages in the Ballabgarh district of the state of Haryana in northern India) compared to a predominately Caucasian community cohort in the USA (Pennsylvania; MoVIES Project) (Chandra et al. 1998), lower prevalence of overall dementia in Malays compared to Singapore Chinese (Kua and Ko 1995) and lower prevalence of overall dementia and AD in Nigerians (Yoruba Nigerians) compared to African Americans in Indianapolis (2.4 times higher) (Hendrie et al. 2001).

Sub-type prevalence (AD and VaD) is also variable. In North America, AD accounts for approximately two-thirds of all cases. In Japan prior to 1990 VaD was found to be more common than AD, although more recent data suggest a Westernization in trend with AD now nearly twice as prevalent as VaD (Shigeta 2004). Similar trend changes have also been observed in Korea (Seoul) (Lee et al. 2002) and Taiwan (Liu et al. 1995, 1998) linked to urbanization, industrialization and lifestyle changes (e.g. alcohol use). In China, VaD is more common in northern regions, with AD more prevalent in the south (Chiu and Zhang 2000). Different reasons have been given including over-diagnosis of VaD and differences in case definition, vascular risk association and relative number of the young-old and oldest-old (Ineichen 1998).

Cross-ethnic comparisons from the UK, the USA and Canada have also found differences in rates between ethnic groups sharing the same territory (Ineichen 1998). In the USA, VaD is significantly more prevalent in individuals of African American and Hispanic origin (vs. Caucasian Americans) (Miles et
In Washington and Hawaii, although individuals of Japanese origin were found to show similar AD estimates to those reported in European-ancestry populations, prevalence was found to be lower when a Japanese diet was adhered to (Hatada et al. 1999; White et al. 1996). Furthermore, although the prevalence of VaD was slightly lower in Japanese Americans than that reported in Japan, it was higher than that reported in European-ancestry populations (White et al. 1996). However, there were differences in diagnostic approaches between countries that may have confounded this finding. In Canada, the prevalence of all dementias was found to be significantly lower in Cree Indians compared to Caucasians (0.5% vs. 3.5%, respectively) (Hendrie et al. 1993); while in the UK, VaD has been found to be more prevalent than AD in individuals of African Caribbean origin vs. British Caucasians (Livingston et al. 2001; Richards et al. 2000).

Age-specific estimates of dementia have been more consistent worldwide with a predicted exponential rise in dementia with age. Prevalence studies indicate that dementia doubles approximately every 5 years after the age of 65 (Jorm et al. 1987). This increase is more marked for females for whom prevalence is higher in the oldest-old compared to males. Collapsed across studies from Europe, North America, Australasia and Japan, prevalence rates for the five-year age groups from 65 years to 85 and over were found to be 1.4, 2.8, 5.6, 11.1, 23.6, respectively (Jorm et al. 1987). A pooling of results from European studies found similar figures (Hofman et al. 1991). Findings from three meta-analyses, the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS) (Matthews and Brayne 2005), and the most recent estimates from Knapp et al. (2007) are reported in Table 1.4.

<table>
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<tbody>
<tr>
<td>60–64</td>
<td>0.7</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>65–69</td>
<td>1.4</td>
<td>1.3</td>
<td>1.4</td>
<td>1.5</td>
<td>1.3</td>
</tr>
<tr>
<td>70–74</td>
<td>2.8</td>
<td>2.4</td>
<td>4.1</td>
<td>2.6</td>
<td>2.9</td>
</tr>
<tr>
<td>75–79</td>
<td>5.6</td>
<td>4.4</td>
<td>5.7</td>
<td>6.3</td>
<td>5.9</td>
</tr>
<tr>
<td>80–84</td>
<td>10.5</td>
<td>8.1</td>
<td>13.0</td>
<td>13</td>
<td>12.2</td>
</tr>
<tr>
<td>85–89</td>
<td>20.8</td>
<td>14.9</td>
<td>21.6</td>
<td>25.3</td>
<td>20.3</td>
</tr>
<tr>
<td>90–94</td>
<td>38.6</td>
<td>27.3</td>
<td>32.2</td>
<td>28.6</td>
<td></td>
</tr>
<tr>
<td>95+</td>
<td>–</td>
<td>50.2</td>
<td>–</td>
<td>–</td>
<td>32.5</td>
</tr>
</tbody>
</table>

