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Epidemiology of old age psychiatry: an overview of concepts and main studies

Chapter: Epidemiology of old age psychiatry: an overview of concepts and main studies

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Part 1 Epidemiology and Neuropsychiatric Disorders in Old Age

This chapter has two parts, the first where we discuss some of the major concepts and methodological issues in the epidemiology of mental disorders in old age, and the second containing a summary of many of the most important studies in this field.

Epidemiology is the foundation of public health and rational planning of services. In the field of old age psychiatry, the information provided by epidemiological research has been highly influential. This chapter reviews the methods used and the more important population-based and combined studies that inform current thinking. However, this work is a dynamic process, as cohorts now and in the future may differ in relation to cultural, psychosocial, and medical factors, which need to be understood as we move forward in time.

In this chapter we will present some of the world demographic data emphasizing the changes in the age distribution witnessed in the last century. Following this, some of the basic epidemiological concepts will be covered. Diving further into the fields of epidemiology and neuropsychology, we will raise the burden of the neuropsychiatric disorders under the new demographic scenario, methodological issues in calculating the epidemiological measures, and the diagnostic methods of identifying such neuropsychiatric conditions. We include an historical perspective, the evolution of the neuropathological findings of the dementias, as well as some of the most influential epidemiological longitudinal studies and combined studies that focus on old age neuropsychological conditions.

Demographic transition

The world population is ageing, with extraordinary reductions in mortality and fertility rates. As a consequence of this 'demographic transition', the older population is growing proportionally faster than the other segments. Indeed, the number of older people has tripled over the last 50 years and will more than triple again over the next 50 years.

According to the United Nations, in 1950 there were 205 million people aged 60 or over worldwide. Fifty-nine years later, this number increased to 737 million. In 2050, it is projected that there will be nearly 2 billion people aged 60+ (Department of Economic and Social Affairs—Population Division, 2010). This demographic transition is a global phenomenon. It was first experienced by high-income countries (HIC), though it has recently become apparent in many of the low- and medium-income countries (LAMIC) (Department of Economic and Social Affairs—Population Division, 2010). Although the proportion of older aged individuals living in HIC is higher, most of the global older population have been living in LAMIC. The projection for 2050 is that six countries will have more than 10 million people aged 80 years or over: China (101 million), India (43 million), US (32 million), Japan (16 million), Brazil (14 million), and Indonesia (12 million). Together they will account for 55% of all those 80 or over in the world (Department of Economic and Social Affairs—Population Division, 2010).

To describe the demographic transition, four phases have been identified. In the first phase, fertility was high and populations grew slowly even in the face of a high level of mortality. Periodic epidemics of plague, cholera, typhoid, and other infectious diseases would in one or two years almost wipe out the gains made over decades. Because overall both rates were in balance, population growth was typically very slow in stage one. Many human populations are believed to have had this balance until the late eighteenth century, when this balance ended in Western Europe.

The second stage begins when epidemics were better controlled and improvements to food supply and sanitation started to emerge. As a consequence, death rates dropped quickly, increasing lifespan. In Europe, the decline in death rates started in the late eighteenth century and carried on for approximately 100 years. As fertility remained high at first, there was an excess of births over deaths which led to population growth.

In the third phase, the imbalance between births over deaths was reduced, as fertility rates dropped for a variety of reasons including access to contraception, urbanization, a reduction in the value of children's work, greater security for the older populations, and an increase in parental investment in the education of children, in addition to other social changes.

In the fourth stage, mortality and fertility are in balance again, but at lower levels. In some countries such as Germany, Italy, and Japan, birth rates have dropped below replacement level, leading to a shrinking of the population.

Fertility rates are now well below the replacement level in many HIC and in 31 LAMIC. The level considered to ensure the replacement of generations is about 2.1 children per woman. Total fertility rate in the HIC has dropped from 2.8 children per woman in 1950–1955 to 1.6 children per woman in 2005–2010. In LAMIC the decline has started later, in the last three decades of the twentieth century, but has progressed faster. From 1950–1955 to 2005–2010, total fertility in the LAMIC dropped by over half from 6.0 to 2.7 children per woman. However, great disparities between HIC and LAMIC still persist (Department of Economic and Social Affairs—Population Division, 2010).

Life-expectancy at birth increased globally by 21 years from 1990–1995 to 2005–2010. The average gain in life-expectancy at birth is 24.6 years in LAMIC and 11.1 years in HIC (Department of Economic and Social Affairs—Population Division, 2010). HIC have experienced an epidemiological transition in parallel with their demographic transition. In the epidemiological transition, pandemics of infection are replaced by degenerative, neoplastic, and man-made diseases caused by the adoption of unhealthy behaviours such as tobacco consumption, poor dietary habits, and a decline in physical activity. This transition has also resulted in a change in the landscape of diagnosis and investigation of the modalities of disease, particularly in the dementias including Alzheimer's disease (AD), Lewy body disease, and frontal temporal dementia, beginning in the early 1900s. Chronic diseases have become the primary causes of not only mortality but also morbidity. This applies for HIC as well as for LAMIC, where this process is underway.

With the shift in the world age demographic, the population that will experience the greatest increase in risk of disease and disability will no longer be infants, but individuals aged 60 years and older. Nonetheless, according to the Save the Children report (2009), child hunger and malnutrition are persistent problems worldwide: one child in three in LAMIC is malnourished, and many of those who survive will experience impaired cognitive development. Both HIC and LAMIC have to face the challenge of increases in chronic disorders, especially those disorders that are prevalent in the older population. This raises issues regarding prevention and treatment as behavioural and genetic risk factors are a hallmark of this era; preventive measurements are less effective; and treatments are more complex, and can be lifelong and therefore expensive.

Basic epidemiological measures

Prevalence

The prevalence of a condition in a population is defined as the total number of cases over the number of individuals in a population at a given time (Box 5.1). It indicates how widespread the condition is and it may be regarded as a snapshot view of the number of affected cases in a population. Prevalence is determined by the duration of a disease and the quantity of

new cases. It is important for developing management and health service planning as well as eradication programmes. As prevalence is measured in cross-sectional settings, it is used to reveal associations with other variables. However, the main disadvantage is that, as it does not account for the existence of a temporal sequence of events, it cannot be used to establish causation and effect of events. Furthermore, in neuropsychiatric syndromes, the prevalence figure is greatly influenced by case definitions and the operational criteria underlying these definitions.

Box 5.1 Basic epidemiological concepts

◆ **Prevalence:**

Number of cases in a population at a given period of time
Population at the same given time

◆ **Incidence:**

◆ **Cumulative incidence:**

Number of new cases in a population at a given period of time
Number of individuals at risk of developing the condition at the same given time

◆ **Incidence density rate:**

Number of new cases in a population at a given period of time
Sum of the follow-up times for each individual at risk of developing the condition

◆ **Lifetime risk:**

◆ Probability of someone of a given age and sex developing a condition during their remaining lifespan

◆ **Disability adjusted life years (DALY):**

◆ Years of life lost due to premature mortality + years lost due to disability for incident cases

Incidence

Incidence relates to new cases and it is a measure of the risk of developing a new condition within a specified period of time (Box 5.1). The incidence rate is expressed either as a cumulative incidence with the number of new cases over some period of time, or as a density rate when the denominator is the sum of the person-time of the at-risk population. The latter is a more precise estimate of the rate of occurrence of a particular disease, especially in cohort studies where the length of time that the participants stay in the study varies. The density rate contrasts the number of new cases with the sum of the time that each person remained under observation and free from disease.

As incidence studies are more expensive and time consuming, most of our knowledge about the occurrence of the neuropsychiatric conditions is based on prevalence rather than incidence studies.

Incidence can be used to determine the impact of management and treatment strategies, to determine risk factors and natural history, and to appropriately allocate future resources (for example, public health initiatives, prevention and intervention strategies, funding for research). It is measured from data obtained in cohort studies: therefore, the temporal sequence of events is implicit, which allows us to infer not only associations, but also causation. However, estimates may be influenced by unexpected changes in the environment, the population tested (e.g. population-specific differences in risk and protective factors), and can be affected by difficulties in certainty of distinguishing new and old cases. The collection of data needed to calculate prevalence and incidence can be challenging and costly. Incidence is difficult to define in neuropsychiatric conditions, as these are syndromal diagnoses, and therefore there is no sudden moment of incidence as onset is almost always gradual, over a period of time.

Lifetime risk

The definition of lifetime risk of a condition is the probability that a person who is currently free of the condition will develop it at some time during the remainder of their expected lifespan (Seshadri and Wolf, 2007) (Box 5.1). The lifetime risk of a disease is the risk over a long period rather than the risk over a year, which is the age-specific annual incidence of the disease (Seshadri and Wolf, 2007). Operationally, the lifetime risk is the conditional probability of developing a disease when

a person has reached the index age and is free of that disease. Its estimation enables a long-term perspective, which is especially useful for chronic conditions such as dementias, where exposure to risk factors in midlife can alter the incidence of disease in later life.

Disability adjusted life years (DALY)

The concept of DALY (Murray, 1994) was designed to measure the global burden of a disease. It has the advantage of aggregating mortality and morbidity in a single tool (Box 5.1). Consequently, it allows the evaluation of burden of diseases with low mortality but which are highly incapacitating. The DALY corresponds to the time lived with disability and the time lost due to premature mortality. This methodology uses epidemiological data and vital statistics, which are normally available even in LAMIC, facilitating international comparisons and evaluations of the impact of international investments and health policies.

DALY is calculated as the sum of the years of life lost due to premature mortality (YLL) in the population and the years lost due to disability (YLD) for incident cases of the health condition:

$$\text{DALY} = \text{YLL} + \text{YLD}$$

The years of life lost (YLL) is calculated from the number of deaths multiplied by the standard life-expectancy at the age at which death occurs, which is derived from the model life-table West Level 26, which has a life-expectancy at birth of 82.5 for women and 80.0 for men. The basic formula for YLL for a given cause, age, and sex is:

$$\text{YLL} = \text{number of deaths} \times \text{standard life-expectancy at age of death in years}$$

To estimate YLD for a particular cause in a particular time period, the number of incident cases in that period is multiplied by the average duration of the disease and a weight factor that reflects the severity of the disease on a scale from 0 (perfect health) to 1 (dead):

$$\text{YLD} = \text{number of incident cases} \times \text{disability weight} \times \text{average duration of the case until remission or death (years)}$$

Additionally, 3% time discounting and nonuniform age weights which give less weight to years lived at young and older ages might be incorporated into the calculation of DALYs. Unequal age-weights are an attempt to capture different social roles at different ages. The young, and often older individuals too, depend on the rest of society for physical, emotional, and financial support. Given different roles and changing levels of dependency with age, it may be appropriate to consider valuing the time lived at a particular age unequally (Murray, 1994).

The epidemiology of neuropsychiatric disorders

Neuropsychology aims to better understand the relationship between the brain and behaviour. This section explores the epidemiology of neuropsychiatric conditions in ageing populations, with a focus on the dementias and depression, including their diagnosis, prevalence, incidence, and risk factors (where available). Evidence will be gathered from longitudinal population-based studies that have included a focus on ageing from across the world.

The global burden of old age neuropsychiatric conditions

Disability adjusted life years (DALY)

From the psychiatric point of view, neuropsychiatric disorders are estimated to contribute to 7.5% of the total DALY of the global population aged 60 years and older. More specifically, AD and other dementias correspond to 4.1% of the total DALY among the older population. This figure is just behind the contribution of ischaemic heart disease (14.4%), cerebrovascular diseases (11.7%), and chronic obstructive pulmonary disease (7.1%) (Department of Health Statistics and Informatics of World Health Organization, 2004).

Table 5.1 shows the global disability burden of the neuropsychiatric disorders among people over 60 years old. Unipolar depressive disorders, AD, and other dementias together correspond to 75% of the burden of the neuropsychiatric disorders among the population aged 60 or over.

Table 5.1 Disability adjusted life years (DALYs) (thousands) in the global population aged 60 or older by sex, 2004

| Cause | Men | Women | Total |
|----------------------------------|---------|---------|---------|
| Unipolar depressive disorders | 1,011 | 2,257 | 3,268 |
| Bipolar affective disorder | 4 | 6 | 10 |
| Schizophrenia | 42 | 67 | 109 |
| Epilepsy | 155 | 149 | 304 |
| Alcohol use disorders | 465 | 75 | 540 |
| Alzheimer and other dementias | 3,366 | 5,878 | 9,244 |
| Parkinson disease | 509 | 540 | 1,049 |
| Multiple sclerosis | 22 | 38 | 60 |
| Drug use disorders | 24 | 8 | 32 |
| Post-traumatic stress disorder | 5 | 19 | 24 |
| Obsessive-compulsive disorder | 25 | 42 | 67 |
| Panic disorder | 11 | 26 | 37 |
| Insomnia (primary) | 155 | 267 | 422 |
| Migraine | 0 | 0 | 0 |
| Total neuropsychiatric disorders | 6,465 | 10,172 | 16,637 |
| Total DALYs (all causes) | 109,688 | 112,817 | 222,505 |

(Source: Department of Health Statistics and Informatics of World Health Organization, 2004.)

It is important to highlight that all estimates presented by the World Health Organization are based on systematic assessments of the available data on incidence, prevalence, duration, and severity of a wide range of conditions, which are themselves often based on inconsistent, fragmented, and partial data from different studies. This means that there are substantial data gaps and uncertainties (Department of Health Statistics and Informatics of World Health Organization, 2004).

Mortality of dementia

(Guehne *et al.* 2005) conducted a review study of the mortality risk in dementia and potential influencing factors, based on population-based samples. They found that apart from the methodological differences between longitudinal population-based studies, which this chapter will later cover intensively, all types of dementia, without exception, were associated with a considerably increased mortality risk. Moreover, the risk of death rises with advancing severity of the disorder. The authors recommended the use of incident dementia cases to calculate the course of dementia and the mean survival time more precisely. For incident cases of dementia, the time of onset of the disorder could be assumed to be the midpoint between baseline and follow-up interview or date of death, provided that the follow-ups were conducted at short intervals. However, only few studies have based their finding on incident cases. Aguero-Torres *et al.* (1999) calculated a mean survival time of 3.0 years among 75-year-old patients with incident dementia, in contrast to a mean survival time of 4.2 years for persons without dementia. (Helmer *et al.* 2001) reported a mean survival time in incident cases of 4.5 years among 65-year-olds and a relative

risk of 1.8 (95% CI = 1.8, 2.7). (Xie *et al.* 2008) observed median survival time of 4.1 years (interquartile range 2.5–7.6) for men and 4.6 years (2.9–7.0) for women. Regarding the influence of education and occupation, some studies have found individuals with dementia and lower education having a *higher* survival time (Helmer *et al.*, 2001; Qiu *et al.*, 2001). A shorter survival time for highly educated individuals with dementia could be explained by their ability to continue living an effective and independent life for longer, resulting in the late recognition of the disease. It is presumed that there is a similarly fast progression of the underlying pathological processes, which means that, because of later recognition, highly educated persons may live with this condition for a shorter period of time, and, therefore, present an apparently higher mortality rate (Guehne *et al.*, 2005).

Mortality of depression

There is a well-established risk of suicide among individuals with depression and this risk is recognized not only among younger patients suffering from depression but also among older people. However, depression, especially in older people, can be a consequence of medical illness and disability, and it may also influence morbidity and mortality through a variety of behavioural and biological mediators (Schulz *et al.*, 2002). A systematic review examining the relationship between depression and nonsuicidal mortality reported that there is evidence supporting an association between the two and the mechanisms that might account for this relationship (Schulz *et al.*, 2002). They assessed the strength of the studies to enter in the revision according to criteria published previously (Wulsin *et al.*, 1999) which involves four components: sample size, measure of depression, choice of comparison group, and factors controlled for. With increasing sample sizes, higher rates of mortality are found. For measures of depression, there are higher rates of mortality when depression is assessed by structured diagnostic interview rather than psychiatric examination, and in turn these are both higher than self-report measures. Interestingly, for comparison groups, matched control groups had higher rates than cohorts, and both more than general population studies. Numerous factors have been controlled for, including age, sex, physical illness, smoking, alcohol, and suicidal behaviour. Of the studies that were restricted entirely to late-life population samples, 10 (67%) disclosed positive reports and 5 (33%), negative reports. Among those positive studies, the relative risks for depression as a predictor of mortality varied from 1.2–4.0, with the majority of studies falling in the 1.5–2.5 range. Depression might increase the likelihood of dying through several factors, such as poor adherence to treatment of comorbidities, poor maintenance of cognitive and physical functioning capabilities, and alienation from social networks. However, these associations do not point to a causal factor. (Schulz *et al.* 2002) proposed that a bidirectional model might be more promising to account for this relationship.

