Dementia in Germany — Past Trends and Future Developments

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"The national strategic goal to prevent AD within a decade is no more difficult, ambitious, or premature than the 1960s Apollo space program. The vision of preventing AD by 2020 is an attainable scientific objective." (Khachaturian and Khachaturian, 2009).

Chapter 1

Introduction

The aging of the population worldwide is an issue that is attracting an increasing amount of attention. In the more developed regions, including Europe and the United States, every fifth person was older than 60 years in 2000. By 2050, this figure will jump to 35%. Worldwide the percentage of people age 60 and above is also rising, and is expected to grow from 10% in 2000 to 21% in 2050 (United Nations, 2005).

The changes in the population structure will lead to far-reaching rearrangements in societies and political systems, as countries adjust to having a higher share of older people. Disability and care need play an important role in an aging population. How many people will be in need of care, and who will care for them?

Dementia and cognitive impairments afflict a high proportion of elderly people who are in need of care and who suffer from chronic illnesses. In past centuries, relatively few people reached the ages at which dementia typically occurs; thus, for a long time, dementia was regarded as a natural consequence of aging. The aging of the population has led to a greater focus on the syndrome: as the number of elderly people has grown, the number of demented people has increased as well.

Today mental and behavioral disorders represent four of the 10 leading causes of disability worldwide, and they are estimated to account for 12% of the global burden of disease (World Health Organization, 2001). European and Northern American studies show that about one-fourth of the population above age 65 suffers from a mental health problem. About 6% to 10% have severe dementia and severe functional psychoses (Bickel, 2003; Hendrie, 1998). For people above age 60, dementia accounts for 11.2% of all years lived with disability.

The number of sufferers from dementia in 2009 is estimated to about 34 million people worldwide (Wimo et al., 2010), an increase of 5 million people within only 5

years (Wimo et al., 2007). About 46% of the demented people live in Asia, 30% in Europe and 12% in North America (Wimo et al., 2003). Estimates of the numbers of dementia patients in Europe for the year 2000 range from 4.624 million Europeans (EU25) between ages 30 and 99 (Eurostat, 2003) to 7.1 million (European Commission, 2004). Due to their higher mean age, more women are affected: 2.9 million women, compared with 1.7 million men (taking the numbers from Eurostat (2003) into account). For the year 2006, the European Community Concerted Action on the Epidemiology and Prevention of Dementia (EURODEM) group (Alzheimer Europe, 2006) estimated that there were about 5.37 million dementia cases. In Germany, about one million people live with dementia (Bickel, 2008; Hallauer, 2002).

The quantification of dementia is very difficult, as the conflicting findings for Europe make clear. Different definitions and measurement methodologies lead to diverging results. A rising awareness might further influence the number of affected cases, because the syndrome is diagnosed earlier and more frequently. Increasing attention is now devoted to the topic, as can be seen from the larger number of journals, programs and initiatives dealing with the topic, and the growing number of studies analyzing the epidemiology of dementia, the prevalence and incidence of dementing illnesses, and the risk factors of the syndrome (Fratiglioni et al., 1999; Larson et al., 1992). Still, the knowledge about dementia is in the early stages.

The dissertation is structured into seven chapters. Following the introduction in the first chapter, the second chapter provides a literature overview of dementia, including its prevalence, incidence rates, trends and determinants; as well as of the efforts undertaken to medicate and prevent the syndrome. In a systematic literature review, we look at the change in dementia prevalence or incidence over time. The main research question is derived from this information: How is the number of people with dementia in Germany going to develop taking past trends and determinants into account?

In the following chapters, the results of empirical analyses for Germany are shown. Chapter 3 presents results on dementia which are calculated with a unique dataset from the German sickness funds, which includes more than 2.3 million people. This is the first time information on prevalence and incidence rates for Germany are calculated with a German dataset for the entire country. Due to its large sample size, results can not only be separated by age, but also by gender and region. Finally, the co-morbidity of people with prevalent and incident dementia is examined in chapter 4.

In chapter 5, data from the Survey of Health, Ageing and Retirement in Europe

(SHARE) are used to analyze severe cognitive impairment. The dataset provides a variety of socio-demographic, lifestyle and physical and mental health variables which help to explain more completely the influencing determinants. Furthermore, the longitudinal design of the data allows for the analysis of trends of severe cognitive impairment.

The results presented in these chapters provide the basis for different projection scenarios of the future number of people with dementia in Germany, which are presented in chapter 6. Projections are always uncertain. On the one hand, all the people who will turn 60 by the year 2050—the group of people most likely to contract the disease—have already been born; but, on the other hand, there are more uncertain factors, such as the development of life expectancy and of dementia prevalence and incidence. So far for Germany, only constant prevalence projections exist. Ziegler and Doblhammer (2010) and Doblhammer et al. (2009) calculated prevalence projections with decreasing prevalences. Here, multi-state projections using incidence rates and different death rates for the demented and not-demented population will be shown.

Dementia is one of the most costly diseases because of the large amount of care sufferers required. Chapter 7 deals with the current costs, and shows why it is so difficult to estimate the true costs of the disease. Furthermore, cost projections until 2050 are shown.

Finally, a conclusion based on the results is provided in chapter 8. What will the future of the aging German population with dementia look like?

Chapter 2

Literature Review—Trends and Determinants of Dementia

2.1 Definition, Types and Measurement of Dementia

2.1.1 Definition and Implications of Dementia

'Mental disorders' and 'mental ill health' are broad concepts which encompass many mental and behavioral disorders. Several hundred somatic disorders are described and classified in standard references, such as the DSM-IV Diagnostic & Statistical Manual of the American Psychiatric Association, 4th edition (American Psychiatric Association, 1994); or the ICD-10, the International Classification of Diseases, 10th edition (World Health Organization, 2006a). Korkeila et al. (2003) established a set of mental health indicators for Europe. They consider two dimensions of mental health. The positive dimension relates to well-being and the ability to cope with adversity. Negative mental health can be seen as psychological distress, and is characterized by the presence of symptoms, such as depression or anxiety, and the diagnosis of psychiatric disorders (European Commission, 2004). Depression, specific phobias, somatoform disorders and alcohol dependence are seen as the most important forms of mental disorders (Wittchen and Jacobi, 2005).

Dementia, which will be our focus here, is the most important age-related mental disorder other than depression (European Commission, 2004).

Definition

The Latin origin of 'dementia' already reveals the meaning of the word: (de-off, out;

mens-mind) out of one's mind. However, it is very difficult to define dementia. First, the term is used to refer to a syndrome with different causes (see section 2.1.2). Second, it is difficult to differentiate dementia in its early stages from the normal cognitive changes that occur at older ages (Fratiglioni and Rocca, 2001; Schaie, 2004). How do the cohort changes that occur in a changing society with increased education and labor market activity (Schaie et al., 2005) affect intelligence, and, therefore, possibly the brain's reserve capacity? Third, it is hard to define dementia cross-culturally because of a different understanding of the syndrome. Fourth, even within a given culture, perceptions of dementia have been changing in recent years, as both the occurrence of the condition and the level of attention have risen. In Europe, dementia was thought to be a natural—and, indeed, normal—consequence of aging until the mid-1970s (Larson et al., 1992). In developing countries it is often still seen as part of normal aging, maybe due to a low degree of awareness of the disease (Chiu and Chiu, 2005). In the following, we look at three more recent definitions from more developed countries.

> "Dementia is not a disease but a pattern of symptoms (or a syndrome, in medical language), which can be caused by an almost infinite number of cerebral and extra cerebral diseases" (European Community, 2005).

> Dementia is "the loss of intellectual functions (such as thinking, remembering and reasoning) of sufficient severity to interfere with a person's daily functioning. Dementia is not a disease itself but rather a group of symptoms that may accompany certain diseases or conditions. Symptoms may also include changes in personality, mood and behavior. Dementia is irreversible when caused by disease or injury but may be reversible when caused by drugs, alcohol, hormone or vitamin imbalances or depression" (Alzheimer Europe, 2006).

> "Dementia is a decline in mental ability that usually progresses slowly, in which memory, thinking, and judgement are impaired, and personality may deteriorate" (Eurostat, 2003).

All the definitions agree that, in dementia, a change in the brain occurs which leads to memory impairment and a change in personality. Dementia hampers the daily living of the person. This is also an indicator for differentiation from normal aging: age-related decline does not usually cause significant impairment of function; it is slower, and people can compensate for this decline (Larson et al., 1992). The condition usually worsens gradually. Three levels of severity are sometimes distinguished. The relationship of the frequency of mild, moderate and severe dementia is 3:4:3 (Bickel, 2005; World Health

Organization, 2006b).

This increased attention also influences the classification of dementia. The handbook Diagnostic & Statistical Manual of the American Psychiatric Association (DSM) provides a good example of these changing definitions. The first edition was released in 1952, and the fifth is planned for 2013. Each edition is adapted to take into account new consolidated findings. Today the DSM-III-R, DSM-IV and DSM-IV-TR (American Psychiatric Association, 1987, 1994, 2000) are among the most widely accepted formal definitions of dementia. A revised DSM-V is planned for 2013 (American Psychiatric Association, 2010). The handbooks describe the syndrome in great detail, and provide guidance for distinguishing dementia from other mental impairments. The International Classification of Diseases and Related Health Problems (ICD), provided by the WHO (World Health Organization, 2006a), is also adapting to changing definitions. The first edition, in which only the causes of death were classified, was introduced in 1893. In 1948, it was extended to diseases. Currently, the 10^{th} edition is used. The diseases are listed into blocks. The organic, including symptomatic, mental disorders are described in block `F00-F09`. These two sources (ICD and DSM), together with the NINCDS-ADRDA criteria, are the guidelines most commonly used in defining and classifying dementia in research (McKhann et al., 1984).

> **ICD-10** "This block [`F00-F09`] comprises a range of mental disorders grouped together on the basis of their having in common a demonstrable etiology in cerebral disease, brain injury, or other insult leading to cerebral dysfunction. The dysfunction may be primary, as in diseases, injuries, and insults that affect the brain directly and selectively; or secondary, as in systemic diseases and disorders that attack the brain only as one of the multiple organs or systems of the body that are involved. Dementia (F00-F03) is a syndrome due to disease of the brain, usually of a chronic or progressive nature, in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgment. Consciousness is not clouded. The impairments of cognitive function are commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behavior, or motivation. This syndrome occurs in Alzheimer's disease, in cerebrovascular disease, and in other conditions primarily or secondarily affecting the brain" (World Health Organization, 2006a).

The **DSM-IV** classifies psychiatric disorders into five axes. Dementia belongs to axis one: 'Clinical disorders; other conditions that may be a focus of clinical attention'. "Although classified as mental disorders because they involve deterioration in mental, behavioral, and emotional functioning, all these brain disorders are probably caused by physical disease, trauma or drug effect and are classified according to the underlying disease state. Categorization occurs according to localization: amnestic (Persisting Amnestic Disorder), cortical (Alzheimer's), frontal, subcortical (Parkinson's Disease) or by etiology: Alzheimer's, Creutzfeldt-Jakob Disease, Head Trauma, Huntington's Disease, HIV Disease, Parkinson's Disease, Pick's Disease, Substance-Induced Persisting, Vascular, Dementia Due to Other General Medical Conditions, Dementia Due to Multiple Etiologies" American Psychiatric Association (2000).

The criteria developed by the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) specifically diagnose AD and exclude other brain diseases. The test takes into account the patient's medical history, as well as the results of a clinical examination, neuropsychological testing and a laboratory assessment (McKhann et al., 1984). It is generally found to be a valid and reliable diagnostic tool (Breteler et al., 1992).

Implications

The definitions outline most of the consequences of the syndrome. Affected persons can suffer from changes in cognitive perception, emotional control, social behavior and motivation. They may experience changes in their personality, become depressed, suffer from sleep disorders or angst, report hallucinations, become aggressive and face constraints in daily living. The gradually deteriorating health state leads to complete dependence, and the initial need for help turns into a full-time care need. People with dementia have a higher institutionalization rate and a higher risk for other diseases, such as hip fracture, urinary incontinence and high blood pressure (Skoog, 2004).

Furthermore, dementia can lead to a higher mortality rate (Bickel, 2005; Dewey and Saz, 2001; Jagger et al., 2000; Kliegel et al., 2004; Kokmen et al., 1996; Werner, 1995b; Wilson et al., 2003), which might be even higher in vascular dementia (VaD) than in Alzheimer's disease (AD) (Dewey and Saz, 2001). In particular, being male, being older and having more severe dementia are factors that can affect survival negatively (Bickel, 2005; Heyman et al., 1997). The average amount of time from the onset of the disease

until death is estimated to be about 4.7 to 8.1 years for AD, and about one year less for VaD (Weyerer, 2005). In industrialized countries dementia is a common cause or underlying cause of death following the development of heart disease, malignant neoplasms and cerebrovascular diseases (Bickel, 2003). In Germany, heart disease and malignant neoplasms together accounted for 70.4% of all causes of death in 2005. Dementia was the leading cause of death in Germany in 2005 in 1.2% of all cases (Statistisches Bundesamt, Gruppe VIII A, 2007). In the US, AD was the leading cause in 2.9% of all cases (Kung et al., 2008). Numbers vary because it is difficult to distinguish between the primary and the underlying causes of death with and from dementia (Ganguli and Rodriguez, 1999) but also because of underreporting on death certificates (Steenland et al., 2009).

2.1.2 Types of Dementia and Pathogenesis

The syndrome of dementia has a wide range of causative disorders. The underlying diseases that result in dementia can be classified into primary degenerative dementia and secondary dementias. Primary dementias are the neurodegenerative forms of the condition, such as Alzheimer's Disease (AD), dementia with Parkinson, Lewy Body Disease, Chorea Huntington or dementia associated with Trisomie 21; as well as vascular forms, such as vascular dementia (VaD); and infectious forms, such as sporadic Creutzfeld-Jakob Disease (CJD); or the inheritable forms Fatal Familial Insomnia (FFI) or Gerstmann-Sträussler-Scheinker Syndrome (GSS). Secondary dementias are caused by nutritive-toxic or metabolic diseases, vitamin deficiency, alcohol or drugs, infections or transmission (e.g., AIDS dementia) or head injury (Beyreuther et al., 2002; Bischoff et al., 2004; European Community, 2005; Priester, 2004; Weyerer, 2005). A full 90% of all dementia-inducing diseases fall under the heading of primary dementia, and are irreversible. About 10% are secondary dementias, which are, in principle, treatable (Priester, 2004), such as hypercalcaemia, subdural haematoma, normal pressure hydrocephalus and deficiencies of thyroid hormone and nutritive-toxic forms; or they are metabolically caused dementias (Stoppe and Staedt, 2002; World Health Organization, 2006b). However, it is important to distinguish between potentially reversible and fully reversible conditions. Studies which look at reversibility find much lower proportions of fully recovered patients (Stoppe and Staedt, 2002).

The most frequent type of dementia today is AD, a neurodegenerative disorder which slowly and progressively destroys brain cells and synapses. It usually occurs in

old age, but can also start before age 60 (early onset AD). Emil Kraepelin (1909) named the disease after Alois Alzheimer, a German psychiatrist who in 1907 first described the structural changes that occured in a brain of a patient with presenile dementia, including senile plaques and neurofibrillary tangles (Alzheimer, 1907). It was not until the 1940s that researchers realized that genes could be responsible for these changes.

The mechanisms leading to AD are not yet fully understood (Lefroy, 2000). AD is a "primary degenerative cerebral disease of unknown etiology with characteristic neuropathological and neurochemical features. The disorder is usually insidious in onset and develops slowly but steadily over a period of several years" (World Health Organization, 2006a).

Knowledge about dementia has increased over the last two decades. Several pathophysiological pathways have been followed by researchers seeking to understand the mechanism of the disease. Beta amyloid (Aβ) plays a central role in the hypotheses of pathogenesis. It occurs when the amyloid precursor protein (APP), a nerve-protecting protein which is usually split by α-secretase, is abnormally split by β- or γ-secretase (Hartmann and Beyreuther, 2002; Masters and Beyreuther, 2006). Two insoluble peptides, Aβ_{1-40} and Aβ_{1-42}, evolve which in a high concentration accumulate in the core of the neuritic plaque and block the synapses. The oligomeric forms of these peptides have shown neurotoxicity in cell culture and animal studies.

Another important role is ascribed to neurofibrillary tangles. They are degenerating neuronal cytoskeletons with thousands of abnormal fibrils which contain abnormally phosphorylated Tau protein. The defective Tau protein accumulates to neurofibrillary tangles and blocks microtubules which support the cytoskeleton and the transport of nutrients and other important substances between the nerve cells (Arendt, 2002; Breteler et al., 1992; Goedert and Spillantini, 2006; Larson et al., 1992; Masters and Beyreuther, 2006). Both amyloid plaques and neurofibrillary tangles disconnect the communication and metabolism of the nerve cells, causing the cells to die. The death of these cells and their synaptic arresting result in dementia.

Aβ is commonly thought to have the biggest impact on AD, and most research concentrates on the pathogenesis of the Aβ. However, some researchers have concentrated on designing therapies intended to prevent the accumulation of the Tau proteins. Newer ideas combine both hypotheses, with Aβ being involved at an early disease stage, and the Tau protein at a later stage (Mandavilli, 2006).

Two processes seem to be connected with AD: oxidation and inflammation. Oxidative stress has an accelerating effect on aging and several diseases, including dementia

(Helmer et al., 2003; Jama et al., 1996). It is caused by increased production of free radicals. When β amyloid breaks down, free radicals are produced, and the resulting oxidation may contribute to neuronal injury in AD (Goodman and Mattson, 1994). The toxic oligomers of Aβ could be the main source of the oxidative damage (Masters and Beyreuther, 2006). Neurotransmitters, such as acetylcholine or glutamate regulate signals between neurons, and play important roles in learning and memory. In AD, less acetylcholine is produced, which slows the signal transmission and causes memory impairment. Meanwhile, glutamate is overproduced. The nerve cells are thus overstimulated and respond with inflammation, which can damage the nerve cells (Kurz and Jendroska, 2002; Masters and Beyreuther, 2006).

Today, AD accounts for about 50%-75% of all dementias (Bickel, 2005; Breteler et al., 1992; European Community, 2005; Eurostat, 2003; Weyerer, 2005). A century ago, this proportion might have been different because of the younger population structure. Most people died before the onset of dementia; 'general paralysis of the insane' caused by syphilis infection was probably the most frequent type of dementia up to the first half of the 20th century (Nitrini, 2005) and VaD was also likely to have been more common (Reed, 2004). Today, VaD is the second most common form of dementia. This disease is caused by many small infarcts of the brain due to vascular disease, including hypertensive cerebrovascular disease (World Health Organization, 2006a). Inflammatory processes in the blood vessels lead to the development of arteriosclerotic plaques. When they detach from the vessel, they block the capillaries, and the nervous tissue suffocates because no oxygen is transported into these areas of the brain (Bischoff et al., 2004; Hamann and Liebetreu, 2002). VaD accounts for about one-fourth of all dementia cases. However, numbers vary: 25%-50% (European Community, 2005), 15%-20% (Weyerer, 2005), 20%-30% (Skoog, 2004), and might be influenced by the region of the study (see Chapter 2.4.4). VaD was perhaps first described by Thomas Willis in 1684 (Reed, 2004), when he noted that "a Palsie often succeeds stupidity, or becoming foolish." For VaD, it seems even more difficult to define and measure the affected population. Studies that have attempted to measure the number of people suffering from VaD have produced varying results, largely because of factors such as the lack of clear diagnostic criteria; the additional use of imaging findings (magnetic resonance or computerized tomography) by some studies, but not by others; and the varying systems of classification of patients with mixed dementia (Fratiglioni and Rocca, 2001).

It is often difficult to distinguish between different forms of dementia and to define the pathogenetic contribution of associated diseases (Palumbo et al., 1997). Hsiung and

Sadovnick (2007) or Beyreuther et al. (2002) give an overview of genetic risk factors of AD, VaD and other dementia forms. The differentiation is, however, made more difficult because mixed pathologies are common. For example, AD and VaD are both present in some cases (World Health Organization, 2006b). In addition, dementias related to Parkinson's Disease and to AD share neuro-anatomic and neurochemical features, and may occur together (Huang et al., 2006; Inzelberg et al., 1998). Newer estimations therefore assume a higher occurrence of AD within the dementias of about 73.7% to 86.5% (e.g., Beyreuther (2008) based on van Oijen et al. (2006); (see section 2.2)), in which AD is considered to be the main cause of dementia among other contributing conditions.

2.1.3 Diagnosis of Dementia

Different types of degenerative disorders with different causes are included in the definition of the term dementia. Neuropsychological assessments that standardize and measure cognition and behavior are necessary to ensure the accurate diagnosis and management of affected people (Tranel, 1992). Many scales have been developed to characterize dementia, some involving questions only, and some involving medical screening or brain autopsy as well. However, when every test uses a different scale, a comparison of results becomes difficult. Kessel (1965) asserts that, for the 1960s, international comparisons are not possible due to poorly calibrated instruments, and because of cross-cultural differences. Early studies are therefore seldom included in cross-cultural comparisons. Analyzing studies before 1945, Werner (1995a,b) shows that the methodologies used were very different from those employed in today's studies. These studies usually included the total population of a certain region. The medical-psychiatric experts of that time (e.g., doctors, supply institutions, government agencies) counted the number of mentally ill persons, and their diagnoses. Whereas these studies were administrative studies, most studies conducted after 1945 were field studies. Out of the total study population, a sample was drawn, and interviews and screenings using newly developed instruments were conducted.

Some of the most frequently used tests to detect a dementia are as follows:

The Mini-Mental State Examination (MMSE) was developed by Folstein et al. (1975), and has been proven to be a valid test of cognitive function. The authors

developed 11 questions on mental functioning designed to test orientation, memory, attention and the ability to name and follow verbal and written commands. The MMSE is used in many recent studies (Wilson et al., 2003). To better differentiate between moderate and severe dementia, Harrell et al. (2000) developed a Severe Mini-Mental State Examination (SMMSE).

The Dementia Detection (DemTect) is a quick and easy-to-implement test used to detect early dementia. The test, which takes between six and eight minutes, examines memory, verbal fluency and calculation abilities (Kessler et al., 2000). A maximum of 18 points can be obtained, and a different weighting procedure is applied for ages above and below 60. The cut-off point is below 11 points.

The Cambridge Mental Disorders of the Elderly Examination (CAMDEX) is a structured interview schedule that is specifically designed to detect mild dementia (O'Connor et al., 1989). It includes a mental state examination, a psychiatric history, detailed cognitive testing and an information interview.

The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) developed a test for detecting AD that entails asking questions from the MMSE related to memory, verbal fluency and constructional abilities. In addition, however, the test but also provides standardized protocols of neuroimaging and neuropathological examinations of the brain (Morris et al., 1988).

Other common tests of dementia or AD include the following:

- Geriatric Mental State Interview (GMS) (Copeland and Dewey, 1991)
- Short Orientation-Memory-Concentration Test of Cognitive Impairment (6 CIT) (Brooke and Bullock, 1999; Katzman et al., 1983)
- Clinical Dementia Rating (CDR) (Hughes et al., 1982)
- Structured Interview for the Diagnosis of a Dementia Alzheimer's Type, Vascular Dementia and Dementia of Other Etiology Orientating on ICD-10 and DSM-IV (SIDAM) (Zaudig and Hiller, 1995)

Although newer tests improve the correct identification of dementia cases (Rockwood et al., 2007), the classification still holds uncertainty. False-positive as well as false-

negative diagnoses occur in a significant proportion of cases. Also the determination of the type of dementia is difficult. As recently as in 2004, it was thought that 100% reliability in diagnosing for AD and other forms of dementia was only possible after death through brain autopsy (Bischoff et al., 2004). However, new methods have been developed which allow for an accurate diagnosis of AD prior to death. The amyloid-imaging positron emission tomography (PET) tracer, or Pittsburgh Compound-B (PIB), (Klunk et al., 2004) detects amyloid plaques in vivo.

For a final diagnosis of the type of dementia, clinical experience and examinations or brain imaging techniques are necessary. Then a classification according to DSM or ICD can be made. The comparability of studies is enhanced and becomes more reliable when the same classification is used. Studies using ICD-10 tend to find lower rates of dementia in general than those using DSM-III-R, which suggests that the ICD-10 employs a stricter definition of dementia of the ICD-10 (Berr et al., 2005).

2.2 Prevalence and Incidence of Dementia

The most common method used to count the number of people suffering from a dementia in a given population is to show the prevalence. This is done by dividing the number of affected people by the total population. Usually the proportion of affected people in certain age intervals in a population is investigated, which also eases the comparability between countries with different age structures. The incidence shows how many newly diagnosed cases occur per 1,000 person-years lived during a certain time. It is very important to differentiate between these two measures. The prevalence does not take mortality into account, which means that differences between age groups or countries could be simply due to a longer or shorter period of survival with the disease in that age group or country. Both together show information about the average length of dementia, and whether mortality with the disease is different from the total population. However, the incidence is a better indicator for estimating a trend in the disease occurrence, or for comparing across countries and age groups, because it excludes the effects of mortality and a different life expectancy with dementia, respectively.

As the population ages and awareness of the disease has grown in recent years, the number of studies and literature reviews regarding the prevalence and the incidence of dementia has also been increasing. Due to the extensive literature in this field, not all existing prevalence and incidence studies could be accounted for. However, all meta-analyses are included.

2.2.1 Prevalence

A study by Werner (1995a) analyzed the first studies done on dementia, as well as psychiatric-epidemiologic studies in general. He found 11 studies conducted before the Second World War. They generally showed low total prevalence rates, with a mean rate of 3.22%. However, comparability is very difficult because of wide methodological differences. As described in chapter 2.1.3, there are large standard deviations because the methods were not standardized. Studies after 1945 generally showed a higher total prevalence in the population, with a mean rate of 19.2%. The author attributed this sudden change to the higher mean age of the population, and to a change in methods. Due to more standardized measurements, the standard deviation also becomes smaller.

In 1987, the first literature review on studies of the prevalence of dementia between 1945 and 1985 was done by Jorm et al. (1987). The authors compared 27 studies, and also found that early studies seem to differ considerably in their prevalence rates. This might, however, be due to methodological problems: specifically, the use of a different definition of dementia, as well as different study design and diagnosis methods (see also Mortimer (1983)). Nevertheless, in 22 studies, Jorm et al. (1987) found that "the relationship between prevalence and age was remarkably consistent." In more recent studies, where more attention was paid to dementia and its measurement, results were based on more common and comparable diagnostic criteria, and the differences between studies became smaller (Hendrie, 1998; Hofman et al., 1991; Jorm and Jolley, 1998; Lopes and Bottino, 2002). Today the prevalence of dementing illnesses is reported to be similar in different regions of the world (Beard et al., 1995) (for a more detailed discussion of regional differences see section 2.4.4).

Age is the most important factor for the prevalence of dementia (see section 2.4.1). Before age 65, dementia is rare. In Germany, about 20,000 people under age 65 are estimated to have a presenile dementia (see chapter 2.1.2), or less than 3% of the total number of all affected people (Bickel, 2005). After age 60 or 65, most studies report a rapid increase in the number of affected people. Many studies found, irrespective of the methodology, that the prevalence of dementia has been doubling every five to six years after age 60 (Jorm and Jolley, 1998; Jorm et al., 1987).

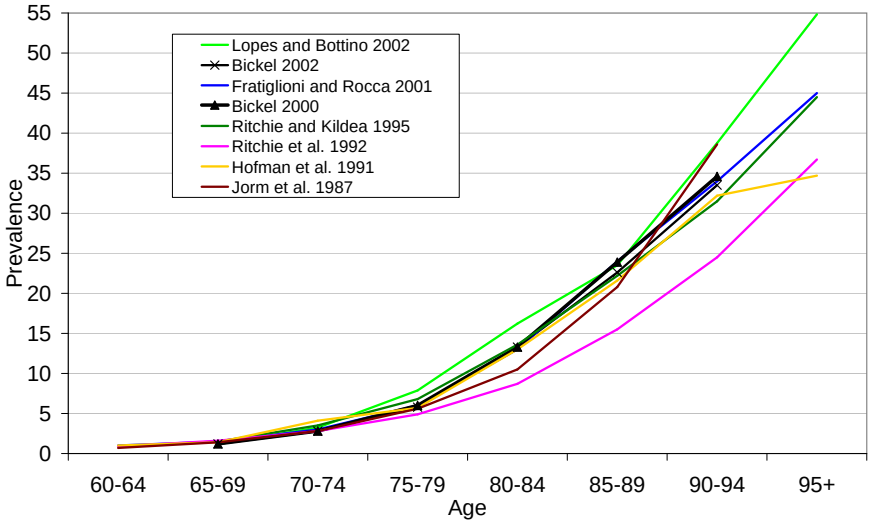
Figure 2.1 shows the prevalence rates from different literature reviews. In the oldest review, Jorm et al. (1987) took 27 of the earliest prevalence studies into account and averaged the results with an exponential model. Studies vary greatly in method and sampling. Hofman et al. (1991) pooled data from 12 European studies conducted between

1980 and 1990, which included the institutionalized population, and used DSM-III or equivalent criteria. Twenty-three data sets were provided by 20 research groups working on the epidemiology of dementia and participating in the European Community Concerted Action on the Epidemiology and Prevention of Dementia Group (EURODEM), which was financed by the European Community. Ritchie and Kildea (1995b) analyzed nine papers in which community and institutionalized population were included, and DSM-III diagnostic criteria were used. The authors criticized the exponential model from Jorm et al. (1987), and suggested a logistic model to allow for a flattening of the curve at the highest ages. (For a more detailed discussion of the debate over whether or not an exponential increase has occurred in the prevalence rates of dementia see chapter 2.4.1.) Three years previously, they published pooled prevalence data on 13 studies conducted since 1980 which were still calculated with an exponential model (Ritchie et al., 1992). Even then, they claimed they were not satisfied with the exponential model because it was a less good fit at the highest ages, and because they saw a slower increase of prevalence rates above age 90. They tried a logistic model, which, however, did not work out due to data constraints. Fratiglioni et al. (1999) averaged results from 35 prevalence studies and Fratiglioni and Rocca (2001) from five meta-analyses. Thirty-eight studies conducted between 1994 and 2000 were analyzed by Lopes and Bottino (2002). The meta-analysis of Lobo et al. (2000) used pooled data from 11 European studies. However, they only provided sex-specific prevalence rates (see chapter 2.4.3). Bickel (2000, 2002) pooled the data from the meta-analyses and calculated the average prevalence. In the 2002 article, two regional results from Germany were also included.

The results for all studies with pooled prevalence rates are similar. The rates are about 1% for people aged 60-64, and they increase to about 35% to 55% for people aged 95 and above. The rates rise steeply with age. Differences between populations for which similar measures are used seem to be small.

When single studies are compared, the results diverge to a greater extent. The variability in the rates may be explained by differences in methodology (Corrada et al., 1995). However, small sample sizes, especially at the highest ages, may also bias results. On the other hand, the results may change within the same study population when different scales are applied. For example, Riedel-Heller et al. (2001b) found higher prevalence rates when using DSM-III-R criteria than when using ICD-10.

Figure 2.1: Prevalence of Dementia according to Meta-Analyses



Source: Different

2.2.2 Incidence

Many prevalence and incidence studies close with the statement that more incidence studies are needed in order to understand better the process of the development and occurrence of dementia: e.g., Fratiglioni et al. (1999); Launer and Hofman (1992); Ritchie and Kildea (1995b); Werner (1995b). This shows the importance of the distinction between prevalence and incidence, especially in the debate about age or aging relatedness (see chapter 2.4.1). And, indeed, the incidence is a much better tool for describing and comparing the disease pattern in and between population(s), because incidence rates are independent of survival. However, incidence studies are more elaborate, costly, and time-consuming to conduct. Thus, Mortimer (1983) still in the 1980s found only a few incidence studies. However, the number of incidence studies has risen considerably in recent years: e.g., Aevarsson and Skoog (1996); Kawas et al. (2000); Kukull et al. (2002); Miech et al. (2002); Nilsson (1984); von Strauss et al. (1999).

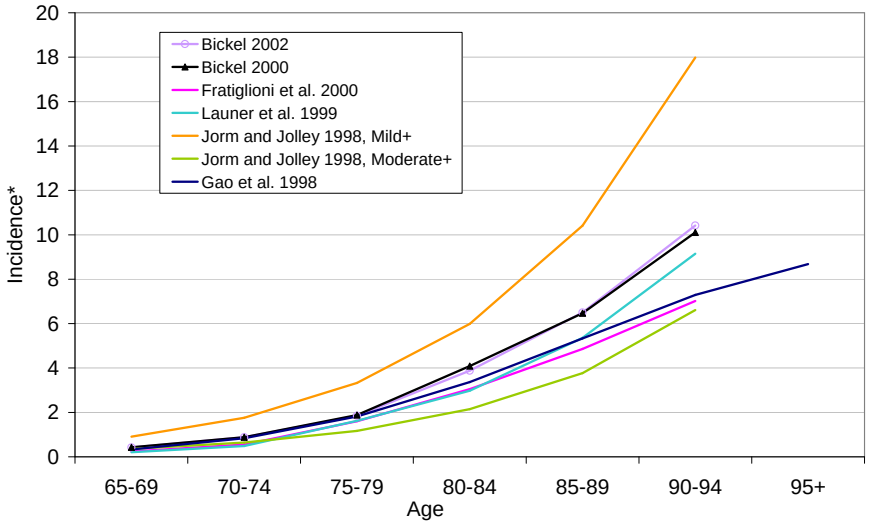
The first literature review on incidence studies conducted between 1966 and 1997 was done by Jorm and Jolley (1998). For the included studies, they found an exponential increase of dementia at ages above 65. As with prevalence, the incidence rates in older incidence studies vary more widely, which again is mainly due to the application of different methodologies. The review further differentiated findings from the studies into mild+ (including mild, moderate and severe cases) rates for Europe, and moderate+ (including only moderate and severe cases) rates for Europe. Newer studies, in which the measurement is more standardized, showed greater consistency in their results and

similar rates in different regions of the world, e.g., Fratiglioni and Rocca (2001); Gao et al. (1998); Kokmen et al. (1996); Kukull et al. (2002); Launer et al. (1999); Launer and Hofman (1992) (see section 2.4.4).

Figure 2.2 shows results of incidence meta-studies, displayed as incidence cases per 100 person-years. Single incidence studies show greater divergence, probably due to different methodology and small sample sizes.

The rates from Fratiglioni et al. (2000) represent pooled data from eight European incidence studies. Gao et al. (1998) applied a mixed-effect model to data from 12 incidence studies of dementia and AD measured with DSM-III. They showed that, while there is no decline in incidence rates at the oldest ages, the increase slows down. Jorm and Jolley (1998) used loess-curve fitting to analyze data from 23 studies. They found an exponential increase in incidence rates up to the highest age group of 90+. The rates found in Bickel (2000) and Bickel (2002) fell in the middle of the results. The author calculated a mean rate of several studies based on three meta-analyses and one single study in the first paper, and on four meta-studies and six single studies in the second paper.

Figure 2.2: Incidence of Dementia according to Meta-Analyses



Source: Different

*There is no consistent use of percentages and incidence per 100 person-years within the studies. Bickel (2000, 2002); Gao et al. (1998) use percentages, while the other studies give rates per 100 person-years.

Incidence studies in general show an increase in the rates with age. The rates seem to be similar throughout the world. The results of these studies are more divergent than for prevalence results. Incidence rates reported from Northern American studies

are generally lower than from European studies, which could be due to methodological differences in case ascertainment and in the study design (Fratiglioni and Rocca, 2001). Results also depend on the test used, as is shown by Fichter et al. (1995, 1996). Their results are based on the SIDAM DSM-III-R test. When they applied other tests, the incidence rates were lower. In addition, Riedel-Heller et al. (2001a) found differences in the incidence rates of the same population measured with DSM-III-R and with ICD-10, respectively. The differences are biggest in the highest age groups. The issue of discrepancies between the prevalence and incidence rates in the highest age groups presented in the literature will be discussed further in chapter 2.4.1.

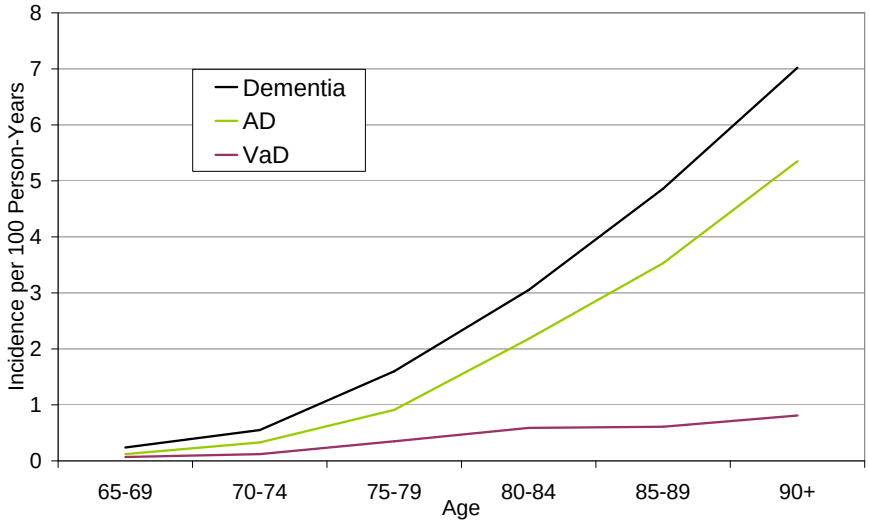
In general, prevalence studies provide an overview of the occurrence of dementia in different age groups in a population. Recent studies, in which the diagnosis of the disease is more standardized, produce comparable results between populations.

Prevalence and incidence have also been studied for different types of dementia, mainly AD and VaD. AD thus appears to be the driving force of the pattern of general dementia, showing a steep increase with age. For example, Ebly et al. (1994); Rocca et al. (1991) showed an increasing proportion of AD to VaD with age. There could be gender and age effects (see sections 2.4.1 2.4.3). For VaD there are diverging results. VaD and AD commonly co-occur, but AD is often seen as the primary cause of the symptoms, and thus they are not easy to distinguish. Fratiglioni and Rocca (2001) suggested that "it is most likely, especially in very old ages, that vascular and degenerative mechanisms contribute to the development of dementia together, and the classification by etiology becomes a matter of attribution." Most studies show a pattern that resembles that of figure 2.3, e.g. Ott et al. (1998).

2.2.3 Dementia Studies in Germany

Not many studies exist in Germany that analyzed the prevalence and incidence of dementia. Studies about dementia are usually regional clinical studies. Prevalence studies were done by Cooper et al. (1992); Fichter et al. (1995); Kliegel et al. (2004); Riedel-Heller et al. (2001b); Wernicke and Reischies (1994). The study by Cooper et al. (1992) was conducted in Mannheim. General practitioners in 24 practices rated 3,737 patients, including people living in institutions over the age of 65. Fichter et al. (1995) analyzed a community sample of 402 people above age 85 from Munich. Wernicke and Reischies (1994) used a sample of 152 people above age 70 from the Berlin Aging Study (BASE), and Riedel-Heller et al. (2001b) included 1,692 people above age 75

Figure 2.3: Incidence of Dementia, AD and VaD



Source: Fratiglioni et al. (2000), Pooled Data from 8 European Studies

from the Leipzig Longitudinal Study in the Aged (LEILA75+) into their study, with 192 of the them living in institutions. The cognitive status of 156 centenarians from the Heidelberg Centenarian Study was analyzed by Kliegel et al. (2004). Bickel (1996) drew a new sample of 2,507 people in Mannheim who died between 1991 and 1993 to analyze prevalence and incidence of care need and dementia. To obtain incidence rates, Fichter et al. (1996), Riedel-Heller et al. (2001a) and Bickel and Cooper (1994) used the same sample from their prevalence studies (see above) to re-analyze the cognitive status about one year later (Bickel and Cooper (1994) 5-8 years).

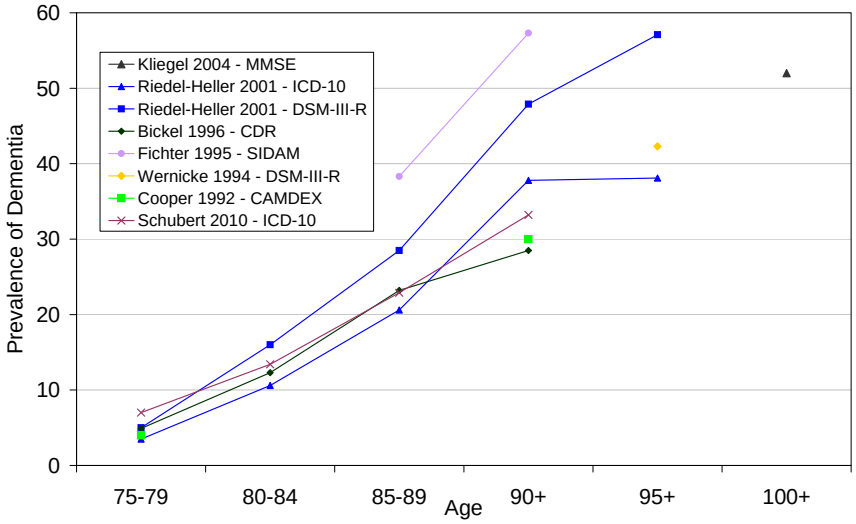
In regional clinical studies typically, a sample of a population is drawn, and medical experts examine people from the sample, diagnosing patients according to a special scale, and in some cases running additional tests, such as an MRT or PET scan. The large amount of time required and the high costs involved often mean that these studies are restricted to a few hundred people. In a newer non-clinical study by Schubert et al. (2010), the authors used data from the public sick funds to calculate prevalences, but the data were drawn from only from one German state, Hessen. The sample comprised nearly 300,000 people in 2005.

Figures 2.4 and 2.5 show the results of prevalence and incidence studies. Different scales are often used to assess dementia which makes it difficult to compare results. Moreover, when results are given for different age groups, some studies only provide graphs and not numbers (Cooper et al., 1992; Wernicke and Reischies, 1994). Cooper et al. (1992) used different tests and scales, and in cases in which a cognitive impairment

was likely, the Cambridge Mental Disorders of the Elderly Examination (CAMDEX) was used to define the severity of dementia. Wernicke and Reischies (1994) used the DSM-III-R for the clinical diagnoses, Kliegel et al. (2004) the MMSE, Fichter et al. (1995) showed results according to the Structured Interview for Diagnosis of Dementia of Alzheimer Type, Multi-infarct Dementia and Dementia of Other Aetiology according to ICD-10 and DSM-III-R (SIDAM), and also presented results according to the DSM-III-R and ICD-10 rated by physicians. In the figure, the physicians result is used, which was the same for both diagnostic criteria. Results were much lower when assessed via interview (for SIDAM/DSM-III-R and SIDAM/ICD-10: age 85-89 23.6% and 13.6% and age 90+ 40.2% and 24.0%, respectively). Riedel-Heller et al. (2001b) also used both the SIDAM/DSM-III-R and SIDAM/ICD-10 in an interview. A retrospective interview with close relatives of the deceased was done to find out about the health status in the study by Bickel (1996). The Clinical Dementia Rating (CDR) was used to estimate the severity of dementia.

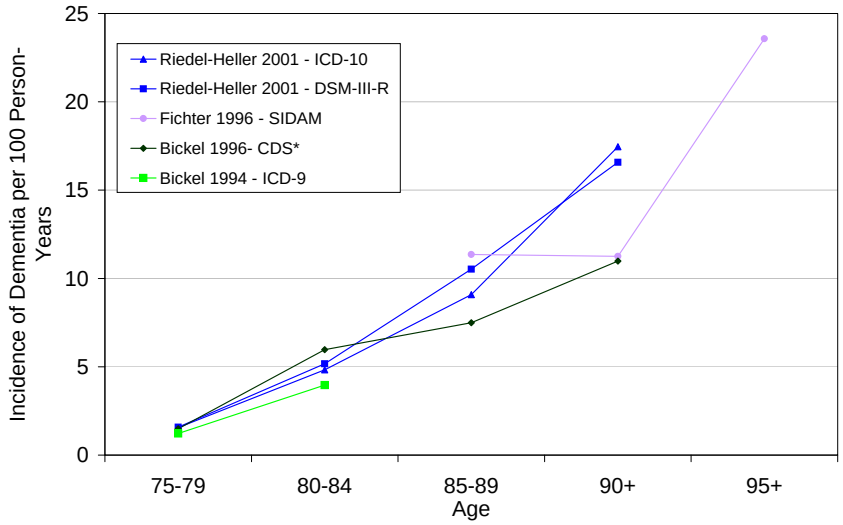
Given the different scales and survey conditions of the studies, the results are relatively close together. Results from the German studies tend to be slightly higher for both prevalence and incidence compared with the meta-studies, with prevalence being particularly high in Fichter et al. (1995) and Riedel-Heller et al. (2001b) (DSM-III-R), and incidence being particularly high in Fichter et al. (1996) and Riedel-Heller et al. (2001a).

Figure 2.4: Prevalence of Dementia in Germany according to Regional Studies



Full Source: Bickel (1996); Cooper et al. (1992); Fichter et al. (1995); Kliegel et al. (2004); Riedel-Heller et al. (2001b); Wernicke and Reischies (1994)

Figure 2.5: Incidence of Dementia in Germany according to Regional Studies



Full Source: Bickel (1996); Bickel and Cooper (1994); Fichter et al. (1996); Riedel-Heller et al. (2001a)

*Incidence rates in per cent are used instead of incidence per 100 person-years
- Bickel and Cooper (1994) use age groups 70-79 and 80+

2.3 Past Trends of Dementia

The increase of the life expectancy and the aging of the population worldwide also increased the interest for the development of health over time. Three general scenarios have been proposed. The pessimistic 'expansion of morbidity' theory assumes that the increase in life expectancy is caused by a reduction in the fatality rate of chronic diseases (Gruenberg, 1977; Olshansky et al., 1991). A more optimistic point of view is presented by those who support the 'compression of morbidity' scenario from Fries (1980). It assumes a fixed lifespan in which the onset of morbidity will be postponed into higher ages. The third, intermediary 'dynamic equilibrium' scenario was proposed by Manton (1982). He assumes that the increase in life expectancy will be associated with a parallel increase in the proportion of healthy and unhealthy years, but that there will be a shift from severe to moderate disability. So far, no consistent pattern for the development of care need and disability could be demonstrated, either across countries or over time. A recent review of trends in diseases and disability rates showed mixed results, but generally supports the theory of dynamic equilibrium (Christensen et al., 2009). Despite the finding that the prevalence of some chronic diseases has increased over time, it seems that people under age 85 experience a postponement of limitations and disabilities. For people above age 85, there are fewer studies with contradictory results, but there is evidence of a leveling off in disability levels for the oldest old on a cohort basis. An increase in the use of assistive living technologies and a changing social perception of disability might support a more positive view of self-perceived health.

In this section, a systematic literature review was done to examine whether a change of dementia prevalence or incidence occurred over time. The databases MEDLINE and PSYCHINFO were used to find all trend studies for dementia. Search terms were ((dementia or Alzheimer$ or (cognitiv$ and impair$))and trend).

Can the rather positive trend that was found for general health be confirmed for dementing illnesses? In the 1980s a negative trend was feared: "A sizeable number of these individuals and their families will derive little enrichment from this extension of their lives because of the cognitive impairment which frequently accompanies the aging process" (Reisberg, 1983). Kramer (1983) shared this pessimistic view, not just because of the aging of the population, but also because the average duration of chronic diseases increased (Kramer, 1983). However, during the 1980s this negative trend was also found for general disability (Crimmins et al., 1989, 1997), which then changed in

the 1990s.

Only few studies looked at the trend of dementia over time. Mortimer (1983) wrote that even if the incidence of senile dementia over time had been documented, "it would be difficult to judge whether one had occurred, given the changes in diagnostic criteria and nosology that have taken place over the past 30 years." Two decades later, there are still only a few studies on the trend of dementia, which makes reaching a clear conclusion difficult. One reason why more trend studies are not available could be that researchers find it very complicated, costly, and time-consuming to gather the necessary longitudinal data. Furthermore, dementia has only recently become more important due to the rising number of people who are affected by the condition, and therefore the necessary level of attention and allocation of resources to treating the disease has only recently increased. However, there is one study that examined the admission to mental hospitals in Stockholm before the 1980s by Larsson et al. (1963). The authors analyzed first admission to mental hospitals in Stockholm for senile dementia in the period 1931-1960 and found no change in the morbidity risk.

When trends in dementia are discussed, studies conducted on two populations are usually cited. The oldest project is the Lundby Study, in which the observation started in 1947. The other study was conducted on a population in Rochester and started in 1975.

2.3.1 Lundby Study, Sweden

Several papers investigated the dementia risk from the Lundby Study. Hagnell et al. (1981) examined 2,550 persons of all ages in the Swedish area of Lundby over a 25-year period: in 1947, 1957 and 1972. In the longitudinal study, nearly all inhabitants could be interviewed for mental disorders and social factors at both follow-ups; the non-response rate was only 1%-2%. In the first follow-up, people who moved out of the parish were also followed. Between 1947 and 1972, a total of 16,057.8 person-years were lived by men, and 15,198.9 person-years were lived by women. In that period, 21 men and 32 women were diagnosed as having severe dementia; when moderate and mild cases were also taken into account, the total numbers were 48 men and 50 women. Hagnell et al. (1981) found a decrease in the incidence of senile and multiple infarction dementia for males and females younger than age 90. Up to age 80, this only held for males, while for females there was a slight increase. They stated that it is essential to differentiate between senile dementia and AD because of their different clinical course

and biochemical changes. "The group of persons that acquire age psychosis in their seventies, with a disease characterized by obvious biochemical changes, can be expected to be less influenced by environmental factors" (Hagnell et al., 1981). This would also support the age-related hypothesis (see section 2.4.1). Their positive finding of a decreased incidence of dementia was supported by Svanborg (1980, in personal communication), who investigated the health of 70-year-old men and women in Gothenburg at two different points in time within five years, and who also found an improvement in psychiatric health.

Rorsman et al. (1986) investigated the same Lundby cohorts as Hagnell et al. (1981), but this time included the total Lundby population, including 1,013 new people who entered the project in 1957. They restricted the analyses to people above age 60. In this study, 2,189.78 person-years were lived by men, and 2,289.78 by women. Twenty-one males with severe, moderate or mild senile dementia were diagnosed, as were 35 cases of multi-infarct dementia. For women, the corresponding numbers were 25 and 26. This time, they found no significant changes in the prevalence of senile and multi-infarct dementia between 1947-57 and 1957-72. The incidence rates were lower in the second period for both senile dementia and multi-infarct dementia, and for all three combinations of severe, severe+medium and severe+medium+mild, except among females, for whom severe multi-infarct dementia was about the same in the two periods. However, the results were not statistically significant.

Another follow-up from the Lundby Study was by Gruenberg et al. (1987), who found an increase in the prevalence of chronic brain syndrome (CBS) from 1947 to 1957. During that time, 38 men and 38 women developed episodes. The prevalence for men and women above age 60 rose from 3.2% to 5.7% between 1947 and 1957. The authors attributed this increase to longer periods of survival with the disease. The mean duration of episodes of people diagnosed in 1947 was 27.6 months; while in 1957, it was 55.2 months. Their paper begins with the words "The old man's friend is dead." People who, at the beginning of the century, suffered from chronic brain syndromes often died from pneumonia, but medical advances postponed death—at the price, however, of higher rates of disability. Gruenberg (1977) expressed this pessimistic view 10 years earlier when he described some diseases in which the prevalence was rising since the late 1930s, when drugs like sulfonamides and penicillin were discovered, and lowered the death rates substantially: "Our methods of 'extending life' have too often been methods of extending disease and disability" (Gruenberg, 1977; Gruenberg et al., 1987). Unfortunately, they therefore do not examine the incidence rates, and

simply write: "There appears to be no reason to assume a change in annual age-specific incidence rates" (Gruenberg et al., 1987).

Rocca and Kokmen (1999) write that we might expect to see a reduced incidence of VaD over time because Broderick et al. (1989) found a decline in the stroke incidence risk for the fifties, sixties and seventies among elderly individuals (but an increase in the eighties). However, only a few data sets are available.

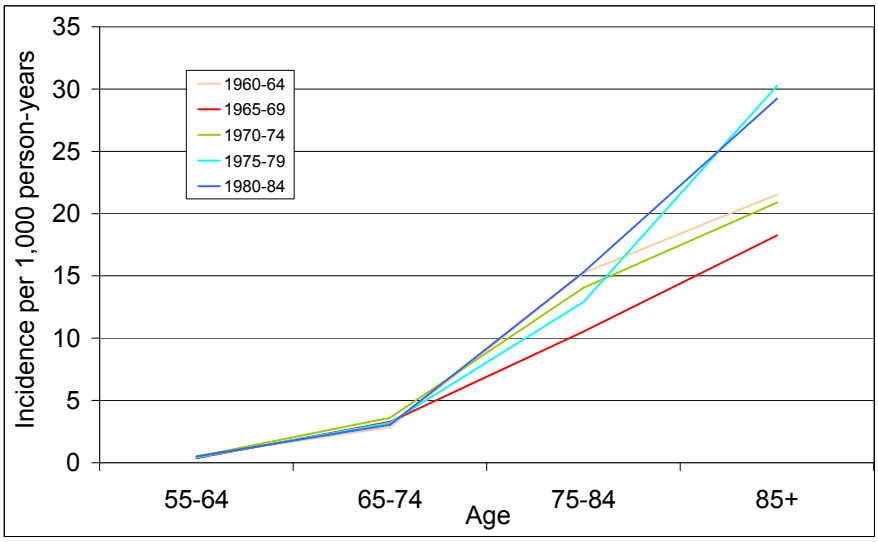
Hagnell et al. (1992) conclude, that the Lundby Study provided data from the fifties to the mid-seventies, and showed stable prevalence and incidence of VaD for males and females for most ages. However, the condition was found to have declined among the 80- to 89-year-olds. They also used the initial cohort from 1947, and the 1957 cohort that was extended by newcomers. A total of 28,497.2 person-years for men and 26,856.1 for women aged 0-109 accounted for 53 and 41 cases of multi-infarct dementia.

2.3.2 Rochester, Minnesota, US

Kokmen et al. (1993) studied the incidence of dementia and AD in Rochester, Minnesota between 1960 and 1984. The city had about 70,000 inhabitants in 1990, and detailed health care records are available from the Mayo Clinic. According to the authors, "Our case-control studies have the advantage of being free of selection and recall biases, inasmuch as all the data were collected from health-care records and were documented long before dementia occurred" (Kokmen et al., 1996). During that period, 1,262 people were diagnosed as having a form of dementia. Patients with an existing dementia who moved to Minnesota were not included in the study. Otherwise, new cases were included. The time was divided into five separate five-year periods. Kokmen et al. (1993) found a U-shaped configuration of both dementia and AD over time. In an earlier study in this community for the period 1960 to 1974, they came to the conclusion that the incidence rates were stable over time (Kokmen et al., 1988). But after that period, the incidence seemed to have increased again. Age-specific incidence rates for dementia in the five periods are displayed in figure 2.6. The highest increase over time has been found for the very elderly aged 85 and over. First, there is a decrease between 1965 and 1974 compared to 1960-64, and a strong increase for people above age 85 after 1975 until 1984. Broken down by the type of dementia, an increase of AD is found, probably due to a decrease in 'unknown cause', but also to a decline in cerebral infarcts. A general decline in cerebrovascular disease in the community for that time occurred. The authors came to the conclusion that the incidence of dementing illnesses was increasing among the

elderly over time. The decrease between the periods 1960-64 and 1965-74 could be due to chance: "because of the inherent difficulties of determining the onset of dementia, a number of prevalent cases, ie, those who had onset of dementia in an earlier time period, might have been included in this first incidence quinquennium." However, they also wrote that the increase might be due to an ascertainment bias: "During the 1970s and 1980s, there has been an increasing awareness of dementing illnesses in general and AD in particular among the health-care community. Indeed, the diagnosis of dementia or AD may be placed on death certificates with greater frequency now than 30 years ago." They further described a possible correlation to the increase in the number of nursing home beds, because a physical examination was required to enter the nursing homes. "In conclusion, the apparent increase in the incidence of dementing illnesses among the very elderly may or may not indicate a true trend" (Kokmen et al., 1993).

Figure 2.6: Incidence Trends of Dementia in Rochester, Minnesota at Different Time Points



Source: Kokmen et al. (1993)

Rocca et al. (1998) reanalysed data from Rochester between 1975 and 1984. This time they looked at differences in the incidence between cohorts. They found that 659 people aged 50 to 99 developed a dementia, with 542 of them developing AD. Between the two periods 1975-79 and 1980-84, no birth cohort effect for dementia or AD could be seen, and the incidence rates remained stable.

Beard et al. (1995) looked at the prevalence of dementia and AD in Rochester, Minnesota at three time points: January 1, 1975; January 1, 1980 and January 1, 1985. A total of 301 people (214 women and 87 men) met the criteria for a dementing illness

in 1975, while 362 people (269 women and 93 men) met the criteria in 1980 and 521 people (386 women and 135 men) met the criteria in 1985. They found no change between 1975 and 1980 (also: Beard et al. (1991)); however, in the last period, the prevalence seemed to have increased more for women. Changes in the incidence or in the survival could be responsible for that increasing prevalence. Since Kokmen et al. (1993) found an increasing prevalence in the same community, the changes could be attributable to both reasons. However, they compared in- and out-migration of the community and found a higher in-migration for the most recent date: "During 1982, a large senior citizens complex initiated an aggressive sales program; we surmise that the increase in prevalence was due, at least in part, to that circumstance." An increase in the number of nursing home beds, and in-migration for that care, could also be a possible explanation. Like Kokmen et al. (1993), they mention the increase in attention to AD and dementia. "Is the increase in prevalence real or artefactual? We suspect that the increase may be due in part to improved recognition by physicians and families, which has partially resulted from the increased reporting in the lay and medical press. ... Under these circumstances, we cannot conclude with confidence that a change in disease frequency has occurred."

2.3.3 Other Trend Studies

Manton et al. (2005) studied the prevalence of dementia in the US elderly population between 1982 and 1999 using data on about 42,000 people from five cross-sections from the National Long Term Care Survey (NLTCS). Severe cognitive impairment (SCI) was measured as "a.) the subject being not able to answer any questions in the Short Portable Mental State Questionnaire (SPMQ), 1982 to 1994 or the Mini Mental State Evaluation (which contains all SPMQ questions), in 1999 and b.) the interviewer consequently determining the necessity, due to severe cognitive impairment, for a proxy to answer questions." They found significant decreases in the prevalence of dementia from 5.7% to 2.9%. This decline was more pronounced for males, but significant for both sexes. It was the result of fewer cases with vascular and mixed dementia, while the proportion of cases with AD stayed about the same. In discussing possible reasons for this decline they mentioned a higher proportion of better-educated people, recent declines in stroke rates and expanded use of neuro-protective medications for selected dementias.

In an overview of trends in severe disability, Lafortune et al. (2007) used trend

data of dementia for Australia, Japan and Sweden. The prevalence changed relatively little (-1.4%) over a short time period for Australia (1998 to 2003). There was a slight increase in Sweden of +1.3% but over a longer period from 1980 to 2004 and also an increase of even +5.4% in Japan between 1989 and 2004.