Prevalence estimates for the oldest-old (90 years and over) remain controversial. Age-specific models, although appearing to hold well for certain age groups (65–85 years), assume that prevalence increases at an exponential rate over time, across all ages (Matthews and Brayne 2005). Very high prevalence rates estimated at 77.6% (Jorm et al. 1988), 61.6% (Jorm et al. 1987), and 39.3% (Ritchie et al. 1992) have been reported in the 95-year-old and over age group. However, this is not consistent with other findings of stability in trend.
for this age group (Ritchie et al. 1992; Wernicke and Reischies 1994). This
could result from older individuals not living as long with dementia as younger
individuals with dementia, or the fact that the survivors into late old age are
relatively resistant to developing dementia. Smaller sample sizes and decreased
response rate in this age group may also influence findings.

**Incidence of dementia**

Incidence of dementia rises rapidly with age. Generally, in people younger than 65
years dementia is rare: early-onset dementia (prior to the age of 65 years) is typically
observed between 40 and 50 years of age and is very uncommon prior to this, and is
generally linked to genetic risk factors (e.g. defect on chromosome 14 and Down’s
syndrome). The incidence of old-age dementia increases exponentially in individu-
als aged 65 and older (Barberger-Gateau and Fabrigoule 1997; Cowan et al. 2000).
This trend, hypothesized to continue with advancing age is found in some, but not
all studies (Matthews and Brayne 2005). Incidence of AD increases from approxi-
mately 0.2% between 60–69 years old, 1% for people who are 70 years old to 3%
for people who are 80 years old to approximately 8% for people who are older than
85 (Barberger-Gateau and Fabrigoule 1997; Patterson and Gass 2001). In contrast,
incidence of VaD does not appear to show an age effect (Brayne et al. 1995).

Gender effects on incidence are controversial. Some studies suggest that female
sex is associated with increased risk. Up to 2000, the number of people with
dementia was estimated at about 25 million people worldwide (approximately
0.5% of the whole worldwide population), of which 59% of cases were female
(Hofman et al. 1991). More recent findings suggest a somewhat stronger pattern of
65% (70% in developed regions and 60% in developing regions) (Fratiglioni et al.
2000). One meta-analysis found a subtype difference indicating that women were
at a higher risk of AD (Black et al. 2001; Dartigues et al. 2000; Jorm and Jolley
1998). Another concluded that women had a higher risk of AD at older ages (above
80 years) and that men had a higher risk of VaD at younger ages, but any differences
in overall age-specific incidence rates were small (Copeland et al. 1999). Cohort
studies in the UK and the USA have consistently reported no gender differences in
the incidence or prevalence of dementia or AD (Edland et al. 2002; Matthews and
Brayne 2005). Increased longevity, increased survival with disease and some
increase in intrinsic vulnerability probably all play a part in female predominance in
some estimates.

Cross-cultural studies reveal lower incidence estimates in Asian populations
compared to North American and European populations, particularly for AD.
However, more recent findings suggest greater convergence in line with
prevalence findings.

In early studies looking at secular changes in the incidence of dementia, no
time trends were detected. In a study based in Rochester, Minnesota, incidence
rates of AD and dementia were stable between 1960 and 1984, except for a
slight increase in the very old (Kokmen et al. 1993). Re-analysis incorporating
more recent data for the period 1975–1985 confirmed previous findings of
absence of a secular trend (Rocca et al. 1998). In the Lundby Study in Sweden
incidence rates for multi-infarct dementia (caused by multiple strokes) and
senile dementias (which typically consist of a group of diseases including
However, more recent data suggest that rates of dementia in the USA have increased from 1984–1990 to 1991–2000 and that this increase was more marked in persons with stroke compared to the stroke-free population (Ukraintseva et al., 2006).

