Dementia – Etiology and Epidemiology

A Systematic Review

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Dementia – Etiology and Epidemiology

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Content

Checklists regarding assessment of study quality for different chapters of this report are included in the electronic version of the SBU report on Dementia diseases at www.sbu.se

Preface

The Swedish Council on Technology Assessment in Health Care (the official acronym is SBU) was founded in 1987. As its name implies, SBU assesses the technologies and methods used in providing health services. Medical and scientific literature from around the world is systematically evaluated and summarized by project groups for these assessments. Striving to keep the needs of the patient at the focus of health care planning, each assessment project investigates not only the medical aspects of treatment options, but also economical, social and ethical aspects.

Assessment projects aim to identify the most effective and, if possible, the most cost-effective interventions. They also aim to identify the technologies already in use that are not adequately supported by scientific evidence. Assessment findings can be used by clinicians, administrators, and policy makers to insure that the limited resources available to health care are allocated in the most appropriate way.

A project group composed of 26 experts (see page 5) was selected to assess the scientific literature on dementia. The project group performed the integrated literature search with guidance from a specially trained librarian. Checklists for rating relevance, study quality and scientific evidence were developed. A detailed description of the methodology used is presented in each volume of this report.

Based on the complete reviews and guided by comments from several external experts (see page 5), the report on dementia was accepted by the SBU Scientific Advisory Committee and the SBU Board of Directors. The Executive Summary and Conclusions were approved by the SBU Board of Directors on December the 20th 2005.

Hopefully, this systematic review will somehow improve the situation for persons with dementia disorders, and for those caring of persons with dementia disorders.

SBU Summary and Conlusions

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1. SBU Summary and Conclusions

Purpose

The purpose of this SBU project was to use systematic database searches and a review of the scientific literature as a starting point to assess the current state of knowledge about dementia disorders from various perspectives. Those perspectives included occurrence, risk factors for development, diagnostics, care, ethical considerations, ethnicity and drug therapies, as well as the health economic aspects.

Objective of the report

The objective of the report is to:

- Analyse current knowledge and values about caregiving in order to help caregivers of dementia patients.
- Support nurses and caregivers in diagnosing and treating people with dementia disorders.
- Describe the key role of family members in caring for people with dementia.
- Provide public officials and other decision makers with a scientific basis for formulating dementia care policy.

SBU's conclusions

Occurrence, risk and prevention

❑ Two thirds of the approximately 140 000 Swedes with a dementia disorder have Alzheimer's disease. The other two leading disorders are vascular dementia (10%) and frontotemporal dementia (5%). Other disorders occur in various combinations with non-dementia

conditions, such as the frequent comorbidity of Lewy body dementia and Parkinson's disease.

- A common denominator of all dementia disorders is that memory and cognitive function is impaired due to neuron death.

- Age is the primary risk factor for developing dementia (Evidence Grade 1). Rising life expectancies are increasing the number of people who develop dementia disorders. Approximately 1% of 65-year-olds and more than 50% of 90-year-olds have a dementia disorder.

  Among people older than 85, a greater percentage of women than men have Alzheimer's disease (Evidence Grade 2).

- Although known genetic changes that cause Alzheimer's disease are rare, the Apolipoprotein E (ApoE) ε4 allele is known to increase the risk (Evidence Grade 1).

- Currently, there is no specific preventive treatment for dementia, but blood pressure monitoring in middle age reduces the risk of developing it later in life (Evidence Grade 2).

- Treatment with antihypertensives reduces the risk of developing vascular dementia later in life (Evidence Grade 2).

- The progression of dementia can be delayed among older people who continue to lead active lives (Evidence Grade 2).

Relationship to other diseases

- Cognitive deterioration due to hypothyroidism or hyperthyroidism is unrelated to dementia but needs to be diagnosed and treated.

- Existing studies show contradictory results with respect to the correlation between low vitamin B_{12} (cobalamin) levels and impaired cognitive function or Alzheimer's disease. There is a moderate correlation between low folic acid levels and impaired cognitive function.

There is a strong correlation between high homocysteine levels and impaired cognitive function.

Treatment with vitamins such as cobalamin or folic acid that lower homocysteine levels does not lead to any improvement in impaired cognitive function.

Diagnosis

- ❑ Currently, there is no simple, reliable test for identifying dementia at an early stage. In their present form, no diagnostic instruments are sufficiently developed to be used for dementia screening.

- ❑ A gold standard is lacking for identifying dementia and ruling out other diseases. Imprecise definitions of the various dementia disorders limit the ability of caregivers to distinguish one disorder from another.

- ❑ Many methods (scales and indices) are used to measure the severity of various symptoms of dementia, such as cognitive deterioration, functional decline and behavioural changes. The insufficient evaluation to which most methods have been subjected makes it more difficult to assess the efficacy of specific care and treatment approaches.

- ❑ Family, friends and caregivers (knowledgeable informants/collateral sources) can provide valuable information to supplement diagnosis and the patient's narrative. Standardised interviews with collateral sources (Evidence Grade 2), as well as the clock drawing test and other simple exercises (Evidence Grade 2), allow general practitioners to perform an initial selection of patients for possible further diagnosis.

- ❑ After a baseline assessment, detection of atrophy of the medial temporal lobe by computer tomography (CT scan) and magnetic resonance imaging (MRI scan), respectively can identify people who have Alzheimer's disease with a high degree of certainty (Evidence Grade 1).

- After a baseline assessment, biochemical diagnostic markers such as cerebrospinal fluid analysis (Evidence Grade 1) and neuropsychological testing (Evidence Grade 1) effectively identify people with Alzheimer's disease.

- Functional diagnosis – positron emission tomography (PET scan) and single photon emission computed tomography (SPECT scan) – has moderate value (Evidence Grade 2), while neurophysiological testing – EEG brain mapping and quantitative EEG – has limited value (Evidence Grade 3) for identifying dementia disorders.

- The apoliprotein E ε4 is a poor marker for the (ApoE ε4 allele for identifying Alzheimer's disease or for differential diagnosis.

- Studies are lacking that have combined different types of testing. As a result, which approaches are most cost-effective is not known with certainty.

Ethical considerations and attitudes

- Because dementia affects almost all areas of life, ethical issues often arise. Values and beliefs – including views about the human condition and the appropriateness of various interventions – influence diagnosis, care and treatment alike. The issues are rarely simple or uncomplicated, but tend to require active moral reflection based on both knowledge and subjective principles.

- People with dementia are sometimes stigmatised. Greater understanding and candour can lead to more objective and compassionate social attitudes.

- Dementia care varies considerably from one Swedish county and municipality to another. The results of the literature search should be used, particularly by the municipalities, for the benefit of patients and their families.

Caring for people with dementia

- In addition to knowledge and objectivity, effective care requires a trusting relationship between the patient and caregiver. Because the studies that have assessed various kinds of care do not generally control for or evaluate the impact of that relationship, the benefits of a particular approach are difficult to determine. Substantial variations with regard to purpose, type of intervention and assessment instrument hamper attempts to summarise the studies as a single evidence grade. A number of studies, though with generally low internal validity, have demonstrated the efficacy of various interventions – such as multisensory stimulation (Snoezelen), music and reminiscence therapy – for improving the quality of life of individual patients.

- Many studies have looked at training programmes and clinical guidance for nurses and caregivers. But given that the studies do not meet suitable criteria for assessing evidence, the most effective approach cannot be identified. Generally speaking, nurses and caregivers need support in the form of training.

- Dementia affects the lives of family members as well as the patient. Psychosocial training programmes (Evidence Grade 2) for family members, along with instruction in dealing with the behavioural problems that accompany dementia (Evidence Grade 3), can alleviate their anxiety and depression.

- While good quality of life is a vital objective in caring for people with dementia, effective methods are lacking for evaluating quality of life from the patient's point of view.

- Existing studies have not found that respite care reduces the community resources that must be devoted to people with dementia or the anxiety experienced by family members. But it offers family members the opportunity to obtain some valuable relief.

Drug therapies

- ❑ Existing studies have not found that treatment with cholinesterase inhibitors (donepezil, galantamine and rivastigmine) affects the progress of mild to moderate Alzheimer's disease. But it offers some improvement of global function and cognition (Evidence Grade 2). However, knowledge about effects for longer than one year is limited.

- ❑ Treatment of mild to severe Alzheimer's disease with memantine can lead to some cognitive improvement (Evidence Grade 3). Knowledge about long-term effects is limited to therapy for six months.

- ❑ Extract of Ginkgo biloba can provide some relief of cognitive and Activities of Daily Living (ADL) impairment (Evidence Grade 3). Knowledge about long-term effects is limited to therapy for six months.

- ❑ Cholinesterase inhibitors commonly cause the adverse effects of dizziness and nausea (Evidence Grade 2).

- ❑ A number of drug groups, such as benzodiazepines and anticholinergics, have undesired effects on cognition (Evidence Grade 1).

- ❑ People with dementia disorders commonly develop depression. Selective serotonin reuptake inhibitors (SSRIs) can provide some relief. The scientific evidence for treating coexisting depression in people with dementia is however limited (Evidence Grade 3).

- ❑ Drug therapies for behavioural symptoms in people with dementia disorders have limited effectiveness (Evidence Grade 3). Increased mortality has been demonstrated in people with dementia who have been treated with atypical antipsychotics. The impact on mortality has not shown up in individual studies but was identified by a meta-analysis (Evidence Grade 2). Corresponding data is lacking concerning older antipsychotics.

- ❑ The health economic studies published so far suffer from methodological flaws and are not conclusive. Because only a few studies contain

empirical data, determining whether drug therapy is cost-effective or not is difficult.

Social impact

- ❑ Approximately half of all people with dementia move to assisted living facilities within 2–3 years after diagnosis. Approximately half of all people with dementia are in assisted living facilities.

- ❑ The burden of dementia in Sweden corresponds to approximately SEK 40 billion (EUR 4.36 billion) a year, a figure that is likely to grow as the size of the elderly population continues to increase. Municipalities bear more than 80% of the costs, which cover care at assisted living facilities and support for those who remain at home.

Additional research needs

Additional research on dementia disorders is required in several areas:

- How the various disorders progress
- Development of diagnostic methods
- Better evaluation of instruments for identifying and measuring cognitive and related symptoms, as well as assessing the quality of life of people with dementia
- Development of caregiving methods, such as guidance, training and studies that focus on the relationship between patient and caregiver
- Clearer ethical guidelines for diagnosis, treatment and care of people with dementia
- Drugs for all categories of dementia that are more effective and cause fewer adverse effects
- Studies that examine the long-term effects and costs of drug therapies.

2. **A General Introduction, Including a Discussion of Alzheimer's Disease**

Introduction

Dementia is a clinical syndrome characterized by "a global deterioration of mental functioning in its cognitive, emotional and conative aspects" [1]. The concept is comprehensive, including several clinical profiles and causes. Dementia usually implies a long period of mental handicap and suffering for the patient, as well as severe strain and financial burden on the patient's family, caregivers and society. Due to increasing life expectancy the number of people suffering from dementia will increase rapidly in both developed and developing countries. More than 25 million people suffered from dementia in 2000. By 2030, that is expected to rise to 63 million, 65% of whom in less developed countries [2]. Figure 2.1 shows the number of scientific publications on major types of dementia in PubMed (Medline) from 1960 to 2004. The rapid increase of publications after 1980 is most pronounced in the field of Alzheimer's disease (AD) and its genetics.

This chapter focuses on the historical background of the identification and classification of dementia syndromes. Dementia, derived from the Latin *demens* (without mind), is an acquired clinical syndrome of long duration and usually progressive. The word dementia has acquired different meanings in different contexts. It may denote a clinical syndrome, regardless of etiology [3], but also implies that the etiology is organic brain disease. Originally, the term was often used synonymously with "insanity" and "madness" in general, but when Kraepelin coined the concept of "dementia praecox" in 1893, it presumed an underlying organic defect [4].

In the 1940s, Mayer-Gross, Guttman [5] and others identified the fundamental defects that constitute the syndrome of dementia. Memory impairment that is evident in learning, retention and recall of both new information and the distant past was considered essential to the diagnosis. However, dementia is more than just forgetfulness [6]. At least one of the following symptoms is usually required as well: impairment of thinking, reasoning, communication, orientation, practical abilities, ie, greater difficulty maintaining learned skills or managing everyday activities, and personality changes resulting in lack of insight and judgment, disinhibition, aggressiveness, emotional bluntness and lack of empathy [1,7]. These key symptoms and various neurological features (sometimes referred to as primary symptoms) are often more directly determined by the location and severity of the brain damage [8–11]. Other psychiatric features, such as anxiety, depression, suspiciousness, delusions, obstinacy and anancastic-like behavior, seem to be more related to the patient's awareness of, and reactions and responses to, cerebral dysfunction and its consequences. These secondary or accessory symptoms are also influenced by the patient's premorbid personality and previous experience, as well as related to better preserved brain functions [12]. However, dementia may evolve according to extraordinary, miscellaneous and variable scenarios, so that a symptom should be interpreted cautiously. What is regarded as a primary symptom in one type or stage of dementia may be a secondary symptom in another [12,13].

The concept of dementia and its classification has developed on the basis of accumulating evidence of clinicopathological entities and presumed etiological factors. Dementia is a clinical diagnosis that evokes strong emotions – patients, relatives, doctors and laypeople fear and avoid it. However, attitudes have changed in recent decades. General knowledge of dementia conditions has increased rapidly. Genetic mutations and other specific etiologies of dementia are recognized, and the first generations of drugs for treatment and amelioration of AD have been made available. Recently introduced terms such as treatable dementia [14,15], reversible dementia [16–18] and mild cognitive impairment (MCI) [19–21] highlight the clinical and etiological variability of such conditions. ICD-10 states that "while some of these disorders are seemingly

irreversible and progressive, others are transient or respond to current available treatments" [6].