Other studies looked at changes in cognitive impairment (CI) with the same diverging results. The negative trends reported for dementia for Sweden (see above) were also found for CI between 1992 and 2002 (Meinow et al., 2006). The two samples of people above age 77 are relatively small, but include the institutionalized population. A study of CI in the US using data from the Health and Retirement Study (HRS) (Langa et al., 2008) showed positive findings: between 1993 and 2002, the prevalence of CI in people above age 70 decreased from 12.2% to 8.7%. This finding for the US was confirmed over a shorter time period between 1993 and 1998 by Freedman et al. (2001). For 1993, they used the Asset and Health Dynamics of the Oldest Old Study; and for 1998, the HRS. But Rodgers et al. (2003), using the same data, showed that only the unadjusted scores suggest an improvement of cognitive functioning. When they controlled for demographic composition and prior exposure to cognitive tests, only a small amount of improvement was found (see methodological discussion further down in 2.3.5).

Two Danish centenarian cohorts from 1895 and 1905 were compared by Engberg et al. (2008). Centenarians born in 1905 living at home showed slightly better performance, while those living in institutions showed slightly worse performance, when compared with the 1895 cohort. In general, however, no significant differences were found.

The following two studies conducted in the UK (Christie, 1982; Christie and Wood, 1990) on illnesses in hospital admission do not meet our criteria for inclusion into trend studies because they did not measure prevalence or incidence rates within the population. However, they were included because they demonstrate the shifting composition of patients. The classification of dementia is based on a study by Roth (1955). He studied 464 patients above age 60 who had been admitted to Graylingwell hospital in Chichester, UK in 1948/49. He classified the patients into five principal diagnostic subgroups: affective psychoses, late paraphrenia, senile psychosis (senile dementia Alzheimer's type or SDAT (AD)), arteriosclerotic dementia (VaD), and acute confusional states. In a first study, Christie (1982) compared these results from Graylingwell with patients from Crichton Royal Hospital, Dumfries, UK, admitted between 1974-76. After adjusting for age and definition problems, there were 143 people from the Graylingwell study and 265 people from the Crichton study left. He found a shift from

functional illness towards dementia, however, "not as a proportion of patients admitted but in the number of beds employed for their care 6 and 24 months after their index admission" (Christie, 1982). Since the analysis did not include age-specific changes, they reflected demographic changes: 22% of the Graylingwell group was above age 79, versus 46% from Crichton. However, in a second study, Christie and Wood (1990) included a second time point 1984-86. Now the proportion of patients above age 79 was constant between 1974-76 and 1984-86, at 46% and 47%, compared to 22% in 1948-49. In general, they found a striking relative and absolute increase in the number of cases of dementia from the 1970s to the 1980s. "This change cannot be explained simply on the basis of demographic change and the high prevalence of SDAT in older age groups since, as already stated, the proportion of patients above and below 80 years was almost constant in the first and second Crichton cohorts. The absence of an increase in the very elderly dementias in our more recent patient population is further evidence for the argument that the characteristics of dementia in the very elderly differ from those in the younger age group" (Christie and Wood, 1990). Since they did not measure prevalence or incidence within the total population, this conclusion is speculative, but it seems that this could reflect a higher prevalence of dementia resulting from the lower death rate for dementia, which fell sharply from 61% to 27%, to 11%.

2.3.4 Trends in VaD and Stroke

A correlation between stroke and VaD is confirmed in many studies (see chapter 2.4.8). After a stroke, the risk of dementia increases significantly (Desmond et al., 2002; Zhu et al., 2000), and therefore a prevention of stroke should decrease the risk of VaD (Ivan et al., 2004).

Seno et al. (1999) investigated the rate of cerebral infarctions in the two time periods 1976-84 and 1985-92 in 310 nursing home residents in Shimane Prefecture, Japan. The 310 people agreed to donate their bodies after death to medical science. They died between 1976 and 1992. While a declining prevalence of cerebral infarctions was found, this is not significant. "The incidence of CI in total life span (both men and women) has not changed in our study. The recent decreasing trend in LI (large infarction) in men may have contributed to the decreasing tendency in the prevalence of vascular dementia." A change in dietary habits might have contributed to this decline. The volunteer sample may also have influenced the results.

Another study on the Rochester population investigated a change in the incidence

of strokes over time (Broderick et al., 1989). The results are based on 2,466 incidence cases from all age groups between 1950-54 and 1975-79. The rate declined by 46% from 213 to 115 per 100,000 population. In the 1980-84 period, it increased again by 17%. This coincides, however, with the introduction of computed tomography, and thus cases could be detected earlier and were less severe. The changes, both the decline and the later increase, were most marked for people above age 85.

A longitudinal study that looks at the development of cardiovascular disease is the Framingham Heart Study. It started in 1948 with 5,209 people aged 28 to 62 years in Framingham, Massachusetts, US. Every two years, physical examinations, laboratory tests and interviews were conducted.

In 1992 Wolf et al. (1992) looked at the stroke incidence of 1,869 men and 2,429 women aged 55 to 64 in 1953, 1963 and 1973. They did not find a significant change in overall stroke and transient ischemic attack incidence or prevalence. However, in women, the incidence of completed ischemic stroke and the stroke severity declined significantly. This might result from an increased awareness and better diagnostic methods of the disease, and thus earlier detection.

Sytkowski et al. (1996) looked at incidence and mortality trends of cardiovascular disease in 1950, 1960 and 1970. In 1950, 757 women and 618 men aged 50-59 formed the baseline study population. In 1960, the study population consisted of 816 women and 586 men; and, in 1970, of 834 women and 598 men, all aged 50-59. For females, the incidence during the whole period declined 21%, while for males, an insignificant decline of 6% occurred, despite a significant decline of 18% that took place during the first decade. In the second period, the incidence was about the same (-0.3%). Cardiovascular disease mortality also declined strongly for females (59%) and males (53%). Improvements in risk factors, such as systolic blood pressure or serum cholesterol level, might have contributed to this development.

Within the Framingham heart study, Mosterd et al. (1999) examined 10,333 participants aged 45 to 74 between 1950 and 1989. The authors found a decline in the prevalence of high blood pressure and in left ventricular hypertrophy. This decline might explain the lower mortality from cardiovascular disease observed since the 1960s.

Garraway and Whisnant (1987) found a decline in stroke incidence between 1950 and 1979 in Rochester, Minnesota. Better control of hypertension might have influenced this development.

For Germany, Fichter (1990) looked at psychiatric illnesses in three communities in southern Bavaria during the 1970s and 1980s. The main focus was on psychiatric illness

in general, but the study also looked at senile dementia. The first sample consists of 1,536 people for the 1970s (no concrete year is given), and the second sample for five years of the 1980s of 1,666 (1,386 of them were follow-ups). The prevalence for both points in time did not differ significantly. When prevalence for both full samples was measured, mild dementia decreased from 1.4% (CI 0.81-1.99) to 0.7% (CI 0.30-1.10), and moderate and severe dementia rose from 1.7% (CI 1.05-2.25) to 1.9% (CI 1.24-2.56). When only the follow-up sample of 1,342 people was taken into account, mild dementia changed non-significantly from 1.2% (CI 0.62-1.78) to 0.7% (CI 0.25-1.15), and moderate and severe dementia rose from 1.2% (CI 0.62-1.78) to 1.9% (CI 1.17-2.63). However, the results were not age-standardized. The author pointed to the five-year aging of the follow-up sample, but did not look at age-specific rates. Thus, these results are not included in the conclusions for trend studies.

2.3.5 Conclusion for Trend Studies

In table 2.1 all trend studies found on incidence and prevalence of dementia, AD and VaD are displayed.

Table 2.1: Trend Studies for Dementia

	Place	Design	Type	Time	Trend
Incidence Studies					
Hagnell et al. 1981	Lundby	Long	Dem	1947, 1957, 1972	-
Hagnell et al. 1992	Lundby	Long	VaD	1950s to mid 1970s	=, - For Ages 80 to 89
Rorsman et al. 1986	Lundby	Long	AD, VaD	1947-57, 1957-72	=, (AD-, VaD+, Not Sign.)
Kokmen et al. 1988	Rochester	Cross-S.	Dem, AD	1960 to 1974	=
Kokmen et al. 1993	Rochester	Cross-S.	Dem, AD	1960 to 1984	U-Shaped
Rocca et al. 1998	Rochester	Cohort	Dem, AD	1975 to 1984	=
Prevalence Studies					
Gruenberg et al. 1987	Lundby	Long	CBS	1947, 1957	+
Rorsman et al. 1986	Lundby	Long	AD, VaD	1947-57, 1957-72	=, (- Not Sign.)
Beard et al. 1991	Rochester	Cross-S.	Dem, AD	1975, 1980	=
Beard et al. 1995	Rochester	Cross-S.	Dem, AD	1975, 1980, 1985	First Period =, Second P. +
Svanborg 1980*	Gothenburg	?	Psy. Health	1970s	-
Manton et al. 2005	US (NLTCS)	Cross-S.	AD, VaD	1982 to 1999	AD=, VaD-

Long=Longitudinal; Cross-S.=Cross-Sectional; Dem=Dementia; CBS=Chronic Brain Syndrome; Psy. Health=Psychiatric Health

+ Increase of Rates

- Decrease of Rates

= No Change of Rates

*Personal Communication with Hagnell (1981)

The table outlines the points of disagreement found in all trend results. Most reviews conclude that no change in prevalence or incidence can be seen (Bickel, 2003; Fratiglioni and Rocca, 2001; Jagger et al., 2006; Werner, 1995b)

The findings from the Lundby Study (except the early study by Gruenberg et al. (1987)) are more positive, showing a decrease or at least a stable development of the rates. Stable or increasing rates are found in Rochester. Studies on VaD in general show a more positive result, presenting a decreasing rate over time.

Prevalence studies in general are less appropriate for measuring a trend effect, because it is not clear if changes in the incidence or in the survival rates affected this change. A change in the survival rates is demonstrated by Christie and Wood (1990); Kokmen et al. (1996). They find a higher rate of survival of patients with dementia over time (Kokmen et al. (1996) for AD between 1975 and 1984, and Christie and Wood (1990) between 1948 and 1986). According to Bickel (2003), these few reports do not provide reliable results about changes in the age-specific incidence trends during the last decades. Grundy (1991) concludes from the Hagnell et al. (1981) study that the incidence might be decreasing. But due to a longer period of survival with the disease, the prevalence might actually be increasing. However, also the incidence studies show contradictory results.

Methodological problems and differences in the study design might influence results, especially in early studies. Often people who drop out—whether due to death, refusal or moving away—are to a higher extent demented (among other factors, such as being older, male, having impaired activities of daily living or poor self-perceived health) (Aevarsson and Skoog, 1996; Matthews et al., 2004). This has to be taken into account when interpreting the results from studies, because many, such as the Lundby Study, do not adjust for this fact. However, the response rate was very high, at about 98%; and when people had died, the nearest relations had been interviewed (Hagnell et al., 1981). The study by Seno et al. (1999) has no attrition at all. However, the volunteer basis of the sample might display a selection effect. Longitudinal studies with high drop-out rates therefore should always investigate attrition; otherwise, the results could be biased. But even if this is done, different results can occur: Freedman et al. (2001) and Rodgers et al. (2003) use the same data to come to different conclusions, as has been shown above. The first study finds a lower prevalence of cognitive impairment, while the second shows only little improvement if demographic composition and prior exposure to cognitive tests are controlled for. However, the authors of the first study also showed that the results are robust to assumptions about missing data, loss of follow-up and

the institutionalized population (Freedman et al., 2002; Freedman and Martin, 2003). Analytical differences might account for the differences; thus, not just a harmonization of the concepts of cognitive-status measurements, but also a harmonization of survey designs and measures is necessary (Freedman and Martin, 2003). Rodgers and Ofstedal (2003) are skeptical about a harmonization of measures across surveys and settings because researchers might not yet have reached the point at which they know how to best measure and model a particular phenomenon. They emphasize the superiority of cross-sectional data for studying aggregate population changes.

These examples show that the best way to study dementia trends has yet to be found. Cross-sectional and longitudinal studies both have advantages as well as drawbacks. There is more general agreement on the measurement of dementia and cognitive impairment, but here the correct implementation is difficult. Finally, different analytical measures influence results.

Besides all the methodological problems, the comparability of studies has improved. In general, there is no sign that the incidence or prevalence of dementia and cognitive impairment has changed. Some studies report stable results, some have found improvements, and some have shown a higher prevalence or incidence. The incidence of VaD seems to have decreased over time due to better medical prevention and detection of strokes and hypertension.

2.4 Risk Factors of Dementia

Because dementia did not become important until recent decades, and because of the complexity of the disease, relatively few risk factors are, as yet, well established. For example, for AD Jorm (1995) found that only three clear risk factors—age, family history and Down's Syndrome—have been verified. The rising awareness, however, led to much more research on underlying mechanisms and possible treatment or prevention. In the newer literature, several risk factors are discussed. Some have been confirmed in replicate studies, while some have been disproved. Table 2.2 shows that only age and family history are highly consistent factors, which means that all the literature agrees in its findings. Table 2.3 shows that for VaD more risk factors seem to be confirmed, especially factors that are related to further vascular diseases.

In the following chapter, the risk factors for dementia are discussed. Due to the vast amount of research on various risk factors, this review does not claim to be exhaustive.

Table 2.2: Risk Factors for Alzheimer's Disease

Risk Factor	Highly Consistent	Somewhat Consistent	Inconsistent	Interactive	Insufficient Data
Age	x				
Family History	x				
APOE $\epsilon 4$		x		x	
Depression		x			
Education		x			
Estrogen-Repl.*		x			
NSAIDS**		x			
Gender			x	x	
Head Injury			x	x	
Smoking			x	x	
Aluminium			x		
Diabetes			x		
Hypothyroidism			x		
Antioxidants					x
Environ. Exp.***					x
Life Styles					x
Zinc					x

* Estrogen-Replacement Therapy

** Nonsteroidal Anti-Inflammatory Agents

*** Environmental Exposures

Source: Bundesministerium für Familie, Senioren, Frauen und Jugend (2002); Hendrie (1998)

Table 2.3: Risk Factors for Vascular Dementia

Risk Factor	Confirmed Risk Factor	Possible Risk Factor
Demographic Factors		
Age	x	
Male Gender	x	
Low Education	x	
Atherosclerotic Factors		
Hypertension	x	
Smoking	x	
Myocardial Infarction		
Diabetes Mellitus	x	
Hyperlipidemia	x	
Genetic Factors		
CADASIL*	x	
APOE $\epsilon 4$		x
Stroke-related Factors		
Volume of Cerebral Tissue Loss	x	
Evidence of Bilateral Cerebral Infarction	x	
Strategic Infarction	x	
White Matter Disease	x	
Silent Cerebral Infarcts		x
Cerebral Atrophy		x
Ventricular Size		x

* Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarct and Leukoencephalopathy

Source: Gorelick (2004)

2.4.1 Age

All the studies agree that age is the most important risk factor for developing dementia (Bickel, 2003, 2005; Breitner et al., 1993; Fichter et al., 1995; Fratiglioni et al., 1999; Hatada et al., 1999; Kokmen et al., 1996; Mortimer, 1983; Nitrini et al., 2004; Ravaglia et al., 2005; Ritchie et al., 1992; Rocca and Kokmen, 1999; Weyerer, 2005) (compare sections 2.5 and 2.2.2). The prevalence of dementia doubles every five years in people over 65: from about 2% for ages 65 to 69, to 8% to 13% for ages 80 to 84, and to 25% to 42% for ages 90+ (Bickel, 2003). Jorm et al. (1987) found an exponential rise in the prevalence until about ages 90-95. Two German studies and one Canadian study showed a prevalence of about 60% after age 95, and other international studies of people above age 100 showed an average prevalence of about 60% for this age group (Bickel, 2005). This is true for general dementia and AD, while different types of dementia might have different age distributions (Fratiglioni et al., 1999; Fratiglioni and Rocca, 2001). For example, some studies found a slower increase with age for VaD than AD (Knopman et al., 2002; Kukull et al., 2002; von Strauss et al., 1999).

Incidence studies of dementia are still rare. The rate is about 0.5% for people aged 60 to 69, and rises to about 1% for people aged 70 to 79, and to 3% for people above age 80. After age 85, findings differ substantially, and are as high as 5% to 10% (Bickel, 2003). Diverging findings for the oldest age groups led to a discussion about an age or aging effect of dementia.

Age vs. Aging

As was seen in the prevalence studies, some incidence studies have also found a plateau (Bickel, 1995) or even a decrease, in the dementia rates for the oldest ages (Johansson and Zarit, 1995). Bickel (2003), however, stated that these findings should not be seen as offering hope that, after a certain age, the risk of developing a dementia is lower. He estimated the morbidity risk, and came to the conclusion that the chances of not suffering from dementia by age 100 is 10% to 20%.

As far back as 2,000 years ago, people thought about aging and health. Galen (AD 129-199) argued that aging per se was not an illness, because illnesses were unnatural, while aging was natural. Aristotle (384-322 BC), by contrast, thought that illness was aging that occurred too early, and that aging was a natural illness (Zaudig and Hiller, 1995). Until the 17th century, dementia was seen as a natural consequence of aging (Bischoff et al., 2004). It was not until the beginning of the 20th century that a new

era started, which today is often associated with the discovery of fibrils in the brain of Auguste D. by Alois Alzheimer (1907).

Many studies have dealt with the question of whether dementia is an age- or aging-related disease. It is a very important question because the answer has far-reaching effects on aging societies, political decisions and research. If dementia is 'age-related', that would mean that it occurs within a specific age range; if it is 'aging-related', it is caused by the aging process itself, and, at a certain advanced age, everybody would inevitably be ill. However, research findings diverge on this issue. In 1983, Mortimer (1983) found a leveling off of dementia incidence after age 75. He used Swedish data from Larsson et al. (1963), but there were only few cases after age 85. However, he also cited three studies that indicated a reduced risk of developing AD in the ninth and tenth decades of life.

Ritchie and Kildea (1995b) reignited the question about an age- or aging-relatedness of dementia in the most recent discussions. Their meta-analysis showed that the increase in age-specific prevalence slows down after age 80, and flattens out to zero at age 95; and that the data would best fit a logistic, instead of an exponential curve. This would mean that the disease is age-related. Only within a certain age range the increase is very strong; but once people are out of that age range, their risk decreases or stays the same, which is shown in stable (leveling off) or even declining rates. If this finding was proven to be true, and dementia could be shown to be a pathological process with a specific age range for being at the highest risk, the consequences would be far-reaching. Instead of preparing for progressive disability, "researchers are justified in searching for aetiological factors other than those implicated in normal ageing, with a view to providing therapeutic intervention" (Ritchie and Kildea, 1995b).

An important contribution to this discussion was introduced by Dewey and Saz (2001). They looked at the prevalence rates estimated by Jorm et al. (1987) (see also chapter 2.5 and figure 2.1) and suggested that they might be too high because the used log model was not appropriate. It would lead in the highest ages to probabilities above 100%, and for young age groups to negative effects. He proposed using a logit model which would lead to lower and more reasonable prevalences in the highest age groups.

Indeed, the article by Ritchie and Kildea (1995b) provoked various reactions. Only two months after its publication, two comments were submitted to the same journal. Winker (1995) noted that two studies that found different results (i.e., increasing prevalence) were not included in the study. The authors' reply pointed to criteria that did not meet their inclusion pattern, and stated: "Our study was designed not to answer

the question but rather to open the matter to debate" (Ritchie and Kildea, 1995a). Giannakopoulos et al. (1995) described their analysis of 43 people above age 95 on senile lesion distribution in the brain that confirmed Ritchie and Kildea's finding: "Retrospective evaluation of clinical data showed that these patients displayed a striking preservation of the cognitive functions and maintained social independence."

Further Studies That Confirm the Finding from Ritchie and Kildea (1995b) That Dementia is Age-Related

Gao et al. (1998) showed in their meta-analysis of 12 incidence studies of dementia and AD measured with DSM-III that there is no decline in the incidence rates at the oldest ages, but that the increase slows down. "For every 5-year increase in age, both dementia and AD incidence rates triple before age 64, double before age 75, and drop down to an increase of 1.5 times around age 85." The authors discussed the possibility of small sample sizes, and the influence of co-morbidity at oldest ages. In general, however, they supported the hypothesis that dementia is age-related. They furthermore argue that studies that find different results are based on logistic models, but that these "results demonstrate that a more complicated relationship between age and dementia and/or AD exists."

Fratiglioni et al. (2000) found in a meta-analysis of eight studies an increasing incidence of dementia up to age 85; subsequently, the increase continues only for women, but not for men.

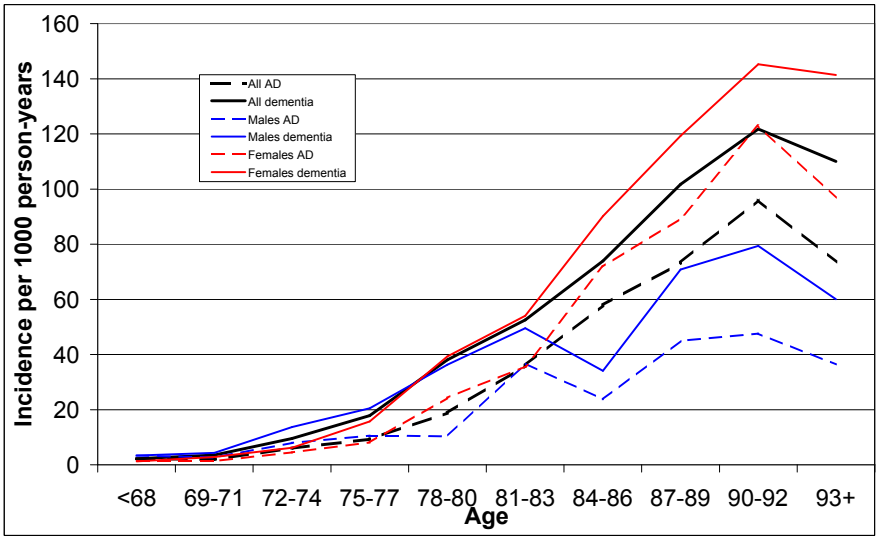
Using pooled data from 12 European studies conducted between 1980 and 1990, Hofman et al. (1991) found similar prevalences for the age groups 90-94 and 95-99, of 32.2% and 34.7%, respectively (see figure 2.1). However, they did not mention this result, and only pointed to the doubling of the rate between age 60 and 94.

Johansson and Zarit (1995) followed and examined 312 people aged 84 to 90 years after two and four years in Jönköping, Sweden. Of this sample, 97 were demented at baseline, and 48 developed a dementia within that period. The authors found a higher mortality of demented people, which keeps the prevalence lower at higher ages. In addition, the incidence rate between ages 86 and 94 was shown to be lower than at ages 84 to 92, which "suggests a decreasing risk with advanced ages."

Miech et al. (2002) found among 3,308 people from the Cache County study in Utah an exponential rise until ages 85 to 90, followed by slower rates of increase after age 93 for men and after age 97 for women. In the age categories 90-92 and 93+, there are 108 and 48 people, respectively. The study group was exceptional because their life

expectancy is almost ten years higher than the average US life expectancy. The rates for dementia and also AD separately are displayed in figure 2.7.

Figure 2.7: Incidence of Dementia and AD in Cache County



Source: Miech et al. (2002)

In the Heidelberg Centenarian Study, Kliegel et al. (2004) found evidence to support the hypothesis that dementia is age-related rather than aging-related. In their sample of 156 centenarians, 91 agreed to be examined. The prevalence rate of moderate and severe dementia is 52%, measured with the MMSE and 59% with the GDS (Global Deterioration Scale (Reisberg, 1983)). Kliegel et al. (2004) followed the persons and found that the cognitive status was a significant predictor of death. After one and a half years, the cognitive functioning of the people did not decline dramatically, and some even performed better. Their findings are in accordance with two Italian studies of centenarians that found prevalence rates of 58% and 62% (Bauco et al., 1998; Ravaglia et al., 1999). Other population-based studies of centenarians vary between 27% in Sweden (Samuelsson et al., 1997), 51% in Denmark (Andersen-Ranberg et al., 2001) and 67-79% in New England (Silver et al., 2001). These variations might be explained by methodological and sampling factors or demographic selection. Kliegel et al. (2004) came to the following conclusion: "Overall, however, reviewing the existing reports, data seem to converge to the conclusion that more than 50% of the persons aged 100 years will show moderate to severe cognitive impairment. Analyzing the performance distribution, individual's performances on the cognitive measures were found to be considerably widespread. Around one fourth of the group seemed to have virtually no

cognitive deficits." However, their results might be influenced by the refusal rate: 50% of the people who refused to take part in the interview gave health-related problems as the reason.

Hall et al. (2005) found in the Bronx Aging Study an increase in dementia after age 85. However, they found that the rate of increase is smaller than rate observed between ages 65 and 85, which they believed suggested that dementia may be an age-related, rather than an aging-related, process.

Wernicke and Reischies (1994) showed a plateau for prevalence rates above age 95 in the Berlin Aging Study (N=156 above age 70, 26 above age 95). When the mild, sub-diagnostic cases were included, a decrease above age 95 could even be seen. They concluded that the exponential increase in dementia does not continue after age 94. Higher mortality seems unlikely in their sample.

Riedel-Heller et al. (2001b) looked at the dementia rates of 1,692 people aged 75 years and older from Leipzig, Germany. Regardless of whether dementia was classified according to DSM-III-R or ICD-10, they showed a leveling off above age 95, though to a greater extent with ICD-10.

Engedal and Haugen (1993) examined 1,029 people above age 75 from Oslo, Norway. Of this sample, 334 were living at home, 518 in nursing homes, and 177 in homes for the aged. No statistical age dependency was found in the samples. In attempting to explain this astonishing finding, they argued that a selection effect into institutions or the high general age of the sample might have influenced the results. But in the total population of Oslo, as well, almost no increase in the prevalence rate between ages 85-89 (26.2%) and 90+ (28.3%) could be found.

A study by Beard et al. (1995) found lower prevalence rates of dementia for males above age 95 than for 90-94-year-old males, whose rates were actually decreasing between 1980 and 1985. However, there was only a small number of males above age 90. For females, the rate was not lower above age 95 compared with ages 90-94, but the increase in prevalence rates after age 85 was lower than at younger ages.

In his Nun Study, Snowdon (2001) found nuns who did not show changes in behavior, even though brain autopsies revealed signs of AD. This could be a sign of brain reserve capacity (see below). He came to the conclusion that AD "is not an inevitable consequence of aging."

The Following Studies Support the Hypothesis That Dementia is Aging-Related:

Jorm and Jolley (1998) collected data from different studies, and found an exponential increase in incidence rates until the highest age group 90+. They argued that it is hard to judge if a leveling off occurs because so little incidence data was available beyond that age.

A meta-analysis by Corrada et al. (1995) looked at 15 AD studies conducted between 1984 and 1993. They applied a logistic regression model and found an increase in risk of 18% with every year of age above age 60. However, the variation between age-specific rates among studies was very high.

An increase in the prevalence of dementia and AD into highest ages was also found by von Strauss et al. (1999). The highest age group is 95+. They stated that their results supported the aging-related hypothesis, and that most studies were in agreement with their findings. They observed that only two studies (Engedal and Haugen, 1993; Wernicke and Reischies, 1994) showed a plateau at the highest ages, which might be due to methodological issues. However, they also admitted that the increase in dementia prevalence with age "was evident among women but unclear among men" (von Strauss et al., 1999). It should be noted, however, that the study population above age 95 is especially small for males, with 17 cases compared with 128 cases for females, respectively.

Ebly et al. (1994) support the aging-related hypothesis with data from the Canadian Study of Health and Aging (1990 to 1992). Results showed that 1,835 people above age 85 living in a community or institution demonstrated no leveling off of dementia prevalence rates. The highest age group was 100-106 (13 cases). Looking at AD and VaD separately, the increase in AD was steeper than for VaD, which led to a shifting proportion of both diseases.

A community-based study in Rotterdam followed 7,046 non-demented people above age 55 (Ott et al., 1998). Of this sample, 162 people developed a dementia. For men, a leveling off occurred after age 85. However, the result is based on two incidence cases (67 person-years) in the age group 90-94, and zero incidence cases above age 95 (nine person-years). For women, the rate increased further at higher ages. When calculating the lifetime risk of developing a dementia, the authors found gender differences: women above age 55 show a higher risk of 35.4%, and men of the same age show an elevated risk of 18.0%. These differences are mainly attributed to the effect of higher life expectancy

and a higher incidence rate among women. This lifetime risk is similar at different ages, and the authors reached a conclusion that supports the aging hypothesis: "Having survived without dementia up to a high age appears not to reduce a person's risk of developing dementia" (Ott et al., 1998).

Other studies that showed no leveling off include the following. Fichter et al. (1995, 1996) analyzed 402 people above age 85 and found for prevalence and incidence no decrease in the rates for the highest age group 95+. Results from Edland et al. (2002) showed no leveling off (age groups 50-54 to 95-99) as well as results from Kukull et al. (2002) (ages 65 to 90+). Bachman et al. (1993) followed the Framingham cohorts from 1976-78 and 1982 for ten years, and found no leveling off of the incidence rates. Of 2,391 people at risk aged 65 to 89, 102 cases of dementia were identified. Only four cases were older than 90.

Table 2.4: Age versus Aging, Studies That Confirm Either Hypothesis

	Measure	Design	Type	N	N (Age**)
Age related					
Fratiglioni et al. 2000	DSM-III	Inci	Dem, AD	835* °	? (85) (m)
Gao et al. 1998	DSM-III	Inci	Dem, AD	17,295°	? (90)
Hall et al. 2005	DSM-III-R	Inci	Dem	488	20* (90)
Larsson et al. 1963	hospitaliz.	Inci	Dem	657*	??(75)
Miech et al. 2002	DSM-III-R	Inci	Dem, AD	3,308	48 (93)
Beard et al. 1995	Expert	Prev	Dem	1,000*	? (90)
Engedal & Haugen 1993	DSM-III	Prev	Dem	1,029	141 (90)
Hofman et al. 1991	DSM-III	Prev	Dem	16,000°	69 (95)
Riedel-Heller et al. 2001a	DSM-III-R	Prev	Dem	1,692	21 (95)
Riedel-Heller et al. 2001a	ICD-10	Prev	Dem	1,692	21 (95)
Ritchie & Kildea 1995	DSM-III	Prev	Dem	25,566°	317 (95)
Wernicke & Reischies 1994	DSM-III-R	Prev	Dem	156	26 (95)
Aging related					
Bachman et al. 1993	MMSE	Inci	Dem, AD	2,391	53 (85-94)
Edland et al. 2002	DSM-IV	Inci	Dem, AD	14,439	? (95)
Fichter et al. 1996	DSM-III-R	Inci	Dem	402	22 (95-99)
Jorm & Jolley 1998	DSM-III	Inci	Dem	? °	? (90)
Kukull et al. 2002	DSM-IV	Inci	Dem, AD	2,356	? (90)
Riedel-Heller et al. 2001b	DSM-III-R	Inci	Dem	1,692	21 (90)
Riedel-Heller et al. 2001b	ICD-10	Inci	Dem	1,692	21 (90)
Corrada et al. 1995	various	Prev	AD	22,091°	18%°°
Ebly et al. 1994	DSM-III	Prev	Dem, AD	1,835	104 (95+)
Fichter et al. 1995	DSM-III-R	Prev	Dem	402	12 (100+)
von Strauss et al. 1998	DSM-III-R	Prev	Dem, AD	1,848	145 (95+)

Inci=Incidence; Prev=Prevalence; m= only males

*Number of demented people, **Age were leveling off is found

°Combined Number from Meta Analysis, °°18% Increase Per Year of Age Above Age 60

? Numbers Not Provided

Settling the Question: Is Dementia an Age- or an Aging-Related Disease?

Most reviews concluded that, in general, the question of whether dementia is age- or aging-related remains open because of contradictory findings and small sample sizes in the oldest age groups (Bickel, 2003; Fratiglioni et al., 1999; Hendrie, 1998). Drachman (1994) brought another aspect into the discussion. He looked at two opposing studies (Ebly et al., 1994; Wernicke and Reischies, 1994) and argued that both studies are prevalence studies. Thus, the decrease in dementia rates at older ages might simply be due to lower survival rates with the disease at older ages. But, on the other hand, AD seemed to be "a disease, not a condition, and may therefore be preventable or treatable. ... But the gaussian curve underlies most biologic variability and suggests that, in at least some of us, the integrity of the brain may survive beyond that of the other vital organs." Ankri and Poupard (2003); Johansson and Zarit (1995) argued that the high incidence did not result in rising prevalences, which might be due to the greater mortality of people with dementia. However, incidence studies also found a further increase of the rates into the highest age group, as table 2.4 shows. Another factor might be the highest age group that is considered. Many studies that support the aging-related hypothesis have small sample sizes in the highest age group, which often is 90+ or 95+. Studies with a decrease in dementia rates frequently found it beyond that age. If dementia is age-related, some factors not related to normal aging exist that have to be investigated. "And regardless, we must continue to search for the keys to postponing cognitive decline—due to disease, to biological decline, or to both" (Drachman, 1994).

Table 2.4 displays incidence and prevalence studies according to whether they tend to confirm the hypothesis that dementia is age-related, or the view that it is an aging-related condition. Both sides look at different 'highest age-groups' and all types of dementia, AD or VaD. One point supporting the age-related hypothesis might be that, in the 'age-related' group, there are more meta-analyses with higher sample sizes in the highest age group. On the aging-related side, there are only two meta-analyses, one with the highest age group only being 90+ (Jorm and Jolley, 1998), and which was based on questionable methods. The model Corrada et al. (1995) used, does not seem to be appropriate to measuring a leveling off in highest age groups. However, even within the same study population (Riedel-Heller et al., 2001a,b), contradictory results can be achieved when calculating prevalences or incidence rates.

A meta-analysis by Ankri and Poupard (2003), who looked at 50 prevalence and

incidence studies that included people above age 85, showed big differences in the rates. Prevalence rates above age 85 varied between 15% and 40% (in 12 European studies between 11.5% and 39% (Berr et al., 2005)), and incidence rates varied between 60 and 100 per 1,000 person-years. They discussed problems that might arise from the study population, the diagnostic criteria or the gender, and came to the conclusion that, beyond age 85 to 90 "the situation is unclear given the small number of studies carried out and the methodological problems inherent in such studies."

In conclusion, the studies show no clear pattern of responses to the question of whether dementia rates level off at the highest ages. An exponential increase seems unlikely, because otherwise a prevalence of 100% would already be attained before age 100, which is not shown in empirical studies (Bickel, 2005; Dewey and Saz, 2001). Researchers agree that aging processes are so fundamental in developing a dementia that nearly everybody would get the disease if he or she were to become old enough (Bickel, 2005). Another reason why some people at the oldest ages do not show signs of the disease might be that they have different brain reserve capacities. Studies showed that some people have incipient AD but no clinical signs of the disease. They might start with a larger brain, which adjusts the malfunction of the brain due to dementia for a longer time (see section 2.4.5).

Selection and Diagnosis Selection

Another reason why prevalence at highest ages does not reach 100% might be the heterogeneity of populations and differential survival. Vaupel and Yashin (1985) described this selection effect in their article. When in a cohort frailer people die first, mortality at the highest ages might actually decrease because more healthy people are left. In a recent study, Christensen et al. (2008) looked at a Danish cohort born in 1905 and the loss of independence—a measure defined as being able to perform ADL and having an MMSE score of at least 23—between 1998 and 2005. On the individual level, the data showed that nearing death increases the risk of being dependent. People who survived until 2005 had the highest level of independence at the first wave of about 70%, compared with about 52% of people who participated only in one follow up. On an aggregate level, however, there was only a slightly increasing risk of loss of independence. The level of independence decreased from 39% to 33%. These results could mean that the aging effect of dementia was slowed by high mortality at the highest ages. While the risk of dementia increased with age on the individual level, it did not rise on the aggregate level due to a selection effect of the more healthy people. A confirmation of these

findings would have far-reaching consequences, because it would mean that increasing life expectancy would not necessarily be accompanied by an increase in disability and dementia levels.

Another explanation could be that diagnoses of dementia are no longer documented at the highest ages. Highest age is often seen as a state of degradation, making it difficult to differentiate between normal aging and senility. Dementia may also be under-diagnosed at these ages because there is no drug to fight the disease, and a diagnosis would not influence decisions about medication.

2.4.2 Genes and Family History

In addition to age, genetic influences seem to be another clear risk factor of dementia and AD (e.g., Breteler et al. (1992); Hendrie (1998); Jorm (1995); Larson et al. (1992)). From a genetic point of view, dementia and especially AD can be classified into a sporadic and a familial form, in which higher dementia rates can be seen within families. Familial forms have to be further differentiated between early- and late-onset dementia. They account for about 25% of all AD cases (Bird, 2008).

Family History

For many people with AD, a higher prevalence of the disease was found within the family. Literature reviews of demented people or people with AD showed an increased risk of dementia and AD when at least one first-degree relative was affected (Henderson, 1988; Jorm, 1995; Larson et al., 1992; van Duijn et al., 1991).

The familial heritability is much higher in pre-senile forms of AD than in late-onset AD, and generally follows an autosomal dominant form. Mutations of at least one of three genes have been found to be important: the amyloid precursor protein (APP) gene on chromosome 21, presenilin 1 (PS-1) on chromosome 14 and presenilin 2 (PS-2) on chromosome 1. For late-onset cases, the situation is more complex and probably involves a number of genetic and other factors (Gorelick, 2004; Hendrie, 1998; McCullagh et al., 2001). In a literature review Williamson et al. (2009), showed several more genes of interest on chromosomes 9, 10 and 11; however, results have to be replicated.

Twin studies offer a unique opportunity to scrutinize the impact of genetic and environmental factors because they exclude influencing factors. It is possible to analyze concordance rates of monozygotic (MZ) twins who have the same genes and have grown up in the same environment, and dizygotic (DZ) twins who share the same environ-

ment and about 50% of the genes (Breitner et al., 1993; Fratiglioni and Rocca, 2001). Heritability is high, but theories differ about to what extent genes and environment contribute to dementia (Karmiloff-Smith, 1998). The risks faced by twins might have been overestimated in older studies (Bickel, 2005), because in old age the onset might not be caused by a higher heritability alone, as sporadic incidence of the disease increases with age (Breitner et al., 1993). A decreasing relative risk of heritability with higher age was found in a meta-analysis by van Duijn et al. (1991). Newer twin studies have reported a concordance rate of 40% to 67% in MZ pairs (Gatz et al., 1997; McCullagh et al., 2001; Williamson et al., 2009). The results often showed that, even when the co-twin did not have dementia, his or her cognitive ability was lower than normal (Gatz et al., 2005).

The estimations of the risk of first-degree relatives also varied. Some authors gave ranges from 24% to over 50% at age 90 (McCullagh et al., 2001). Other reviews assumed that in 5% to 20% of the cases AD is more often found within families (Bischoff et al., 2004; Mandavilli, 2006; Weyerer, 2005). Farrer (1997) came to the conclusion that less than 2% of AD cases are genetically caused. In a study about inter-familial and intra-familial phenotypic heterogeneity in familial Alzheimer's disease Lopez-Alberola et al. (1997) found only a weak genetic influence on the degree of phenotypic heterogeneity in late-onset familial AD. Some studies found no significant influence at all: in a prospective meta-study, Launer et al. (1999) analyzed people with a history of dementia in two or more first-degree family members. They had a non-significant increased risk of AD of 1.6. They argued that, in earlier cross-sectional studies, the risk might have been overestimated because of a possible report bias of informants. Another longitudinal study found no statistical neurocognitive decline in children whose parents had AD over a 20-year period (Jarvik et al., 2005). The results regarding gender difference were also inconsistent: some found no differences (van Duijn et al., 1991), while some found a higher risk among women (Payami et al., 1996).

Another correlation seems to exist between dementia and Down's Syndrome (DS). In a meta-analysis, van Duijn et al. (1991) showed a relative risk of AD of 2.7 for first-degree relatives of patients with DS. However, the relative impact on dementia was small; it is found in association with early-onset cases, but not in the senile form of the disorder (Henderson, 1988). But also a direct correlation between DS and AD has been shown to exist. Wisniewski et al. (1985) scanned the brains of 100 patients with DS and found senile plaques and neurofibrillary tangles in 56 brains, 49 of them above age 30. Over the age of 40, a large proportion of people with DS developed cognitive

impairments, the profile of which resembled that of changes in AD (Teipel, 2006).

Apolipoprotein E

Since the early 1990s, the association between apolipoprotein E (APOE) and AD has been studied extensively. APOE is involved in processes regarding the degeneration and regeneration of nervous tissue. Recent studies have suggested an involvement of APOE in the process of amyloid formation in the brain (Bischoff et al., 2004; Tsai et al., 1994), and in the direct regulation of brain lipid metabolism and synaptic functions through APOE receptors (Bu, 2009). APOE has three common alleles, $\epsilon 2$, $\epsilon 3$ and $\epsilon 4$, that determine six genotypes in the population. Many studies found an increased risk for developing AD among people with APOE $\epsilon 4$, e.g. Bickeböller et al. (1997); Farrer et al. (1997); Kang et al. (2005); Miech et al. (2002); Nitrini et al. (2004); Palumbo et al. (1997); Panza et al. (2003); Seshadri et al. (1995). But other forms of dementia were also associated with APOE $\epsilon 4$, e.g., all forms of dementia (Slooter et al., 1998), VaD (Frisoni et al., 1994), dementia with Lewy bodies (DLB) (Lamb et al., 1998), dementia in Parkinson's Disease (PD) (Huang et al., 2006), other frontal type dementias (Frisoni et al., 1994), as well as early stages, such as MCI (Feskens et al., 1994; Tyas et al., 2007). The findings suggest that the $\epsilon 4$ allele is associated with accelerated neurodegeneration in several diseases (Bu, 2009). The reason might be that APOE $\epsilon 4$ binds more avidly to $\beta A4$ amyloid than the $\epsilon 3$ protein and this bonding may promote the deposition of $\beta A4$ in senile plaques (Benjamin et al., 1996; Corder et al., 1994).

Across the world, there is a wide variation in the frequency of the $\epsilon 4$ allele, ranging from only 5% in the Amish to over 40% in some aboriginal populations. In Caucasian populations, the frequency is about 8% to 16% (Hendrie, 1998) (some prevalence rates given for Europe are higher, with an estimated 20% to 24% of the population having at least one APOE $\epsilon 4$ (Staehelin, 2004)), while in Japanese and Chinese studies, the frequency was found to be about 2% to 8% (Asada et al., 1996; Yamagata et al., 1997; Yen et al., 2001). APOE $\epsilon 3$ allele is the most common in all populations, and the $\epsilon 2$ is the least common, at below 10% (Farrer et al., 1997; Frölich et al., 2002).

The APOE $\epsilon 4$ allele was not only found to increase the risk of AD: the mean age of onset was shown to decline by about six to eight years for people with two $\epsilon 4$ alleles, compared to people with no $\epsilon 4$ allele (Benjamin et al., 1996; Sando et al., 2008; Tsai et al., 1994). The severity and rates of progression did not seem to be greater (Weiner et al., 1999). The risk is age-specific, with the greatest differences seen in people with and without the allele in middle-age groups of about 60 to 69, and is therefore lower

before age 60 than the risk of early-onset AD, and after ages 75 or 80 (Bickeböller et al., 1997; Corder et al., 1994; Farrer et al., 1997; Panza et al., 2000; Sando et al., 2008; Yamagata et al., 1997). The $\epsilon 4$ allele might cause other selection effects before the onset of AD, and thus the frequency might decrease with increasing age among the late-onset AD cases (Tsai et al., 1994). After age 100, it may no longer be an important risk factor for AD (Asada et al., 1996; Panza et al., 2003; Yamagata et al., 1997).

Regarding the selection effect, Weiner et al. (1999) found no significant increase in the history of heart disease, depression, or head injury, with an increasing number of $\epsilon 4$ alleles. The homozygous $\epsilon 4$ group was found to have higher levels of education than the heterozygous or $\epsilon 4$-absent group, which also excludes possible negative early life effects of $\epsilon 4$ on cognition.

The gender effect is not quite clear. Most studies have not found significant differences in the risk of developing AD or dementia between men and women (Farrer et al., 1997; Slooter et al., 1998; Tsai et al., 1994). Other studies have found higher odds ratios for women, indicating that women with at least one $\epsilon 4$ allele are at higher risk than men of developing AD (Palumbo et al., 1997), including late-onset familial AD (Payami et al., 1996). A gender effect among Caucasians and possibly Hispanics, but not Japanese, on the risk of APOE $\epsilon 3/\epsilon 4$ might explain the difference, with a diverging prevalence of homozygous $\epsilon 3/\epsilon 4$ alleles (Farrer et al., 1997). Farrer et al. (1997) concluded that women may have a higher susceptibility to AD than men regardless of APOE genotype. Other factors, such as estrogen (see section 2.4.12) might play a role. Bickeböller et al. (1997) also found similar odds ratios for men and women; however, in the control population, men were shown to have this allele significantly less often than women (10.9% vs. 16.7%) (which might be a selection effect). This could provide an explanation for the higher age-specific prevalence of AD in women (see section 2.4.3).

In some studies, a family history of dementia further increased the $\epsilon 4$ associated risk for dementia (Slooter et al., 1998). This was not confirmed in all studies (Corder et al., 1994).

Table 2.5 shows the results of studies on the effect of APOE on dementia. The odds ratio of people with AD who have one or two $\epsilon 4$ alleles are compared with people who do not have this allele. Bickeböller et al. (1997) analyzed a French sample and found for the control group of about 1,000 people that 14.9% carry the $\epsilon 4$, while 8.0% and 77.1% carry the $\epsilon 2$ and $\epsilon 3$ allele. From the 417 people with AD, however, 34.4% had the $\epsilon 4$ allele. Brain autopsies of 52 people with AD and of 16 without who died in nursing homes in the Oslo area showed a much higher risk for people with the $\epsilon 4$ allele

(Benjamin et al., 1996). Tsai et al. (1994) examined 77 patients with AD and 77 without in the US. They confirmed that this allelic variant may be an important risk factor for susceptibility to AD in the general population. Lamb et al. (1998) compared 108 cases of AD, 49 cases of dementia with Lewy bodies (DLB) and 101 control cases from a prospective clinicopathologic study in Newcastle, and confirmed the established finding of an increased frequency of the APOE $\epsilon 4$ allele in AD and in DLB. The prevalence of the $\epsilon 2$ allele was found to be lower in people with AD (not significant compared with the control group), but not in people with DLB (significantly higher than the AD group). Huang et al. (2006) conducted a meta-analysis of APOE and dementia in PD. They found that people with PD develop dementia more often when they have an $\epsilon 4$ allele. The $\epsilon 2$ allele had no protective effect. Inzelberg et al. (1998) found no higher frequency of the APOE $\epsilon 4$ allele in demented and non-demented patients with PD. Patients with PD in general had no higher prevalence of the allele compared with the control group. They suggested possible influences on the result, such as an earlier development of AD for people with $\epsilon 4$ and a later development of PD, which would cause these people to be seen as AD, rather than as PD, cases. Yamagata et al. (1997) showed for a Japanese sample an association between $\epsilon 4$ and nonfamilial AD. Palumbo et al. (1997) differentiated between late- and early-onset AD, possible AD, VaD and age-associated memory impairment. They found an effect of $\epsilon 4$ on late-onset and possible AD, but not on the other forms of dementia. However, the samples they used were quite small (between 12 (VaD) and 64 people (late-onset AD)). Yen et al. (2001) and Wang et al. (1997) confirmed the lower prevalence of the $\epsilon 4$ allele in the Chinese and Taiwanese population. The effect of the allele on the risk of developing AD was, however, shown to exist. This might explain the generally lower prevalence of AD in Asian populations. Using a relatively large sample of 4,227 nurses from the Nurses Health Study, Kang et al. (2005) confirmed that women with $\epsilon 4$ often have worse cognitive performance. They additionally controlled for cardiovascular disease (CVD) and CVD risk factors, and found that women with both $\epsilon 4$ and CVD or CVD risk factors (except diabetes type 2) had a higher risk than those without $\epsilon 4$ or CVD/CVD risk factors. Thus, people with APOE $\epsilon 4$ might also have an increased risk of CVD. The authors suggested that prevention of CVD could reduce the cognitive decline associated with the APOE $\epsilon 4$ allele.

Table 2.5: Effect of APOE $\epsilon 4$ on the Occurrence of Dementia

	Design	Type	Age	N Patients/Controls	OR*
Feskens et al. 1994	Incidence	MCI	70-89	48 / 265 (Males)	2.9 (1.3-6.4)
Slooter et al. 1998	Incidence	Dementia	all	134 / 997	Homo: 11.2 (3.6-35.2)
Slooter et al. 1998	Incidence	Dementia	all	134 / 997	Hetero: 1.7 (1.0-2.9)
Slooter et al. 1998	Incidence	AD	all	97 / 997	Homo: 6.2 (1.4-28.2)
Slooter et al. 1998	Incidence	AD	all	97 / 997	Hetero: 1.8 (1.0-3.1)
Slooter et al. 1998	Incidence	Dementia	all	96 / 736	Unrelated: 1.7 (1.0-3.1)
Slooter et al. 1998	Incidence	Dementia	all	26 / 235	Family: 4.8 (1.5-15.6)
Tyas et al. 2007	Incidence	MCI	75+		1.87
Benjamin et al. 1996	Prevalence	AD	***	52 / 16	33.4 (6.4-173.6)
Bickeboller et al. 1997	Prevalence	AD	all	417 / 1,030	2.7 (2.0-3.6)
Bickeboller et al. 1997	Prevalence	AD	60-69	38 / 93	4.1 (2.3-7.5)
Corder et al. 1994	P. (Unrelated)	AD	60+	115 / 243	4.4 (2.9-6.7)
Corder et al. 1994	P. (Family)	AD	60+	150 / 197	3.9 (2.6-5.9)
Farrer et al. 1997	Prevalence	AD	all	5,930 / 8,607 (Meta)	$\epsilon 4/\epsilon 4$** 14.9 (10.8-20.6)
Farrer et al. 1997	Prevalence	AD	all	5,930 / 8,607 (Meta)	$\epsilon 3/\epsilon 4$** 3.2 (2.8-3.8)
Farrer et al. 1997	Prevalence	AD	all	5,930 / 8,607 (Meta)	$\epsilon 2/\epsilon 4$** 2.6 (1.6-4.0)
Hong et al. 1996	Prevalence	AD	65+	56 / 57	3.0 (1.1-8.0)
Huang et al. 2006	Prevalence	PD	60+	163 / 295 ****	1.6 (1.0-2.5)
Kang et al. 2005	Prevalence	Poor Perf.	70-80	4227	Hetero 1.39 (1.06-1.83)
Kang et al. 2005	Prevalence	Poor Perf.	70-80	4227	Homo 2.62 (1.38-4.96)
Palumbo et al. 1997	Prevalence	AD	65+	64 / 40	6.1
Panza et al. 2000	Prevalence	AD	all	109 / 92	2.1 (1.2-3.9)
Panza et al. 2000	Prevalence	AD	<65	28 / 92	6.6 (1.4-30.9)
Sando et al. 2008	Prevalence	AD	all	376 / 561	$\epsilon 4/\epsilon 4$** 12.9
Sando et al. 2008	Prevalence	AD	all	376 / 561	$\epsilon 3/\epsilon 4$** 4.2
Sando et al. 2008	Prevalence	AD	all	376 / 561	$\epsilon 2/\epsilon 4$** 3.2
Tsai et al. 1994	Prevalence	AD	60+	77 / 77	4.6 (1.9-12.3)
Wang et al. 1997	Prevalence	AD	55+	98 / 98	3.9 (1.7-9.2)
Yamagata et al. 1997	Prevalence	AD	54+	163 / 198	4.0 (2.6-6.4)
Yen et al. 2001	Prevalence	AD		50 / 50	6.0 (1.3-55.3)

*Odds ratio for APOE $\epsilon 4$ present vs. absent; **Odds ratio compared with $\epsilon 3/\epsilon 3$; ***Elderly Residents from a Nursing Home

****Meta analysis, Controls are people with Parkinson's Disease

Some studies have shown that APOE $\epsilon 4$ not only increased the risk for AD, but also that $\epsilon 2$ could have a protective effect as can be seen in table 2.6. AD patients had this allele less often than people in the control population (Bickeböller et al., 1997; Corder et al., 1994). The effect was not always significant, probably due to small sample sizes and the low prevalence of the $\epsilon 2$ allele, and varied between populations (Benjamin et al., 1996; Farrer et al., 1997; Hong et al., 1996; Yamagata et al., 1997).

Table 2.6: Protective Effect of APOE $\epsilon 2$ on the Occurrence of Dementia

	Design	Type	Age	N (Patients/Controls)	OR*
Slooter et al. 1998	Incidence	Dementia	All	134 / 997	0.5 (0.2-1.1)**
Slooter et al. 1998	Incidence	AD	All	134 / 997	0.4 (0.1-1.0)**
Bickeboller et al. 1997	Prevalence	AD	All	417 / 1,030	0.5 (0.3-0.98)
Corder et al. 1994	P. (Unrelated)	AD	60+	115 / 243	0.25 (0.10-0.62)
Corder et al. 1994	P. (Family)	AD	60+	150 / 197	0.48 (0.15-1.51)
Farrer et al. 1997	Prevalence	AD	All	5,930 / 8,607 (Meta)	$\epsilon 2/\epsilon 2$ 0.6 (0.2-2.0)**
Farrer et al. 1997	Prevalence	AD	All	5,930 / 8,607 (Meta)	$\epsilon 2/\epsilon 3$ 0.6 (0.5-0.8)**
Panza et al. 2000	Prevalence	AD	65+	81 / 92	0.14 (0.05-0.43)
Panza et al. 2000	Prevalence	AD	<65	28 / 92	0.10 (0.01-0.79)
Sando et al. 2008	Prevalence	AD	all	376 / 561	$\epsilon 2/\epsilon 3$ 0.9 (0.5-1.4)**
Sando et al. 2008	Prevalence	AD	all	376 / 561	$\epsilon 2/\epsilon 2$ 0.7 (0.01-7.6)**
Yamagata et al. 1997	Prevalence	AD	54+	163 / 198	0.81 (0.31-2.06)

*Odds Ratio for APOE $\epsilon 2$ Present vs. Absent

**Odds Ratio Compared with $\epsilon 3/\epsilon 3$

In conclusion, most studies confirmed the APOE $\epsilon 4$ allele as a major genetic risk factor for sporadic AD and other forms of dementia. People with APOE $\epsilon 2$, on the other hand, developed AD less often. However, not all people with the $\epsilon 4$ allele developed the disease, and not all people with the $\epsilon 2$ allele are protected.

Seshadri et al. (1995) calculated the lifetime risk of people aged 65 with no family history of AD. The risk for all people was about 15%. Differentiated by APOE $\epsilon 4$ allele, the risk increased to 29% for people with the allele, and to 9% for people without it. Slooter et al. (1998) calculated the lifetime risk for men and women at age 55. Men with at least one $\epsilon 4$ allele had a risk of 26%, while women had a risk of 46%. Without the allele, the risk decreased to 11% for men, and to 28% for women. The higher risk for women is attributable to their greater life expectancy and their higher a priori risk.

A determination of APOE genotypes could be an important tool for identifying people with an increased risk (Tsai et al., 1994). Approximately 20% of dementia cases are attributable to the APOE genotype (Slooter et al., 1998). However, this leaves 80% of the cases unexplained. More of the factors that contribute to or prevent the disease must be determined.

To date, the APOE $\epsilon 4$ allele is the best established genetic risk factor for sporadic AD. There are more genetic risk factors, but the studies that have explored these factors are too numerous to be addressed here in detail. A comprehensive database that catalogs all genetic association studies in the field of AD can be found at `www.alzgene.org` (Bertram et al., 2007). So far, 40 potential AD susceptibility genes have been pinpointed [accessed in June 2010], and 12 of them have strong epidemiological credibility.

Study results on the genetic and familial influence on AD and dementia vary greatly. The relative importance of genes as risk factors for AD is not yet entirely clear, and seems to have been overestimated in early studies (Bickel, 2005; Larson et al., 1992).

Familial causes are believed to contribute to about 25% of all AD cases, and less than 1% are caused chromosomal by DS, which leaves 75% as the result of unknown factors (including gene/environment interactions) (Bird, 2008). This means that most people develop the disease without an accumulation of events within the family, and that non-genetic factors play an important role.

2.4.3 Gender

While the literature appears to agree that women are at higher risk of developing depression and general mental health problems (European Commission, 2004; Wittchen and Jacobi, 2005), existing research provides no definite answers to the question of whether a gender difference exists in the incidence or prevalence of dementia (Bickel, 2005; Mortimer, 1983). Some studies found a higher incidence or prevalence for women (Aevarsson and Skoog, 1996; Ebly et al., 1994; Manton et al., 2005; Ravaglia et al., 2005), while others stated no differences (Cooper et al., 1992; Edland et al., 2002; Hall et al., 2005; Hofman et al., 1991; Kokmen et al., 1993, 1989; Kukull et al., 2002; Wernicke and Reischies, 1994). Only a few studies worked out higher (insignificant) rates for severely demented males between ages 70-79 (Nilsson, 1984).

The following table 2.7 provides an overview of existing dementia studies that explore gender. Many studies only looked at dementia in general, or dementia and AD, because it is the biggest subgroup, and the usually small sample can still be interpreted for AD. VaD is analyzed less often.