### Variation across regions

Given cultural, demographic and ethnic variability in incidence and prevalence, there is a need for further cross-national and cross-cultural epidemiological studies in indigenous as well as migrating populations. At present it is difficult to establish to what extent findings are merely an artefact of methodology (e.g. sampling procedures and diagnostic criteria), differential exposure to risk factors (e.g. education, health care, cardiovascular disease), demographic changes (e.g. increased numbers of the oldest-old), cultural views on ageing (status of dementia as a ‘devastating disease’), response rates or survival trends (Fratiglioni et al. 1999). It is also conceivable that differences reflect real geographical and ethnic variations. A marked geographical dissociation in Europe between the north and south, linked to differences in vascular risk factors has been proposed to account for the higher incidence rates in the oldest-old of north-western countries (Finland, Sweden, Denmark, the Netherlands, and the United Kingdom) compared to southern countries (France and Spain) (Fratiglioni et al. 2000). This division is further supported by north–south regional findings of differences in MRI-detected white matter lesion (WML) pathology (Launer et al. 2006). Greater WML pathology linked to progression of dementia has been observed in southern Europe relative to northern and central European countries. However, this differential based on vascular risk was not replicated in MRC CFAS. Here comparison of incidence across five sites (urban and rural settings) in England and Wales associated with different patterns of vascular risk and mortality failed to find cross-site variation (Matthews and Brayne 2005).

### Risk factors

The pathological origin and aetiology of dementia remain unknown. Treatment and prevention will largely depend on the level of understanding of the underlying biological and environmental factors associated with increased risk both in current, as well as future cohorts of older people. Although methodological factors do contribute importantly to reported variations in prevalence, it is also thought that variability could reflect factors relevant for disease pathogenesis or expression in various populations or subgroups (Corrada et al. 1995). Conclusions from previous studies have determined that dementia is a complex, multi-factorial process that is essentially under genetic control (Salib 2000). However, there is also compelling evidence for a predominantly acquired (environmental) form of AD. Indeed, Kumar et al. (1991) reported detailed neuroanatomical, neuropsychological and neuropathological examination of three monozygous twin pairs containing an individual with onset of AD disease between ages 50 and 60 years. All three twins remained well and each disease-free pair had been AD-free for over a decade. While this does not rule out the operation of genetic influences in the affected
members of the pairs, this finding suggests that any such predisposition would have been exaggerated substantially by environmental variation between twin pairs that accelerate disease onset.

Age

Age is the strongest risk factor for dementia. The incidence of dementia has been found to rise exponentially from 65 to 90 years of age (Jorm and Jolley 1998). Beyond this, controversy remains as to whether this trend continues: if dementia is an inevitable consequence of ageing or whether risk plateaus so that some individuals over a reasonable lifespan would never develop the disease (Goa et al. 1998; Matthews and Brayne 2005). Age findings are complicated by the lack of consensus as to exactly what cognitive changes occur as a function of the normal ageing process and where the boundary between normal and pathological ageing lies. Furthermore, the extent to which age is responsible for disease, rather than as serving as a proxy for as yet unidentified age-related factors which lead to disease is unclear.

Family history and genetics

Dementia risk can increase two- to four-fold among individuals who have at least one first degree relative with dementia (Devi et al. 1999; van Duijn et al. 1991). This effect is stronger for those where a relative had early onset and with increased longevity. Risk increases from 5% up to the age of 70, to 33% up to the age of 90 years (Lautenschlager et al. 1996). However, while the familial occurrence of dementia may reflect shared environmental factors, there is strong evidence to support a genetic link (Black et al. 2001). In very rare cases (less than 5%), AD can be inherited in an autosomal dominant pattern. This occurs when a single abnormal gene on one of the first 22 non-sex chromosomes is inherited. Disease onset is typically in the beginning of middle age (Bird 1994). By the age of 40 almost all individuals with Down’s syndrome have neuropathological changes consistent with AD, although onset can be modified by gender and apolipoprotein (ApoE) (Prasher et al. 1997; Schupf et al. 1998). Furthermore, mutations on the presenilin genes on chromosome 14 (PSI) and chromosome 1 (PSII), which have been found to alter the production or deposition of beta-amyloid in the brain (Selkoe 2001), have been linked to autosomal dominant familial Alzheimer’s disease. Phenotypic heterogeneity reflects differences in site and nature of mutation, with PSI linked to early onset and complete penetration, and PSII linked to variable onset and incomplete penetration (Boteva et al. 1996; Levy-Lahad et al. 1995; Rogaev et al. 1995). These risks are most important in the early onset dementia groups, also including Huntington’s disease.