The concept of pseudodementia emerged during the 1880s to deal with patients who eventually recovered from a dementia-like clinical state. The symptoms of cognitive, emotional and conative dysfunction were regarded as secondary to a non-organic mental disorder. The term *demence melancholique* [22] had been used earlier until Carl Wernicke introduced the word pseudo-dementia to refer to "chronic hysterical states, mimicking mental weakness". The terms pseudodementia and depressive pseudodementia were little used until the 1950s [23–25]. Although the designations have been criticized [26,27], they may be justified in stressing the importance of a thorough diagnostic workup for the identification of treatable organic and non-organic mental disease [28–31].

The syndrome of dementia shares many symptoms with other organic brain syndromes. Focal brain lesions may cause severe amnesia, dysphasia and personality change. Long-lasting delirious states in the elderly that may be drug induced and multifactorially determined can simulate dementia very closely. Thus, dementia is described as an acquired disturbance of multiple higher cortical functions, but without clouding of consciousness. This requirement is further elaborated in ICD-10 [6], which suggests that a confident diagnosis requires clinical evidence of a certain duration, such as six months. General agreement on the clinical concept of dementia as described in ICD-10 and DSM-IV [32] appears to be within reach, although the distinction with delirium remains somewhat indistinct, considering that delirium is often superimposed on dementia. The primary criterion for diagnosis of dementia is evidence of a decline in both memory and thinking, leading to significant impairment of functioning compared with previous levels. However, the way in which poorer functioning manifests largely reflects the social and cultural setting in which a patient lives. The unmasking of a progressive brain disease may depend on the interaction of various organic, psychological and socioeconomic factors.

Furthermore, the choice of criteria for diagnosing dementia may have very significant implications for the actual number of subjects who are identified as having the condition [33].

Normal versus pathological aging of the brain

The line between normal and abnormal cognitive changes with age remains indistinct. Normal aging is due to physiological processes over a person's lifetime, in which the biological clock controls development and survival of nerve cells. That does not exclude a spectrum of variable levels of health or a continuum *within* normal aging, as well as *between* normal and pathological aging. At one end there are individuals with "successful aging" [34]. At the other end, we find frail, easily incompensated people. According to the "threshold hypothesis" of normal aging, the reserve slowly diminishes and a critical level may be reached. Alternatively, someone may start with a low reserve and more easily reach the threshold for the clinical manifestation of dementia as they age [35,36].

Concepts such as "benign senescent forgetfulness" [37,38], "age associated mental impairment" (AAMI) [39–41] and "mild cognitive impairment" (MCI) have been adopted to indicate alternative interpretations of cognitive decline with increasing age. The criteria for AAMI, developed by a National Institute of Mental Health work group [39], were at least 50 years of age, complaints of memory loss in everyday life, memory performance on standardized tests at least one standard deviation below the average for young adults, and the absence of dementia. AAMI is not a widely accepted diagnostic entity [38,41], while MCI has become the most widely used concept in research on early cognitive deficits indicating an illness that leads to dementia [42]. AAMI is similar to the concept of age-related cognitive decline (ARCD) presented by DSM-IV (1994). MCI patients perform memory tasks at 1.5 standard deviations below age-matched controls that cover the spectrum between normal aging and dementia. Of the elderly population 5–10% develops dementia, and 4–12% of MCI patients are expected to develop AD each year [43–45]. An alternative to the MCI concept is that of "age-associated cognitive decline" (AACD) developed by the International Psychogeriatric Association (IPA) [46]. AACD is characterized by difficulties in any cognitive area, with a predictive value comparable to that of MCI [44].

History of nosological classification

Despite the fact that dementia is a clinical concept, most classifications have been based primarily on neuropathological criteria and presumed etiological factors, and less on clinical characteristics. Apoplexy was a well-known clinical phenomenon even in antiquity, as was its sequels, including paresis and changes of mentation and behavior. Thomas Willis offered a description of vascular dementia (VaD) in 1672 and made crucial observations on cerebrovascular circulation [47]. Hemorrhage long remained the dominant pathophysiological explanation of stroke. The early 19th century saw the introduction of the concept of softening, as well as its association with arterial occlusion and infarction in stroke [48]. In an 1854 classification of mental diseases [49], Baillager distinguished *paralysie générale* from *démence incoherente* and *démence simple*. Kahlbaum described *vesania progressiva apoplectica*, as well as *dementia paralytica, dementia aquisita* and *presbyophrenia* [50]. The 1896 edition of Kraepelin's psychiatry textbook broke organic brain syndromes down into diffuse and localized brain diseases, strongly associating dementia with aging [51]. The work of Alzheimer and others modified this perspective, and the 1910 edition of the textbook [52] presented AD as a presenile dementia, a term coined by Binswanger in 1894 [53]. However, cerebral arteriosclerosis was regarded as the major cause of organic dementia, while post-apoplectic and arteriosclerotic dementia were used synonymously.

The classification of dementia has been a controversial issue since the evolution of modern neuropsychiatry in the late 19th century. Arnold Pick reported an association between circumscribed cortical degeneration, aphasia and behavioral changes in some cases of dementia [54,55]. Alzheimer presented a pathological account of this lobar atrophy in 1911 [56]. Onari and Spatz [57] and Stertz [58] established the clinicopathological entity of Pick's disease in the 1920s. Schneider suggested a three-stage model, dominated by frontal lobe symptoms, to describe its clinical course [59]. Mallison [60] and Sjögren et al [61], van Mansvelt [62], Escourolle [63], Schenk [64], Delay and Brion [65] and Constantinides et al [66] – just to mention some of the more important contributors – further elaborated on the consistency and variability of clinical and

histopathological findings in Pick's disease. The concept of frontotemporal dementia (FTD) and its diagnostic criteria have evolved mainly during the last two decades based on several clinical and pathological studies [67] (Appendix 2.1). Clinical and pathological consensus documents [68] have described the spectrum of FTD, and frontotemporal lobar degeneration (FTLD) later on, more recently including classification attempts based on biomarkers such as genetics [69–72].

International and national boards and work groups have gradually taken over responsibility for disease classification. However, the principles remain far from an ideal multiaxial classification based on free combinations of the predominant syndrome and "causal or precipitating factors", as suggested by Essen-Möller [73,74]. The 5th edition of DSM [32] offers guidelines for diagnosis of one type of primary degenerative dementia – dementia of Alzheimer type (DAT) (Appendix 2.2) – and one type of VaD – multiinfarct dementia (MID) (Appendix 2.3). These two dementia disorders are subclassified as "uncomplicated" or "combined with delirium, delusions or depression". Such subclassification that emphasizes the natural course and variability of a progressive disease had already been called into question by Alzheimer [75]. ICD-10 offers four main categories of dementia: DAT, VaD, dementia in diseases specified elsewhere (such as Pick's disease and Creutzfeldt-Jacob's disease), and dementia "not otherwise specified" [6]. DAT (F00, Appendix 2.4) is subclassified with respect to early vs late onset, typical vs atypical clinical features, and pure or combined with VaD. VaD (F01, Appendix 2.5) is broken down in terms of type of onset and predominant involvement (cortical vs subcortical). A 1990 Swedish consensus report from dementia research centers in Lund, Göteborg, Stockholm and Umeå [76] offered a clinical classification based on predominant clinical features, as well as type and location of the brain disease [76,77]. Diagnosis should rely on a thorough analysis of the patient's history and a standardized clinical examination. Three main etiology-based categories were primary degenerative dementia, VaD and other secondary dementias. Primary degenerative dementia was broken down into 1) frontotemporal, 2) temporoparietal, 3) subcortical and 4) other predominance. The 1994 Lund-Manchester consensus statement on FTD [67] and the 1998 consensus on FTLD [68] further elaborated the criteria for the first group.

Subclassification of VaD

Despite early achievements with regard to subclassification of dementia caused by vascular lesions, most textbooks have tended to favor homogeneous concepts, such as arteriosclerotic psychosis, arteriosclerotic dementia and – more recently – MID and VaD. A 1988 classification on a clinical and pathoanatomical basis added strategic infarct dementia (SID), incomplete infarction and small vessel infarct disease to the list [78]. DSM-III-R [79] recognized the clinical picture and risk factors for MID, and DSM-IV [32] has retained this integrated view of MID (now called VaD) with a subclassification based on "predominant clinical features". ICD-10 of 1992 recognized 6 subtypes of "vascular (formerly arteriosclerotic) dementia", which includes such entities as "VaD of acute onset", "subcortical VaD", "mixed cortical and subcortical VaD", "other VaD" and "VaD unspecified" in addition to MID [6]. Subcortical VaD with extensive diffuse demyelination and small focal infarctions was also referred to as "Binswanger's encephalopathy"[6]. Moreover, ICD-10 points out its common coexistence with AD.

The state of California Alzheimer Disease Diagnostic and Treatment Center (ADDTC) proposed the first set of criteria for the diagnosis of "ischemic vascular dementia" (IVD) in 1992, describing probable, possible, and definite IVD, as well as "mixed dementia" [80]. VaD was also defined in terms of brain imaging, thereby extending the concept to include MID, "single stroke dementia" and Binswanger's disease. The criteria developed by the National Institute of Neurological Disorders and Stroke (NINDS) and the Association Internationale pour la Recherche et l'Ensignement en Neurosciences (AIREN) [81] elaborated on the cause-effect relationship between cerebrovascular disease and symptoms of dementia (Appendix 2.6). With the goal of facilitating treatment and epidemiological research, it emphasized the need of clinical and neuroimaging criteria for early and specific diagnosis of probable, possible and definite VaD. Future dementia research will probably pay more attention to the clinical and neuropathological overlap between VaD and AD [82]. The possibility of a common etiology (or pathogenesis) or co-localization of brain pathologies has been pointed out [83]. The various efforts to devise a lasting classification of mental deterioration and dementia associated with cerebrovascular disease illustrate the limitations of the

present terminology. The validity of the VaD diagnosis is often challenged – especially at a mild preclinical stage – for which alternatives such as vascular cognitive impairment (VCI) have been suggested [84].

The subclassification of VaD must consider its neuropathological and clinical heterogeneity. Classification may employ different approaches, such as the primary vascular etiology, location of brain lesions or the predominant clinical picture that also considers the presence of Alzheimer pathology [85–87]. Pathological subclassification of 175 VaD cases showed that small vessel disease (SVD) was twice as common as large vessel disease and dementia due to hypoxic-ischemic lesions. Moreover, SVD occurred five times as often as the other types [88].

Other secondary dementias

Most classifications of dementia include a third major category, sometimes called "other secondary dementias". This category contains miscellaneous types of dementia, including the majority of presently treatable conditions, such as those caused by hydrocephalus [89–91], endocrine, metabolic and nutritional disorders [92,93], infections and exposure to toxic factors. There are substantial geographic, ethnic and socioeconomic variations with regard to the presence of some of these etiological variables. The further development of neuroimaging, biochemical markers, genetic markers and treatment strategies will gradually add to our knowledge in this field. Neuropathology remains the gold standard for definitive diagnosis of dementia. A decline in post mortem examinations will severely limit our knowledge of normal aging and the true prevalence of different types of dementia.

Fact Box 2.1 *Nosology: Questions to be posed regarding AD, VaD, FTD and other dementia diseases.*

What are the major dementia diseases from a clinical and brain morphological point of view?

Does AD-type pathology exist in normal aged brains? If so, to what extent?

Do vascular lesions occur in normal aged brains? If so, to what extent?

Is post mortem differentiation possible between AD pathology compatible with dementia and AD-type changes in the cognitively normal individual?

Is post mortem differentiation possible between cerebrovascular pathology compatible with dementia and cerebrovascular changes in the cognitively normal individual?

Is there any defined level of brain pathology associated with MCI?

How many concomitant brain changes – or symptoms and signs – of other types can be accepted as part of a diagnosis of "pure AD"?

Who decides what constitutes "mixed dementia"?

Alzheimer's disease

Aims

A search of the literature aimed at identifying the "entity of Alzheimer's disease" with regard to the abovementioned parameters. That included distinguishing Alzheimer's disease (AD) from normal aging, mixed AD-VaD and other forms of dementia.

The purpose was to not to examine clinical diagnostic (including neurochemical, neurophysiological and symptomatological) features or to cover complete diagnostic neuropathology, other than to describe AD as an entity.

The search was structured so as to identify and analyze publications that were central, validating or valuable from another point of view. It focused on work related to clinical symptomatology and brain morphology, including qualitative and quantitative considerations.

Because historical papers and clinical descriptive, as well as clinicopathological studies, are structured in a variety of ways, a study-to-study group comparison was not feasible. Instead, each study or report was assessed and evaluated on its own merits.

Background

AD is the most common disorder leading to dementia among both neurodegenerative and all types of dementias. The disease (as well as the concept itself) is well known and yet unfamiliar due to its multifaceted presentation. AD is recognized as being not one disease, but a group of similar disorders, a syndrome that varies according to factors related to age, etiology, heredity, etc. The clinical syndrome and neuropathological profile are viewed as well established but remain the subject of discussion regarding heterogeneity and subtypes, age characteristics and epidemiology, heredity and familial association, brain morphologic-pathologic substrates and characteristics, and possible vascular components (and thereby etiology as well).

AD – evolution of the disease concept

As far as we know, AD is the most prevalent single cause of severe dementia. However, that view, along with the classification of dementia, may change in the future based on new knowledge and insights. Ever since Alzheimer's oral presentation entitled "Über einen eigenartigen schweren Erkrankungsprocess der Hirnrinde" in November 1906 [94] and its publication in 1907 [95], AD has been described with increasing precision. The case notes on 51-year-old Auguste D contain several core features of AD, such as progressive cognitive impairment with memory failure, spatial disorientation, deceptions and delusions. Within five years, the disease had progressed to profound dementia and death. At necropsy, the brain was found to be generally atrophied, and Alzheimer found numerous plaques and neurofibrillary tangles throughout the cerebral cortex. He was impressed by the severity of the pathological changes and the early age of onset. The medical records, including the patient's attempts to write her name and Alzheimer's meticulous notations, which were rediscovered 90 years later, further improved our knowledge of this first diagnosis of AD [96]. Alzheimer encouraged

his colleague Perusini to publish four cases [97]. One of them (probably Auguste D) features beautiful illustrations of amyloid plaques and tangles but no significant signs of arteriosclerosis. Perusini claimed that these cases represented an independent disease that needed to be distinguished from senile dementia. Kraepelin, who shared that view, introduced the term "Alzheimer's disease" in the 8th edition of his psychiatry textbook [52]. In 1910, Fischer described 19 cases of psychosis with senile plaques and tangles [98]. In accordance with the emerging view that AD starts early, he preferred to call them presbyophrenics by virtue of their advanced age. However, as early as 1911, Alzheimer was also describing an Alzheimer type of encephalopathy among patients with late onset dementia [99].