Table 2.7: Gender Differences in the Occurrence of Dementia

	Design	Type	N	Remarks
Higher Rates for Females				
Bickel & Cooper 1994	Incidence	Dem, AD	458	Tendency
Fratiglioni et al. 2000	Incidence	Dem, AD	Meta	8 Studies, Europe
Nitrini et al. 2004	Incidence	Dem, AD	?	Above Age 85
Ott et al. 1998	Incidence	Dem	7,046	
Andersen et al. 1999	Incidence	AD	Meta	4 Studies, 85+
Gao et al. 1998	Incidence	AD	Meta	12 Studies
Jorm & Jolley 1998	Incidence	AD	Meta	23 Studies, Tendency
Kawas et al. 2000	Incidence	AD	1,236	Not Sign.
Launer et al. 1999	Incidence	AD	Meta	4 Studies
Miech et al. 2002	Incidence	AD	3,308	Above Age 85
Aevarsson & Skoog 1996	Incidence	AD, VaD	347	Ages 85-88, N.S.
Ravaglia et al. 2005	Incidence	AD, VaD	937	Not Sign.
Lobo et al. 2000	Prevalence	Dem, AD	Meta	11 Studies, Europe
Manton et al. 2005	Prevalence	Dem, AD	42,000	
von Strauss et al. 1999	Prevalence	Dem, AD	1,848	77+
Ebly et al. 1994	Prevalence	Dem	1,835	85+
Engedal & Haugen 1993	Prevalence	Dem	1,029	75+
Fichter et al. 1995	Prevalence	Dem	1,692	75+, Tendency
Lopes & Bottino 2002	Prevalence	Dem	Meta	38 Studies
Cooper et al. 1992	Prevalence	AD	3,737	No Sign. Given
Ebly et al. 1994	Prevalence	AD	1,835	Not Sign.
Jorm et al. 1987	Prevalence	AD	Meta	27 Studies
Kokmen et al. 1989	Prevalence	AD	12,000	
Higher Rates for Males				
Fichter et al.1996	Incidence	Dem	402	85+, tendency
Nilsson 1984	Incidence	Dem	385	Ages 70-79, Not Sign.
Jorm & Jolley 1998	Incidence	VaD	Meta	23 Studies, Tendency
Jorm et al. 1987	Prevalence	VaD	Meta	27 Studies, Tendency
Rocca et al. 1991a	Prevalence	VaD	Meta	5 Studies, Europe
No Gender Differences				
Bachman et al. 1993	Incidence	Dem, AD	2,391	
Edland et al. 2002	Incidence	Dem, AD	14,439	
Kukull et al. 2002	Incidence	Dem, AD	2,356	
Hall et al. 2005	Incidence	Dem	488	
Jorm & Jolley 1998	Incidence	Dem	Meta	23 Studies
Kokmen et al. 1993	Incidence	Dem	12,000	
Riedel-Heller et al. 2001b	Incidence	Dem	1,692	75+
Andersen et al. 1999	Incidence	AD	Meta	4 Studies
Fratiglioni et al. 2000	Incidence	VaD	Meta	8 Studies, Europe
Cooper et al. 1992	Prevalence	Dem	3,737	
Fichter et al. 1995	Prevalence	Dem	402	85+
Hofman et al. 1991	Prevalence	Dem	Meta	8 Studies, Europe
Jorm et al. 1987	Prevalence	Dem	Meta	27 Studies
Kokmen et al. 1989	Prevalence	Dem	12,000	
Wernicke & Reischies 1994	Prevalence	Dem	156	70+
Ebly et al. 1994	Prevalence	VaD	1,835	Above Age 85
Lobo et al. 2000	Prevalence	VaD	Meta	11 Studies, Europe
von Strauss et al. 1999	Prevalence	VaD	1,848	77+

In a general model Jorm et al. (1987) combined data from 15 studies which provided gender-specific information and investigated no difference between male and female prevalence rates. Looking at these studies separately results were contradictory. Some studies showed no difference between the genders, and others reported higher rates for males or for females. However, within the three studies that looked at AD, significantly higher rates for women were found (also in Cooper et al. (1992); Gao et al. (1998); Miech et al. (2002); von Strauss et al. (1999)). Jorm and Jolley (1998) observed no sex difference in the prevalence and the incidence of dementia, but a trend towards higher rates for AD in women and higher rates for males in VaD. In addition, other studies found no difference for dementia, but a higher rate for women when only AD was taken into account (Andersen et al. (1999); Fratiglioni et al. (2000); Kokmen et al. (1989); Launer et al. (1999); Ott et al. (1998)). Edland et al. (2002), however, found no difference in the incidence of AD in the US. These results are in line with other US studies, but not with European and Asian studies, in which AD incidence was shown to be higher for women. Some studies investigated additional age differences: e.g., higher prevalence rates for men until about age 80, higher rates for women above age 80 (Beard et al., 1995; Bickel, 2005; Hatada et al., 1999; Hofman et al., 1991; Nitrini et al., 2004), and higher rates for women at old age 85+, but no difference before this age (Nitrini et al., 2004). Studies that analyzed VaD, on the other hand, often found no sex differences (Fratiglioni et al., 2000; Knopman et al., 2002) or higher rates for males (Gao et al., 1998; Hagnell et al., 1992; Kukull et al., 2002; Ott et al., 1998; Rocca et al., 1991; Rocca and Kokmen, 1999; Seno et al., 1999).

These often contradictory studies also provided different explanations for their findings. Kokmen et al. (1989) suggested that the higher rate for women with AD should not mark sex as a risk factor; instead, it could more likely "reflect variability in timing of diagnosis relative to the actual onset of dementia and the longer survival of women subsequent to onset." The longer survival of women with AD relative to men with AD is confirmed by Kokmen et al. (1996). Bickel (2005) also argued that the prevalence of dementia is higher in women than in men, due to their higher life expectancy and their longer periods of survival with the disease. However, Aevarsson and Skoog (1996) also found higher incidence rates, and suggested that a possible "explanation for the higher incidence in women could be that men in this age group are a surviving elite and, therefore, less vulnerable to dementia compared with women." Other studies provided a biological explanation, and argued that estrogen replacement in postmenopausal women might improve the memory performance and reduce the risk of developing AD

(Henderson et al., 1994) (see section 2.4.13).

Also the APOE $\epsilon 4$ allele might play a role. A gender-specific efficacy of APOE in redistributing cholesterol during nerve repair might exist (Payami et al., 1996) (see section 2.4.2).

These studies demonstrated that gender is a "somewhat consistent," but still interactive risk factor. For general dementia, there were contradictory results. For AD, the risk seemed to be higher for women. Meanwhile for VaD, no gender difference, or a slightly higher risk for men, was found.

2.4.4 Region/Ethnicity

Region

It is difficult to say if regional differences exist. Early studies concluded that, while there might be differences in the prevalence rates of dementia between regions, "their magnitude is impossible to assess with existing data" (Jorm et al., 1987). Differing study designs and methodology make comparisons too unreliable. The number of studies about prevalence and incidence of dementia has grown and the methodologies used have become more comparable. Most studies were, however, from Europe or North America, while only a few were from Asia, Southern America or Africa.

Nonetheless, Wimo et al. (2010), who estimated the magnitude of dementia occurrence for different regions across the whole world, assumed that the age-specific prevalence is similar worldwide. They used the same prevalence data from Fratiglioni and Rocca (2001) for all regions (see figure 2.2). Most of the 34 million demented people across the world in the year 2009 lived in the most populated regions, with Asia making up 48% of the cases; Europe, 26%; and North America, 12%. In relative terms, developed regions have a higher proportion of demented people because of their older populations. In earlier calculations, Wimo et al. (2003) conducted sensitivity analyses with continent-specific data. Results showed a slightly lower number of demented people—24.24 million instead of 25.54 million—which is mainly due to lower figures from Asia and Africa. The authors noted that the dementia occurrence might, however, be different across the regions. But because data were missing or studies had methodological problems for many countries, they used the data from Fratiglioni and Rocca (2001). Hofman et al. (1991) also concluded that the prevalence from pooled data on Europe was similar to other continents. This was confirmed by Hatada et al.

(1999), who compared the prevalence in Japan with European studies; Nitrini et al. (2004), who compared Brazil with Asian and Western studies; and Fratiglioni et al. (1999), who reviewed 36 prevalence studies from different continents.

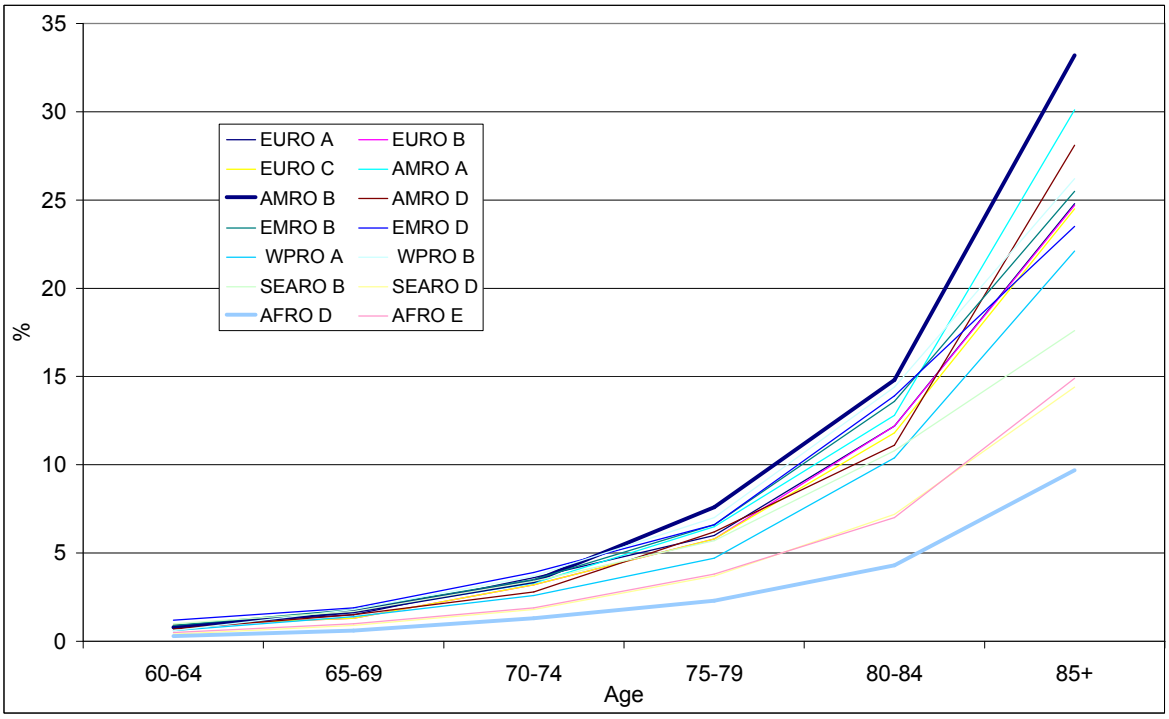
In a meta-analysis of dementia in Africa, Ineichen (2000) found only few studies for the whole continent. The most frequently cited study on dementia prevalence is from Nigeria (Hendrie et al., 1995). The authors estimated the prevalence rates among people above age 65 in two communities: 2,494 Africans in Nigeria, and 2,212 African-Americans in Indianapolis, US, who lived in the community, as well as 106 African-Americans living in nursing homes. Rates of dementia were much lower for the African sample (2.29%) than for the US sample (community: 4.82%; community and nursing home together: 8.24%). However, methodological problems might exist. Fratiglioni et al. (1999) excluded these results from their pooled prevalence estimates, and suggested that the lower prevalence in this study could be due to lower survival or methodological differences, and that the rates should be confirmed by incidence data. They did not use the data but concluded that possible ethnic variations cannot be excluded. In a paper by Ferri et al. (2005), international experts were asked to estimate the worldwide prevalence rates on the basis of the reviewed studies, and, unlike Fratiglioni et al. (1999), they did not exclude the study on Africa by Hendrie et al. (1995). On the contrary, they "seemed to be strongly influenced by the one study of good methodological quality from sub-Saharan Africa (Hendrie et al., 1995), for which the reported prevalence was very much lower than in developed countries." Hendrie (1998) himself posited differential levels of mortality between the two sites as an explanation for the different rates. Further possible reasons for these discrepancies could be, according to Ineichen (2000), that demented people are concealed by the family due to stigma, poor access or reluctance to seek medical care, or even due to a lack of awareness of the symptoms as a disease.

The estimation of worldwide prevalence by Ferri et al. (2005) took different geographical rates into account. The authors calculated the number of demented people in 2001 and came to about the same number as Wimo et al. (2003): 24.3 million people worldwide. However, on the basis of the Hendrie et al. (1995) study, they assumed a much lower prevalence in Africa of 0.49 million, compared with 1.25 million estimated by Wimo et al. (2003). Nevertheless, caution should be exercised because prevalence rates cannot take mortality into account. Since mortality is very high in Nigeria, the lower prevalence could be attributable to this fact. Incidence rates are needed to illustrate true differences. Furthermore, the results would be more reliable if other studies

could confirm them. Breteler et al. (1992) also pointed to methodological differences between studies when diverging results between countries were found.

Figure 2.8 displays the different estimates across regions as provided by Ferri et al. (2005).

Figure 2.8: Prevalence of Dementia in Different Regions of the World



Source: Ferri et al. 2005

AMRO-the Americas
EURO-Europe
EMRO-north Africa and the middle east
AFRO-Africa
SEARO-south Asia
WPRO-western Pacific
Patterns of Child and Adult Mortality, from A (lowest) to E (highest)

While dementia in general was often thought to be similar across regions (McDowell, 2004), the literature showed that the most prevalent types of dementia vary between countries, regions and ethnic groups.

For example, Fratiglioni et al. (1999) came to the conclusion that, while little geographical variation in prevalence and incidence of dementia exists, the relative incidence of AD and VaD seems to differ between continents or ethnic groups. AD is, in general, the most prevalent form of dementia (Cooper et al., 1992; Ebly et al., 1994; Edland et al., 2002; Kokmen et al., 1989; Ravaglia et al., 2005; Reed, 2004). However, the ratio varies across the continents. Fratiglioni et al. (1999) showed a higher prevalence of AD

in Europe and North America than in Asia. Newer studies from Asia showed a lower proportion of VaD (31% instead of 38%), which led them to the following conclusion: "it seems that most of the inconsistency present in the literature is due to the estimate of vascular dementia occurrence, rather than AD" (Fratiglioni et al., 1999). The authors sought to attribute these discrepancies to variations in diagnostic criteria and procedure, dementia duration or different age structure. However, these effects might be a real, since Hatada et al. (1999) showed a trend towards a decreasing VaD/AD ratio in Japan, which he calls "westernization" (see below). In addition, Jorm and Jolley (1998) found in their meta-analysis that studies in East Asian countries have found a lower incidence of AD relative to Europe and North America. The authors argued that this could be due to the lower prevalence of APOE $\epsilon 4$ allele in the Japanese population (see section 2.4.2, also true for the Chinese population).

Different reasons account for this varying prevalence of AD and VaD: "Given that a large proportion of cases of VaD are related to stroke (Gorelick et al., 1999) and that hypertension, atherosclerosis, and stroke vary with the genetic composition, dietary habits, and lifestyle of different populations, we would expect some international variation in the incidence of VaD" (Rocca and Kokmen, 1999). And indeed, many studies have confirmed the presence of this difference. Rocca et al. (1991) compared five European studies published by the EURODEM group, and found considerable differences across countries, with some countries not even showing an increase in VaD prevalence with age, but a flattening of the curve.

In a literature review by Jorm et al. (1987), studies from Finland and the US showed no difference between VaD and AD, while studies from Japan and Russia reported a higher prevalence of multi-infarct dementia, and all other studies reported higher prevalence for Alzheimer's disease. For Japan, this result is consistent with a high rate of strokes. Hatada et al. (1999) generally confirmed this finding of higher VaD prevalence in Japan; however, compared with older studies, they found a lower VaD/AD ratio that is narrowing to European numbers. They call this trend the "westernization" of dementia prevalence. While the results produced by Seno et al. (1999) in an incidence trend study of people in nursing homes moved in the same direction, they were not significant. In general, Jorm (1991) concluded that AD is the more common form of dementia in white populations, whereas VaD is more common in East Asian populations. In their incidence literature reviews, Jorm (1991); Jorm and Jolley (1998) reported a lower incidence of AD in East Asian countries than in Europe and the US (also Reed (2004)), but also that the exponential rise with age tends to be steeper.

At the same time, however, differences were found between countries located on the same continent. Fratiglioni et al. (2000) showed differences for Europe between eight incidence studies, in which the proportion of AD accounted for about 60% to 70%. Regional differences may exist, with higher rates of dementia and AD being found in northwestern countries, and lower rates in southern countries (also found by Moise et al. (2004)). Eurostat (2003) showed the highest prevalence rates for Sweden and Italy (14.9 and 13.7 per 1,000 inhabitants) and the lowest rates for Portugal and Ireland (10.4 and 8.4 per 1,000 inhabitants).

Skoog (2004) and also Aevarsson and Skoog (1996) found for Sweden an almost equal prevalence of VaD and AD. Skoog (2004) stated that this might be due to a precise measurement of cases of stroke, which were classified as VaD if a person reported a history of cerebrovascular disease. Aevarsson and Skoog (1996) emphasized the co-occurrence and interaction of both diseases, and the difficulty of distinguishing between them.

Urban/Rural differences

In early studies, no differences between urban and rural areas were apparent (Mortimer, 1983). Henderson (1988) found mixed results for four studies. Three studies included in a literature review by Jorm et al. (1987), which encompassed only rural areas, reported lower prevalence rates of dementia. Nilsson (1984) looked at an urban sample of people aged 70 to 79. He suggested that the higher incidence in his study relative to the results from Hagnell et al. (1981), who studied a rural sample, might be due to the different urban/rural settings. Corrada et al. (1995) found in a meta-analysis of 15 studies higher incidence rates in urban/rural mixed areas than in urban areas, but no differences between solely urban and rural areas.

Ethnicity

Other studies did not investigate the differences by country, but by ethnic origin. Kukull et al. (2002) found no differences between white and non-white (African-American and "other") people, but only a small number of non-white people were included in the study. Some have concluded that Caucasian populations have a higher incidence of AD than Asian people (Fratiglioni et al., 1999; Fratiglioni and Rocca, 2001; Henderson, 1988). Conversely, Asian and, possibly, black populations could be at higher risk of VaD than Caucasian populations. African-Americans had a higher frequency of dementia and

AD than Caucasians in a US study (Plassman et al., 2007). Controlled for education, gender and APOE genotype, the risk was still higher, but no longer significant.

Nitrini et al. (2004) found a lower incidence rate of dementia for a Brazilian community relative to rates found in European and North American studies. The APOE $\epsilon 4$ allele might be one reason for the lower rates in Spanish and Latin American populations (see chapter 2.4.2).

Many studies that looked at the prevalence or incidence of VaD showed different results. The possible reasons for these variations might include (1) the difficulty of classifying the so-called "mixed" cases, or people who show signs of cerebrovascular and primary degenerative features; (2) the disagreement over criteria and evaluation tools; (3) the use or non-use of imaging findings and (4) the definition of the range of severity of the disease, as discussed by Rocca and Kokmen (1999).

Dementia prevalence and incidence seems to be quite similar across continents. "Nonuniform studies from diverse regions of the world still provide remarkably similar incidence and prevalence rates." If diverging results are found, this is often attributed to variations in the definitions of dementia or the study design: "This occurrence is likely attributable to the unusual case definition criteria used" (Kokmen et al., 1996).

However, when different types of dementia were taken into account, the ratio between AD and VaD varied. AD is usually the most prevalent form of dementia, but in Europe and Northern America, VaD is less common than in Asian countries.

2.4.5 Education and Lifestyle

Socio-economic class is a clear indicator for general physical health (Marmot et al., 1984; Townsend and Davidson, 1992). In addition, belonging to a higher socioeconomic class has a protective function for general mental health (European Commission, 2004). By contrast, people with low levels of education, material disadvantages and long periods of unemployment are more susceptible to mental disorders. While there appears to be a correlation between dementia and socioeconomic class and education these are not clear-cut risk factors. Many studies showed that people with higher levels of education are less likely to develop AD, dementia or MCI (Bickel, 2005; Kawas et al., 2000; Kukull et al., 2002; Launer et al., 1999; Manton et al., 2005; Nitrini et al., 2004; Ravaglia et al., 2005; Richards et al., 2004; Tyas et al., 2007; Yen et al., 2001). Other studies have failed to confirm the hypothesis that socio-demographic factors, such as education, occupation, marital status, and type of dwelling, differ significantly between patients

with AD and their age- and gender-matched control subjects (Henderson, 1988; Kokmen et al., 1996).

Higher intellectual activity also leads to a higher cognitive reserve, which compensates for dementia selected brain lesions (Boyle et al., 2008; Katzman et al., 1988; Richards et al., 2004). Epidemiologic studies have shown "that the association between AD and education occurs primarily with the clinical manifestation of disease, rather than with the underlying pathology. This finding prompted the interpretation of education as a marker for cognitive reserve" (McDowell, 2004). People with higher levels of education are able to cope better or longer with the different scales that measure dementia. Additional studies should therefore consider this possibility in generating dementia scales or indices. For example, Crum et al. (1993) suggested that less educated people can be still cognitively normal at a lower number of points than higher educated people of the same age. This distinction is, of course, hard to include, especially because there are cohort differences in intelligence caused by changes in society and the expansion of education (Schaie et al., 2005).

Education and socio-economic class influence many other lifestyle factors, such as social engagement, mental and physical training, nutrition, smoking, and alcohol use.

Psychosocial factors such as engagement in activities and the performance of complex work have positive effects, while inactivity, loneliness, low mood and social isolation have negative effects (Carlson et al., 2008; Karp, 2005; Ravaglia et al., 2008). Also being married and not living alone have protective influences on mental health: elderly people who live with a partner or spouse have lower levels of depression than people who live alone. In addition, living with children or having frequent contact with them acts protectively (Buber and Engelhard, 2006). Wang et al. (1997) and Håkansson et al. (2009) confirmed this positive relationship of being married as protective against dementia and AD. Social activities and interaction play an important role in staying mentally active, through communication and caring for others.

Meta-analyses have shown that regular physical activity is likely to reduce the risk of VaD (Aarsland et al., 2010) as well as AD (Hamer and Chida, 2009). There is strong evidence that physical activity reduces the risk for many chronic diseases such as cardiovascular disease, hypertension, diabetes, as well as the risk for inflammation. It might increase the blood supply and stimulate angiogenesis, brain perfusion and neurovascular integrity (Aarsland et al., 2010; Hamer and Chida, 2009; Lautenschlager et al., 2008).

Regular low to moderate alcohol consumption could be protective against dementia,

as a meta-analysis has shown (Peters et al., 2008); while alcohol abuse seems to be negatively connected (Lindsay et al., 1997). Some studies found a protective effect of moderate alcohol consumption for red wine (Larrieu et al., 2004; Mehlig et al., 2008) and argued that the flavonoids could act as antioxidants. However, these results should be interpreted with caution. The amount of "moderate" intake often is unclear and the negative effects of regular alcohol intake have to be taken into account. Furthermore, moderate alcohol consumption could be associated with a moderate and more healthy lifestyle in general (Peters et al., 2008). The slightly higher risk often seen among the group without alcohol consumption compared with the low intake group could be influenced by the presence of some recovered alcoholics and by a selection effect of more unhealthy people into this group.

Smoking seems to be a risk factor for dementia, although not all studies confirmed this finding (Henderson, 1988; Hendrie, 1998). Most studies showed an increased risk (Breitner et al., 1993; Launer et al., 1999; Meyer et al., 1988; Solfrizzi et al., 2004), others found no correlation (Lindsay et al., 1997), while one found a protective effect of light smoking, but an increased risk for heavy smokers (Wang et al., 1997) and some even a protective effect of smoking (Graves et al., 1991). Riggs (1996, 2000) ascribed findings that suggest smokers face an increased risk, as well as findings that show the risk is decreased, to the different survival rates of smokers and nonsmokers. The toxic effects of smoking might increase the risk of becoming demented, but smokers experience higher mortality, and thus only a few selected smokers are left at high ages. Results might also be influenced by the study design. However, most studies found an increased risk for AD for smokers (Merchant et al., 1999). In a meta-analysis Anstey et al. (2007) looked at ten, two, and five studies analyzing the risks that smokers face of developing AD, VaD and any dementia, respectively. They found that elderly smokers had a significantly higher risk of developing all three conditions than people who had never smoked. The effect was shown to persist for current smokers vs. former smokers for AD, but not for VaD and dementia, and no difference was found to exist between ever smokers (there are different measures of "ever" in different studies) and never smokers, and former smokers vs. never smokers. The authors concluded that elderly people who currently smoke have an increased risk of developing dementia and cognitive decline relative to never smokers. Smoking cessation seems to have a positive effect on VaD and dementia, perhaps because of the reduced risk of developing conditions like cardiovascular disease, which is a risk factor for VaD in itself. In a recent meta-analysis, Cataldo et al. (2010) controlled for tobacco industry affiliation, and found an

influencing effect. Fourteen cohort studies without tobacco industry affiliation showed a significantly increased relative risk of AD of 1.45 for smokers.

A head trauma may also contribute to the development of dementia. (A head trauma could be caused by an accident which is, of course, not a "chosen" lifestyle. It also often occurs among boxers and can lead to a "Dementia Pugilistica.") A pooled analysis by Mortimer et al. (1991) and other studies confirmed that a head trauma is a risk factor (Breitner et al., 1993; Henderson, 1988), but not all studies are in line with these results (Henderson, 1988; Hendrie, 1998; Kokmen et al., 1996; Launer et al., 1999). An explanation for the possible correlation between a head trauma and dementia is that traumas release β-amyloid, which produces diffuse plaques, and which in turn lead to AD (Larson et al., 1992).

There is increasing evidence that some lifestyle factors could influence the development of AD and that many of them are potentially modifiable (Flicker, 2010). Most importantly, higher education seems to lead to a greater awareness of the importance of health and prevention. People with higher levels of education have been found to have healthier lifestyles than less educated people, including better diets (see next section) and exercise habits, social engagement, cognitive stimulation, better adherence to medical checkup schedules, and lower rates of smoking and excessive alcohol use. Better lifestyles, however, act as protection against some diseases that contribute to the development of dementia, such as high blood pressure.

2.4.6 Nutrition

Many studies dealing with risk factors of AD and dementia focus on nutrition, especially antioxidants. Oxidative stress has an accelerating effect on aging, diseases and cognitive decline (see section 2.1.2) (Helmer et al., 2003; Jama et al., 1996). Antioxidants such as vitamins A, C, E which are contained in some fruits and vegetables such as citrus fruits, cabbage and tomatoes, might have a protective effect. Helmer et al. (2003) found within the PAQUID study of people who develop dementia a significantly lower concentration of vitamin E two to nine years before the onset, and a non-significantly lower concentration of vitamin. The authors proposed two hypotheses concerning the relationship between dementia and vitamins. On the one hand, nutritional deficiencies in elderly people can increase oxidative stress. On the other hand, the increase in oxidative stress might already be an early sign of dementia because more free radicals

are produced. Because vitamin plasma concentrations are determined up to nine years before the onset of dementia, they inferred that it should rather be a contributing factor to the disease (Helmer et al., 2003). Other studies confirmed the positive effect of antioxidants on cognitive functioning (Gray et al., 2003; Jama et al., 1996), dementia (Cherubini et al., 2005) and also on PD (de Rijk et al., 1997). However, not all studies have confirmed this effect (Kalmijn et al., 1997; Luchsinger et al., 2003; Weuve et al., 2008).

In a literature review on the effect of omega-3 fatty acids on cognitive function and dementia lssa et al. (2006) found support for the protection hypothesis. Three studies showed a lower incidence of dementia for people with higher levels of fish consumption. In one study, omega-3 fatty acids were successfully used as a treatment for dementia. Only one prospective study found no influence on cognitive function. Other studies confirmed a protective effect of eating fish on cognitive functioning (Kalmijn et al., 1997; Larrieu et al., 2004; Morris et al., 2005). Studies also showed that high intake of unsaturated, unhydrogenated fats had a protective effect on AD, while consuming saturated or trans-unsaturated fats increased the risk (Morris et al., 2003; Pope et al., 2003). The negative effect of the high intake of polyunsaturated fatty acids was not confirmed by Kalmijn et al. (1997).

Other protective supplements might include folate (Kado et al., 2005; Kang et al., 2005) and dietary niacin (Morris et al., 2004). Giem et al. (1993) discovered more dementia incidence cases for "heavy" meat eaters than for vegetarians. Luchsinger et al. (2004) did not find an increased risk of AD with higher levels of plasma homocysteine, which occurs when low levels of folate, vitamin B6 and B12 are prevalent. Another study by Aisen et al. (2008) did not show an effect for vitamin B supplementation. Low levels of vitamin D could influence the dementia risk, not just directly, but also because they are also connected to many risk factors of AD and dementia, such as age, sex, obesity, smoking, low bone density, inflammation, diabetes, depression and several cardiovascular pathologies, including hypertension (Dyer, 2008; Grant, 2009).

Generally findings support the assumption that a healthy diet might have a protective effect on dementia.

2.4.7 Diabetes Mellitus

Literature about diabetes mellitus (also called type 2 diabetes, and in the following diabetes mellitus or diabetes) is not quite consistent about the relation of this disease and dementia. Diabetes might develop from dementia, as is described in the co-morbidity section 4.1, but it could also represent a risk factor and abet the development of dementia. Diabetes mellitus is part of the metabolic syndrome, a combination of disorders that increase the risk of developing cardiovascular disease and diabetes, which also has a direct link into AD pathology. Senile plaques and neurofibrillary tangles both show "advanced glycation endproducts (AGEPs)," or oxidation products of proteins which are associated with hyperglycemia and diabetes (Finch and Cohen, 1997). While an accumulation of AGEPs occurs during aging in normal brains, the extent of this accumulation is unknown, which makes the estimation of correlations difficult. The blood glucose level increases with age, and a higher level is inversely correlated with cognitive functioning. Older reviews of 13 studies about the correlation of diabetes and AD found inconsistent results (Finch and Cohen, 1997). Five studies showed no correlation, two showed a positive correlation, and six even found a negative correlation. One major problem the authors cited as a possible reason for these findings is the exclusion of strokes in most AD classifications. People with diabetes have a higher stroke risk. It is possible that people with diabetes are initially diagnosed with AD, but then suffer a stroke and are shifted to the mixed dementia or VaD group: "there is a discrimination against even a provisional diagnosis of AD if a subject shows evidence of diabetes. Virtually any evidence of vascular impairment may suffice to disqualify the designation of 'pure AD' and classify the individual as mixed or vascular dementia" (Finch and Cohen, 1997). On the other hand, AD could have a real positive effect on diabetes: weight loss is common in AD patients, and weight loss is also commonly recommended for diabetes patients in order to decrease insulin level. The authors concluded that it is not yet possible to establish a relationship between the two diseases, and that longitudinal studies are needed to "evaluate the possibility that an initial age-related hyperglycemic state is reversed by the cachexia and weight loss common to later stages of AD."

Recently, eight newer studies, all based on incidence rates, were compared in a database from the Alzheimer Research Forum (Weuve et al., 2008). All studies showed a higher risk for people with diabetes of developing AD, four of them with significant results. When a summary measure was calculated, people with diabetes were found to have a 51% higher risk of developing AD. Among the possible explanations for this find-

ing are links between the pathogenesis of AD and dementia, and between diabetes and vascular diseases, including impaired glucose/energy metabolism, altered insulin signaling pathways, mitochondrial dysfunction, oxidative stress and inflammation (Bierhaus and Nawroth, 2009). The meta-analysis of incidence studies (Weuve et al., 2008) did not exclude the many cases in which AD and vascular disease co-occur, and in which a higher risk of developing AD with diabetes is more consistently found. Thus, vascular factors might partially explain the association between diabetes and AD. The authors also pointed to the role of hyperinsulinemia that often occurs in type 2 diabetes and might increase the level of the Aβ protein (Farris et al., 2003; McDermott and Gibson, 1997; Watson et al., 2003). A higher insulin level also seemed to increase the cognitive decline in non-diabetic individuals (Okereke et al., 2008; van Oijen et al., 2008; Young et al., 2006). They concluded that diabetes plays an important role in the development of AD, and that more effort has to be put into the prevention of the disease through exercise and weight reduction. Treatment of AD patients with diabetes medication might have a positive effect (Craft, 2006); however, the relationship of type 2 diabetes treatment and cognitive outcomes are uncertain (Weuve et al., 2008).

In conclusion, most studies worked out that having diabetes mellitus is associated with a higher risk of developing cognitive decline (Fontbonne et al., 2001), dementia (Craft, 2009; Luchsinger et al., 2004) and AD (Kopf and Frölich, 2009; Weuve et al., 2008). Also studies that looked at the metabolic syndrome found an increased risk of AD (Vanhanen et al., 2006).

Other metabolic diseases that might influence the dementia risk include malnutrition and obesity. Some studies have discovered that unintended weight loss occurred before the onset of or parallel to the development of dementia (Barrett-Connor et al., 1998; Henderson, 1988; Stewart et al., 2005). Barrett-Connor et al. (1998) analyzed how the weight loss and dementia influence each other. They found that weight loss occurs before clinical signs of dementia can be seen. None of the persons from the study group suffered from depression, which also could have explained their low appetite. The fact that unintended weight loss precedes dementia can be used as an early sign of the onset of dementia, merits more attention.

The relationship between obesity and dementia has not been often analyzed, and so far the results have been contradictory. Rosengren et al. (2005) and Skoog (2004) found an increased dementia risk when people have a high BMI, but Dahl et al. (2008) found

a lower risk. Fitzpatrick et al. (2009) differentiated between midlife obesity, which has been shown to increase the risk, and late-life obesity, which does not appear to elevate the risk relative to the normal-weight population. A discussion has taken place about the definition and measurement of overweight, and the importance of taking intended and unintended weight changes into account (Dahl et al., 2008; Fitzpatrick et al., 2009; Hazzard, 2009). Although not all studies found a link between obesity and AD, there might be a direct link from the metabolic syndrome. Luchsinger and Gustafson (2009) assumed that there is a common mechanism linking the continuum of obesity and type 2 diabetes with AD, which may include hyperinsulinemia, advanced products of glycosylation, cerebrovascular disease and products of adipose tissue metabolism.

2.4.8 Cardiovascular Disease

Several studies showed a correlation between cardiovascular disease and AD or dementia (Pope et al., 2003). Many studies concentrated on strokes, a principal form of cardiovascular disease. They found an increased risk of dementia and VaD after stroke (Desmond et al., 2002; Ivan et al., 2004; Knopman et al., 2002; Patterson et al., 2007a; Pendlebury and Rothwell, 2009; Rocca and Kokmen, 1999; Tatemichi et al., 1992; Zhu et al., 2000). The reason for this higher risk may be the stroke itself (Pendlebury and Rothwell, 2009), as well as a combination of vascular and degenerative pathologies that underlie the development of dementia after stroke (Ivan et al., 2004).

2.4.9 Hypertension

Hypertension is such a factor. The better treatment of high blood pressure has a declining effect on the stroke risk (Garraway and Whisnant, 1987) and on dementia and AD (Hajjar et al., 2005; Qiu et al., 2003). Reversely, untreated high blood pressure increases the risk of dementia (Khachaturian et al., 2006; Lindsay et al., 1997; Skoog, 2004; Skoog et al., 1996; Wu et al., 2003).

However, literature findings regarding AD and hypertension have been inconsistent. Some studies have found a lower risk of hypertension for people with AD (Guo et al., 1996; Morris et al., 2001; Sanderson et al., 2002). Lower blood pressure could cause less cerebral blood flow and accelerate the mental decline. Causality could also work the other way round: AD could cause low blood pressure. The longitudinal study from Skoog et al. (1996) showed that people with high blood pressure at age 70 have a higher risk of developing dementia at ages 79-85. However, the blood pressure decline in

the years before developing dementia was found to be stronger than for non-demented people.

Newer reviews about the correlation between hypertension and dementia have come to the conclusion that midlife, and possibly late-life, hypertension increase the risk. In the years before the diagnosis of dementia, the blood pressure seems to decline. These age-specific correlations might explain the contradictory results found before (Ngandu, 2006; Pope et al., 2003).

2.4.10 Depression

Depression is very common in old age, especially among women. Bereavement, loneliness, physical illness and institutionalization are common factors among the elderly that can lead to a depression and furthermore influence the onset of dementia (Devanand et al., 1996; European Commission, 2004; Kokmen et al., 1996).

However, the relationship between depression and dementia is complex. The onset of depression could also happen before the cognitive decline. Both illnesses influence each other (European Commission, 2004), which makes it difficult to determine the direction of influence: Do people with depression become demented more frequently, or do demented people become depressed more often? Some studies came to the conclusion that depression might be an early manifestation rather than a predictor of AD (Bassuk et al., 1998; Chen et al., 1999). Depressed people might also score low on dementia scales due to this illness, so special care must be taken to avoid misdiagnosis (La Rue et al., 1986). New research has revealed another connection between the two diseases: Sun et al. (2008) found a high plasma Aβ_{42} level in elderly depressed people, which is also a risk factor for AD. It might be a subtype of depression which indicates an early manifestation of AD.

2.4.11 Parkinson's Disease

AD and Parkinson's Disease (PD) are both neurodegenerative disorders. Similar molecular mechanisms occur in both diseases (McCullagh et al., 2001; Tsigelny et al., 2008) and increase the likelihood of co-occurrence. In addition to AD, people with PD may also suffer from Lewy body dementia. Most PD patients have cortical changes, while only about 10% have subcortical changes (Lieberman, 1997). In a literature review of 17 studies Brown and Marsden (1984) found that a wide range of PD patients developed a dementia (no differentiation by type), from 0% to 81% with an average of 35%. The

authors assumed that this proportion was too high because of methodological problems and misdiagnoses, and estimated that about 10% to 15% of PD patients had an additional risk of dementia. In the Rotterdam study, people with PD had a 2.8-fold risk of developing dementia (de Lau et al., 2005). A higher familial aggregation of PD and AD was shown in a study by van Duijn et al. (1991), but not in a study by Levy et al. (2004).

2.4.12 Other Risk Factors

Many other minor risk factors have been considered which cannot be addressed here in detail. For each single factor, a few studies and contradictory results make them too unreliable to include. Further risk factors of dementia might include social or environmental factors (Brandt et al., 1993; Skoog, 2004) or negative life events (Skoog, 2004). In particular, accompanying illnesses could increase the risk of developing a dementia, such as atrial fibrillation, coronary heart disease (Skoog, 2004), atherosclerosis (van Exel et al., 2002), cerebral white-matter lesions (Miyao et al., 1992), oxidative and inflammatory stress (McCullagh et al., 2001), occupational exposure to pesticides and fertilizers (Lindsay et al., 1997) or delirium (McCusker et al., 2001). Examples of environmental factors that could contribute to the development of the disease include aluminum or silica intake with the drinking water. Rondeau et al. (2008) found a higher dementia risk among people with a high aluminum and a low silica intake. Studies have often produced contradictory results, such as those that have examined the role of aluminum. The metal can cause abnormal phosphorylation of tau, which is a major component of the neurofibrillary tangle (McCullagh et al., 2001) but studies showed mixed results regarding the effects of aluminum intake, and it is unclear whether an influence exists (Henderson, 1988; Hendrie, 1998; McCullagh et al., 2001). Henderson (1988) analyzed nine studies with regard to AD and parental age. Two of the studies found an increased risk with higher maternal age, and only four studies included paternal age, with no correlation established. Rocca et al. (1991) analyzed four studies with regard to maternal age. Not all the results are significant but they suggest a higher risk associated with late (after age 40) but also with early (before age 19) maternal age. Henderson (1988) did not find a correlation between AD and fertility. Results for thyroid disease are contradictory (Henderson, 1988).

In a recent study caring partners of people with dementia were found to have a six-fold higher risk for incident dementia (Norton et al., 2010). Possible explanations

for this higher risk might be assortative mating, a shared lifestyle, and caregiving stress. However, the question was brought up if dementia was infectious. Although a direct infection is extremely unlikely, common infections could boost the outbreak of AD (Balin and Appelt, 2001).

The amount of literature on possible further risk factors is too vast to include it here. A more detailed description of risk factors for cognitive health is provided, for example, by Hendrie et al. (2006) or the AlzRisk database (Weuve et al., 2008).

2.4.13 Protective Factors

While the amount of literature covering protective factors is small, table 2.8 shows an overview of consistent and less consistent factors (Bundesministerium für Familie, Senioren, Frauen und Jugend, 2002; Hendrie, 1998).

Some studies that have analyzed the negative effect of APOE $\epsilon 4$ extended their research to APOE $\epsilon 3$ and APOE $\epsilon 2$ and found a protective effect, as has been shown in section 2.4.2.

The effect of education was discussed in section 2.4.5. Most recent studies worked out a protective effect of higher education. People with higher education have been shown to have a higher cognitive reserve, and they might also lead healthier lifestyles.

Table 2.8: Protective Factors for Dementia

Protective Factor	Highly Consistent	Somewhat Consistent	Inconsistent	Insufficient Data
ApoE2, ApoE3	x			
Education		x		
Estrogen-Repl.*		x		
NSAIDS**		x		
Antioxidants			x	
Social Contact		°		(x)
Antihypertensiva		°		(x)

* Estrogen-Replacement Therapy

** Nonsteroidal Anti-Inflammatory Agents

° Own Re-Allocation Based on Literature Findings

Source: Bundesministerium für Familie, Senioren, Frauen und Jugend (2002)
Hendrie (1998)

Two medical interventions that might be protective against AD and dementia are estrogen-replacement therapy for postmenopausal women, and the use of nonsteroidal anti-inflammatory agents (NSAIDS). However, the mechanisms behind both interventions are not quite clear, and not all studies confirmed positive effects (see section 2.5.1). Mixed study results on the effect of antioxidants, such as vitamins or omega-3 fatty acids make them inconsistent factors (see section 2.4.6).

Although social contact in this table is allocated to the "insufficient data" column, many study results show a protective effect of marriage and other social engagements e.g., in activities and work (see section 2.4.5). Therefore, a re-allocation into the "somewhat consistent" column is suggested.

Study results on the risk of hypertension on dementia are mixed (see section 2.4.8). However, newer reviews show that a distinction between midlife and late-life hypertension has to be made. Recent studies about the effect of antihypertensive drugs on dementia show positive results (see section 2.4.8, 2.5.1) and therefore, a re-allocation into the "somewhat consistent" column is suggested.

2.5 Medication and Prevention

2.5.1 Medication and Therapy

Up to now no drug exists that can cure dementia. However, some existing drugs can palliate the aetiopathology by about 8 to 12 months (Förstl, 2008; Kurz and Jendroska, 2002).

Currently, two kinds of drugs are approved for treatment of AD. Acetylcholinesterase inhibitors (AChEI) (e.g., donepezil, rivastigmin, galantamin, huperzine A; tacrin is an older drug which is not used anymore due to strong side effects) are designed to inhibit or at least slow the degradation of acetylcholine, one of the most important neurotransmitters. They improve cognition and memory in early and moderate disease stages (Birks, 2006; Black et al., 2007; Mount and Downton, 2006; Münch, 2000b; Roberson and Mucke, 2006; Wang et al., 2009), but they are also used in more severe stages (Korczyn, 2008; Winblad, 2009). It does not seem to improve cognition for patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL), a genetic form of subcortical ischaemic VaD (Dichgans et al., 2008). A second class of drugs, N-methyl-D-aspartate (NMDA) antagonists, were approved in 2002 in Europe and can also be used to treat more severe dementia

cases. The NMDA antagonist memantine prevents over-stimulation of the glutamate (Bischoff et al., 2004; Mount and Downton, 2006; Roberson and Mucke, 2006). Although AChEI and NMDA antagonists are currently the most frequently used drugs, the general efficacy of AChEI after mild to moderate disease stages is not certain. Both drugs have been called into question because they cannot stop the accumulation of Aβ, and therefore the disease progresses (Lemstra et al., 2007; Mount and Downton, 2006). Furthermore, not all people respond to them, and some even experience side effects.

New research concentrates on medication with different mechanisms trying to fight amyloid plaques, neurofibrillary tangles and neuroinflammation. The most promising approaches target the deposition of Aβ: γ secretase-inhibitors try to counteract the cleavage of APP into Aβ_{1-40} and Aβ_{1-42}. And β secretase-inhibitors prevent that Aβ_{1-42} proteins accumulate as plaques (Masters and Beyreuther, 2006; Mount and Downton, 2006; Roberson and Mucke, 2006). In a recent study, Cirrito et al. (2008) were able to decrease this process substantially in a mouse model. If the deposition of Aβ could be reduced in humans, it could provide major insights into therapeutic interventions.

Other kinds of drugs exist that were not initially developed against dementia. Statins were first prescribed to treat high cholesterol levels. Having a high-serum cholesterol concentration and high systolic blood pressure in midlife, and particularly the combination of these risk factors, have been shown to increase the risk of developing AD in later life (Kivipelto et al., 2001). Studies based on this knowledge found that people who take statins (Jick et al., 2000) and antihypertensive medication (Khachaturian et al., 2006) have a lower risk of dementia. The statins delay the progress substantially when taken early during the disease process. A recent review concluded that no effect could be seen and statins cannot therefore be recommended for the prevention of AD (McGuinness and Passmore, 2010).

Section 2.1.2 shortly described how the inflammatory process could be involved in the pathogenesis of AD. Some trials therefore used nonsteroidal anti-inflammatory agents (NSAIDs), such as indomethacin or aspirin. Some protective effects of these drugs have been shown in some studies (Henderson, 1988; Stewart et al., 1997; Zonderman, 2005), but not in all (de Jong et al., 2008; Hanlon et al., 1997; Henderson, 1988; Kang et al., 2007). Newer studies assumed that these drugs have different mechanisms: instead of preventing inflammation, the NSAIDs block the γ-secretase activity, which leads to a reduction of Aβ_{1-42} (Eriksen et al., 2003). Other studies could show that inflammation is also caused by Advanced Glycation Endproducts (AGEs) within

the amyloid plaques. AD patients who are treated with AChEI, as well as with the antioxidant thioctacid, have been shown to have a better cognitive outcome (Münch, 2000a). In a meta-analysis about antioxidants that come from green tea polyphenols, soy isoflavone and nicotine, Zhao (2009) drew positive conclusions, ascribing them preventive and even therapeutic effects. Generally, however, antioxidants vitamins A and C and nootropica such as ginkgo biloba mostly do not have a protective effect, and the results of vitamin E studies remain controversial (Bickel, 2005; Bischoff et al., 2004; DeKosky et al., 2008; Mount and Downton, 2006; Weyerer, 2005).

The effect of estrogen replacement in postmenopausal women also remains unclear (Bickel, 2005; Combarros et al., 2008; Kurz and Jendroska, 2002; Pope et al., 2003). The hormone most likely acts in several ways, and reduces the β-amyloid deposition, improves the cerebral blood flow and suppresses APOE (McCullagh et al., 2001). There is increasing evidence that estrogen-replacement therapy has a protective effect on the onset of cognitive impairment and AD (Henderson, 1988; Kawas et al., 1997; Tan et al., 2005; Waring et al., 1999; Zonderman, 2005), but not all studies confirmed the effect (Petitti et al., 2008). In addition, for males hormone effects were analyzed with contradictory results. A low free testosterone index could increase the risk for AD (Zonderman, 2005), but, while Lu et al. (2006) did not find a significant improvement in cognition for men treated with a testosterone therapy, an overall improvement in quality of life was shown.

Currently several trials with new drugs are conducted of which the results are being awaited. There is not just one mechanism that researchers are trying to stop or even reverse; different kinds of drugs have been developed which concentrate on fighting the β-amyloid plaques and the neurofibrillary tangles. Other trials which are still going on aim directly at the nerve cells and the nerve growth factor (NGF) (Bischoff et al., 2004; Roberson and Mucke, 2006) and are seeking not only to stop the process, but also to stimulate the growth of new nerve cells.

Until recently, the most hopeful research going on in the fight against AD were vaccines which were successfully tested on mice (Brendza et al., 2005; Maier et al., 2006). A first trial on 300 humans was started in 2001 by Elan and Wyeth, with an amyloid vaccine AN-1792 (Gilman et al., 2005). Although the trial had to be stopped after few months because some people had developed meningoencephalitis, the vaccine had reduced Aβ plaques and improved memory significantly (Hyman and Growdon, 2006; Mandavilli, 2006). A new nonviral vaccine has shown positive results on mice

(Okura et al., 2006), but the study on humans failed: it showed a clearance of amyloid plaques but it failed to halt the neurodegeneration (Holmes et al., 2008).

Another backlash against ongoing trials came from a review about 18-month-long phase II and phase III trials for AD drug development, none of which showed significant improvements in patients (Schneider and Sano, 2009).

However, because so many trials are going on that target different brain mechanisms, the outlook for the future is hopeful. Tanzi (2008) provided an overview of promising recent drug developments aimed at treating and preventing AD by targeting the neurotoxic peptide Aβ. Drugs that seek to clear Aβ molecules out of the brain or to block Aβ from forming neurotoxic aggregates include the following: an intravenous IV-IgG injection (Gammargard, Baxter International), Alzhemed (Neurochem), a drug that is taken orally, known as GAG-mimetic, PBT2 (Prana Biotechnology), a "metal protein attenuation compound" (MPAC) that prevents Aβ from aggregating and from forming neurotoxic Aβ oligomers by stripping zinc and copper from Aβ and AZD-103 (Transition Therapeutics) and a compound, known as inositol that is designed to break down Aβ aggregates. Another class of drugs is developed to regulate the generation of Aβ in the brain: LY450139, gamma-secretase inhibitor (Lilly), Flurizan (Myriad), E2012 (Esai) and CTS-21166 (CoMentis) (Tanzi, 2008). He concluded that the outlook for these studies is good to excellent, and that hope exists that at least one of the trials can successfully be finished and used to treat AD. After reviewing drug development trials, Sabbagh (2009) has also come to the positive conclusion that, even within the next decade, treatment of AD will become available.

Further ongoing trials with promising results are from Tobinick and Gross (2008), who showed an improvement of cognitive function in an AD patient after perispinal administration of etanercept, a biologic antagonist of TNF-alpha which is involved in the pathogenesis of AD. Wischik et al. (1988) developed a promising tau-based therapy. In a phase II clinical trial of a disease modifying treatment in 321 patients, the cognitive decline could be stopped (Wischik et al., 2008). Studies carried out on mice also show promising results: Serneels et al. (2009) discovered that deactivating the Aph1B γ-secretase in AD mice led to reduced formation of plaques. From these positive results, new medicines could be developed that reduce this process. Rozkalne et al. (2009) workec out that, after a single dose of anti-Aβ immunotherapy in mice, a lasting benefit to the morphology of cortical neurons occurred, which implies substantial plasticity of neural circuits despite a continued presence of plaques. The development of amyloid-lowering therapies for treatment of AD has been suggested by Wilcock et al. (2009). An

amyloid-β vaccination not only reduced amyloid pathology but also blocked nonmutant tau pathology and neuron loss. Crouch et al. (2009) demonstrated that an increasing intracellular copper bioavailability can restore cognitive function in mice by inhibiting the accumulation of neurotoxic Aβ trimers and phosphorylated tau. Schilling et al. (2008) succeeded in reducing pyroglutamate Aβ by inhibiting glutaminyl cyclase.

The treatment of dementia patients also includes the non-cognitive symptoms, such as depression, aggressiveness, agitation, delusions or hallucinations. A huge problem is that the patients often can no longer express their pain (Kurz and Jendroska, 2002). Due to the diversity of the existing drugs some countries have developed treatment guidelines. In Germany, for example, guidelines have been issued by the German Association for Gerontopsychiatry and -psychotherapy (DGGPP) (Deutsche Gesellschaft für Gerontopsychiatrie und –psychotherapie (DGGPP) und Bundesverband Deutscher Nervenärzte (BVDN), 2000). Meanwhile, in the UK, the National Institute for Health and Clinical Excellence and Social Care Institute for Excellence have developed the NICE guidelines.

So far, only medication has been described. However, many other interventions designed to improve the environment and the quality of life of demented people have been developed. Non-medicative cognitive interventions, such as psychological competence training, or painting, dancing or music therapies, are important forms of interaction that can help people with dementia and their carers, even in advanced disease stages (Buschert et al., 2009; Kurz and Jendroska, 2002; Weyerer, 2005).

In conclusion, we can assume that no single class of compound or single mechanism of action will be sufficient to treat this complex illness; instead, a combination of drugs and therapies targeting various aspects will evolve into some form of rational therapy (Kurz and Jendroska, 2002; Masters and Beyreuther, 2006; Roberson and Mucke, 2006).

2.5.2 Prevention

The previous sections explained that dementia is not a single disease with a straightforward solution, and so far not even the mechanisms leading to AD and some other dementias are fully understood. However, research about dementia has increased tremendously in recent decades, and little by little details are revealed which slowly seem to complete the puzzle. This led many studies to a positive conclusion about future developments. Somewhat ambitiously, a "roadmap for the prevention of dementia" has

even been drawn up by Khachaturian et al. (2008), which leads to a plan to "prevent Alzheimer's disease by 2020" (Khachaturian and Khachaturian, 2009; Khachaturian et al., 2009). It is a call for thinking "outside the box" (Khachaturian et al., 2008), and the need to rethink and radically change current paradigms for drug discovery and development of therapy. The meetings summarized the current knowledge about dementia, and researchers developed new ideas to enhance research and set the roadmap for the prevention of the disease: drug developments not only for the treatment, but even more for the prevention of the disease, have to be developed. New therapeutic targets must be discovered, scientific barriers must be identified and surmounted and new technologies are in development. Moreover, societal and cultural barriers need to be overcome (Khachaturian and Khachaturian, 2009; Khachaturian et al., 2008, 2009).

Just recently, a special issue of the *Journal of Alzheimer's Disease* was dedicated to the prevention of AD. Also from these articles an overall hopeful conclusion was drawn that prevention is possible: "Despite the glacial pace of clinical progress over the last 100 years, it is encouraging that our present knowledge of AD risk factors offers fertile avenues of exploration that can focus on significant interventions to help delay or prevent the onset of dementia" (de la Torre, 2010b).

The previous section 2.5.1 showed that no drug capable of stopping or reversing AD is on the market, yet, but many trials with different goals are ongoing. Although some of them have failed, many have been producing promising results and reviews. In the end, there are reasons to be optimistic that helpful drugs will soon be found (Sabbagh, 2009; Tanzi and Bertram, 2008). Furthermore, many medical interventions are being developed, such as brain insulin receptors, statin therapy, dietary interventions, and lowering of serum homocysteine (Gorelick, 2004).

Further hope comes from studies which look at risk factors that can be influenced. There are various potentially treatable risk factors, and studies have concluded that, in general, the fight against the risk factors that can be influenced also should lead to a prevention or delay of dementia (Flicker, 2010; Jorm, 1995; Lautenschlager, 2002). In particular, the risk factors for VaD are treatable, such as hypertension, smoking, alcohol abuse, diabetes, stroke, serum cholesterol and lifestyle. Some studies have already confirmed that treatment of hypertension has reduced the risk of dementia (Forette et al., 1998; Gorelick, 2004; Kang et al., 2007; Kivipelto et al., 2001; Patterson et al., 2007a; World Health Organization, 2006b). Lifestyle factors play an important role in the prevention discussion. They seem to influence the dementia risk directly, as well as indirectly via their effect on other diseases, which in turn influence the dementia risk (see

also sections 2.4.5 to 2.4.12). A healthy lifestyle comprises healthy nutrition, physical and mental activity, moderate alcohol consumption and no smoking. Many studies assumed a preventive effect of a healthy lifestyle (Depp et al., 2007; Kornhuber, 2004). An additional factor for maintaining optimal cognitive function is the participation in a social network (Barnes et al., 2007).

Not all studies shared this level of optimism. The mere presence of a potentially treatable risk factor might not imply that a change in that factor would lead to an equal change in dementia risk. Randomized controlled studies are needed to study the effects (Patterson et al., 2007b). Furthermore, Brayne et al. (2006) concluded that reducing the risk for dementia at a given age is connected with an increasing life expectancy, and thus that the cumulative risk remains high.

To prevent a disease early on, detection of it is very important. The early stages may be the optimal time for interventions that have the potential to slow or even stop the AD process (Morris, 2006; Nitrini, 2005). Many studies on mild cognitive impairment (MCI) came to the conclusion that it is a pre-state of AD (Bennett et al., 2005; Morris, 2006; Tyas et al., 2007). Therefore, many recent studies have concentrated on these changes from normal cognitive functioning to MCI (Tyas et al., 2007). But, even before the onset of MCI, structural brain changes appear. In some patients who eventually developed MCI, decreased grey matter volume was found while they were still cognitively normal (Smith et al., 2007). Early screening with revised criteria could make it possible to diagnose the disease in an early state or even before the onset.

Age still remains the biggest risk factor for a dementia, and given the aging of the population, it can be expected that the number of patients who develop dementia will grow if no prevention or cure is found. But many factors offer hope that dementia can be treated or even prevented: earlier detection is possible, many drug trials are ongoing, and several diseases and lifestyle factors exist that can be influenced with a healthy lifestyle. The optimistic goals set by several dementia researchers may seem challenging but the factors mentioned above give hope that it can be achieved, if not by 2020, then soon thereafter (Khachaturian and Khachaturian, 2009).

2.6 Conclusion and Research Questions

The last chapter provided a literature overview of the epidemiology of dementia, risk factors of the disease, trends over time and medical interventions.

Many problems still have to be overcome in order to provide reliable research results regarding the occurrence and determinants of dementia and trends over time. Varying definitions and measurement scales of dementia exist. However, in recent years, some common measurements which will increase the comparability of the studies have been agreed upon. Previously, preference has been given to prevalence studies, but in recent years the number of incidence studies has been rising. The importance of incidence data that excludes the effect of different mortality and survival with the disease has been acknowledged. An expensive and time-consuming longitudinal study design will be necessary to collect incidence data. Most newer studies showed remarkably similar prevalence and incidence rates of dementia across different regions of the world. When results deviated, methodological problems, rather than real effects, were often mentioned.

Despite an increasing awareness of the disease and the greater resources devoted to research, knowledge of the risk factors for dementing illnesses is still rather rudimentary. Since Jorm (1995) made this observation, the number of studies on dementia risk factors has increased even more. Nonetheless, the number of highly consistent risk factors that has been identified remains limited. Age is universally recognized as the biggest risk factor. After age 65, the prevalence of dementia doubles about every five to six years. Other factors have also been established, such as family history or carrying the APOE $\epsilon 4$ allele. But other than these factors, which cannot be influenced, several risk factors have been proposed that are not yet fixed. A number of lifestyle variables have been shown to be somewhat consistent in causing a higher risk of dementia. Generally, we can conclude that a moderate lifestyle offers some protection against dementia. People "who remain socially and physically active, involved, and intellectually curious have a lower risk for developing AD. Apathy, however, is a common very early symptom of AD, occurring before the onset of memory loss..." (Hendrie, 1998). It is also known that having certain diseases increases the risk of dementia. These diseases are often associated with an unhealthy lifestyle (but also with genetic causes), such as diabetes mellitus or hypertension. A problem that arises when seeking confirmation of risk factors is that the strong association between cognitive decline and mortality limits the ability to identify risk factors for cognitive decline in old age. This is due to the interaction of factors contributing to cognitive decline and death (Wilson et al., 2003). Another problem is that studies often only look at single risk factors, and only few investigate the interaction between them. The outcome of single factors on dementia could be different when other factors are present, and thus it is important to look at and control

for as many risk factors as possible at the same time. Often it is difficult to extend the study design due to time and cost restraints. Another drawback of many studies is that they do not include people living in institutions. The institutionalized population has a higher prevalence and a higher level of severity of dementia. They are also likely to be different in terms of co-morbidity and other possible risk factors. Further research is needed to disentangle the effect of interacting risk factors of dementia, and interacting factors contributing to cognitive decline and death.

Despite the mixed results in trend studies, epidemiological reviews often take a positive view of the future. This confidence is based on the advancements in medical progress and treatment that have occurred in recent decades, and the hope for further progress. Furthermore, the expansion of education since the 1960s might lead to higher cognitive reserves in future elderly people. The higher reserve could enable an individual with high premorbid intelligence to "sustain greater cognitive loss before reaching the threshold for interference with everyday functioning" (Jorm, 1995).

Additional research with longitudinal design and larger samples, especially for the very old ages, is needed in order to investigate the trends for dementia, AD and VaD, and to identify other treatable risk factors for the disease.

Research Question

From these literature findings, several research questions arise which we will look at in more detail in the next chapters. First, the insufficient data situation in Germany will be addressed. Prevalence and incidence of dementia by age, gender and region are calculated in chapter 3 using a large sample from the German sickness funds. In the next chapter 4, the co-morbidity of dementia patients is analyzed. The literature findings are inconclusive if co-morbidity is higher or lower in dementia patients. Here we include not just diseases that have already been explored in the literature, but all possible ICD-10 (three-digit-codes) diagnoses. Chapter 5 follows the question about further determinants of dementia and severe cognitive impairment. What other factors are there that act on the disease, and which of these can be influenced? With a large European dataset, several socio-demographic variables, including living conditions and physical and mental health, are investigated. Finally, chapters 6 and 7 look at the future: How is the number of people with dementia and the associated costs going to develop? Given the aging of the population, the most important question that arises is the following: Will the total number of people rise in line with the increase in the number of elderly, or can some factors be influenced in order to minimize age-

specific incidence and prevalence? The results from the previous chapters are used to calculate projections and to make assumptions about different models with changing life expectancy and changing dementia incidence. Chapter 7 points to another important challenge for the society: How are the costs of one of the most expensive diseases going to develop? Here, not only the changing number of people with the disease, but also changing societal background and medical expenses have to be taken into account.