Methodology

Prevalence and incidence are heavily influenced by study design, methodological differences, population uptake, and cultural factors (Brayne, 1993). This has hampered worldwide comparisons. However, there are strong examples of standardized methods across combined studies, such as used in the 10/66 study discussed later in this chapter.

Case definition

To study disease incidence, prevalence, duration, and severity, the definition of what is a case is important. For some conditions, such as most infectious and parasitic diseases, this is a straightforward process. By isolating the aetiological agent or antibodies against the agent, the presence of disease can be determined. In some individuals this may manifest in clinical symptoms, while in others it may not. However, with neuropsychiatric disorders the diagnostic process is less clear since diagnosis is mainly based on a combination of symptoms, their quantity, and intensity. Therefore, there is more difficulty in conceptualizing what is a mental disorder and in determining whether it is present or not. This is particularly difficult among the older population, since medical comorbidity is common and may affect symptom profiles and interfere with functioning through, for example, polypharmacy and disease-related effects on mood and other mental functions.

Cultural aspects

Cultural concepts of diseases may lead to different expectations of what is considered mentally normal. World-views towards ageing vary immensely and as a consequence cultural concepts influence the awareness of diseases, especially mental disorders, and the utilization of services.

There have been examples over time of studies examining native and migrant populations. In a study of Cree Indians living on two reserves in Manitoba (Canada), age-adjusted prevalence of dementia was equivalent to whites living in Winnipeg (4.2% both groups), but AD prevalence was lower (0.5% vs. 3.5% in whites) (Hendrie *et al.*, 1993). In the UK, vascular dementia has been found to be more prevalent than AD in individuals of African-Caribbean origin (vs. British whites) (Richards *et al.*, 2000; Livingston *et al.*, 2001). (Paraiso *et al.* 2011) found that dementia in an urban area of Benin (West Africa) was slightly more prevalent than in a rural area of Benin, but the rate was similar to that recorded in other cities in

LAMIC.

Besides genetic factors, other features could explain different prevalence estimates for dementia between different populations. First, symptoms have to be perceived as an abnormal feature. Variation in the environment, including education and social meaning of cognitive changes with ageing, all influence how soon individuals seek medical help. Furthermore, different approaches to cognitive testing may direct towards a diagnosis.

In a study of impressions of the onset and diagnosis of dementia among African-American, Chinese, and Latino family caregivers in the US, minority ethnic groups were found to convey striking crosscultural similarities in the characterization of initial memory changes as normal ageing (Mahoney *et al.*, 2005). As dementia symptoms progressed, however, cultural differences emerged. Normalization of cognitive symptoms until the precipitation of one critical event appeared to be most prolonged among African-Americans; Chinese seemed to be the most concerned about stigmatization.

In the clinical setting, patients or carers have to perceive a symptom as an abnormal feature to seek help and for the person to be defined as a case. In contrast, in most of the epidemiological studies, a case is defined by means of structured questionnaires in which responses will be balanced to check against a set of operational criteria; therefore, it does not rely solely on an informant's opinion, but on informant standardized information, which in essence can minimize cultural bias.

Diagnostic methods

The World Health Organization (WHO) suggested that the most standardizable, countable and comparable units of observation in case-finding techniques should be based on symptoms. Moreover, the data collected should then be further organized into syndromes, and, in a third stage, into recognized diagnostic entities (WHO Expert Committee on Mental Health, 1960).

Attempts have been made to deal systematically with the concepts and methods of assessment. However, depending on the system of diagnostic classification used for case definition, an individual can be identified as being a case according to one system, but not a case on another. For most neuropsychiatric disorders, different diagnostic classification systems include different combinations of symptoms that reflect impairments in cognitive, emotional, and social abilities to inform the process of diagnosis. Therefore, the use of different criteria jeopardizes comparisons between studies, as they may classify the participants differently (e.g. diseased vs. not-diseased) (Erkinjuntti *et al.*, 1997).

(Erkinjuntti *et al.* 1997) examined the effects of six commonly used classification schemes on the prevalence of dementia in a population-based cohort of older people. The classification schemes used were the Third Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) (American Psychiatric Association, 1980), the DSM-III-R (American Psychiatric Association, 1987), the DSM-IV (American Psychiatric Association, 1994), the Ninth Edition of the international classification of diseases (ICD-9) (World Health Organization, 1977), the ICD-10 (World Health Organization, 1992), and Cambridge Mental Disorders of the Older Population Examination (CAMDEX) (Roth *et al.*, 1986). They found that although there was substantial overlap among the groups of persons identified by the various systems, the frequency of dementia varied depending on the scheme used. The frequency of dementia was 3.1% using the ICD-10, 4.9% with CAMDEX, 5.0% with ICD-9, 13.7% with DSM-IV, 17.3% with DSM-III-R, 20.9% according to the Canadian Study of Health and Aging (CSHA) clinical-consensus method (1994), and 29.1% with the DSM-III criteria. However, while dementia prevalence varied depending on the diagnostic criteria used, the frequency of dementia increased with increasing age for each classification method.

The ICD has existed for more than a century; it is global, multidisciplinary, and multilingual and is ratified by all 193 WHO member countries. On the other hand, the DSM developed by the American Psychiatric Association focuses specifically on mental disorders and it does not have such an international approach. As diagnosis in psychiatry is mostly descriptive and based on a collection of symptoms, the ICD and DSM diagnostic classifications are functionally equivalent in clinical settings. However, in epidemiological studies where structured interviews are usually employed, such differences become more important (Andrews *et al.*, 1999).

Another methodological issue regarding the diagnosis of dementia or its subtypes is that diagnostic criteria have changed over the years as new investigations became available. To illustrate this, the diagnosis of probable dementia with Lewy bodies (DLB) was initially based simply on clinical criteria, such as the presence of dementia, visual hallucinations, fluctuations, and parkinsonism (McKeith *et al.*, 1996). However, the third report of the consortium on DLB international workshop (McKeith *et al.*, 2005) included dopamine transporter imaging among the diagnostic criteria. This technique is a functional imaging of the dopamine transporter and defines integrity of the nigrostriatal dopaminergic system. Regarding neuropathological criteria, originally the only requirement for DLB was the presence of Lewy bodies somewhere in the brain of a patient with a clinical history of dementia, whereas the new criteria take into account the extent of Lewy body-related

pathology and AD-type pathology in assessing the degree of certainty that the neuropathological findings explain the DLB clinical syndrome. Moreover, the use of new immunohistochemical staining techniques such as alpha-synuclein have been proposed to replace the former ubiquitin immunohistochemistry, as alpha-synuclein has been shown to be a more sensitive and specific method for detecting Lewy bodies.

Diagnostic criteria for vascular dementia and AD have also changed according to the influence of available technology. (Roman *et al.* 1993) emphasized the importance of brain imaging to support clinical findings for vascular dementia. For AD, as the amyloid-imaging positron emission tomography (PET) tracer, termed Pittsburgh Compound-B (PIB) (Klunk *et al.*, 2004), provides quantitative information on amyloid deposits in living subjects, it is likely that fairly soon this technique will be introduced into diagnostic criteria for AD.

This instrumentalization of medicine impacts on epidemiology as medical diagnosis, theoretically, becomes more accurate and effective, but at the same time these technologies might label individuals as diseased without them having experienced any symptoms at all, and without knowing if they will ever present symptoms of the given disease. From an epidemiological perspective, the critical fact here is how these newly suggested criteria perform in samples representative of the general population. It is important to highlight that although dementia is considered a progressive disorder, in population settings, the course of the deterioration of the symptoms is not always inexorable, especially when the symptoms are mild.

Classification problems also emerge when attempts to define the transitional state between 'normal' ageing, pathological decline, and progression into dementia are made. Although several classification systems claim to represent this intermediate stage, their criteria differ slightly, so different outcomes are to be expected. To illustrate this, (Matthews *et al.* 2008) compared the 2-year outcome of 16 different classifications in the same population-based setting. They found that the overall progression was highest in classifications in which impairment extended to memory and nonmemory domains, such as multiple domain mild cognitive impairment (m-MCI) (14.3%), mild neurocognitive disorder (MNCD) (31%), and mild cognitive disorder (MCD) (29%). On the other hand, the conversion rate for age-consistent memory impairment (ACMI) was 0.3% and for age-related cognitive decline (ARCD) was 4%, showing that they captured a lower-risk group in the population with greater stability and reversion to normality.

In many clinical research centres, the diagnosis of dementia is made based on a consensus approach, which relies on a multidisciplinary panel of expert clinicians who meet to review detailed information on various aspects of a given person, such as clinical examination, informant reports of cognition, behaviour, functional impairment, and neuropsychological diagnosis. This process allows each study participant to be individually considered in detail (Weir *et al.*, 2011). However, in such cases, the diagnosis process is inevitably influenced by the clinicians' philosophy, personality, discipline, culture, and inherent biases. Although clinical examination is of extreme importance, in the context of epidemiological research, to assure cross-study comparisons, it is crucial to standardize the process of data collection, such as cognitive function, activities of daily living (ADL), physical health, and behavioural and psychological symptoms of dementia. Otherwise, study validity might be jeopardized by between-clinician variability and changes in diagnostic criteria over time (Brayne *et al.*, 2011).

In the context of psychiatric studies, the Present State Examination was developed as a standardized instrument (Wing *et al.*, 1967). This instrument was adapted by (Copeland *et al.* 1976) to become the Geriatric Mental State (GMS) Examination, which was designed to detect dementia, depression, and other mental illness in the older population by generating diagnostic algorithms (Copeland *et al.*, 1986) validated against the clinical diagnostic process based on the DSM-III-R. The aim was to introduce a more structured approach to diagnosis that could be used by nonclinicians. Unlike clinicians who quickly narrow down to the presenting diagnosis, structured interviews systematically explore each diagnostic criterion before assigning a diagnosis. Studies with a large number of participants make a quasiclinical diagnosis possible by adopting this diagnostic algorithm based on the assumption that interviewers are trained to administer questions or conduct examinations in a standardized manner (Brayne *et al.*, 2011). Recently there has been renewed interest in the algorithm approach (Weir *et al.*, 2011).

Interviews

Data collection can be made by means of a written questionnaire, telephone interview, and face-to-face interview with participants or their informants, or even extracted from case records and death certificates. Semistructured interviews are preferred when there is the need to gather qualitative data, whereas in structured interviews standardization is easily obtained in detriment of qualitative information. In structured interviews, there is a tightly scripted text from which the interviewers are not supposed to deviate. Examples of highly structured interviews are the CAMDEX (Roth *et al.*, 1986) and the Geriatric Mental State Examination/Automated Geriatric Examination Computer Assisted Taxonomy (GMS/AGECAT). The neurological examination in the CAMDEX is more comprehensive than the GMS. The 10/66 study, which demands that the data are highly standardized due to cross-country data collection, has used two approaches for dementia diagnosis: one based on GMS/AGECAT and the other based directly on DSM-IV criteria.

Interviewers

In large-scale surveys, there is a tendency to recruit nonclinical interviewers to collect the data, provided the interview is structured. Naïve trained interviewers are known to be very adept at administering structured interviews in a consistent manner. Depending on what is included in the assessment protocol, there may still be a need for qualified professionals. For example, if a physical examination is intended, a doctor would normally be required (Butler and Brayne, 1998). In some multistage studies, lay interviewers are used in the first stage and medical doctors in subsequent stages, as in the ALPHA Liverpool study (Saunders *et al.*, 1993) and in the Nakayama study (Ikeda *et al.*, 2001). In the Soham study, a clinician administered the CAMDEX to all participants (Brayne *et al.*, 1997).

Sampling

To define the sampling frame of a study, the site of the study has to be defined, as well as the sample procedure. The study site might be defined geographically or, for example, be composed of individuals registered in a specific organization, such as a primary care trust, hospitals, healthcare system, retirement community, nursing home, or participants of an electoral register. The sample procedure might include the entire population above a certain age, or use a sampling strategy to select a representative subgroup of manageable size, such as random selection or systematic selection. Furthermore, stratification according to age groups, sex, and other variables can be used so as not to overrepresent groups.

Population-based studies

Few studies are truly representative of the whole population. Many others would be more accurately described as population derived: for example, many exclude individuals in institutions. There are studies where a general population defined by geographical boundaries is the sampling frame (Poels and Last, 2008). It is well known that referral of patients can cause population bias, affecting the results of epidemiological studies (Sackett, 1979). According to the Goldberg–Huxley model of the pathway from the community to the hospital in terms of psychiatric care, there are five levels and four filters (Goldberg and Huxley, 1980). People with severe illnesses pass more easily through the filters to secondary professional care than do people with common mental disorders.

Referral not only is influenced by the condition itself but also may vary according to burden of symptoms, family recognition of a problem, access to healthcare, popularity of the condition, and the presence of specialized centres nearby (Brayne, 1993). Furthermore, specialized patient research groups derived from referrals typically use stringent selection criteria so that patients are usually selected to have fewer comorbid conditions. As an example, the occurrence of behavioural symptoms among patients with dementia is often the triggering event for recognition and referral to healthcare rather than the cognitive impairment itself (Lawlor, 2002). It is therefore important to differentiate between population-based studies and community-based studies. Where the first is potentially of use for generalizing the findings to the whole population, the latter often is restricted to members of a selected community that does not necessarily represent the population. An example is the Nun study, where the entire community of nuns was involved in a long-term longitudinal study (Snowdon *et al.*, 1996). However, it is likely that this religious community is very different from any general population sample and therefore that the nature of risk exposure and outcome may be different from the general population. However, depending on the research question, some findings might be suitable for generalizing purposes.

Another point that should be highlighted is that some studies may exclude individuals who live in institutions. Many countries do not have the possibility of sampling from both general and institutionalized populations. This may lead to underestimation of prevalence and, in longitudinal terms, underestimation of decline or mortality. (Larson *et al.* 2004) reported findings from a survival study of community-dwelling patients with AD, where men had a median survival of 4.2 years from their initial diagnosis and women had a median survival of 5.7 years. These estimates were longer than the ones of the Canadian Study of Aging (Wolfson *et al.*, 2001), where the median survival was 3.17 years for men and 3.36 years for women. These differences may well be due to the fact that the Canadian Study of Aging included nursing-home residents, who were doubtless at a later stage of the disease.

Stratification

Some epidemiological studies of dementia have used more than one-stage diagnostic procedures to optimize resources. In the first stage, a brief and inexpensive screening instrument (such as the Mini-Mental State Examination (MMSE)) is administered, followed by more complex, time-consuming, and expensive tests in the second stage. Typically, all those people who screen positive (e.g. below a cut-off score on the MMSE), along with a random sample of the rest, are seen again using more comprehensive diagnostic tools, which usually include a structured clinical assessment, a more extensive multidomain test of cognitive function, and a structured interview with an informant. The second-stage assessment may also include a physical examination, brain scan, and collection of biological samples. Although a multistage design makes

diagnostic procedures more efficient, it carries a serious problem of refusal or nonavailability. Furthermore, it is more prone to bias due to incorrect analysis of partially verified data, where the screened negative participants who were not selected for the second stage are considered as true negatives or are simply excluded from the analysis. As a consequence, sensitivity and specificity are poorly estimated (Yu and Zhou, 2012). Other studies, to overcome these biases, randomly select the participants for the second stage, weighting towards cognitive impaired persons to allow for inferring the sample results back to the whole population (The Medical Research Council Cognitive Function and Ageing Study (MRC CFAS), 1998). But the analyses are rarely indicated with full attention to the multiple stages and rates of dropout (Matthews, 2005). This overinflates power in that the reported confidence intervals are in fact too narrow.