Medical opinion concerning the nosological classification of AD has gradually changed, particularly over the past 25 years. The single most important scientific meeting on AD and related conditions was arranged by the CIBA Foundation in November 1969. The publication a year later updates the clinical and pathological research on AD, as well as its relationship to other dementias and to aging [100]. Robert Katzman's landmark 1976 editorial on AD, entitled "A Major Killer", strongly endorsed the concept that senile and presenile forms of AD are a single disease "whose etiology must be determined, whose course must be aborted and ultimately a disease to be prevented" [101]. AD became a major challenge to the scientific community. A large body of research from medicine and basic sciences has contributed to our present understanding of dementia by providing new diagnostic techniques, neuroimaging, molecular genetics, neurochemistry, epidemiology, neuropathology and clinical trials.

The terminology of AD

The natural course of AD, the first clinical signs, progressive deterioration and clinical stages have been studied and described by means of different methods and models. The patient's age at clinical onset, before and after age 65, early and late onset, was the basis of the initial distinction between presenile AD and senile dementia (SD). Moreover, it was asserted that the diagnosis of AD relied on the occurrence of focal parietal lobe features [102]. SD has often been used as an unspecified

dementia syndrome with onset that is late or regardless of age [6], albeit this clinical distinction has often been questioned [103]. SD should not be confused with the abbreviation for "semantic dementia" in recent literature [104,105]. Dementia of Alzheimer type (DAT) was introduced by DSM-IV to include early onset AD (EOAD) and late onset AD (LOAD), corresponding primarily to AD type II and type I respectively in ICD-10. LOAD is also called senile dementia of Alzheimer type (SDAT).

According to ICD-10, the "presumptive" clinical diagnosis of AD should be based on the following criteria: insidious onset with slow deterioration, absence of indication of other systemic or brain disease that can induce a dementia, and absence of apoplectic onset or focal neurological signs early in the disease [6]. The NINCDS-ADRDA work group for standardization of clinical criteria for diagnosis of AD [106] (Appendix 2.7) recommended the terms "possible AD" and "probable AD". The criteria for probable AD include dementia established by clinical examination and documented by the mini-mental state examination (MMSE) [107], dementia test score [108] or a similar examination, and confirmed by neuropsychological tests, deficits in two additional areas of cognition, progressive deterioration of memory and other cognitive functions, no disturbance of consciousness, onset between the ages of 40 and 90, most often after 65, and absence of systemic disorders or other brain disease that could account for the progressive deficits. The diagnosis of probable AD is supported by progressive deterioration of specific cognitive functions, such as aphasia, apraxia and agnosia, impaired daily activities and altered patterns of behavior, family history of similar disorders, laboratory results showing normal lumbar puncture, normal or non-specific EEG changes, evidence of cerebral atrophy on CT with progression documented by serial observation. Other clinical features are considered to be consistent with the diagnosis, rendering probable AD uncertain or unlikely. The term possible AD was intended for atypical presentations in the presence of second systemic or brain disorder sufficient to produce dementia but not deemed to be the cause of the dementia. The terminology is recommended in order to highlight the possibility of major comorbidity, neurological or otherwise. Although clinical variability with typical and atypical AD is strongly emphasized [6], variants such as the "Lewy body variant of AD" has virtually become a disease entity

of its own [109–111] (Appendix 2.8). Attempts to single out familial and sporadic non-familial forms of AD have resulted in the abbreviations FAD and SAD.

The clinical picture in AD

This chapter reviews the literature on the clinical features and natural course of AD with specific reference to early manifestations, clinical pathological correlates and differential diagnosis. A large number of publications have analyzed and described AD, often on the basis of incomplete or nonexistent neuropathological data. In 1910, Perusini confirmed Alzheimer's clinical observations, adding visual dysgnosia, epileptic seizures and extrapyramidal signs to the clinical repertoire [97]. He also pointed out the possibility of differentiating AD from arteriosclerotic dementia based on its slow progressive course and lack of focal neurological signs. Other early studies often reported Parkinsonian symptoms in AD [112–114].

The clinical picture for presenile AD includes a number of symptoms and signs with varying relationships to the distribution of the brain lesions. Selection of diagnostic criteria must consider both the frequency and specificity of these symptoms and symptom clusters. The majority of AD patients develop dysmnesia, dysphasia, dysgraphia, dysgnosia, dyspraxia and spatial disorientation, indicating bilateral involvement of the neuronal network in the temporal limbic structures and the temporoparietal association cortex [115–118]. That does not exclude significant individual variations with regard to symptoms and course of the disease. Of special interest is the influence of vascular factors, both as a dynamic component of AD in general and as a manifestation of the frequent co-occurrence of AD and cerebrovascular disease [82,119–122]. Neuropathological investigation may reveal the contribution of vascular vs neurodegenerative changes, based if possible on an examination of the entire brain in order to cover all regions and different types of damage [123].

Most clinicopathological studies of AD identify pronounced correlations between different aspects of mental deterioration on the one hand and regional variation and the progress of degeneration on the other [124].

However, certain areas are largely spared until advanced stages. The relative sparing of primary projection areas, the anterior cingulate gyrus and the frontal lobes corresponds closely to findings of relatively high retained motility, perception and habitual personality traits [116,117]. Clinical manifestations in AD have been shown to be partially related to the patient's age characteristics [125,126]. Subtypes have been based on clinical features, such as contributions of language dysfunction, extrapyramidal features and myoclonia, as well as other epileptic seizures and logoclonia [127,128]. Moreover, genetic and other etiological backgrounds to subtypes of AD have been identified.

Age at onset of AD

Clinical recognition of AD must be based on knowledge of the natural course of the brain disease. AD usually starts insidiously and develops slowly over many years, so that onset can be dated only imprecisely. The psychiatric symptoms in the prodromal phase, such as irritability, anxiety, suspiciousness, depression, passivity and self-centeredness [129–131], are non-specific. The mean age at onset in autopsy proven EOAD is 53–57 [132] with death 2–20 years later [125]. However, both age at onset and disease duration vary considerably from study to study, based on autopsy proven cases and in families with identified mutations [133]. Passing the threshold from the presymptomatic/preclinical phase into the first early clinical stage may be caused by various somatic (particularly cerebrovascular) events and psychological factors as well [121,134,135]. Alzheimer's first patient died after 4.5 years, Sjogren et al [136] reported a mean duration of 7.1 years for EOAD, and Lauter found a mean duration of 5.8 years in 203 autopsy proven presenile cases [125]. Duration is inversely related to the patient's age at onset. Several studies indicate a mean duration of about 6 years (2–10 years) in LOAD [132,137]. Although a few studies have indicated that early age at onset is associated with a more rapid clinical course, the majority of studies find no significant age-related differences [138–144].

Patients in families with presenile AD usually show a similar age at onset [145], but a large range has been reported in families with a uniform genetic basis [133].

Because of poor premorbid assessment, clinical onset may be especially difficult to determine in patients with Down's syndrome and DAT. The Alzheimer encephalopathy in Down syndrome dementia (DSD) starts developing before age 20 [146–149]. Thus, the "presymptomatic" phase may last as long as 20–40 years. Beyond that age, DSD patients exhibit pronounced progressive cognitive decline involving language and spatial functions, as well as epileptic seizures. That evolves alongside a significant decrease of regional blood flow in the temporoparietal cortex, together with progressive EEG pathology [150,151].

Rate of disease progression

The clinical course of AD is characterized by insidious onset and a slow progressive course, terminating in severe global dementia and death. However, disease progression exhibits significant heterogeneity with regard to both clinical profile and rate of deterioration. Various predictors for the rate of cognitive decline and survival have been studied but generated few consistent, significant findings. The complex etiology of greatly reduced survival in AD is only partly known [152]. A longitudinal study by Knesevich et al of 40 subjects with LOAD found that aphasic patients had a more rapidly progressive course [153]. Conversely, the absence of aphasia was associated with a higher prevalence of familial cases and a slower rate of progression. The problem was to keep speed of progression and duration of dementia apart. The study clearly demonstrates the confounding effect of aphasia on the use of any narrowly based methods for staging dementia.

Mayeux et al reviewed the clinical records of 121 consecutive, well-diagnosed AD cases with an emphasis on initial and neurological manifestations [128]. The authors suggested 4 subgroups of progression over 4 years: a benign group (6%) with little or no progression; a myoclonic group (10%) with severe intellectual decline; an extrapyramidal group (28%) with severe deterioration and frequent psychotic symptoms, and typical AD cases with no clinical manifestations other than dementia. However, there was no post mortem verification or clinicopathological correlation. A follow-up study of probable AD (mean 2.8 ± 1.6 years) by Stern et al also reported an association between extrapyramidal signs or psychotic symptoms [154]. No fewer than 37% of the patients showed

extrapyramidal signs at the initial examination. Myoclonus was associated with a more aggressive course and was related to disease duration. A five-year follow-up of 92 EOAD cases by Heyman et al found severity of memory and language impairment to be predictors of institutional care and death, even more so in younger patients with the same degree of dysfunction [139]. Cumulative mortality was 24% after five years, as opposed to the expected 9.5%. Autopsy confirmed the AD diagnosis in 14 of 23 deaths.

Berg et al analyzed the ability of brief measures to predict the severity of dementia [155]. Among such measures are the Blessed dementia scale (BDS) and Pfeiffer's short portable mental status questionnaire (SPMSQ). A third measure was the face-hand test (FHT). Berg and Stourandt stressed the advantage of using several measures in longitudinal studies, although predicting progression based on any of these assessment instruments turned out to be difficult [156].

Huff et al studied the rate of progression in 77 AD patients by repeatedly administering the BDS [137]. The bimodal distribution of age at onset with a dividing line at age 65 was suggested in order to identify the possible existence of two AD populations. The mean age at onset was 55.9 ± 4.8 in the early onset group and 72 ± 4.4 in the late onset group. Repeated assessment with the BDS showed a progression rate of 0.52 points per month for EOAD and 0.78 points per month for LOAD. Many studies, including Drevets and Rubin in 1989 [157], report an association between psychotic symptoms and accelerated cognitive deterioration, while a study by Ortof and Crystal [143] of 54 patients clinically diagnosed with AD found no significant influence of age at onset, duration of illness or family history of dementia. Jost and Grossberg analyzed 100 autopsy confirmed AD patients who had a mean duration of symptom onset until death of 9.3 years with a standard deviation 6.0 years [158]. Rapid progression was associated with aphasia, extrapyramidal symptoms and psychosis.

Nyth et al described a subgroup of AD patients with late onset, rapid progression, comparatively early presentation of frontal and confusional symptoms, and only a mild parietal clinical picture [159].

There are few longitudinal studies on clinical subtypes of DAT. Chui et al studied 146 patients with dementia and AD who had been diagnosed in accordance with DSM-III criteria and for whom VaD had been ruled out by means of a modified Hachinski IS [160]. The duration of symptoms exceeded one year in all cases. Of the total sample 44.8% had a first-degree relative with symptoms of dementia. Aphasia was found in 60%, extrapyramidal signs in 44.5%, a hyperactive muscle stretch reflex without clonus in 18.5%, a history of seizures in two cases and myoclonic twitchings in 6.2%. Subtypes of AD with respect to presence of aphasia, a positive family history, extrapyramidal signs and myoclonus were analyzed. Corroborating Pearce [114] and Seltzer and Sherwin [161], no relationship between extrapyramidal dysfunction and age at onset was identified. Early onset, rather than family history, appeared to predict the early development of language disorder.

There are few longitudinal prospective studies on the clinical features of AD. A retrospective review by Eustace et al [162] of database information on patients with probable AD [106] studied baseline and accumulated prevalence in 52 AD patients who were repeatedly followed for two years. Significant differences emerged between baseline and accumulated prevalence. The clinical assessment was based on the reports of informants and scoring by means of the BEHAVE-AD [163]. Activity disturbances, such as wandering, purposeless and inappropriate activities, were common, persistent symptoms over time, whereas paranoid and delusional ideation and aggressiveness were less common but relatively persistent. Affective symptoms were least common. However, duration of the disease was not included in this study – nor was any information concerning the general severity of cognitive symptoms.

Staging AD

Well-defined instruments for staging dementia are needed. Although a typical clinical course may be identifiable in the majority of AD cases, there are pronounced individual variations that can influence the diagnostic and therapeutic process. Such variations may be a result of not only the distribution and severity of the brain disease, but premorbid personality, comorbidity, medication and socio-economic factors as well.

The three-stage (initial, manifest and terminal) model proposed by Sjögren in 1952 can generally describe the clinical course of AD [61]. The following clinical description is based primarily on this staging, which has been used by a large number of publications on AD and for comparisons of clinical subtypes.

Other assessment instruments have been employed for operationally defined staging of dementia. Reisberg et al [13,164] developed the Global Deterioration Scale (GDS) by using Piaget's stages of development of intellectual processes throughout childhood [165]. Interobserver and test reliability and comparisons with the MMSE have been included in several studies [123,129,166–170].