Chapter 3

Dementia in Germany—Based on Data from the German Sickness Funds in 2002 (GKV Data)

3.1 Data and Method

3.1.1 Data

In 2007, data from the public sickness funds on more than two million people (Stichprobendaten von Versicherten der gesetzlichen Krankenversicherung nach §268 SGB V, (Lugert, 2007)) were made available for open research by the Forschungsdatenzentren der Statistischen Ämter des Bundes und der Länder (Research Centers of the German Statistical Offices). It is possible to analyze the complete medical ambulatory and stationary treatment during the year 2002, including diagnoses, costs and pharmaceutical prescriptions by age, sex and region. This unique dataset was drawn from more than 350 sickness funds, 23 regional associations of statutory health insurance physicians (Kassenärztlichen Vereinigungen (KV)), the German Federal (Social) Insurance Authority (Bundesversicherungsamt (BVA)), the National Provider of Social Security Services (Bundesversicherungsanstalt für Angestellte (BfA)) and the German Institute of Medical Documentation and Information (Deutsches Institut für medizinische Dokumentation und Information (DIMDI)) (translations used from: Kassenärztliche Bundesvereinigung (2007)). The 3% random sample is based on a birthday sample. Every person born on the 11^{th} day of any of the 12-month period is included in the data.

In general, this data mirrors the characteristics of the total German population

very well. There are 2,301,015 people in the sample: 1,226,736 females (53.3%) and 1,074,279 males (46.7%). Of the total German population, 51.1% were women and 48.9% were men on December 31st , 2002. To reflect the 18.2% of the German population who live in the Eastern part, and the 81.8% who live in the Western part (Human Mortality Database, 2008) of the country, our sample includes 413,233 people from East Germany (18.0%) and 1,887,782 (82.0%) from West Germany. The death probability is slightly higher, or 1.14% in the data, compared with 1.02% in the total population. The differences between the data and the total population can be ascribed to the different age profiles of people insured in public and in private sickness funds. People in private sickness funds are, on average, younger (Niehaus, 2006). The age structure in our sample is slightly older than in the total population, e.g., 24.0% of the total population were older than age 60 in 2002, as are 25.0% of the people in our data. Just 320 people in the data are aged 100 or above, or 0.014%, while in the total population the proportion of people aged 100+ is 0.008% (Human Mortality Database, 2008). Therefore, our data comprises more women and more death occurrences.

Of the total German population, 70.7 million people, or about 86% of the population, were insured by public sickness funds in 2002. A further 8.0 million people, or nearly 10% of population, were privately insured. Of the remaining 4%, most were eligible for benefits because they were on welfare ('anspruchsberechtigt als Sozialhilfeempfänger'), and some were covered as members of the police forces, the German Federal Armed Forces, or alternative civilian services (Freie Heilfürsorge der Polizei, Bundeswehr und Zivildienstleistenden). Only about 188,000 people (0.23%) were not insured in 2003 (Statistisches Bundesamt & Robert Koch Institut, 2007), primarily because their income was above the assessable income limit (Beitragsbemessungsgrenze) beyond which people can choose their insurance mode (Wahner-Roedler et al., 1997).

3.1.2 Method

Diagnoses in the data are encoded on the 'International Classification of Diseases and Related Health Problems', 10th Revision (World Health Organization, 2006a). Dementia was measured here when any of the following diagnoses were asserted:

- `F00` Dementia in Alzheimer's disease
- `F01` Vascular dementia
- `F02` Dementia in other diseases classified elsewhere
- `F03` Unspecified dementia
- `G30` Alzheimer's disease

In addition to all dementia types, two major subtypes were taken into account separately: AD with the ICD-10 codes F00, or G30 and VaD with code F01. Further differentiation, e.g., between dementia accompanied with morbus Pick F02.0 or with Creutzfeldt-Jakob Disease, F02.1 was not possible because only three-digit ICD codes are given. Furthermore, the small sample sizes of these minor subtypes and the classification accuracy of general practitioners might make analysis of these subtypes imprecise. Some 58% of new cases were diagnosed by general practitioners.

All people who had a diagnosis (ambulatory or in-patient) of dementia in the year 2002 were counted as prevalence cases. In a comparative analysis (not shown), 'unstable' cases—defined as cases that are coded as demented in one quarter, but not in the following quarters (and also did not die)—were excluded from the prevalence rate. The effect of this consistent coding problem is small and can therefore be neglected. The effect of under-acquisition of mild dementia cases is probably larger.

The incidence was slightly more difficult to assess. Although the data refer only to one year, 2002, the ambulant diagnoses can be distinguished by quarters. (The in-patient diagnoses are reported for the whole year, but since dementia is not an acute state, the diagnosing is most probably done ambulantly by the general practitioner. Of the new dementia cases, 58% were diagnosed by a general practitioner, and a further 17% and 14% of the diagnoses were made by specialists for mental disorders or internists). Thus, in a next step incidence rates of dementia were calculated. In the ideal case, the dementia status for every person for every quarter of the year 2002 should be known. Only people without the disease are exposed to the risk of an incidence of dementia. The prevalent cases in quarter 1 were removed from this analysis. The incidence rate of the healthy people consequently results from people who develop dementia in the following quarters 2, 3 or 4. We assumed that a person who has dementia goes to the doctor regularly and therefore gets a record every quarter (otherwise we could miss prevalent cases in quarter 1, and count them as incidence in the next quarters). Schubert et al. (2007) found that, on average, dementia patients had 11 additional doctor visits. Eisele et al. (2010) confirmed a considerable increase in utilization of ambulatory medical services by patients before, during and after the diagnosis of dementia in Germany. Hallauer et al. (2000) also found a higher frequency of consultations, according to different states of AD: results showed about 14 doctor contacts on average for people with an MMSE between 10 and 26. Severe cases with an MMSE below 10 have only five doctor contacts per year. This is still more frequent than once a quarter, and thus these results support the assumption that incidence rates can be calculated from the data. In

reality, this might not be true, and we do not only count true incidence cases. Not all people will go to the doctor every quarter, and we could count a prevalence case from quarter 1 who was coded '0' because he did not go to the doctor as an incidence case in quarter 2. Over-reporting might also occur because of misdiagnosis. For example, because in the early stages the disease is hard to distinguish from other mental illnesses, a person coded as demented in quarter 2 may no longer be diagnosed as demented in quarter 3.

In an effort to overcome these problems, we have only measured 'stable' cases. Only incidence cases for the quarters 2 or 3 who also had the diagnosis in the following quarters (but also if they died) are counted (the code can be found in the appendix, code 8). These half-year incidence cases were adjusted for the whole year in order to calculate a one-year incidence rate.

3.2 Prevalence of Dementia Based on GKV Data

3.2.1 Dementia Prevalence by Age

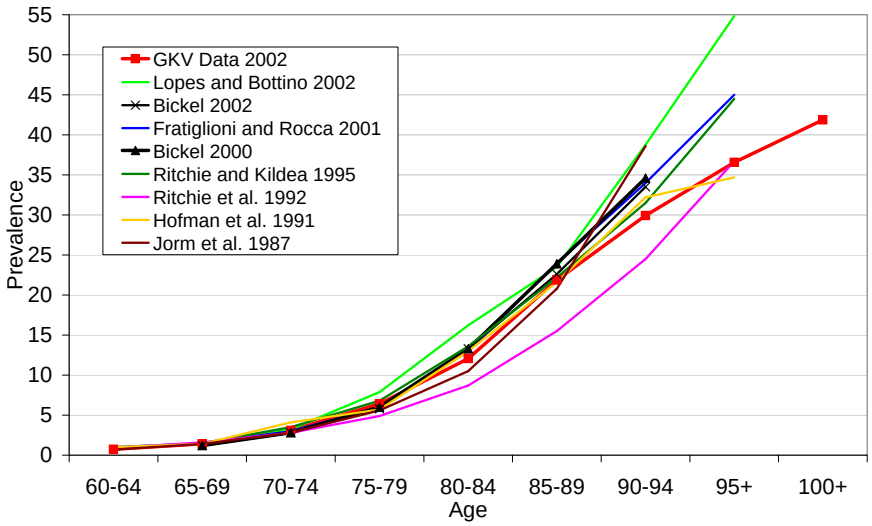
Of all the people in the sample, 1.43% had some kind of dementia. Above age 60 (65) a prevalence of 5.28% (6.96%) is seen, which is in accordance with Bickel (2000), who concluded that, on average, 7.2% (6% to 8.8%) of the population above age 65 are affected. Our age-specific results are similar compared with the results of international meta-analyses discussed in chapter 2.5. The prevalence is in the middle of these international results, as is shown in figure 3.1 (red line with boxes). The results are very close to the rates Bickel (2000) and Bickel (2002) found when he calculated the mean of meta-analyses (black line with triangles and black line with crosses).

The size of the data-set allows for an extension of the highest age group to 100+. A slowing of the increase in the prevalence rate could be seen, but no leveling off could be detected (see discussion of an age/aging effect in section 2.4.1). When the age group 105+ was analyzed as an extra category, the rate dropped from 43% for the age group 100-104 to 27% for the age group 105+. However, only 15 cases were included in the highest age group.

3.2.2 Dementia Prevalence by Age and Gender

Differentiated by gender, we found a much larger prevalence for women, at 1.91%, than for men, at 0.88%. Above age 65, the prevalence increased to 8.26% for women and

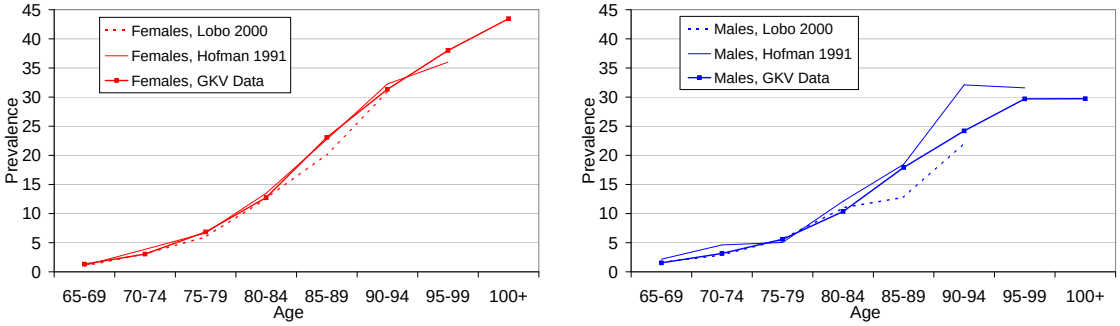
Figure 3.1: Prevalence of Dementia in International Meta-Analyses and in Germany above Age 60



Source: Different

4.82% for men. As can be seen in figure 3.2, age-specific prevalence rates correspond well with data from, for example, Lobo et al. (2000) (until age 90+) or Hofman et al. (1991) (until age 95+). Hofman et al. (1991) found only a small increase in the prevalence for males from ages 90-94 to 95+. In the GKV data the prevalence for males at age group 95-99 is 30% and does not increase at ages 100+. For women, there is, however, a further increase to 43%. The differences are significant from age 75 onwards as table 3.1 shows.

Figure 3.2: Prevalence of Dementia in International Meta-Analyses and in Germany by Age (65+) and Gender



Source: Hofman et al. (1991); Lobo et al. (2000), GKV Data, own calculations

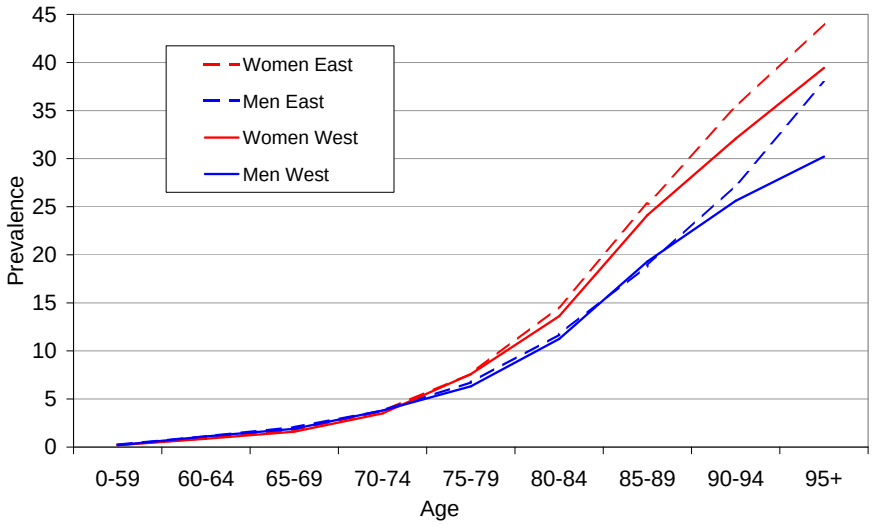
Table 3.1: Prevalence of Dementia in Germany by Age (60+) and Gender, and Confidence Intervals, GKV Data 2002

	Females		Males	
Age	Prevalence	CI	Prevalence	CI
60-64	0.6	[0.6-0.7]	0.8	[0.8-0.9]
65-69	1.3	[1.2-1.4]	1.5	[1.4-1.6]
70-74	3.1	[2.9-3.2]	3.2	[3.0-3.3]
75-79	6.8	[6.6-7.1]	5.6	[5.3-5.9]
80-84	12.8	[12.4-13.1]	10.3	[9.9-10.8]
85-89	23.1	[22.4-23.7]	17.9	[16.9-18.9]
90-94	31.3	[30.4-32.3]	24.2	[22.5-25.9]
95+	38.0	[35.7-40.4]	29.7	[25.2-34.2]

3.2.3 Dementia Prevalence by Age, Gender and Region

Below age 80, the rates are similar in West and East Germany. Differences can be found above age 80. Higher rates exist in East Germany for both sexes, especially above age 90. However, although the regional differences are not significant, the gender difference is more pronounced, as can be seen in figure 3.3.

Figure 3.3: Prevalence of Dementia in Germany by Age, Gender and Region



Source: GKV Data, own calculations

Table 3.2: Prevalence of Dementia in Germany by Age (60+), Gender and Region, and Confidence Intervals, GKV Data 2002

	West Germany		East Germany	
Age	Prevalence	CI	Prevalence	CI
Females				
60-64	0.6	[0.6-0.7]	0.6	[0.5-0.8]
65-69	1.3	[1.2-1.4]	1.4	[1.2-1.5]
70-74	3.0	[2.9-3.2]	3.1	[2.8-3.4]
75-79	6.9	[6.6-7.1]	6.8	[6.3-7.3]
80-84	12.6	[12.3-13.0]	13.2	[12.4-14.0]
85-89	22.9	[22.2-23.6]	23.9	[22.4-25.5]
90-94	30.7	[29.7-31.8]	34.1	[31.7-36.5]
95+	37.7	[35.3-40.2]	42.6	[36.8-48.4]
Males				
60-64	0.8	[0.8-0.9]	0.8	[0.7-1.0]
65-69	1.5	[1.4-1.6]	1.6	[1.3-1.8]
70-74	3.2	[3.0-3.4]	3.0	[2.7-3.4]
75-79	5.6	[5.3-5.9]	5.5	[4.9-6.2]
80-84	10.3	[9.8-10.9]	10.4	[9.2-11.5]
85-89	18.0	[16.9-19.2]	17.3	[14.9-19.7]
90-94	24.0	[22.1-25.9]	25.0	[21.0-29.1]
95+	28.3	[23.6-33.1]	35.3	[24.5-46.2]

3.2.4 The Number of Demented People in Germany in 2009

When the age-specific prevalence rates are multiplied by the number of people in the corresponding age groups, the sum of these age-specific numbers of demented people gives the total number of demented people. Since we do not only have age-specific prevalence rates, but also further differentiation by gender and region, we multiplied these rates with gender- and region-specific population data from the Human Mortality Database for the year 2009 (Human Mortality Database, 2008). Although the age structure of people in the GKV data is slightly older than in the total population, we nevertheless took the age structure of the total population into account because we did not assume different prevalence rates between people insured in the public sickness funds and those insured privately. The age profile is slightly older in East Germany: 30.8% of the East German women are older than age 59, compared with 27.5% of the West German women, while for males the difference in the percentages above the age of 59 is smaller, at 23.7% in the East and 22.5% in the West. Because there are many more elderly women, the number of affected women is also much higher. Using our method, we found that a total of 1.12 million demented people above age 60 lived in Germany in 2009. Of these, about 595,000 were women in West Germany, 169,000 were women in East Germany, 288,000 were men in West Germany, and 71,000 were men in East Germany.

Table 3.3: People with Dementia in Germany in 2009 by Age (60+), Gender and Region (in 1000)

	West Germany		East Germany		
Age	Females	Males	Females	Males	
60-64	11	14	3	3	
65-69	27	29	8	9	
70-74	57	52	17	14	
75-79	92	56	26	15	
80-84	147	67	41	15	
85-89	173	51	46	10	
90-94	58	13	18	3	
95+	30	5	10	1	
60+	595	288	169	71	
Total 60+					1,123

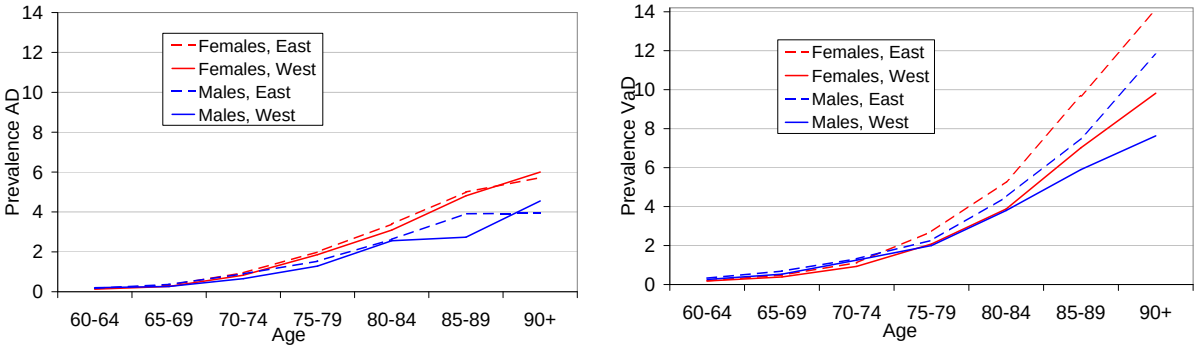
3.2.5 Alzheimer's Disease

Although the literature confirmed that AD is the most prevalent form of dementia, this fact is not reflected in the data, where only 23.2% of all dementias were coded as AD. This is most probably a diagnosis problem, which will be discussed at the end of the section. The age-specific prevalence for AD is low in our data, and probably does not show the real prevalence. While the split by gender and region shows the expected higher prevalence among women, it does not seem to differ between the regions and even shows a tendency towards lower rates in East Germany (see left figure 3.4, results are not significantly different).

3.2.6 Vascular Dementia

Nearly one-third, or 32.2%, of all dementia cases are coded as VaD. The results show a slower increase in the prevalence with age than for general dementia. Gender differences occur only after age 80, where prevalences for women increase more strongly than for men. They are higher in East Germany than in West Germany. Particularly interesting is the apparent interaction of gender and region: for AD and for dementia in general, gender was shown to be the more important determinant in old age, as a higher incidence was found among women, while for VaD it is the region that has the stronger influence. East German women have the highest prevalence, followed by East German men and West German women. In the highest age group, 90+, East German women have nearly a two-fold prevalence relative to West German men (14.1% and 7.6%), as can be seen in figure 3.4. Results are significantly different for females above age 75 and for males above age 90 (not shown).

Figure 3.4: Prevalence of Alzheimer's Disease and Vascular Dementia in Germany by Age, Gender and Region



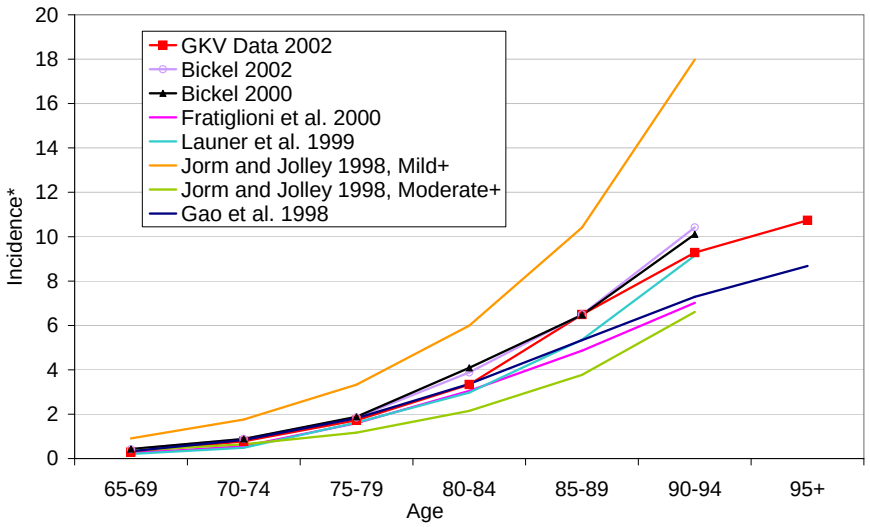
Source: GKV Data, own calculations

3.3 Incidence of Dementia Based on GKV Data

3.3.1 Dementia Incidence by Age

The incidence rate in comparison with meta-analyses is shown in figure 3.5. The rates from the meta-analyses correspond quite well (see section 2.2.2); only the rates from Jorm and Jolley (1998) mild+ for Europe have a steeper increase with age than other studies, largely because mild cases that are measured with different scales are also included.

Figure 3.5: Incidence of Dementia in Germany in Comparison with Meta-Studies



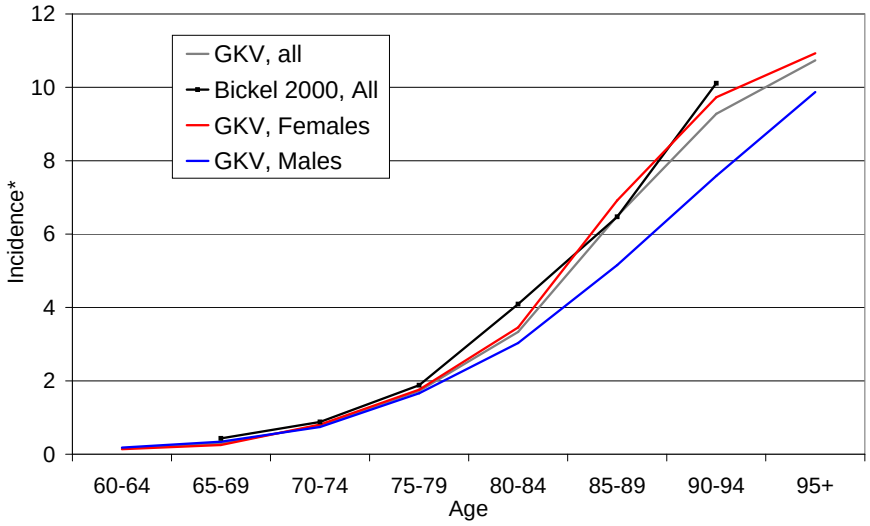
Source: Different

*There is no consistent use of "incidence per 100 person-years" and incidence in percent in the meta-analyses. Results from the GKV data show rates per 100 person-years. See also figure 2.2.

3.3.2 Dementia Incidence by Age and Gender

Figure 3.6 and table 3.4 show gender-specific incidence rates for Germany. Gender differences also show a higher incidence for women, or 1.63 per 100 person-years, compared with 0.93 per 100 person-years for men. The higher prevalence thus does not only result from a lower mortality with the disease, but also from a higher risk of developing a dementia. Table 3.4 shows that the results are not significantly different except for ages 85 to 89.

Figure 3.6: Incidence of Dementia in Germany in Comparison with Bickel (2000) and Additionally Separated by Gender



Source: Bickel (2000), GKV Data, own calculations

* Bickel (2000) shows incidence in percent, the rates from the GKV Data are per 100 person-years. When percent is calculated with GKV Data (not shown), only above age 85 is a very slightly lower rate seen.

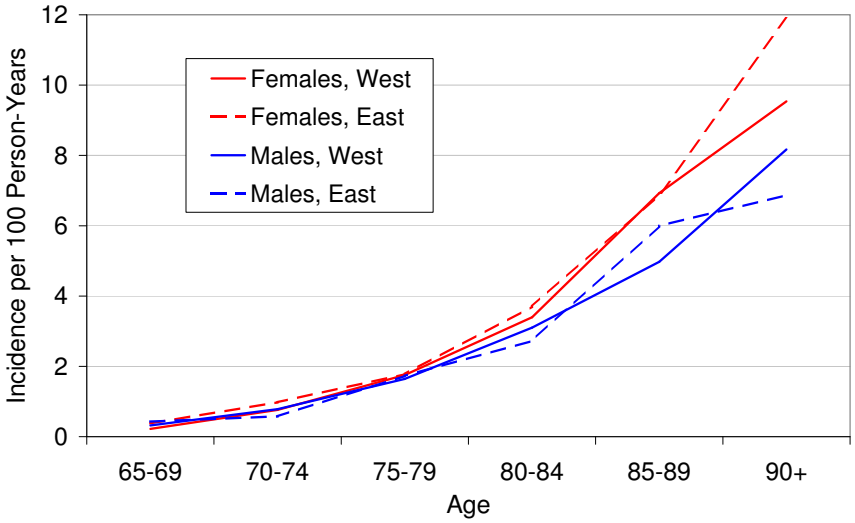
Table 3.4: Incidence Rates of Dementia in Germany by Age (60+) and Gender, and Confidence Intervals, GKV Data 2002

	Females		Males	
Age	Incidence	CI	Incidence	CI
60-64	0.14	[0.10-0.17]	0.18	[0.14-0.23]
65-69	0.25	[0.20-0.30]	0.34	[0.28-0.41]
70-74	0.81	[0.70-0.91]	0.74	[0.63-0.86]
75-79	1.76	[1.60-1.92]	1.66	[1.44-1.87]
80-84	3.46	[3.19-3.72]	3.03	[2.64-3.42]
85-89	6.92	[6.37-7.47]	5.16	[4.32-5.99]
90-94	9.73	[8.85-10.61]	7.59	[6.08-9.09]
95+	10.93	[8.91-12.94]	9.87	[5.84-13.91]

3.3.3 Dementia Incidence by Age, Gender and Region

In figure 3.7 and table 3.5 the incidence rates, additionally separated by region, can be seen. Above age 80, the higher prevalence of dementia for East Germans is also reflected in higher incidence rates. Only East German men above age 90 do not show an additional increase relative to the age group 85-89, and they are even seen to have a lower incidence than West German men above age 90. Due to small case numbers, it was not possible to split incidence into age groups higher than 90+. Confidence intervals show that the differences between East and West Germany are not significant.

Figure 3.7: Incidence of Dementia in Germany by Age, Gender and Region



Source: GKV Data, own calculations

Table 3.5: Incidence of Dementia in Germany by Age (65+), Gender and Region, and Confidence Intervals, GKV Data 2002

	West Germany		East Germany	
Age	Prevalence	CI	Prevalence	CI
Females				
65-69	0.22	[0.17-0.27]	0.38	[0.24-0.52]
70-74	0.76	[0.65-0.88]	0.98	[0.73-1.23]
75-79	1.75	[1.57-1.94]	1.78	[1.41-2.15]
80-84	3.40	[3.11-3.69]	3.70	[3.07-4.34]
85-89	6.93	[6.32-7.53]	6.88	[5.58-8.19]
90+	9.54	[8.67-10.40]	11.90	[9.77-14.03]
Males				
65-69	0.32	[0.25-0.39]	0.43	[0.27-0.59]
70-74	0.78	[0.65-0.92]	0.58	[0.36-0.80]
75-79	1.64	[1.41-1.88]	1.73	[1.22-2.24]
80-84	3.10	[2.66-3.54]	2.73	[1.87-3.58]
85-89	4.97	[4.06-5.88]	5.99	[3.85-8.14]
90+	8.17	[6.58-9.76]	6.87	[3.78-9.96]

3.3.4 The Number of New Dementia Patients in Germany in 2009

Table 3.6 shows the number of incident cases for the year 2009 (when the rates from 2002 are applied for 2009). About 263,100 people above age 60 developed the disease in that year, or 277,500 in the total population. Due to the age structure, many more women are affected. Incidence before age 60 is rare; only pre-senile dementia cases occur before age 60. When our result was multiplied with the according population, we still found that about 14,400 people in 2009 were diagnosed with the disease (not shown).

Table 3.6: Number of People (in 1,000) with Incident Dementia in Germany in 2009 by Age (60+) and Gender

	West Germany		East Germany		
Age	Females	Males	Females	Males	
60-64*	2.4	3.0	0.6	0.7	
65-69	4.5	6.0	2.3	2.4	
70-74	13.9	12.3	5.3	2.6	
75-79	22.0	15.6	6.4	4.3	
80-84	34.5	18.0	9.9	3.5	
85-89	40.4	11.6	10.2	3.0	
90-94	17.1	4.3	5.6	0.8	
60+	134.8	70.8	40.2	17.3	
Total 60+					263.1

*For ages 60-64 incidence rates for total Germany are used.

3.4 Conclusion

The research centers of the Statistical Offices Germany provide a unique dataset for analyzing dementia in Germany. So far, all studies for Germany and most studies worldwide have used much smaller samples than this dataset provides. Furthermore, most calculations about dementia prevalences worldwide rely on meta-analyses or small-scale studies. For Germany, so far calculations were done with mean rates of meta-analysis. This is now the first study based on a large German dataset that shows new information on age-specific prevalence and incidence rates for dementia for the year 2002. The results distinguish from the mean rates from meta-analysis from Bickel

(2000, 2002) insofar, as not only rates into highest ages up to age-group 100+ were calculated, but they were additionally separated by gender and region.

Age is the biggest risk factor for developing a dementia (see section 2.4.1). The prevalence in our data increases from below 1% at ages 60-64 to 42% at ages 100+. The incidence rises from 0.16% at ages 60-64 to about 10.7% at ages 95+. From age 60, the prevalence doubles about every five years until about age 85; thereafter, the intervals at which doubling occurs become longer. Rates from meta-studies and mean rates from meta-studies are very much in line with our results.

Pre-senile dementia before age 60 or 65 is rare. For Germany, the prevalence is estimated at about 20,000 people under age 65 (Bickel, 2002). Our results show slightly higher rates (not shown), with the incidence rate indicating that about 21,000 new patients under age 65 would have been diagnosed in 2009. A different age structure in 2009 compared with Bickel (2002) could result in more cases. Younger patients (<65) also have a much higher mortality than older patients, relative to non-demented people of the same age, which would lead to fewer differences between prevalence and incidence. However, our prevalence rate also leads to higher numbers of affected pre-senile people.

Older studies often suppose an exponential increase after age 60 or 65. In recent years, as the number of studies has increased and data on higher ages have become more reliable, this assumption is being questioned, and a debate about this issue, ignited by Ritchie and Kildea (1995b) has been taking place (see section 2.4.1). Most newer epidemiological articles have concluded that an exponential increase is unlikely (Bickel, 2002, 2003, 2005; Dewey and Saz, 2001), because otherwise a prevalence of 100% before the age of 100 would occur, which is empirically not confirmed. A number of German studies has found a slowing of the increase in higher age groups (Kliegel et al., 2004; Riedel-Heller et al., 2001b; Wernicke and Reischies, 1994), but not all (Fichter et al., 1995; von Strauss et al., 1999). Most incidence studies do not provide a reliable basis for answering this question, because the highest age group often is 90+, which is not sufficient for assessing a leveling off. Most studies, including incidence studies, have concluded that the age-aging question ultimately cannot be solved because of contradictory results and methodological problems, especially because of the small sample sizes and the difficulties in assessing people in the highest age groups (Bickel, 2003; Fratiglioni et al., 1999; Hendrie, 1998). Our results show a prevalence of 43% for people aged 100 years and older. When the age group 105+ is analyzed as an extra category, a drop in the rate from 43% for age group 100 to 104 to 27% can even be seen. The results have to be interpreted with caution because the sample size of the population

105+ is small (15 people, and four are diagnosed with dementia). However, it shows that the risk does not seem to be inevitable, not all people in the highest age groups develop the disease. Also most other studies do not reach prevalences of 100% in the highest age groups. In addition, the increase in the incidence rates, which until age 85 is exponential, slows down after that age. Nevertheless, it is often assumed that aging processes are so instrumental in developing dementia that nearly everybody would get the disease if he or she became old enough (Bickel, 2003, 2005). For the future, however, there is hope that higher education and a healthier lifestyle can preserve cognitive reserves that help to postpone dementia into higher ages.

The mean rate of dementia incidence calculated from meta-studies (Bickel, 2000, 2002) comes closest to our result. However, there could be a bias in the mean rate regarding the choice of included studies, methodology, etc. The fact that our results are a little lower could be a trend effect: our data are from the year 2002, while data from the studies used for the mean rate are from 1991-93 (Bickel, 1996), 1966-1997 (Gao et al., 1998; Jorm and Jolley, 1998), 1988-1996 (Launer et al., 1999) for the mean rate from Bickel (2000), and from Bickel (2002) additionally from 1988-91 (Letenneur et al., 1994), 1980s-1990s (Hebert et al., 1995), 1991-96 (The Canadian Study of Health and Aging Working Group, 2000), 1980s-1990s (Fratiglioni et al., 2000), 1992-95 (Di Carlo et al., 2002), 1997-99 (Riedel-Heller et al., 2001a). Thus, our results could reflect a decrease in the incidence over time. However, the slight divergence could also be due to measurement differences. To measure real incidence changes over time, a longitudinal study is more adequate (see section 2.3).

Applying our rates to the German population, there were about 1.12 million people with dementia in 2009, and about 277,000 new cases occurred within this year. The risk to have and to get a dementia increases with age, and it is higher for women than for men. Up to now, no study has calculated different rates for West and East Germany. We find that of the 1.12 million demented people above age 60, there were about 595,000 women in West Germany, 169,000 women in East Germany, 288,000 men in West Germany and 71,000 men in East Germany. Of the new cases diagnosed in 2009 among people aged 60 and over, 134,800 were West German women, 70,800 were West German men, 40,200 were East German women and 17,300 were East German men. Prevalences and incidence rates are higher for East German women and men over age 85. Only East German men over age 90 have a lower incidence than West German men in that age group. The greatest difference was found for VaD prevalence, where the regional difference was even stronger than the gender effect.

A potential point of criticism could be the diagnosis method. Most studies measuring dementia are specially designed for this purpose and are conducted with standardized tests and specialists. Our dataset is not specially designed for detecting dementia prevalence or incidence, as it comes from the health funds and comprises all diagnoses people had within one year. Of the dementia diagnoses in our data, 58% are made by general practitioners, and 32% by neurologists or internists. A study of dementia diagnoses and cognitive impairment detection by general practitioners in Mannheim, Germany, found a comparable level of accuracy (Cooper et al., 1992). In a study about the accuracy of incident diagnoses of general practitioners in Germany, Pentzek et al. (2009) found that nearly half of all cases are missed. The diagnosis is sometimes overestimated in depressed and frail patients, but people living alone tend to be underestimated. However, the exclusion criteria included consultation only by home visits and residence in a nursing home. The advantages of the GKV data are that no exclusion exists, the institutionalized population is included, there is no problem of drop-out due to factors such as severe illness or resistance, and there is no possible reporting bias due to self-selection into the study. Furthermore, diagnoses by specialists, as well as by general practitioners, are included. Thus, the possibility of under-representation has to be considered, but it should be much lower in the GKV data.

Another drawback could be the measurement of dementia in the German health system using the ICD-10 scale. Studies that use ICD-10 criteria tend to find lower rates than studies using DSM-III-R. Criteria of the ICD-10 seem to be more restrictive (Berr et al., 2005). This could lead to an underreporting of people with mild dementia, and therefore an underestimation of the total scope of dementia. With our rates, we capture a total number of 1.12 million people above age 60 with dementia in 2009. The numbers are in accordance with other estimations (Bickel, 2008). By taking milder cases into account, others have estimated that as many as two million people may be affected (Bickel, 1999, 2000; Priester, 2004). The first symptoms of the disease are difficult to differentiate from normal cognitive aging. It is impossible to assess the true prevalence of a disease that begins gradually, progresses slowly, and lacks any clear signs of specificity of cognitive impairment (Bickel, 1999). Taking these uncertainties and the possible underreporting of mild cases into account, the prevalence and incidence rates shown in this analysis appear to provide reasonably accurate estimates of the number of people with moderate and severe dementia in West and East Germany by age and gender.

Further differentiations by dementia types and a differentiation between ambulatory and in-patient treatment are possible in our data. However, a very low prevalence of AD is shown, even though it is the most common form of dementia. The low rates are most likely attributable to diagnosis problems. The data are from the year 2002, and as recently as 2004 it was believed that AD could only be diagnosed with certainty using brain scans after death (Bischoff et al., 2004). Today, new but still costly methods can distinguish the disease from other dementias before death (Ikonomovic et al., 2008; Klunk et al., 2004). General practitioners are probably reluctant to diagnose AD, and therefore place many patients into the group 'unspecified dementia' `F03`. Furthermore, today's treatment concept against dementia is still limited and a more precise diagnosis would not change therapy in many cases. The coding into the group 'unspecified dementia' could also be the reason for the regional differences we find within the low prevalences for AD. Doctors in East Germany might code patients more often into this group. The proportion of dementia cases diagnosed as VaD, 32.2%, seems to be in line with the literature (see section 2.1.2), which, however, gives quite a wide range of about 25%-50% (European Community, 2005), 15%-20% (Weyerer, 2005) or 20%-30% (Skoog, 2004). These varying results might be partly attributable to the difficulties of defining the exact diagnostic criteria for the disease, and partly due to the high number of people who suffer from a mixed dementia of AD and VaD. Depending on the study design, the examination form and the allocation of the mixed dementias, diverging results appear (Fratiglioni and Rocca, 2001). Because for general practitioners in the DKV it is difficult to diagnose AD, they might slightly more often allocate VaD when at the same time other risk factors are present, such as circulatory disorders, cardiovascular diseases or diabetes. The age- and gender-specific prevalences are slightly higher than those found, for example, in the meta-study by Lobo et al. (2000), the results of which generally indicated quite a low prevalence of VaD, or 16%. The higher rate for women is confirmed in the results from Lobo et al. (2000), but not in other meta-studies, which found no gender difference or even higher prevalences for men (Jorm and Jolley, 1998; Jorm et al., 1987; Rocca et al., 1991).

In our results, prevalence and incidence are higher for women after age 70 than for men of the same age. Before that age, the risk is slightly higher for men, which has only a small impact because rates are very low. In the literature, dementia has not been shown to be a consistent gender-specific risk factor. A differentiation by type of dementia, however, shows clear tendencies for higher rates of AD among women (see section 2.4.3). The risk of developing VaD, on the other hand, seems to be equal

in most studies, or even higher for men. Given that AD is the most common type of dementia, representing more than 75% of all cases, it is plausible to assume that most cases from our data coded as 'unspecified dementia' suffer from AD or a mixed form of AD and VaD. Therefore, our results confirm that women have a higher risk of developing AD. When we analyze VaD separately, we also find a higher risk for women. The above described difficulties in getting a specific diagnosis of AD and the frequent occurrence of mixed dementias could lead to an increase in the diagnosis of VaD, when risk factors occur at the same time in the co-morbidity anamnesis. In the next chapter 4, a higher prevalence of hypertensive diseases and problems with the circulatory system for women is confirmed. Lifestyle differences could account for these differences. People in East Germany have worse lifestyles than their West German counterparts: their diets are less healthy, they are less likely to exercise, they have higher smoking rates, and they are more likely to suffer from obesity (Gesundheitsberichtserstattung des Bundes, 2006). An unhealthy lifestyle not only increases the risk of developing dementia (Helmer et al., 2003; Hendrie, 1998; Merchant et al., 1999), it also raises the risk of developing other diseases, such as cardiovascular disease or diabetes (Gorelick, 2004; World Health Organization, 2006b), which in turn increase the risk of developing dementia, especially VaD.

Many other diseases have been detected as risk factors for dementia (see sections 2.4.6, 2.4.10, 2.4.12, 2.4.8, 4.1). Morbidity plays an important role in developing and managing the disease. In the next chapter we look at the co-morbidity of demented people and morbidity in the quarter before dementia occurs.

Chapter 4

Co-Morbidity of Dementia in Germany—Based on GKV Data

4.1 Co-Morbidity of Demented People

In the literature review in chapter 2, single diseases were shown to be risk factors for dementia. The risk of dementia is highest at the same ages at which many other diseases occur. But do some diseases simply occur more often in dementia patients, or can certain diseases be identified that may lead to the development of a dementia? Often an interconnection of mental and physical health is described. Physical frailty can lead to cognitive decline (European Commission, 2004; Michel et al., 2005), but a causality also exists the other way round: low cognitive performance at baseline increases the risk of physical disability (Greiner et al., 1996). Cognitive and functional impairments appear complementary, with each precipitating the decline of the other.

Some studies looked at co-morbidity in dementia patients in general, with contradictory results (Henderson, 1988; Sanderson et al., 2002; Wolf-Klein et al., 1988; Zekry et al., 2008). Early studies found a lower co-morbidity among AD patients. Wolf-Klein et al. (1988) found in a sample of 348 patients from a geriatric clinic in New York between 1981 and 1986 that AD patients had significantly fewer diagnoses than patients with a normal mental status or patients with an abnormal but non-AD mental status (e.g., VaD, depression, psychoses, or mental retardation). Male AD patients had on average 2.9 accompanying diseases, while normal and non-AD abnormal mental status patients had averages of 5.0 and 5.5. For females, the respective co-morbidity was 2.8, 5.4 and 4.6. Males with AD suffered less often from hypertension, heart disease and 'cerebrovascular accident', while surgery, especially prostatectomies, occurred

more often. In women, hypertension, heart disease, arthritis, urological disease and hearing problems were found less often in AD patients than in patients with normal mental status; and hypertension, cardiac and cerebrovascular disease and arthritis were found less often in both groups. When both sexes were taken together, diabetes rates were also shown to be significantly lower in the AD group. The authors speculated that selection and evaluation bias could account for this result, as could the possible inability of patients to verbalize or remember problems. However, they came to the conclusion that the sample is representative because patients in the non-AD abnormal mental status group would have had the same difficulties in verbalizing problems, but have co-morbidity similar to that of the normal group. They further speculated that the loss of recall in AD patients might decrease the mental stress of life, which is a risk factor for developing hypertension and heart and cerebrovascular disease. The lower diabetes risk might "be related to a beneficial effect of hyperglycemia. It is recognized that aging is associated with hyperglycemia of varying degrees. There could be a compensatory effect by higher blood glucose concentration in overcoming a transport or metabolic impediment to glucose in the elderly brain" (Wolf-Klein et al., 1988). However, other reasons for this result might exist: of all the patients, only 16% of males and 27% of females were diagnosed as AD patients, while of all the abnormal mental status patients the proportion only increases to 34% and 40% males and females. Given that we now know that more than two-thirds of all dementia patients are AD cases, we may assume that many people have mixed pathologies of AD and VaD. Furthermore, a certain diagnosis of AD was not possible until a few years ago. Thus, diagnoses made in the early 1980s are questionable, especially because no brain biopsies or autopsies were done at that time. Financial constraints and a lack of cooperation from patients influenced the completion of the procedure (Wolf-Klein et al., 1988). Thus, there could still be a selection bias in the data.

A lower number of co-morbid conditions in cognitively impaired people was also found by Landi et al. (2001). To overcome problems related with retrospective studies, such as recall problems, they performed a longitudinal study on 1,787 community-living patients above age 65 between 1997 and 1999. Of this sample, 44% were cognitively normal, 22% had moderate impairments and 34% had severe impairments. ADL and IADL difficulties were much higher in impaired patients. Demented people were significantly more likely to have unintended weight loss and behavior problems. However, the average number of diseases was about the same in all groups: 3.0, 3.4 and 3.3 for people with severe, moderate and no impairment, respectively. Severe diseases, such

as hypertension, congestive heart failure, pulmonary disease, cancer, diabetes, arthritis and osteoporosis, were less often found in the group with most impairments, while stroke, PD and pneumonia were found more often. Landi et al. (2001) concluded that it is unclear, whether AD protects against certain diseases or whether these results are due to memory problems. They also made the interesting suggestion that differing drug use could play a role. Certain drugs, such as those used to treat hypertension, are associated with a lower incidence of cognitive problems. Nevertheless, higher levels of cognitive impairment were shown to lead to higher mortality. This might be caused by a greater impact of ADL functional limitations than of other clinical conditions on survival, by a varying likelihood of being examined and diagnosed with dementia or by an insufficient assessment of medical conditions in severely demented patients. In addition, people with more co-morbidities could be institutionalized more often and are thus not included in the study.

Sanderson et al. (2002) analyzed hospital discharge data on 15,013 people with dementia from South Carolina from the years 1998/99 and compared the results with 15,013 controls. They found a higher number co-morbid conditions for people with AD, multi-infarct dementia (MID) and dementia associated with a medical condition (MED) of 7.97, 8.13 and 7.20, respectively, compared with controls who had on average 6.99 conditions. Their results showed that most demented people suffered from AD (77%), 12% had an MID, and 11% had an MED. The ten most common co-morbidities among people with AD were shown to be fracture of the neck of femur, urinary tract infection, convulsions, osteoarthritis, osteoporosis, decubitus ulcer, syncope and collapse, dysphagia, congestive heart failure and essential hypertension. For MID and MED, convulsion was the most common co-morbid condition, followed by cerebral infarction and chest pain for MID, and complication of nervous system device and obstructive hydrocephalus for MED. In addition, they analyzed co-morbidity with essential hypertension, diabetes mellitus, congestive heart failure, atrial fibrillation and anemia. However, people with AD and MED were found to have a decreased risk of developing these diseases; with the exception of anemia, but the elevated risk was not shown to be significant. MID was found to be associated with a lower risk of developing congestive heart failure and an increased risk of having diabetes. In an effort to explain why no correlation between MID and hypertension and atrial fibrillation was found, the authors suggested that people are more often diagnosed with cerebral artherosclerosis. The findings in the literature regarding AD and hypertension are inconsistent, as has been discussed in section 2.4.8. Lower blood pressure might cause a cognitive decline, but it might

also be caused by AD. A longer observation period is necessary to obtain the risk of midlife hypertension on late-onset dementia. Diabetes was lower in AD and MED patients and higher in MID patients. When the analysis was restricted to people without vascular conditions, the risk was also found to be higher in AD patients. Hypertension and diabetes were shown to increase the risk of atherosclerosis and brain infarctions, which in turn increase the risk of AD. They do not provide an explanation for the lower risk of developing AD among people with atrial fibrillation and congestive heart failure. "Since the cross-sectional nature of this study does not allow for the correct exposure-outcome temporal sequence, longitudinal studies are necessary to confirm our findings" (Sanderson et al., 2002).

A longitudinal study was done by Zekry et al. (2008), who followed 349 patients from the Geriatric Hospital of Geneva University (HOGER) over the age of 75 for four years starting in 2004. The 43% of the sample with dementia and the 11% of people with MCI were similar to the control group in terms of age, sex, educational levels, smoking habits and alcohol intake. Non-demented people were more likely to live alone, and demented people were more likely to live in a nursing home. The lower the cognitive status of a patient, the lower were his or her functional abilities, as measured by ADL, IADL and functional independence measure (FIM), and the lower was his or her nutritional status, as measured by the mini nutritional assessment (MNA). The BMI of demented people was found to be lower at hospital admission, but not significantly lower at discharge. Co-morbidity, as measured by the Charlson co-morbidity index (CCI), was shown to be similar in demented and non-demented people. Dementia patients were found to be more likely to suffer from cerebrovascular disease, stroke and hypertension.

In addition, Marengoni et al. (2009) found a lower number of co-morbid conditions in demented patients. The results of their cluster analysis showed that the diseases that most likely accompany dementia are depression, hip fracture, cerebrovascular disease, visual impairment and deafness.

The findings of these studies have failed to provide a clear answer to the question of whether co-morbidity is higher in dementia patients, but they have confirmed that certain diseases occur more frequently among demented than among non-demented study participants. Often co-morbidities of mental disorders have been found to lead to a reduction of the quality of life (Wittchen and Jacobi, 2005).

It is difficult to say whether the co-morbidity of people with dementia is really lower, or if it is just a bias effect. One reason for the lower number could be that retrospective

studies often miss diagnoses of dementia patients, because these patients may only complain of cognitive problems (Marengoni et al., 2009; Zekry et al., 2008).

4.2 Co-Morbidity of Demented People in Germany in the GKV Data

In the following, we look at the diseases that accompany dementia according to the GKV data. Are demented people more likely than non-demented people to contract other diseases, and which diseases occur most often?

Of the 562,707 people above age 60 in the sample, about 9% did not seek medical advice at all during the year 2002. Of the 91% who did, about 90% sought ambulatory care and 25% needed stationary care. Which diseases did people with and without dementia suffer from most frequently?

The following risk factors of dementia were determined in the GKV data (the order occurs according to the order in the ICD-10):

- HIV [B20-B24]
- Diabetes [E10-E14]
- Malnutrition [E40-E46]
- Obesity [E65-E68]
- Depression [F32-F33]
- Chorea Huntington [G10]
- Parkinson's Disease [G20-G22]
- Hypertensive Diseases [I10-I15]
- Ischaemic Heart Disease [I20-I25]
- Cerebrovascular Disease [I60-I69]
- Pneumonia [J12-J18]
- Arthrosis [M15-M19]
- Osteoporosis [M80-M82]
- Down's Syndrome [Q90]

Furthermore we controlled for all other disease groups*:

- Certain infectious and parasitic diseases [A00-B99]
- Neoplasms [C00-D48]
- Diseases of the blood, blood-forming organs and immune mechanism [D50-D89]
- Endocrine, nutritional and metabolic diseases [E00-E90]
- Mental and behavioral disorders [F00-F99]
- Diseases of the nervous system [G00-G99]
- Diseases of the eye / ear [H00-H95]
- Diseases of the circulatory system [I00-I99]

- Diseases of the respiratory system [J00-J99]
- Diseases of the digestive system [K00-K93]
- Diseases of the skin and subcutaneous tissue [L00-L99]
- Diseases of the musculoskeletal system and connective tissue [M00-M99]
- Diseases of the genitourinary system [N00-N99]
- Diseases during pregnancy and perinatal Period [O00-P96]
- Congenital malformations, deformations, chromosomal abnormalities [Q00-Q99]
- Abnormal clinical findings, injury, poisoning, external causes[R00-Z99]

*The above specified risk factors were taken out of the respective categories, e.g., the disease group 'Certain infectious and parasitic diseases' [A00-B99] does not include 'HIV' [B20-B24].

Table 4.1 shows the prevalence of the above specified diseases during the year 2002 for people over age 60. Of all the people in the sample over the age of 60, 5.4% suffered from a dementia. Injuries and external causes were, at a rate of 72.3%, found to occur quite frequently among the elderly. Meanwhile, 56.4% of all people in this group had musculoskeletal diseases. Diseases of the circulatory system occurred quite frequently, with an overall rate of 51.4%, and 52.7% were found to have hypertension. But people also suffered frequently from problems with eyes or ears (50.0%), metabolic diseases (49.0%), diseases of the digestive system (41.5%), infections (44%) and diseases of the genitourinary system (42.8%).

Table 4.2 shows the prevalence of various risk factors for people above the age 60 with and without dementia, additionally separated by survival status. Because demented people are, on average, older, and because they are more likely to develop several diseases, the results were age-standardized. From the table it can be seen that people with dementia often have a higher prevalence of other diseases as well. The correlation was found to be highest for cerebrovascular diseases, diseases of the nervous system, PD, and psychiatric disorders. For example, 12.5% of the surviving women and 14.4% of the surviving men aged 60 and above without dementia were found to be suffering from cerebrovascular disease, while 37.6% of the surviving women and 47.1% of the surviving men above age 60 with dementia were shown to suffer from cerebrovascular disease. Mental diseases, diseases of the nervous system and depression were highly correlated with dementia. A doubling of the prevalence was found to occur in surviving males and females with dementia. Neoplasms (not for surviving males) and obesity showed a negative correlation. Table 8.1 (shown in the appendix 8) displays the results further differentiated by 10-year age groups: 60-69, 70-79, 80-89 and 90+. Generally, with increasing age the overall morbidity increases and the difference between people with and without dementia and an additional co-morbidity becomes smaller.

Table 4.1: Prevalence of Diseases for People above Age 60

Risk Factor*	ICD-10 Block	%
Infections	A00-B99	44.0
HIV	B20-B24	0.3
Neoplasms	C00-D48	25.3
Blood Diseases	D50-D89	10.7
Metabolic Diseases	E00-E90	49.0
Diabetes	E10-E14	24.2
Malnutrition	E40-E46	0.2
Obesity	E65-E68	11.6
Mental Disorders	F00-F99	24.3
Dementia	F00-F03, G30	5.4
Depression	F32-F33	13.7
D. of Nervous System	G00-G99	24.6
Chorea Huntington	G10	0.02
Parkinson's Disease	G20-G22	2.0
Eye/Ear Diseases	H00-H95	50.0
D. of Circulatory System	I00-I99	51.4
Hypertensive Diseases	I10-I15	52.7
Ischaemic Diseases	I20-I25	28.3
Cerebrovascular Diseases	I60-I69	15.6
Respiratory D.	J00-J99	36.4
Pneumonia	J12-J18	3.7
D. of Digestive System	K00-K93	41.5
Skin Diseases	L00-L99	27.2
D. of Musculoskeletal System	M00-M99	56.4
Arthrosis	M15-M19	29.0
Osteoporosis	M80-M82	11.8
D. of Genitourinary System	N00-N99	42.8
Chromosomal Abnormalities	Q00-Q99	8.8
Down's Syndrome	Q90	0.01
Injury, External Causes	R00-Z99	72.3

D.= Diseases

*The above specified risk factors were taken out of the respective categories, e.g., the disease group 'Certain infectious and parasitic diseases' `[A00-B99]` does not include 'HIV' `[B20-B24]`

Table 4.2: Prevalence of Risk Factors and Other Disease-Groups for Females and Males above Age 60 with and without Dementia by Surviving Status (Age-Standardized)

	Survived				Died			
	No Dementia		Dementia		No Dementia		Dementia	
	F	M	F	M	F	M	F	M
Infections	46.6	40.4	56.1	54.0	43.6	41.4	42.8	46.5
HIV	0.27	0.25	0.60	0.39	0.21	0.45	0.04	0.27
Neoplasms	24.8	25.5	26.5	29.7	47.5	46.6	29.4	32.3
Blood D.	10.0	10.1	15.3	15.1	21.2	20.2	19.0	21.7
Metabolic D.	51.6	44.2	58.0	51.7	47.2	41.1	51.8	52.3
Diabetes	21.7	24.3	33.3	35.8	31.3	31.5	34.0	36.6
Malnutrition	0.09	0.09	0.63	0.48	0.91	0.94	5.05	2.74
Obesity	13.2	9.6	15.3	11.7	12.7	9.0	13.4	9.8
Mental Disorder	25.7	18.6	57.1	57.2	28.8	25.8	50.6	59.7
Depression	16.9	7.2	35.2	22.7	18.6	9.4	30.2	16.8
Nervous System	25.0	20.9	48.4	51.6	29.3	27.2	44.4	51.7
Chorea H.	0.02	0.02	0.41	0.74	0.01	0.06	0.27	0.33
Parkinson's D.	1.3	1.7	9.0	11.8	2.3	2.7	13.1	13.6
Circulatory System	51.6	46.9	62.6	61.6	59.0	61.0	59.5	68.8
Hypertensive D.	53.1	49.4	60.0	57.0	51.3	48.8	50.4	53.5
Ischaemic Heart D.	23.9	31.0	32.1	38.3	28.7	39.1	31.9	44.7
Cerebrovascular D.	12.5	14.4	37.6	47.1	22.0	23.6	44.1	47.3
Respiratory D.	35.3	36.9	42.9	46.1	37.9	45.2	40.0	54.4
Pneumonia	2.6	3.4	6.2	9.2	10.8	15.6	20.1	30.3
Digestive D.	40.5	40.3	52.6	55.0	49.5	47.3	48.8	54.7
Skin D.	27.3	25.1	41.0	39.0	24.4	22.5	43.8	42.2
Musculoskeletal D.	59.6	52.8	59.1	55.9	43.1	39.9	45.3	37.4
Arthrosis	32.0	23.9	31.9	25.4	19.2	15.7	15.9	18.6
Osteoporosis	16.9	3.2	19.2	4.7	14.0	3.9	16.3	4.3
Eye/Ear D.	50.2	46.5	53.6	53.0	30.0	29.0	35.2	32.1
Genitourinary D.	46.5	38.8	52.8	51.7	40.8	38.0	46.2	53.1
Chromosomal A.	9.2	8.8	9.5	9.3	5.6	5.8	5.7	4.9
Down's Syndrome	0.01	0.01	0.29	0.31	0.00	0.03	0.00	0.00
Injuries, Ext. C.	73.9	66.9	89.4	87.0	73.6	70.7	67.4	67.7

F=Females, M=Males

D.=Disease; A.=Abnormalities; Ext. C.=External Causes

In table 4.3 odds ratios of the risk of being demented depending on several diseases are shown, separated by gender and survival status and controlled for age and region. The following model was used to estimate the risk:

$$ln[\frac{p_d}{1-p_d}] = \beta_0 + \sum_{i=1}^{8} \gamma_i \times age_i + \delta_j \times region_j + \sum_{k=1}^{30} \epsilon_k \times D_k \qquad (4.1)$$

where p_d stands for the probability of having a dementia (by gender and survival status); β_0 for the constant, *age* for 5-year age-groups from age 60, *region* for East and West Germany, 'D' for 30 ICD disease groups, and γ, δ and ϵ are the regression coefficients.

The age effect is confirmed showing a strong increase of dementia prevalence with age. The increase is higher for people who survive and for surviving females than for surviving males. A higher risk was found for East Germans which is not significant for females who died. The following lines show that several diseases increase the risk of having a dementia disregarding gender and survival status. Especially PD, Chorea Huntington and DS were found to increase the risk strongly (the last two diseases have small sample sizes which explain the results for people who died) but also cerebrovascular diseases, mental disorders, diseases of the nervous system, depression, injuries and other external causes and malnutrition, furthermore pneumonia and skin diseases. With some diseases the risk for a dementia is slightly lower such as neoplasms, hypertensive diseases, obesity, metabolic disorders (without diabetes, malnutrition and obesity), musculoskeletal diseases, arthrosis, chromosomal abnormalities (without DS) and some are not significantly different: infections, HIV, osteoporosis, diseases of the circulatory system, respiratory diseases, or blood diseases.

Separate regression models for AD and VaD were run (not shown). As expected, the risk for VaD was higher when vascular diseases were prevalent, such as hypertensive, ischaemic and cerebrovascular diseases, diabetes, but also osteoporosis. The risk for AD was higher compared with VaD when at the same time people had DS, PD or Chorea Huntington. While the risk to be diagnosed with VaD was 36% higher in East Germany, there was no gender difference. For AD there was hardly a regional difference while it was 25% lower for males.