Screening tool: a focus on the MMSE

The MMSE is one of the most widely applied tools in clinical and research practice to screen for cognitive impairment and dementia. However, there are disagreements regarding the best cut-off score to distinguish impaired versus not-impaired (e.g. 18, 21, 22, 24, or 26) and whether cut-off scores should be adjusted for age and education levels. In high-functioning samples, the MMSE is found to suffer from ceiling effects, and in low-functioning samples, from floor effects too. Both extended, such as the extended mental state examination, (Huppert *et al.*, 2005) and abbreviated versions, such as the 11-item version used in the European Prospective Investigation into Cancer (EPIC-Norfolk (Matthews *et al.*, 2011)), have been created to overcome these issues. Further, due to copyright law restrictions, new brief and free screening tests that also measure cognitive function, such as the Sweet-16 (Fong *et al.*, 2011), are becoming available and are likely to become widely used.

Influence of other variables

Performance on cognitive tests may be influenced by many factors other than cognitive impairment, such as educational background, cultural experiences, prior testing experience, emotional and physical states, the testing environment, use of medicines, and measurement error. This makes it difficult to control and compare such measurements in different studies even if the same tool is used to assess cognition. Furthermore, most tests currently used are subject to ceiling and floor effects (The Medical Research Council Cognitive Function and Ageing Study (MRC CFAS), 1998; Morris *et al.*, 1999).

Missing data

Almost all studies have some missing observations. Missing data can arise for two main reasons: missing values due to nonresponse at baseline, death, or dropout of the study, and item nonresponse. Longitudinal and multistage studies are especially prone to be subject to missing data due to death or dropout. The main concern is that in those cases, missing data are not at random and do affect final estimations. Participants with cognitive impairment are more likely to drop out from a study than healthy individuals. (Chatfield *et al.* 2005) performed a systematic review to investigate large population-based studies of the older population that report on attrition between waves of a follow-up in a systematic manner. The review concentrated on dropout due to refusal, sickness, inability to locate individuals, and individuals moving away from a defined study area. They found that increasing age and cognitive impairment were the two main independent factors related to increased attrition. People who were very ill or frail had higher dropout rates, and people in worse health were less likely to be contactable on a second occasion. As these factors are not preventable, the authors suggested that oversampling of these groups in the initial phases could be used to ensure that sufficient numbers of participants remain at follow-up. Also, the follow-up methods can be adjusted to ensure maximum participation in those individuals with cognitive impairment. The length of the interview can be modified and a proxy interview can be used in a wider range of situations (Chatfield *et al.*, 2005). (Saxton *et al.* 2009) compared rates of MCI and rates of progression to dementia using different MCI diagnostic systems and, regarding dropouts, they found that MCI status at baseline was significantly associated with dropouts lost to follow-up. Obviously, loss of participants also reduces the power of a study.

Missing data are even more common in retrospective studies, in which routinely collected data are subsequently used for a different purpose. When information is gathered from participants' medical records, the notes often do not point to whether or not a participant has the aimed risk factor. It is unwise to assume that the answer is not present when there is no indication that the risk factor was present (Altman and Bland, 2007). There is no really satisfactory solution to the problem of missing data. The main ways of handling missing data in analysis are omitting variables or individuals who do not have complete data; or imputation, whereby missing values are estimated from that individual's available data (Altman and Bland, 2007). Ignoring missing data in the analysis is a common approach; however, it might bias the results, as the data are rarely missing at random in cohort studies. Although imperfect, multiple imputation is recommended for handling missing data. Such models not only can control for the fact that dropout has occurred, but also, where available, may include information on the reason for dropout. Following imputation, sensitivity analysis can be run to check for similarity in observed associations in the restricted (e.g. complete-case analysis) compared to the imputation-derived dataset.

Age, period, and cohort effects

Age, period, and cohort effects are closely interrelated, as age is the result of a given year (period) minus the year of birth (cohort). Szklo and Nieto (2007) proposed a definition of age, period, and cohort effects, where age effect is the change in the rate of a condition according to age, irrespective of birth cohort and calendar time; cohort effect is the change in the rate of a condition according to year of birth, irrespective of age and calendar time; and period effect is the change in the rate of a condition affecting an entire population at some point in time, irrespective of age and birth cohort. To better understand age and cohort effects definitions, it is easier to approach them by fixing one parameter.

Age effect: let us suppose that the prevalence of a condition was measured in a single group of people born in the same year (single birth cohort) in wave-1. Five years later, the prevalence of the same condition was measured again (wave-2), and 10 years later (wave-3) in the same original group of people. If the prevalence of this condition changes between waves, this is a representation of an age effect.

Cohort effect: this can be obtained when a study is interested in looking at a prevalence of a condition only at a given age (let us say 60 years) and does so by recruiting 60-year-old individuals in wave-1, a different group of 60-year-old individuals in wave-2, and a third 60-year-old group in wave-3. If the prevalence of this condition changes between waves, this is a representation of a cohort effect, as, in fact, the different birth cohorts were compared longitudinally. The cohort effect can be seen as a result of the risk factors and environmental exposures that are present in early life or are typical for a given generation.

Period effects: these are the consequences of any phenomenon occurring in a specific point in time, which affects the entire population, reflecting in changes in prevalence of a given condition across all age groups and birth cohorts (Szklo and Nieto, 2007). This is the case of wars, new curative treatments, vaccines, etc.

Regarding dementia, age effects are well established across studies, but cohort effects are controversial. In the Lundby study, from 1947–1972 to 1972–1997, a decrease in the incidence of dementia was found in all age groups except in the 40–49 interval (Bogren *et al.*, 2007). Whether or not it is a true cohort effect or an artefact is not known. On the other hand, (Rocca *et al.* 2011) analysed data from four studies to verify if declines in age-specific prevalence and incidence rates for dementia have occurred in recent years. Three of those were community-based studies: one conducted in Rochester, Minnesota (1975–1994) (Knopman *et al.*, 2006), the Indianapolis branch from the Indianapolis-Ibadan Dementia Project (1992–2001) (Hendrie *et al.*, 1995), the Chicago Health and Aging Project (1997–2008) (Hebert *et al.*, 2010), and a national survey, the Health and Retirement Study (<http://hrsonline.isr.umich.edu>) (Juster and Suzman, 1995). In the Minnesota cohort, there were no differences in incidence across the 10 birth cohorts, but a marginal decline for dementia was observed. The Chicago Health and Aging Project did not find a relationship between calendar year of evaluation and disease incidence, which suggests no change in incidence over time. In the Indianapolis-Ibadan Dementia Project, although they found that the 2001 cohort had higher levels of hypertension, diabetes, and stroke, there were no differences in the prevalence of dementia. The Health and Retirement Study did not assess dementia directly, but ‘cognitive impairment consistent with dementia’ (CI-D) based on a 35-point cognitive scale or proxy’s assessment of the respondent’s memory for those who were not self-respondents. The authors reported that the prevalence of CI-D had an absolute decrease of 3.5% points, and a relative decrease of nearly 30.0%. Furthermore, the prevalence of some cardiovascular risk factors increased significantly, but higher levels of education were found in the most recent cohort.

The ZARADEMP project (Lobo *et al.*, 2007) investigated possible cohort effects regarding the prevalence of dementia in Zaragoza, Spain, for 1988 versus 1994. The authors found that there was stability in the global prevalence of dementia over time, but a decrease among men aged between 70 and 84 years. It is interesting to note that the prevalence of dementia in men found in the first cohort was also higher than in European, pooled data reported during the EURODEM Concerted Action study (Lobo *et al.*, 2000). Although in ZARADEMP the two time points were probably too close together to detect differences in environmental exposure, the authors pointed out that the Instituto Nacional de Estadística (<http://www.ine.es/>) had reported improved control of potential risk factors for dementia, such as smoking habits, diabetes, and cardiovascular disorders in Spain.

Despite these methodological challenges, considerable attempts have been made to compare and combine findings from epidemiological studies that focus on the most common and debilitating neuropsychiatric disorders in old age psychiatry, including dementia and depression. These studies are presented in this chapter.

The importance of neuropathological studies in the epidemiology of dementia and its subtypes

‘Plaques’ in cerebral grey matter were first described by Blocq and Marinesco in 1892 and related to the pathology of senile dementia by Simchowicz, who named them as ‘senile plaques’ (Blessed *et al.*, 1968). In 1907, the neuropathological findings of neurofibrillary tangles in the degenerated neurons and senile plaques deposited in the cortex were first linked to a presenile

dementia syndrome (Alzheimer *et al.*, 1995). At first, this combination of presenile dementia, neurofibrillary tangles, and senile plaques, described by Alois Alzheimer, was recognized as a rare disease separated as a distinct entity from senile dementia, and was baptized as Alzheimer's disease (Berrios, 1990; Zilka and Novak, 2006). These ancient reports were based on case reports and small groups of patients.

It was not until 1966 that an investigation of the nature and extent of the relationship between plaque formation and mental deterioration in old age was undertaken in a clinic-based study (Roth *et al.*, 1966) conducted on patients admitted to a psychiatric hospital, a geriatric hospital, and several wards in a general hospital. The severity of dementia in individuals during life was ascertained to determine whether this bore any relationship with mean plaque counts in cerebral grey matter. These assessments were repeated at 6-monthly intervals on survivors. Roth *et al.* concluded from the results of 37 patients that, far from being irrelevant for the pathology of old-age mental disorder, the density of plaque formation in the brain was highly correlated with quantitative measures of intellectual functioning. When the sample was expanded to 60 patients the results were consistent, showing a highly significant correlation between mean plaque counts and scores for dementia and performance in psychological tests (Blessed *et al.*, 1968). The plaques seen in authenticated cases of AD were indistinguishable on light microscopy from those investigated in their study. This observation led to the realization that half or more cases of senile dementia were associated with the same neuropathology that characterized the early onset dementia of AD.

Significant knowledge of the clinical features and the neuropathology of the different types of dementia has come from observations on the brains of individuals with dementia from nursing homes, acute medical units, hospitals, and ordinary postmortem series (Zaccai *et al.*, 2006). However, the nature of these services can lead to selection bias, which influences the findings of the studies. (Schneider *et al.* 2009) investigated the differences in neuropathological findings from persons with and without dementia in clinical versus community-based settings. They compared the neuropathology underlying no cognitive impairment, MCI, and dementia from two community-based cohorts and one clinic-based cohort. They found that community-based participants with probable AD showed less severe AD pathology and more often had infarcts and mixed pathologies; while those with MCI more often had infarcts and mixed pathologies. Also, clinic-based individuals had more Lewy bodies and atypical pathologies. Based on these results, the authors concluded that the spectrum of pathologies underlying cognitive impairment in clinic-based cohorts differs from community-based cohorts (Schneider *et al.*, 2009).

For extrapolation of results to the population to be valid, research must be conducted on a true population sample, or on groups with well-characterized biases.

As dementia is a chronic and progressive disorder, it is impossible to determine the exact point when an individual became demented. In addition to uncertainty regarding symptom onset is a lack of certainty in diagnosis. In interobserver studies, the clinical diagnosis of AD is not 100% correct in all cases (Holmes *et al.*, 1999; Xuereb *et al.*, 2000; Richards and Brayne, 2010; Scheltens and Rockwood, 2011). Some classification criteria, such as the NINCDS—ADRDA, rely on histopathological confirmation to diagnose AD as a definite condition (McKhann *et al.*, 1984). As a consequence, AD is therefore framed as a neuropathological entity in spite of the fact that the diagnosis of AD in living patients is made on the basis of clinical information (Richards and Brayne, 2010). In contrast, dementia is a syndrome rather than a neuropathological diagnosis (Xuereb *et al.*, 2000), and so a clinical diagnosis of AD assumes dominance of Alzheimer pathology as the cause of dementia in those patients.

The pathological criteria for AD were derived from brains originally from a highly selective clinical sample. However, the brains of people included in truly population-based neuropathological studies of dementia have a high percentage of mixed pathologies, which challenges the pathology-led model of diagnosing definitive AD. The first study to disclose such a pattern in a systematic way reported on autopsied brains of 101 participants (Xuereb *et al.*, 2000). These findings were ratified when the sample was augmented to 213 brains (Brayne *et al.*, 2009), where 22% of the brains of participants clinically diagnosed as having dementia had mixed pathologies. (White *et al.* 2002) in the Honolulu-Asia Aging study also presented similar findings on 285 donated brains, where 16% of the clinically demented decedents had mixed pathologies. The Hisayama study, based on 275 autopsied brains, reported an even higher proportion of mixed pathologies (34%) among those with clinical dementia (Noda *et al.*, 2006). Also, the neuropathology group from the CFAS cohort have emphasized the high prevalence of vascular pathology in this population and the common occurrence of a mixture of both AD and vascular pathology (Neuropathology Group, 2001).

Part 2 Review of Major Studies in Old Age Psychiatry

This section summarizes some of the most important and informative epidemiological studies on cognitive and other mental changes in old age. Three main types of study are discussed: combined studies; studies that have used a synthesis of the literature with data from several sources; and longitudinal studies. There are several difficulties in examining epidemiological

studies in the context of dementia; for example, some studies report on overall dementia estimators, whereas others restrict their reports to AD, using this term almost as a synonym of dementia, disregarding the existence of mixed pathologies.

Combined studies

In this section, the following combined studies for the epidemiology of dementia are presented: the EURODEM initiative and the 10/66 Dementia Research Group.

The EURODEM initiative

In the early 1990s, there was a collaborative initiative of all major European groups working on the epidemiology of dementia, organized by EURODEM, EC Concerted Action on the Epidemiology of Dementia (Hofman *et al.*, 1991). A total of 20 centres took part and contributed original data of 23 population studies published between 1980 and 1990, from which 12 were included in the analysis. Those studies that were methodologically similar and suitable for comparison were selected to describe geographical differences and to provide an overall estimate of the prevalence of dementia in Europe. The study confirmed the steep rise of dementia prevalence with age, showing that within 5-year age groups the prevalence of dementia almost doubles from the age group 65–69 onwards. No major differences were noticed regarding sex; however, the overall estimates were somewhat larger for men than for women until the age of 75 years and somewhat larger for women over the age of 75 years. These patterns were similar across the 12 studies (Hofman *et al.*, 1991). Only 2% of cases were found in those less than 65 years.

An incidence phase of the EURODEM initiative was conducted and included results of analyses based on pooling the data from the studies conducted in Denmark, France, the Netherlands, and the UK (Launer *et al.*, 1999). In Denmark, the Odense Study (Andersen *et al.*, 1997) had a baseline cohort of 3,346 persons; in France, the PAQUID study (Letenneur *et al.*, 1994) included 3,777 individuals at baseline; in the Netherlands, the Rotterdam study (Ott *et al.*, 1995) had a baseline cohort starting from 65 years of 5,265 persons; and in the UK, the MRC-ALPHA study (Saunders *et al.*, 1992) had a baseline cohort of 5,222 participants. In this pooled analysis of individuals 65 years and older, 528 incident dementia patients were reported and 28,768 person-years of follow-up. Incidence rates for dementia were similar across studies and increased with age; at 65 years of age, the incidence rate for dementia was 2.5 (95% CI = 1.6, 4.1), and at 90+ years the rate was 85.6 (95% CI = 70.4, 104.0) per 1,000 person-years. The study investigated potential risk factors for dementia, and found that current smoking and low levels of education increased the risk of dementia significantly. A history of head trauma with unconsciousness, female gender, and family history of dementia, did not increase risk significantly.

The 10/66 Dementia Research Group

The 10/66 Dementia Research Group (www.als.co.uk/1066/) brings together researchers with an interest in ageing in LAMIC, including determination of the prevalence and incidence of dementia and noncommunicable diseases (Prince *et al.*, 2007).