Perhaps the clearest genetic risk associated with dementia, particularly AD is the apolipoprotein E (ApoE) gene. This is a plasma protein involved in cholesterol transport and neuronal repair. ApoE has three common variants, the E2, E3 and E4 alleles. Individuals can inherit any combination of these. The E4 allele is a risk factor for Alzheimer’s disease (AD). Within a lifetime the estimated risk of developing AD is 15% for the general population with an increase to 29% for those possessing an E4 allele (Seshadri et al. 1995, 1997).
Lifetime risk also increases with the number of E4 alleles: homozygous carriers are at a greater risk than heterozygous carriers or those who do not carry the E4 variant. However, these findings are modified by age, gender and ethnicity: risk differentials diminish after the age of 70, in some (Farrer et al. 1997; Osuntokun et al. 1995), but not all studies (Bryan et al. 1996), and the effect is weak in Hispanics, Africans, African Americans and Chinese (Farrer et al. 1997). Whether this is a result of differences in the population distribution of ApoE alleles or due to differences in the environmental impact on gene expression is unclear. While this association is strong in many non-population-based studies, it is not always found in population settings and instead appears to be related to specific aspects of cognition (Small et al. 2004; Yip et al. 2002).

While the relationship between dementia and specific mutations including PSI, PSII, and Down’s syndrome is definitive, the relationship between ApoE and dementia is less clear. Exactly how ApoE is involved in the pathogenesis of AD is still not known: ApoE E4 is neither necessary nor sufficient for dementia and rather appears to operate as a risk modifier. The clinical role of ApoE testing remains unclear and therefore is not recommended for routine testing in susceptible individuals (Patterson et al. 2001).

**Exercise 1.2** Is dementia inherited?

Someone hears you are working with people with dementia and approaches you with deep concern on their face. ‘My mother, aunt, uncle and grandmother all had dementia. Is it inevitable that I too will get it?’

How would you reply?

List three sources of evidence to suggest that the person is at an increased risk of developing dementia.

List three sources of evidence to suggest that they are not.

**Lifestyle risk factors**

Risk findings for alcohol and smoking are not consistent. Alcohol has been found to have a protective effect in moderate drinkers with a five-fold increase in dementia in both abstainers and those who drink heavily (Anttila et al. 2004; Orgogozo et al. 1997). However, Orgogozo et al. (1997) found a link between increasing alcohol consumption and VaD. With regard to smoking, after adjusting for age, ApoE, education, cardiovascular and respiratory factors, Tyas et al. (2003) found an increased risk of AD with medium and high levels of smoking, but not for very heavy levels of smoking. Smoking is known to cause cardiovascular and respiratory diseases which are both risk factors for AD. For heavy smokers it could be that they are not living long enough to develop dementia. In some studies alcohol and smoking (never, past and current) are neither strongly protective nor predictive (Doll et al. 2000), while in others both have been associated with an increase in the age-specific onset rate of AD (Bryan 2000). Conflicting results as to the direction of association between smoking and AD may be due to survival bias and methodological differences across studies. Yet, if smoking and drinking do confer increased risk of
dementia, educational programmes on prevention and cessation will become important public health priorities.

Healthy diet spanning across life may have a protective effect. A role for dietary antioxidants (from foods containing vitamin E especially vegetables, beta-carotene, omega-3 and vitamin C) in preventing or delaying dementia has been found (Engelhart et al. 2002). Higher adherence to a Mediterranean diet (high in fruit and vegetables, grain, and unsaturated fats, and low in meat and dairy products) has recently been found to significantly lower the risk of developing AD, even after adjusting for age, gender, ethnicity, education, caloric intake, weight, smoking and comorbid conditions (Scarmeas et al. 2006). However, these findings have not been replicated, particularly in clinical trials (the most rigorous form of clinical research to determine the impact of an intervention). Inconsistency in findings and questions regarding the accuracy of diet measurement suggests that no definitive evidence exists for dietary recommendations for the prevention of dementia beyond general exhortation of healthy diet and lifestyle to minimize vascular risk.