Table 4.3: Risk of Being Demented Depending on Age, Region and Several Diseases

	Females				Males			
	Survived		Died		Survived		Died	
	OR	p	OR	p	OR	p	OR	p
Age 60-64	1		1		1		1	
Age 65-69	2.20	***	1.52	°	1.61	***	1.70	**
Age 70-74	4.67	***	2.98	***	2.89	***	3.39	***
Age 75-79	9.69	***	4.49	***	4.56	***	4.40	***
Age 80-84	17.04	***	6.95	***	7.84	***	7.97	***
Age 85-89	31.84	***	10.28	***	13.08	***	12.55	***
Age 90-94	46.07	***	13.29	***	20.50	***	12.58	***
Age 95-99	65.52	***	14.37	***	28.03	***	17.51	***
Age 100+	111.67	***	17.02	***	61.40	***	13.02	***
West Germany	1		1		1		1	
East Germany	1.16	***	1.09		1.11	**	1.23	*
Infections	1.04		1.08		1.04		0.99	
HIV	1.57		1.01		1.04		1.32	
Neoplasms	0.78	***	0.64	***	0.82	***	0.57	***
Blood D.	1.13	**	0.95		0.95		0.99	
Metabolic D.	0.91	***	1.07		0.91	**	1.16	*
Diabetes Mellitus	1.30	***	1.10	*	1.23	***	1.03	
Malnutrition	4.09	***	1.34	°	2.28	***	1.07	
Obesity	0.90	***	0.75	**	0.87	**	0.75	*
Mental Disorder	2.40	***	1.92	***	3.01	***	2.53	***
Depression	1.46	***	1.23	***	1.56	***	1.20	*
Nervous System	1.33	***	1.16	**	1.66	***	1.50	***
Parkinson's D.	3.03	***	2.19	***	3.33	***	2.57	***
Chorea Huntington	13.79	***	13.08	*	15.07	***	0.85	
Eye/Ear D.	0.75	***	0.97		0.75	***	0.91	
Circulatory System	1.06		1.05		1.06	°	0.96	
Hypertensive D.	0.90	***	0.91	*	0.87	***	0.84	*
Ischaemic Heart D.	1.01	°	0.91	*	0.87	***	0.88	*
Cerebrovascular D.	2.27	***	1.51	***	2.77	***	1.80	***
Respiratory D.	0.98	**	1.03		0.91	**	0.97	
Pneumonia	1.60	***	1.57	***	1.59	***	1.54	***
Digestive D.	1.17	***	0.98		1.04		0.95	
Skin D.	1.49	***	1.71	***	1.31	***	1.80	***
D. of Musculosc. S.	0.68	***	0.88	**	0.73	***	0.76	***
Arthrosis	0.89	***	0.95		0.90	***	0.95	
Osteoporosis	1.00	*	0.98		0.96		0.99	
D. of Gen. S.	1.02		1.34	***	1.09	**	1.30	***
Chromosomal. A.	0.86	***	0.77	*	0.77	***	0.68	**
Down's Syndrome	36.31	***	-		14.00	***	-	
Injuries	2.15	***	1.82	***	1.81	***	2.01	***
No Disease	0.59	***	0.93		0.58	***	0.84	
Constant	0.00	***	0.02	***	0.01	***	0.01	***
-2 Log-Likelihood	102167.1		12907.9		44423.0		6856.7	
Adjusted R-Square	0.316		0.260		0.277		0.315	

D.=Diseases, S.=System, Gen.=Genitourinary, A.=Abnormalities

***p≤0.001, **p≤0.01, *p≤0.05, °p≤0.1

On average, ambulatory doctors diagnosed 8.5 different diseases from the above-mentioned 30 risk factors and diagnosis groups, per person seeking advice in 2002. People above age 60 without dementia had on average 7.4 out of the 30 risk factors and diagnosis groups, while people with dementia had 11.2. When only the 14 risk factors for a dementia described above were taken into account, people above age 60 without dementia had on average 1.9 risk factors, and people with dementia had 4.2. The following table 4.4 shows the average number of risk factors that people with and without dementia suffer from, additionally controlled for age, gender and death. The average number of risk factors increased the most between ages 60-79 and 80-89 among non-demented people, by 0.6 diseases. Meanwhile, since co-morbidity is already very high when dementia occurred at younger ages, the average number of risk factors increased only by 0.2 among older demented people. However, non-demented 90+-year-old people did not have more co-morbidities relative to 80-89-year-olds, while among demented people in this age group the number actually decreased by 0.3. Nearing death also had an impact, although less than dementia (only deaths in 2002 can be identified). For 60-79-year-old people, those who died within the year 2002 had on average 0.6 more risk factors and other accompanying diseases. This difference decreased with age to 0.4 and 0.2 diseases for 80-89- and 90+-year-olds. Females had on average 0.4 diseases more than males, and East and West Germans hardly differ, with 0.1 more diseases in East Germany.

Table 4.4: Average Number of Risk Factors for Demented and Non-Demented People above Age 60

		West Germany				East Germany			
		Females		Males		Females		Males	
	Age	No D	D	No D	D	No D	D	No D	D
Survived									
	60-79	1.9	4.2	1.6	3.9	2.0	4.4	1.6	4.0
	80-89	2.5	4.4	2.1	4.1	2.7	4.7	2.3	4.5
	90+	2.4	4.0	2.0	3.9	2.6	4.3	2.3	4.0
Died									
	60-79	2.3	4.4	2.0	4.3	2.4	4.8	2.1	4.3
	80-89	2.5	4.4	2.3	4.2	2.9	4.8	2.7	4.6
	90+	2.3	4.1	2.2	3.7	2.5	4.5	2.3	4.1

D.=Dementia

4.3 Predictors of Dementia

The previous section explained the accompanying diseases of people with dementia. However, these results do not reveal causality: Have these diseases had an influence on the development of dementia, or are they more likely to develop in patients who already have dementia? In this subsection, we look at the influence of diseases on the incidence of dementia. The first two quarters of the year were combined into the first half-year and the last two quarters into the second half-year. We started by excluding prevalence cases in the first half-year of the year 2002 and checked for certain diseases. Then, in the second half-year, we compared people without dementia and this disease in the first half-year, and dementia incidence cases with this disease in the first half-year.

Table 4.5 shows the odds ratios of the risk of having an incident dementia depending on certain diseases in the previous half-year. First of all the risk increases strongly with age, more so for women but without a regional difference.

Several diseases increased the risk of incident dementia in the following half-year: PD, cerebrovascular diseases, mental disorders and depression nearly doubled the risk. Furthermore, diseases of the nervous system, diabetes mellitus, diseases of the circulatory system, skin diseases and injuries increased the risk. Stronger increases were found for males with Chorea Huntington and for females with DS, but again, case numbers were very small. A lower risk was found when neoplasms, metabolic disorders (without diabetes, malnutrition and obesity), obesity, eye/ear diseases, diseases of the musculoskeletal system, or arthrosis occur in the first half-year.

Table 4.5: Risk of Incident Dementia Depending on Age, Region and Several Diseases before the Onset

	Females		Males	
	OR	p	OR	p
Age 60-64	1		1	
Age 65-69	2.31	***	1.54	***
Age 70-74	5.18	***	2.97	***
Age 75-79	10.14	***	5.07	***
Age 80-84	16.99	***	8.76	***
Age 85-89	29.82	***	13.53	***
Age 90-94	36.70	***	19.41	***
Age 95-99	45.53	***	19.30	***
Age 100+	67.63	***	52.21	***
West Germany	1		1	
East Germany	1.05		0.95	
Infections	0.97		0.98	
HIV	1.29		0.95	
Neoplasms	0.82	***	0.87	*
Blood D.	1.15	**	0.95	
Metabolic D.	0.85	***	0.85	*
Diabetes Mellitus	1.15	***	1.13	*
Malnutrition	1.12		1.70	
Obesity	0.75	***	1.00	
Mental Disorder	1.94	***	2.32	***
Depression	1.70	***	1.90	***
Nervous System	1.21	***	1.66	***
Parkinson's D.	2.01	***	3.00	***
Chorea Huntington	-		7.88	**
Eye/Ear D.	0.89	***	0.86	**
Circulatory System	1.14	*	1.16	°
Hypertensive D.	0.97		1.01	
Ischaemic Heart D.	1.03		0.99	
Cerebrovascular D.	1.80	***	2.12	***
Respiratory D.	0.94	°	0.99	
Pneumonia	1.00		1.06	
Digestive D.	1.00		0.97	
Skin D.	1.20	***	1.08	
D. of Musculoskeletal System	0.84	***	0.85	**
Arthrosis	0.83	***	0.90	°
Osteoporosis	0.90	*	0.97	
D. of Genitourinary System	1.00		0.98	
Chromosomal Abnormalities	0.96		0.88	
Down's Syndrome	38.09	***	-	
Injuries, External Causes	1.28	***	1.29	***
No Disease	-		-	
Constant	0.00	***	0.00	***
-2 Log-Likelihood	39417.4		18476.3	
Adjusted R-Square	0.150		0.135	

D. = Diseases

***p≤0.001, **p≤0.01, *p≤0.05, °p≤0.1

4.4 Discussion

In this section, we confirmed results from the literature that have shown that people with dementia suffer more frequently from several diseases than people without dementia (compare sections 2.4.8, 2.4.11, 2.4.7, 2.4.10 and 2.4.12), but also that other diseases and disease groups increase the risk.

However, results from the literature regarding the number of co-morbid conditions are not in agreement, with some studies even finding a lower number in people with dementia. In this data, a much higher co-morbidity was found in people with dementia. It was found to be slightly lower in males and West Germans, and the difference between demented and non-demented people was shown to decrease with age, mainly because of an increasing multi-morbidity of non-demented people. In the GKV data all physicians' diagnoses from one year are recorded, and thus there is no problem of recall bias, as it might be the case in surveys. But some studies also use a special co-morbidity index to compare people with and without dementia. Here all diseases measured with the ICD were taken, which might have included a higher total number of diseases, and could therefore increase the chance of co-morbid conditions. It is, however, important to include all possible diseases, as many were found to increase or sometimes even decrease the risk.

When we looked at special risk diseases, we could confirm literature results. People with a prevalent dementia were found to have a more than three-fold risk of also having cerebrovascular diseases, including stroke. People with a new diagnosis of dementia had a more than 2.6-fold risk of having a cerebrovascular disease in the quarter before than people without. A combination of vascular and degenerative pathologies that may lead to the development of dementia after a stroke may be the reason for this higher risk (Ivan et al., 2004). Hypertension, which might be such a factor, was not confirmed as a risk factor in all studies (see 2.4.8), and was shown to have a significant negative but not strong effect in the GKV data; thus more factors must play a role. However, it is mid-life hypertension and not accompanying hypertension that was found to play a role and thus cannot be measured here with data from only one year. The treatment of hypertension or the treatment with antihypertensive drugs might have a positive effect (Marengoni et al., 2009).

Depression was also worked out to be much higher when dementia is prevalent in both the literature (see 2.4.10) and in the GKV data by a factor higher than two. It is not quite clear which disease is the risk factor for the other, as they seem to influence

each other: a depression is accompanied by low energy and low social participation levels, which are considered vital for cognitive fitness. But a cognitive impairment is also accompanied by low levels of self-confidence and social participation and can therefore lead to depressive symptoms. The GKV data showed that people with incident dementia have a higher risk of suffering from depression in the first half-year. The assumption that depression is a risk factor was confirmed, but the reverse causality was not analyzed.

The metabolic syndrome is believed to increase the risk of dementia. The syndrome is made up of several diseases. One of it which might increase the level of the aβ protein and thus the dementia risk is diabetes mellitus (see 2.4.7). A review of 13 studies about the correlation of diabetes and AD (Finch and Cohen, 1997) showed inconsistent results. However, a newer review, which only included eight studies with incidence rates (Weuve et al., 2008), showed a higher risk for people with diabetes of developing AD: on average, the eight studies found that people with diabetes have a 51% higher risk of developing AD. In the GKV data, the risk was 15% higher for females and 13% for males when all other diseases were controlled for, too. Meanwhile, people with diabetes had a 24% higher risk also to have a prevalent dementia. Obesity (Skoog, 2004) was sometimes thought to be a risk factor for dementia due to the increased risk for heart disease and stroke. However, results in the GKV data even showed a lower risk for prevalence and for incidence. Longitudinal studies are needed to follow weight change, which might be a better indicator than the crude classification into 'normal weight', 'overweight' and 'underweight'. This finding could also be due to a measurement problem. In dementia studies, the weight and height of all people is examined, but in this data, obesity might only be coded if a direct problem with it occurred, and not as underlying diagnosis. This might lead to underreporting: table 4.1 shows a prevalence of obesity of only 11.6% while the true number is more than twice as high (Statistisches Bundesamt & Robert Koch Institut, 2007). Malnutrition has been found more frequently in people with dementia in both the literature (Henderson, 1988) and in the GKV data. People suffering from malnutrition in half-year 1 had a 50% higher risk of developing an incident dementia. When both diseases co-occurred, the risk nearly tripled. Weight loss is not only a symptom of dementia, but it can also precede the disease and may be a warning factor. Insulin resistance is a factor that some metabolic diseases—including endocrine and nutritional diseases such as diabetes, obesity and dyslipidemia—have in common. Reduced brain insulin was also associated with some processes leading to AD (Craft, 2009).

Also DS is a risk factor for dementia (Breitner et al., 1993; Henderson, 1988; Mor-

timer et al., 1991) (see 2.4.12). DS here was connected with an 11-fold risk of also having dementia, but the risk is 38-fold for females and zero for males with incident dementia. The life expectancy of people with DS has risen tremendously in recent decades, from about nine years in 1929 to more than 60 years today. A higher amyloid accumulation due to an additional copy of the amyloid precursor protein (APP), located on chromosome 21, is the main factor for brain changes in people with DS, nearly all of whom show cognitive impairments with profiles similar to AD above age 40 (Teipel, 2006). In our analysis, only people above age 60 were included. People above age 60 with DS are a very select group in which nearly all people show already signs of (prevalent) AD.

Another disease which highly increases the dementia risk is PD. The rates of PD were three times higher for prevalent dementia and two to three times higher in new dementia cases. Results from the GKV data confirmed the literature findings (see section 2.4.11).

Additionally, a head trauma could be connected with higher amyloid levels in the brain and could therefore lead to AD (Breitner et al., 1993; Henderson, 1988; Mortimer et al., 1991) (see 2.4.12). Here, based on the GKV data only, the whole category 'Abnormal clinical findings, injury, poisoning, external causes `[R00-Z99]`' was taken into account. People with prevalent dementia had a nearly two-fold risk, and people with new dementia had a nearly 30% higher risk of being in this category. The causal pathway is unclear: a fall could lead to the above-mentioned higher release of β-amyloid, however, people with dementia are also more limited in their functional limitations which leads to downfalls.

A group with a significantly lower risk for both, prevalent and incident dementia, were people with neoplasms. Cancer is not often analyzed as a risk factor for dementia, and the few studies that exist have diverging results. One study found a non-significant higher risk among people who survived cancer. The authors suggested that the treatment might lower the cognitive reserve, which increases the risk of dementia (Heflin et al., 2005). A longitudinal study by Roe et al. (2005) showed a significantly lower incidence for both the development of dementia among people who have cancer, and vice versa.

The high co-morbidity for people with dementia that was found in the results from the GKV data, together with results from the diagnosis group 'no other diagnosis', showed that people with dementia had a much lower risk of being in that group, or 40%, and that nobody who developed a new dementia in the second half-year was in that group in the first half-year.

In conclusion, we can say that co-morbidity is much higher in people with dementia: on average, they had 4.2 co-diseases based on the above specified 14 risk factors, while people without dementia had 1.9 co-diseases. The number of co-morbid conditions increased with age, while the difference between the groups demented/not demented decreases only slightly. People who died had on average 0.4 more co-morbidities. A further differentiation by dementia status showed nearly no difference. This explains that dementia has a much higher influence on (the selected) co-morbidity than death. Regardless of dementia status, women had more co-morbidities, on average 0.4.

The true number of co-morbidities among people with dementia is difficult to analyze, not only because dementia occurs at high ages, but also because of the higher mortality associated with certain diseases. A selection effect could evolve from the different mortality rates seen in some studies. However, in this study we could control for this factor because the complete doctors' diagnoses from the entire year of 2002 are given. Thus, no disease was overlooked due to a higher focus on dementia. Additionally, the information regarding the survival status was considered to be reliable because of the German registration system.

Many diseases that were found in the literature were confirmed here, not only as accompanying diseases that develop as a result of the neurodegeneration, but also as risk factors. From the analysis it could not be always clear if a factor was accompanying the disease or a risk factor because dementia develops over a much longer period and the incidence marks just the time of the first diagnosis. However, the risk factors could still influence the disease progress. The most important diseases found as co-morbidities and risk factors include cerebrovascular and diseases of the circulatory system; mental diseases, such as depression and diseases of the nervous system; as well PD and metabolic disorders.

This is an important finding because the development and progression of many of these diseases can be influenced. If their prevalence could be reduced, dementia prevalence might also be reduced.

Chapter 5

Determinants and Trends of Severe Cognitive Impairment (SCI)

In the last chapter, the occurrence of dementia and co-morbid diseases were described. In this chapter, we will look at determinants of the disease in more detail. Are there any conditions or risk factors some people are exposed to more frequently that increase their risk of developing dementia? In the literature review in chapter 2 several risk factors have been shown to influence the risk. From these results we hypothesize that higher education and a healthy lifestyle reduce the risk of developing dementia. Furthermore certain diseases such as cardiovascular diseases or diabetes and bad physical and mental health condition in general should increase the risk. To explore this question, we are using a new data-set, which is described in the first section. Second, we outline our results on different determinants. The descriptive cross-sectional results provide an overview of the distribution of the risk factors among the demented and the total population. Finally, we look at multivariate longitudinal results regarding determinants and incident dementia.

5.1 Data - The Survey of Health, Ageing and Retirement in Europe (SHARE)

The Survey of Health, Ageing and Retirement in Europe (SHARE) (`www.share-project.org`) is a cross-national panel survey of micro data on health, socioeconomic status and social and family networks. More than 40,000 individuals aged 50 or over from 11 countries participated in the baseline wave in 2004. Countries from all parts of Europe are

included: from Scandinavia (Denmark and Sweden), Central Europe (Austria, France, Germany, Switzerland, Belgium, and the Netherlands) to the Mediterranean (Spain, Italy and Greece). In 2005/06 Israel also joined the first wave. Data for the second wave were collected in 2006/07 in the above-mentioned countries, as well as in Ireland and two new EU member states, the Czech Republic and Poland. It has a panel, as well as a cross-sectional dimension: the same people from wave 1 were followed in wave 2, and, to adjust for panel attrition, new samples were drawn. The third wave was conducted in 2008-09, data will be available soon. This analysis includes 11 countries: Denmark, Sweden, Austria, France, Germany, Switzerland, Belgium, the Netherlands, Spain, Italy and Greece. Israel, the Czech Republic and Poland were excluded from the analysis because these countries were not surveyed in both waves. The data were restricted to people above age 60 to make results comparable to those described in the previous the chapters. In both waves there are more than 17,000 people who meet the criteria.

5.1.1 Data Problems - Exclusion of the Institutionalized Population

One major drawback of the SHARE data is that it mainly excludes the institutionalized population. Since the amount of care needed by dementia sufferers is very high in the end stage of the disease, these people often have to move into institutions (Hallauer, 2002; Jakob et al., 2002). Jagger et al. (2000); Jakob et al. (2002); Ruitenberg et al. (2001) show that the prevalence of dementia is much higher in institutions than in private households. Yet the SHARE data only allows us to look at people with cognitive impairments who live at home, with a few exceptions. For a more detailed description of the institutionalized population in the SHARE data, the problems and the creation of the variable 'institutionalized population' the reader is referred to the appendix.

Table 5.1 shows the proportion of people in homes for the elderly/nursing homes in the included countries: only a handful of people per country belong to these categories, except in the Netherlands, where about 12% are listed, and in Sweden and Denmark with about 4%. But the distribution is different than would be expected from reading the methodology report (see above), as even Austria, France, Italy and Switzerland have at least a few people listed. There is an expected clear difference between northern and southern European countries: in northern Europe, there are more people living in institutions.

Table 5.1: Proportion of the SHARE Population in Special Housing for the Elderly and Nursing Homes (Nursing Homes Only in Wave 2)

	Wave 1	Wave 2
Greece	0.1	0.0
Italy	0.2	0.3
Spain	0.3	0.6
Austria	0.5	1.7
Belgium	0.5	1.8
France	0.8	1.2
Switzerland	1.3	1.8
Germany	1.9	2.9
Sweden	4.0	3.7
Denmark	4.2	4.8
Netherlands	12.3	10.0
Total	2.3	2.6

According to the results from the literature, the countries with higher proportions of people living in institutions are generally found in Northern and Western Europe. By contrast, Southern and Eastern European countries tend to have lower rates of institutionalization among the elderly. For example, in 2000, only 1.8% of men and 4.5% of women above age 75 lived in collective households in Italy, as did 2.7% of men and 5.1% women in the Czech Republic. But the proportion of the population aged 75+ living in institutions in 2000 was higher in the Netherlands, Finland, France and Belgium: about 6% to 7% of men and about 11% to 12% of women in Finland and France, and 14.6% in Belgium and the Netherlands. Germany is in the middle, with 3.8% of men and 9.3% of women in this age group living in institutions (Gaymu et al., 2006). It is difficult to compare these numbers with the results in table 5.1 because, on the one hand, not all countries include the institutionalized population, and, on the other, there are different definitions of 'people in institutions' in general, and 'people in homes for elderly/nursing homes' found in the SHARE data, and also between countries (Van Oyen, 2001).

5.1.2 Data Problems - Weights

SHARE provides cross-sectional weights for waves 1 and 2. One problem stated in the methodological report is that countries that do not include the institutionalized population in their sampling frames have a potential problem in calibrating against population

totals that include these people (which is true for all countries but Switzerland) (Börsch-Supan and Jürges, 2005). In the same report, problems with the computation of proper variances are described [p. 35]. A possible temporary solution may be to carry on as if in every country there was a single-stage random sample with unequal sampling probabilities. The 'individual calibrated weight for the main and vignette sample together' (wgtaci) is not only a weight, but has also been calibrated to population totals.

The weighted numbers from the country samples provided by SHARE are readjusted (divided by population numbers in order to produce the same sample sizes) so that it is possible to calculate, for example, standard errors (see also Börsch-Supan and Jürges (2005), [p. 36]). When all countries are combined to create a bigger sample, an additional weight is calculated which equalizes the sample sizes of all countries.

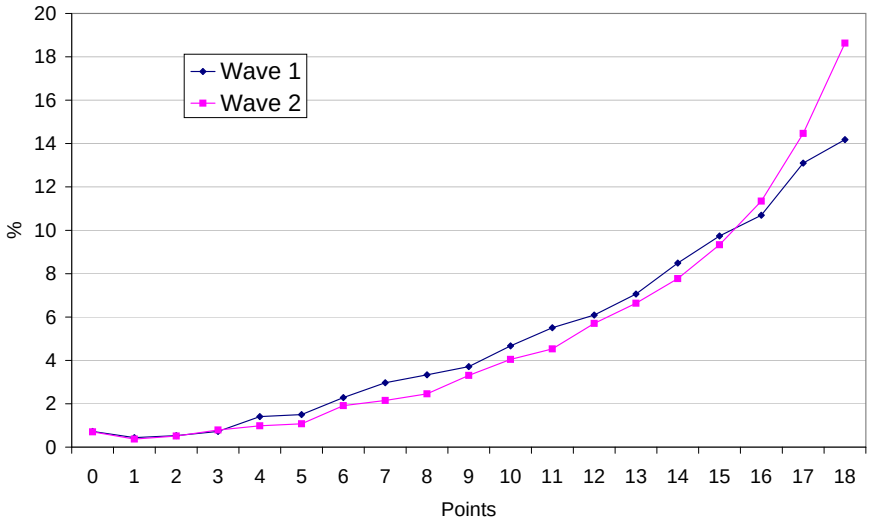
5.1.3 Operationalization: The 'Cognitive Function' Variable

Several variables exist in the SHARE data that measure the cognitive function. From these a new variable is created as a basis for the analyses. Questions are partly based on the mini-mental-state examination (MMSE) and the Dementia Detection (DemTect) scale (see section 2.1.3), but cannot be ascribed to one scale. Several items are captured: *orientation, numeracy, verbal fluency* and *recall*. The block CF 'cognitive function' in the SHARE data also comprises questions about self-rated reading and writing skills; however, in the second wave, there are too many missings and thus the two items were excluded from a generic 'cognitive function' variable. The questionnaire can be found at: `http://www.share-project.org/t3/share/new_sites/Fragebogen/ma-Gene.pdf`. From these five items—*orientation, numeracy, verbal fluency, recall 1 and recall 2*—a new variable *'cognitive function'* is created for this analysis here with a maximum of 18 points (for a more detailed description of the operationalization, see the appendix).

The results for both waves can be seen in figure 5.1. Of all people above age 60, 14% reached 18 points in wave 1, compared with 19% in wave 2. The proportion of people achieving fewer points is declining, and less than 1% of the people have three, two, one or zero points.

Seven is the cut-off point: people who achieve seven or fewer points are defined as having a 'severe cognitive impairment' (SCI). It is difficult to determine the cut-off point for cognitive impairment. Here, seven points are chosen because at this level 10% of the population with the lowest cognitive performance are included. The category is

Figure 5.1: Relative Frequency of the 'Cognitive Function' Variable in Wave 1 and Wave 2



Source: SHARE Data, own calculations

called SCI and not dementia, because the diagnosis of dementia has to be ascertained by a medical professional and cannot be assigned after only a cognitive function test has been performed. It might also comprise more mild cases of cognitive impairment because the prevalence of dementia above age 60 found with the GKV data is 5.3% (chapter 3). The results are shown in table 5.2. Of the people above age 60, 10.9% show signs of SCI in wave 1, and 8.8% in wave 2.

Another problem that can occur involves age and education. The average cut-off point might be too high for an older person with a low level of education because he or she cannot remember things or calculate well, but is experiencing normal cognitive aging. It could also be too low for a younger person with higher education and impairments who gets some points simply due to better training. To overcome this problem of the inclusion or non-inclusion of wrong cases, some studies have suggested adjusting the scale for age and education, e.g. Crum et al. (1993) who give a possible table for classification of the MMSE score. Taking this idea into account for the new variable *'cognitive function 2'* which is derived from the variable *'cognitive function'*, two age groups 60-79 and 80+, and two educational groups, one with a high level of education (13+ years), and the other with a lower level of education (fewer than 13 years), are distinguished. People aged 60 to 79 with high education were rated on a stricter scale, starting at zero points and going up to eight points, which indicates severe cognitive impairment. Meanwhile, people above age 80 with low education were rated on a less

stringent scale of zero to six. People aged 60 to 79 and with low education, and people above age 80 and with high education, were kept in the grouping described above from zero to seven.

When education is taken into account, we find that there are slightly fewer people with severe impairment (table 5.2). The results by age and education show that the re-classification leads to only slight changes for people aged 60-79 with high education. Their risk is found to be lowest because of their younger age and the higher education, and because the stricter measurement scale increases the prevalence only by 0.3% to 1.5%. For people above age 80, the prevalence was found to decrease from 31.9% to 25.2%. This is because, with low education and seven points they are no longer classified as SCI. The change for the total prevalence in table 5.2 therefore comes primarily from a decrease in the number of people above age 80 with severe problems. Missing education cases (1.1% in wave 1 and 6.6% in wave 2) were treated as low-educated; because this is the biggest group, this classification minimizes mistakes. It means that some of the people above age 80-more so in the second wave, but to a lesser extent in both groups-might have higher levels of education and might thus actually be in the lower group if they have borderline cognitive status points. There could be a very slight underestimation, but this effect is very small and does not explain the difference between waves 1 and 2. When age-standardized results are calculated to keep possible age differences between the waves into account, about the same results are obtained. For the following analyses the variable *'cognitive function 2'* is used because it excludes the above mentioned problems.

Finally, table 5.2 shows that people who drop out of the survey after the first wave generally have a worse cognitive status in wave 1.

In the second wave, the variable 'Alzheimer's Disease, dementia, organic brain syndrome, senility or any other serious memory impairment' (diagnosed by a doctor) is requested. Unfortunately, it does not exist in the first wave, and therefore cannot be used for longitudinal analysis. However, this group will be included in the general descriptive analysis regarding determinants and support. The diagnosis of AD, other dementia or other memory impairment (in the following called MEM) applies to 2.3% of the sample.

Missing Information on Cognitive Function

The cognitive status from the new created variable 'cognitive function 2', which is used for the following analyses, is missing for 3.1% in wave 1, and from 3.3% in wave 2. For

Table 5.2: Prevalence of Severe Cognitive Impairment (in %) above Age 60 in the SHARE Data, 11 Countries, in Wave 1 (2004/05) and Wave 2 (2006/07)

Age, Edu, Points SCI*	Wave 1	Wave 2
Cognitive Impairment		
60-79, Low, 0-7	8.1	6.1
60-79, High, 0-7	1.2	0.3
80+, Low, 0-7	31.9	25.6
80+, High, 0-7	12.3	9.4
All	10.9	8.8
Cognitive Impairment 2		
60-79, Low, 0-7	8.1	6.1
60-79, High, 0-8	1.5	0.8
80+, Low, 0-6	25.2	20.0
80+, High, 0-7	12.3	9.4
All	9.9	7.9
Cognitive Impairment 2 for Panel-Attrition		
60-79, Low, 0-7	10.8	
60-79, High, 0-8	2.5	
80+, Low, 0-6	32.2	
80+, High, 0-7	17.1	
All	13.3	

*Age-group, Education, Points counting SCI

people who drop out after the first wave, this information is missing more often, 5.2%.

In both waves, people for whom the information about the cognitive status is missing are on average older than the people who answered the questions. About 50% refused to answer the block of questions in the SHARE questionnaire, chose 'don't know', or the responses to the items 'refusal' and 'don't know' were missing as well. They also often refused answers to other blocks, such as physical health, and reported much more frequently health problems such as ADL or IADL limitations. Furthermore, about 60% (58% wave 2) of the missing cases have a proxy respondent; this is the case for 15% (18%) of respondents in the cognitively severely impaired group, compared with less than 2% (3%) in the other groups. The interviewer information about "the respondent 'never' or 'almost never' understood the questions" was highest for the group with missing information on the cognitive status (17.5% (19.9%)), and second-highest for the severely impaired group (6.7% (9.4%)). This provides strong evidence that the group with missing information about the cognitive status is highly selective and is therefore not excluded, but is treated separately. A new variable 'missing cognitive status, proxy respondent' (MiP), includes those who had a proxy respondent (1.7% (1.9%)) and those who misunderstood the questions of the interview (never, almost never, now and then) (0.1% and 0.2%).

5.2 Cross-Sectional Results - Severe Cognitive Impairment in the SHARE Countries

The weighted average of the variable 'cognitive function' of all people above age 60 is 13.35 (95% CI: 13.29-13.42) in the first wave, and increases significantly to 13.91 (95% CI: 13.85-13.97) in the second wave. The DemTect scale developed by Kessler et al. (2000) has some different questions, but also 18 points as a maximum. The average score of non-demented people above age 60 was 15.4 (SD 2.1) and the cut-off points were eight for 'possible dementia', 9-12 for 'moderate cognitive impairment' and 13-18 for 'normal cognition' (Kessler et al., 2000). The average score in the DemTect is higher than the average in this scale and thus the lower cut-off points we use seem justified. Kessler et al. (2000) found in discriminant analyses with a cut-off score of $\geq$11 in the DemTect that 92% of patients and controls were correctly classified.

The country-specific mean values can be seen in table 5.3. The results, as well as all following results, are age-standardized to ensure that no age effect exists. The

Mediterranean countries, especially Spain and Italy, have a lower score of 10 and 11 points, while people in Greece, France and Belgium have average scores of 13 points, and the other countries reach about 14-15 points. In all countries there is a significant increase in the mean value of the cognitive function in the second wave.

It is difficult to say if the country differences can be interpreted as real differences. Literature reviews about regional differences in dementia prevalence in section 2.4.4 are contradictory and also contradict these results. The lower cognitive score, especially in Spain, Italy and Greece, could be influenced by the sampling procedure. People with care needs and cognitive problems are more likely to live with their families in these countries, which increases the chance that they will participate in the SHARE survey. In Northern and Western European countries, they often move into special housing for the elderly, which are not included at random, and therefore a more healthy sub-population might be captured. For the descriptive analyses all countries are pooled and thus the differences are neglected. In the multivariate analyses the countries are included as control variables.

Table 5.3: Mean Scores of Cognitive Impairment above Age 60 in 11 SHARE Countries, Age-Standardized

	Wave 1		Wave 2	
Country	Mean	CI	Mean	CI
Spain	10.04	[9.82-10.25]	10.54	[10.30-10.77]
Italy	10.97	[10.77-11.16]	11.86	[11.67-12.04]
Greece	12.58	[12.41-12.74]	13.06	[12.90-13.21]
France	12.99	[12.79-13.18]	13.40	[13.19-13.60]
Belgium	13.31	[13.15-13.46]	14.07	[13.91-14.24]
Netherlands	14.02	[13.84-14.21]	14.68	[14.51-14.86]
Austria	14.13	[13.92-14.34]	14.93	[14.68-15.18]
Germany	14.18	[14.01-14.35]	14.82	[14.65-15.00]
Denmark	14.54	[14.30-14.78]	14.91	[14.73-15.09]
Switzerland	14.73	[14.46-14.99]	15.72	[15.07-15.48]
Sweden	14.76	[14.59-14.93]	15.29	[15.13-15.45]
All Countries	13.35	[13.29-13.42]	13.91	[13.85-13.97]

The cognitive status of people living in special housing for the elderly and nursing homes is lower than for the total population; the mean over all countries is about three points lower: 10.28 in wave 1 and 10.65 in wave 2. The mean of the population in private households does not differ significantly from the total population; the numbers of people in institutions provided in the sample are too low to have an impact. The biggest difference is seen for the Netherlands: without the institutionalized population, there is an increase in the mean number of points by 0.37 in the first and 0.24 points in the second wave. All other differences are far smaller.

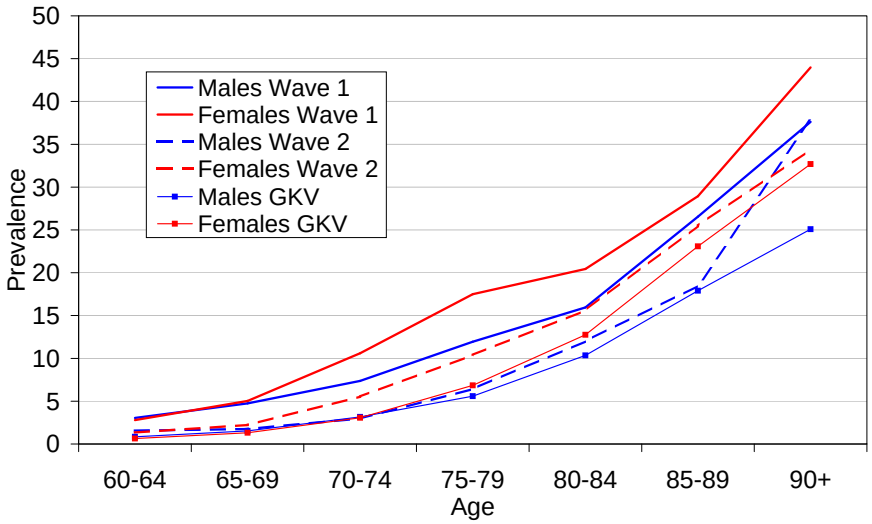
5.2.1 Determinants of Severe Cognitive Impairment

Many factors influence the prevalence of dementia and SCI, as has been discussed in chapter 2.4. In the SHARE several variables are included to analyze SCI: age, gender, education, partnership status, number of children, physical health and certain illnesses. Age has shown to be the main risk factor. Our data also shows that people with SCI are on average older: the mean age in wave 1 is 77.7, compared with 71.4 for the total sample, while in wave 2 the mean age is 79.7, compared with 71.6 years for the total sample. The proportion of women is higher in the group of people with SCI compared with the total population. The age-specific prevalence by gender is displayed in figure 5.2. Results on dementia from the literature and from own analyzes with data from the German Sickness Funds (GKV data), (see chapters 2.4.1 and 3) are confirmed for SCI: the risk increases with age and is higher for females than for males. The level for SCI is higher, which is expected because of the higher total prevalence. The comparison is done to set the prevalence and further down the incidence of SCI in relation with the prevalence and incidence of dementia to see to what extent the results on determinants obtained in this chapter can be assigned for demented people in general.

The comparison between the waves shows a lower prevalence among both males and females in the second wave over all age groups. Over age 90, there is a wider difference between the women in waves 1 and 2, and a narrowing for males. However, this relationship is inverse to the proportion of the missing cases.

Table 5.4 shows the distribution of the demographic variables. The groups with SCI and 'missing cognitive status, proxy respondent' (MiP) are significantly older than the total sample, including many more elderly people over age 75 and fewer below. In the second wave, the age distribution of the two impaired groups seems to be slightly older than in the first wave. In the total sample, the age profile seems to be stable. The

Figure 5.2: Prevalence of SCI in 11 SHARE Countries in Comparison with the Prevalence of Dementia in Germany with the GKV Data



Source: SHARE Data, GKV Data, own calculations

proportion of women is higher in the SCI and lower in the MiP group compared with the total population, while living with a partner does not seem to be different between the groups. Maybe men have more often a proxy respondent in case of severe health constraints. Education is differentiated into low and high education for people below and above 13 years of education and training. In the total sample, more people have high education than people in the SCI and MiP groups. There is no clear tendency regarding the number of children.

The table shows that there is a large degree of age dependence in belonging to a group. Therefore, in the following, all results are calculated as age-standardized rates. When the variables for this table 5.4 are age-standardized, there is still a gender effect in the SCI group showing a higher proportion of women than in the total population, of 60.4% (62.0% wave 2), compared with 56.5% (56%). In the MiP group, the proportion is lower, at 49.1% (52.1%). We also find that the effect of low education persists: 95.6% (97.7% wave 2) of people in the SCI group have low education, while this proportion in the total population is about 83.8% (82.0%), and in the MiP group it is 86.1% (89.8%). Rates of childlessness are about 20% for all groups in both waves. The proportion of people with a partner is about 60% (62.8%) in the total sample, and only 50.9% for the SCI group, but increases to 60.0% in the second wave, or 59.6% (66.0%) for MiP.

Table 5.4: Distribution of Several Demographic Variables in the Two Waves for the Total Sample, the 'Severe Cognitive Impairment' Group and the 'Missing Cognitive Status' Group (in %)

	Total Sample		SCI group		MiP group	
Variable	W1	W2	W1	W2	W1	W2
Age						
60-64	24.9	24.7	7.2*	5.6*	10.7*	9.4*
65-69	21.9	21.4	10.7*	6.6*	7.7*	9.7*
70-74	19.7	18.4	17.8	12.4*	15.8	11.4*
75-79	15.2	15.5	22.6*	20.5*	15.0	16.3
80-84	11.1	12.2	20.2*	26.3*	21.3*	18.8*
85-89	4.8	5.6	12.8*	18.6*	15.1*	21.1*
90+	2.4	2.1	8.7*	10*	14.4*	13.4*
Gender						
Females	56.5	56.0	60.4*	62*	49.1*	52.2*
Males	43.5	44.0	39.6*	38*	50.9*	47.8*
Education						
Low	83.8	82.0	95.6*	97.7*	86.1	89.8*
High	16.2	18.0	4.4*	2.3*	13.9*	10.2*
Partner						
With	60.0	62.8	50.9*	59.9	59.6	66.0
Without	40.0	37.2	49.1*	40.1*	40.4	34.0*
Children						
0	21.4	19.7	19.6*	17.8*	19.2	19.7
1+	78.6	80.3	80.4	82.2	80.8	80.3

W1=Wave 1, W2=Wave 2

Variables gender, education, partner and children are age-standardized

*Difference to total sample (same wave) is significant on the 5% level.

General Health Measures

In this section, general physical and mental health measures of the total population and the SCI and the MiP sub-populations are shown. The operationalization and data problems are described in the appendix.

Generally, we can see in table 5.5 that people in the groups with SCI and MiP have significantly more health constraints than people in the total sample. People with MiP have even higher constraints than SCI people. For example, 14% of the total sample have an ADL limitation in the first wave. This proportion rises in the SCI group to more than one-fourth (27.9%) and in the MiP group to more than one-third (38.3%). While for the total population all physical health constraints are about stable or even decrease slightly over time, they increase in the two other groups. This finding is in accordance with the item 'health is worse in the second wave', to which a higher proportion in the SCI and MiP groups respond with 'yes'. There is no consistent difference in obesity, but, more importantly, these groups are more likely to have a BMI of less than 18.5, and to suffer from weight loss of at least 10 kilos.

In addition, the mental health of the SCI and MiP populations is worse than in the total population. Depression occurs nearly twice as often in the SCI group and in the MiP group in the second wave. The self-rated QoL and optimism levels are much lower in the SCI group and the participants more often say they are not prepared for the future. Results for the MiP group are unreliable due to a very high number of missing cases, as is also the case for most other mental health questions.

The lifestyle variables smoking, drinking and exercise were included. Current and past smoking do not show clear effects; the proportion of ex-smokers is somewhat lower in the SCI group, but higher in the MiP group. The proportion of people who drink alcohol almost daily is quite high in the total population, or about every fourth person. Except in the first wave for the SCI group, this proportion is a little lower for the SCI group in the second wave and for MiP. Moderate alcohol consumption is lower in the SCI and MiP groups, or about half that of the total population. More than half of the cognitively impaired people in the SCI and MiP groups drank no alcohol at all within the last six months, or only about one-third in the total population (the numbers do not add to 100% because there is another category 'light drinking', which measures drinking one to three times a month). The proportion of people over age 60 doing 'no sports or activities that are vigorous' is only about 50% in the total population and even rises in the SCI and MiP groups. Also moderate activities ('activities requiring a

moderate level of energy') are much less common.

Table 5.5: Health of the Total Population, People with Severe Cognitive Impairment and People with Missing Cognitive Status (Age-Standardized)

	Total Sample		SCI		MiP	
	W1	W2	W1	W2	W1	W2
Health Behavior						
Current Smoker	14.1	14.0	15.4	11.4*	7.1*	16.6*
Ex-Smoker	27.8	28.8	20.4*	18.7*	34.9*	29.9
Alcohol ≥5/week	26.5	25.6	25.2	17.5*	18.6*	19.6*
Alcohol 1-4 /week	21.8	22.8	10.0*	8.9*	10.8*	12.8*
No Alcohol	33.1	32.7	55.5*	63.1*	61.1*	56.1*
No Vigorous Act.	50.3	49.0	72.1*	75.1*	72.7*	80.2*
No Moderate Act.	15.5	15.2	32.9*	43.2*	37.7*	50.8*
Physical Health						
1+ ADL Limitations	14.0	13.4	28.0*	34.4*	38.9*	46.0*
1+ IADL Limitations	22.7	21.9	43.0*	54.7*	52.3*	60.5*
Long-Term Illness	54.6	51.4	64.5*	70.2*	74.6*	78.6*
2+ Chronic Diseases	49.9	47.6	56.9*	61.3*	48.2	54.5*
Sev. Limited Activities	16.3	16.5	26.5*	34.3*	46.3*	52.1*
Health 2nd Wave Worse		30.6		51.9*		59.0*
BMI < 18.5	1.7	1.9	2.2*	2.7*	3.4*	7.3*
BMI ≥30	16.2	17.5	18.1*	22.9*	11.0*	18.4
Lost Weight (≥10 kg)		4.6		8.0*		15.6*
Mental Health						
Depression (EURO-D)	26.9	22.6	50.9*	52.7*	36.4*	49.5*
QoL Low (CASP-12)	35.0		60.0*		34.5°	
Optimism Low	36.6	33.2	51.1*	48.8	39.3°	55.2*°
Future - Not Prepared	9.3	9.3	20.3*	12.7*	13.4*	29.2*°

W1=Wave 1, W2=Wave 2

*Difference to total sample (same wave) is significant on the 5% level.

No data available if cell is empty.

°Large proportion of missing cases.

Morbidity

In the following, the prevalence of certain diseases which were diagnosed by a medical doctor within the total and the SCI and MiP populations are examined. Results in table 5.6 show that the prevalence is higher for most diseases when people are cognitively impaired, especially cerebral vascular diseases, diabetes mellitus, arthritis or rheumatism and PD, but also heart and chronic lung diseases. The prevalence of cancer and tumors seems to be a little lower in cognitively impaired people.

Table 5.6: Morbidity of the Total Population, People with Severe Cognitive Impairment and People with Missing Cognitive Status (Age-Standardized)

	Total Sample		SCI		MiP	
	W1	W2	W1	W2	W1	W2
Heart Problems (+ Attack)	15.7	14.8	17.2*	20.2*	20.1*	23.8*
High Blood Pressure	36.7	39.0	35.9	42.1	30.0*	28.4*
High Blood Cholesterol	20.8	22.1	21.4	24.1*	16.1*	20.8
Cerebral Vasc. D. (+ Stroke)	5.2	4.6	9.1*	11.5*	15.8*	22.9*
Diabetes Mellitus	11.5	12.5	19.2*	20.9*	16.4*	15.3*
Chronic Lung Disease	6.3	6.3	9.1*	9.5*	5.3*	10.4*
Asthma	5.0	4.9	4.8	5.7*	2.6*	2.5*
Arthritis or Rheumatism	23.3	23.9	29.5*	34.7*	20.9*	23.2
Osteoporosis	9.6	10.7	11.1*	11.9*	7.9*	9.0*
Cancer or Malignant Tumor°	6.7	5.0	4.8*	3.0*	7.9*	9.0*
Benign Tumor°		2.5		1.3*		1.0*
Stomach Ulcer°°	6.2	4.0	7.4*	5.5*	4.0*	3.1*
Parkinson's Disease	1.1	1.1	3.0*	3.6*	3.7*	4.6*
Cataracts	12.3	10.6	11.5	8.7*	10.3*	9.3*
Hip or Femoral Fracture	2.8	2.5	3.7*	3.9*	3.7*	4.3*
Other Conditions	16.4		21.7*		24.5*	
Alzheimer's D., Dementia**		2.1		9.4*		20.0*

W1=Wave 1, W2=Wave 2
*Difference to total sample (same wave) is significant on the 5% level.
**'Alzheimer's disease, dementia, organic brain syndrome, senility or any other serious memory impairment': Question was only asked in Wave 2.
°'Benign Tumor' is asked separately in the second wave, which should explain the lower numbers for the category 'Cancer or Malignant Tumor'
°°Stomach, Duodenal or Peptic Ulcer

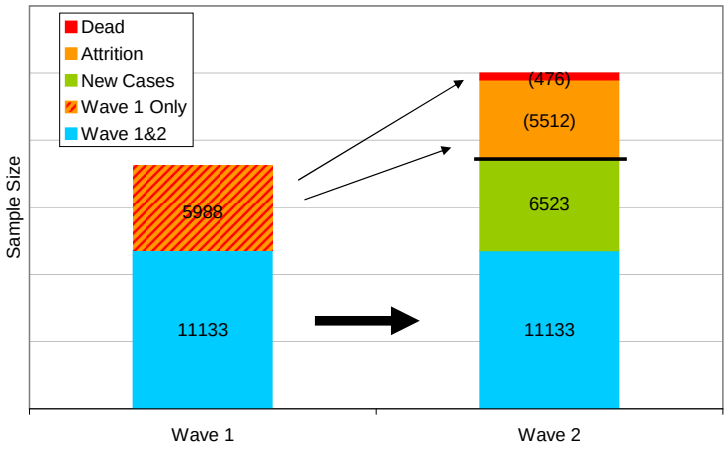
The prevalence of 'AD, Dementia, Senility' increases in the SCI group to 9.4%, compared with 2.1% in the total population. It increases even more in the MiP group to 20.0%.

5.3 Longitudinal Results - Changes in Cognitive Status and Health over Time

For the longitudinal analysis, 11,133 people provide information about changes over time. Figure 5.3 furthermore shows that the panel attrition rate is 32%, and 2.8% drop out because of death. Panel attrition by country shows that rates range from 20.8% in Greece to 49.0% in Germany.

Often systematic differences exist between these groups relative to the longitudinal group, they differ in their age and gender distribution. The mean age in the group participating in both waves is significantly lower, at 70.0 years, than in wave 1, at 71.7 years. In the two groups, 'Waves 1&2' and 'Attrition' (not including people who died), about 54.4% and 55.2% are females. In the group of people who died, 46.6% are females. Only 50.6% of people who died lived with a partner, while 68.9% in the attrition group and 68.6% in the longitudinal sample live with a partner.

Figure 5.3: Sample Composition of the SHARE Data (Ages 60+) in Waves 1 and 2



Source: SHARE Data

Table 5.7 shows that regardless of what health definition is examined, people who died are found to have been in worse health. This is also true, but to a lesser and sometimes insignificant degree, for people who only participated in wave 1 and then dropped out for reasons other than death ('attrition'). This is also true for the proportion with SCI; it is much higher for people who died shortly after wave 1, and it is also significantly higher for people who dropped out after wave 1. The mean number of cognitive points decreased for each group. The health behavior was rated as worse regarding physical activities. Alcohol consumption was lower among people who died,

but less difference is seen for people who participated only in wave 1 relative to the longitudinal sample. The proportion of people who were current or ex-smokers is higher in the group of people who died.

Table 5.7: Proportion of People in Bad Health/with Support Differentiated by Participation in Both Waves, Attrition and Death after Wave 1

	Wave 1&2	Attrition°	Died
Health Behavior			
Current Smoker	13.2	14.2	24.3*
Ex-Smoker	29.1	27.5	38.1*
Alcohol ≥5/week	27.7	24.9*	24.6
Alcohol 1-4 /week	22.5	21.1	17.4
No Alcohol	31.4	35.4*	45.5*
No Vigorous Act.	47.1	52.9*	71.5*
No Moderate Act.	13.0	16.4*	32.3*
Physical Health			
1+ ADL Limitations	12.4	13.5	28.2*
1+ IADL Limitations	19.9	23.6*	40.4*
Long-Term Illness	53.0	55.9	72.5*
Sev. Limited Activities	14.4	17.6*	32.7*
BMI < 18.5	1.3	1.6	3.4*
BMI ≥30	17.4	15.4*	19.6
Mental Health			
Severe Cognitive Impairment	8.1	12.0*	18.4*
Mean Number of Cog. Points	11.2	10.7*	9.6*
Depression (EURO-D)	25.5	26.9	38.7*
QoL Low (CASP-12)	34.0	37.0	49.1*
Optimism Low	35.5	38.6	49.0*
Future - Feel Not Prepared	8.9	9.2	15.9*

*Difference to wave 1&2 is significant on the 5% level

°Attrition due to other reasons but death

5.3.1 Incident Severe Cognitive Impairment

The strength of longitudinal data are that the same people can be followed and status changes analyzed. This makes it possible to not only look at the prevalence of SCI, but also at the incidence: people without SCI in wave 1 who enter this status group in wave 2. In wave 1, 7.3% of the people in the longitudinal sample have SCI, and in wave 2, 6.1% have SCI. 3.0% of all people had this condition in both waves, from

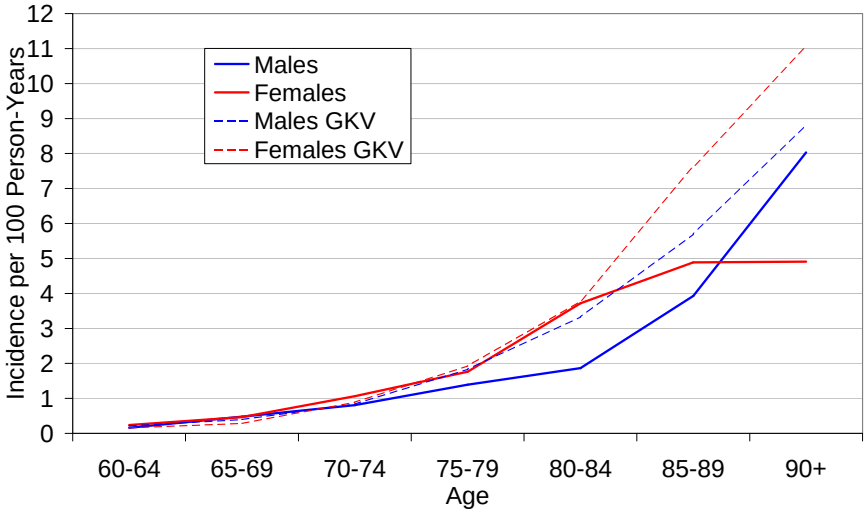
0.45% with SCI in wave 2 the cognitive status in wave 1 is missing. Substracting the prevalent cases and the missings leads to 2.65% incident cases, a rate of 2.82% over a period of about 2.35 years. If all SCI-missing cases from wave 1 were incident cases, the proportion would rise to 3.30%. Of the incident cases, 72% seem to have been already moderately cognitively impaired in wave 1 with a score of between eight and twelve points. Yearly incidence rates (the average interview time of 2.35 years between the two waves is taken as a calculation basis) show an increase with age in figure 5.4. It is stronger for women, but stagnates at ages 80-84. For males, the increase starts later but continues steadily.

A comparison with the incidence dementia rates from the GKV data (incidence for women and men above age 60 is 1.63 and 0.93 per 100 person-years) shows just a slightly lower incidence until about ages 75-79 for males and ages 80-84 for females. After these ages, a lower increase occurs for males, and a dispersion takes place among women, with a much stronger increase for females seen in the GKV data. If the missing cases (cognitive status in wave 1 is missing, in wave 2 SCI) were included into the graphs, the trajectories would have had the same pattern on a slightly higher level; e.g., at age 90+ males would have had an incidence of 8.2 cases per 100 person-years, instead of 8.0; and females would have had an incidence of 5.6 cases per 100 person-years instead of 4.9. Since the prevalence of SCI in figure 5.2 is higher than the prevalence of dementia in the GKV data, the SCI incidence was also expected to be slightly higher. The finding that it is lower might be an underestimation of true cases either because of panel attrition or because of missing answers within the data.

Another way to look at cognitive developments is to examine the changes in the number of points. To create this new variable the 18-point scale built for waves 1 and 2 is taken, and the difference between the waves is measured. On average, the cognitive function is not worse in the second wave, as can be seen in figure 5.5; the mean of the new variable is 0.013, and is not significantly different from zero. Positive values indicate a decrease in the number of cognitive points. The interquartile range is 2.0, 89% of the changes are within four and negative four points. People with no cognitive change (including a one-point decrease to a one-point increase) have the lowest mean age of about 68.8. People with decreasing cognitive function are on average older than people with no change or an improvement: 71.2 years with two to four points, and more than 73 years when a greater decrease happens. Extreme cases are briefly described in the appendix (8).

Table 5.8 shows the changes over time regarding some health behaviors, physical and

Figure 5.4: Incidence of SCI in 11 SHARE Countries in Comparison with the Incidence of Dementia in Germany with the GKV Data



Source: SHARE Data, GKV Data, own calculations

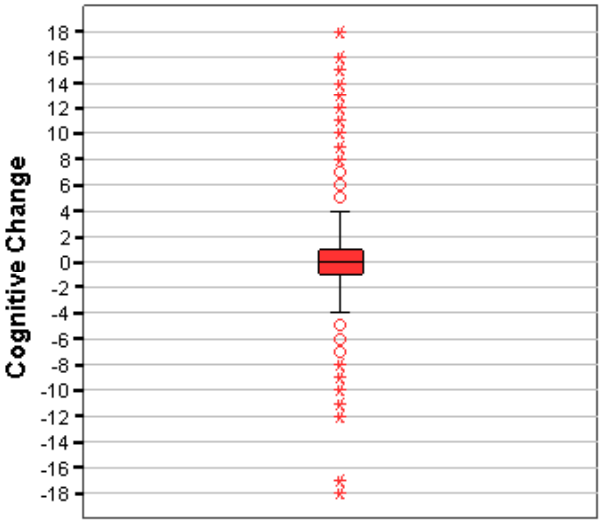
mental health variables, as well as changes in the partnership status, body weight and living arrangements (i.e., private households or institutions). The first column shows the results for the total population, and the second a comparison with the incident SCI population (2.7%). In column 3 are the results for the group which shows a decrease in cognitive status of at least five points (5.3%).

In the appendix (section 8) in table 8.2, results for additional risk groups are shown: people with missing information about the cognitive change, with a proxy interview or a poor understanding of the questions (1.5%) in column 4, and people with an incident proxy interview in wave 2 (2.5%) and with proxy interviews in both waves (1.4%) are in columns 5 and 6. These people are believed to belong to highly selected groups with missing information or proxy interviews due to a poor cognitive status.

The first two variables in table 5.8 below show the living arrangements in private vs. institutional homes, and with/without partner. Large differences can be seen in housing: people in any of the groups with cognitive impairment in columns 2 and 3 are significantly more likely to move into institutions than people from the total population. People with incident SCI or a strong cognitive deterioration are also significantly more likely to live in institutions. Most people live together with a partner, disregarding the cognitive status.

The next four variables show the health behavior of the population. While in the total population and in the cognitive change group the proportion of non-smokers is just

Figure 5.5: Cognitive Changes between Wave 1 and Wave 2 in the SHARE Data



Source: SHARE Data, own calculations

over half, it rises in the SCI group to 68.0%. The chances of stopping smoking between the two waves is non-significantly higher for people with cognitive impairment. They also have lower alcohol consumption and drink less between the waves. Stable 'much moderate activities' are most widespread in the total population. This proportion decreases considerably in all cognitively impaired groups. The decrease in activities between the two waves is strongest in the SCI group. A stable body weight is most prevalent in the total population. All other groups have a higher loss of body weight, but also a higher proportion of weight gain.

Significant differences can be seen for the three physical health variables. A stable condition without ADL, IADL or limited activities is highest within the total population; all other groups have a high stable prevalence of these limitations, and also a high incidence in wave 2. The two groups with proxy interviews are in the worst health state by far.

The situation is similar regarding mental health: the prevalence and incidence of people with depression is significantly higher in the cognitively impaired groups compared with the total population. The self-estimated QoL and optimism levels in wave 1 (QoL only wave 2: see appendix) are lowest for the SCI group.