Cross-sectional comprehensive one-phase surveys have been conducted of all residents aged 65 and over of geographically defined catchment areas in ten LAMIC (India, China, Nigeria, Cuba, Dominican Republic, Brazil, Venezuela, Mexico, Peru, and Argentina), with a sample size of between 1,000 and 3,000 in each site. Overall, 14,960 individuals completed the prevalence study. Response proportions varied between 72% and 98% (Llibre Rodriguez *et al.*, 2008). Two approaches were used for dementia diagnosis. The first was based on a regression equation developed in the 10/66 international pilot study that uses coefficients derived from the GMS/AGECAT (Copeland *et al.*, 1986), Community Screening Instrument for Dementia, and ten word-list learning tasks (Prince *et al.*, 2003). This approach has been validated for crosscultural settings and is sensitive to educational status (a large proportion of older aged individuals in LAMIC have little or no education), and regional variation, particularly associated with diversity in language and culture. The second approach applied DSM-IV criteria directly (American Psychiatric Association, 1994). For diagnosis of dementia subtypes the following criteria were used: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) AD criteria (McKhann *et al.*, 1984), National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN), vascular dementia criteria (Roman *et al.*, 1993), and Lewy body dementia criteria (McKeith *et al.*, 1992).

10/66 study: dementia

Across 10/66 regions, dementia prevalence varied between 5.6% and 11.7% using the regression equation. When DSM-IV criteria were applied directly, prevalence varied between 0.4% and 6.4%. Prevalence determined by the 10/66 equation was higher at every site, and generally double that estimated using direct application of the DSM-IV criteria (Llibre Rodriguez *et*

et al., 2008). Comparison of the prevalence of dementia reported in the EURODEM meta-analysis with prevalence reported using the DSM-IV criteria in the 10/66 sites found large variation: the prevalence in urban Latin American sites was about four-fifths of that in Europe, the prevalence in the Chinese sites was just over half, and that in rural Latin American and Indian sites only between a quarter and a fifth (Llibre Rodriguez *et al.*, 2008).

10/66 study: depression

Depression, anxiety, and the co-occurrence of anxiety and depressive syndromes have been investigated amongst the 10/66 centres (Prina *et al.*, 2011). Anxiety was measured by using the GMS/AGECAT and depression was assessed according to ICD-10 and EURO-D criteria.

The prevalence of depression according to the ICD-10 was reasonably consistent across Latin America and India (range 4.9–13.8%) but was much lower in the Chinese site. A similar pattern was also found for the distribution of anxiety (range excluding China: 2.3–8.9%). The prevalence of co-occurring anxiety and depression ranged between 0.9% and 4.2% across sites. Having both disorders was linked to higher disability scores than having anxiety or depression alone. This has major implications for treatment outcome, which is found to be worse in individuals with comorbid anxiety and mood disorders compared to individuals suffering from depression alone (Prina *et al.*, 2011).

10/66 study: summary

The 10/66 Dementia Research Group focuses on the study of dementia diagnosis among populations in LAMIC. Their population-based surveys will provide a unique resource for comparative descriptive research of not only prevalence and incidence, but also its effects, risk factors and costs, interventions, estimations of need, roles of racial mixture, micronutrient deficiency, and cardiovascular disease.

Synthesis of literature

In this section, the following studies for the epidemiology of dementia are presented: Worldwide Prevalence and Incidence of Dementia; Delphi consensus study; Meta-analysis of dementia incidence; World Alzheimer Report 2011.

Worldwide Prevalence and Incidence of Dementia

The Worldwide Prevalence and Incidence of Dementia (Fratiglioni *et al.*, 1999) paper reviews the prevalence and incidence data for dementia reported in the international literature in the last 10 years. Results from 36 prevalence and 15 incidence studies reported from 1989–1999 found an increase in dementia with age. Worldwide dementia prevalence was estimated to be 0.3–1.0 per 100 people in individuals aged 60–64 years and 42.3–68.3 per 100 people in individuals aged 95 years and older. Incidence rates ranged from 0.8–4.0 per 1,000 person-years in people aged 60–64 years, and increased to 49.8–135.7 per 1,000 person-years when the population was older than 95 years. Geographical variation in prevalence and incidence was low, with differences between countries largely reflecting methodological rather than real differences. Regarding the dementia subtypes, AD was always the leading type of dementia in all continents. However, the relative proportions attributed to AD and vascular dementia seemed to differ among continents and multiethnic communities of western countries. North America had the highest relative proportion of AD among all the dementing disorders (74.5%), whereas Asia had the least relative proportion of AD (46.5%). The prevalence of vascular dementia ranged from 10.0% in North America to 38.1% in Asia. Differences in diagnostic criteria and procedures might account for these inconsistencies.

Delphi consensus study

Alzheimer's Disease International convened an international group of experts to generate up-to-date evidence-based estimates for the prevalence of dementia for each world region (Ferri *et al.*, 2005). The authors used the Delphi consensus method, which in essence derives quantitative estimates through the qualitative assessment of evidence where studies of widely different design and quality can be assessed. When published information is scarce, experts can make inferences using other data from comparable contexts. Although studies varied widely in quality, methodology, and dementia outcome definition, the only inclusion criterion was that the study should be population-based. They found that the seven countries with the largest number of people with dementia in 2001 were: China (5.0 million), the European Union (5.0 million), the US (2.9 million), India (1.5 million), Japan (1.1 million), Russia (1.1 million), and Indonesia (1.0 million). They estimated that 24 million people had dementia in 2005 and that this amount would double every 20 years, to 42 million by 2020 and 81 million by 2040, assuming no changes in mortality and no effective prevention strategies or curative treatments.

Meta-analysis

Jorm and Jolley (1998) conducted a meta-analysis of the age-specific incidence of all dementias, including AD and vascular dementia. The inclusion criteria were: case finding should be based on a field survey or studies of medical and social agencies, excluding purely hospital-based case register studies; age-specific incidence of dementia had to be reported for age groups spanning 10 years or less; the study had to involve a population-based sample rather than volunteers; incidence rates had to be reported for mild or moderate dementia; and data needed to calculate the standard errors of incidence rates had to be available or accessible from the authors. The final analysis was based on data from 23 studies and showed that the incidence of both dementia and AD rise exponentially up to the age of 90 years, with no sign of levelling off, whereas the incidence of vascular dementia varied greatly. There was no sex difference in dementia incidence, but women tended to have a higher incidence of AD in very old age and men tended to have a higher incidence of vascular dementia at younger ages. East Asian countries had a lower incidence of dementia than European countries.

World Alzheimer Report 2011

The Alzheimer's Disease International World Alzheimer Report 2011 was based on a series of systematic reviews conducted by an independent research group to collate and review all of the available evidence relating early diagnosis of and early intervention in dementia (Alzheimer's Disease International, 2011). They reported the crude prevalence estimates of dementia in individuals aged 60+ in 2010 ranging from 2.7% in Africa to 6.5% in the Americas (world prevalence estimate = 4.7%). They highlighted that current evidence suggests that available drug treatments and psychological and psychosocial interventions can be effective in ameliorating symptoms for people with dementia and in reducing strain among their carers during the early stages of the disease. The report also stresses that interventions for carers may be more effective in allowing them to continue to provide care at home, avoiding or delaying institutionalization of the person with dementia, when applied earlier in the disease.

Longitudinal studies

Numerous longitudinal studies on the epidemiology of depression and dementia, including its subtypes, have been undertaken in the last 50 years. We present a selection of the main, truly population-based, longitudinal studies throughout the years to illustrate methods and findings:

- ◆ Lundby study
- ◆ Iceland birth cohort
- ◆ Reykjavik study
- ◆ Gothenburg study
- ◆ Cambridge City over-75s Cohort Study (CC75C)
- ◆ Framingham study
- ◆ Established Populations for Epidemiologic Studies of the Elderly (EPESE)
- ◆ Gospel Oak study
- ◆ Cognitive Function and Ageing Study (CFAS)
- ◆ Rotterdam study
- ◆ Vantaa 85+
- ◆ Personnes âgées QUID (Paquid)
- ◆ Italian Longitudinal Study of Ageing (ILSA)
- ◆ The Three-City study (3C)
- ◆ The English Longitudinal Study of Ageing (ELSA)
- ◆ Newcastle 85+ study
- ◆ Epidemiological Clinicopathological Studies in Europe (EClipSE)

This cannot be comprehensive. In all of these studies we will focus on the papers that disclosed figures for prevalence and incidence of dementia and depression, and comment on possible additional findings in those papers.

Lundby study

The first and the longest comprehensive prospective study of an entire community with a focus on psychiatric epidemiology was conducted by Essen-Möller in 1947 (Essen-Möller *et al.*, 1956). This study had a unique place in the field of

epidemiology of not only old age psychiatry but also psychiatry overall, since it involved participants aged 15 years and over. The aim was to observe the entire population of a community in the south of Sweden, notionally called Lundby, to study individual traits and morbidity in a general population, not in patients. All but 1% of the 2,550 adult inhabitants of Lundby aged 15 years and over were examined (Henderson and Jablensky, 2010). This cohort was further re-examined in 1957, 1972, and in 1997. In addition to the psychiatric interview, and unlike most other surveys, information was obtained from multiple sources: face-to-face interviews, informants and community nurses, general practitioners, death registers, the Swedish psychiatric register, the national hospital inpatient register, and the local outpatient register. In 1972, the investigators were able to obtain sufficient information to reach a diagnosis on 99% of the cohort, and in 1997 on 94%.

The Lundby strategy is a marked contrast to today's large-scale surveys. Information was obtained by psychiatrists, who were free to explore the respondents' symptoms and behaviour at interview, rather than by lay interviewers who were required to complete a symptom checklist and follow a tightly scripted text from which they must not deviate.

Lundby study: dementia

The prevalence of all-cause dementia in both sexes in the Lundby study according to age group are shown in Table 5.2 (Hofman *et al.*, 1991).

Table 5.2 Prevalence of dementia (all types) in both sexes in the Lundby study according to age group

| Age group | Prevalence (%) | Number of cases | Number of groups studied |
|-----------|----------------|-----------------|--------------------------|
| 30–59 | 0.0 | 0 | 971 |
| 60–64 | 0.5 | 1 | 191 |
| 65–69 | 1.7 | 3 | 177 |
| 70–74 | 4.8 | 6 | 126 |
| 75–79 | 7.9 | 6 | 76 |
| 80–84 | 17.8 | 8 | 45 |
| 85–89 | 15.8 | 3 | 19 |
| 90–94 | 27.3 | 3 | 11 |
| 95–99 | 0.0 | 0 | 1 |

(Source: data extracted from Hofman *et al.* 1991.)

Male and female age-standardized first-incidence rates of dementia every fifth year from 1947–1997 are shown in Fig. 5.1. In both men and women, a trend of decreasing dementia incidence can be observed from 1947–1997 (Bogren *et al.*, 2007). The data between waves were gathered from all available sources, such as registers and case notes.

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Fig. 5.1

First-incidence rates of dementia in the Lundby study.

(Adapted with permission from Bogren, M., Mattisson, C., Horstmann, V., Bhugra, D., Munk-Jorgensen, P., and Nettelblatt, P. (2007), 'Lundby revisited: first incidence of mental disorders 1947–1997', *Australian and New Zealand Journal of Psychiatry*, 41 (2), 178–86. (c) Sage, 2007.)

This finding was unexpected and may be explained by the fact that the study ran when different principles of classification were used, possibly affecting diagnostic conclusions, or even because there was a difference in study waves regarding the number of supplementary sources of information concerning outpatient care and key informants, which in 1947–1972 was greater than in 1972–1997 (Bogren *et al.*, 2007). An alternative explanation is that it might be a genuine cohort effect, as the incidence of dementia could have fallen due to factors such as less medical comorbidity or healthier lifestyle.

Lundby study: depression

The median age at first onset of depression was reported to be around 35 years and the recurrence rate was about 40%. Transition to other diagnoses was registered in 21% of the total sample, alcohol disorders in 7%, and bipolar disorder in 2%. Five percent committed suicide, with increased risk of suicide associated with male sex and increased depression severity. Although figures are not specific for older individuals, the Lundby study showed that after the first onset of depression, 6% of men and 10% of women developed organic disorder or dementia (Mattisson *et al.*, 2007).

Lundby study: summary

The Lundby cohort has been followed prospectively during a period of great transition in society, which encompasses increased welfare, urbanization, and a change of societal structures, including development of public healthcare and education, entrance of women into the labour market, birth control, changes in family structure, lessening of the cohesive power of family, church, and community, and changing roles of men and women. Biological and physical factors have also undergone change, including changes of lifestyle (diet and tobacco use) and the availability of medical care, such as new drug therapies, as well as changes in the physical environment (Bogren *et al.*, 2007). Moreover, with the increase in life-expectancy, it is possible to distinguish two different profiles for the older old and the recent old.

Iceland birth cohort

The Iceland birth cohort consisted of all Icelanders born in the years 1895, 1896, and 1897, and focused on the investigation of psychiatric diagnosis. The study was completed in four phases: the first spanning from 14–61 years (Helgason, 1964); the second from 61–75 years; the third from 75–81 years; and the concluding phase extending from 81–87 years (Magnusson, 1989). Information on the mental health of each proband was collected from several different sources. In each phase, every general practitioner in the country was interviewed in a systematic manner by a psychiatrist, asking about mental symptoms of the probands in the cohort. Next, all records from every hospital and nursing home in the country were studied and crosschecked with the data provided by the general practitioners. When it was not possible to collect sufficient information to make a psychiatric diagnosis, other key informants were contacted, such as relatives, local nursing staff, and neighbours. This method of data collection is referred to as the indirect method since the information on mental and physical health did not come directly from the persons.

Diagnoses of psychiatric conditions were divided into three groups: the dementia syndrome, affective disorders, and other mental disorders. The accuracy of the information in the initial phases of this study depended on how well the informants knew the proband. In the last phase of the study, however, an interview scheme that covered the major symptoms and signs of mental disorders in the aged population was implemented to allow validation of the indirect method.

Iceland birth cohort: dementia

Dementia syndrome was initially diagnosed using information acquired from probands and records. Individuals were categorized according to severity as either mildly or severely demented. At later study stages, the participant was interviewed using the shortened version of the Geriatric Mental State Schedule. This allowed psychiatric diagnoses based on the computerized program AGE CAT (Copeland *et al.*, 1986). Comparison of dementia prevalence across methods indicated a tendency of the indirect method to overdiagnose. The average age was 87 years. Indeed, 46% of participants considered to be demented by the indirect method were not demented according to AGE CAT, whereas only 3% of the probands diagnosed as not having dementia by the indirect method were diagnosed as having dementia by AGE CAT (Magnusson, 1989). The prevalence of dementia according to the indirect method was 27% and according to AGE CAT was 17%. Most disagreement was in the group of participants considered to have mild dementia.

When examining the course of mild dementia in this cohort, Magnússon and Helgason (1993) found that many cases diagnosed as mild dementia by the indirect method had no or very few cognitive symptoms when the AGE CAT was applied. Almost 30% of cases of mild dementia diagnosed by the indirect method before the age of 75 years had no symptoms of dementia at the age of 81 years and more than 10% continued to have mild symptoms. Similar results were found at the age of 87 years.

Iceland birth cohort: depression

The prevalence of depression according to the indirect method was 8.7% and it was unaffected by age (Magnusson, 1989).

Iceland birth cohort: summary

The study demonstrates how prevalence can be influenced substantially by information sources. While indirect methods have their advantages (e.g. avoids retrieval problems in patient groups), within the context of psychiatric illness, reliability of diagnoses derived from indirect data is questionable. Indeed, depression and dementia were in many cases not known to the family doctor (Magnússon and Helgason, 1993).