The first stage of GDS is preclinical dementia. Stage 2 involves the presence of very mild subjective complaints but no objective evidence of dementia. This stage is compatible with the diagnoses of AAMI and ARCD, as well as possible AD. Once dementia has been clinically diagnosed, there are five possibilities. GDS stages 3 and 4, roughly corresponding to mild and moderate dementia respectively, score 15–25 on the MMSE. GDS stage 5, indicating moderately severe dementia, scores 10–19. GDS stages 6 and 7, suggesting severe and very severe dementia respectively, score below 10 [171–173]. The in-between stages of GDS have no operational definitions. The mean annual rate of decline on the MMSE for AD is approximately 3 points (range of 4 to 5) [174–176]. The rate of decline appears to be predicable for groups of patients, though not for individual cases, and is reasonably constant as long as the floor effect is not reached [138].

Kraemer et al examined two proposals for staging patients after onset of AD using the MMSE and GDS [169]. The study was based on 206 patients. Neuropathological data was available for 46 patients, 89% of whom had been confirmed as definite AD with or without other diagnoses, such as LBD or ischemic vascular changes. The hypothesis was that stages are scientifically relevant when there is heterogeneity among patients with respect to the timing and course of the disease. The stages may contribute to evaluation of response in research using stage matched patients. However, any valid staging system must satisfy

certain criteria, including operationally defined stages, interobserver and test reliability. Futhermore, the stages must be exhaustive and exclusive, as well as progressive with death occurring in the final stage. There must be a sufficient number of stages to absorb most of the heterogeneity of the process. Finally, the stages must have clinical validity, such as a strong correlation with treatment responsiveness and survival type. Both the MMSE and GDS were operationally defined with documented interobserver and test reliability [107,170]. Kraemer et al found a strong correspondence, but also some discrepancies, between the two staging systems [169]. The MMSE (24–30) corresponds to GDS-2 and GDS-3, the MMSE (15–23) corresponds to GDS-4 and the MMSE (8–14) corresponds to GDS-5. Discrepancies occur in the latter stages, and the MMSE 4 and MMSE 5 are less clearly related to GDS-6 and GDS-7. Staging stability was determined by means of two successive observations, usually about six months apart. The conclusion was that the MMSE system may be more limited than the GDS in some respects. The question is whether these staging systems lead to new insights about the course of AD that could be important for clinical decision making and research strategies. A staging system that focuses more on specific neurological, physical, behavioral, social or economic changes might turn out to be preferable to the GDS (which is based on functional change) or the MMSE (which is based on cognitive change). In short, we believe that there is a need for *several standard staging systems* in the field.

The first stage of AD

The first stage of AD is by definition a period during which the patient and relatives report symptoms that are considered indicative of a process that leads to dementia. However, there may already have been symptoms and signs that are subsequently looked upon as a first manifestation of the disease. These "preclinical" prodromal changes are often noted by the patient, causing various emotional reactions and behavioral changes. Such early expressions may sometimes be impossible to recall later on. Cognitive deficits in the early stage, sometimes called the "forgetfulness phase" [177], are mainly subjective. The person notices a tendency to misplace things, as well as difficulty in remembering names and appointments. Nevertheless, these impairments do not interfere signi-

ficantly with daily activities, though they are often accompanied by anxiousness and depressed mood. A paper by Kral entitled "Senescent forgetfulness: benign and malignant" discussed the prognostic value of such observations for indicating very mild questionable AD or normal aging [37]. He considered the malignant form to be characterized by inability to recall past events – not simply relatively unimportant facts associated with an experience, but the experience itself. By contrast, in benign senescent forgetfulness, the experience itself could be recalled.

The patient at this early stage of AD is often aware of and attempting to understand the functional decline. That leads in turn to various emotional reactions and coping strategies [11,178–180]. An illustration of this situation is the following poem, published 10 years before the clinical debut of dementia and 20 years before death. The author developed a slowly progressive dementia with memory failure, disorientation and confusional episodes. He suffered two small vascular attacks during his last two years. The neuropathological examination revealed an Alzheimer encephalopathy with temporal limbic accentuation and a small striatal infarction. The poem (see page 41) has been translated into English, and publication has been approved by his relatives [181].

The mental changes associated with AD start during the initial stage of 2–4 years [136]. People close to the patient usually notice a loss of short-term memory, while the patient may be even more embarrassed by impaired long-term memory. The patient may also show signs of dysphasia, dysgraphia and an impaired sense of locality, although it may be concealed and compensated for in various ways. Receptive dysphasia and dysgraphia are easily overlooked and may be explained as impaired hearing or vision in elderly patients. Dysphasia is reported in about 25% of presenile AD cases, and handwriting changes may also appear early [132].

Many symptoms during the first stage of AD are rather non-specific and experienced mainly by the patient. Awareness of cognitive failure continues, at least partly, for many years, and the patient employs various strategies to conceal disabilities and maintain a facade. The patient complains of tiredness and lack of concentration, becomes less active and efficient. Anxiety, depression and paranoia are common.

The Head of the Water Lily

There is a devil in my head
He is sneaking around
beating with a hammer
breaking the keys
one note a month
I must be careful
not to play the broken ones
But it is becoming more and
more difficult.

He is wrecking ganglions
and breaking connections
I suddenly feel it in a finger
A sensory cell that refuses to
function
I notice it in something beautiful
that I once saw and now have
lost.

He crushes neurons
where my memories are stored
Scratches with needles in a record
spills the nucleic acids around
– all turning into ink
spilled out on the table by a child
streaming along channels, along
the vessels
turning into patterns no one can
understand.

A devil is sneaking around in my
head
He is beating with a hammer
in the grey matter of the brain
he is spoiling dreams, friends,
tones, birds, visions, flowers,
Everything is sinking down!

Author anonymous

Recent research that focuses on the earliest phase of AD has offered a varied and complex clinical picture. A study by Oppenheim of 83 patients with probable AD found that the earliest objective signs of disease in 44 cases (53%) was something other than memory impairment [182]. Twentyseven patients (32.5%) exhibited psychiatric symptoms, such as withdrawal, suspiciousness, general anxiety, irritability and aggressiveness. Nine patients (11%) had neurological signs, while eight patients (9.6%) showed impaired housekeeping and signs of non-coping type. The author suggested the possibility of a "prememory" stage of AD, with subtle behavioral changes that may be forgotten or escape notice.

Based on 363 AD cases, Wilson et al studied the correlation between informant descriptions of premorbid personality and the risk of developing AD [183]. He found a correlation between proneness to distress and decline in episodic memory, but the distress could not be related to AD pathology in deceased cases. A study by La Rue et al on the first symptoms of dementia concluded that more than one informant should be questioned whenever possible [184]. Multiple initial symptoms were usually reported. Persson and Skoog reported impairment of memory and language, along with a low number of remembered dreams, as early subclinical manifestations of AD and VaD [185]. However, the reports of spouses and young relatives often differed at the onset of the disease.

There are few prospective studies on the initial symptoms of AD and other dementias. We have not determined the consistency of symptom patterns or how reliably they can be ascertained from the reports of relatives [184,186]. A study by Green et al of 1 953 subjects with AD and 2 093 of their unaffected relatives reported a significant association between depressive symptoms and AD [187]. Families in which depression had occurred within one year before onset of AD showed a higher correlation than families with depressive symptoms that had occurred earlier. A modest correlation remained for families in which depressive symptoms had first occurred more than 25 years before the onset of AD. There appear to be two sources of the association between depression and later development of AD. Depression may be an early symptom of the dementia process. If appearing in the distant past, it may indicate a predisposition to later vulnerability.

The second (manifest) stage of AD

The second (manifest) stage of AD brings with it progress of mental deterioration dominated by dysmnesia, dysphasia, dyspraxia, dysgnosia and spatial disorientation. This symptom pattern has a strong relationship with the temporoparietal cortical involvement of the disease [61,103, 116,118,126,188,189]. The emotional changes are described as emotional fading, lack of vitality and apathy. However, the patient's habitual personality traits and capacity for social interaction may be relatively intact. The amiability and cautiousness that has been considered rather typical of AD may also be due to the relative sparing of the frontal lobe cortex

and anterior limbic structures, whereas restlessness, agitation, irritability and confabulation are more prevalent in AD with pronounced frontal cortical or frontal subcortical white matter involvement [103,117,190–194]. Fainting spells, severe dizziness, autonomic failure and fluctuations of the clinical course are not uncommon in AD [116], and clinical suspicion of concurrent cerebrovascular disease often arises, sometimes to be autopsy proven [120,195–199]. Although personality alterations are often reported in AD cases, many patients maintain non-verbal emotional contact even at an advanced stage. That contrasts with the lack of emotional concern and empathy in FTD [67,200]. The duration of the second stage of AD has been estimated at 2–4 years.

Expressive and receptive language impairment increases in AD patients, although not necessarily at the same rate of progression. Speech becomes aspontaneous and hesitant, with deficits of naming and word comprehension [201]. Expressive speech might deteriorate to an almost incomprehensible and fragmented level, with repetition and paraphasia. The language dysfunction is similar in several respects to the transcortical sensory aphasia described by Wernicke [201]. Dysgraphia, dyscalculia, finger dysgnosia and right-left disorientation may sometimes develop as a fairly full-blown Gerstmann syndrome. Logoclonia, a clonic type of stuttering, is reported with varying prevalence, sometimes as high as 1/3 of early onset cases – usually at a late stage, but occasionally early in the course of the disease [61,116,200].

Alzheimer reported significant writing impairment in his first patient: "when writing she reduplicated the same syllable and forgot some others and in general finished very rapidly by stopping". Writing is now recognized to be impaired early and to decline considerably as the disease progresses [202]. Several studies have shown that the agraphia in AD is independent of demographic variables, such as age, education and duration of dementia. They correlate rather with visuoconstructional dysfunction, as well as the global severity of dementia. Dysgraphia in AD is different from that of normal aging, characterized by poorly constructed letters, omission or overrepetition. Words and letters are repeated, and patients with mild to moderate AD give a visual impression of studious

and hesitant writing. The agraphia in AD shows significant correlations with cortical dysfunctions in the left temporoparietal region [202–206].

Difficulties at the early stage seem to be associated with semantic difficulties in organizing written text. The Nun Study investigation of written language following individuals decades before the official onset of AD, indicated some pathology [207]. Penniello et al reported a decrease in blood flow in the temperoparietal region in patients with alexia, agraphia and impairment of comprehension [203]. A study by Lambert et al of probable AD found writing from dictation to be a predominant but non-isolated lexical deficit that was independent of lexical and semantic capacity [205]. Hughes et al found writing deficits (errors in spelling difficult words) at the early stage of DAT [208]. Luzzatti et al found the whole spectrum of dysgraphic taxonomy in 23 patients suffering from mild to moderate DAT, with little correlation between dementia severity and the two types of dysgraphia [209].

Classical Gerstmann syndrome, which is associated with lesions of the left hemisphere's angular gyrus, consists of finger agnosia, right-left disorientation, acalculia and agraphia. This symptom constellation is common in the second and third stage of AD, but may also be detectable at an early stage, albeit less severe. Wingard et al analyzed data on 71 patients with probable AD who were still capable of understanding commands of the MMSE [210]. The four signs of Gerstmann syndrome did not cluster as a distinct syndrome, but finger naming correlated significantly with right-left orientation.

Hand movements and the generation of writing movements are complex processes involving the integration of different faculties. Kinematic analysis of handwriting movements in AD have shown significantly less automated accurate and regular writing than healthy controls. There may be an influence of extrapyramidal motor symptoms, but the changes cannot be explained by age and medication. Longitudinal studies of hand motor dysfunction in AD will be clinically relevant for evaluation of treatment [211].

Down's cases often show a chronologic association between the onset of dementia and the first epileptic seizure as well as appearance of EEG pathology. Myoclonic twitchings, which are unexpectedly common in AD, are reported in FAD, SAD and DSD. Differential diagnoses against Creutzfeldt-Jakob's disease of extended duration may be difficult and cannot be based on the EEG findings. Myoclonia also appears in some rare hereditary forms of dementia, such as progressive myoclonic epilepsy [212,213] and Gerstmann-Sträussler-Sheinker disease [214].

Episodic deterioration with severe anxiety and delirious states is common during the second stage of AD, as patients become increasingly sensitive to all kinds of psychological and somatic strain, including that caused by various medications, especially anticholinergic drugs. Hypersensitivity to atropine and cholinergic impairment of neuroendocrine control have also been found in Down's syndrome [215–217]. Confusional episodes and pronounced clinical fluctuations in AD appear to be related to the presence of white matter lesions of ischemic type, as well as to vascular risk factors, such as arterial hypertension [218]. Previous hypotension, as well as the development of low and orthostatic blood pressure, are common findings in both AD and other dementias [120,219–221].

Falls and fractures are common in orthostatic and hypotensive patients, the incidence being above 50% in AD and VaD cases [222,223]. The complex etiology is a combination of aging, autonomic weakness, heart failure, medication, inactivity etc. Elmståhl et al reported that AD patients had significantly lower blood pressure at rest than age matched healthy controls [224]. The maximum blood pressure drop during standing often appeared after 10 minutes.

Spatial dysfunction is often reported early in AD as a decreased sense of locality in new surroundings. This impairment can easily be masked by a more cautious and restrictive lifestyle, and phobia-like reactions may appear. The syndrome constellation of dysphasia, dyspraxia, dysgnosia and spatial disorientation has been strongly correlated with degeneration and dysfunction of the temporoparietal cortex [116,125,126]. However, the various cognitive dysfunctions may start and progress independently,

possibly related to asymmetry in the cortical involvement [225]. During the second stage of AD, increasing visuospatial dysfunction may affect recognition of localities, objects and family members, and later even the reflection of the patient's own face in a window or a mirror (mirror sign), possibly provoking psychotic reactions [145,226].

Dyspraxia increases during the second stage of AD, causing difficulties in using technical equipment, and later in dressing and eating properly as well. Driving problems are observed early in AD. Left-right insecurity in AD is easily observable given that most elderly people in Sweden learned to drive before the country switched to right-hand traffic in 1967. However, AD patients are typically self-critical and anxious about their driving difficulties, so that they accept their doctor's advice to give it up voluntarily. By contrast, FTD patients may continue to drive dangerously against their doctor's recommendation [227].