Table 5.8: Health Behavior, Physical and Mental Health of the Total Population, Incident SCI Population and People with a Deterioration of the Cognitive Status of ≥5+ Points (Proportion in %) (Age-Standardized)

		Total Pop.	Incid. SCI	Cogn. Ch. 5+
Housing°	Move into Institution	1.6	4.1 *	3.7 *
	Services / Nursing	1.1	2.7 *	2.4 *
	Private Household	96.8	93.2	93.6
	Moved out of Inst.	0.5	0.0	0.3
Partner	Loss of P in W2	2.8	1.8	4.6
	No P Stable	30.7	32.5	31.2
	P Stable	66.0	65.7	63.5
	New P in W2	0.5	-	0.7
Smoking	Smoked Never	56.6	68.0 *	59.2
	Current S. (W1&W2)	10.6	8.6	10.0
	Ex-Smoker	28.1	15.7 *	23.4 *
	Stopped S. in W2	2.8	7.0	5.0
	Started S. in W2	1.7	0.4 *	2.2
Alcohol	No A. Stable	23.7	44.8 *	29.4 *
	Little A. Stable	9.2	3.8 *	5.1 *
	Moderate A. Stable	13.6	5.6 *	8.3 *
	Much A. Stable	19.7	9.9 *	16.7
	Less A. in W2	19.0	23.4	21.6
	More A. in W2	14.9	11.3	17.5
Moderate Activities	No Act. Stable	7.2	21.9 *	11.6 *
	Moderate A. Stable	7.0	7.5	6.7
	Much Act. Stable	55.2	24.3 *	42.8 *
	Less Act. in W2	18.2	40.0 *	26.5 *
	More Act. in W2	12.3	5.1 *	11.0
Weight	Loss of >10 Kilo	3.1	6.2 *	5.8 *
	Loss of 3-10 Kilo	19.1	24.6	23.5
	About Stable	61.9	43.8 *	51.1 *
	Gain of 3-10 Kilo	13.0	16.3	14.5
	Gain of >10 Kilo	2.8	9.0 *	5.1 *
ADL	No ADL W1, ADL W2	6.8	21.5 *	12.3 *
	ADL 1+ Stable	7.1	14.4 *	7.8
	No ADL Stable	81.7	58.9 *	73.5
	ADL W1, No ADL W2	4.5	5.2	6.4
IADL	No IADL W1, IADL W2	10.7	31.2 *	21.2 *
	IADL 1+ Stable	12.2	25.1 *	15.4
	No IADL Stable	70.6	36.2 *	57.0 *
	IADL W1, No IADL W2	6.5	7.4	6.4
Limited Activities	W1 no, Sev LA W2	8.8	21.6 *	16.1 *
	Sev Lim Act Stable	7.6	13.1 *	8.3
	No Sev Lim Act Stable	77.4	57.4 *	70.0 *
	Sev LA W1, No W2	6.2	7.9	5.5
Depression	No D W1, D W2	9.5	19.9 *	18.1 *
	D Stable	13.4	34.9 *	19.2*
	No D Stable	65.5	34.2 *	51.8*
	D W1, No D W2	11.7	11.0	10.9
QoL (CASP-12)	High Qol W1	37.5	20.2 *	32.6*
	Medium Qol W1	29.2	20.0 *	27.4
	Low Qol W1	33.3	59.8 *	40.0*
Optimism	High Optimism W1	24.6	13.8*	19.6*
	Medium Optimism W1	40.4	35.6	38.8
	Low Optimism W1	35.0	50.7 *	41.6*

*Difference to total population is significant on the 5% level.
°'Housing with Services for Elderly'. Includes nursing homes in wave 2.

5.3.2 Determinants of Incident Severe Cognitive Impairment

So far only descriptive results have been shown. Multivariate analysis can exclude effects that exist between explaining variables. To find out more about the influence of various factors on incident SCI, we have run logistic regressions:

$$\begin{aligned} ln[\frac{p_i}{1-p_i}] = \beta_0 + \sum_{i=1}^{6} \gamma_i \times age_i + \delta \times sex + \sum_{k=1}^{10} \epsilon_k \times coun_k + \sum_{l=1}^{3} \zeta_l \times prox_l + \\ \sum_{m=1}^{2} \eta_m \times edu_m + \sum_{n=1}^{3} \theta_n \times part_n + \sum_{o=1}^{4} \iota_o \times inst_o + \sum_{p=1}^{5} \kappa_p \times weig_p + \\ \sum_{q=1}^{4} \lambda_q \times smok_q + \sum_{r=1}^{6} \mu_r \times drink_r + \sum_{s=1}^{6} \nu_s \times act_s + \sum_{t=1}^{14} \xi_t \times I_t \end{aligned} \quad (5.1)$$

$$\begin{aligned} ln[\frac{p_i}{1-p_i}] = \beta_0 + \sum_{i=1}^{6} \gamma_i \times age_i + \delta \times sex + \sum_{k=1}^{10} \epsilon_k \times coun_k + \sum_{l=1}^{3} \zeta_l \times prox_l + \\ \sum_{m=1}^{2} \eta_m \times edu_m + \sum_{n=1}^{3} \theta_n \times part_n + \sum_{o=1}^{4} \iota_o \times inst_o + \sum_{u=1}^{3} o_u \times adl_u + \\ \sum_{v=1}^{3} \pi_v \times iadl_v + \sum_{w=1}^{4} \rho_w \times limac_w + \sum_{x=1}^{5} \sigma_x \times depr_x + \sum_{y=1}^{3} \tau_y \times casp_y \end{aligned} \quad (5.2)$$

where p_i stands for the probability of incident dementia, β_0 for the constant, *age* for 5-year age-groups from age 60, *sex* for males and females, *coun* for the 11 included countries, *prox* for the variable 'proxy interview', *edu* for high, low or missing education, *part* for the variable 'living together with a partner' and the development over time, *inst* for the variable 'living in an institution' and the development over time, followed by the health behavior variables *weight*, *smoking*, *drinking*, *activity* and their changes between the two waves, and several illnesses in wave 1 (I). In the second equation the demographic and living condition variables are followed by the physical and mental health variables *adl*, *iadl*, *limited activities*, *depression*, *CASP–12* and their changes over time. γ to τ are the regression coefficients.

Excluded from the analysis were prevalence cases from wave 1 and people with missing information about their cognitive status as well as one person with missing information about ADL and IADL. This left 9,977 people, of whom 295 (2.96%) had an incident SCI in wave 2. Different models are calculated, and the results are displayed

in tables 5.9 and 5.10. The lifestyle variables from both waves are taken into account to see if the status stayed stable or if it changed.

In table 5.9, lifestyle factors and illnesses are analyzed. Model 1 shows the effects for age, gender and country. The risk increases strongly with age, but then decreases slightly in the highest age group, or ages 90+. In the first model, women have a significantly higher risk of developing a SCI. Compared with Germany, Sweden, the Netherlands, Denmark, Greece and Switzerland have lower risks, while higher risks are found for Spain and Italy. Meanwhile, Austria, France and Belgium are shown to have roughly the same risk levels as Germany. In the following models, the effects for age persist; regardless of what other variables are included, the risk of developing an SCI is found to increase strongly with age. For gender, the effect is no longer significant when education is included. When lifestyle variables are included the effect reverses: females have a lower risk, but not significantly so. The fact that the interview involved a proxy respondent is a good indicator that the person has mental difficulties; this effect is especially clear when a proxy person is present in both waves. Education is also shown to have a strong influence, with higher education showing significantly protective effects. Partnership status is not found to have significant effects before living in an institution is controlled for. Meanwhile, the risk of developing incident SCI is shown to increase for people who live alone in both waves, relative to people living with a partner in both waves; however, when other variables are included, the significance vanishes. People who are living in or moving into an institution are found to have a much higher risk of developing incident SCI. Changing body weight is also identified as a risk factor, regardless of whether it is a decrease or an increase. Including lifestyle variables into the model shows a significant improvement of it. The findings indicate, for example, that ex-smokers have a significantly lower risk compared with people who never smoked, and that people who did not drink alcohol within the last six months before the interview in both waves had a significantly higher risk than moderate drinkers (about three to four times a week). Doing no moderate activities ('activities that require a low or moderate level of energy, such as gardening, cleaning the car, or taking a walk'), or decreasing the level of activity between the two waves, is found to increase the risk. Some illnesses in wave 1 are shown to increase the risk of incident SCI: high blood pressure sufferers who had a stroke, diabetes, chronic lung disease and asthma have an increased risk, and people with cataracts have a lower risk. The effects for stroke and diabetes become less significant when lifestyle factors are controlled for.

Table 5.9: Logistic Regression Results for Determinants of Incident SCI – Health Behavior and Illnesses

		Model 1		Model 2		Model 3		Model 4		Model 5	
		OR	p	OR	p	OR	p	OR	p	OR	p
Age	60-64	1		1		1		1		1	
	65-69	2.43	***	2.30	***	2.18	**	2.29	***	2.20	***
	70-74	3.69	***	3.12	***	2.77	***	3.10	***	2.81	***
	75-79	8.51	***	7.18	***	5.95	***	7.31	***	6.28	***
	80-84	16.34	***	11.61	***	8.78	***	11.70	***	9.42	***
	85-89	37.93	***	24.95	***	17.63	***	25.37	***	18.73	***
	90+	25.58	***	14.22	***	8.63	***	14.64	***	9.32	***
Gender	Males	1		1		1		1		1	
	Females	1.38	*	1.17		0.80		1.23		0.82	
Country	Germany	1		1		1		1		1	
	Austria	0.80		0.73		0.66		0.76		0.68	
	Sweden	0.35	**	0.35	**	0.44	*	0.38	**	0.49	*
	Netherl.	0.49	*	0.38	**	0.45	*	0.39	*	0.45	*
	Spain	3.78	***	3.30	***	2.71	***	3.48	***	2.89	***
	Italy	2.13	**	1.66	◦	1.53		1.68	◦	1.59	
	France	0.99		0.88		1.01		0.90		1.05	
	Denmark	0.50	◦	0.41	*	0.57		0.43	*	0.60	
	Greece	0.53	*	0.47	*	0.45	*	0.49	*	0.45	*
	Switzerl.	0.32	*	0.24	*	0.38	◦	0.24	*	0.37	◦
	Belgium	0.66		0.65		0.75		0.66		0.73	
Proxy	No Proxy			1		1		1		1	
	P in W1			2.66	◦	2.52	◦	2.46		2.38	
	P in W2			10.37	***	7.45	***	9.68	***	7.02	***
	P W1&2			22.43	***	17.72	***	22.12	***	17.38	***
Education	Low			1		1		1		1	
	High			0.16	***	0.19	***	0.17	***	0.19	***
	Missing			0.63		0.60		0.64		0.63	
Partner	Partner			1		1		1		1	
	P. Loss			0.71		0.59		0.72		0.60	
	No P.			1.17		1.05		1.18		1.09	
	New P.			0.00		0.00		0.00		0.00	
Institution	Priv. HH			1		1		1		1	
	Move in I			3.96	***	2.62	*	3.61	***	2.48	*
	Live in I			4.00	***	2.90	*	3.49	**	2.61	◦
	Move out			0.00		0.00		0.00		0.00	
	Miss			1.33		1.16		1.40		1.22	
Weight	Stable					1				1	
	> -10kg					1.93	*			1.90	*
	-10 to -3kg					1.32	◦			1.35	◦
	3 to 10kg					1.48	*			1.44	◦
	> 10kg					1.86	*			1.76	◦
	Miss					2.15	*			2.18	*
Smoking	Never					1				1	
	Stopped					1.07				1.16	
	Ex Sm.					0.72	◦			0.68	*
	Current					0.99				0.94	
	Started					0.56				0.62	
Drinking	Mod					1				1	
	No					2.16	*			2.08	*
	Rarely					0.83				0.82	
	Often					0.74				0.72	
	Less					1.46				1.44	
	More					1.11				1.08	
	Miss					6.65				6.55	
Activity	High					1				1	
	No					2.90	***			2.75	***
	Mod					1.53				1.53	
	Less					2.22	***			2.19	***
	More					1.04				1.00	
	Miss					0.57				0.54	
								...	...	...	...

*Continued on Next Page...

Table 5.9 Continued

		Model 1		Model 2		Model 3		Model 4		Model 5	
		OR	p	OR	p	OR	p	OR	p	OR	p
Illnesses*	Heart Attack							0.93		0.85	
	High Blood Pr.							0.90		0.90	
	High Blood Ch.							0.88		0.96	
	Stroke							1.79	*	1.49	°
	Diabetes							1.45	*	1.20	
	Chr. Lung D.							1.69	*	1.65	*
	Asthma							0.54	°	0.47	*
	Arthritis							1.09		1.06	
	Osteoporosis							1.02		0.98	
	Cancer							1.16		1.19	
	Stom. Ulcer							1.24		1.31	
	Parkinson's D.							2.19		1.86	
	Cataracts							0.66	*	0.65	*
	Hip Fract.							1.11		1.14	
Constant		0.01	0.00	0.01	0.00	0.01	0.00	0.01	0.00	0.00	0.00
-2 Log-Likelihood		2248.7		2078.2		1971.5		2051.9		1950.7	
R-Square		0.172		0.242		0.285		0.252		0.293	

***p≤0.001, **p≤0.01, *p≤0.05, °p≤0.1

*1. A heart attack including myocardial infarction or coronary thrombosis or any other heart problem including congestive heart failure
2. High blood pressure or hypertension
3. High blood cholesterol
4. A stroke or cerebral vascular disease
5. Diabetes or high blood sugar
6. Chronic lung disease, such as chronic bronchitis or emphysema
7. Asthma
8. Arthritis, including osteoarthritis or rheumatism
9. Osteoporosis
10. Cancer or malignant tumor, including leukaemia or lymphoma, but excluding minor skin cancers
11. Stomach or duodenal ulcer, peptic ulcer
12. Parkinson's disease
13. Cataracts
14. Hip fracture or femoral fracture
15. None

In table 5.10, the influence of subjective and objective physical and mental health measures is analyzed. While constraints in ADL do not show a significant effect, people with IADL—regardless of whether these are persistent, new or only reported in wave 1—have a higher risk of incident SCI. Having severe limitations in activities in both waves, or only in wave 2, is also shown to increase the risk. Mental problems have an influence on incident SCI: people with a stable depression and an incident depression in wave 2 have a higher risk compared with people without depression. A low QoL estimation also increases the risk (borderline significance). The number of missing cases is very high for this variable. Inclusion of the 'optimism' variable did not improve the model, and is therefore excluded.

Table 5.10: Logistic Regression Results for Determinants of Incident SCI - Physical and Mental Health

		Model 6		Model 7	
		OR	p	OR	p
		Exp(B)	Sig.	Exp(B)	Sig.
Age	60-64	1		1	
	65-69	2.06	**	2.08	**
	70-74	2.46	***	2.45	***
	75-79	5.12	***	4.97	***
	80-84	7.19	***	7.13	***
	85-89	14.00	***	14.00	***
	90+	7.52	***	7.66	***
Gender	Males	1		1	
	Females	1.01		0.91	
Country	Germany	1		1	
	Austria	0.71		0.76	
	Sweden	0.39	**	0.41	*
	Netherlands	0.44	*	0.44	*
	Spain	3.78	***	3.24	***
	Italy	1.65	°	1.26	
	France	0.89		0.70	
	Denmark	0.42	*	0.43	*
	Greece	0.52	*	0.46	*
	Switzerland	0.24	*	0.29	*
	Belgium	0.67		0.62	
Proxy	No Proxy	1		1	
	P in W1	2.22		2.21	
	P in W2	7.01	***	7.25	***
	P in W1 & W2	13.75	**	22.46	***
Education	Low	1		1	
	High	0.18	***	0.19	***
	Missing	0.70		0.67	
Partner	Partner Loss	0.57		0.48	°
	No Partner	1.08		1.08	
	Partner	1		1	
	New Partner	0.00		0.00	
Institution	Private HH	1		1	
	Move in	3.21	***	3.44	***
	Live in I	3.58	**	3.33	**
	Move out	0.00		0.00	
	Missing	1.50		1.41	
ADL	No ADL stable	1		1	
	New ADL in W2	1.35		1.17	
	ADL stable	0.88		0.75	
	ADL only W1	1.06		0.99	
IADL	No IADL stable	1		1	
	New IADL in W2	2.99	***	2.58	***
	IADL stable	3.46	***	2.92	***
	IADL only W1	1.70	*	1.58	°
Lim Act.	No Lim. stable	1		1	
	New Lim. W2	1.57	*	1.36	
	Lim. Stable	1.60	*	1.24	
	Lim. only W1	0.99		0.85	
Depression	No Depr. Stable			1	
	New Depr. W2			2.29	***
	Depr. stable			2.32	***
	Depr. only W1			1.13	
	Missing			2.78	
CASP 12	High			1	
	Medium			0.98	
	Low			1.51	°
	Missing			1.78	*
Constant		0.00	***	0.00	***
-2 Log-Likelihood		1976.8		1930.3	
R-Square		0.28		0.30	

***p≤0.001, **p≤0.01, *p≤0.05, °p≤0.1

5.4 Discussion

In this chapter, determinants and trends of SCI of people above age 60 in Europe are examined. The basis for analysis is a European longitudinal sample from 11 countries with more than 17,000 people in each wave cross-sectionally, and more than 11,000 people for a longitudinal analysis.

The SHARE provides a detailed questionnaire on cognitive function from which a new variable *'cognitive function 2'* with a scale of 18 possible points is created. A final diagnosis of dementia requires further professional examination and therefore the worst cognitive status, measured when seven or fewer points are gained, is called SCI. It is nevertheless assumed that the SCI group reflects or at least comprises demented people.

Generally, all results could be influenced by a non-random sample, as has been described above. Furthermore, the results could be influenced by missing cases from participating people: for some people, the cognitive status variable could not be created due to missing answers in one or both waves. Additional analyses in the appendix in table 8.2 show that people with missing cognitive status, with a proxy interview in wave 2 or in both waves even have worse physical and mental health and lifestyles. Thus, the results presumably underestimate the true risk of bad health and bad lifestyle on incident SCI.

When seven points are taken as the cut-off, the self-defined prevalence of SCI in the first wave 2004 for the 11 European countries is slightly higher than the prevalence of dementia in Germany in 2002, as calculated using the GKV data. It decreases in the second wave, narrowing to the prevalence of the GKV data. The better cognitive status in the second wave could be a true effect, but it could also be influenced by a learning effect. In the second wave, most respondents are already familiar with the test (Freedman et al., 2002; Rodgers et al., 2003) (compare section 2.3.5). The longitudinal results between 2004/05 and 2006/07 could indicate slight cognitive improvements, but they have to be interpreted with caution.

The higher prevalence of SCI in the SHARE data compared with dementia prevalence in the GKV data results from the use of a different definition, in which more cases are included in the SCI group who might not be severely demented, but who are more moderately impaired. If the SCI variable were to reflect dementia more closely, we would expect to find a lower prevalence in the SHARE because of the exclusion of the institutionalized population. Dementia and SCI prevalence are much higher in institutions, as has been described above, which makes it most probable that there is

an underestimation of SCI in the total population with the SHARE data.

The same fact might be responsible for the country differences: the higher proportion of the elderly population who are institutionalized in Northern European countries (Börsch-Supan et al., 2005; Doblhammer and Ziegler, 2006; Gaymu et al., 2006; Iacovou, 2000) could lead to a lower prevalence of SCI in the population living in private households, if people with SCI were to move more often to institutions. In the data, a low degree of inclusion of institutionalized people thus leads to an overestimation of the mean cognitive points. Southern European countries, where people in need of care are more often looked after in the family (Börsch-Supan et al., 2005; Gierveld et al., 2001; Tomassini et al., 2004), would then have a lower mean in cognitive function. If tables 5.3 and 5.1 are compared, this statement seems confirmed for Southern European countries: Spain, Italy and Greece are among the countries with the lowest institutionalization rates, and they also have the lowest mean in cognitive function. However, France also has a comparatively low mean, and some of the other countries with higher institutionalization rates do not vary greatly in the mean point of cognitive function—e.g., Austria, Germany, Netherlands, Denmark, and Switzerland—but they do vary in the proportions of the population in institutions, with Sweden, Netherlands and Denmark having the highest proportions. If the population in institutions is excluded from the analysis, the mean number of points does not increase significantly, except in the Netherlands. Thus, the country differences, with higher points seen in Central and Northern Europe might be less pronounced when institutional settings are considered, but they still seem to exist. No final conclusion regarding the cognitive status within Europe can be drawn. With the SHARE we find a lower cognitive status in Southern Europe, literature results in section 2.4.4 show contradictory results.

Some people did not answer the part 'cognitive functioning' in the questionnaire. A closer look at this group revealed that these missing cases were not random. The people were older and were much more likely to have help in answering the interview questions, or to have problems understanding the questions, and were therefore taken as an extra group. If these missing cases resulted from not understanding and not being able to answer the questions due to low cognitive functioning, the true number of SCI would be underestimated. These assumptions are affirmed in table 5.6, where the proportion of people with AD is highest in the MiP group, at 20.0%. By contrast, the proportion is 2.1% in the total population, and 9.4% in the SCI population.

The results confirm determinants of prevalent SCI shown in the literature review in Chapter 2. First, SCI is found to increase strongly with age. The prevalence above

age 90 is about 45% for males and 54% for females in wave 1, and 47% and 43% in wave 2. Results from the logistic regression show a decrease in the oldest age group of 90+. This could again be an effect of the under-representation of the institutionalized population: the most severe cases occur at the oldest ages, when institutionalization is also highest. Attrition, especially of the less healthy people, is also highest at these ages and therefore the true risk might be higher in this age group.

The cross-sectional results in table 5.4 and the logistic regression results in table 5.9, model 1 controlling for age and country show a higher prevalence for females than for males. But the gender effect vanishes when more variables are included into the regression. Institutionalization plays an important role: elderly women are more likely to live alone, which itself is a risk factor. However, living alone is also a risk factor for attrition when bad health occurs, which should decrease the risk in the model. But when institutionalization is controlled for, the effect of loneliness without a partner seems to be stronger. The risk for women is even lower than for men when lifestyle variables are included. Women seem to have a healthier lifestyle, which decreases their risk. It is not significant in the models shown, but in a model in which all the variables were included at the same time (not shown, most other variables do not change, -2 Log-Likelihood=1852.9, R-Square=0.332) it would be 34% lower (p=0.02).

People with SCI problems are more likely to move into institutions than people without these. The differences between Northern/Western and Southern Europe can be explained with cultural differences towards family ties, but, in general, moving into an institution is more likely for people without a spouse or a child, especially when a care need exists (Börsch-Supan et al., 2005). This fact should also lead to a gender imbalance, since more elderly women today live without a partner. We find, however, about the same proportion of women in the two groups 'participation only in wave 1' and 'participation in waves 1&2'. A selection effect already seen in the first wave of fewer single women could account for this fact. In addition, the risk of developing incident SCI is much higher for people with a proxy respondent during the interview, and for people who live in or move into institutions, which was expected given other literature findings.

Results regarding the health of people with SCI and MiP also confirm general findings in the literature. Many studies have found a correlation between mental health and cognitive functioning (see chapter 2.4.10) which is confirmed here. Optimism levels and felt QoL are lower in people with SCI and MiP, and they feel less prepared for the future. This is no surprise if people know about their diagnosis and about the progressive,

currently untreatable course of the disease, and taking into account the accompanying symptoms and diseases, such as depression. The prevalence of depression is found here to be higher in people with SCI and MiP and confirms literature results. Depression is also confirmed as a risk factor for incident SCI, but since a persistent as well as a new depression show increased risks, the causality cannot be determined. People who rate their QoL (CASP-12) in wave 1 as low have a higher risk of developing incident SCI. All physical health measures have a higher age-standardized prevalence in the cognitively impaired groups, with clear differences seen in ADL and IADL. People with worse physical health overall generally also have a higher risk of incident SCI. More severe limitations, like ADL constraints and 'severe limitations in daily life' seem to be less influential than limitations with IADL. It is hard to interpret causality given that people with stable IADL are at high risk, as are people who do not have constraints in wave 1 but in wave 2, and the other way round. For ADL and limitations, the risk is about the same for people with and without these constraints in wave 1 only. The risk is highest for those with new constraints in wave 2, which therefore seem to accompany the development of incident SCI, rather than to be a causal factor. People who have a declining cognitive status can still manage their most basic body functions, like dressing and bathing (ADL), during the early stages of their disease. By contrast, certain instrumental activities such as going shopping, preparing a meal or making phone calls, are likely to become more difficult at an early point in the disease. It is the change in daily routine and a progression in the mental decline which then leads to more severe limitations.

Results on accompanying diseases confirm the results obtained with GKV data in chapter 4. People with SCI have a higher co-morbidity, especially cerebral vascular diseases, diabetes mellitus, arthritis or rheumatism, PD and heart and chronic lung diseases.

Lifestyle variables also in general support the literature findings, a low and decreasing activity status and changes in weight occur more often in the group with SCI and MiP. On the one hand, a low activity status leads to a lower metabolism, which influences the risk of SCI negatively; but, on the other hand the disease also leads to less movement because people feel more insecure. SCI can lead to weight loss, as has been discussed in chapter 4. Being overweight can cause other metabolic diseases, such as diabetes which is a risk factor for dementia. Some results from the lifestyle variables were unexpected: e.g., that alcohol consumption is lowest in the SCI and MiP group, and that the proportion of current and ex-smokers is not higher in people with SCI. One

influencing factor might be the short study time. For all lifestyle variables in general, a longer observation period is necessary. The influence of the variables on the cognitive status takes place over a longer period and changes just shortly before the survey might already have occurred, but long-term effects still influence the outcome. People who are ill change their drinking and smoking behavior.

Results from the SHARE data confirm several risk factors of SCI described in chapter 2. Age, gender, education and lifestyle, physical and mental health as well as some diseases influence the risk for cognitive impairment. Furthermore, results between the two waves might indicate a positive time trend with a better cognitive status in the second wave. The results are important for assumptions about future trends of age-specific dementia prevalence and incidence shown in the next chapter.

Chapter 6

Projections of the Number of People with Dementia in Germany until 2050

6.1 Past Projections of the Occurrence of Dementia for Germany and Worldwide

The number of people worldwide who were suffering from dementia in 2009 has been estimated to about 34.4 million (Wimo et al., 2010). The aging of the population worldwide is going to lead to an increase in the number of people with dementia. This future increase has strong implications and poses huge challenges for policy makers and society as a whole.

Most early projections could not access reliable and comparable data, and therefore relied on assumptions. On the one hand, disability trends in the 1970s and 1980s in general were not favorable, and negative projections for trends in dementia were made (e.g. by Kramer (1983), but numbers are not comparable since different measures were applied). On the other hand, older studies underestimated the increase in life expectancy, and therefore predicted there would be fewer demented people than there actually are today (Häfner and Löffler, 1991).

In making these projections, researchers often assume that prevalences are similar worldwide (see section 2.4.4). For example, Wimo et al. (2003) applied the same prevalence data from Fratiglioni and Rocca (2001) for all regions. They estimated that the number of dementia cases will increase to about 63 million people in 2030, and to 114 million people in 2050 (table 6.1). Based on the assumption that there were 24.3 million demented people in 2001, Ferri et al. (2005) estimated an incidence of 4.6 million new

cases per year, which results in about 81.1 million demented people in 2040. Moreover, they predicted that the proportion of sufferers who live in developing countries will rise from 60% in 2001 to 71% in 2040. Ferri et al. (2005) used DISMOD-II software to analyze the results of reviewed prevalence articles from different regions of the world, producing estimates of incidence rates from information on prevalence, remission and mortality. They assumed a much lower prevalence in Africa of 0.49 million people, compared with 1.25 million in Wimo et al. (2003).

Brookmeyer et al. (2007) took changing prevalences into account. If the disease onset could be delayed by 2 years, there would be 22.8 million less AD cases in 2050, 84.0 million instead of 106.8 million when constant prevalences were applied.

Projections for Europe by Wancata et al. (2003) took different prevalence and incidence studies from Europe into account and calculated a mean over all studies. The number would more than double to 16.2 million cases, however, the increase is less steep than worldwide, where the numbers would nearly quadruple. The age structure in Europe is older and the proportion of people with dementia higher. In other regions of the world, especially Asia, the population structure is still younger, but is going to age much faster during the next decades. Therefore, also the number of people with dementia is increasing faster.

In Germany, projections of the possible development of the numbers of people with dementia are rare. Table 6.1 shows the existing studies conducted from 2000 onwards. They all used constant prevalences, as have most of the worldwide projections. Bickel (2001) estimated that the number of demented people will increase from about 0.93 million in 1996 to 2.05 million people in 2050. He used population projections from the 9^{th} coordinated population projection from the Statistical Office (Statistisches Bundesamt Deutschland, 2000). They are a mean of age-specific prevalences of several studies (Bickel, 2000). Bickel et al. (2006) used prevalences from 2000 (Bickel, 2000) and the population projection from the 10^{th} coordinated population projection from the German Statistical Office (Statistisches Bundesamt Deutschland, 2003) with the medium increase in life expectancy variant. Bickel (2008) used the same prevalences from 2000 (Bickel, 2000) and population projections from the 11^{th} coordinated projection from the German Statistical Office, a variant (V1,W2) with 'basic' life expectancy and high migration assumptions. This is surprising since life expectancy is always corrected to higher values in subsequent population projections, as has been shown above, and because migration has been rather low in Germany in recent years. Hallauer (2002) used the mean prevalences of several studies from Bickel (2002), which take into account two

Table 6.1: Projections of Demented People (in Million)

	Year				
	2000*	2020	2030	2040	2050
Worldwide					
Wimo et al. (2003)	25.5		63		114
Ferri et al. (2005)	24.3 (2001)	42		81.1	
Brookmeyer et al. (2007)	26.6 (2006)				106.8 (AD only)
Brookmeyer et al. (2007)	26.6 (2006)				84.0** (AD only)
Europe (39 countries)					
Wancata et al. (2003)	7.1				16.2
Germany					
Bickel (2001)	0.93 (1996)	1.39	1.56	1.81	2.05
Bickel (2008)	0.94	1.55	1.82	2.20	2.62
Bickel et al. (2006)	0.94	1.41	1.69	1.92	2.29
Hallauer (2002)[1]	1.13		1.95		2.8
Hallauer (2002)[2]	1.13			3.0	3.5
Priester (2004)	0.99 (2002)	1.50	1.74	2.03	2.36
Kern and Beske (2000)	1.3 (1997)	1.98	2.21		

*or divergent year (in brackets)

** if onset of disease is delayed by 2 years

[1] Prevalences from Bickel (2002), Population from Statistisches Bundesamt Deutschland (2000)

[2] Prevalences from Bickel (2002), Population from Birg and Flöthmann (2000)

more studies than the mean prevalences from Bickel (2000), but which result in only very slight differences. Two different population projections were applied: the 9th projection from the German Statistical Office and projections from Birg and Flöthmann (2000), with a higher increase in life expectancy. Although Hallauer (2002) and Bickel (2001) both used nearly the same prevalence and the 9th population projection, Hallauer (2002) projected much higher numbers of demented people. He used variant 2a, in which higher life expectancy and migration are assumed than in the medium variant Bickel (2001) used. In a second projection, Hallauer (2002) used population projections from Birg and Flöthmann (2000), who assumed an even higher life expectancy than the high variant from the Statistical Office; thus, in this projection, the number of expected demented people in 2050 increases when constant dementia prevalences are applied. Priester (2004) used constant mean prevalences from several studies from Bickel (1999) and the 10th population projection from the Statistical Office. According to this assumption, the number of demented people will rise from 0.99 million in 2002 to about 2.36 million demented people in 2050. However, since the prevalences from Bickel (1999) only measure moderate and severe dementia, Priester (2004) estimated that the total numbers, including cases of early dementia, could rise to five million people in 2050. An older projection is from Kern and Beske (2000), who projected constant prevalences from the 4th family report issued by the Ministry of Family, Senior Citizens, Women and Youth (Bundesministerium für Familie, Senioren, Frauen und Jugend, 1986) using the 8th population projection from the Statistical Office (Statistisches Bundesamt Deutschland, 1994). Despite this fact (life expectancy increase is rather low), the projected numbers are quite high: they increase from 1.3 million in 1997 to 2.2 million in 2030. Even as the population projection appears to underestimate the aging effect, the numbers from the 4th family report from 1986, which were taken as dementia prevalences, actually include 'psychiatric illnesses' in general, and thus appear to overestimate the prevalence.

Although all studies were based on prevalences and assumed no change over time, and most studies were based on prevalences from Bickel (2000, 2002), they produced quite different results, which demonstrates that the outcome of dementia projections depends largely on the underlying population projections.

Doblhammer et al. (2009) and Ziegler and Doblhammer (2010) calculated prevalence projections based on the GKV data (see further down). In addition, in order to enhance the projection method, multi-state projections based on incidence rates are calculated.

6.2 Multi-State Projections of the Total Population and the Population with Dementia for Germany

It is impossible to make precise predictions because too many determinants and coincidences are involved. Projections distinguish from predictions insofar, as they demonstrate possible future developments. Projections can show what most likely will happen if all the factors that can determine future developments are carefully taken into account (Vaupel et al., 2006). In our case, we are interested in the present and past developments of mortality and dementia. What course will the current trend take? What factors can possibly influence the further development of mortality and dementia? We do not have to take fertility into account. Since we project the population above age 60 until the year 2050, all the people involved were already born in 2006. The youngest cohort that turns 60 in 2050 was born in 1990. We do not take migration into account. The following section describes the data and method used, assumptions about the future development of mortality and dementia, and shows the projection results: the increase of the total and the demented population until the year 2050.

6.2.1 Data and Method

Two projections were made and compared: dynamic multi-state projections, and population projections with static transition rates of dementia. First, dynamic multi-state projections are shown; the static prevalence projections are further down in section 6.2.4.

The multi-state method was developed by Rogers (1980). The multi-state model allows us to include different health states into the projection. Here the states 'healthy' and 'demented' were considered with the possible transitions:

- 'healthy' → 'demented',
- 'healthy' → 'dead'
- 'demented' → 'dead'.

Recovery from dementia was not assumed. There are only a few treatable types of dementia which, however, should ideally be coded with ICD-10 codes other than the ones used here (although some of them may be in the category `F03`, 'Unspecified Dementia').

For the projections, the program Population-Development-Environment (PDE) was used. It was developed at the International Institute for Applied Systems Analysis IIASA in Laxenburg, Austria (Dippolt et al., 1998).

First, we needed the starting population of demented and non-demented people in 2006. The total population was taken from the Human Mortality Database (Human Mortality Database, 2008) and multiplied using the prevalence rates from the GKV data 2002. No change in the prevalence between 2002 and 2006 was assumed.

Second, we used incidence rates for demented and non-demented people, all calculated with the GKV data shown in section 3.3, table 3.5. The five-year incidence rates were interpolated with STATA into single-year rates with the command 'cipolate', a module which cubicly interpolates the values. The population was projected with single-year age groups until age 89; the last age group is 90+. The highest age group for the incidence rate by sex and region that can be obtained from the GKV data is 90+. PDE has problems with mortality rates above 0.4, which would occur if the rates were to be extrapolated into higher ages. Other rates above that age are erratic and the proportion of people above age 90 within the age group 60+ is small (about 4%). It therefore seems justified to use 90+ as the highest age group. The projections were done separately for West and East Germany and were compared with projections for all Germany.

Furthermore, death rates of the non-demented and the demented population in West and East Germany are necessary for the projections. Demented people have much higher death rates, as can be seen in table 6.2 and figure 6.1. These results are consistent with literature findings (Bickel, 2005; Dewey and Saz, 2001; Jagger et al., 2000; Kliegel et al., 2004; Kokmen et al., 1996; Werner, 1995a; Wilson et al., 2003). Mortality might be higher in VaD than in AD (Dewey and Saz, 2001), and being male, older and having more severe dementia are also factors that negatively affect survival (Bickel, 2005; Heyman et al., 1997). The excess mortality is highest at younger ages, and decreases with increasing age. In a literature review, Dewey and Saz (2001) did not find significant results. This is partly due to study designs and small samples. They concluded, however, that the data suggest a slower increase of mortality risk for people with dementia compared to those without. Starting from a much higher level, our results show strong evidence for a slower rise in mortality among demented people, which may be due to the competing risk of other diseases at higher ages. A clear gender difference can be seen as well: the rate ratio difference is higher for females than for males. The higher mortality risk of males relative to females might lower the excess

risk of dying from dementia because they already have a higher risk of dying from another disease. The differences between West and East Germany are smaller than the gender differences. East German females above age 85 seem to have higher death rates. For males, small sample sizes make an interpretation difficult. After the rates were interpolated, a slightly higher risk for East Germans could be seen.

Table 6.2: Death Rates for the Demented and Non-Demented Population in West and East Germany per 100 People in 2006

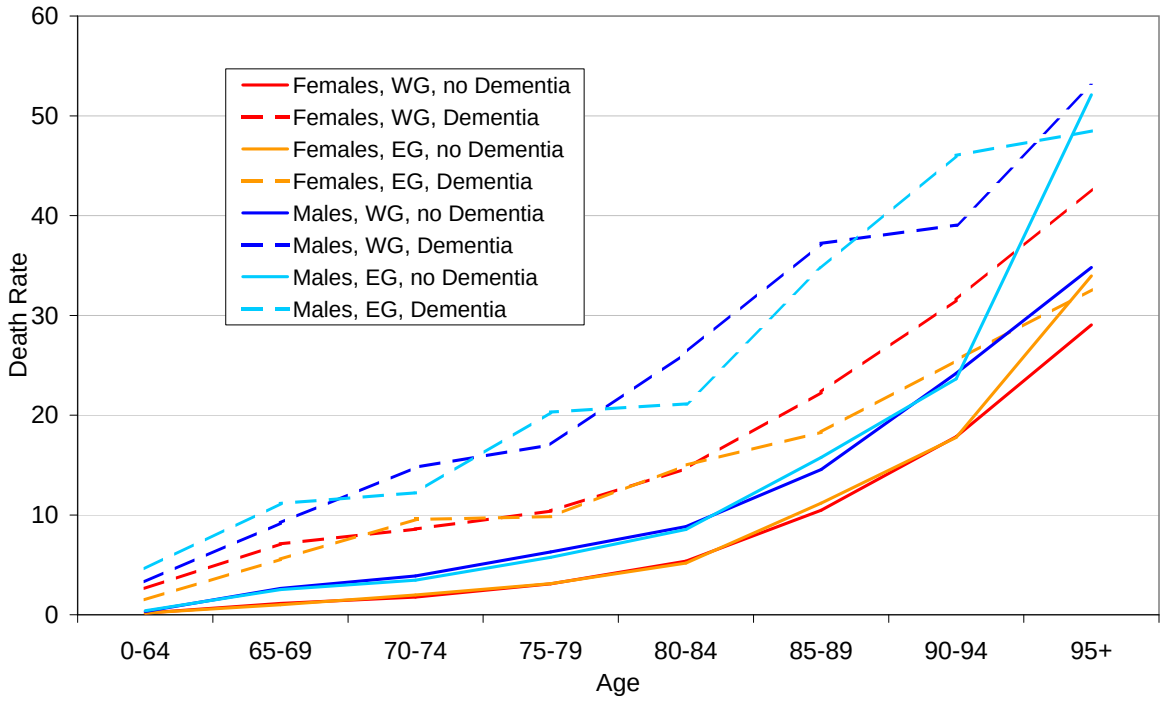
	East Germany				West Germany			
	Females		Males		Females		Males	
Age	No D.	D.	No D.	D.	No D.	D.	No D.	D.
0-64	0.17	2.64	0.32	3.30	0.18	1.50	0.41	4.61
65-69	1.14	7.11	2.65	9.20	1.00	5.57	2.53	11.14
70-74	1.77	8.59	3.89	14.76	1.99	9.55	3.46	12.21
75-79	3.11	10.40	6.30	17.04	3.12	9.85	5.75	20.30
80-84	5.38	14.65	8.84	26.27	5.19	14.97	8.54	21.14
85-89	10.48	22.31	14.56	37.20	11.18	18.31	15.77	34.73
90-94	17.84	31.55	24.19	39.06	17.78	25.49	23.63	46.03
95+	29.04	42.63	34.81	53.02	33.96	32.58	52.10	48.48
90+	19.71	33.94	25.73	41.49	20.15	26.93	27.37	46.56

D.=Dementia

Source: HMD, GKV Data, own calculations

Results of the projections depend primarily on the assumptions about life expectancy and incidence rates. Since dementia increases steeply with age, assumptions about life expectancy are very important. Three different scenarios regarding life expectancy were considered. In scenarios 1 and 2, life expectancy rises to 83.2 and 85.3 years for males, and to 87.3 and 89.4 years for females. These figures are nearly in line with the 'basic' and 'high life expectancy' variants of the 11^{th} coordinated population projection of the German Statistical Office (Statistisches Bundesamt Deutschland, 2006), in which life expectancy rises to 83.5 and 85.4 years for males, and to 88.0 and 89.9 years for females, respectively. However, the increase in life expectancy has so far always been underestimated (Oeppen and Vaupel, 2002) and adjusted in the subsequent scenarios of the coordinated population projection of the German Statistical Office (Statistisches Bundesamt Deutschland, 1994, 2000, 2003). In recent decades, a decrease in mortality, especially at older ages, contributed to the increase in life expectancy (Vaupel et al., 2006). Therefore, a third scenario with a high increase to 88.0 and 92.1 years for males and females, respectively, was calculated. To achieve this life expectancy, mortality

Figure 6.1: Death Rates for Demented and Non-Demented Population in West and East Germany per 100 People



WG=West Germany, EG=East Germany
Source: GKV Data, HMD Data, own calculations

had to decrease by 1.7% and 1.5% per year for non-demented males and females, respectively; and 0.5% and 0.4% per year for demented males and females for the low life expectancy variant. The values for the medium variants are 2.1%, 1.9%, 1.0% and 0.85%; and the values for the high variants are 2.6%, 2.6%, 1.5% and 1.3%. The life expectancy at age 60 in 2006 for non-demented people is about twice as high as for demented people. For demented people, life expectancy was assumed to rise more slowly than for non-demented people in the low scenario 1 (the increase in life expectancy of the non-demented population is higher when fewer medical advancements occur), nearly in the same proportion in the medium scenario 2 and in about the same proportion in the high scenario 3. The assumption here was that, in general, a greater increase in life expectancy is partly caused by medical advancements, and the higher it is, the more beneficial it is also for demented people.

Furthermore, a model with constant mortality was calculated to show in comparison the development if nothing were to change. Table 6.3 shows the life expectancy at age 60 of the demented and non-demented populations for all scenarios, separately for West and East Germany.

Table 6.3: Life Expectancy in 2006 and 2050 at Age 60 for the Total, Demented and Non-Demented Population according to Different Life Expectancy Scenarios by Gender and Region

	Germany		West Germany		East Germany	
Life Expectancy	$e_{60(m)}$	$e_{60(f)}$	$e_{60(m)}$	$e_{60(f)}$	$e_{60(m)}$	$e_{60(f)}$
Total Population						
2006	20.0	24.3	20.1	24.3	20.0	24.6
2050 Low	25.3	28.6	25.4	28.4	25.2	29.1
2050 Medium	27.2	30.6	27.2	30.1	27.1	30.6
2050 High	29.6	33.1	29.7	32.9	29.4	33.6
Non-Demented Population						
2006	21.1	25.7	21.2	25.8	21.1	26.0
2050 Low	28.7	32.6	28.8	32.6	28.7	33.1
2050 Medium	31.0	35.0	31.1	35.0	31.1	35.7
2050 High	34.3	38.5	34.3	38.5	34.4	39.4
Demented Population						
2006	9.9	12.6	9.7	12.7	9.3	13.3
2050 Low	11.4	14.5	11.2	14.6	10.8	15.2
2050 Medium	13.1	16.6	12.8	16.6	12.5	17.3
2050 High	14.9	18.8	14.7	18.8	14.4	19.7

The increase in life expectancy during the 1990s and the beginning of the new century has been steeper in East than in West Germany, with East German levels nearly reaching West German levels in 2006. Because of this greater rate of increase, results for 2050 even show slightly higher life expectancies for East German women.

The second influencing factor for our projection results is the incidence rate. In a first step, constant rates were applied to the population projections. For a second variant, we determined how the incidence rates had to decrease until 2050 in order to maintain a dynamic equilibrium, such that the proportion of years with and without dementia is equal to the rates seen in 2006. For example, if an 80-year-old woman currently has an additional life expectancy of 8.9 years, of which 1.7 years, or 20% of this time, are spent with dementia, how does the incidence rate have to change so that again 20% of the life expectancy of 80-year-old women are spent with dementia in 2050? These results would represent a dynamic-equilibrium of the life expectancy with and without dementia: total life expectancy increases, and the absolute number of years

with and without dementia increases, but the proportion of years with and without dementia stays the same. If the proportion of life expectancy with dementia were shown to be higher than today, the results would support the expansion-of-morbidity hypothesis; but if it were found to be lower, the results would support the compression-of-morbidity hypothesis (for an overview of the hypotheses, see section 2.3). To obtain a dynamic equilibrium, the incidence for each age must change differently because of the increasing life expectancy. For example, the incidence at age 80 would have to decrease much more for an equilibrium to be attained at age 60 than at age 80. The younger the age for the dynamic equilibrium that is chosen, the more the incidence at each age above would have to decrease. Here, age 80 was chosen to demonstrate the effect of the dynamic equilibrium, because most people with dementia are aged 80+ and the incidence rises steeply beyond that age.

The status quo scenario and the three different life expectancy assumptions, combined with two different incidence assumptions, result in seven scenarios:

1. Status Quo Scenario - constant mortality and constant incidence
2. Scenario 1.1 (Low) - low increase in LE and constant incidence
3. Scenario 1.2 (Low) - low increase in LE and dynamic incidence
4. Scenario 2.1 (Medium) - medium increase in LE and constant incidence
5. Scenario 2.2 (Medium) - medium increase in LE and dynamic incidence
6. Scenario 3.1 (High) - high increase in LE and constant incidence
7. Scenario 3.2 (High) - high increase in LE and dynamic incidence

(LE=Life Expectancy)

6.2.2 Projection of the Total Population

The increase in the total elderly population above age 60 can be seen in table 6.4. If mortality and dementia rates were to stay constant, there would only be a slight increase in the elderly population of 0.9 million to about 21.4 million people. A small increase in life expectancy would make a difference of 5.1 million, while a large increase would mean 7.7 million more people than today. If the dementia incidence rates were

to decrease, the total number of people would increase because the mortality of non-demented people would be lower.

Table 6.4: Total Population above Age 60 (in Million) according to Different Life Expectancy Scenarios by Region

Life Expectancy	Dementia Rate	Germany	West G.	East G.
2006		20.5	16.0	4.5
2050 Constant	Constant	21.4	16.9	4.4
2050 Low	Constant	25.4	20.2	5.3
2050 Low	Dynamic	25.7	20.5	5.3
2050 Medium	Constant	26.7	21.2	5.5
2050 Medium	Dynamic	27.2	21.6	5.6
2050 High	Constant	28.2	22.3	5.8
2050 High	Dynamic	28.9	22.9	6.0

G.=Germany

The table cannot display the dynamic of the change. For example, in the constant model the absolute number of people above age 60 rises only slightly, by 0.9 million between 2006 and 2050. But it does not show that, until 2031, it rises to 25.4 million people above age 60, and decreases thereafter to 21.4 million in 2050. Figure 6.2 shows this dynamic for the total population. Table 6.5 and Figure 6.3 show the population increase separately for males and females.

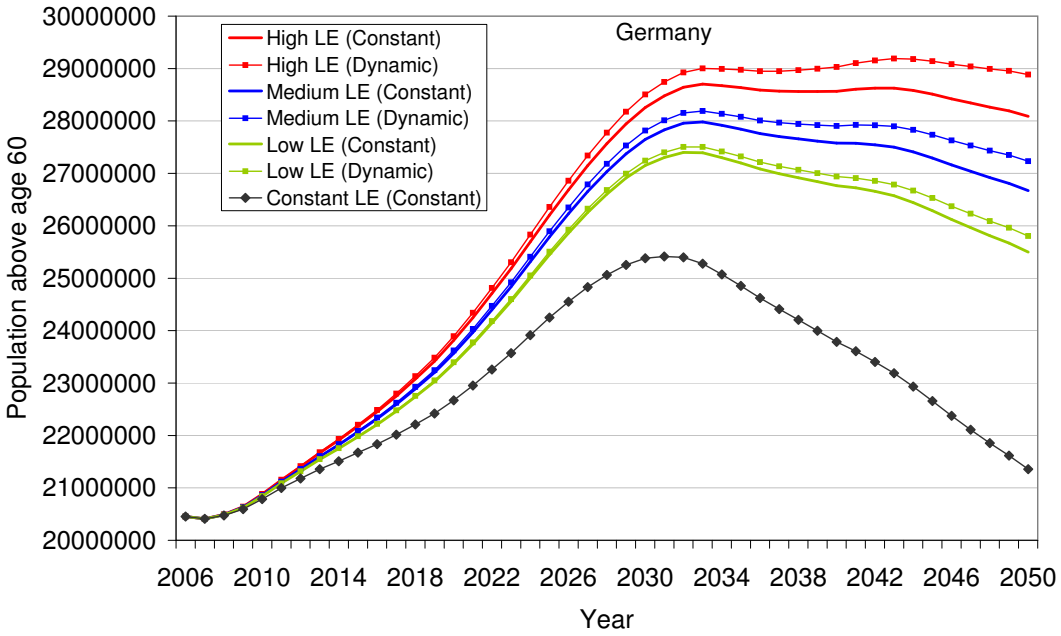
Until about 2030, we see a steep increase in the number of people above age 60, regardless of the model. Between the small and the large increase in the life expectancy models, there is a difference of about 1.5 million people. In the low and medium (and static) variant, the number of people above age 60 decreases again, while it is nearly stable in the high variant. Differentiated by gender, we found the same effect for males and females; however, the increase in the total number is much higher for males. On the one hand, this is the result of a higher rising life expectancy at present, while on the other, we see that previous male cohorts are still suffering from high losses from the two World Wars. More and more cohorts are entering old age who have not been involved in the war (Doblhammer and Ziegler, 2006).

While we see a general increase in the population above age 60 until about 2030, and a stagnation or even a decrease thereafter, the picture looks quite different for the 80+ population. Since this information is more important for the projections because of the higher incidence at higher ages, we display the increase of the total and gender-separated population in figure 6.4.

Table 6.5: Total Population above Age 60 (in Million) according to Different Scenarios by Gender and Region

Life Expectancy	Dementia Rate	2006	2020	2030	2040	2050
Males						
Germany						
Constant	Constant	8.82	10.23	11.63	10.74	9.53
Low	Constant	8.82	10.64	12.68	12.53	11.98
	Dynamic	8.82	10.65	12.72	12.61	12.13
Medium	Constant	8.82	10.74	12.95	12.99	12.63
	Dynamic	8.82	10.77	13.03	13.15	12.91
High	Constant	8.82	10.87	13.27	13.52	13.40
	Dynamic	8.82	10.91	13.39	13.75	13.80
West Germany						
Constant	Constant	6.94	8.02	9.24	8.58	7.52
Low	Constant	6.94	8.33	10.06	9.98	9.44
	Dynamic	6.94	8.34	10.09	10.05	9.56
Medium	Constant	6.94	8.42	10.27	10.34	9.95
	Dynamic	6.94	8.44	10.34	10.47	10.18
High	Constant	6.94	8.52	10.52	10.76	10.56
	Dynamic	6.94	8.55	10.62	10.94	10.88
East Germany						
Constant	Constant	1.88	2.21	2.39	2.16	2.01
Low	Constant	1.88	2.30	2.62	2.55	2.53
	Dynamic	1.88	2.30	2.63	2.56	2.56
Medium	Constant	1.88	2.32	2.68	2.65	2.67
	Dynamic	1.88	2.33	2.69	2.68	2.73
High	Constant	1.88	2.35	2.75	2.76	2.84
	Dynamic	1.88	2.36	2.77	2.81	2.92
Females						
Germany						
Constant	Constant	11.64	12.44	13.75	13.04	11.83
Low	Constant	11.64	12.73	14.48	14.24	13.52
	Dynamic	11.64	12.75	14.52	14.33	13.68
Medium	Constant	11.64	12.83	14.70	14.59	14.04
	Dynamic	11.64	12.85	14.79	14.76	14.32
High	Constant	11.64	12.95	14.98	15.04	14.69
	Dynamic	11.64	12.99	15.11	15.28	15.09
West Germany						
Constant	Constant	9.05	9.69	10.88	10.45	9.42
Low	Constant	9.05	9.92	11.45	11.39	10.78
	Dynamic	9.05	9.93	11.48	11.46	10.90
Medium	Constant	9.05	10.00	11.63	11.69	11.21
	Dynamic	9.05	10.02	11.70	11.82	11.44
High	Constant	9.05	10.09	11.85	12.03	11.71
	Dynamic	9.05	10.12	11.95	12.22	12.03
East Germany						
Constant	Constant	2.59	2.75	2.87	2.60	2.40
Low	Constant	2.59	2.81	3.03	2.85	2.75
	Dynamic	2.59	2.82	3.04	2.86	2.78
Medium	Constant	2.59	2.83	3.07	2.90	2.83
	Dynamic	2.59	2.84	3.09	2.94	2.88
High	Constant	2.59	2.86	3.14	3.01	2.98
	Dynamic	2.59	2.87	3.17	3.06	3.06

Figure 6.2: Development of the Total Population above Age 60 until 2050 according to Different Scenarios

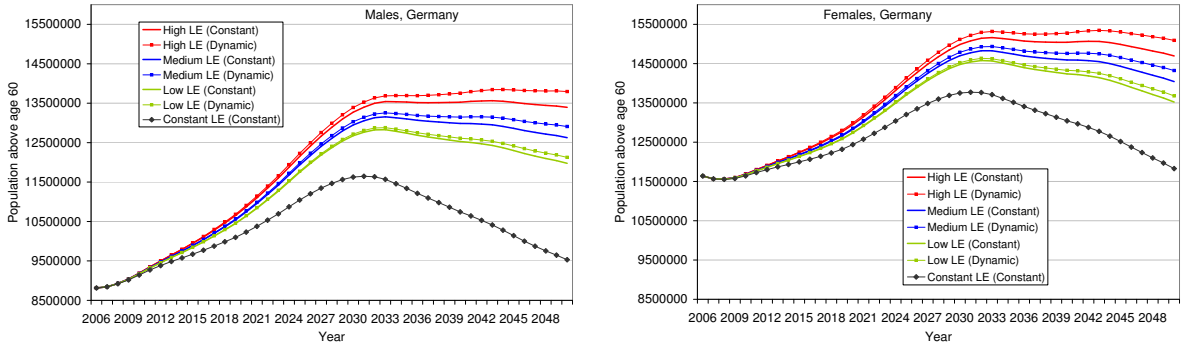


LE = Life Expectancy
Legend: the first term describes the life expectancy variant, the dementia variant is given in brackets.
Source: own calculations

The number of people above age 80 will more than double in the low life expectancy variant, and more than triple in the high variant. Again, the increase is stronger for males than for females. The small amount of stagnation after the hump around the mid-2020s comes from cohorts born around the end of the Second World War, when period fertility decreased for a short period, only to resume thereafter at the previous level, and to even increase during the 1960s with the baby boom. Only after 2050 will smaller cohorts in their eighties return.

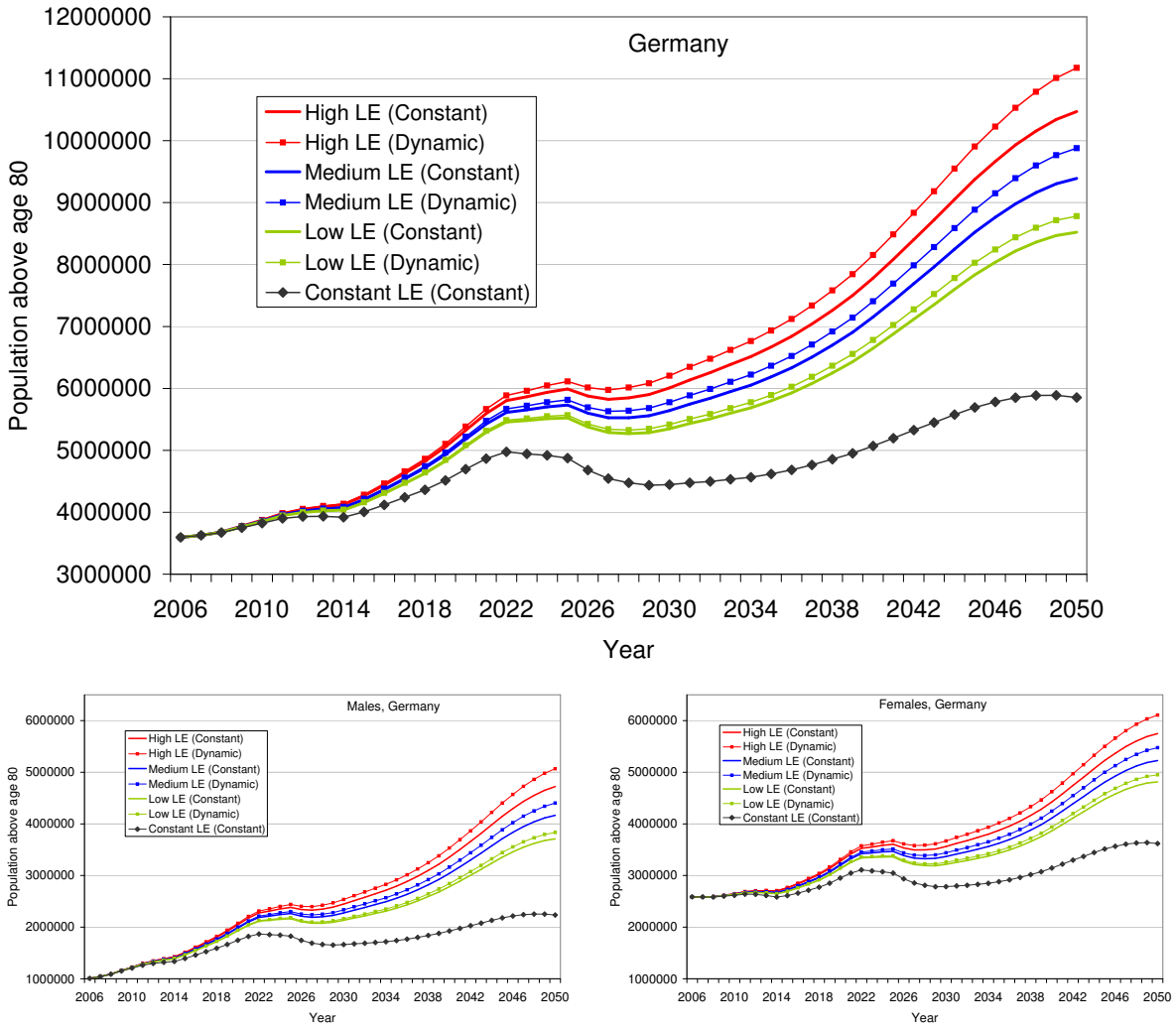
An West-East comparison shows a similar development of the population in figure 6.5 and table 6.5, with a strong increase until 2030, and then a stagnation or even a decline. In the mid-2030s, a greater decline is observed in East Germany for brief time, which might have been caused by a greater decline in fertility after the baby boom in the beginning of the 1970s. However, due to public policies designed to support families, fertility increased slightly in the early 1980s, which is again reflected in the over-60 population in the 2040s.