Reykjavik study (Age, Gene/Environment Susceptibility Study: AGES-Reykjavik)

The Reykjavik study started in 1967 and comprised a random sample of 30,795 participants born in 1907–1935 in Reykjavik, Iceland (Harris *et al.*, 2007). The study was performed in six waves—1967–1969, 1970–1972, 1974–1979, 1979–1984, 1985–1991, and 1991–1996—and the study sample was divided into six groups by birth date within month. Each group was invited to participate in specific waves of the study. One group attended at all waves, another at two, and the remaining only once. In 2002, 11,549 participants were still alive and 5,764 were re-examined during 2002–2006, as a part of the Age, Gene/Environment Susceptibility (AGES)-Reykjavik study. In this substudy, the oldest group of the original study was not recruited. The AGES-Reykjavik study aimed to evaluate the common mechanisms leading to diseases in neurological, cardiovascular, musculoskeletal, and metabolic systems. Participants underwent comprehensive assessments which included a questionnaire, clinical examination, cognitive battery, and images of the brain and retina (Harris *et al.*, 2007). The response rate was 72%.

Reykjavik study: dementia

Dementia case ascertainment was based on the AGES-Reykjavik study cohort and followed a three-step procedure (Qiu *et al.*, 2010). All participants were screened on the MMSE (Folstein *et al.*, 1975) and Digit Symbol Substitution Test (DSST) (Wechsler, 1981). Screened positives on either of the tests were administered another more complete diagnostic test battery. Those who screened positively on the Trails A and B (Reitan, 1992) or the Rey Auditory Verbal Learning Test (Rey, 1958) went for a final assessment that included a proxy interview and a neurological examination. The diagnosis of dementia and subtypes was made by means of a consensus including a geriatrician, neurologist, neuropsychologist, and neuroradiologist. Dementia was diagnosed according to the guidelines of the DSM-IV (American Psychiatric Association, 1994). AD, according to the criteria of the NINCDS-ADRDA (McKhann *et al.*, 1984), and vascular dementia followed the criteria of the State of California AD Diagnostic and Treatment Centers (Chui *et al.*, 1992). Of the 3,906 participants, 132 (3%) were diagnosed with dementia, including 66 with AD, 31 with vascular dementia, and 20 with both. The group also explored whether microvascular damage, indicated by cerebral microbleeds and retinal microvascular signs, was associated with cognitive impairment and dementia. People with multiple cerebral microbleeds had lower scores on tests of processing speed and executive function, and this difference was greater if there were multiple cerebral microbleeds in the deep hemispheric or infratentorial areas. All these associations were independent of major cardiovascular factors, white matter hyperintensity, and cerebral infarcts.

As the AGES-Reykjavik study is a single-wave substudy based on a survival cohort, there are no incidence data available. Furthermore, the temporal relationship of retinal and cerebrovascular lesions to cognitive dysfunction could not be established, nor a possible protective role of the cerebral microbleeds.

Reykjavik study: depression

Data on depressive symptoms were collected during the AGES-Reykjavik study and included the Geriatric Depression Scale (GDS) (Yesavage, 1988), depression history, and medications. However, reports of these findings are yet to be published.

Reykjavik study: summary

This large population-based cohort has made several contributions to the understanding of risk factors for myocardial infarcts and cancers (Harris *et al.*, 2007). Data on genetic and other new risk factors and their relationship with more specific themes for old age psychiatry have been collected and publication is awaited.

Gothenburg study

In 1986–1987, all 85-year-old people born between 1 July 1901 and 30 June 1902 in Gothenburg, Sweden, and registered for census purposes in Gothenburg were invited to take part in a health survey. This study was conducted as part of a series of longitudinal gerontological population studies (Rinder *et al.*, 1975). Participants from both the community and institutions were

invited. Some of the later publications from this group disclose amalgamated results from this cohort and the study of women in Gothenburg, 1968–1969 (Bengtsson *et al.*, 1973).

Gothenburg study: dementia

A systematic subsample of 826 individuals underwent psychological and psychiatric examination comprising questions about background factors, ratings psychiatric symptoms and signs, ratings of signs common in dementia, and tests of mental functioning. Response rate was 63% ($n = 494$). After examination, an interview with a close informant was carried out (Skoog *et al.*, 1993). There were 147 cases of dementia, according to the DSM-III-R criteria (American Psychiatric Association, 1987), a prevalence of 30%. Subjects with dementia were further investigated with CT scans and classified into subtypes of dementia: AD, according to the NINCDS-ADRDA classification (McKhann *et al.*, 1984), was present in 43% of the participants, vascular dementia based on the criteria proposed by (Erkinjuntti *et al.* 1988) was found in 47%, and dementia due to other causes was diagnosed in the remaining 9%. The 3-year mortality rate was 23% in subjects without dementia, 42% in patients with AD, and 67% in patients with vascular dementia. Individuals diagnosed as having mixed dementia were included in the vascular dementia category. The population at risk comprised of 347 individuals was re-evaluated 3 years later (Aevansson and Skoog, 1996). Among them, 188 (54%) took part in a neuropsychiatric examination at the age of 88. Information on 132 withdrawals (deceased and refusals) was obtained from medical records or other sources. Sufficient information was thus obtained on 320 participants (92% of the population at risk). Sixty-three (20%) developed dementia during the study period. Of these, 42 cases were diagnosed from the neuropsychiatric examination, and 21 deceased or refusals from medical records or other information. The incidence of dementia was 90/1,000 per year, within which the incidence of AD was 36/1,000 per year and vascular dementia 39/1,000 per year (Aevansson and Skoog, 1996).

The group also investigated the role of blood pressure on dementia at 75, 79, and 85 years (Skoog *et al.*, 1996) in participants free from dementia at 70 years. They found that participants who developed dementia at age 79–85 had higher systolic and diastolic blood pressures at 70 years of age. However, just before dementia onset, blood pressure declined, and was then similar to or lower than that of participants without dementia. Although the sample was representative of survivors at age 79 years, only 11 participants had dementia and, at age 85 years, 18, which makes it difficult to extrapolate these findings. The group further investigated this relationship in a different but larger cohort and published similar findings (Joas *et al.*, 2012).

Gothenburg study: depression

The contribution of this cohort in terms of depression was based on an investigation of the relation between depression and the 3-year incidence of first-ever stroke. The diagnosis of depression was made according to DSM-III-R (American Psychiatric Association, 1987) criteria and included the categories major depression, dysthymia, and depression not otherwise specified. The diagnoses were based on symptoms during the month preceding the examination and observed symptoms during the psychiatric examination. Among all 85-year-olds, 93 had a history of stroke and 19% were diagnosed with depression. Depression at baseline (hazard ratio (HR) = 2.7, 95% CI = 1.5, 4.7) was related to increased incidence of first-ever stroke during follow-up. Depression increased stroke risk among not only participants without dementia but also those with dementia. However, stroke history at age 85 years (baseline) was not associated with clinical depression.

Gothenburg study: summary

This study emphasizes the magnitude of dementia in the very old, showing that almost 10% of persons between the ages of 85 and 88 develop dementia each year. This cohort showed a high prevalence and incidence of vascular dementia with the caveat that clinically defined mixed dementias were included in the vascular dementia diagnosis. Depression was quoted as a predictor of stroke.

Cambridge City over-75s cohort study (CC75C)

The first cohort study especially devoted to investigating dementia from a population perspective and determining the clinicopathological correlates of dementia was the Cambridge City over-75s Cohort Study (CC75C) (<http://www.cc75c.group.cam.ac.uk>). The original prevalence phase of the study is known as the Hughes Hall Project for Later Life, and the incidence survey, which was launched 2 years later, is known as the Cambridge Project for Later Life (Fleming *et al.*, 2007). The study began in 1985. A representative sample of 2,609 individuals aged 75 years and over living in Cambridge city, UK, were surveyed (O'Connor *et al.*, 1989), approximately one-third of all residents in this age range. All people in this age group in six family practices were approached and one in three from a seventh practice. Respondent rate was 95% and 40% of the oldest old in Cambridge took part (Brayne *et al.*, 1992), so the sample was representative of the whole population in terms of age distribution, sex, and accommodation, according to the Office of Population Censuses and Surveys (OPCS).

Each survey has included a detailed cognitive assessment, including at least the MMSE (Folstein *et al.*, 1975), usually its extended version, and, in the majority of interviews, the Cambridge Cognitive Exam (CAMCOG) (Roth *et al.*, 1986). Subsamples have had detailed psychiatric assessment using the CAMDEX, detailed neuropsychological assessment, informant interview, and additional tests.

A consensus diagnosis for dementia status at death was made consistent with DSM-IV (American Psychiatric Association, 1994) criteria using postmortem review of all interviews, including proxy informant data, death certificates, and retrospective informant data after death, but blinded to neuropathology findings. Dementia was rated by severity and, where possible, subtypes were identified (Brayne *et al.*, 2009). The study is still ongoing, representing an exceptional duration for a population-based cohort, although there are now very few survivors, all aged over 100.

CC75C: dementia

The total prevalence of all grades of dementia was 10.5%. Estimates of prevalence increased with age including: 4.1% (75–79 years), 11.3% (80–84 years), 19.1% (85–89 years), and 32.6% (90 years or over) (O'Connor *et al.*, 1989). Annual incidence rates for dementia also increased with age, approximately doubling every 5 years: 2.3% for participants initially aged 75–79 years, 4.6% for participants aged 80–84 years, and 8.5% for participants aged 85–89 years (Paykel *et al.*, 1994).

CC75C: depression

Using questionnaire information, diagnoses according to DSM-III-R criteria (American Psychiatric Association, 1987) were made. In addition, the interviewing clinician rated each person for 'severity of depressive symptoms' on a 5-point scale: none, minimal, mild, moderate, and severe (Girling *et al.*, 1995). The population-estimated prevalence of major depressive disorder, based on DSM-III-R criteria, was 2.4% (95% CI = 0.9%, 4.0%) and, based on the CAMDEX criteria, was 3.0% (95% CI = 0.7%, 5.3%). Five percent of persons diagnosed as having dementia according to the CAMDEX criteria also received a diagnosis of depression. Around one in five people with dementia were rated as mildly or moderately depressed (Girling *et al.*, 1995).

CC75C: neuropathology

Using data from the brain donation programme, neuropathological analyses on tissue from a representative sample of the older population have been undertaken. The neuropathological protocol was based on the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) method, with additional features to allow Braak staging of neurofibrillary pathology. The first 101 brains were reported by (Xuereb *et al.* 2000), with half having developed dementia by death. The median age group was 86–90 years. This study found that tangles and neuritic plaques were highly intercorrelated. Significant, but weaker, correlations were also found between plaques and vascular amyloid, plaques and white-matter pallor, tangles and vascular amyloid, and between tangles and white-matter pallor. Microvascular infarcts showed no relationship to any of these measures (Xuereb *et al.*, 2000).

Results after over 200 donations had occurred have also been reported (Brayne *et al.*, 2009). The overall burden of pathology was generally high across all participants, with most brains showing sufficiently extensive lesions to suggest pathological classification of dementia, whether or not the donor had been clinically demented before death. However, participants with a clinical diagnosis of dementia did generally have a greater burden of pathology than those without dementia.

CC75C: summary

The main contribution for our understanding of this genuinely population-based study with substantial numbers of brains was the heterogeneity of lesions found in very old populations. Further, there was considerable overlap in the pathologies found in the demented and nondemented, and the pathological overlap between those diagnosed as having different subtypes of clinical dementia. This indicates that when assessing dementia during life, particularly in the older old, a focus on a single pathology has limited utility.

Framingham study

Established in 1948, the Framingham study (Dawber *et al.*, 1951) began as a longitudinal population-based cohort study of cardiovascular disease and associated risk factors, which enrolled 5,209 volunteers (55% woman). Comprehensive physical examinations of the Framingham cohort have been obtained on a biennial basis. During biennial examination 14 or 15 (January 1976 through March 1978), a dementia-free inception cohort was established. Among 2,828 persons who were seen for physical examination, response rate was 75% and complete data were available for 1,085 participants aged 65 years or older, who agreed to complete a brief neuropsychological screening battery (Linn *et al.*, 1995). Starting with examination 17 (1982/1983) and on all successive biennial examinations, an MMSE was administered. Participants falling below

age-education adjusted levels were evaluated by a neurologist and neuropsychologist to determine if dementia was present and, if so, to ascertain dementia type. By using the criteria of Cummings and Benson (1986), dementia was considered to be present by the neurologist if the participant demonstrated a compromise in at least three areas of mental activity, including language, memory, visuospatial skills, personality or behaviour, and cognition, and if there was no disturbance in consciousness. Dementia severity was judged by criteria similar to those in the DSM-III-R (American Psychiatric Association, 1980). A neuropsychologist who was unaware of the dementia diagnosis made by the neurologist also saw the participants. If a person's performance was more than one standard deviation (SD) below published age-adjusted normative values on at least three of the seven neuropsychological tests used, they were considered to have cognitive impairment consistent with dementia. Dementia was considered present by the panel if the following three criteria were met: (1) cognitive impairment—if the neurologist found moderate or severe dementia to be present, and the neuropsychologist independently confirmed the presence of cognitive impairment consistent with dementia; (2) cognitive decline—evidence that the person had definite deterioration in cognition from a pre-existing level of functioning; and (3) duration of cognitive impairment of at least 1 year (Linn *et al.*, 1995).

Framingham study: dementia

The prevalence of dementia was 30.5/1,000 for men and 48.2/1,000 for women and increased with advancing age. Cases of probable AD constituted 55.6% of all dementia cases. The prevalence of AD was 11.7/1,000 for men and 30.1/1,000 for women and also increased with advancing age. Prevalence of dementia and probable AD were greater for women than men. The women to men ratio of prevalence for cohort members 75 years of age and older was 1.8 for all cases of dementia and 2.8 for cases of probable AD (Bachman *et al.*, 1992).

To determine the incidence of dementia and AD (Bachman *et al.*, 1993), people previously free of dementia and falling below the 1 SD cut-off score on screening tests were evaluated further to verify whether dementia was present and, if so, the type of dementia, following the procedure described above. All new cases arising in this cohort over a maximum of 10 years of follow-up were ascertained. The incidence of dementia increased with age, doubling in successive 5-year age groups. Dementia incidence rose from 7.0/1,000 per year at ages 65–69 to 118.0/1,000 at ages 85–89 for men and women combined. The incidence of probable AD also doubled with successive quinquennia, from 3.5 at ages 65–69 to 72.8/1,000 at ages 85–89 years. Incidence of dementia and of probable AD did not level off with advanced age and was not different in men and women.

Framingham study: depression

In 1990, at the start of the 22nd biennial examination cycle, 1,753 people from the original cohort were still alive. Of these, 1,166 (67%) attended the 22nd biennial examination, and among them, 949 (81%; 604 women, 345 men) were dementia free and were assessed for depressive symptoms. These participants were followed for up to 17 years (average follow-up 8 years) for incident dementia to examine the association between depressive symptoms at baseline and risk of incident dementia (Saczynski *et al.*, 2010).

During the 17-year follow-up period, 164 participants developed dementia; 136 of these cases were AD. A total of 21.6% of participants who were depressed at baseline developed dementia, compared with 16.6% of those who were not depressed. Depressed participants, defined by scores of at least 16 on the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977), had more than a 50% increased risk for dementia (HR = 1.72, 95% CI = 1.04, 2.84) and AD (HR = 1.76, 95% CI = 1.03, 3.01). Results were similar when participants taking antidepressant medications were included. For each 10-point increase on the CES-D, there was significant increase in the risk of dementia (HR = 1.46, 95% CI = 1.18, 1.79) and AD (HR = 1.39, 95% CI = 1.11, 1.75). Results were similar when persons with possible MCI were excluded.

Framingham study: summary

Another important contribution of the Framingham study to the field of dementia was the estimation of the lifetime risk of dementia. A group of 2,794 participants without dementia who were 65 years or older were followed up for a maximum of 29 years (42,233 person-years). There were 400 cases of incident dementia of all types and 292 cases of incident AD. The lifetime risk of any dementia was estimated at more than 1 in 5 in women and 1 in 6 in men, and the lifetime risk of AD about 1 in 5 for women and 1 in 10 for men (Seshadri *et al.*, 2006).