Neurological symptoms, such as increase of muscle tone with an uncharacteristic non-Parkinson character, appear in 20–80% of early onset cases. Tremor and cogwheel phenomena are observed comparatively late. A more Parkinsonian picture seems to be frequent in patients with degeneration of extrapyramidal structures, either with or without Lewy bodies. The differential diagnosis against Parkinson's disease and Lewy body dementia is of growing importance for pharmacological treatment of cognitive and neurological symptoms.

Generalized epileptic seizures and myoclonia have been reported in more than 50% of early onset AD cases [112,200,219]. The prevalence of myoclonus in AD increases steadily during disease progression, and up to 50% of patients eventually develop myoclonus. Early onset, more rapid progression or family appearance are associated with myoclonus appearance. The appearance can involve sporadic large myoclonic twitchings or repetitive small ones. The occurrence may be addressed with action or stimulus induced [228].

The clinical importance of basal ganglia degeneration and extrapyramidal clinical features in AD was pointed out early despite ambivalence about the linkage between organic intellectual impairment and Parkin-

sonism. The concept of subcortical dementia that was introduced included Parkinson's disease, Huntington's disease, supranuclear palsy and multiple system atrophy [229–231]. Sjögren et al described changes in motility of an akinetic-hypertonic character in 7 AD cases [136]. Such symptoms were ascribed to the involvement of basal ganglia [113] in frontal lobe degeneration [136] or to a supranuclear type of extrapyramidal disorder [114]. The association between extrapyramidal signs and pathological findings has recently become the key issue for understanding degenerative dementia with cortical and subcortical Lewy bodies. Ditter and Mirra analyzed 20 neuropathologically confirmed AD brains, 11 of which showed Parkinson's disease changes [232]. Extrapyramidal signs, such as rigidity, bradykinesia and even tremor, were observed in 34% of AD patients. This rigid bradykinesia picture has been variously described in 28–67% of AD patients [233–235].

Tyrrell and Rossor further analyzed the extrapyramidal signs associated with AD in 1988 and 1989 [236,237]. Kleist defined the phenomenon of gegenhalten or "counter pull" as a pure motor negativism that resists changes of position [238]. These types of flexibility, which are often observed in AD, have been linked to the extrapyramidal rigidity of Parkinson's disease but may also be caused by the patient's inability to understand instructions, and would therefore be similar to dyspraxia.

The presence of olfactory dysfunction has been reported in several forms of organic dementia, most often in AD, sometimes associated with Lewy bodies rather than the Alzheimer pathology [239]. Esiri and Wilcock found neurofibrillary tangles and cell loss in the anterior olfactory nucleus of AD patients, illustrating the fact that olfactory sensory pathways are significantly affected by the disease [240]. It has been suggested that the olfactory tract may provide a portal of entry to the brain for any putative pathogenetic agent that could be responsible for induction of senile plaques and/or neurofibrillary tangles [241]. Animal studies have shown the presence of both cholinacetyltranferase and acetylcholinasterase in the olfactory epithelium [242]. In referring to a study by Graves et al 1999 [244], Burns [243] pointed out the need for further research into whether olfactory dysfunction may be a marker for early AD. One major problem so far has been the lack of reliable test procedures.

AD patients, with or without apparent extrapyramidal signs, may also exhibit problems with walking and trunk movements. Their gait is described as slow, unsteady, and clumsy. Terms such as "frontale Gangstörung" (frontal gait disorder) and gait apraxia have been introduced [245,246]. Alexander et al reported problems walking difficulties in 50% of AD patients three years after diagnosis [247]. A recent study by Della Sala et al found walking difficulties in 40% of 60 AD patients, as revealed by a standardized test for assessment of walking skills [248]. Their figures differed from the prevalence detected by simple clinical observation. Sjögren et al emphasized the peculiar gait disturbance, adding that the terminal stage of the disease also exhibits "marche a petit pas" (small step gait) [136]. A study by Della Sala et al found a strong association between gait apraxia and dementia severity [248]. The neurological feature was considered to be a sequel of mesial bilateral frontal damage related to a more advanced stage of AD [249]. Gait apraxia should be regarded as a possible cause of walking difficulties, falls and fractures in AD patients. A slow, stiff, stooped gait with "curtseying" at the knees has been described in a family with chromosome 14-linked AD [145].

The third (terminal) stage of AD

The third (terminal) stage of AD usually starts after more than four years and may last for one to many years. The mental deterioration continues, involving most cognitive functions, verbal as well as nonverbal. The patient becomes apathetic to one degree or another and verbal communication becomes sporadic and unreliable. As a result, relatives and staff may have difficulty knowing whether their voices or faces are being recognized any longer. However, even patients in an advanced stage close to death may offer adequate comments and specific reactions, suggesting that problem solving and recognition may still be possible, consistent with the neuropathology of the individual case.

Several studies have recognized the presence of a Klüver-Bucy like syndrome and its neuropathological basis in AD [112,200,250]. Visual agnosia, severe amnesia and hyperorality may be present and associated with the temporal limbic damage. However, hypersexuality and bulimia are rather uncommon in AD and more prevalent in FTD [200]. With increasing duration, neurological features, such as incontinence,

primitive reflexes and extrapyramidal symptoms become more prevalent. On the whole, incontinence is rather uncommon as an early symptom in uncomplicated AD.

The clinical differentiation between AD on the one hand and VaD and mixed AD-VaD on the other is complicated by the high frequency of delirious episodes and fluctuations of the clinical state in LOAD. However, symptoms that usually indicate ischemic brain disorder may also appear among early onset cases and at an early stage of the disease. Twenty-five percent of presenile cases reported episodes of severe headache, and 1/3 suffered from spells of dizziness during the first years of the disease. Such symptoms have been related to the presence of white matter disease (WMD) in autopsy proven AD [251,252].

During the third stage, verbal communication becomes more restricted and extrapyramidal features become prevalent, as do also epileptic seizures and myoclonic twitchings. As many as 40–50% of AD patients eventually develop myoclonus [128,228,253]. Vocally disrupted behavior, screaming and noise making of varying intensity have been reported in presenile AD and LOAD, as well as and in AD of Lewy body type [254,255]. Finally, the patient becomes bedridden, incontinent and in a great need of permanent care. Postural changes, low and labile blood pressure and syncope attacks may further complicate the clinical picture [222,223].

Subclassification of AD

The establishment of subtypes of AD has been based on clinical profile, early manifestations, clinical course, neuroimaging, age at onset, familial appearance, neuropsychological characteristics, neuropathology, genetic markers, biochemical markers etc.

Kurtz et al searched for evidence of phenomenological subtypes and failed to identify qualitative subtypes within the spectrum of the cognitive phenomenology of AD [256]. Language function, praxis and perceptual ability were normally distributed in the patient sample, and pronounced memory failures seemed to be present in all patients.

However, the authors did not rule out the possibility of clinical subtypes based on neuropsychological test results. The study was based on a sample of 90 patients with mild or moderate AD.

EOAD and LOAD

The heterogeneity of AD with respect to age at onset is still an open question. The clinical distinction between AD and senile dementia was traditionally a clear one. Temporoparietal lobe symptoms, such as apraxia, agnosia, aphasia and spatial disorientation, were prevalent in AD, while the principle ingredient in senile dementia was more general intellectual and personality deterioration. This was questioned by others who claimed to have demonstrated focal phenomena in senile cases as well, albeit tending toward decreasing focalization with increasing age [125,126]. Lauter analyzed data from 203 autopsy proven AD cases with clinical onset before age 70. The clinical diagnoses were correct in all but 63 cases, and the autopsy revealed additional arteriosclerotic changes in 71 cases. Spatial disorientation was already reported during the first stage of EOAD, while aphasia, apraxia, agnosia and iterative restlessness were characteristic of the second stage. During the third and final stage, there were motor (including oral) stereotypies. The duration of each clinical stage was about two years, and the progress of deterioration could unexpectedly stop for a certain period of time. Habitual personality traits and insight were often preserved, although colored by anxiousness and bewilderment. There was general language involvement, but communication often remained possible for many years. Paranoid ideation was found in 39% of the patients, epileptic seizures (starting often at an early stage) in 32% and extrapyramidal features in 48%.

Lauter compared EOAD cases to 52 AD cases with onset after age 70 and autopsy proven [126]. The mean age at onset for EOAD was 73.3 and the mean duration was 3.5 years. Of the 52 cases, 85% showed arteriosclerotic changes of brain vessels, including focal ischemic lesions in 13 cases. A comparison between EOAD and LOAD found that memory failure was just as common, but that confabulation, delusions and disturbances of the sleep-wakefulness rhythm were more prevalent in the LOAD group. The analysis indicated a clinical continuum, with

increasing prevalence of dysgnosia, dyspraxia, neurological signs and epileptic seizures in EOAD groups. These age-related clinical differences are supported by rCBF studies showing temperoparietal flow decrease in EOAD, as well as frontal and potential rCBF reduction in LOAD [257].

A prospective study of AD with post mortem verification reported similar clinical patterns dominated by dysmnesia, dysphasia, dyspraxia and spatial disorientation in both groups, while confabulation, restlessness and agitation were somewhat more prevalent in the LOAD group [132]. Moreover, confusional episodes, fluctuating course and hallucinosis were more common in the LOAD group, while grand mal, myoclonia and increase of muscle tone were found to the same extent in both groups. A study by Mayeux et al of 121 consecutive patients with AD found an association between earlier onset on one hand and severe intellectual decline, functional impairment and reports of myoclonus on the other [128]. A study by Sevush et al of 150 clinically diagnosed AD patients found significant correlations between early onset and reduction of spontaneous speech, reading and writing, as well as right-left disorientation, while late onset was associated with dysfunction of long-term memory, orientation and object naming [258]. A study by Lawlor et al also associated greater language and praxis difficulties and depression with early onset [259]. However, a study by Selnes et al of 133 patients with possible AD could not confirm this difference in language dysfunction between EOAD and LOAD [260].

However, age at clinical onset is difficult to estimate in retrospect. A CERAD analysis by Koss et al of 421 patients with probable AD compared those first studied before age 65 (n = 98) to those with clinical onset after age 65 (n = 323) [261]. No autopsy data were available, but clinical follow-up and a standardized procedure for clinical and neuropsychological assessment were employed. A larger percentage of early onset cases had problems with language, concentration and clock drawing, whereas a greater percentage of patients in the late onset group were found to have problems with memory and/or time orientation. The main conclusion was that late entry AD patients are difficult to recognize on clinical grounds. A study by Imamura et al of 150 consecutive patients with mild to moderate AD who had been diagnosed clinically found that those

with EOAD performed a good deal more poorly on the word comprehension and sequential command subtests than those with late onset, who performed more poorly on the picture naming test [262].

Some authors have reported more severe neuropathological changes in EOAD than in LOAD [263–265]. A clinical comparison by Blennow et al found that a symptom profile that included parietal predominance was associated with lower age at onset and the presence of clinical vascular features [266]. However, autopsy proof was not available. This study, as well as subsequent publications by the Göteborg study group, also highlighted the importance of subcortical symptoms and neurological features in AD. The frontal severity of symptoms was related to the severity of the disease. That is in agreement with neuroimaging studies that used PET [267], SPECT [268] and EEG analysis [269,270]. The age-related decrease in focalization is also in agreement with neuropathological studies [87,116,119,120].

Brun and Englund pointed out early the clinical importance of ischemic WMD in patients with clinical and neuropathological evidence of AD [119]. WMD is found in both EOAD and LOAD, with a clinical coupling to arterial hypotension and orthostatism, often (though not exclusively) in patients previously treated for arterial hypertension [252]. Blennow and Wallin suggested a heterogeneity of clinically diagnosed AD in one earlier onset group with severe memory dysfunction and temporoparietal involvement, as opposed to LOAD, which had a less focalized symptom pattern [271]. Wallin and Blennow confirmed a high prevalence of extrapyramidal signs in both EOAD and LOAD, with a positive correlation between the prevalence of these symptoms and the degree of dementia [272].

There are both similarities and differences between rCBF in EOAD and LOAD. Twentyeight EOAD and 27 LOAD cases were studied and compared to 22 FTD and 44 VaD cases that had been diagnosed clinically in a prospective study of dementia. There was a significant focal flow decrease in the temporoparietal association cortex for both AD types, with a significant frontal flow decrease in the frontal cortex for LOAD [273].

Frontal lobe features in AD

The predominant symptom pattern in AD of memory failure, aphasia, apraxia, agnosia and spatial disorientation is strongly related to the distribution and severity of degenerative changes. However, several studies have shown clinical heterogeneity related to age at onset, disease duration, genetic factors and pathological correlates such as frontal lobe involvement and incomplete white matter infarctions [160].

Frontal lobe symptoms, including executive dysfunction, are often reported in AD [274]. Frontal lobe features, such as disinhibition and euphoria when present, seem to be associated with later onset, longer duration and slower rate of progression [123,275]. However, most clinicopathological studies of AD find a relative sparing of frontal lobe cortex and anterior cingulate gyrus [87,116], while few reports on AD indicate pronounced frontal lobe involvement. Brun and Gustafson published data on four female AD patients with a mean disease duration of 9.5 years at death, all with pronounced frontal lobe involvement [276]. The Alzheimer encephalopathy in these cases was pronounced in the limbic and temperoparietal areas, and even more so in the frontal lobes, with accentuating widening of sulci and the ventricular system. The clinical picture in two cases was that of a rapid progressive course at an early stage. Early dysmnesia dominated in three cases, and all patients developed dysphasia, dyspraxia and dysgnosia, three of them extrapyramidal signs as well. Loss of insight was prominent in three cases, with euphoria observed in two cases and emotional lability and inadequate laughing in two cases. These symptoms, indicative of frontal lobe involvement, were in close agreement with the rCBF pathology.