**Vascular factors**

Vascular factors and conditions, including history of stroke or transient ischaemic attack (TIA), diabetes mellitus, hypertension, congestive heart failure and obesity are major risks for cognitive decline and dementia by accelerating Alzheimer-type changes in the brain. Indeed, vascular disease is thought to reduce blood flow to the brain and hypoperfusion (decreased blood flow through an organ) has been found to cause oxidative stress, neurodegeneration and cognitive decline (de la Torre 2002). The hypothesis that both the clinical expression and severity of dementia (including AD and VaD) are mediated at least in part by the presence of cerebrovascular disease is supported by imaging findings where individuals with lacunar infarcts in the basal ganglia, thalamus or deep white matter have a higher prevalence of dementia compared to those without infarcts (Snowdon et al. 1997). Stroke and hypertension accelerate atrophy and degenerative changes resulting from neuronal shrinkage or loss (de la Torre 2002). The aggregation of risk factors is suggested to have a greater impact on the development of dementia than each factor independently. Furthermore, the relationship between vascular factors and dementia has been found to be moderated by various genetic and non-genetic factors including ApoE and age. Attention to these modifiable risk factors will have important implications for reducing the incidence and prevalence of dementia.

**Exercise 1.3 Can we prevent dementia?**

Health promotion and prevention of chronic illness in later life are now common approaches in the government’s approach to health care. Get a hold of last week’s newspaper and leaf through looking for examples of health promotion in relation to chronic health conditions including dementia.

List all the examples that you find.

How many of the examples have to do with dementia?

What do you think is the reason for this?
Hypertension and anti-hypertensives

Mid-life hypertension (high blood pressure) has been associated with impaired cognitive function even in otherwise healthy individuals. It has been suggested that for every 10 mmHg rise in blood pressure the risk of impairment to cognitive function rises 7% (Peters 2001) although some studies have found no association between high blood pressure, its reduction and cognitive function. Traditionally it is VaD that has been considered affected by hypertension and the alleviation of it. However, recent data suggest that vascular factors may influence the clinical expression of AD although the extent to which this reflects a true increase in the risk of AD rather than the combination of AD and small strokes is not clear (Bennett 2000). Nonetheless, hypertensive treatment has been found to reduce the incidence of AD (Peters 2001) although it is currently difficult to separate the effects of blood pressure reduction and/or the direct action of the anti-hypertensives themselves on the preservation of cognitive function. For example, while some medications (e.g. diuretics) may have adverse effects on cognitive function, others (e.g. some angiotensin converting enzyme (ACE) inhibitors) are known not to have a deleterious effect (Peters 2001).

Mild cognitive impairment

Clinical criteria dictate that the onset of dementia is preceded by a prodromal state of mild cognitive decline and, unsurprisingly, individuals with mild cognitive impairment (MCI) have been found to be at increased risk of dementia conversion compared to normal unimpaired individuals (5–15% per year versus 1–3%, respectively). However, although defined as a risk factor for AD, the clinical course of MCI is not always pathological. While in some studies impairment has been associated with increased risk of progression to AD, in others, individuals remain stable or even show improved cognitive functioning at follow-up (Portet et al. 2006). Variability is probably due to population selection, threshold for impairment, follow-up interval and operationalization of criteria. Indeed, rates of conversion to dementia are generally highest among clinic-based samples and for definitions of MCI where a memory impairment predominates. Yet the diagnosis of MCI remains difficult. Many forms have been identified (Stephan et al. 2007). Due to a lack of standardized diagnostic criteria the prevalence in older populations has varied widely between studies (3–36%) with an incidence of 8–58% per thousand per year (Busse et al. 2003). Furthermore, defining what distinguishes this condition from normal age-associated changes, early dementia and dementia itself is unclear. Whether this condition is distinct from early AD has been questioned and there is growing evidence that this, and related systems, are unstable in population-based studies.

Education

People who have less than six years of formal education are reported to have a higher risk of developing dementia, particularly AD (Black et al. 2001). Education as a protective factor has been linked to the ability to compensate
for cognitive decline, thus delaying the diagnosis of dementia (Mortimer 1988). It has also been hypothesized that this effect may be mediated by brain reserve/size (Schofield et al. 1997). Whether it is education itself that makes a difference or other related factors such as occupational status and income level that can account for these effects is unclear.