Established Populations for Epidemiologic Studies of the Elderly (EPESE)

The goals of the Established Populations for Epidemiologic Studies of the Elderly (EPESE) project were to describe and identify predictors of mortality, hospitalization, and placement in long-term care facilities and to investigate risk factors for chronic diseases and loss of functioning. The survey elicited information from persons 65 years of age and older in four

different geographic locations in the US: East Boston, New Haven, Iowa, and North Carolina. The baseline data cover demographic characteristics (age, sex, race, income, education, marital status, number of children, employment, and religion), height, weight, social and physical functioning, chronic conditions, related health problems, health habits, self-reported use of dental, hospital, and nursing home services, and depression.

In East Boston, individuals eligible for the study were identified through a total community census performed concurrently with the baseline interview in 1982. In Iowa, the sample was not truly populational since interviews were attempted with all eligible individuals enumerated using a list from the area's Agency on Aging, supplemented by additional listings from local informants. New Haven used a stratified random sample of clusters of households. The sample was stratified for three types of residence, including public housing for the older population, private housing for the older population, and elsewhere in the community. Men were oversampled to attempt to achieve balance in the sex distribution of the sample. In North Carolina, area sampling was used at the first stage of the design to obtain a sample of 1,980 census blocks, block clusters, and enumeration districts. The sample was designed so that it would consist of at least 50% black older persons. The investigation of dementia was conducted using the sampled persons members of the Duke EPESE (Established Populations for Epidemiologic Studies of the Elderly) (Heyman *et al.*, 1991), which focused on five adjacent counties, one primarily urban and the other four mostly rural, in the Piedmont area of North Carolina. The last stage of the sampling procedure consisted of selecting one older person at random from each household in which there were residents aged 65 years and older. Of 5,223 persons selected for the sample, 4,164 were successfully interviewed, yielding a response rate of 80%. Of these, 2,259 (54%) were black and 1,905 (46%) were nonblack. The sampling design permitted the development of weights, which took into account age, sex, race, geographic location, number of old people in the household, and nonresponse, so that it was possible to project data from the Duke EPESE sample to the same age population of other areas.

A brief screen of cognitive function, the Short Portable Mental Status Questionnaire (SPMSQ) (Pfeiffer, 1975), was administered at baseline, and, according to the authors by using the adjusted scores, little race or education bias is found. The case finding procedure involved a trichotomization of the SPMSQ scores, that is, the total EPESE sample was divided into persons with scores below the cut-off for cognitive impairment, those with one point better than the cut-off, and, finally, those with two points better than the cut-off. The selected participants were seen by a neurologist who administered a semistructured interview which involved a medical and psychiatric history and physical and neurological examinations. Based on these measures, a diagnosis of dementia and, specifically, of AD was made, using the DSM-III and NINCDS-ADRDA (McKhann *et al.*, 1984). The severity of the dementia, when present, was rated on the Clinical Dementia Rating scale, which includes information for rating the individual in six cognitive and behavioural categories: memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care (Hughes *et al.*, 1982). The project attempted to compare the prevalence and the incidence of dementia between black and all other participants.

EPESE: dementia

For the 1986 and 1987 survey, when the baseline data were collected, the estimated prevalence of dementia was 8.9% for black men, 19.9% for black women, 3.3% for white men, and 2.9% for white women. The overall estimated prevalences for blacks and whites were 16% (95% CI = 7.9, 24.1) and 3.0% (95% CI = 0, 6.9), respectively (Heyman *et al.*, 1991). The overall prevalence of dementia among blacks was significantly higher than in whites. However, the same difference was not found in the 1989 and 1990 survey, where the prevalence of dementia was 7.0% (95% CI = 2.1–11.9) for blacks and 7.2% (95% CI = 2.2, 12.2) for whites. Prevalence for black men (7.8%, 95% CI = 0.1, 15.5) exceeded that for black women (6.6%, 95% CI = 0.3, 12.9), but gender prevalence values for whites were reversed (men: 4.4%, 95% CI = 0.0, 10.3; women: 8.7%, 95% CI = 1.5, 16.0) (Fillenbaum *et al.*, 1998).

The 3 year incidence of dementia between the two surveys, 1986–1987 and 1989–1990, was found to be 5.8% (95% CI = 2.6, 9.0) for blacks and 6.2% (95% CI = 2.7, 9.7) for whites. Neither race nor gender differences were significant (Fillenbaum *et al.*, 1998).

EPESE: depression

To address the influence of socioeconomic variables in the association between racial differences and late-life depression, basic needs, income, and education variables, controlling for sex, age, and functional status were examined (Sachs-Ericsson *et al.*, 2005). Data for this analysis were derived from the Duke EPESE. Before adjusting for socioeconomic variables, African-American older people had more depressive symptoms than white older participants in the cross-sectional analyses. However, after the inclusion of socioeconomic variables, the relationship was inverted, such that white-Americans were significantly more likely to endorse depressive symptoms than African-Americans. In the longitudinal analyses, after controlling for baseline depressive symptoms, race was unrelated to depressive symptoms 3 years later.

EPESE: summary

The study highlights the importance of race and demographic and sociodemographic factors in determining estimates of disease prevalence and incidence. These findings reinforce that there is room for improvement of chronic conditions by reducing socioeconomic disparities.

Gospel Oak study

This was a longitudinal prospective study based on the Gospel Oak electoral ward in north London (Livingston *et al.*, 1990b). Its main purpose was to detect those persons likely to be suffering from dementia or depression or to be impaired in performing ADL. The electoral ward had an estimated population of 6,136 living in 3,000 households and had higher rates of most indices of deprivation than the average for England and Wales at the time.

Interviews took place in 1987. The sample consisted of all women aged over 60 and men over 65 who were residents of this area. All participants were interviewed using the Standard Comprehensive Assessment and Referral Evaluation (CARE) (Gurland *et al.*, 1984). This instrument is composed of six screening scales that assess depression, organic brain syndrome, subjective memory impairment, sleep disorder, somatic symptoms, and activity limitation. The depression and dementia scales have been further refined to become depression and dementia diagnostic scales (the Dementia Diagnostic Syndrome scale), which refer to syndromes of cognitive impairment and depressed mood severe enough for further clinical intervention (Kay *et al.*, 1964). The final sample for interview consisted of 932 participants (women over 60, men over 65), who represented 15.2% of the ward population. The response rate of available people was 87.2%.

Gospel Oak study: dementia

On the six screening scales, 8% were identified as cases of organic brain syndrome, 27% as depressive cases, 25% with subjective memory complaints, 33% had sleep disorders, 32% had limitation in performing activities, and 24% had somatic symptoms. After the refinement for identifying syndromes of cognitive impairment (the Dementia Diagnostic Syndrome scale), dementia prevalence at screening was estimated as 4.7%. However, this value increased to 7% when the residents of the local authority home were included.

Eighty percent of the 60 people initially identified by screening were further assessed using the GMS/AGECAT instrument (Copeland *et al.*, 1986), a psychiatric interview, and neuropsychological testing (Livingston *et al.*, 1990a). Among those participants, 43 were diagnosed as having dementia of any type based on the psychiatric diagnosis. For the whole Gospel Oak population, the overall prevalence for dementia of any type was 6.1% (43/705). AD prevalence, according to the NINCDS-ADRDA criteria (McKhann *et al.*, 1984), was 3.1% (22/705). Multi-infarct dementia (0.01%, 1/705), mixed dementia (0.7%, 5/705), and secondary dementia (0.7%, 5/705) were rare. In contrast, diagnosis based on the GMS/AGECAT resulted in a prevalence of organic case of 4% (28/705). GMS/AGECAT was more likely to diagnose as 'organic' those participants whom the psychiatrists diagnosed as having AD. The total dementia prevalence as diagnosed by the psychiatrists was higher (6.1%) than reported at screening (4.7%), where the prevalence was calculated according to the Dementia Diagnostic Syndrome scale.

In 1990, 502 participants were successfully rescreened using the Short CARE. Six percent of the rescreened participants were identified as incident dementia cases based on screening (Boothby *et al.*, 1994) and 1.6% according to the Dementia Diagnostic Syndrome scale. However, by means of clinical diagnosis, the overall annual incidence of dementia in persons over 65 years was 2%.

Gospel Oak study: depression

Depression varied according to place of residence; 17.3% (122) of the population living at home were classed as probably suffering from pervasive depression as measured using the depression diagnostic scale. Excluding those individuals who also were diagnosed as having dementia reduced the prevalence of depression to 15.9%. On the other hand, prevalence increased to 18.5% when the residents of the local authority home were included. Depression was not associated with age (Livingston *et al.*, 1990b).

Gospel Oak study: summary

Additional research questions within the framework of the Gospel Oak study have focused on the association between cigarette smoking and alcohol drinking and incident cognitive impairment (Cervilla *et al.*, 2000). Participants were asked whether they had ever smoked, and among those who smoked, currently or in the past, information was obtained on the average number of cigarettes smoked a day and on the number of years they had smoked for. Participants were also asked about the amount of alcohol used before or after the age of 65. Current smokers were nearly four times more likely to be cognitively impaired than non (never) smokers or ex-smokers, after adjusting for baseline cognitive function, depression,

occupational class, education, handicap, and alcohol consumption before and after the age of 65. Alcohol drinking was not a risk factor for incident cognitive impairment. The finding that current smokers but not ex-smokers are at higher risk of developing cognitive decline is of great public health relevance for smoking prevention and smoking cessation campaigns and policies targeting prevention of cognitive impairment.

Cognitive Function and Ageing Study (CFAS)

CFAS is a multidisciplinary, multiphase, population-based study, which involved five identical sites including Cambridgeshire, Gwynedd, Newcastle, Nottingham, and Oxford. An additional site was based in Liverpool, but the sampling and interview structure base were different. The study was designed to cover three main areas related to dementia and ageing: epidemiology, neuropathology, and policy (Brayne *et al.*, 2006). The fieldwork began in 1991 (Chadwick, 1992).

Background information on the demographics of the populations sampled was collected from the OPCS 1990–1991 census, to enable comparison with regional and national data. The population sample was drawn from the Family Health Service Authorities lists. These are registers of the general practitioners, which provide a nearly total population enumeration in the areas chosen for study, including individuals living in institutions. Individuals aged 65 years and over were selected for participation.

Trained interviewers administered structured interviews at the respondents' homes, which included the GMS, the MMSE (Folstein *et al.*, 1975), and basic information on residence, marital status, social class, and main occupation during working life (Elias *et al.*, 1993); social and service contacts (Wenger, 1989); physical health and wellbeing, including vascular risk factors (Launer *et al.*, 1992); ADL as measured by the Townsend scale (Townsend, 1979); and regular medication use (prescribed and over the counter). CFAS also includes a brain donation programme, with a total of 456 brains donated up to August 2004 (Matthews and Brayne, 2005). It is estimated that in 2012 around 500 brains will have been donated.

From the five identical sites, 13,004 individuals were screened (85% response from eligible sample). Following screening, a 20% subsample was selected based on age and cognition, weighted towards the older and more cognitively frail, to complete a more in-depth baseline interview shortly afterwards, with a repeat at 2 years. Further screen and assessment interviews with the whole sample who remained in the study were carried out (see www.cfes.ac.uk) for full details on the study design) (Brayne *et al.*, 2006).

The ALPHA Liverpool study fits within the framework of the CFAS but started earlier than the other five centres (Saunders *et al.*, 1993). The Liverpool Family Practitioner Committee central computerized list of general practice patients was used as a sample frame. From this list, all patients aged 65 years or over with Liverpool addresses were selected. To provide a check on diagnosis and to enable subclassification of GMS/AGECAT organic disorder into dementia types, a subsample of individuals received a second-stage assessment and informant interview conducted by psychiatrists. The informant interview consisted of the History and Aetiology Schedule (HAS) which is drawn upon by the HAS/AGECAT.

CFAS: dementia

CFAS has reported on the UK population prevalence and incidence of dementia as well as extensively on cognition and MCI. In the population aged 65 years and over, the standardized (to the England and Wales population estimates for 1991) dementia prevalence was estimated as 6.6% (95% CI = 5.9, 7.3). This was based on dementia defined as an AGECAT organicity rating scale of 3 and above (1998). Dementia prevalence across the centres did not vary greatly, although there was some evidence of nonsystematic fluctuation in individual age- and sex-specific groups.

Dementia incidence estimated between the first two waves of interviews increased with age, from 7.4 (95% CI = 3.6, 16.1) per 1,000 person-years at age 65–69 years to 84.9 (95% CI = 63.0, 107.8) per 1,000 person-years at age 85 years and above. The rate of increase for both sexes was marked, and continued into the oldest age groups. It was estimated that approximately 180,000 new cases of dementia occur in England and Wales each year. There is no convincing evidence of variation across sites, and incidence rates did not reflect the variations in the prevalence of possible risk factors in these sites (Matthews and Brayne, 2005). CFAS has also provided profiles of cognition weighed back to the UK population based on the MMSE, extended MMSE, and CAMCOG scores (including total score and subdomain scores of orientation, language (expression and comprehension), memory (learning, recent, remote), praxis, attention, calculation, and perception) (Williams *et al.*, 2003; Huppert *et al.*, 2005).

The scope and operability of 16 different terms reflecting cognitive decline intermediate to normal ageing and dementia, and quantification of their prevalence and longitudinal course of disease, have also been undertaken (Matthews *et al.*, 2008). Across the 16 definitions, prevalence estimates were found to vary substantially (range 0.1–42%). As expected, prevalence tended to increase for those definitions that capture a broader state of impairment, including, for example, Subjective Memory

Complaint (SMC) and Cognitive Impairment No Dementia (CIND), and was less frequent for more restrictive definitions including Amnesic Mild Cognitive Impairment (A-MCI). Rates of progression to dementia also varied and tended to be low. Overall, dementia progression was highest for more broadly defined concepts, and those that capture greater levels of cognitive decline, particularly in older individuals. Across definitions, at 2 years' follow-up, most individuals had remained stable, reverted to normal, or developed impairment outside the intermediate range. In the neuropathological analysis, MCI was found to be associated with an increased risk of neurodegenerative and vascular pathologies (Stephan *et al.*, 2012a, 2012b).

In terms of risk factor analyses, CFAS has shown that a simple measure of self-rated health (SRH) was associated with a higher risk of death and functional and cognitive impairment. The associations remained after adjustment for age, gender, functional ability, and MMSE at baseline: comparing those who rated their health as excellent and good, hazard ratios for risk of death and functional and cognitive impairment were 0.8 (95% CI = 0.8, 0.9), 0.6 (95% CI = 0.5, 0.7), and 0.7 (95% CI = 0.5, 0.9), respectively (Bond *et al.*, 2006).

Results from the neuropathological analyses have found that multiple neuropathological features determine the overall burden of dementia, including mixed vascular and Alzheimer lesions together with other changes such as atrophy (Neuropathology Group, 2001; Matthews *et al.*, 2009; Savva *et al.*, 2009; Wharton *et al.*, 2011). Furthermore, the relationship between the clinical manifestations of dementia and the neuropathological findings varies with age, such that there is considerable overlap in the burden of neuropathological features of AD between groups of the oldest old persons with dementia and those without dementia. Even in participants who died without dementia, the burden of Alzheimer's-type disease in the population increased with increasing age.

In the Liverpool study, GMS interviews were obtained with 5,222 (87%) of the 6,035 in the study area. A total of 444 GMS/AGECAT organic cases were identified at phase 1 and a sample of them was randomly selected for reinterview at phase 2. Among the available 205 participants who were assessed by psychiatrists to verify the clinical diagnosis, dementia was diagnosed in 84% ($n = 172$) of the organic cases. At wave 2, 328 were diagnosed as cases of organic disorder (of whom 120 were from wave 1 and 208 were new cases), and 232 in wave 3 (of whom 54 were from wave 1 and 53 from wave 2, leaving 125 new cases). Comparison of the confidence intervals for the age-specific rates by sex showed no significant sex difference for the incidence rates of undifferentiated dementia (Copeland *et al.*, 1999).