Figure 6.3: Development of the Male and Female Population above Age 60 until 2050 according to Different Scenarios



LE = Life Expectancy
Legend: the first term describes the life expectancy variant, the dementia variant is given in brackets.
Source: own calculations

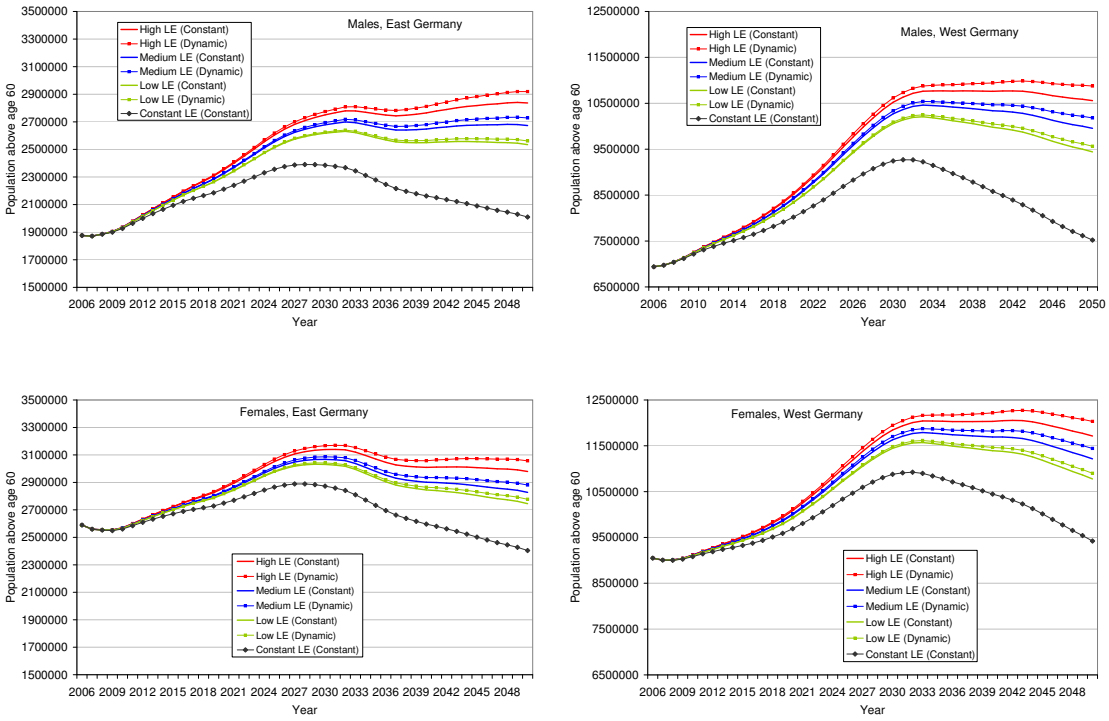
Figure 6.4: Development of the Total, Male and Female Population above Age 80 until 2050 according to Different Scenarios



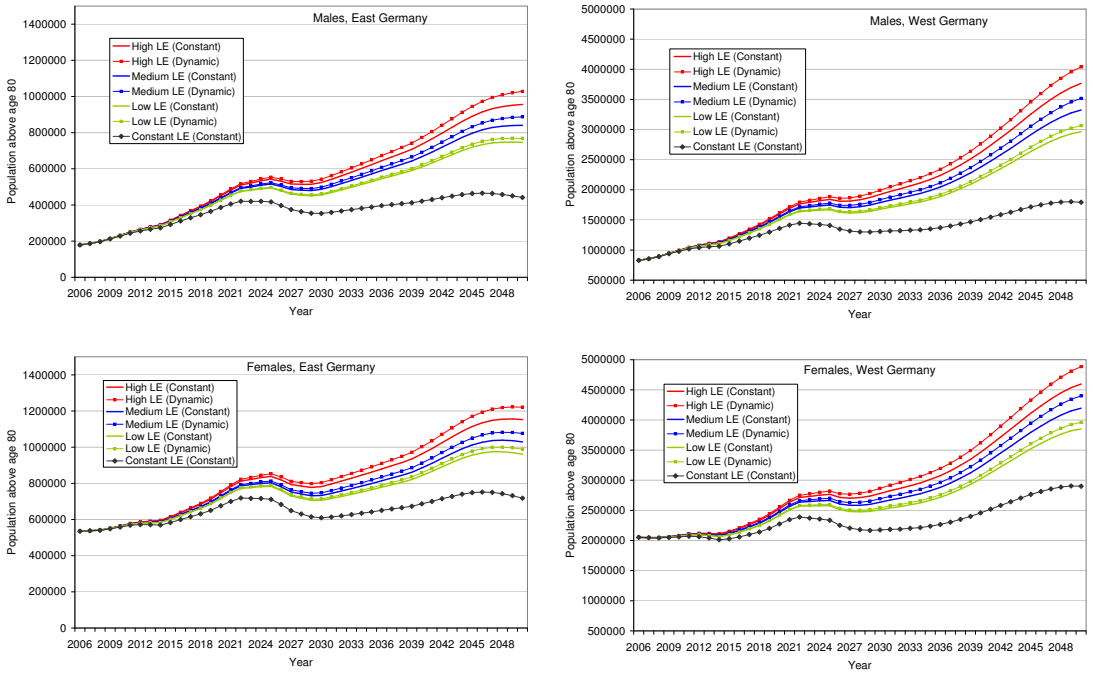
LE = Life Expectancy
Legend: the first term describes the life expectancy variant, the dementia variant is given in brackets.
Source: own calculations

Figure 6.5: Development of the Male and Female Population above Age 60 and Age 80 until 2050 according to Different Scenarios in West and East Germany

Age 60+



Age 80+



LE = Life Expectancy
Legend: the first term describes the life expectancy variant, the dementia variant is given in brackets.
Source: own calculations

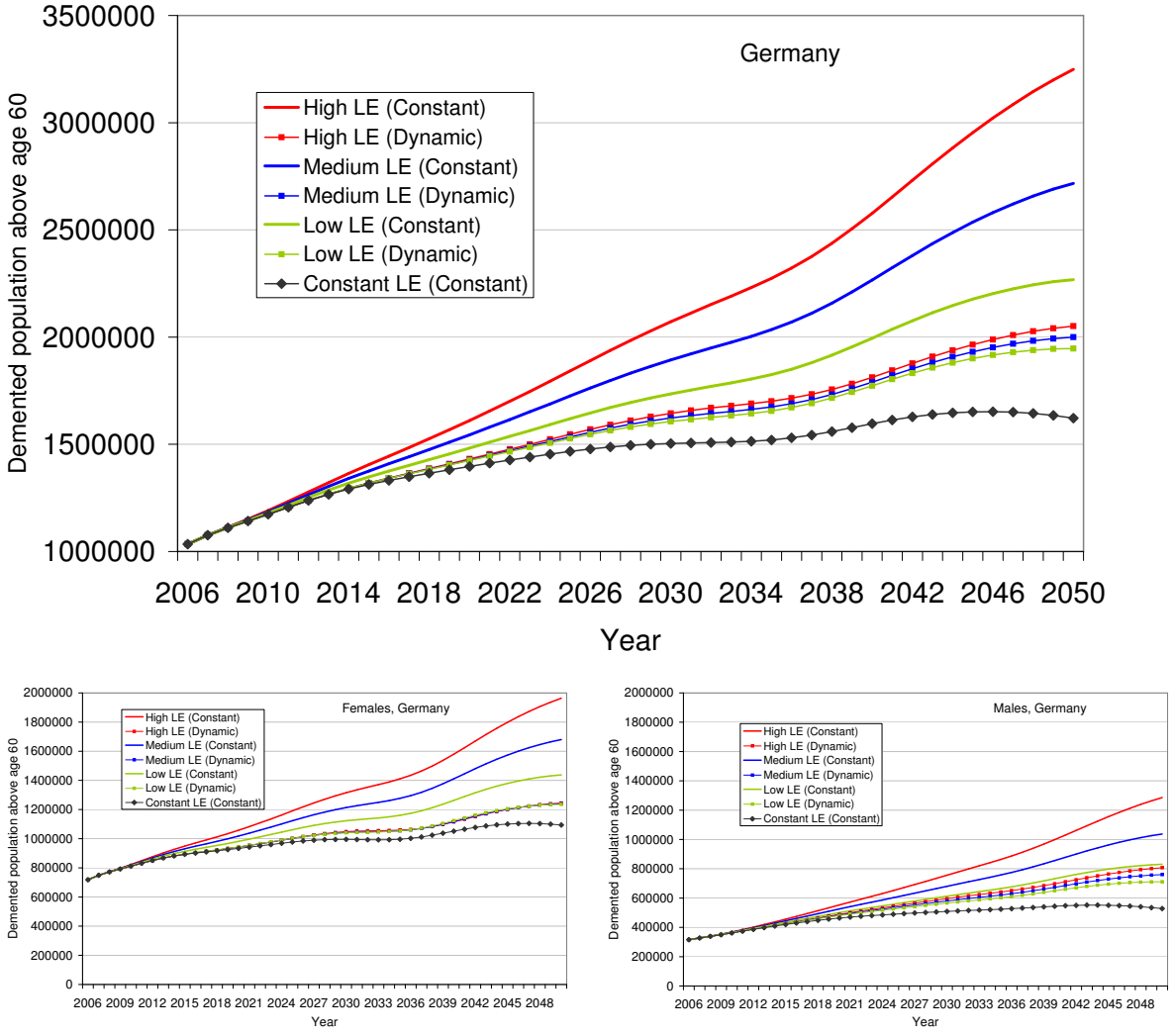
6.2.3 Projection of the Demented Population

The following graphs, 6.6 and 6.7, and table 6.6 show the increase in the number of demented people above age 60 and age 80, according to the different variants. The most important finding is that the number of people with dementia is going to rise, no matter how life expectancy develops. Even if mortality were to stay the same as it is today, there would be an increase from about 1.03 million people today to about 1.62 million in 2050, which is due to an increasing average age even within the age group 60+. But if life expectancy were to increase at a low level, and no changes in dementia rates were to occur, there would be 2.27 million demented people in 2050. If, however, there is a large increase in life expectancy, the number might rise to 3.25 million. With a dynamic equilibrium, the numbers of demented people would not differ much between the different life expectancy variants, rising to 1.95 and 2.05 million, respectively.

Table 6.6: Demented Population above Age 60 in 2050 (in Million) according to Different Life Expectancy Scenarios by Region

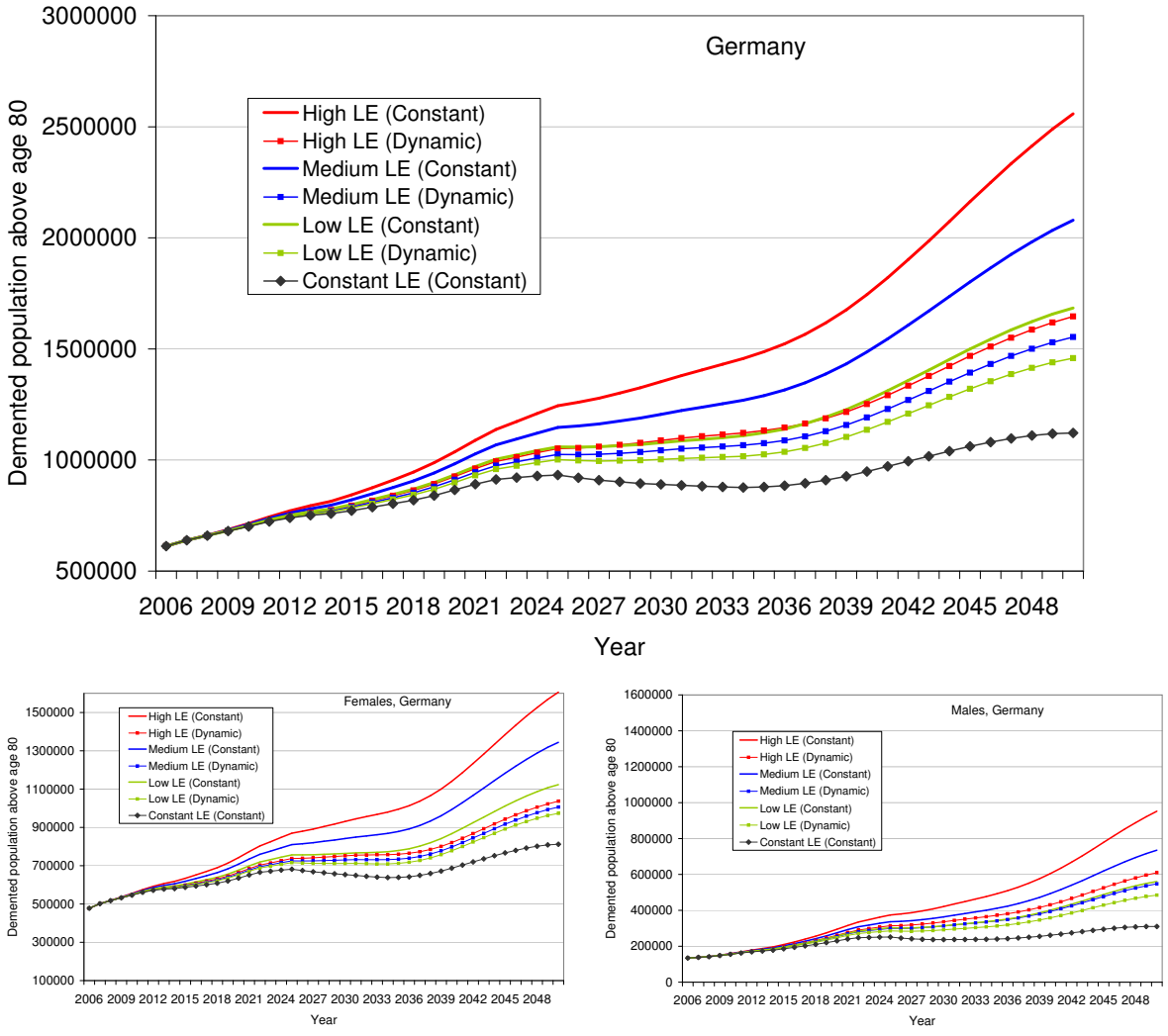
Life Expectancy	Dementia Rate	Germany	West Germany	East Germany
2006		1.034	0.813	0.221
2050 Constant	Constant	1.622	1.267	0.355
2050 Low	Constant	2.268	1.771	0.497
2050 Low	Dynamic	1.947	1.515	0.432
2050 Medium	Constant	2.717	2.127	0.590
2050 Medium	Dynamic	2.000	1.556	0.444
2050 High	Constant	3.249	2.541	0.708
2050 High	Dynamic	2.052	1.590	0.461

Figure 6.6: Development of the Demented Population above Age 60 until 2050 according to Different Scenarios



LE = Life Expectancy
Legend: the first term describes the life expectancy variant, the dementia variant is given in brackets.
Source: own calculations

Figure 6.7: Development of the Demented Population above Age 80 until 2050 according to Different Scenarios



LE = Life Expectancy
Legend: the first term describes the life expectancy variant, the dementia variant is given in brackets.
Source: own calculations

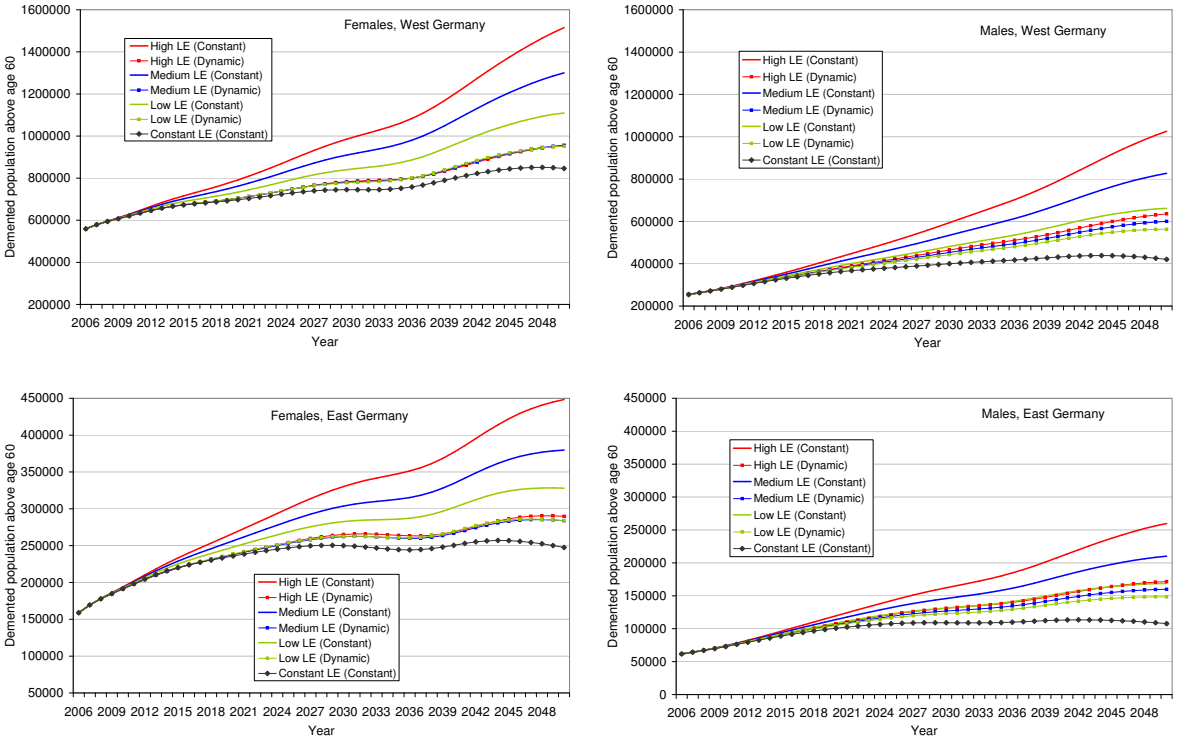
Figure 6.8 and table 6.7 show the results differentiated by region. Since many more people above age 60 live in West Germany, or 16.0 million (78%), compared with 4.5 million people in the East; more demented people also live there, or 0.81 million (79%), compared with 0.22 million. This is a proportion of 5.1% in West Germany and 4.9% in East Germany. But because the incidence is slightly higher in East Germany, the increase until the year 2050 will also be slightly higher in this region: according to the different scenarios, the increase will, in the low life expectancy and dynamic equilibrium model, be at least to 1.77 million (78%) demented people in the West and 0.50 million demented people in the East, or 8.8% and 9.4% of the total population, respectively. The highest scenario - large life expectancy increase and constant dementia rates - shows an increase to 2.5 (78%) million demented people in West Germany and 0.71 million demented people in East Germany, or 11.4% and 12.2% of the total population, respectively.

Table 6.7: Demented Population above Age 60 (in 1000) according to Different Life Expectancy Scenarios by Gender and Region

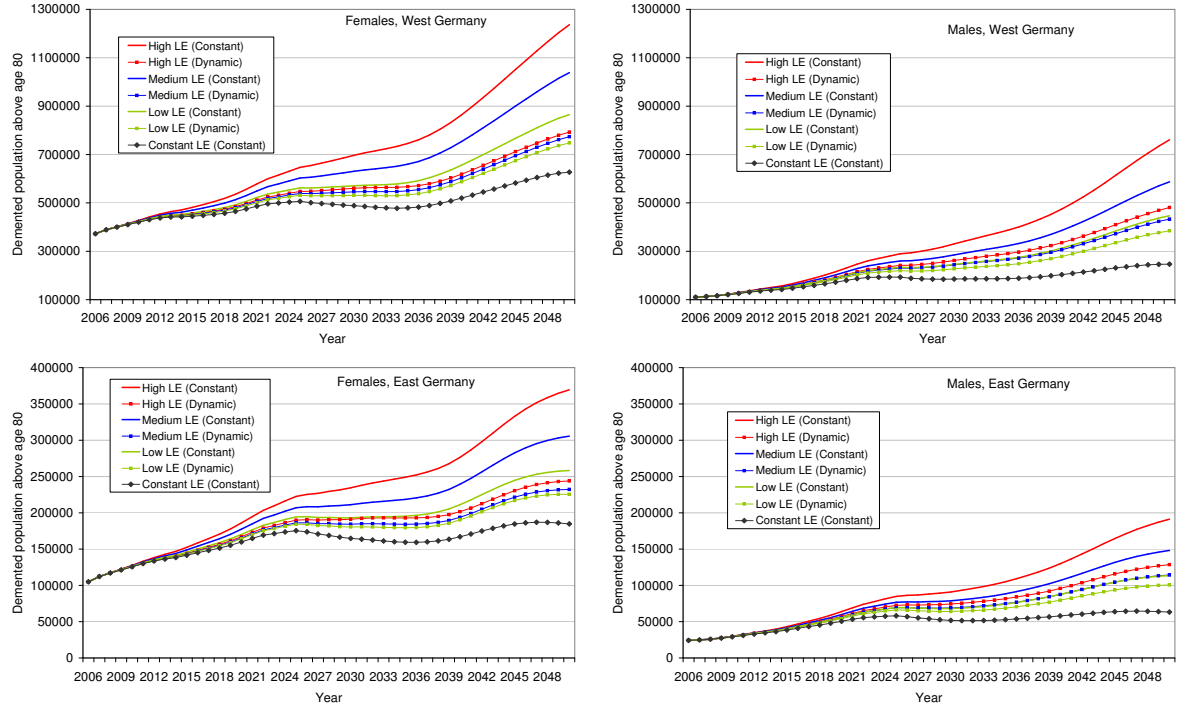
Life Expectancy	Dementia Rate	2006	2020	2030	2040	2050
Males						
Germany						
Constant	Constant	316	464	509	544	528
Low	Constant	316	501	613	732	830
	Dynamic	316	481	566	650	712
Medium	Constant	316	526	680	856	1037
	Dynamic	316	485	580	673	760
High	Constant	316	553	756	998	1286
	Dynamic	316	489	596	698	807
West Germany						
Constant	Constant	254	363	400	431	421
Low	Constant	254	392	481	580	662
	Dynamic	254	376	443	512	563
Medium	Constant	254	412	534	678	827
	Dynamic	254	379	453	529	600
High	Constant	254	433	594	791	1026
	Dynamic	254	382	465	547	636
East Germany						
Constant	Constant	62	101	109	113	108
Low	Constant	62	109	131	152	169
	Dynamic	62	105	123	138	148
Medium	Constant	62	114	146	178	210
	Dynamic	62	106	127	144	160
High	Constant	62	120	162	207	260
	Dynamic	62	107	131	151	172
Females						
Germany						
Constant	Constant	718	933	995	1052	1094
Low	Constant	718	982	1123	1263	1437
	Dynamic	718	944	1040	1124	1235
Medium	Constant	718	1018	1214	1410	1680
	Dynamic	718	942	1043	1117	1240
High	Constant	718	1058	1316	1579	1963
	Dynamic	718	942	1049	1115	1244
West Germany						
Constant	Constant	559	697	745	801	846
Low	Constant	559	734	840	961	1109
	Dynamic	559	705	778	854	952
Medium	Constant	559	762	910	1076	1300
	Dynamic	559	705	780	850	956
High	Constant	559	792	985	1203	1515
	Dynamic	559	704	784	846	955
East Germany						
Constant	Constant	159	236	250	250	247
Low	Constant	159	248	283	302	328
	Dynamic	159	239	262	269	284
Medium	Constant	159	257	304	334	380
	Dynamic	159	238	262	267	284
High	Constant	159	267	330	377	448
	Dynamic	159	238	265	269	290

Figure 6.8: Development of the Demented Male and Female Population above Age 60 and Age 80 in West and East Germany until 2050 according to Different Scenarios

Age 60+



Age 80+



LE = Life Expectancy
Legend: the first term describes the life expectancy variant, the dementia variant is given in brackets.
Source: own calculations

6.2.4 Prevalence Projections

In a next step, prevalence projections were calculated. The population was projected with five-year age groups until age 94, while the last age group was 95+. Different scenarios with different life expectations for 2050 were calculated. The status quo scenario was done with constant prevalences and constant mortality to show the pure age structure effect. Scenario 1 projected increases in life expectancy to 82.61 years for males and to 87.51 for females, scenario 2 projected increases to 84.30 years for males and 89.08 for females, and scenario 3 projected increases to 87.90 years for males and 92.52 years for females. Scenarios 1 and 2 are roughly in line with the increase in life expectancy for the 'basic' and 'high' variants from the 11^{th} coordinated population projection from the German Statistical Office (Statistisches Bundesamt Deutschland, 2006), while scenario 3 has higher life expectancy assumptions. The life expectancies used here in the prevalence projections are similar but not equal to the multi-state projections. In the prevalence projections the total population was projected. In the multi-state projections, the total life expectancy is a combination of the non-demented and the demented populations, which is not equal to obtain.

In a second step, the population projection results were multiplied by the dementia prevalence. Each scenario was multiplied by two prevalences: constant prevalences and prevalences which resemble the dynamic equilibrium in life expectancy with and without dementia. Thus, seven different scenarios were obtained:

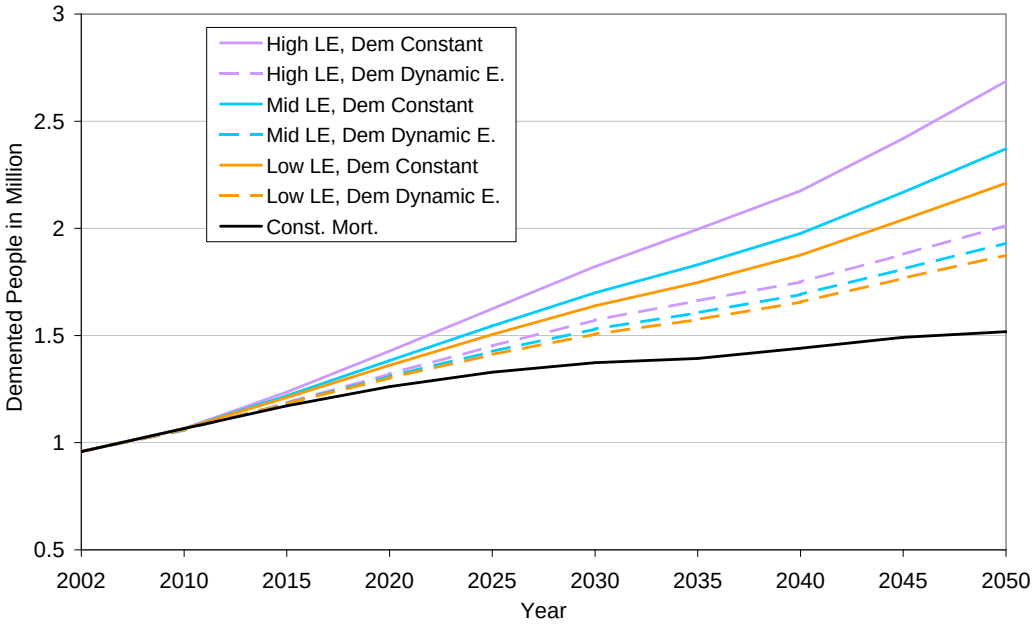
1. Status Quo Scenario - constant mortality and constant prevalence
2. Scenario 1.1 (Low) - low increase in LE and constant prevalence
3. Scenario 1.2 (Low) - low increase in LE and dynamic prevalence
4. Scenario 2.1 (Medium) - medium increase in LE and constant prevalence
5. Scenario 2.2 (Medium) - medium increase in LE and dynamic prevalence
6. Scenario 3.1 (High) - high increase in LE and constant prevalence
7. Scenario 3.2 (High) - high increase in LE and dynamic prevalence

(LE=Life Expectancy)

When constant dementia prevalences were assumed, only the expected number of elderly people influenced the change in the number of demented people. Even with

constant mortality, the number of demented people above age 60 would increase from 0.96 million people in 2002 to 1.52 million simply because of the changing age structure (see figure 6.9, black line). With rising life expectancy, the increase is much higher: constant dementia prevalence and high increases in life expectancy to 87.9 and 92.5 years for males and females, respectively, would lead to 2.7 million demented people in 2050. If a dynamic equilibrium in dementia-free life expectancy could be achieved at ages 80-84, the increase in the number of demented people would be less steep, but still roughly double. The results are displayed in table 6.8 and figure 6.9.

Figure 6.9: Projected Number of People above Age 60 with Dementia according to Different Scenarios



LE = Life Expectancy
Legend: the first term describes the life expectancy variant, the second the dementia development
Source: own calculations

A comparison of the projection results of the multi-state projections, the prevalence projections and projections with own prevalences and population projections from the German Statistical Office (Statistisches Bundesamt Deutschland, 2006) are shown in table 6.9. From the 11th coordinated population projections from the German Statistical Office (Statistisches Bundesamt Deutschland, 2006) the two variants 1-W1 and 2-W1 were used, which assume a constant fertility rate of 1.4 and a net migration of 100,000 people. They differ in their 'basic' and 'high' life expectancy assumption, which equals our low and medium variant, as described above.

The results show higher numbers of demented people for the medium and high

Table 6.8: Total and Demented Population above Age 60 in 2002 and 2050 according to Different Life-Expectancy and Dementia Prevalence Scenarios (in Million)

		2002		2050					
				Low LE		Medium LE		High LE	
	e(0)	75.9	81.5	82.6	87.5	84.3	89.1	87.9	92.5
Population	Age	M	F	M	F	M	F	M	F
Total	60-64	2.848	2.958	2.149	2.148	2.170	2.159	2.206	2.176
Population	65-69	2.073	2.305	2.066	2.164	2.098	2.180	2.152	2.208
	70-74	1.584	2.021	1.894	2.056	1.940	2.081	2.021	2.123
	75-79	0.983	1.855	2.234	2.544	2.320	2.596	2.475	2.686
	80-84	0.499	1.190	2.010	2.472	2.134	2.560	2.364	2.717
	85-89	0.228	0.696	1.221	1.699	1.347	1.812	1.592	2.020
	90-94	0.083	0.329	0.552	0.906	0.650	1.018	0.857	1.240
	95+	0.013	0.070	0.152	0.258	0.176	0.287	0.229	0.346
	60+	8.310	11.42	12.28	14.25	12.84	14.69	13.90	15.52
	60+ all	19.735		26.526		27.526		29.413	
Demented	60-64	0.024	0.019	0.018	0.014	0.018	0.014	0.019	0.014
Population	65-69	0.032	0.030	0.032	0.029	0.032	0.029	0.033	0.029
Constant	70-74	0.050	0.062	0.060	0.063	0.061	0.064	0.064	0.065
Dementia	75-79	0.055	0.127	0.125	0.174	0.130	0.178	0.138	0.184
Rates	80-84	0.052	0.152	0.208	0.315	0.221	0.327	0.245	0.347
	85-89	0.041	0.161	0.219	0.392	0.241	0.418	0.285	0.466
	90-94	0.020	0.103	0.134	0.284	0.157	0.319	0.207	0.389
	95+	0.004	0.027	0.045	0.099	0.052	0.111	0.068	0.133
	60+	0.277	0.681	0.840	1.370	0.913	1.458	1.059	1.627
	60+ all	0.958		2.210		2.372		2.686	
Demented	60-64			0.015	0.012	0.015	0.011	0.014	0.011
Population	65-69			0.027	0.024	0.026	0.023	0.025	0.022
Dynamic	70-74			0.051	0.053	0.050	0.052	0.048	0.049
Equilibrium	75-79			0.106	0.148	0.106	0.145	0.104	0.138
	80-84			0.176	0.268	0.180	0.266	0.183	0.260
	85-89			0.185	0.333	0.196	0.340	0.214	0.350
	90-94			0.113	0.241	0.128	0.260	0.156	0.291
	95+			0.038	0.084	0.043	0.090	0.051	0.100
	60+			0.713	1.163	0.743	1.187	0.794	1.220
	60+ all			1.875		1.931		2.014	

LE=Life Expectancy, F=Females, M=Males

multi-state projections, compared with the prevalence projections. The results from the StBA projections are higher than the prevalence projections. The results for the dynamic equilibrium are close, at around two million people regardless of the scenario.

Table 6.9: Comparison of Projection Results of the Demented Population above Age 60 (in Million) for 2050

Life Expectancy	Multi-State Projections	Prevalence Projections	StBA Projections*
Constant Dementia			
Low	2.26	2.21	2.37
Medium	2.71	2.37	2.74
High	3.26	2.69	-
Dynamic Dementia			
Low	1.95	1.88	
Medium	2.00	1.93	
High	2.05	2.01	

*Variants 1-W1 and 2-W1 from the 11th coordinated population projection are multiplied with own dementia prevalences.

6.2.5 Dementia-Free Life Expectancy (DFLE)

The increasing life expectancy has led to a discussion about the development of the accompanying health status. Is there an 'expansion of morbidity' (Gruenberg, 1977; Olshansky et al., 1991) because medical advancements keep chronically ill people alive longer, or do these advancements help us to 'compress morbidity' into later life (Fries, 1980) (see section 2.3)? In order to measure life expectancy in good and bad health, a concept of 'health state expectancy' (HSE) (Robine et al., 2003) was developed by Sanders (1964) and Sullivan (1971). A general model of the health transition was developed by the World Health Organization (1984). The concept of the mortality survival curve was extended by survival curves in good health and without disability. Healthy Life Years (HLY) are defined by the World Health Organization (2004) as the "average number of years that a person can expect to live in 'full health' by taking into account years lived in less than full health due to disease and/or injury." It combines the life table with prevalence rates for which practically any measure of health can be used: e.g., self-perceived health, activities of daily living or chronic morbidity (European Health Expectancy Monitoring Unit (EHEMU), 2009).

We used this concept to measure 'dementia-free life expectancy' (DFLE). It was calculated using the Sullivan Method (Sullivan, 1971),

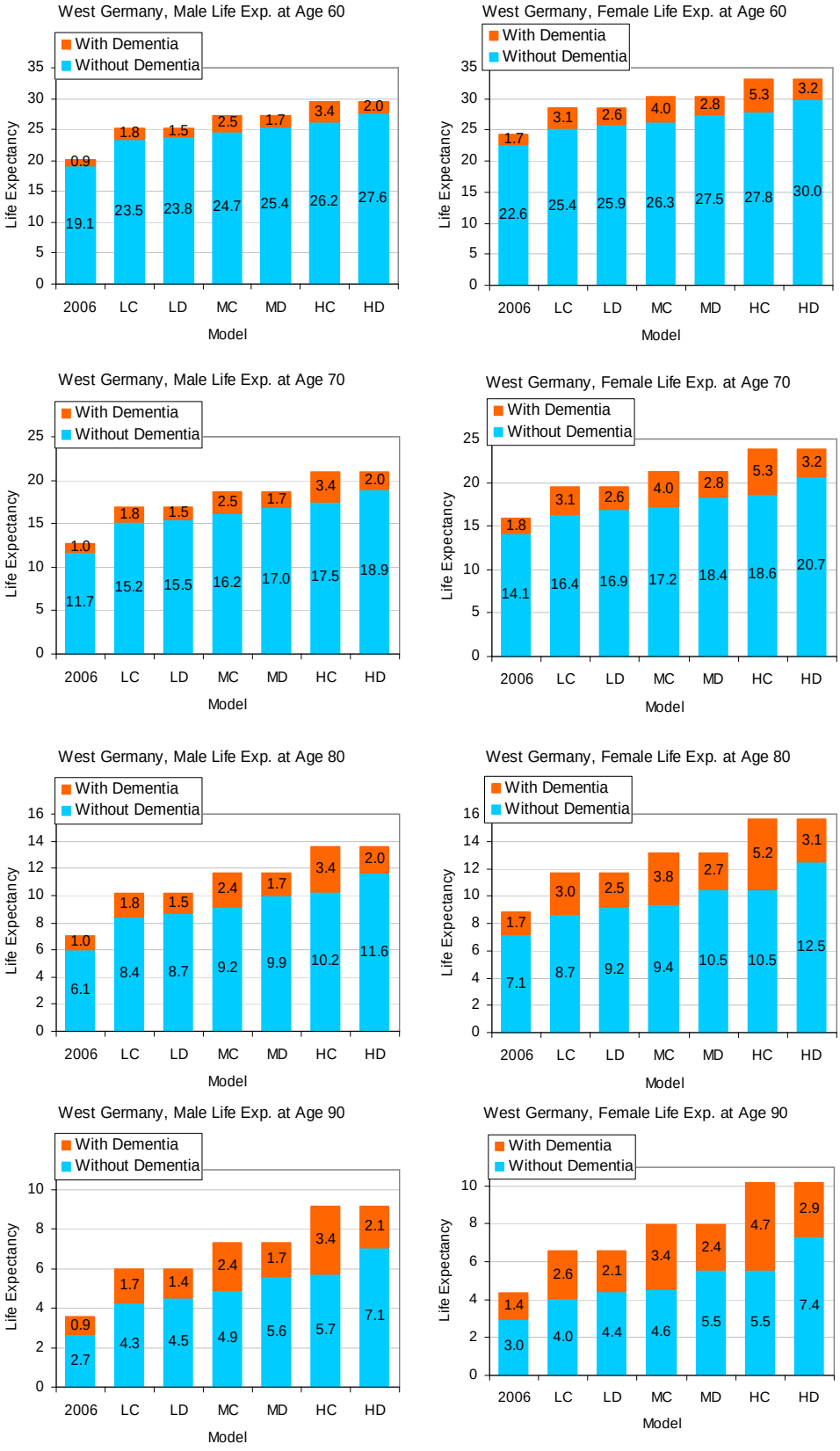
$$e_x = \frac{1}{l_x}\sum_{i=x}^{W} L_i = \frac{1}{l_x}\sum_{i=x}^{W} L_i(H) + \frac{1}{l_x}\sum_{i=x}^{W} L_i(D) \tag{6.1}$$

where the life expectancy e at age x is calculated by dividing the sum over all years lived in the age interval L_i by the surviving people l in that age interval. The total life expectancy can then be split into life expectancy without and with dementia when it is multiplied with the proportion of people in that age interval without (H) and with dementia (D).

We calculated age-specific prevalences of dementia from the multi-state projection results from each scenario, and combined them with a life table. Results from the prevalence projections were similar (not shown). Results for people at ages 60, 70, 80 and 90 for West and East German males and females are shown in figures 6.10 and 6.11. For example, an average 80-year-old West German man in 2006 has a total further life expectancy of 7.1 years, of which he may be expected to spend 6.1 years without and 1.0 years with dementia, or a proportion of about 14.3%. A small increase in life expectancy and constant dementia rates would lead to 8.4 years without and 1.8 years with dementia in 2050, or a proportion of 17.3%. A dynamic equilibrium would lead to 8.7 years without and 1.5 years with dementia, or a proportion of 14.3%. The proportion is the same as in 2006. Since the transition rate is higher for West German men and East German women, their life expectancy with dementia is also higher compared with East German men and West German women, respectively.

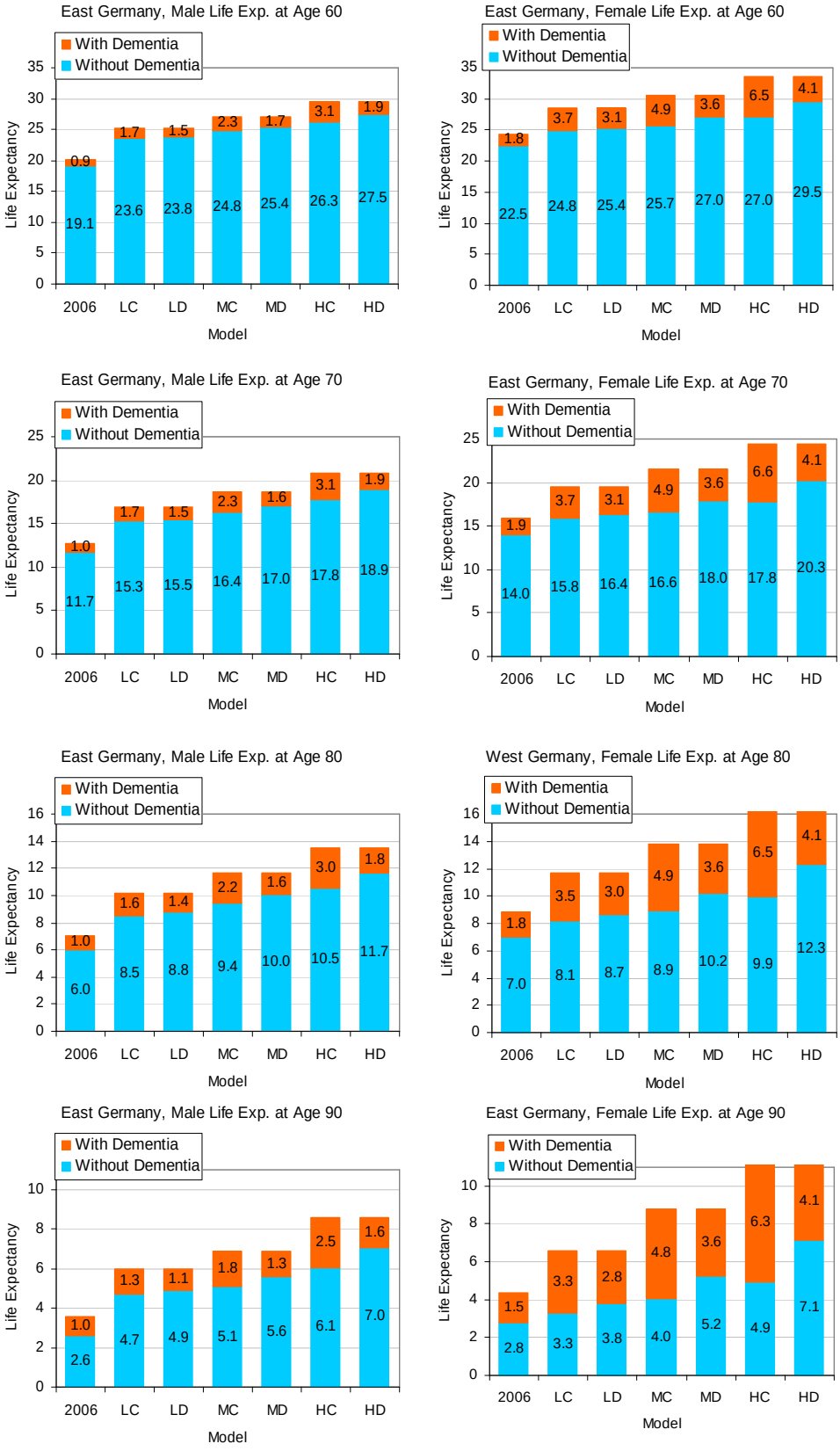
Using the standard life-table method, it is only possible to calculate the true dynamic equilibrium for one age onward (here, 80+ is chosen) because of a constraint of the Sullivan Method. It implicitly assumes that death rates are similar for both the non-demented and demented populations, but that the rates change differently for different ages. However, the results we obtained for other ages are close to the dynamic equilibrium: they are somewhat higher at younger ages before age 80, very close at the middle ages around age 80 and slightly lower at higher ages. For example, an average 90-year-old West German woman has an additional life expectancy of 3.0 years without and 1.4 years with dementia, or 32%. The high life expectancy and dynamic rates model leads to 7.3 years without and 2.9 years with dementia in 2050, or 28.7%.

Figure 6.10: Dementia-Free Life Years and Years with Dementia for West German Males and Females in 2006 and 2050 for Different Scenarios



L=Low Life Expectancy, M= Medium Life Expectancy, H=High Life Expectancy
C=Constant Dementia Incidence Rates, D=Dynamic Equilibrium Development
Source: own calculations

Figure 6.11: Dementia-Free Life Years and Years with Dementia for East German Males and Females in 2006 and 2050 for Different Scenarios



L=Low Life Expectancy, M= Medium Life Expectancy, H=High Life Expectancy
C=Constant Dementia Incidence Rates, D=Dynamic Equilibrium Development
Source: own calculations

6.2.6 Discussion

These results make clear that the increase in life expectancy is the driving factor of the development of the number of demented people if no strong change in the incidence occurs. Table 6.9 shows an increase to at least 2.3 million demented people in Germany if life expectancy increases slowly. But, in the more likely event that a large increase in life expectancy takes place and assuming, there are no changes in incidence rates, it would rise to 2.7 or 3.3 million people in 2050 in the prevalence and multi-state projections, respectively. This difference of more than half a million people also underlines the importance of the method used. The prevalence projection simply estimates the total population and multiplies the results with the prevalence rates. The multi-state projections should be more exact because they use the incidence rate, which does not depend on whether the survival rate and the different death rates for demented and non-demented people are taken into account. But this comparison implies that the calculated incidence and death rates lead to the correct—and the calculated— prevalence rates. On the one hand, the different death rate could be a reason for the higher result. The higher death rate among demented people decreases this subpopulation faster, while the lower rate among the non-demented population increases this subpopulation faster. This, however, increases the potential for incident cases. Thus, the total population in the multi-state model with high life expectancy and a constant dementia rate should be higher than the total population in the prevalence model, with high life expectancy explaining the higher number of demented people, with a higher number for potential incident cases. However, the population is about the same, at 28 and 29 million people above age 60. On the other hand, the incidence rate we used might be too high, or the mortality for demented people might be too low. The prevalence of a disease results from the incidence and the duration of that disease. Thus, a projection with constant mortality and incidence rates should lead to about the same prevalences as in the starting population. When Ziegler and Doblhammer (2009) compared the prevalences from 2006 with the ones from 2050 in the constant mortality and constant transition rate model, they found about the same age-specific prevalences in 2050 for males, but slightly higher prevalences for females, especially above age 75. This could mean that the incidence rate for women is too high, or that the death rate is too low, which would in turn increase the number of people with dementia in our projections.

Combining our prevalence rates with the population projections from the Statistical Office Germany led to somewhat higher results than our own prevalence projections,

although life expectancy is about the same and the prevalence rate is exactly the same. The two variants of the StBA include a net migration of 100,000 people, which simply increases the total population. In recent years, net migration has been below 100,000 (from 2004 until 2007: 82,500; 79,000; 22,800 and 43,900). It is very difficult to project migration and to get reliable and age-specific data; therefore, we leave it out of our models. If it were to increase again, the total population would increase too. The age profile of migrants is usually younger than that of the German population, and their health is better when they arrive. The so-called 'Healthy Migrant Effect' (Lechner and Mielck, 1998) states that migration is a stressful event which more unhealthy people tend to avoid. But the longer they stay, the more they lose their health advantage, and the potential of people to develop dementia increases earlier or later, depending on the age structure of the migrants.

Our results with the constant rates are higher than most results from other projections for Germany. The highest number was so far projected by Bickel (2008), who projected 2.62 million people in 2050. It is based on his own prevalence rates combined with the 'basic' life expectancy and high migration model from the 11th coordinated projection from the German Statistical Office. The high number results from the high migration assumption rather than from the life expectancy development. Most projections tend to underestimate the increase in life expectancy. In recent decades, there has been a linear increase in life expectancy (Oeppen and Vaupel, 2002), which came primarily from mortality decreases at higher ages (Vaupel et al., 2006). So far, no end to the increase in life expectancy is in sight; thus the high life expectancy scenario is the most likely development.

However, the constant dementia rate scenario is not necessarily the most likely development. The literature review and the results about the determinants of dementia have shown that there are possible influenceable factors of the disease. On the basis of these findings a decreasing dementia rate has been modeled. If it is possible to decrease dementia incidence rates such that a dynamic equilibrium is achieved, the increase in the number of sufferers would be more moderate, or about two million people, regardless of developments in life expectancy. The decrease in the rates had to be greater in the medium and high life expectancy models to achieve a dynamic equilibrium. The dynamic equilibrium demonstrates an equal proportion of dementia-free life-years (DFLE). But even this dynamic equilibrium with an equal proportion of years with and without dementia means an actual increase in total years with dementia because of the higher life expectancy. If the transition rates decreased more slowly, we had an

expansion; but if they decreased more quickly, a compression of morbidity would occur.

The neglect of the further strong increase in life expectancy has far-reaching consequences. The increase in the total elderly population and the population with dementia will most likely be higher than generally assumed if no change in dementia rates occurs. As the demographic change will already be putting society under pressure, having to supply more care for the elderly than anticipated is a very big challenge, especially as political reforms have failed in the past because of these underestimations (Vaupel and von Kistowski, 2005). Best effort is needed to postpone the onset of dementia into higher ages and decrease the number of affected people. If a lower number of demented people would diminish the very high cost burden is less clear and depends on a large number of factors as is described in the next chapter.

Chapter 7

Projections of the Costs of Dementia in Germany until 2050

7.1 Total Costs of Dementia Worldwide

Dementia is one of the most costly disease groups. This is mainly due to the very high care need of demented people (Bickel, 2001; Weyerer, 2005; World Health Organization, 2006b). Of the cognitively unimpaired people with chronic disabilities, only 7% are in need of care, while this proportion rises to 80% for severely demented patients (Schäufele, 1994).

The costs associated with dementia and AD are usually classified into direct, indirect and intangible costs (Moise et al., 2004). These mainly involve indirect costs, such as unpaid care by family members and the lost added value to the national economy. Direct costs are driven by institutional care. Medical diagnosis and treatment play only a minor role in the costs. In the final months of dementia, care within the family is barely feasible, and many patients have to move into institutions (for example, in Germany about 80% (Bickel, 2001)). The very high indirect costs are not the only reason it is difficult to estimate the total costs of dementia. Other hidden costs have to be included, such as health problems of caregivers (stress and depression), higher average hospital costs of dementia patients, co-morbidities and underdiagnoses (Schwam et al., 2007; Weyerer, 2005). A methodological framework for the estimation of the cost of illness given by Rice (1967) shows the problems of covering all involved costs. Direct costs not only include expenditures for prevention, detection, treatment, rehabilitation, research, training and capital investment in medical facilities; but also for construction, government public health activities, voluntary health agencies and the net costs of

insurance. The indirect costs include the loss of output to the economy: earnings, losses in employment output, housewives' services, transfer payments and taxes. Difficult to measure are intangible costs, such as pain and grief.

Wimo et al. (2010) estimated the total worldwide societal costs of dementia in 2009. On the basis of 34.4 million people, they calculated total costs of US $ 422 billion. The costs can be split into direct costs of US $ 279 billion (66%) and indirect costs for informal care of US $ 142 billion (34%). They found that, within just four years, the costs had increased by 34% (18% in fixed prices). The highest costs occur in North America and Europe. The cost calculations from Wimo et al. (2010) (and for the year 2005: Wimo et al. (2007)) were based on prevalences from Fratiglioni and Rocca (2001). For the direct costs, a relationship between costs per demented person and GDP per person was assumed. Informal care costs were difficult to estimate, because there often is no market value for caregiver time. The authors used the UN classification of working activities group 07900 'providing unpaid caregiving services to household members' (International Monetary Fund, 2005). An institutionalization rate of 27% was taken into account, which, however, increased to 50% in a sensitivity analysis.

In the member states of the European Union, the costs of all mental problems were estimated to be between 3% and 4% of gross national product (European Commission, 2004). Dementia has a large impact on these total costs. For the EU27 states, Wimo et al. (2008) estimated total costs of € 130 billion in 2005, which amounts to costs of € 21,045 per person. For the UK, annual costs in 2007 were estimated at £ 25,472 (€ 37,000) (Knapp et al., 2007).

A study for the US showed total costs of US $ 77,447, of which US $ 43,066 (56%) were indirect costs, including a weekly amount of 47 care hours; and US $ 34,381 were direct costs (MetLife Mature Market Institute & LifePlans Inc., 2007).

In the first meta-analysis of the costs associated with dementia in the 1980s and early 1990s Wimo et al. (1997) found large differences in results. Their main conclusion was that more research is needed. Cost studies were rare at that time, and differed widely in methodology and outcome measures. Some years later, differences between countries were still large because it is difficult to estimate indirect costs.

Bickel (2001) analyzed international studies and found that the annual per patient costs of dementia ranged from about € 25,000 to 50,000. Moise et al. (2004) analyzed total costs for AD for five studies conducted in OECD countries. Their findings indicated that costs ranged from US $ 19,529 in Spain to US $ 44,301 in the US (see table 7.1).

In a review by Leung et al. (2003) an even greater range was found in 23 studies of US $ 6,000 to $ 75,000 per person per year. The large difference might be explained by the fact that studies with the lowest cost estimates did not include indirect costs, and that the highest estimates were in studies which included hospital or institutional care.

Table 7.1: Total Costs of Dementia and Alzheimer's Disease

	Country	Year	Severity	Costs (Pat/Year)*
All Severity Levels Combined				
Wimo et al. (2007)	World	2005	All	10,765
Wimo et al. (2008)	EU 27	2005	All	21,045**
MetLife 2007	USA	2005	All	77,447
Wimo and Jonsson (2001)	Sweden	2000	All	34,365
Hallauer et al. (2000)	Germany	2000	All	43,767***
Hessel et al. (2004)	Germany	1994	All	30,700**
Bickel (2001)	Meta	1990s	All	25,000-50,000***
Leung et al. (2003)	Meta	80s-90s	All	6,000-75,000
Boada et al. (1999)	Spain	1998	All	19,529
Fagnani et al. (1999)	France	1993	All	23,542
Hux et al. (1998)	Canada	1991	All	28,868
Ernst and Hay (1994)	USA	1994	All	44,301
Differentiated by Severity Level				
Quentin et al. (2009)	Meta°	1990s	Mild	14,100 - 29,100**
Quentin et al. (2009)	Meta°	1990s	Moderate	21,500 - 35,100**
Quentin et al. (2009)	Meta°	1990s	Severe	24,100 - 68,000**
Quentin et al. (2009)	Meta°°	1990s	Mild	10,500 - 22,900**
Quentin et al. (2009)	Meta°°	1990s	Moderate	18,300 - 43,900**
Quentin et al. (2009)	Meta°°	1990s	Severe	20,700 - 64,700**
Hallauer et al. (2000)	Germany	2000	Mild	5,000***
Hallauer et al. (2000)	Germany	2000	Moderate	42,500***
Hallauer et al. (2000)	Germany	2000	Severe	90,000***

* Costs per patient per year in 2000 US $ PPP

** in €

*** in €: German 'Mark' was transferred into € with an exchange rate of 2:1

° Studies in community-dwelling patients

°° Studies with augmenting proportions of institutionalized patients

–Costs for dementia shown by Bickel (2001); Hessel et al. (2004); Quentin et al. (2009); Wimo and Jonsson (2001); Wimo et al. (2008, 2007), other studies show AD costs.

Quentin et al. (2009) were the first to conduct a meta-analysis of cost-of-illness studies of dementia by severity grade. They found a large range of research results, but a clear trend towards higher costs with increasing severity. Sadik and Wilcock (2003) found that the direct costs in all countries increase with the severity grade, but

that this was not the case for indirect costs. With the severity of the disease, the institutionalization of patients was also found to increase, which in turn caused many informal caregivers to increase their paid working hours. The costs were shifted from the family to the society. This finding is also reflected in lower total costs in studies which include institutionalized dementia patients (Quentin et al., 2009).

7.2 Total Costs of Dementia in Germany

Cost estimations for the around one million demented people in Germany range from € 10 to 44 billion per year (Bischoff et al., 2004; Hallauer et al., 2000; Hessel et al., 2004). For example, Hessel et al. (2004) assumed that the yearly costs were € 30,700 per patient, which resulted in total costs of € 27.8 to 37.7 billion in 1994.

In Germany, the total cost of illness in 2004 added up to € 224.9 billion (10.6% of the GDP) (Statistisches Bundesamt & Robert Koch Institut, 2007). The total amount consist of costs for the final consumption of health goods and services and investments in the health sector, such as research. Since 1995, the total costs also included expenditures for care need and arrangements for rehabilitation to facilitate return to work.

Of these total costs, 10.1% (€ 22.8 billion) were incurred in treating mental and behavioral disorders. This was the fourth largest cost group after diseases of the circulatory system, diseases of the digestive system (including diseases of oral cavity, salivary glands and jaws) and diseases of the musculoskeletal system and connective tissue. Other costly disease groups include neoplasms (€ 9.8 billion), endocrine, nutritional and metabolic diseases (€ 6.7 billion) and diseases of the respiratory system (€ 5.8 billion). Within the group of mental and behavioral disorders, dementia and depression together account for nearly half of the costs, € 6.1 billion and 4.2 billion, respectively. Nearly two-thirds of these direct costs are related to inpatient and daytime care (Weyerer, 2005).

However, the main reason why dementia is one of the most costly disease groups is because of the indirect costs incurred, as discussed above. Hallauer et al. (2000) calculated that more than € 43,700 per year are spent to treat each AD patient. After breaking down these costs, they found that 67.9% are indirect costs incurred by the family providing care, while 29.6% are payments made by the patient's long-term care insurance (GPV) and 2.5% are payments made by the public sickness funds (GKV). They further differentiate between the costs of treating AD patients for several severity grades, measured with the MMSE scores of 21-26, 15-20, 10-14 and 0-9. While costs

for the GKV stayed nearly constant, the burden for the GPV and the family increased steeply as the MMSE scores declined. The yearly contribution of the GPV in the early stages was about € 3,000, and increased to about € 23,000. While there was no need for care by the family in the early stages, the need increased to 2.75, 9.85 and 13.94 hours per day, which equals expenses (mainly lost income) of about € 12,500, 46,000 and 68,000 per year, respectively. The total amount spent in the early stages of cognitive decline added up to less than € 5,000 per year, and increased to more than 90,000 Euro per year. In a US study, a drastic cost increase was also found, rising from US $ 9,451 for people with mild dementia, to US $ 36,794 for people in severe disease stages (Hux et al., 1998).

7.3 Ambulant and In-Patient Costs of Dementia in Germany in the Public Sickness Funds (GKV)

Using the GKV data (see chapter 3), the direct costs of doctor visits, medication and hospitalization of people with dementia can be calculated. In the first section, a short overview of health care costs for all people is provided. The second section shows costs for people with dementia above age 60.

7.3.1 Total Health Care Costs of the Public Sickness Funds (GKV)

Of all people in the sample, 84.5% were insured for the whole year in 2002. The other 15.5% either changed sickness funds or had died. They are evenly distributed over the year, with peaks at the end of the months. As changes in sickness funds are rare after the age of 60, 97.7% of those who did not die were insured the whole year.

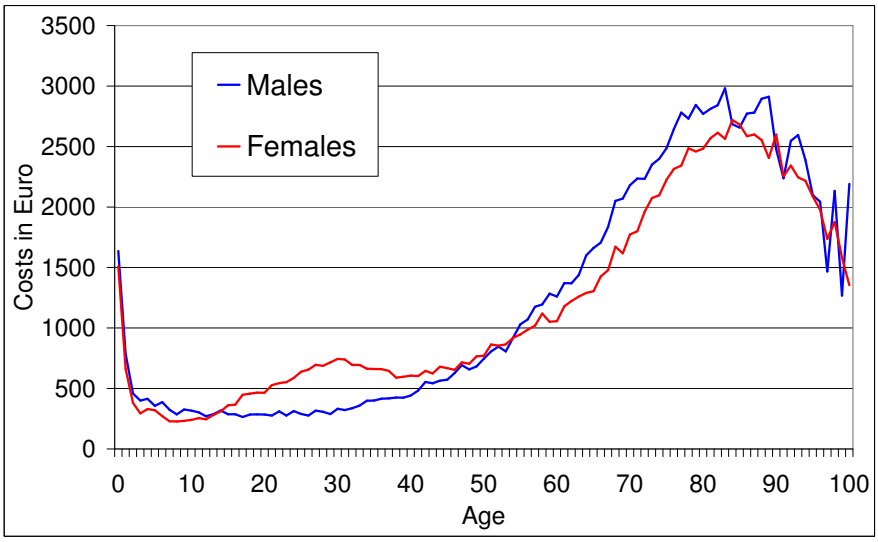
In a first step, the total costs of ambulatory and in-patient treatment were calculated. On average, a person produced total costs of € 897.80 per year. For the 70.7 million people insured in public sickness funds this added up to an amount of € 63,5 billion (total expenditure of the public sickness funds in 2002 were € 133 billion; total health costs € 224.9 billion (Statistisches Bundesamt & Robert Koch Institut, 2007)).

The average ambulatory costs per person calculated only for people who were actually treated amount to € 339.94. When divided by all people, insured costs decline to € 287.65. People who were hospitalized stayed on average 17.9 days, and cost € 4,358.75. The average over all people amounts to 2.5 days and € 610.15. These two

numbers then add up to total costs of € 897.80 per person. If only those people who are insured the whole year (or who died) were taken into account, the costs increased to € 983.58. This is not surprising because the average frequency of doctor visits will increase over a longer insurance period, and because more young people are excluded from this calculation, since they change sickness funds more often.

Figure 7.1 displays the mean age-specific costs. After relatively high costs for newborns, costs are lowest for children and teenagers, and rise thereafter. Costs increase steeply after age 50, but start to decline after age 85. Higher costs for women between ages 15 to 45 can be ascribed to costs incurred during and after pregnancy. At all other ages, the costs are higher for men.