Head injury

Head trauma with loss of consciousness is a risk factor for dementia in some but not all studies (Bennett 2000; Haan and Wallace 2004; Salib 2000). Several hypotheses have been offered to explain the association, including neuronal damage, which reduces neuronal reserve and causes release of amyloid (Bennett 2000). An interaction between head injury and ApoE E4 has also been reported (Bennett 2000; Kukull and Ganguli 2000) with the potential explanation that the E4 allele is associated with inadequate neuronal repair and deposition of beta-amyloid after injury (Kukull and Ganguli 2000). The hypothesis of head trauma as a risk factor for AD comes from the observation of neurofibrillary tangles, indistinguishable from those seen in AD in the brains of boxers with dementia pugilistica (Breteler et al. 1992). However, the possibility that head trauma may be a consequence of an early stage of the dementia cannot be excluded. For example, although an association has been consistently found in case-control studies, there is considerable opportunity for recall bias for events that occurred long before disease onset and the association has not also been confirmed in population-based studies.

Other risk factors

Other risk factors include brain tumour, kidney failure, liver disease, thyroid disease, vitamin deficiencies (B12, folic acid, thiamine), chronic inflammatory conditions (such as certain forms of arthritis), a history of episodes of clinical depression, stress, inadequate mental exercise, exposure to aluminium, pesticides and other toxins (see van der Flier and Scheltens (2005) for an overview). The unique risk associated with each and the timing of their effect are still yet to be determined. Furthermore, there is no age cut-off at which the major risk factors for disease become insignificant.

Summary of risk

A number of risk and protective factors for dementia, in particular AD, have been reported in the literature. The general conclusion is that the pathophysiology of dementia is very complex and may include genetic, physiologic, psychological, as well as lifestyle elements, some of which may be linked. In fact, the multi-environmental and genetic risk factors for dementia suggest that it is a clinical syndrome analogous in aetiology to cancer (Jones 1997). The heterogeneous genetic influences on dementia have probably contributed substantially to difficulties in the detection of host or environmental factors associated with modified disease. There is a need to better understand both the genetic and environmental mechanisms that may modify these effects. These alleged linkages offer the basis for potential intervention for the prevention or
the slowing down of those processes that lead to disease (Nourhashemi et al. 2000). Because of the number of people who are expected to be affected by dementia, just shifting the prevalence curve slightly to the right could have a huge impact on numbers and a substantial effect on health care costs depending on the extent to which survival is lengthened.

Studies that combine clinical and pathological assessment have a special role in the search for potential risk factors. A small number of ongoing longitudinal epidemiological studies include a post-mortem brain donation programme (e.g. the Nun Study, the Religious Orders Study, the Baltimore Longitudinal Study on Aging, the Medical Research Council Cognitive Function and Ageing Study, the Cambridge City Over-75s Cohort Study (CC75C); the Vantaa 85+ Study, the Cache County Study). This provides researchers with an opportunity to examine the neuropathology and molecular biology underlying the changes associated with dementia and link risk factors directly to brain pathology to understand how risk factors lead to clinical disease.

Disability and mortality associated with dementia

Disability

Dementia is one of the leading causes of non-fatal disability in the developed world and by 2030 it is predicted that dementia will be the third leading cause of years of life lost due to death and disability (measured using the concept of disability adjusted life years (DALYs) which combines a measure of the average years of life lost due to disease with the years lived with disability) in high-income countries (Mathers and Loncar 2006). Indeed, in developed countries dementia accounts for more than half of all DALYs in the domain of burdensome neuropsychiatric disorders (Murray and Lopez 1996). In the WHO Global Burden of Disease (GBD) report (WHO 2003), it was estimated that the disability from dementia is higher than almost all conditions with the exception of spinal cord injury and terminal cancer. The World Health Organization Report 2003 estimated that for people aged 60 years and over dementia contributed 11.2% of all years lived with disability, while stroke contributed 9.5%, musculoskeletal disorders 8.9%, cardiovascular disease 5.0% and all forms of cancer 2.4%. With increasing pressure on health care budgets, accurate estimations of the type and distribution of dementia in addition to the burden it causes are necessary to help quantify health care needs and highlight areas for future research into curative and preventative strategies.