CFAS: depression

The age and sex prevalence of depression standardized to the 1991 population of England and Wales was 8.7% (95% CI = 7.3, 10.2). No relationship between depression prevalence and age was found. However, high deprivation, high disability, and two or more comorbid illnesses were associated with a greater prevalence of depression (McDougall *et al.*, 2007). Previous neuropathology studies have found an association between depression and markers of neurodegenerative and nonAD pathology, including neurofibrillary tangles, diffuse and neuritic plaques, Lewy bodies, brain atrophy, and cerebrovascular disease (Thomas *et al.*, 2001; Wilson *et al.*, 2003; Sweet *et al.*, 2004; Jellinger, 2009). In the CFAS neuropathology resource, depression ($n = 36$ out of 153 nondemented participants at death) has been associated with subcortical Lewy bodies (Tsopelas *et al.*, 2011). In contrast to early findings from other studies, no association was found between depression and cerebrovascular or Alzheimer pathology, although depression was associated with neuronal loss in the hippocampus as well as in some of the subcortical structures investigated (nucleus basalis, substantia nigra, raphe nucleus) (Tsopelas *et al.*, 2011). It is important to note that despite the strong statistical association with depression in the samples where subcortical Lewy bodies or neuronal loss were detected, these neuropathological features were relatively rare, and most cases of depression found in this sample were not associated with any subcortical pathology. This suggests that subcortical pathology may account for a small number of cases of late-life depression in the population.

In the ALPHA Liverpool study, the relationship between depression and risk of incident dementia was also investigated (Chen *et al.*, 2008). The risk of dementia was significantly increased with level 4 depressive syndromes derived from the GMS/AGECAT. The multiple adjusted HR is 2.47 (95% CI = 1.25, 4.89) and 2.62 (95% CI = 1.18, 5.80) at 2- and 4-year follow-up, respectively. The effect was greater in younger participants.

CFAS: summary

Estimates of prevalence and incidence of dementia, cognitive decline, and depression from the CFAS represent true population estimates due to study design. This has important implications for gauging the consequence of each disease (e.g. burden of care, cost) from a true population perspective. The CFAS collaborators have begun collecting information on a new sample of individuals aged 65 years and older that builds on the original CFAS study design. This new study is called the Cognitive Function and Ageing Study II (CFAS-II) and includes centres in Cambridgeshire, Newcastle, Nottingham, and CFAS Wales: Gwynedd and Swansea. This study will provide baseline information on approximately 12,500 people aged 65 and

over in 2008–2011, and will follow them up over time, with a 2-year phase confirmed (2014). The data collected will provide important information on generational and geographical differences, including details on those living in institutions. CFAS-II will allow the estimation of new patterns of the number of people with dementia and disease comorbidity.

Rotterdam study

The Rotterdam study (<http://www.epib.nl/research/ergo.htm>) is a single-centre population-based prospective dynamic cohort study of individuals aged 55 and over that started in 1990 in Ommoord, a suburb of Rotterdam. The main objective has been to investigate the prevalence and incidence of risk factors for chronic diseases in the older population, including cardiovascular, neurological, locomotor, and ophthalmologic diseases.

Baseline measurements were obtained between 1990 and 1993 and all participants were subsequently examined every 2–3 years. In total, 7,983 (78%) persons took part, including 897 persons living in one of the six homes for older people. In 2002, another 3,011 participants (55 years of age since 1990) were added to the cohort, which comprised a total of 10,994 persons. In 2006, the cohort was further expanded by 3,932 persons aged 45 years and over. The total Rotterdam study population encompasses 14,926 participants. In 1995 and 1999 random subsets of the Rotterdam study underwent neuroimaging, and from 2005 onwards magnetic resonance imaging (MRI) has been implemented into the core protocol of the Rotterdam study. Up to January 2011, a total of 5,886 brain MRI scans have been obtained, which includes multiple scans from the same person (Ikram *et al.*, 2011).

Regarding old age psychiatric conditions, the Rotterdam study addresses questions about the prevalence and incidence of various types of dementia and of Parkinson's disease, and also verifies the determinants of such conditions. Participants were screened for dementia using a brief cognitive test including the MMSE and GMS. Once screened positively, participants were then seen by a physician with the CAMDEX, and those who were still suspected of dementia were examined by a neurologist, had a MRI of the brain, and were tested by a neuropsychologist. No interviews were done on those who screened negatively (MMSE 26–30).

Rotterdam study: dementia

Of the 10,275 eligible individuals, 7,528 (73%) were screened for dementia, and 6.3% of them were diagnosed as having dementia. Overall, 72% of the dementias were of Alzheimer type, 16% were vascular dementia, 6% were Parkinson's disease dementia, and 5% were other dementias (Ott *et al.*, 1995). At follow-up, 5,571 (79%) participants were rescreened for dementia. The overall incidence was 10.7/1,000 person-years (Ott *et al.*, 1998). Dementia subtype clinical diagnosis was determined in 98% of the cases. AD was diagnosed in 61%, mixed dementia of Alzheimer with cerebrovascular disease was detected in 12%, vascular dementia in 14%, and other dementias in 13%.

Results from the neuroimaging data show that white matter lesions are related to impairment of subcortical functions (Breteler *et al.*, 1994), but also that changes affecting the microstructural integrity of normal white matter before these can be visualized using conventional MRI are also associated with cognitive function (Vernooij *et al.*, 2009b). Those changes, such as mean diffusivity and fractional anisotropy, correlate directly with the amount of myelin in the white matter and to a lesser extent also to axonal count. They can be measured using the diffusion tensor imaging technique in the MRI.

Regarding cerebral microbleeds, their spatial distribution was found to follow the known topographic distribution of amyloid angiopathy implicated in AD (Vernooij *et al.*, 2009a). They were present in 1 in 5 persons over the age of 60 and in over 1 in 3 in persons aged 80 years and older (Vernooij *et al.*, 2008; Poels *et al.*, 2010). Furthermore, the presence of these numerous microbleeds, especially in a strictly lobar location, was associated with worse performance on cognitive tests, even after adjustment for vascular risk factors and other imaging markers of small vessel disease (Ikram *et al.*, 2011). These results suggest an independent role for microbleed-associated vasculopathy in cognitive impairment.

Rotterdam study: depression

Depressive disorders were assessed by a two-step procedure that included completion of the Dutch version of the original Center for Epidemiological Studies Depression Scale (CES-D), and for those who screened positive for depressive symptoms a clinical psychiatric evaluation was undertaken. A strong relationship was observed between severe coronary and aortic calcifications and depressive disorders (odds ratio (OR) = 3.89, 95% CI = 1.55, 9.77; and OR = 2.00, 95% CI = 1.02, 3.96, respectively). Although the analysis cannot establish a causal role of atherosclerosis due to the cross-sectional nature of the study, it provides evidence that a generalized atherosclerotic process is associated with late-life depression (Tiemeier *et al.*, 2004).

Rotterdam study: summary

The Rotterdam study has extensive information from a wide variety of sources, such as biological and MRI-based data, that can be used to help untangle the association between health and health-related risk factors and poor mental health. The high prevalence with MRI scans has helped with understanding the association between white matter lesions and cognitive impairment.

Vantaa 85+

The Vantaa 85+ study is a prospective population-based study which was established in 1991 (Polvikoski *et al.*, 1995). The study population included all individuals who were born before 1 April 1906 and were aged 85 years or over living in the city of Vantaa in southern Finland ($n = 601$). Clinical examination was possible of 553 (92%) participants and a neuropathological examination of 304 (51%). A neurologist and a trained public health nurse performed the clinical evaluations, which included a structured general and neurological examination. Data were systematically collected on health, health-related behaviour, and medication. Cognitive function, depression, and functional abilities were also assessed. Survivors were re-examined in 1994, 1996, 1999, and 2001. The entire study population is now deceased.

Dementia was diagnosed using DSM-III-R criteria, AD by NINCDS-ADRDA criteria, and vascular dementia using the NINDS-AIREN criteria. Initial blood samples for DNA analysis were obtained from 550 of the 553 persons examined.

Vantaa 85+: dementia

AD was clinically diagnosed in 16% of the Vantaa 85+ cohort. In contrast, the prevalence of AD was 33% (Polvikoski *et al.*, 2001) when defined neuropathologically according to the CERAD protocol (Mirra *et al.*, 1991). Forty-one (55%) of the 74 individuals with neuropathological AD were either in the no-dementia group or had dementia of nonAlzheimer's type clinically defined (Polvikoski *et al.*, 2001). The incidence of dementia was 8.1/100 person-years (Ahtiluoto *et al.*, 2010).

In this study, the authors also investigated the relation of diabetes to dementia, AD, and vascular dementia based on the fact that population-based longitudinal studies have shown controversial findings regarding diabetes as an independent risk factor for dementia. When the prevalence of dementia was split among those with and without diabetes, no association was found between dementia and diabetes after adjusting for sex, age, education, cardiovascular conditions, and apolipoprotein E (APOE) e4 allele frequency. However, the incidence of clinically defined dementia in participants free of dementia at baseline ($n = 355$) was almost twice as high in patients with diabetes (12.1 person-years, 95% CI = 8.5, 17.2) than nondiabetic (7.2 person-years, 95% CI = 5.7, 9.0) individuals, even after adjustments for age, sex, education, and APOE e4 status (Ahtiluoto *et al.*, 2010). One possible explanation for the difference between the findings for prevalence and incidence is that the dementia duration was shorter in diabetic compared to nondiabetic participants, probably due to the diabetes-related increase in mortality.

Regarding the neuropathological findings, the proportion of individuals with beta-amyloid and neurofibrillary tangles was lower in diabetic compared to nondiabetic individuals. In contrast, the proportion of participants with cerebral infarctions was significantly higher in diabetic compared to nondiabetic persons, even after adjustments for age at death, gender, education, APOE, and dementia status.

Vantaa 85+: depression

Depressive symptoms were investigated using the Zung Depression Status Inventory (DSI) (Zung, 1972), which is a 20-item semistructured, interviewer-rated depression instrument with scores ranging from 25 to 100. Higher scores indicate more depressive symptoms. In the general population aged 85+ there was a very low prevalence of depression (1.1% for clearcut clinical depression and 4.1% for minimal to mild depression). Among participants with dementia, vascular dementia was significantly more common in individuals with higher depression scores (40 points or more on the DSI). There was no association between DSI score and dementia severity.

Vantaa 85+: summary

The Vantaa 85+ study is one of the few autopsy-controlled, prospective, and population-based studies available on the prevalence of dementia in the very old population.

Personnes âgées QUID (Paquid)

Paquid was the first large French epidemiological study on dementia. It is an interdisciplinary study designed to investigate cerebral and functional ageing. Residents living in two administrative areas of southwestern France (2,797 in Gironde and 1,504 in Dordogne) were randomly chosen from the electoral lists. A cohort of 3,777 participants aged 65 or over was interviewed. This cohort was complemented by a random sample of 380 institutionalized persons (Létenneur *et al.*, 1993a).

Trained psychologists administered a standardized questionnaire at home. Baseline variables included sociodemographic factors, living conditions and habits, subjective health measures, dependence in ADL (Katz *et al.*, 1970) and instrumental activities of daily living (IADL) (Lawton and Brody, 1969), and the Rosow and Breslow scale (Rosow and Breslau, 1966). Depressive symptomatology was also assessed. Intellectual functioning was examined through an extensive test battery that included an evaluation of global mental status, visual memory, verbal memory, verbal fluency, visuospatial attention, and simple logical reasoning.

After the psychometric evaluation, the psychologists completed systematically a standardized questionnaire, allowing determination of the DSM-III criteria for dementia. Patients who met the DSM-III criteria for dementia were seen by a neurologist who applied the NINCDS-ADRDA criteria to indicate the aetiology of the deterioration. Persons were re-evaluated following the same procedure as used for the baseline screening at 1, 3, and 5 years after the initial visit in Gironde and 3 and 5 years after the initial visit in Dordogne. However, to improve the sensitivity of the detection of incident cases, respondents were selected for the neurological examination if they met the criteria for DSM-III-R dementia or if they had experienced a cognitive decline of more than two points on the MMSE.

Paquid: dementia

The overall prevalence of dementia was estimated based on the Gironde data and was 4.3%. No difference was found between men and women (Letenneur *et al.*, 1993b). Of the 5,554 contacted subjects, 3,777 (68%) agreed to participate in the study. Risk factor analysis found greater risk for AD in people with fewer years of formal education. The overall incidences of dementia and AD were estimated at 1.59/100 person-years and 1.17/100 person-years, respectively. The incidence of AD was higher in women than men after 80 years of age, whereas the incidence was higher in men before the age of 80. This different progression of the incidence according to sex was not found when other dementias were analysed (Letenneur *et al.*, 1999).

Paquid: depression

To estimate the predictive relationship between depressive symptoms and incident dementia, (Fuhrer *et al.* 2003) investigated 16,373 person-years of observation. Baseline prevalence of depressive symptomatology was 12.9% for men and 14.7% for women. The OR for the age-adjusted association between elevated depressive symptoms and onset of dementia was 2.0 (95% CI = 1.4, 2.8). However, after adjusting for gender, education, and cognition, the risk was reduced to 1.3 (95% CI = 0.8, 2.0), but these associations were significantly different between men and women. Men who had high depressive symptoms were more than three times as likely (OR = 3.5, 95% CI = 1.9, 6.5) than men with low depressive symptoms to develop incident dementia. This effect was not replicated for women. A possible explanation for this finding could be due to sex differences in vascular disease. It was found that the risk of dementia for men with hypertension who were depressed was 50% higher than for normotensive depressed men.

Paquid: summary

Paquid is an interdisciplinary study on cerebral and functional ageing, made up of a cohort of 3,777 community residents living in two administrative areas of southwestern France. The epidemiological basis of the programme focused on the incidence, natural history, and nongenetic risk factors of dementia.

Italian Longitudinal Study of Ageing (ILSA)

ILSA is a population-based, longitudinal study aimed at determining the health status of people aged 65–84 years (Maggi *et al.*, 1994). Common chronic conditions were investigated along with potential risk and protective factors. ILSA was also designed to assess age-associated physical and mental functional changes. A random sample of 5,632 people, stratified by age and sex using an equal allocation strategy, was gathered from the demographic lists of the registry office of eight municipalities including: Genoa, Segrate (Milan), Selvazzano-Rubano (Padua), Impruneta (Florence), Fermo (Ascoli Piceno), Napoli, Casamassima (Bari), and Catania. The baseline examination started in March 1992. The case identification for all conditions was based on a two-phase procedure, consisting of a screening phase, administered by lay interviewers, and, for those who screened positive, a clinical assessment run by specialists according to the condition. The final diagnosis of dementia was made according to the DSM-III-R criteria, for AD based on the NINCDS-ADRDA criteria, and for vascular dementia and other dementias according to ICD-10. From the total population sampled, 5,462 were eligible and 84% took part in the home interview and 64% participated to the clinical examination (The Italian Longitudinal Study on Aging Working Group, 1997)

ILSA: dementia

Among the 3,497 persons included in the baseline wave, the prevalence of dementia was 7.2% for women and 5.3% for men (The Italian Longitudinal Study on Aging Working Group, 1997). The follow-up phase was conducted on 2,498 individuals free of dementia who were reassessed after a mean period of 3.8 years. The incidence rate of overall dementia was of 12.5/1,000 person-years (Di Carlo *et al.*, 2002).

ILSA: depression

Depressive symptoms were investigated using the Italian version of the 30-item GDS (Yesavage *et al.*, 1982). Further investigation sought to determine the possible impact of depressive symptoms on the rate of progression to dementia in individuals diagnosed with MCI (Panza *et al.*, 2008). Among the 2,963 participants, 139 prevalent patients with MCI were diagnosed at baseline. During 3.5-year follow-up, 14 patients with MCI progressed to dementia, of whom nine had a GDS over 10. The association between depressive symptoms and rate of progression to dementia in MCI was not significant (Relative Risk (RR) = 1.42, 95% CI = 0.48, 4.23).