Figure 7.1: Mean Costs of the GKV in Germany in 2002 by Age and Gender



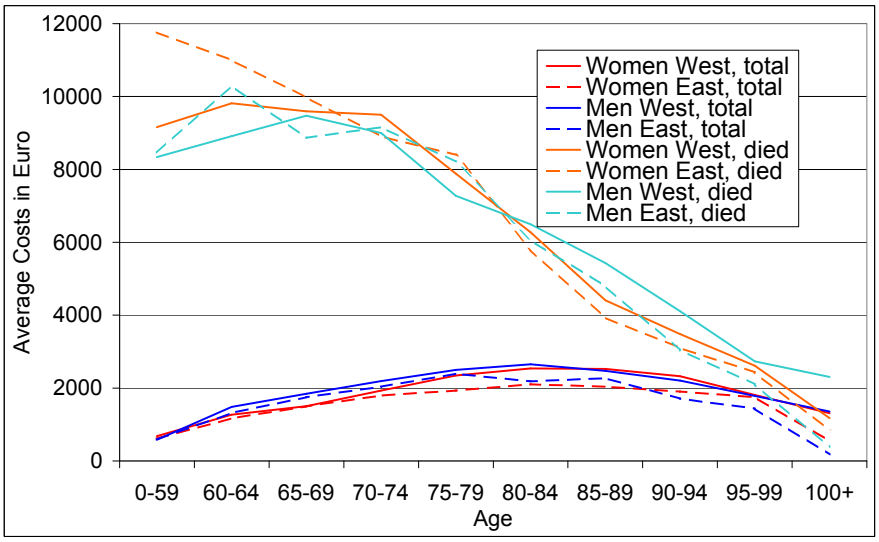
Source: GKV Data 2002, own calculations

Costs in East Germany are lower than in West Germany. The difference is greater for women, especially between the ages of 25 and 45, and above age 74. But the findings also show that less money is spent on elderly men in East Germany than in West Germany. Above age 75, the regional difference is greater than the gender difference. For the age group 100+, cost differences between West and East Germany of more than € 760 for women and more than € 1,170 for men appear.

In figure 7.2, the costs incurred by people who died during the year 2002 are displayed by age, sex and region, in comparison with the total population by age, sex and region. In younger ages costs for people who die are much higher than for the total population but with increasing age there is a steep decrease in the costs. Older people

die more quickly, and are therefore less costly to treat than younger people. Cost restrictions for elderly might also play a role. These results are also found by Brockmann and Gampe (2005); Niehaus (2006).

Figure 7.2: Total GKV Costs in Germany in 2002 by Age, Gender and Region



Source: GKV Data 2002, own calculations

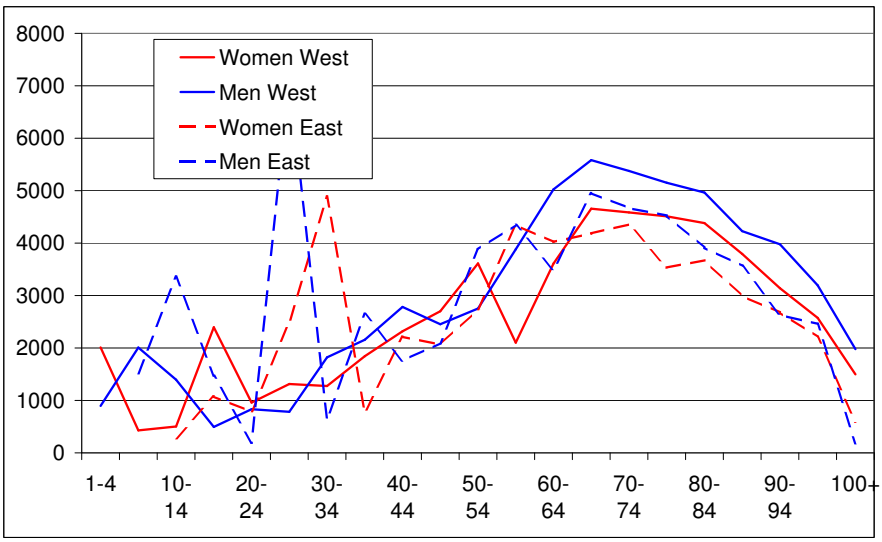
7.3.2 Costs of Dementia in the Public Sickness Funds (GKV)

As has been described above, dementia leads to very high indirect costs. Direct costs are driven by institutional care. Medical diagnosis and treatment play only minor roles in these costs. Nevertheless, it is important to also look at the treatment costs.

A methodological problem arises when calculating the costs of dementia with the GKV data. Costs in these data are given per doctor visit and it is not possible to calculate the costs incurred in treating the disease of dementia by itself. Co-morbidity increases with age, and is high for people with dementia. Thus, the total costs per dementia case include the cost of treating accompanying diseases.

Gender differences persist for people with dementia, with higher costs seen for males than for females. Between the regions, the costs are higher in West than in East Germany. Presenile dementia seems to be less costly than dementia after age 60, which could also be a co-morbidity effect at higher ages. However, numbers are low and large fluctuations appear. Costs are highest between ages 60 to 84, and decrease thereafter.

Figure 7.3: Total GKV Costs of a Dementia Patient in Germany in 2002 by Age, Gender and Region



*Costs are total GKV costs per person with dementia. Costs are given per doctor visit, it is not possible to calculate pure dementia costs.
Source: GKV Data 2002, own calculations

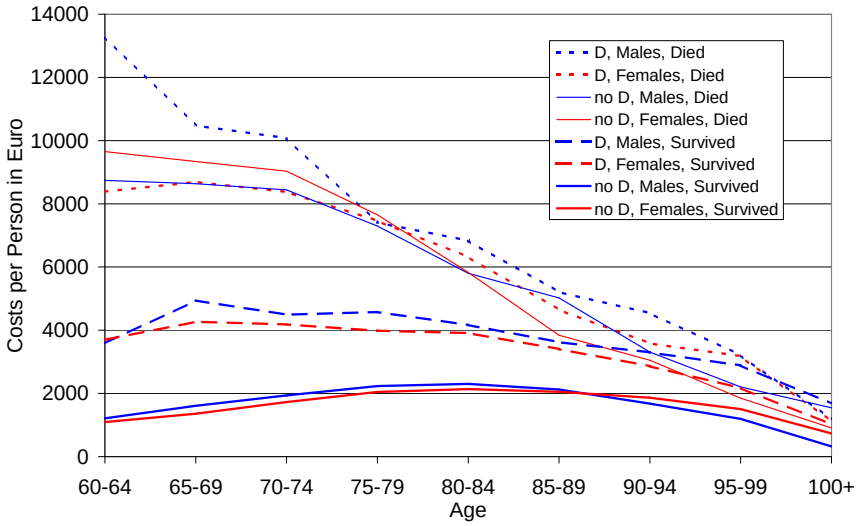
The data allow us to distinguish between ambulatory and in-patient diagnoses. Since in-patient treatment is much more expensive, we differentiated between the two kinds of diagnoses. Dementia is not an acute illness. It develops gradually, and, after being diagnosed, patients receive medication and start to require care. For ambulatory de-

mentia, we found about the same prevalence rates as for total dementia. For in-patient dementia, rates are lower, ranging from 0.15% in the age group 60-64 to 5.84% for ages 95+ (of the total population). The results again reveal a regional effect, especially for the highest ages. Above age 80, people with dementia in West Germany are treated more often in hospitals. Above age 90, a gender difference within the regions shows lower rates of in-patient treatment for men.

The next figure 7.4 shows the differences in the costs incurred by demented and non-demented males and females, and takes into account whether people survived the year. Death is confirmed as the main cost factor. Especially at younger ages, the costs for people who die in that year are higher, and range between € 8,385 (9,652) on average for women aged 60-64 with (without) dementia, up to € 13,280 (8,739) for males aged 60-64 with (without) dementia. Costs decrease with every age group, to less than one-third above age 95. The difference between the costs incurred by demented and non-demented people who died is small. It is slightly higher for males, and for females above age 80. For the people who survive a greater cost effect appears: people with dementia incur costs which are, on average, about twice as high as those incurred people without dementia. The costs are also higher at younger ages. Men and women without dementia who are between the ages of 60 and 64 incur average costs of € 1,212 and € 1,093. More than three times as much money is spent on people with dementia who are in the same age group: € 3,582 for males and € 3,696 for females. The cost differences for demented and non-demented people do not converge as strongly with age as the cost differences between survivors and the deceased. The decreasing difference between the groups with the lowest and highest spending (surviving males without dementia (€ 324) and surviving males with dementia (€ 1,678)) above age 100 is mainly due to the decreasing costs of dying.

Death is an important factor in the costs, as the period prior to death is often marked by acute treatment and/or hospitalization, which is more expensive than general doctor visits. Many studies have found that proximity to death is the main factor that drives costs (Brockmann, 2002; Lubitz and Riley, 1993). The small cost difference between people who die with and without dementia confirm this. Acute treatment leads to the highest costs, especially at younger ages. The large age gradient might arise because older people tend to be weaker, have a different disease pattern and have higher co-morbidity, and may therefore die more quickly (which would make their treatment less costly). However, cost rationing is found: elderly patients often receive less costly treatment than younger patients with the same disease, and the effect is stronger for

Figure 7.4: GKV Costs Incurred by Demented and Non-Demented People Who Survive or Die in Germany in 2002 by Age, Gender and Region



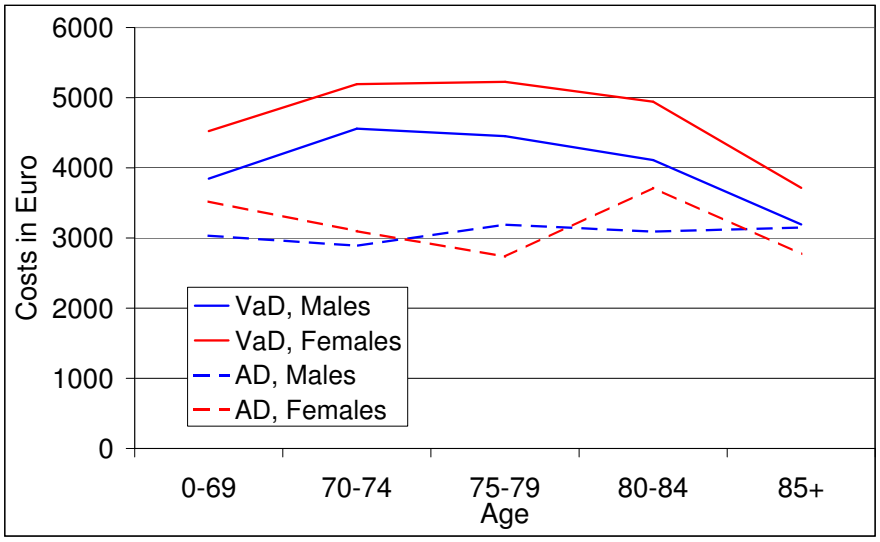
Source: GKV Data 2002, own calculations

those who die (Brockmann, 2002). Among survivors, dementia leads to higher ambulatory and in-patient costs, due to a high number of regular doctor visits, high drug costs and higher in-patient costs of these patients compared with not demented people (Hallauer et al., 2000). Hallauer et al. (2000) calculated detailed dementia costs for different severity stages of dementia, and found that, at the more moderate stages, doctor visits and drug costs are especially high, while at the more severe stages, in-patient care increases. On average he found that doctor consultation and treatment costs amounted to € 1,015 per patient, which is much lower than the € 3,890 we found. However, our costs also include treatment for the accompanying diseases. Costs are usually higher for males than for females, except for surviving males without dementia above age 90, and for males without dementia who died before age 80. Selection effects might leave the fittest males, who require less health care. Presenile dementia is rare and might be more often incorrect in the data, and is therefore left out. Treatment for this form of dementia seems to be less costly than for dementia between ages 60 and 95 (not shown) (which could also be due to a co-morbidity effect at higher ages). However, numbers are low and large fluctuations appear. Between the regions, the costs are higher in West than in East Germany (not shown). Costs are highest between ages 60 to 84, and decrease thereafter. Before age 60, the costs of death are higher, and the general treatment costs are lower, for demented people as well (not shown).

Costs for AD and VaD

Figure 7.5 shows the costs of dementia differentiated by type. Costs for VaD are higher than for AD, especially for women with VaD. Higher co-morbidity with more cost-intensive cardiovascular illnesses might be the sources of these higher costs.

Figure 7.5: GKV Costs of Vascular Dementia and Alzheimer's Disease in Germany in 2002 by Age and Gender



Source: GKV Data 2002, own calculations

7.4 Future Costs of Dementia in Germany

7.4.1 Past Projections of the Dementia Costs

Only a few cost projections exist for Germany. Hessel et al. (2004) estimated average costs of € 34.6 billion for the year 1994 (average costs per patient with brain disorders of € 30,700). Under constant conditions, costs would add up to € 60 billion in 2020 and more than € 100 billion in 2050. For the US, Schneider and Guralnik (1990) also projected a steep increase in the costs for dementia by 2040 of between 150% and 300%, based on different mortality assumptions.

Ziegler and Doblhammer (2008) projected ambulatory and total costs for Germany until 2050 assuming constant and decreasing dementia prevalences. With high life expectancy increases total costs would more than triple. A strong decrease in the prevalence of 1% per year at each age would increase the costs—if they stayed constant—by

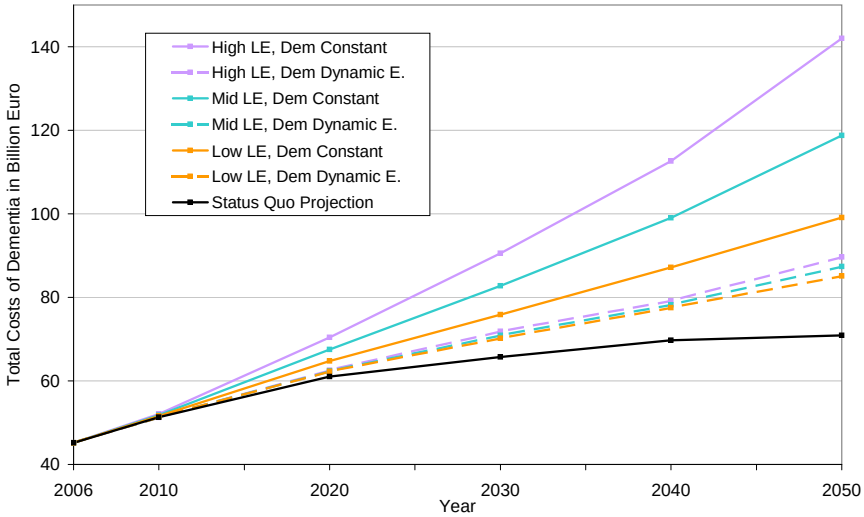
70%. Ambulatory costs increase less steep due to a different cost pattern. With higher age and severity the indirect care costs increase but not necessarily the ambulatory costs. However, they only make up a small proportion of the total costs.

7.4.2 Projections of the Total Dementia Costs for Germany

For the cost projections, the results from the multi-state population projections were combined with total costs per person. The cost estimates from Hallauer et al. (2000) of € 43,700 are used. Only constant costs are applied.

Results are displayed in figure 7.6. For the 1.03 million people with dementia in 2006, total costs amount to about € 45 billion. The change in the population structure would, even under constant mortality and dementia rate conditions, lead to an increase to about € 71 billion. Assuming that no change in the dementia incidence rates occurs, that costs remain constant, and the increase in life expectancy is relatively small, there will nonetheless be a steep increase in costs to nearly € 100 billion. If the increase in life expectancy is large, they are expected to rise to € 142 billion. A dynamic equilibrium would slow the increase to € 85 to 90 billion, according to the life expectancy scenario.

Figure 7.6: Projections of the Total Costs of Dementia in Germany until 2050



Source: own calculations

With constant costs and the highest life expectancy scenario, the 3.3 million demented people would cause a tripling of the costs. A tripling of the costs was also projected by Hessel et al. (2004) for the same time span between 1994 and 2040. Still, a decrease in the incidence rates to a dynamic equilibrium would lead to a nearly twofold increase in costs.

The indexed increase for the cost calculations is shown in table 7.2. The increase in total costs by 2050 is 57% for the status quo, and 214% for the scenario with the highest gains in life expectancy, but a constant dementia rate. If a dynamic equilibrium could be achieved, the costs would roughly double.

Table 7.2: Indexed Increase of the Total Costs of Dementia until 2050 according to Different Scenarios

Life Expectancy	Dementia Incidence	2006	2020	2030	2040	2050
Status Quo	Constant	100.0	135.1	145.4	154.3	156.9
Low	Constant	100.0	143.3	167.8	192.9	219.3
	Dynamic E.	100.0	137.8	155.3	171.5	188.3
Mid	Constant	100.0	149.3	183.1	219.1	262.7
	Dynamic E.	100.0	138.0	156.9	173.1	193.4
High	Constant	100.0	155.8	200.3	249.2	314.2
	Dynamic E.	100.0	138.4	159.0	175.3	198.4

7.4.3 Discussion of the Cost Projections Results

Cost projections of dementia are difficult to obtain, and the results rely on several uncertainties. On the one hand, the number of future dementia patients upon which these cost projections are based is a product of several assumptions which might deviate from actual future developments. On the other hand, projections of future costs are subject to an even greater degree of uncertainty. First, the true total costs today are difficult to assess, as was shown in the previous section 7, and the range of estimates is wide. Second, it is too simple to take an average amount and apply it evenly to all patients. The costs of dementia depend not only on the disease stage, but also on the age and gender of the patient, co-morbidity and the proximity to death (section 7). Third, changes over time are difficult to estimate. The care arrangement, changes in mortality, the economic development and medical progress (Comas-Herrera et al., 2003, 2006) have to be taken into account.

The care arrangement is dependent on the familial situation of the patient. Are there spouses and children present who are able and willing to provide care at home? Institutional care is very expensive, but caring for a spouse or parent also causes a loss of gross national product. Moreover, care for mentally impaired people is more difficult to provide than for physically disabled people. Dementia is the main factor

in institutionalization, and the prevalence of dementia is, at 34% to 88%, much higher in the institutionalized population (Agüero-Torres et al., 2001; Jagger et al., 2000; Jakob et al., 2002; Klein, 1996; Ruitenberg et al., 2001). Still, the majority, or about 60%, of the intermediate and severely ill dementia patients in Germany are cared for in families (Bischoff et al., 2004). This places a large amount of responsibility and a heavy burden on the family. The introduction of long-term care insurance (LTCI) in Germany in 1995 *(Pflegeversicherungsgesetz (SGB XI))* aimed to support familial care at home (Theobald, 2004). But more support and acceptance in society for people who care for family members at home is needed if higher institutionalization rates are to be avoided. Changes in the labor market include higher participation rates among women aged 45 to 65, who are also most likely to be the daughters of people in need of care, and who have so far also been the main caregivers. Thus, arrangements have to be provided which enable them to balance the demands of family, job and care provision. Care at home is positive in two respects: elderly people in need of care could stay at home and the higher cost of institutions could be avoided. Ziegler and Doblhammer (2006) found that, until about 2030, the development of the familial situation is rather positive: more elderly people will be living with a partner and at least one child. This means that a large number of potential caregivers are available up to 2030, and that an increase in institutionalization rates could be slowed if caregivers are supported in this difficult task. Only thereafter does the proportion of childless people again increase. The combined effects of rising rates of childlessness and divorce will mean that more people will live alone, which will aggravate the care situation in Germany.

Mortality decreases could result in a longer period with dementia, and thus in higher costs. A shift in the onset of the disease has a large impact because disease costs are also shifted into higher ages. The financial situation of the LTCI system is dependent in part on future economic developments. Medical research is very expensive, and the costs associated with developing new technologies and treatments could have a greater impact than the aging of the population. However, earlier treatment of patients could help to delay the onset of the disease, and reduce otherwise high indirect care costs. Thus, medical progress is not necessarily going to lead to increases in health care expenditures (Brockmann, 2002). These few examples demonstrate that future cost estimates are highly debatable, especially as unit-care costs and inflation have not yet been included. It was not possible to take into account a possible shift in the age structure in making these total cost calculations. Higher ages have been shown to cause lower ambulatory and in-patient costs (tables 7.3 and 7.4. However, it would not be appropriate to

apply the age-, sex- and mortality-specific increase in the proportion of ambulatory and in-patient costs, because the indirect costs might have a completely different pattern. Hallauer et al. (2000) did not give age-specific costs, but instead provided estimates of costs according to the severity of dementia, which, however, cannot be measured using the GKV Data.

The future development of care is, of course, also dependent on progressions in treatment, or even on a possible cure for the disease. But the treatments already available also have to be used more effectively. While there is currently no cure for dementia, there are some drugs that can slow the progression of the disease. However, studies that have analyzed the utilization pattern of dementia patients have shown that only a few patients received appropriate medication. For example, Küsgens et al. (2008) found that, in the first quarter of their disease, only 29.0% of German AD patients received a prescription for AChE, and only 23.5% were given a prescription for memantine. Rychlik (2007) also came to the conclusion that only about 25% of patients receive treatment. However, he calculated this number from the total amount of all prescribed anti-dementia drugs divided by the number of patients. Another study shows that the prescribed total amount of AD drugs would be sufficient for 23% of patients; however, nearly 50% of patients received drugs, which means that the daily dosage is about half the dosage suggested by the guidelines (INSIGHT Health, 2008). Results based on the GKV Data showed that, in 2002, only 12.2% of all dementia patients were taking the dementia drugs Aricept (4.3%), Axura (5.7%), Ebixa, Exelon, or Reminyl. When the more specific diagnosis of AD is given, 20% were found to have received this treatment in West, and 25% in East Germany. More knowledge about appropriate medications is needed, as is more knowledge about the guidelines used by general practitioners. Younger and healthier patients receive treatment more frequently. Drugs might be less appropriate for older and more frail people (Küsgens et al., 2008), but costs and other restrictions might also affect prescribing habits. A German study about the long-term cost-effectiveness of donepezil showed that, while the drug may be cost-effective, the reimbursement system in Germany does not support its use (Teipel et al., 2007). The value of a better quality of life for the patient and the carer, and the opportunity costs for carers, should be taken into account to a greater degree. A slower disease progression could reduce the need for care, and thereby result in a shift away from institutions. This would, however, also mean a greater burden for the family, and would lead to a greater demand for outpatient support services and other new service modalities, such as outpatient clinics and expanded AD day programs

(Sloane et al., 2002). Changes in the family structure could lead to the development of more technologies that will enable elderly to live independently at home, even in case of illness. This lowers the costs for institutionalized care, but also requires investments in the development of these technologies.

Future costs cannot be estimated simply on the basis of the future number of demented people and the associated costs. It is not aging per se which leads to higher costs, but time to death (Westerhout and F., 2005). But even if the costs associated with dementia could be reduced, a substantial investment in research might first be necessary.

These projections can, therefore, only represent an average estimate based on all patients, and serve as an example of how the costs could develop under these conditions. Despite these uncertainties, making these projections still seems worthwhile. The average amount given by Hallauer et al. (2000) seems to be about average or just a little higher than the average compared with other cost estimates in table 7.1. By using the GKV data, we might have captured more cases with moderate and severe dementia and fewer with milder forms of the disease, which are less expensive to treat. The lower and higher costs associated with milder and more severe cases, respectively, and furthermore the different costs for people who survive or who die, and people who are younger or older, might more or less equal out to the estimated average amount.

It is important to have an estimate of future developments. The high likelihood of an increase in the costs associated with the care and treatment of demented people has to be taken into account in future societal planning.

Chapter 8

Conclusion

As population aging trends are observed all over the world, mental illnesses and especially dementia are attracting considerable societal, political and medical interest. The proportion of people suffering from dementia in the coming years will be especially high in developed countries. But the increase will also be substantial in developing regions, where aging is gaining ground.

Dementia has so far been a progressive disorder. In the later stages it leads to a loss of personality and to complete dependency which makes the disorder very severe for both, the patient and the carer. Having dementia is also associated with increased co-morbidity and mortality.

This is the first study that has looked at the prevalence and incidence rates of dementia for Germany using a very large dataset. The data which were drawn from the 2002 records of people who were members of the German sickness funds (GKV) have a sample size of more than 2.3 million people. The size of the dataset allows us to differentiate not only between age groups, but also by gender and region. Furthermore, the co-morbidity of demented people was determined. Using another dataset, the Survey of Health, Ageing and Retirement in Europe (SHARE), further socio-demographic and health risk factors were analyzed. Understanding past trends and determinants is important for deriving hypotheses about the future development. The results of these analyses were used to model possible future scenarios, and to calculate projections of the number of people with dementia up to 2050. In a last step, the costs associated with dementia, one of the most expensive diseases there is, were projected.

Several risk factors for dementia were determined and confirm literature results, of which age is the strongest. Before age 60, a rare form of early onset dementia exists, but thereafter, prevalence increases strongly, with a doubling in rates seen every five to

six years. In the highest ages the increase is slower. More research is needed in order to see if dementia is an age- or aging-related disease or if the slower increase is due to a selection effect. The prevalence in the GKV data is in the middle of international meta-studies, and increases from 0.6% for females and 0.8% for males aged 60-64, to 38% and 30% for females and males above age 95. Results show a higher risk for females than for males, a finding that is not consistently confirmed in the literature. Multivariate analyses show that several lifestyle factors such as education, social contact and healthy behavior might account for this difference. So far, results on regional differences from the same studies are rare. Using the GKV data, a slightly higher risk is found in East Germany compared with West Germany, especially above age 80.

Further risk factors could be confirmed using the SHARE data, including education, living with a partner, physical and mental health and co-morbidity. Having high levels of education and a healthy lifestyle seem to be factors that push the onset of the disease into higher ages. People with higher levels of education build up a higher cognitive reserve, and might be able to cope longer with decreasing brain function. Having more education also leads to a healthier lifestyle. Many lifestyle factors have shown a protective effect: good nutrition that includes fruits and vegetables (antioxidants) and fish (omega-3 fatty acids), moderate wine consumption (flavonoids), no smoking, and, most importantly, physical and mental exercise combined with social activity. A healthy lifestyle furthermore influences the prevalence of many other diseases, such as hypertension, diabetes and cerebrovascular diseases, which are all additional risk factors for dementia. Thus, having a healthy lifestyle lowers the risk of developing dementia both directly and indirectly. Genetic factors could not be determined using the GKV or the SHARE data. While family history seems to be more important in the rare early-onset form of AD, it is less influential in late-onset dementia. Many studies have confirmed that apolipoprotein E is a risk factor, but more research is needed in order to confirm the influence of other genes.

Trend studies on dementia have been rare up to this point, largely because the illness has only recently become the focus of medical and societal interest. The resources necessary for this type of research are considerable, as these studies take a long time and are costly. Only recently has the number of studies on dementia and cognitive impairment increased. The few studies that exist show inconsistent results. However, because of the recent increase in the amount of research on dementia, studies often end with an optimistic outlook on the chances of reducing dementia prevalence. Further medical advances could help to delay the onset of the disease, as could improvements

in the treatment of cerebrovascular risk factors and hypertension, and increased educational levels among younger cohorts.

On the basis of the findings summarized above, this study has developed several scenarios and projects the number of people with dementia for Germany up to 2050. Three different life expectancy scenarios —two that are similar to the 'basic' and 'high' variant of the Statistical Office (Statistisches Bundesamt Deutschland, 2006) and a higher variant—were combined with dementia rates. Two different variants were chosen for each life expectancy scenario regarding dementia rates: in the first, they are left constant; and in the second, on the basis of the literature review about determinants, trends, and medical research, a decreasing rate to a dynamic equilibrium is applied. Assuming that rates remain constant, the number of people with dementia would increase to between 2.3 and 3.3 million, depending on whether a small or large rise in life expectancy occurs. If a dynamic equilibrium should occur—meaning that the same proportion of further life expectancy at, for example, age 80 will be spent with and without dementia, irrespective of the development of life expectancy—the number would be lower, at about two million affected people.

But how likely is a decrease in dementia rates? How much do the rates have to decrease for a dynamic equilibrium to occur? If a dynamic equilibrium is assumed, 77-year-old people will have the same incidence rate as today's 80-year-olds. In other words, the age-specific incidence of today's 77-year-olds would have to be valid for 80-year-olds in 2050. The incidence among people aged 86 today would have to apply to age 90 in 2050. To achieve a decrease in the prevalence of 1% per year, the prevalences of today's 76- and 84-year-olds would have to be shifted to ages 80 and 90, respectively (see Doblhammer et al. (2009)). For 2002, Ziegler and Doblhammer (2009) found a difference of three months between West and East German 80-year-olds, and of 1.5 years for 90-year-olds. Since medical care is roughly the same in both parts of the country (Kibele and Scholz, 2009; Luy, 2009) the main reason for these gaps could be differences in lifestyle behavior. Less healthy diets and lower levels of activity often lead to obesity, cardiovascular diseases and diabetes, which are risk factors for dementia. Given this difference between West and East Germany today, a decrease of three to four years over a period of 40 years seems possible.

The review by Christensen et al. (2009) showed that, while the prevalence of chronic diseases is expected to increase, the levels of disability arising from these diseases will be less severe and disabling. A compression of morbidity thus seems less likely, but

a dynamic equilibrium is feasible. Medical advances, assistive living technologies and changing social perceptions of disability might lessen the impact of chronic diseases, and give hope for a postponement of dementia into higher ages.

Chapter 2 showed not only that many of the risk factors associated with dementia can be influenced, but also that there are many promising medical studies that could produce effective treatments, or even a cure, for the disease. Thus, several approaches for battling the disease already exist. These include medical research into treatments for dementia, medical research into diseases that are risk factors for a dementia, and increased awareness of the importance of healthy lifestyles for healthy aging. "If we recognize the common sense notion that how you take care of your brain and the rest of your body will affect your cognitive abilities when you're older, we will recognize that preventing dementia is a lifelong activity" (Whitehouse, 2007). Some researchers are optimistic that the fight against AD by 2020 is "an attainable scientific objective" (Khachaturian and Khachaturian, 2009). Most studies are not that concrete about the time frame, but often conclude with a positive assessment of the future:

> "New pathophysiologic leads in concert with epidemiologic evidence will in the near future hopefully result in improvement in the prognosis of Alzheimer patients" (Breteler et al., 1992).
>
> "In spite of what has seemed to be an endless search for cause and cure, those involved are now cautiously optimistic that a useful outcome will be achieved within the next decade. It is postulated that successful inroads will have been made towards eliminating the devastating effects of AD - not cure, but prevention" (Lefroy, 2000).
>
> There "is a strong possibility of substantially delaying the onset of symptoms in future generations, while managing efficiently and with compassion people currently affected by AD" (Gauthier et al., 1997).
>
> "Recently, however, researchers have made tremendous progress toward understanding the molecular events that appear to trigger the illness, and they are now exploring a variety of strategies for slowing or halting these destructive processes. Perhaps one of these treatments, or a combination of them, could impede the degeneration of neurons enough to stop Alzheimer's disease in its tracks. Several candidate therapies are undergoing clinical trials and have yielded some promising preliminary results. More and more

researchers are feeling hope–a word not usually associated with Alzheimer's" (Wolfe, 2006).

"The prevention of Alzheimer's Disease is an ambition that may not be fully achievable in the near term, although delaying disability might be achievable. We find that modest advances in therapeutic and preventive strategies, resulting in even small delays in the onset and progression of Alzheimer's Disease, can significantly reduce the global burden of the disease" (Brookmeyer et al., 2007).

"With the many exciting prospects now in the pipeline and the steady flow of insights into disease pathogenesis [...] AD should be more fully stocked at the next major anniversary of Alzheimer's discovery" (Roberson and Mucke, 2006).

"Perhaps the most important message from the Rotterdam Study is the great potential for prevention or postponement of neurological diseases in elderly people" (Hofman et al., 2006).

"Alzheimer's disease is incurable but preventable." (de la Torre, 2010a).

In addition, news headlines heralding progress made by dementia researchers appear almost every week.

"Research reveals some of Alzheimer's secrets,"(Reuters Health, Feb. 26, 2009).

"Progress toward an Alzheimer's drug that saves brain cells," (Eurekalert, March 19, 2009).

"New research highlights dramatically reduced risk of developing dementia," (Eurekalert, March 23, 2009).

"Breakthrough in Alzheimer's Research," (Eurekalert, Aug. 12, 2009).

"Can Alzheimer's disease be prevented? Researchers explore potential interventions in a special issue of the Journal of Alzheimer's Disease," (Eurekalert, June 14, 2010).

Moreover, recent studies that have found that brain changes can be detected before clinical signs can be seen give reason to hope that progress can be made. The earlier the disease is detected, the greater the effectiveness of treatments designed to prevent the occurrence and halt the progress of the disease.

We should, however, guard against too much optimism about the outlook for reducing the number of dementia sufferers. No cure for dementia currently exists, and even if small advancements can soon be achieved, the change in the population structure, including a rise in the elderly population, will lead to an increase in the number of affected people. The status quo projection showed that, even without mortality changes, the pure aging effect will increase the number by about 60%. A dynamic equilibrium would also increase the number of affected people. Results of a European study on the number of people in need of care have shown that, even if all the years gained in life expectancy are years in good health, and a compression of morbidity occurs, the number of dementia sufferers is set to increase simply because of the changing age structure (Doblhammer and Ziegler, 2006).

The increase in the number of people with dementia is going to present significant challenges for the society. The number of potential caregivers is going to diminish, not only because of the changing age structure, but also because of the increasing labor force participation among women aged 40 to 65, who currently serve as the main caregivers. Thus, fewer potential caregivers are faced with the prospect of having to care for more patients. In the final stages of the disease, demented people are fully dependent on support. This not only places a large burden on caregivers; it also implies financial constraints for families and for society as a whole due to high opportunity costs. In the final stages, institutional care is often inevitable.

Thus, the considerable costs already incurred in treating and caring for patients with one of the most expensive diseases may be expected to further increase. The exact amount of this increase is difficult to estimate because many different cost areas are involved, which are usually broken down into direct, indirect and intangible costs. The indirect care costs are the highest because, in the final stages of dementia, people are completely dependent on the help of other people. For the cost projections an amount of € 43,700 per person, determined by Hallauer et al. (2000), is used. As discussed in section 7.4, it is questionable to use one single amount, while disregarding age, gender, the form of dementia, and the degree of severity state of the disease. However, more exact calculations are difficult to obtain due to data problems, and thus this average

amount seems the best possible compromise. In 2006, the costs incurred in caring for the around 1.03 million people with dementia total costs already amounted to about € 45 billion. If no changes in dementia incidence occur, and life expectancy increases are low, the costs will rise to nearly € 100 billion. If life expectancy increases are large, the amount will rise to € 142 billion. A dynamic equilibrium would slow the increase to € 85 to 90 billion, according to the life expectancy scenario, if costs would stay constant. It is difficult to estimate a change in the costs per person, because in addition to calculating changes due the progression of the disease, it is also necessary to take into account changes in mortality, co-morbidity, the family or institutional care status, opportunity costs, state allowances, assistive technology, medical progress leading to the development of new medications and changes in the incidence rates. The cost projections are a calculation example under constant cost conditions. These projections show, however, that the trend will most likely be upwards. Even if medical advances lead to a postponement of the onset of the disease or a decrease in the severity, costs might remain high because of the large investments in research. However, even a small amount of progress and a slight reduction in the burden borne by the patient and the carer should justify higher costs.

In conclusion, we can predict with some confidence that the number of demented people and the accompanying costs are going to increase in Germany through 2050. However, given the progress that has been made, it is possible that the aging of the population will not lead to a parallel increase in demented people. New research and better utilization of available treatments, combined with a healthier lifestyle and higher educational levels, will most likely slightly postpone dementia incidence rates to higher ages. The anticipated increase in life expectancy, which would, if dementia rates were to remain constant, lead to more than three million people developing dementia, can be counteracted with medical progress, promotion of better lifestyles and the building of greater cognitive reserves due to higher educational attainment. If a postponement to a dynamic equilibrium could be achieved, and thus the same proportion of further life expectancy with the disease remains as it is today, a doubling of the number of people with dementia to about two million would occur. Society has to be made aware of these changes, which include not just an increase in the number of patients and in the costs of their care and treatment, but also the related problems, such as the changing population structure, and the burden that will fall upon family caregivers or institutional care settings.

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Appendix

Code for Measuring Incidence Cases in GKV Data (Section 3.1.2)

```
inzi_23q=0;
if dem_1=1 then inzi_23q=2;
if dem_1=1 & dem_2=1 then inzi_23q=2;
if dem_1=1 & dem_2=0 & dem_3=0 & dem_4=0 then inzi_23q=0;
if dem_1=0 & dem_2=1 & dem_3=1 & dem_4=1 then inzi_23q=1;
if dem_1=0 & dem_2=1 & dem_3=0 & dem_4=1 then inzi_23q=1;
if dem_1=0 & dem_2=1 & dem_3=1 & dem_4=0 then inzi_23q=0;
if dem_1=0 & dem_2=1 & dem_3=0 & dem_4=0 then inzi_23q=0;
if dem_1=0 & dem_2=0 & dem_3=1 & dem_4=1 then inzi_23q=1;
if dem_1=0 & dem_2=0 & dem_3=1 & dem_4=0 then inzi_23q=0;
if dem_1=0 & dem_2=1 & ef3_411=1 then inzi_23q=1;
if dem_1=0 & dem_2=0 & dem_3=1 & ef3_411=1 then inzi_23q=1;
```

[inzi_23q=incidence in quarter 2 or 3, (0=no, 1=yes, 2=prevalence)
dem_1, dem_2, dem_3, dem_4=dementia prevalence in quarter 1 to 4, (0=no, 1=yes)
ef3_411=death, (0=no, 1=yes)]

Table 8.1: Prevalence of Risk Factors and Other Diseases for Females and Males above Age 60 with and without Dementia by Surviving Status and Different Age-Groups

		Survived				Died			
		No Dementia		Dementia		No Dementia		Dementia	
	Age	F	M	F	M	F	M	F	M
Infections	60-69	50.4	38.8	61.2	53.4	47.4	42.9	58.0	48.0
	70-79	45.7	42.5	50.3	53.9	41.3	40.5	48.8	47.2
	80-89	39.6	42.6	46.4	50.3	32.7	37.8	39.6	44.5
	90+	32.1	37.1	42.1	48.9	24.8	28.1	36.3	38.7
Neoplasms	60-69	26.4	20.8	28.3	24.8	53.4	47.1	33.0	30.1
	70-79	24.3	29.4	24.6	35.0	44.2	47.6	29.3	33.2
	80-89	22.7	34.8	21.8	36.0	30.4	44.2	23.9	37.0
	90+	18.2	31.3	17.8	36.7	19.2	32.0	18.9	29.9
Blood D.	60-69	8.7	8.1	14.8	13.5	22.1	20.6	18.2	25.2
	70-79	11.3	11.6	16.5	16.0	22.2	20.5	23.6	20.5
	80-89	12.6	14.0	17.5	18.2	17.0	19.6	18.8	22.9
	90+	12.2	12.4	14.4	19.7	12.8	14.3	16.3	18.6
Metabolic D.	60-69	52.3	44.4	60.4	51.6	49.3	42.0	61.4	52.8
	70-79	54.9	47.4	58.3	54.3	49.1	43.3	54.7	52.4
	80-89	47.8	41.8	50.3	48.9	40.3	37.3	51.6	49.4
	90+	35.8	30.4	38.4	37.7	34.7	32.0	43.0	42.7
Diabetes M.	60-69	17.4	21.9	32.2	34.7	29.1	30.5	38.6	36.6
	70-79	26.0	27.2	36.1	38.4	37.3	34.5	43.8	41.1
	80-89	30.0	28.7	37.8	35.3	35.9	30.6	41.3	36.6
	90+	27.0	21.7	33.1	28.6	26.9	25.6	34.2	27.7
Obesity	60-69	15.2	11.2	19.7	14.7	14.2	10.6	15.9	8.1
	70-79	13.7	9.7	11.7	9.7	14.2	9.1	10.9	6.8
	80-89	7.7	5.6	7.1	5.6	6.2	4.5	5.4	4.6
	90+	3.5	2.3	3.9	1.2	3.3	1.9	3.5	1.5
Mental Disorder	60-69	27.8	19.3	62.1	62.3	30.7	28.4	61.4	64.2
	70-79	24.3	18.1	52.1	52.9	25.7	22.4	49.0	53.3
	80-89	22.6	17.7	46.6	45.9	23.8	21.1	46.7	49.8
	90+	23.6	18.4	44.9	43.6	27.0	25.5	45.0	43.0
Depression	60-69	16.2	6.3	38.3	24.6	19.1	9.4	34.1	17.9
	70-79	17.9	7.4	35.3	21.2	19.4	8.9	29.1	19.2
	80-89	18.4	9.2	28.6	19.4	16.2	9.8	24.7	15.3
	90+	15.0	10.4	20.9	14.4	11.8	10.2	17.5	12.5
Nervous System	60-69	23.7	18.5	53.7	54.4	30.5	27.1	61.4	59.3
	70-79	26.1	22.4	44.2	50.3	29.2	27.2	44.9	49.7
	80-89	28.9	26.0	41.0	45.4	27.5	26.5	38.7	42.3
	90+	26.7	25.2	36.2	41.7	25.4	24.7	33.1	33.8
Parkinson's D.	60-69	0.6	0.8	8.6	10.2	1.9	1.5	10.2	12.2
	70-79	1.7	2.0	10.7	15.0	2.7	3.2	16.2	18.5
	80-89	3.0	3.6	10.4	14.4	4.7	6.2	12.5	18.8
	90+	3.0	4.1	7.2	13.2	4.3	5.4	7.0	9.1
Circulatory System	60-69	45.6	38.4	58.1	56.1	54.4	56.0	62.5	72.4
	70-79	56.5	52.8	68.1	66.9	66.1	66.2	74.2	77.9
	80-89	64.4	62.9	72.9	74.8	68.4	71.8	77.7	76.3
	90+	66.8	66.2	74.2	77.2	68.3	68.6	77.4	79.6

Table 8.1 continued

		Survived				Died			
		No Dementia		Dementia		No Dementia		Dementia	
	Age	F	M	F	M	F	M	F	M
Hypertensive D.	60-69	47.1	45.2	58.2	53.1	47.6	47.3	52.3	52.8
	70-79	60.4	54.9	64.6	62.6	58.9	52.1	62.3	59.1
	80-89	62.9	55.8	66.0	61.8	56.2	51.1	61.1	52.9
	90+	57.9	47.5	58.6	52.2	49.7	43.3	54.7	49.4
Ischaemic Heart D.	60-69	16.6	23.3	26.6	31.5	21.3	33.5	25.0	44.7
	70-79	29.6	37.0	39.3	46.0	39.4	44.9	44.1	52.6
	80-89	38.8	44.9	45.8	50.0	42.0	50.2	47.1	48.3
	90+	40.2	44.9	42.9	51.6	41.7	43.2	44.7	47.6
Cerebrovascular D.	60-69	7.4	9.1	33.6	44.3	16.6	19.0	47.7	43.9
	70-79	15.1	17.0	43.6	52.4	26.6	27.1	51.4	58.2
	80-89	24.0	25.0	47.6	53.2	37.0	35.7	54.7	60.6
	90+	32.1	30.7	46.8	50.2	38.0	37.6	50.2	45.1
Respiratory D.	60-69	36.3	34.6	45.3	44.6	38.4	43.4	48.9	49.6
	70-79	35.5	39.1	39.2	47.4	38.6	48.0	43.9	60.3
	80-89	33.8	41.5	38.1	46.9	33.6	47.1	41.1	52.4
	90+	31.0	39.8	38.6	48.1	30.5	44.9	42.7	50.0
Pneumonia	60-69	2.2	2.5	5.2	7.8	10.2	13.7	20.5	28.5
	70-79	2.8	3.9	7.0	10.0	10.8	17.0	21.9	34.5
	80-89	3.7	5.3	8.5	13.4	13.1	19.6	23.8	30.6
	90+	5.6	6.8	9.7	16.2	13.5	18.5	23.3	31.1
Digestive D.	60-69	39.5	38.2	52.5	54.4	50.7	48.4	53.4	57.7
	70-79	42.7	42.5	54.6	55.6	50.2	46.3	53.7	54.4
	80-89	42.6	44.9	52.4	55.0	44.6	45.7	53.2	51.8
	90+	38.8	41.1	50.8	51.7	41.1	43.8	48.9	51.5
Skin D.	60-69	27.4	22.8	41.6	39.4	24.2	21.8	47.7	41.5
	70-79	27.4	26.4	38.2	38.9	25.1	22.3	43.2	43.3
	80-89	28.4	30.5	41.9	39.7	27.0	26.0	45.4	45.3
	90+	29.0	31.7	45.4	49.6	28.6	28.1	48.1	50.6
Musculoskeletal D.	60-69	60.4	53.3	60.3	56.2	43.5	40.8	51.1	38.2
	70-79	61.4	53.6	59.5	57.3	44.9	39.4	45.3	44.2
	80-89	57.8	52.3	53.5	51.6	38.5	38.2	41.7	38.1
	90+	47.4	48.2	48.2	49.9	30.8	33.9	38.9	36.6
Arthrosis	60-69	27.4	20.5	29.0	21.9	15.7	13.2	13.6	18.7
	70-79	37.1	26.5	35.8	28.4	24.2	17.0	23.0	19.2
	80-89	39.9	30.1	38.9	31.4	25.7	21.9	29.5	22.0
	90+	36.8	29.5	39.5	33.7	27.6	25.9	33.7	27.1

Due to small sample sizes analyzes for Malnutrition, Osteoporosis, Chorea Huntington and Down's Syndrome could not be split into smaller age groups

Data Problems—Exclusion of the Institutionalized Population

It is difficult to determine how many interviews were done in institutions. A report outlining the initial results from wave 1 (Börsch-Supan et al., 2005) states that, in the baseline, no institutionalized population is included except in Denmark and Sweden (p. 10). The report later explains that Sweden, Denmark and, to a certain extent, the Netherlands include institutionalized respondents in wave 1 (p. 36). On page 30 the reader is referred to the appendix to find out more about the target population: "Only exceptionally it became possible to identify people in institutions (homes for elderly) in the sampling frame. What applies to each country is detailed in the Appendix." On pages 39, 43, 51 and 66 the report states that the target population for Austria, France, Italy and Switzerland "does not include individuals living in institutions for elderly, in prisons and similar institutions." Information for Denmark, Germany, Greece, the Netherlands, Spain and Sweden (on pages 41, 45, 49, 57, 60, 63) show that the "target population includes individuals living in institutions for elderly, but not individuals living in prisons and similar institutions." For Spain (Page 60) "dwellings with more than 20 individuals are removed from the frame, so prisons and similar institutions do not appear. Small institutions for the elderly could be on the list." In the second wave, the transitions into institutions such as nursing homes and assisted living facilities was followed (Börsch-Supan et al., 2005).

The data give the following information about institutions: two variables collected information about the 'type of building', with the possible answer categories being Category 7, 'A housing complex with services for the elderly'; and Category 8, 'Special housing for the elderly (24-hour care)', respectively. Variable 'IV010_' is answered by the household respondent if the interview is in the house of the respondent, variable 'HO036_' applies only if the interview is not in the house of the respondent. Another variable 'HC029_' collects information on living in an institution during the last twelve months with the answer categories 'no', 'yes, temporarily' and 'yes, permanently'. In the second wave, the variable 'CV178_' gives information about the place of interview: 'private household' or 'nursing home'. For this analysis the variables 'IV010_' (applied on individual level), 'HO036_' and 'CV178_' are used.

Operationalization of the 'Cognitive Function' Variable in Section 5.1.3

From the five items-orientation, numeracy, verbal fluency, recall 1 and recall 2-a new variable *'cognitive function'* is built with a maximum of 18 points in the following way. *'Orientation'* is measured with four questions about the day of the week, day of the month, month and year. If all questions are answered correctly, four points are awarded, while if one mistake is made, just three points are given, and so on. For the *'recall'* task, 10 simple words are read aloud by the interviewer, and the respondent is asked to recall as many as he or she can. A maximum of four points are given when at least five items are recalled, followed by three points for four items, two points for three items, and one point for at least two items. After the *'numeracy'* and *'verbal fluency'* questions, the respondent is again asked to recall the words he was read before. The second *'recall 2'* test is less strict, and four points are given for four items, three points for three items, and so on. *'Numeracy'* comprises some calculation tests. If the first question, in which the respondent is asked to subtract 10% from 1,000, is answered correctly, the third question, in which the respondent is asked to calculate two-thirds of 6,000, is posed. If this is answered correctly, then the fourth question about compound interest is asked, and a maximum of four points is given if the answer is correct. If the first question is answered incorrectly, a maximum of two points can be attained if the second question, in which the respondent is asked how much half the price of a sofa that costs 300 Euros would be, is answered correctly (Christelis et al., 2006). For the *'verbal fluency'* test, the respondent is asked to name as many animals as he or she can in one minute. One point is given if at least 10 animals are listed, two points for 14 animals, and three points for at least 17 animals.

Operationalization of the General Health Variables in Section 5.2.1

The health measure '2+ chronic diseases' is based on question PH006 "Has a doctor told you that you had any of the conditions on this card?" (main questionnaire part PH). The person is shown a card with 14 illnesses in Wave 1, and 17 illnesses in Wave 2. In Wave 2, there is one additional disease, 'Alzheimer's disease, dementia, organic brain syndrome, senility or any other serious memory impairment', while the other two additional points are sub-divisions of two illnesses already prevalent in Wave 1.

Mental health information comes from the main questionnaire part MH, and from the drop-off questionnaire. Depression is measured using the EURO-D scale, which lists 12 items on how people feel and perceive their life are collected. Depression is diagnosed if more than three items are answered negatively (main questionnaire, section mental health (MH)) (Dewey and Prince, 2005). For the first wave, the variable 'eurodcat' was provided, for the second wave it was generated analogically.

The variables 'optimism' and Quality of Life 'QoL' are from the 'drop-off' file. QoL is defined as the degree of satisfaction of human needs, with the most important domains being control, autonomy, self-realization and pleasure. For the operationalization, a new short form CASP-12 (C=control, A=autonomy, S=self-realization and P=pleasure) was designed by von dem Knesebeck et al. (2005) (question 2 in drop-off questionnaire, only wave 1), based on the CASP-19 scale developed by Hyde et al. (2003). Possible answers are 'often', 'sometimes', 'rarely' and 'never'. The variables were recoded such that 'often' was always the negative answer. Points from one, 'often'; to four, 'never', were given, and the sum over all variables calculated. A possible range from 12 to 48 indicated very low to very high QoL. In contrast to the authors (von dem Knesebeck et al., 2005), here three groups of QoL were classified: high, medium and low. Below 35 points a low QoL was allocated.

The variable 'optimism' is based on question 3 (question 1 in wave 2) of the drop-off questionnaire. It combines seven statements about people's lives and feelings. Respondents are asked how strongly they agree or disagree with these statements. The new variable is broken down into 'high', 'medium' and 'low' optimism. One item from the 'optimism' scale is 'I'm always optimistic about my future'. Because it is seen as a very important item, it was also taken as a single item here (the answer categories 'strongly disagree' and 'disagree' were taken together.

Unfortunately not all people filled in the drop-off questionnaire, because it was only handed to respondents who had completed the main questionnaire. The response rate is between 70% in Sweden and 93% in Greece (Börsch-Supan and Jürges, 2005). In wave 2, the questionnaire was changed, and for example, question 2 with the QoL (CASP-12 items) not no longer asked in the drop-off questionnaire. Furthermore, it was only given to respondents who had not already answered the questionnaire in wave 1. Thus, it is not possible to follow changes in respondents' answers, over time, and the response rate is much lower. For the people above age 60 in the 10 countries studied here, we have information on depression, QoL (only wave 1) and optimism for 66% of the sample in wave 1, and for only for 23% in wave 2.

Extreme Cases in the Cognitive Change Variable in Section 5.3

One case had a decline of 18 points, from the highest possible number to no points at all. After the person was carefully checked and found to be free of disease, and to have had only few doctor visits, no depression, no proxy etc., he/she was taken out of the analysis. Two people demonstrated this change in reverse, going from zero to 18 points, and were also taken out after checks were made. Here uncooperative behavior or contextual factors during the interview might have led to missings in the first wave, and many further missings for other variables as well. One person had an increase of 17 points. During the first wave, the person had four diseases, so the test results might have been influenced by medication. Seventy-four people had an increase of at least eight points (eight to 12 points, except the one person with 17 points), which might represent true changes, but could also indicate measurement problems in either wave. The mean age of this group is 71.5.

Risk Groups in Table 5.8

The table shows changes over time for several socio-demographic and health variables. The first column displays the results for the total population, and the second for the incident SCI population. In column 3 are the results for the groups with a decrease in cognitive status of at least five points. A decrease of at least five point is found in 589 people. More than 32.9% are in the SCI group in wave 2, compared with only 3.4% in wave 1. For 437 people, the cognitive change is missing, either because the cognitive status is missing in wave 1, wave 2 or in both waves. Again, a correlation between the missings and the general health of these people is assumed, and those with a proxy interview and those who poorly understood the questions are placed in the risk group 'missing cognitive change', to which 163 people belong (column 4). The last two groups (columns 5 and 6) are built from the criteria 'proxy interview'. One group consists of those who do not have a proxy interview in wave 1, but are 'incident proxy' cases in wave 2 (277 people), and another group of 150 cases with a proxy interview in both waves. The cognitive status of people who had a proxy interviewer in both waves is mostly either SCI or missing: in wave 1.88%; and in wave 2.95%.

Most importantly physical health of the additional groups is even worse than the health of the incident SCI or strong cognitive decline group which is also true but to a lesser extent for mental health. The new groups also move significantly more often into institutions.

The health behavior is more difficult to interpret. There is no difference in the smoking behavior, and furthermore, we find not only a higher proportion of people with a strong weight loss but also with a strong weight gain. Expected results for people in the groups with cognitive impairments are a lower alcohol consumption and a lower activity status.

Table 8.2: Health Behavior, Physical and Mental Health of the Total Population, Incident SCI People and Several Other Risk Groups of Cognitive Impairment (Proportion in %) (Age- Standardized)

		Total Pop.	Incid. SCI	Cogn. Ch. 5+	Missing Cog. Ch.	Incid. Proxy	Proxy Both W.
Housing°	Move into Inst.	1.6	4.1*	3.7*	6.2*	5.6*	21.7*
	Services/Nursing	1.1	2.7*	2.4*	0.8	0.9	5.6*
	Private HH	96.8	93.2	93.6	93.0	93.2	70.5*
	Moved out of I.	0.5	0.0	0.3	0.0	0.2*	2.2*
Partner	Loss of P in W2	2.8	1.8	4.6	5.8	3.4	4.0
	No P Stable	30.7	32.5	31.2	29.5	22.0*	47.3*
	P Stable	66.0	65.7	63.5	64.7	74.5	48.8*
	New P in W2	0.5	-	0.7	-	0.1*	-
Smoking	Smoked Never	56.6	68.0*	59.2	57.6	54.7	56.6
	Current S. (W1&2)	10.6	8.6	10.0	11.3	13.6	4.1*
	Ex-Smoker (W1&2)	28.1	15.7*	23.4*	21.8	25.3	21.1
	Stopped S. in W2	2.8	7.0	5.0	8.7*	4.9	7.0
	Started S. in W2	1.7	0.4*	2.2	0.1*	1.4	1.5
Alcohol	No A. Stable	23.7	44.8*	29.4*	37.8*	35.4*	52.6*
	Little A. Stable	9.2	3.8*	5.1*	3.6*	5.8*	0.6*
	Moderate A. Stable	13.6	5.6*	8.3*	4.5*	4.5*	3.8*
	Much A. Stable	19.7	9.9*	16.7	13.6	15.8	9.8*
	Less A. in W2	19.0	23.4	21.6	27.3	22.2	5.6*
	More A. in W2	14.9	11.3	17.5	10.3	13.0	6.7*
Moderate Act.	No A. Stable	7.2	21.9*	11.6*	20.2*	24.5*	40.7*
	Moderate A. Stable	7.0	7.5	6.7	4.6	4.0	9.9
	Much A. Stable	55.2	24.3*	42.8*	27.2*	25.0*	9.2*
	Less A. in W2	18.2	40.0*	26.5*	36.1*	31.3*	19.1
	More A. in W2	12.3	5.1*	11.0	9.0	12.6	0.2*
Body Weight	Loss of >10 Kilo	3.1	6.2*	5.8*	8.2*	12.7*	5.1
	Loss of 3-10 Kilo	19.1	24.6	23.5	28.5	30.0*	19.7
	About Stable	61.9	43.8*	51.1*	36.4*	34.8*	43.6*
	Gain of 3-10 Kilo	13.0	16.3	14.5	16.4	14.5	22.6*
	Gain of >10 Kilo	2.8	9.0*	5.1*	10.6*	8.1*	8.9*
ADL 1+	No W1, W2 Yes	6.8	21.5*	12.3*	17.6*	24.3*	19.4*
	ADL Stable	7.1	14.4*	7.8	10.1	26.0*	37.6*
	No ADL Stable	81.7	58.9*	73.5	66.5	47.3*	40.2*
	Yes W1, No W2	4.5	5.2	6.4	5.9	2.4*	2.8
IADL 1+	No W1, W2 Yes	10.7	31.2*	21.2*	30.6*	28.4*	11.5
	IADL Stable	12.2	25.1*	15.4	23.1*	33.1*	62.6*
	No IADL Stable	70.6	36.2*	57.0*	41.6*	31.8*	21.9*
	Yes W1, No W2	6.5	7.4	6.4	4.7	6.6	4.1
Limited Act.	No W1, W2 Yes	8.8	21.6*	16.1*	21.0*	27.7*	12.6
	Sev Lim Act Stable	7.6	13.1*	8.3	9.9	23.5*	44.9*
	No Lim Act Stable	77.4	57.4*	70.0*	62.2*	44.6*	36.1*
	Yes W1, No W2	6.2	7.9	5.5	6.9	4.2	6.4
Depression	No D W1, D W2	9.5	19.9*	18.1*	29.1*	15.6*	6.2
	D Stable	13.4	34.9*	19.2*	19.5	20.9*	41.5*
	No D Stable	65.5	34.2*	51.8*	42.3*	41.4*	34.7*
	D W1, No D W2	11.7	11.0	10.9	9.1	22.1*	17.7
QoL (CASP-12)	High Qol W1	37.5	20.2*	32.6*	28.8*	20.6*	19.4*
	Medium Qol W1	29.2	20.0*	27.4	26.6	19.4*	13.2*
	Low Qol W1	33.3	59.8*	40.0*	44.5*	60.0*	67.4*
Optimism	High Optimism W1	24.6	13.8*	19.6*	15.6*	14.1*	20.1
	Medium Opt. W1	40.4	35.6	38.8	39.1	31.6*	31.6*
	Low Optimism W1	35.0	50.7*	41.6*	45.3*	54.3*	48.2*

*Difference to total population is significant on the 5% level.
°'Housing With Services for Elderly'. Includes nursing homes in wave 2.

Abbreviations

- AD - Alzheimer's Disease
- ADL - Activities of Daily Living
- APOE - Apolipoprotein E
- CI - Cognitive Impairment
- DFLE - Disability-Free Life-Expectancy
- DS - Down's Syndrome
- GKV - German Sickness Funds
- IADL - Instrumental Activities of Daily Living
- LTCI - Long-Term Care Insurance
- MCI - Mild Cognitive Impairment
- MEM - Dementia or Memory Impairment in SHARE
- MiP - Missing Cognitive Status, Proxy Respondent
- MMSE - Mini Mental State Examination
- OR - Odds Ratio
- PD - Parkinson's Disease
- SCI - Severe Cognitive Impairment
- SHARE - Survey of Health, Ageing and Retirement in Europe
- QoL - Quality of Life
- VaD - Vascular Dementia