A representative sample by Gislason et al of 451 85-year-old patients diagnosed frontal lobe syndromes in 86 cases (19%) [277]. Seventyfive (87%) of them met the DSM-III-R criteria for other types of dementia, mainly AD (50.7%) and VaD (49.3%). Thus, frontal lobe features were common in AD for this age group.

A complicating factor for understanding clinical and pathological correlates is the presence of WMD in the majority of AD cases, somewhat more common in LOAD [119]. AD and WMD patients with incomplete

infarction show a less focal temporoparietal pattern and more symptoms of vascular type, such as vertigo, fainting and clinical fluctuations. In addition to arterial hypotension, cardiovascular disease occurs more frequently in these cases [120].

Psychotic features in AD

ICD-10, DSM-III and DSM-IV all suggest subclassification of AD with respect to the presence of other symptoms, such as hallucinations and delusions. Psychotic features are common in AD [152,278]. Alzheimer's first case showed delusions of jealousy as an early symptom and auditory hallucinations later in the course of the disease. Hallucinations and illusions are reported in about 25% of EAOD cases and 50% of LOAD cases [279]. Psychotic symptoms in the EAOD group appear to correlate more strongly with the severity of cognitive deterioration, while delusions in LOAD cases are associated more with hallucinations and confusional traits. Functional brain imaging in AD has revealed a complex relationship between deceptions and delusions on the one hand and cortical and subcortical dysfunction on the other [279–283].

A four-year follow-up by Wilson et al of 410 people with probable AD that had been diagnosed clinically reported hallucinations in 41% and delusions in 55% of the cases [284]. Hallucinations, but not delusions, were associated with a more rapid decline on each cognitive measure. Delusions were generally more common than hallucinations, which occurred more sporadically in AD. Ballard et al reported hallucinations in 27% and paranoid delusions in 44% of 48 AD cases [285]. A study by Burns of 78 patients with probable AD reported auditory hallucinations in 9.5% of the cases, visual hallucinations in 12.9% and delusions in 15.7% [152]. The hallucinations were not significantly related to the severity of dementia, although subjects with very mild dementia did not experience auditory hallucinations. Burns also found that 12.5% misidentified other people and 4% misidentified their own reflection in a mirror (mirror sign) [286]. A study by Mendez suggested that person misidentification in dementia begins with an altered sense of familiarity for a familiar person [287]. Drevets and Rubin studied delusions, misidentifications and hallucinations throughout the course of LOAD [157]. The rates of psychosis ranged from 42% to 84%, while psychotic symptoms

were associated with accelerated cognitive deterioration but not with increased mortality. A review by Wragg and Jeste of 21 studies reported the prevalence of delusions during the course of AD ranging from 10% to 73% and of hallucinations from 21% to 49% [288]. The presence of psychosis has been associated with more advanced age [289,290].

The development of hallucinations and delusions in patients with AD show a complex etiology and often seem to be precipitated by sensory impairment, such as blindness, deafness and inadequate polypharmacy [279]. A correlation between psychosis and frontal lobe syndromes has been described in AD [279,291].

The accumulated prevalence of psychiatric symptoms during the course of AD has been studied under various conditions. Johansson and Gustafson followed a sample of dementia patients treated at a psychogeriatric day hospital by means of a standardized clinical evaluation during an average of 21 ± 14 months [292]. The clinical features were related to clinical diagnoses, and their first appearance was early, late or intermittently during the course of dementia. Delirious episodes characterized by periods of markedly impaired cognition, disorientation and clouding of consciousness were the most prevalent reaction types reported in all patients with AD or mixed AD-VaD and in 89% of patients with VaD. This high prevalence was probably due to close communication between the patient and the contact person, allowing for early recognition of clinical changes and the appearance of new symptoms, even those of short duration. Delirious episodes in AD are probably more common than generally thought and have a heavy impact on the patient's cognition and independence. The assessment of psychotic features in AD should also consider the complex interaction between the patient, family and clinical setting, as well as the current pharmacological treatment and somatic illness. Misidentification of friends and relatives was reported in 50% of AD patients and 1/3 of patients with mixed AD-VaD. Ten percent of AD cases, both with and without vascular signs, failed to recognize themselves in the mirror (mirror sign). Visual hallucinations were prevalent in all dementia groups, most prevalently in AD (53%). Auditory hallucinations were reported in only a few

cases. Delusions, defined as ideas of persecution ranging from pronounced distressfulness to fixed delusions, were prevalent and reported in about 2/3 of all AD and mixed AD-VaD cases. This study also indicates that emotional and behavioral symptoms that appear during the course of dementia may well be dealt with by the limited use of psychotropic medication at the day hospital, which provides flexible care and support for AD patients living at home [292].

Deutsch et al studied the frequency and type of psychotic symptoms in patients with probable AD (n = 170) [293]. Delusions were reported in 43.5% of the cases, most frequently of persecutory type (73%) and ideas of reference (14.9%) and 29.6% of the patients showed physical aggression, frequently preceded by delusions and misidentification. Delusions were significantly associated with physical aggression but accounted for only 3.5% of the variance. Among misidentifications, the idea that the house was not the patient's was present in 51%, of cases, that strangers were living in the house in 29,4% and that the reflection in the mirror was someone else (mirror sign) in 21.6%. An interesting finding was that episodes of physical aggression occurred during interactions of caregivers with the patient and that verbal aggression occurred in situations where the patient was being instructed by the caregiver. Several studies of AD have reported certain psychotic features, such as "the mirror sign", "the TV sign" and Capgras syndrome, probably with a more specific association to temporoparietal cortical dysfunction and the later stages of the disease [294].

Bylsma et al analyzed the relationship between delusions and patterns of cognitive impairment in 180 patients with probable AD [295]. They assessed the clinical features with the Columbia University Scale for Psychopathology in Alzheimer's Disease (CUSPAD). The study showed an association with functional impairment, although deluded patients showed better attention than non-deluded patients. Stern et al assessed functional abilities with the BDS [296]. Fortyfive patients (25%) showed delusions (theft or abandonment). There were no demographic differences between deluded and non-deluded patients. The delusions were most often described as simple, non-systematic and unelaborated. It has been suggested that delusions in AD are caused by efforts to understand

and interpret anomalous perceptual experience. Moreover, visual hallucinations are significantly associated with impaired visual acuity and cognitive impairment [297]. Delusions, especially paranoid, in dementia are inversely related to cortical atrophy and thus appear to require a relatively intact cerebral cortex [204,298,299].

Aarsland et al reported verbal aggressiveness, physical aggression or both in 35% of 75 cases of probable or possible AD [300]. These behaviors were usually rated as being of mild or moderate severity. There was no association with clinical findings of depression, but psychosis predicted 22% of the variations in aggressive behavior. No relationship was identified between increasing severity of dementia and aggressive behavior. When it comes to individual cases, the impact of premorbid personality straits, medication, psychological environment and concomitant medical illness must be considered [301].

Hirono et al reported evidence of delusions or hallucinations in 51.8% of 228 patients with AD [302]. Patients with Parkinsonism were excluded from the study, 94 patients had delusions only, 3 had hallucinations only and 21 had both. Eightyeight patients had delusions of theft, 10 patients had delusions of being conspired against, 58 patients had misidentifications and delusion, 42 had delusions that someone was in the house, 11 had delusions that the house was not their own and 6 had delusions that television personalities were present in the home. Sixteen patients had visual hallucinations and 14 had auditory hallucinations.

Awareness and insight

The retention of awareness of deficits by AD patients is diagnostically significant and helpful in early diagnosis, as well as in distinguishing among subtypes of dementia. Early loss of insight tends to suggest FTD rather than AD [189,193,303–306]. Insight is a complex concept that consists of several constructs, including the ability to re-label certain mental events as pathological, the recognition of disease and the degree of compliance with treatment [179]. Using the three-stage model of AD, Schneck et al suggested that insight was retained at the initial forgetfulness stage, lost during the early confusional phase and absent in the final dementia stage [177]. A study by Verhey et al of 103 AD cases found that

impaired insight correlated significantly with GDS scores [307]. Mullen et al [179] argued that the co-occurrence in AD patients of depressed moods with preserved insight is readily understandable [308]. Depressed mood is related to increased awareness of functional decline, and depressed AD patients tend to rate their memory functions lower than do non-depressed patients [180].

An AD patient's awareness of different types of deficits varies over time [178], presumably influenced by premorbid personality factors and defense mechanisms [309,310]. In agreement with Green et al [311], a study by Ott et al [178] of 26 patients with early AD concluded that disruption of memory awareness may be more severe than disruption of the ability to monitor more functional aspects of behavior. No relation was found between unawareness of dementia and the presence of depression. Thus, AD patients have the capacity to minimize their functional deficits. Weinstein et al pointed out that, despite assertions of denial in formal interviews, patients frequently exhibited awareness of their impairments in other contexts and situations [312].

Dialysis dementia of Alzheimer type

The third most common element on Earth, aluminum, has known neurotoxic effects and is suspected to be involved in the etiopathogenesis of AD. In the 1970s, Crapper et al reported an elevation of brain aluminum in patients with AD [313]. Both long-lasting and reversible dialysis encephalopathies with elevations of aluminum, senile plaques and neurofibrillary tangles have been described [314,315]. Dialysis encephalopathy syndrome is characterized by cognitive decline (memory failure, lack of concentration and spatial dysfunction), speech disturbance (stuttering-like dysarthria and nominal dysphasia), motor symptoms and signs (dyspraxia, tremor, multifocal myoclonia), epileptic seizures and atypical EEG (general slowing that includes episodic high-voltage bilateral 2–3 Hz activity with bifrontal dominance) [316–318]. Thus, striking similarities exist between clinical and neuropathological findings in both AD in general and dialysis encephalopathy in particular. However, the accumulation of aluminum in degenerating neurons presently appears to be secondary to the degenerative process of AD.

AD in Down's syndrome

Struwe published evidence of an association between Down's syndrome (DS) and AD in 1929 [319], and Jervis suggested in 1948 [320] that a large percentage of DS patients developed an Alzheimer encephalopathy after age 40. There is a strong neuropathological and clinical similarity between EOAD and Down's syndrome dementia (DSD) [146,321]. The development of the Alzheimer pathology in DS seems to start early [322], suggesting that the dementia has a long preclinical stage [322,323]. Prevalence figures for AD in DS vary from 15% to 51% for adult patients [324,325]. A prospective study found that the prevalence of dementia was 8% from age 35 to 40 and 55–75% above age 50 [326]. Epidemiological studies have indicated a significant association between AD and family history of DS [327,328]. DSD develops slowly, albeit sometimes more rapidly than AD in non-DS cases for similar age. Memory failure, disorientation, a reduction of language functions, myoclonic twitchings and generalized epileptic seizures are reported. There is often a temporal association in DSD between the appearance of the first signs of cognitive decline and the onset of epileptic phenomena. Few prospective clinical studies of DSD have been conducted. A longitudinal study of 22 DS patients indicated a pronounced cognitive decline of AD type above age 40 [150]. Dalton et al found a selective reduction of short-term visual retention above age 35 [329]. Spatial disorientation and receptive dysphasia were early indications of a cognitive decline – as well as a progressive rCBF decrease in the parietal cortex from previously normal rCBF results – in elderly DS patients [150]. The EEG abnormality of progressive slowing is very similar to that in non-DS AD. However, clinical evaluation of DS patients is difficult due to their poor verbal communication, including dysarthria. The arterial mean blood pressure is low, below even that of manifest non-DS AD patients. Thus, hypertension is a less convincing vascular risk factor in DSD [330].

Clinical features in familial AD

Familial aggregation of AD has been recognized for many years. However, it has been difficult to discriminate for, given that such aggregation reflects random clustering due to high prevalence of AD and non-random clustering due to exposure to shared environmental risks or inheri-

ted factors [331]. Several large multigeneration AD kindreds have been reported ever since Schottky published the first kindred of this type in 1932 [332]. Age at onset in the large FAD kindred varies from family to family, with a range of mean age at onset from 30 to 80, while the duration of the disease is relatively consistent, regardless of age at onset. The mean duration was 8.8 ± 4.4 years in 24 kindreds evaluated by Bird et al [333]. Lopez et al described a large kindred in which 128 individuals were identified [283]. Six with EOAD were autopsy proven, 93 had probable EOAD and 29 had possible EOAD. The most common initial symptoms in the Lopera family were progressive memory failure, language difficulties, personality changes and, later on, gait difficulties, seizures and myoclonus. A common feature of the affected patients was severe headache, both preceding and during the course of the disease. Only 2 of 12 non-affected subjects from the largest families reported headache. That is consistent with the findings in other families [334].

Clinical differences between FAD and SAD have been reported, although with inconsistent results. Duara et al compared 113 FAD subjects with a mean age of onset of 70.6 to 198 SAD subjects with a mean age of onset of 73.1 [335]. Duration of the disease was similar (4.1 and 3.9 years respectively). There were no differences between FAD and SAD with respect to praxis, language, balance, seizures, hallucinations, depression or delusions. Moreover, no differences in any of the MRI variables of ventricular volume and subcortical white matter lesions appeared among the 242 subjects. Both FAD (n = 47) and SAD (n = 50) cases showed a metabolic reduction in the parietal and temporal lobes. These findings do not support the notion that FAD is a different disease than SAD, although there was a relatively poorer language performance in SAD patients and a positive association between EOAD and longer duration. Luchins et al compared the clinical findings in 172 FAD and 290 SAD cases without identifying any significant differences in age at onset, duration, gender, aphasia, dyspraxia or family history of DS [336]. However, they found an association between familial aggregation and a more rapid deteriorating course of AD. That was not confirmed by Haupt et al, who compared 23 FAD patients with 67 SAD clinically diagnosed patients [337]. A Swedish family, reported first in 1946 and followed up in 1998, with six affected cases and four generations involved

showed similar age characteristics and clinical manifestation. The clinical picture was typically temporoparietal. Other predominant symptoms were logoclonia, myoclonic twitchings, major motor seizures, psychomotor slowness with a stiff stooped gait and rapid weight loss [145,338]. The symptom pattern was explained by the consistent and severe involvement of cortical and central gray structure and linked to chromosome 14. Holmes and Lovestone comparing familial and sporadic LOAD did not find any major clinical differences, with the exception of early age at onset in the familial group [339]. Matsubara-Tsutsui et al described a family presenilin-1 mutation and a somewhat atypical AD clinic [340]. AD affected six individuals in three generations. Early symptoms were memory impairment, spastic paresis and apraxia.