ILSA: summary

This cohort has produced results on the prevalence of not only neuropsychological conditions, such as dementia, but also general medical disorders, such as myocardial infarction, angina, arrhythmia, congestive heart failure, peripheral arterial disease, hypertension, diabetes, stroke, parkinsonism, distal symmetric neuropathy of lower limbs, and disability. These data are of great importance for planning of health services, to evaluate the real needs for assistance, and to study those factors that determine the transition from independence to loss of autonomy.

The Three-City study (3C)

The main objective of the 3C study is to estimate the risk of dementia attributable to vascular diseases or vascular risk factors, and to provide data for modelling the expected impact of vascular risk reduction on the incidence and prevalence of dementia (<http://www.three-city-study.com/>). Other objectives are to study incidence and risk factors of stroke, to provide data on incidence and risk factors of coronary diseases, and to analyse temporal trends in the incidence and prevalence of incapacities and loss of autonomy (Alperovitch *et al.*, 2002). Recruitment was undertaken based on the electoral registries of three French cities (Bordeaux, Dijon, Montpellier) and included individuals aged 65 years, between 1999 and 2011. The acceptance rate was 37% (9,693) of the selected people who could be contacted.

Data were collected during face-to-face interviews using standardized questionnaires. Baseline workup included extensive assessment of vascular risk factors including blood pressure measurements; ultrasound examination of the carotid arteries; measurement of biological parameters such as blood glucose, urea and electrolytes, and lipids; cognitive functioning; and a clinical diagnosis of dementia. Cerebral MRI examinations were also performed in a subsample of 3,442 persons aged between 65 and 79 years. Participants have been re-examined, on average, every 2 years. The third wave of follow-up examinations started in 2006 and is due for completion in 2012.

Dementia was diagnosed using a three-step procedure (3C Study Group, 2003). First, screening was based on a thorough neuropsychological examination by trained psychologists. From the initial 9,693 cohort, 7 participants had to be excluded as they aged less than 65 years. Second, the participants who were suspected of having dementia on the basis of their neuropsychological performance were examined by a neurologist. Four percent of the participants refused to take part in the medical interview. Finally, all suspected dementia cases were analysed by a common independent committee of neurologists according to DSM-IV criteria. The committee reviewed by teleconference all potential cases of dementia of the three study centres to obtain a consensus on diagnosis and aetiology based on all existing information. With regard to the different subtypes of dementia, AD was diagnosed according to the NINCDS-ADRDA criteria, and vascular dementia based on history of vascular disease, Hachinski score (Hachinski, 1994), and MRI whenever possible (Raffaitin *et al.*, 2009). To date, baseline vascular risk has been investigated and prevalence of vascular disease at baseline explored (3C Study Group, 2003).

3C: dementia

Baseline prevalence of dementia was 2.2% (3C Study Group, 2003). During 4 years of follow-up, 0.84 incident dementia cases per 100 person-years (95% CI = 0.72, to 0.95) were validated (Raffaitin *et al.*, 2009). The authors investigated the relationship between incident dementia and metabolic syndrome, defined according to the National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III) criteria (Grundy *et al.*, 2005). Metabolic syndrome was present in 15.8% of the study participants, and its presence increased the risk of incident vascular dementia but not AD over 4 years (Raffaitin *et al.*, 2009). High triglyceride level was the only component of metabolic syndrome that was significantly associated with the incidence of all-cause (HR = 1.45, 95% CI = 1.05, 2.00) and vascular (HR = 2.27, 95% CI = 1.16, 4.42) dementia. Diabetes, but not impaired fasting glycaemia, was significantly associated with all-cause (HR = 1.58, 95% CI = 1.05, 2.38) and vascular

(HR = 2.53, 95% CI = 1.15, 5.66) dementia. It is worth highlighting that one of the challenges in studies that use all the available information to diagnose subtypes of dementia is that it is difficult to avoid the circular process of the diagnosis of vascular dementia, which might result in overemphasizing the strength of relationships.

3C: depression

The relationship between metabolic syndrome and depression was also investigated. Both metabolic syndrome and depressive symptoms increased during old age (Akbaraly *et al.*, 2011). Over the 4-year follow-up, 827 (18.6%) new cases of depression measured by the CES-D (Radloff, 1977) were observed. Participants with metabolic syndrome were more likely to develop depressive symptoms (OR = 1.73, 95% CI = 1.02, 2.95) compared to participants without metabolic syndrome, even after adjusting for sociodemographic characteristics, smoking, alcohol consumption, and health status factors such as treatment, cognitive deficit, disability, BMI, and self-report history of cerebrovascular disease at baseline. However, this association was not significant within the older age groups (70–75; 75–80; and 80–91). Regarding the specific components of metabolic syndrome, low HDL cholesterol was associated with increased odds of new-onset depressive symptoms in those aged 65–69 years. These results suggest that onset of late-life depression (after 70 years old) does not share the same aetiology and risk factors as onset of depressive symptoms in middle aged and ‘young’ old people. However, the results could also be due to different response rates or bioresources at different ages.

3C: summary

This is a population-based study that focuses on the investigation of the association between vascular health, cerebrovascular disease, and risk of cognitive decline and dementias. New data collected from the third wave of follow-up will be important for looking at the long-term impact of vascular disease and its risk factors on cognitive health.

The English Longitudinal Study of Ageing (ELSA)

ELSA is an interdisciplinary data resource on health, economic position, and quality of life as people age (<http://www.ifs.org.uk/elsa>). The aim is to explore the relationships between health, functioning, social networks, and economic position. The sample was drawn from households that had previously responded to the Health Survey for England (HSE). The HSE is an annual cross-sectional household survey that collects a wide range of health data and biometric measures. The main HSE samples were designed to be representative of the English population living in private households. Fieldwork for the first wave of ELSA began in March 2002 and spanned 12 months, being completed in March 2003. All households with one or more 50+-year-old individuals were eligible for participation. In the first wave, 12,100 individuals were interviewed. The survey achieved a household response rate of 70%; approximately 96% of individuals responded within households.

Topic areas covered at wave 1 included: individual and household characteristics; physical, cognitive, mental, and psychological health; social participation and social support; housing, work, pensions, income, and assets; and expectations for the future. A shorter interview was attempted with a proxy informant if the eligible sample member was unable to respond because of physical or mental ill health, or cognitive impairment. All those interviewed in person were asked for permission to link their responses to administrative data sources. Respondents at wave 1 comprise the baseline study and individuals have been reapproached every 2 years, including those in institutions.

(Langa *et al.* 2009) reported a crosscultural comparison between cognitive performance of older adults in the Health and Retirement Study (HRS) in the US and the ELSA. As cognitive function is a key determinant of independence and quality of life among older adults, the authors sought to identify sociodemographic and medical factors associated with differences in cognitive function between the two countries. The overall response rate among all eligible respondents was 87% for the 2002 HRS and 67% for ELSA. The final study samples included 8,299 individuals from the HRS and 5,276 individuals from the ELSA. The main findings were that despite a higher prevalence of cardiovascular risks and cardiovascular disease among older US adults, they performed significantly better than their English counterparts on tests of memory. While the authors were unable to confidently identify the cause or causes of this US ‘cognitive advantage’, higher levels of education and wealth, lower levels of depressive symptoms, and more aggressive treatment of cardiovascular risks such as hypertension were pointed as possible important contributing factors (Langa *et al.*, 2009).

ELSA: dementia

Although there are no data available on dementia in the ELSA study yet, some interesting results regarding cognition have been published. (Llewellyn *et al.* 2008) investigated whether psychological wellbeing is associated with cognitive function. They found that higher levels of psychological wellbeing were associated with better global cognitive function and performance in multiple cognitive domains, after controlling for the influence of depressive symptoms and a wide range of

additional potential confounders.

ELSA: depression

The associations between dual sensory loss (hearing and vision) with onset and persistence of depression were investigated (Chou, 2008). There were 469 new cases of depression out of the 2,844 older participants who were not depressed at baseline (16.5%); and among the 938 depressed at baseline, 549 (58.5%) were also depressed at follow-up. Visual loss was found to be a robust predictor of both onset and persistence of depression, but dual sensory loss was not.

ELSA: summary

ELSA data are being used to explore the dynamics of ageing, to inform policy debates and for comparative analysis with the HRS in the US and the Survey of Health and Retirement in Europe (SHARE). ELSA is still ongoing.

Epidemiological Clinicopathological Studies in Europe (EClipSE)

EClipSE harmonizes the neuropathological and longitudinal clinical data of brain donors from three population-based prospective longitudinal studies of ageing in Europe that included a brain donation programme: the CFAS (baseline 1989–1993), the CC75C (baseline 1985), and the Vantaa 85+ (baseline 1991) study (EClipSE Collaborative Members, 2009) (www.eclipsestudy.eu). The project was created to address the lack of statistical power within individual studies for specific analyses assessing relationships between data collected during life and neuropathology at death. All three studies interviewed participants at regular intervals, gathering information on sociodemographic details and health status in addition to cognitive function, including dementia diagnosis. Neuropathological parameters include neocortical and hippocampal neuritic plaques, diffuse plaques, tangles, cerebral amyloid angiopathy and atrophy, lacunes, infarcts, white matter pallor, Braak stage, and brain weight. This study is the largest dataset of its type in the world, with brain donor sample sizes of 241 (CC75C), 304 (Vantaa), and 548 (CFAS).

EClipSE: dementia

The potential protective role of education for dementia was explored within the EClipSE study (Brayne *et al.*, 2010). Although almost all older people have some pathology in their brain at death but have not necessarily died with dementia, the relationship between education and brain pathology at death was investigated, testing the hypothesis that greater exposure to education reduces the risk of dementia through either protection from pathology or compensatory mechanism. Education during earlier life was recorded in number of years. Incident dementia was detected through follow-up interviews, complemented by all the available sources of information, such as retrospective informant interviews, death certificate data, and linked health/social records after death. Dementia-related neuropathologies were assessed based on the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) protocol (Mirra *et al.*, 1991). Included were 872 brain donors, of whom 56% were diagnosed as having dementia at death. The main findings in this study were that longer years in education were associated with decreased dementia risk at death (OR = 0.89, 95% CI = 0.83, 0.94). Moreover, education did not protect individuals from developing neurodegenerative and vascular neuropathology by the time they died, but it did appear to mitigate the impact of pathology on the clinical expression of dementia before death. In other words, for a specific pathological burden, those participants who remained in education for longer, earlier in life, were at reduced dementia risk in older age. These results support the 'brain reserve hypothesis' (Stern, 2002; Valenzuela, 2008) where greater exposure to education reduces the risk of clinical dementia by compensating for the pathological burden later in life, rather than being protective against the accumulation of pathology.

Geographical and cross-cultural differences such as education should be taken into account when interpreting the study results. During the early mid-twentieth century the educational systems differed considerably between the UK (CFAS and CC75C) and Finland (Vantaa 85+). Participants from CFAS and CC75C completed an average of 9 years of formal education, while participants from the Vantaa 85+ study completed approximately four. However, even after controlling the analysis regarding education and dementia for study site differences, age, and sex, the results remained strongly associated.

EClipSE also investigated the significance of rarer and 'disregarded' pathologies, such as Pick bodies, severe neuronal loss, gliosis, and granulovacuolar degeneration, along with brainstem plaques, tangles, neuronal loss, gliosis, pigmentary incontinence, and Lewy bodies in relation to dementia in the population. A total of 627 individuals with clinical dementia were assessed. All pathologies were associated with dementia when controlling for plaques and tangles, except Hirano bodies, granulovacuolar degeneration, and brainstem plaques, which shows that dementia in old age is associated with a broad range of pathological and anatomical substrates (Keage *et al.*, 2012).

EClipSE: depression

Depression has not yet been studied within the EClipSE data resource.

EClipSE: summary

The EClipSE study represents a unique resource of neuropathological and longitudinal clinical data of brain donors in Europe. Data from three studies were combined: CFAS in England and Wales, CC75C in England, and the Vantaa 85+ study in Finland. The finding that education can mitigate the impact of pathology on the clinical expression of dementia combined with the understanding of lifecourse factors supports investments in health and education in early life.

Newcastle 85+ study

The focus of the Newcastle 85+ study is the oldest old. The main aim is to examine health trajectories and outcomes as the cohort ages, and their associations with underlying biological, medical, and social factors. All individuals born in 1921 who were permanently registered with a participating general practice in Newcastle upon Tyne or North Tyneside primary care trusts in the UK were sampled (Collerton *et al.*, 2007). The baseline sample will be followed until the last participant has died. Of the 1,470 people eligible to participate, 1,042 participated, three having health assessment only, 188 having general practice record review only, and 851 having both (Collerton *et al.*, 2009).

For most diseases, prevalence was determined on the basis of a review of data from general practice records alone. The targeted common old age chronic diseases include: hypertension, ischaemic heart disease, cerebrovascular disease, peripheral vascular disease, heart failure, atrial flutter or fibrillation, arthritis, osteoporosis, chronic obstructive pulmonary disease or asthma, diabetes, hypothyroidism, hyperthyroidism, cancer diagnosed within the last 5 years, eye disease, dementia, Parkinson's disease, and renal impairment.

Newcastle 85+ study: dementia

Screening for dementia was based on the standardized MMSE score. Using the sMMSE score, moderate or severe cognitive impairment was found in 12.5% (105/840) of participants, of whom 53% (56/105) had no diagnosis of dementia in their general practice records. Therefore, the prevalence of undiagnosed cognitive impairment was estimated at 7%.

Newcastle 85+ study: depression

Depression was assessed using the GDS. Similar results were disclosed for depression as for dementia: 8.4% of the participants (65/772) had a GDS score suggestive of severe depression, of whom 82% (53/65) had no diagnosis recorded in their general practice records in the previous year.

Newcastle 85+ study: summary

Overall, this large cohort of 85-year-olds showed good levels of both self-rated health and functional ability despite significant levels of disease and impairment. Hypertension, ischaemic heart disease, atrial fibrillation, depression, and dementia may, however, be underdiagnosed among this age group.

Conclusion

There is a continuous need for further epidemiological research in old age psychiatry as the world population is ageing. Neuropsychiatric conditions, such as depression and dementia, cognitive impairment, and behavioural and functional decline, place a considerable onus on the health, social, and economic systems. Of particular importance is the potentially large impact on resources and care worldwide. Indeed, the cost of dementia is significant, not only in terms of personal cost, but also on societal resources (Alzheimer's Disease International, 2011). As highlighted in this chapter, many large population-based cohort studies have been undertaken in the ageing population, worldwide and in Europe, in order better to identify patterns of disease and disease risk factors.

There is, however, no standardized approach to the diagnosis of dementia, cognitive dysfunction, and depression. As a result, estimates of disease prevalence and incidence that have been reported across studies may vary, not due to true differences but as a result of methodology. Reported estimates could also vary across studies as a result of differences in the presence of risk and protective factors across individuals and as a result of cultural variation. Such variability is important to identify, especially for the development of preventative strategies (such as those linked to modifiable factors such as diet, educational exposure, and health-related comorbidity). Furthermore, the type of information collected and method of assessment is variable across the studies. For example, some studies report cardiovascular disease comorbidity (self-reported or objectively measured), brain-related changes (determined through neuroimaging), psychiatric-related comorbidity (e.g. behavioural and psychological symptoms of dementia), blood-based biomarkers (including nutritional and genetic risk markers), and

neuropathology. No single study has included all the measures required to completely map the full spectrum of risk/protective factors and the determinants of disease progression. Summarizing the results across all studies suggests that with the age demographic transition, the impact of dementia and age-related conditions is and will continue to be considerable. Better methodology for extracting and weighting data across studies will be important for future synthesis of cross-study analysis and for informing the design of new cohort studies focused on the life-course of ageing populations.

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