The disability associated with dementia is unevenly distributed across the world and is greater in developed countries. Furthermore, it is also related to age and gender, being greater in females and in the oldest-old. However, increases in male life expectancy and a shift in the age demographic of developing countries are predicted to result in an increased number of elderly individuals and non-communicable diseases, such as dementia, in these groups.

Mortality

It is estimated that in the high-income countries AD and other dementias are the seventh leading cause of death, accounting for 3.6% of total deaths. Studies
from developed countries report a median survival time after the onset of
dementia symptoms ranging from 5.0 to 9.3 years (Walsh et al. 1990), while in
developing countries the reported median survival is 3.3 years for all demented
individuals and 2.7 years for those with AD (Chandra et al. 1998).
Overall, individuals with dementia have poorer survival and a shorter life
expectancy than those without, with the risk of mortality greater the earlier the
disease onset.

Debates and controversies

To what extent do classification concepts of mild cognitive impairment (MCI)
accurately capture those at risk of progressing to dementia? The clinical course
is not always pathological: while in some studies impairment has been
associated with increased risk of progression to AD, in others, individuals
remain stable or even show improved cognitive functioning at follow-up. The
lack of consistency in definition may explain the resulting discrepancy conver-
sion rates.

Diagnostic criteria for Alzheimer’s disease and for vascular dementia are
mutually exclusive. Yet mixed forms are common. Do we not need accepted
criteria for mixed dementia?

Should the same factors (e.g. life expectancy and diet) be taken into
consideration when estimating prevalence of dementia across the developed and
developing world? How accurate are our calculations and what assumptions
are we making?

What are the risk and protective factors for dementia? Question of the risk
associated with exposure to aluminium and the role of genetic and environmen-
tal factors (e.g. alcohol, smoking, diet) in moderating risk.

Conclusion

Dementia is set to become a worldwide epidemic. Accurate estimates of both
prevalence and incidence are necessary not only as a foundation for health and
social policy but also to generate awareness. Of particular importance is a focus
on developing countries where there is to be a more rapid demographic shift
resulting in an increase in the number of elderly individuals and non-
communicable diseases. The global challenge to policy makers is two-fold: (1)
to implement immediate policy and infrastructure for the future provision and
health care for the older population in all regions of the world; and (2)
development of preventative strategies and treatment to delay disease onset and
progression. Application of these measures is critical in less-developed countries
which have a shorter timeframe to adjust to an ageing population. Findings
from developed countries show that the prevalence of chronic diseases and level
of disability can be ameliorated with appropriate health care and prevention
strategies. Opportunities missed by developing counties may have devastating
economic and social consequences.
Further information

The Cognitive and Functional Ageing Study (CFAS) is a large longitudinal multi-centre population-based study of cognitive decline and dementia in people aged 65 and over living in the UK.

The World Health Organization is the directing and coordinating authority for health within the United Nations system.

The Alzheimer Research Forum is an independent non-profit-making organization. Its website reports on the latest scientific findings, from basic research to clinical trials; creates and maintains public databases of essential research data and reagents, and produces discussion forums to promote debate, speed the dissemination of new ideas, and break down barriers across the numerous disciplines that can contribute to the global effort to cure Alzheimer’s disease.

Alzheimer’s Disease International is an umbrella organization of national Alzheimer Associations around the world.

The Alzheimer’s Research Trust is a research charity for dementia in the UK. It is dedicated to funding scientific studies to find ways to treat, cure or prevent Alzheimer’s disease, vascular dementia, Lewy Body disease and fronto-temporal dementia.

The report of the United Nations Department of Economic and Social Affairs, Population Division, entitled World Population Ageing 2000, presents the current assessment of the status of the world’s older population and prospects for the future. It provides a description of global trends in population ageing and includes key indicators of the ageing process for each of the major areas, regions and countries of the world.

References


Principles and perspectives


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Prevalence and projections of dementia


Prevalence and projections of dementia