Dementia with Lewy bodies (DLB)

The clinical phenotype of DLB shares many features with dementia in Parkinson's disease (Parkinson's disease with dementia (PDD)) and AD. A fundamental question concerns the clinical implication of Lewy bodies in different cortical and subcortical regions. Some studies have found no correlation between regional densities of cortical Lewy bodies and clinical symptoms of DLB [341]. Other studies have identified significant correlations between LBD density, especially in the temporal neocortex, and cognitive impairment [342] in PD, as well as high LBD density in amygdala and parahippocampus, associated with visual hallucinations [343]. The presence of α-synuclein and Alzheimer encephalopathy suggests the possibility of a combination of pathologies behind the clinical manifestation. The clinical picture of DLB that includes extrapyramidal signs, fluctuations, visual hallucinations, neuroleptic sensitivity, multiple falls, auditory hallucinations, delusions, syncopy and transient loss of consciousness has been related to pathological data in most cases studied post mortem. Whole brain semi-serial sectioning shows that the neuropathological picture is complex, varying among individual cases that sometimes exhibit a very similar clinical appearance. In addition, there are indications that the clinical picture is influenced by sensory disabilities, such as deafness and reduced vision, as well as low and labile blood pressure [344].

Ditter and Mirra studied 20 cases of AD, 11 of which showed neuropathological features of PD [232]. Extrapyramidal signs were more common in PD pathology patients ($p < 0.05$). Rigidity occurred in 80% of patients with PD pathology but only 14.3% of those without PD pathology ($p < 0{,}01$). In the PD group, bradykinesia and masked face were always observed in association with rigidity. Neither tremor nor myoclonus was observed in any of the patients.

Chapman et al reported a significant association between visual hallucinations, visual acuity and verity of cognitive impairment in 50 patients with probable AD [297]. Cataracts were significantly associated with visual hallucination, and no patients with normal acuity had hallucinations.

Differential diagnosis against VaD and non-Alzheimer's degenerative dementia

Perusini pointed out clinical differences between AD and VaD, and the early descriptions of Pick's disease touched on the possibility of differential diagnosis on clinical grounds [57,61,62,65]. Recognition of AD was based on the patient's clinical similarity to descriptions provided by leading clinicians like Sjogren et al [136] and Mayer-Gross et al [1]. Differentiating among dementias presents many difficulties, especially at an early stage, and no single available diagnostic technique can solve all of these problems. No mental symptoms in and of themselves are pathognomonic of AD or any other type of dementia. The symptom constellations, the timing of the disease's appearance and the clinical course are what is important. Thus, the clinical diagnosis of AD should rely on a broad assessment of both psychiatric and neurological features.

The introduction of MID was soon followed by the presentation of the Ischemic Score (IS) rating scale by Hachinski and coworkers [345]. The IS, which is based mainly on the clinical description of arteriosclerotic psychosis [1], has a scoring procedure thought to correlate with cerebral ischemic changes found in autopsy studies [346,347] (Appendix 2.9).

The IS was originally validated against rCBF findings in dementia, yielding a bimodal distribution with patients classified as MID scoring ≤7 and those classified as AD scoring <4. The wide use of the IS in research and clinical work may justify further clarification of some of the items used. "Fluctuating course" refers to varying severity of the symptoms of dementia during a particular day and among different days, as well as typical episodic return to a relatively efficient level [35]. This episodic improvement in VaD, which is also found in delirious states, probably points to the potential viability of dysfunctional brain regions. "Nocturnal confusion", which is observed in all types of dementia and delirium, is probably too non-specific to offer significant discriminative diagnostic value [303,348]. "Depression" refers to a fairly stable lowering of mood tone, uninfluenced by the presence of "emotional incontinence" (item 8 of the IS). "Somatic complaints" refer to symptoms such as headache, giddiness, tinnitus, general malaise and precordial discomfort. Evaluation of the various IS items is heavily dependent on the reliability of available data, as well as routines for somatic investigation and documentation.

The clinical differentiation between AD and VaD (and other primary degenerative dementias) based on IS has been validated against diagnoses based on EEG and angiography [349], rCBF measurements [350,351], clinical diagnosis supported by EEG and CT findings [348], and post mortem diagnosis [303,352,353]. Rosen et al proposed that the items of fluctuating course, nocturnal confusion, relative preservation of personality, depression and evidence of associated arteriosclerosis be excluded from the original IS and suggested a modified version with a diagnostic cut-off point at a score of 6 [352]. By contrast, Molsa et al found that the items of stepwise deterioration, fluctuating course, relative preservation of personality, emotional incontinence, history of stroke and focal neurological symptoms had the highest discrimination value between AD and VaD in 85 dementia cases diagnosed post mortem [353]. On the other hand, only 1 out of 6 mixed cases were correctly identified. The mean ischemic score was 2.8 in 28 AD cases and 8.9 in 11 MID cases.

Gustafson and Nilsson applied the ischemic score to clinical data from a longitudinal study of early onset dementia [303]. IS was combined with

two other rating scales, one for diagnosis of AD, the other for identification of Pick's disease and other types of FTD. The homogeneity of the IS was tested using item analysis of data from 57 patients (33 deceased, 28 of whom with post mortem diagnosis) [354]. The AD scale includes twelve features that describe the clinical picture of AD, whereas the FTD scale is based on 9 items that partially overlap those of the AD scale. An AD score greater than 5, particularly above 8, points to an AD diagnosis. Moreover, the AD score correlates significantly ($p < 0.001$) with the duration of dementia in presenile AD. The 9-item rating for diagnosis of FTD is based on the early clinical picture of FTD. Thus, there is no correlation between the score and duration. The two rating scales are recommended for use in combination with the IS. Differential diagnoses, which are based on the scoring profile, have been validated against both rCBF data [350] and autopsy findings [78].

Erkinjuntti analyzed the validity of the IS for differential diagnosis between AD and VaD, confirming that "abrupt onset", "stepwise deterioration" and "fluctuating course" clearly distinguished AD from VaD [355]. Equally useful were "history of stroke," "focal neurological symptoms and signs" and CT evidence of vascular lesions, whereas nocturnal confusion and depressive symptoms did not contribute to differential diagnosis. Fischer et al studied the sensitivity and specificity of Hashinski's IS in patients with AD, MID, mixed dementia and Pick's disease, using neuropathological diagnosis as the point of reference [356]. The results indicated that IS is a sensitive test for VaD and that the scoring as modified by Rosen et al did not improve diagnostic accuracy [352]. On the other hand, the IS was insufficiently sensitive to diagnose primary degenerative dementia, and IS labeled 21% of these patients as having a vascular etiology. The authors warned against the uncritical application of IS to large samples in epidemiological studies.

In 1997, Moroney et al published a large meta-analysis of the Hashinski IS in 312 cases with pathologically verified dementia, AD, MID and mixed type [357]. Using the standard cut-offs, the scale was highly accurate (sensitivity of 89% and specificity of 89) in discriminating between MID and AD. Although nocturnal confusion and depression were non-discriminating, the results suggest that the scale performed well in some

respects. The conclusions concerning AD cases were somewhat limited by the fact that five of the six centers involved did not specify the extent of white matter changes in relation to the diagnosis of AD and only one center examined the entire brain histologically.

Alafuzoff et al showed the limitations of the DSM-III criteria for differential diagnosis between AD and VaD [358]. The post mortem verification rate was only 52% for AD and 39% for MID. That was ascribed to insufficient criteria for the diagnosis of mixed VaD and AD. A study by Risse et al of 25 patients with DSM-III criteria for primary degenerative dementia and NINCDS-ADRDA criteria for probable AD found a non-AD post mortem in no fewer than 32% of the cases [359].

There are few studies of clinical differentiation based on combinations of various diagnostic rating scales. Hooten and Lyketsos [188] analyzed the AD and FTD scales [303] using the original items. They tested the scales in conjunction with a complete neuropsychiatric examination, including an executive interview, mini-mental state examination and informant-based questionnaire. The conclusions for the AD scale were a sensitivity of 0.983 and specificity of 0.824. Moreover, with an increasing cut-off score, sensitivity decreased and specificity increased in differentiating AD from FTD. Higher scores were more indicative of AD. The sensitivity of the FTD scale was high at 0.949, with a specificity of 0.825. As the cut-off score increased, sensitivity decreased, while specificity increased in differentiating FTD from AD. Higher FTD scores were more indicative of FTD. The cut-off score on the AD scale was 5.25, while the cut-off score on the FTD scale was 4.75, almost identical to the original scoring procedure [303].

Differential diagnosis of AD against FTD is often possible to achieve based on well-defined clinical criteria, neuropsychological testing and brain imaging. Some of these clinical differences are clearest at an early stage of the disease. The initial stage of FTD is dominated by emotional and personality changes, loss of insight, disinhibition, progressive reduction of speech and memory failure. Severe dyspraxia and spatial disorientation develop comparatively late. The rating scale for differential diagnosis among AD, Pick's disease and VaD have been analyzed

and validated against rCBF data, autopsy findings and cerebrospinal neurotransmitter levels. In 1987, Gustafson compared clinical findings in FTD and AD patients of similar age and found significant differences [200]. Early dysmnesia, dyspraxia, spatial disorientation, logoclonia, increased muscular tension, grand mal and myoclonia were more prevalent in AD. Early loss of insight, restlessness, stereotyped speech (palilalia), mutism in combination with relatively preserved receptive speech and early normal EEG were more prevalent in FTD.

The Lund-Manchester consensus is recommended as a guideline for clinical recognition of FTD, but not as a rating scale for differential diagnosis [67]. Swartz et al used a multivariate step-wise discriminant analysis and largely confirmed the validity of the clinical features [189]. Miller et al evaluated the Lund-Manchester research criteria for FTD [306]. The study showed that "loss of personal awareness", "hyperorality", "stereotyped and perseverative behavior", "progressive reduction of speech" and "preserved spatial orientation" differentiated 100% of FTD and AD subjects. Items related to physical affect findings did not differ between FTD and AD. Loss of personal awareness, dietary changes, perseverative behavior and reduction of speech were the most clearly differentiating items. Bathgate et al used a semi-structured questionnaire for differential diagnosis among FTD, AD and CVD [192]. The behavioral changes that strongly differentiated FTD from AD were loss of emotions and insight, selfishness, disinhibition, personal neglect, gluttony, sweet food preferences, wandering motor and verbal stereotypies, loss of pain, echolalia and mutism, all of them more prevalent in FTD. Irritability, hypersexuality and hypersomnia did not discriminate. Ikeda et al confirmed previous findings that changes in eating habits was significantly more common in FTD than AD [360]. Nedjam et al found that FTD patients confabulated significantly more than AD on episodic memory tasks and a frontal executive task [361]. However, there were no correlations between their performance on the frontal executive task and the tendency to produce confabulation. De Deyn et al [362] recently presented a behavioral assessment scale that differentiates FTD from AD based on observational studies [67,68,200]. The clinical and behavioral assessment scale offers reliable discrimination of FTD from AD.

The diagnosis of AD is mainly clinical, supported by various diagnostic tools – post mortem, pathological or a combination of the two. Various clinical publications have studied the validity of different sets of clinical criteria vs pathological diagnostic criteria. Nagy et al compared NINCDS-ADRDA and DSM-III-R criteria on 73 consecutive cases that had come to necropsy in the OPTIMA-study [363]. The sensitivity of the individual clinical criteria was rather low, ranging from 35% to 56% regardless of the histopathological protocol used. A high detection rate for AD was obtained when the cohorts of NINCDS-ADRDA "possible DAT" and "probable DAT" were combined. Sensitivity exceeded 90% independent of histopathological protocol. However, specificity was a poor 40–61% for such a combination. On the other hand, the predictive value of a diagnosis ranged from 89% to 100%. That suggests that the diagnostic criteria should be recommended for research purposes, albeit with caution given that the negative predictive value in clinical practice may be relatively poor.

The NINCDS-ADRDA criteria for AD were originally formulated with the aim of differentiating between AD and VaD. A study by Varma et al of 56 patients with post mortem diagnoses found a high sensitivity (0.93) for probable AD, but also a low specificity (0.23) given that 77% (n = 26) of pathologically confirmed FTD cases met the NINCDS-ARDRDA criteria for AD [364].

Kosunen et al compared clinical diagnosis of AD based on NINCDS-ADRDA [365], or VaD according to DSM-III [79], with post mortem diagnoses based on the CERAD-criteria [366]. Ninety-six percent of 28 probable AD patients met the definite (pathological) AD criteria. By contrast, clinically diagnosed VaD patients frequently showed coexistent AD changes, while pure VaD was rare.

Ikeda et al reported several significant changes in food preferences, appetite and eating habits in FTD but not in AD patients [360]. There were 43 AD patients with a mean age of 68 and mean MMSE score of 20.6, as well as 23 FTD patients with a mean age of 61 and mean MMSE of 23. Swallowing problems were rare at this stage of dementia, but FTD patients showed both loss of and increase in appetite, overeating and

other eating changes. They also liked sweet food more than before, as well as drank more soft drinks, tea, coffee and alcohol. Other eating changes included tendencies to eat in a stereotyped way and order and at the same time of day. Among other oral changes were tendencies to overfill the mouth, eat non-edible foods and smoke more heavily [227].

Attitudes toward dementia

Attitudes of the general public towards dementia and people with dementia have changed over time, especially the past 30 years. Weekly magazines, daily papers, novels, radio and television have devoted increasing attention to the causes and treatment of dementia, particularly AD. These reports often reflect great interest and knowledge, stressing the magnitude of the problem and the importance of new research findings, often predicting a major breakthrough in the near future.

Dementia was earlier defined as progressive and irreversible with little hope for the patient and low expectations by the doctor. However, knowledge among the general population, as well as clinical experience, has changed attitudes toward the diagnosis and treatment of dementia conditions. In other words, dementia has become treatable.

Anonymity is a crucial element of the stigmatization of people with dementia. Thus, it is important that both famous and ordinary people step forward to tell about themselves or a relative with the disease. Rita Hayworth was diagnosed with AD, and her daughter made a major contribution to the establishment of Alzheimer Disease International (ADI). The importance of Ronald Reagan's announcement that he had AD cannot be overestimated. When Swedish reporter Gunilla Myrberg interviewed the wife of an EOAD patient on the radio in 1985, there was a massive and unexpected effect from listeners all over the country. As a result, the Swedish Alzheimer Association got off to a flying start in 1986 and the interviewee was the first chairperson. Maj Ödman, another familiar voice on Swedish radio, edited a small informational publication in 1988 entitled "A neglected national disease. Present debate on Alzheimer's and other dementia diseases" [367]. A 1987 obituary suggested for the first time that money be donated to Alzheimer's research in memory of the deceased. *To Become the Mother of Your Mother*, a 1988

book by well-known author Maj Fant, described her mother's progressive dementia, arguing for better understanding and care of everyone with the disease [368]. In 1990, prominent politician Gösta Bohman wrote about his wife's illness in *The Saga of Gunnel* [369]. Ulla Isaksson, one of Sweden's leading writers, published a novel in 1994 based on her relationship with Erik Hjalmar Linder, her husband and an AD patient. Entitled *The Book about E*, it was later adapted for the screen [370].

Current literature is paying a good deal of attention to dementia, introducing new and different perspectives, such as small children's observations and reflections when a grandparent or other close relative becomes forgetful or absent minded. The lack of information on dementias in earlier standard Swedish encyclopedias is surprising. However, AD, FTD, VaD and other dementias have made their appearance more recently in the *National Encyclopedia* (1989), *Bra Böckers stora läkarlexikon* (1997) and children's literature. September 21 is now International Alzheimer's Day.

General attitudes toward dementia are changing, although not as rapidly as had been expected. Only a minority of the estimated 25 000 Swedes who develop dementia each year are properly examined and diagnosed. That cannot be due to a lack of financial resources. A more likely explanation is skepticism about the benefits of early diagnosis and drug treatment [371]. Resources and principles for clinical diagnosis of dementia vary widely within Sweden, even when comparing neighboring health. Hopefully, such inequalities reflect ignorance and lack of training rather than unfavorable attitudes toward dementia patients.

With the exception of cancer, few diseases have fascinated professionals and laypeople as much as AD. That is probably due to growing awareness that people, both they themselves and their relatives, run a relatively high risk of developing the disease. Several studies have shown the difficulty and ambivalence that doctors face about disclosing a dementia diagnosis to patients and families. De Lepeleire et al reported that 36% of 521 general practitioners always or usually disclosed the diagnoses [372]. Seventy-five percent of the doctors saw the benefits of adopting such an open, rationalistic approach. Ouimet et al studied this topic

from the point of view of relatives [373]. Of 204 interviewees age 65 and older, nearly all would want to know if they were diagnosed with dementia. Moreover, 78% would want disclosure for their potentially afflicted spouses if medication was about to become unavailable. That increased to 97% if medication was available, illustrating the impact of potential treatment on attitudes toward dementia. Among other determinants of such attitudes are access to medical services, as well as the initiatives and financial resources that have been devoted to research. Lowin et al calculated the UK's direct costs for AD at £7–9 billion, substantially more than for stroke (£3.2 billion), heart disease (£4.05 billion) and cancer (£1.6 billion, including informal care) [374]. When it came to research, the UK spent 75% as much on AD as stroke, 10% as much on AD as heart disease and 3% as much on AD as cancer.

AD – clinical and pathological correlates

AD – a strictly neuropathological entity?

The initial descriptions of dementia cases, which involved clinically observed mental deterioration and post mortem identified brain changes [56,94,95,113], are still valid in a simplified sense. Subsequent works have refined and expanded upon rather than changed the accumulated concept of AD [65,115,136]. Thus, some of the cardinal microscopic features are those described in the very first works, namely neurofibrillary tangles (NFT) and senile or neuritic plaques (SNP), the presence of which specifically marks the disease [108,375–379]. NFTs consist of filaments of the microtubule-associated protein tau in its hyperphosphorylated form [380]. The complex protein is shaped as paired helical filaments, which build the neurofibrillary tangle along with straight filaments. The protein is visualized for microscopy by means of silver stainings. It is seen as filling the neuronal soma and later as dispersed in fragments throughout the neuropil [376]. The number of NFTs has been shown to correlate significantly with the severity of symptoms and to increase with AD progression [377,381]. Based on a large volume of studied material, Braak and Braak demonstrated the neuropathological differentiation of progressive AD in 6 defined stages, with the brunt of early pathology appearing in the hippocampus [118]. However, NFTs

also occur in elderly without dementia, especially in the hippocampus [382,383]. Thus, when it comes to NFTs, the distinction between normal aging and AD is quantitative and region-associated rather than qualitative – the matter remains unresolved. Nevertheless, the finding of neocortical NFTs and a sufficient number of amyloid plaques in combination is diagnostic for AD.

SNPs vary in morphological shape and composition. With contributions from degenerated neuritis that are prominent to a greater or lesser extent, degenerated glial processes and microglial constituents form a nest around a proteinaceous core of amyloid fibrils [384].

Deposition of the beta-amyloid (ßA4) protein in neuritic plaques and meningocortical blood vessels is a regular feature of AD [385,386]. It is thought to play a major, if not pathogenetic, role in the pathology of AD and regarded as one of the specific components that adhere to the pathology criteria for AD diagnosis [378,387]. However, the primary ßA4 load of soluble and insoluble protein seems to vary in severity and extent, not strictly coinciding with the severity of other neurodegenerative disease parameters.

The core amyloid consists of ßA4, originating from proteolytic cleavage of the transmembranous glycoprotein amyloid precursor protein, for which the normal appearance, while not the function, is known. Although it has been established that an AD diagnosis is consistent with the presence of SNPs [56,378,387], SNPs are also common in the brains of elderly without dementia [388,389], exhibiting higher visibility than immunohistochemical and silver [383], as well as conventional hematoxylin-eosin, stainings. The notion that the amount of plaque is correlated with the duration and severity of dementia has been refuted [390], and SNPs have not been found to morphologically increase in step with other disease parameters [87,391]. Some of these discrepancies may relate to the fact that SNPs dissolve and decrease in number in most advanced stages [87,392]. The amyloid is hypothetically eliminated through transportation along perivascular channels, a concept corroborated by the abovementioned finding of plaque dissolution [393].

Mutation of the amyloid precursor protein gene in familial AD is shown to increase ßA4 production [394]. However, while ßA4 is a core feature of AD, it is not pathognomonic for the disease. It is found to occur in various types of cerebrovascular disease, including VaD [395,396], with minimal or no AD [397–399] and may not be as specific to disease development and progression as has been hypothesized.

The neurons affected by the disease are severely damaged and ultimately lost [87,400] to an extent that correlates with the severity of clinical deterioration [116,401,402]. Other components of visible damage include neuropil threads and glial reactions (astrocytosis and microglial response) [87,118,403]. The microvacuolization seen in outer cortical lamina during early to mid-phase degeneration indicates a fairly recent loss of neurons, often coincides with the gliotic reaction and precedes the collapse that appears as narrowing of the cortical ribbon [65,87,116,404,405]. Some features repeatedly discussed in early works, granulovacuolar degeneration and Hirano bodies, were never shown to be consistent and specific traits, nor to have particular significance for the disease [406,407].

A particular micromorphological trait to acknowledge is that of Lewy bodies (LBs), which are intraneuronal ubiquinated inclusions containing the aggregated α-synuclein protein, by means of which they are detected immunohistochemically. Studies referred to in subsequent documents that formulate criteria are those that present data from clinicopathological correlations [111,408–411]. LBs, even previously with Parkinson's disease, are detected in people with various neurological diseases and are occasionally found in the non-impaired elderly. They may appear in the brains of clinically and neuropathologically diagnosed AD patients [344,412,413]. Conversely, clinical LB dementia may be found to have an underlying substrate of AD, with mild to prominent concurrent degeneration of the substantia nigra and with WMD [344], some of them exhibiting cortical-subcortical LBs to a variable extent [414]. Thus, it may be reasonable to regard DLB as a variant of AD with less prominent AD pathology and concomitant nigral degeneration, concomitant WMD or both [415]. Despite numerous publications in the field, the significance of LB pathology in AD is still an unresolved issue and

the role played by these structures in determining disease development remains uncertain [383].

Clinicopathological correlation studies

Proceeding from differing focuses and perspectives, several authors have offered descriptions of the clinical *and* pathological signs of disease in AD cases [61,116,117,196,198,358], such as the presence of concurrent white matter pathology [252,416,417], correlations with clinical symptoms of LB dementia [344] and the particular group of Down's syndrome patients [146,149,418].

Some studies have also attempted to demonstrate the relative possible role or impact of plaques and tangles for the neuropathological diagnosis of AD based on established clinicopathological criteria [419]. The patient group in this particular study was generalized as AD (probable and possible AD in 46 of 49 cases) – however, neuropathological analyses of 6 sampled brain areas revealed that only 30 of 49 were pure AD – the remaining ones exhibiting another concurrent disease. A more extensive sampling might have shown an even greater number of non-Alzheimer pathologies. In order to stage the disease, other researchers have detailed the progressive development of ßA4 formation in association with other neurodegenerative changes, as related to certain clinical parameters [420]. The clinical part of this meticulous pathology study is limited to assessment with the Blessed Dementia Scale [108], but retrospective evaluation of the NIA and Reagan Institute criteria revealed that only 7 of the 26 cases studied would be definite AD and another 7 would be probable AD.

A rough indication of validity in both the clinical and neuropathological diagnostic setting is the analysis of agreement between clinical and neuropathological diagnoses. Agreement over specified diagnoses was better than 80% in the experience of the authors. One study reported it as 88% [421], while the NINCDS-ADRDA Work Group Study found 81–88% [422]. The authors of the latter study demonstrated that universally accepted clinical and neuropathological criteria for AD are essential. An allegedly high kappa index of agreement for clinical interrater diagnosis of "dementia/non-dementia" reported by some studies would not suffice

to serve its purpose [423]. Without post mortem follow-up in at least a significant percentage of the deceased, clinical skills may deteriorate – as illustrated by the above study, in which 10% of a dementia cohort were clinically reclassified as VaD after neuroimaging and 65% of the diagnoses were altered following neuropsychological assessment.

The promotion of neuropathology as the gold standard for diagnosis and nosology necessitates the proper use of morphology. Clinicopathological studies exhibit a large variability with regard to not only the choice of clinical assessment, but also the nature and comprehensiveness of the pathological work-up. Only rarely are both aspects covered comprehensively. Due to the distinct nature of AD-related pathology, its identification is easy and adequately convincing, though not necessarily for AD per se. During neuropathological follow-up on sampled tissue from different brain regions, identification of plaques and tangles in AD-typical areas (where they are expected to be particularly numerous) may be reported as such but is insufficient without a quantitative or semi-quantitative assessment such as the one that appears in the NIA Working Group Recommendations [424] and is applied by the CERAD protocol [387]. Many presentations leave the interpreter with uncertainty as to whether the pathology described actually crosses the threshold of clinically detectable dementia. Furthermore, and equally problematic, is that numerous studies fail to preclude any significant additional pathology of non-Alzheimer type. Neuropathology must take further responsibility for defining guidelines, such as minimal acceptable levels for verifying diagnosis in different clinical diagnostic and research settings (Appendix 2.9). Attempts have been made, but existing recommendations are not generally or fully complied with. Thus, this kind of initiative is long overdue [422]. The lack of such guidelines hampers progress and often leaves the task of assessment hostage to neuropathology itself.

Classification and criteria

Several research groups have attempted over the years to establish diagnostic neuropathological criteria for AD [378,387,388,422], to recommend compliance with consensus criteria [424], to establish a grading system for severity of brain disease [87,118] or to validate existing dia-

gnostic criteria [363]. The CERAD classification, one of the most widely used systems, aimed at overcoming the limitations of previous protocols that US and Canadian neuropathologists showed to have been applied by relatively few [425]. The CERAD protocol, which permits the combined evaluation of clinical data and easily applied morphology along with patient age, offers several obvious advantages. However, one problem is that it does not allow for a safe assessment (ie exclusion) of other, confounding disease, such as mixed AD-VaD [426]. Gross examination for the exclusion of other pathology is insufficient, even for cerebrovascular disease unless it is of a large-lesion type. Furthermore, the few samples recommended for microscopic preparation happen to be suboptimally located for identifying the brunt of pathologic changes, including WMD [87,116].

Delineation of AD against normal aging

The focus of AD diagnosis should be on the distinction between healthy brain aging and early AD. Two key papers by Tomlinson et al provide essential insights into the gray zone between them [382,388]. Later studies added information regarding the manifest but very early (mild) phase of AD [427]. Amyloid plaques in the neocortex were shown to discriminate very elderly people with AD from age-matched controls without dementia, while neocortical tangles correlate more closely with the degree and duration of dementia [428,429]. The occurrence of amyloid plaques in early AD and preclinical stages suggests a possible future target of therapeutic initiatives.

AD and vascular manifestations

Besides the group of pure AD, a large category presents a spectrum of vascular lesions [82,83,430], from mild, inconspicuous pathology to a modest number of small infarcts [121,195,196,198] to a full-blown picture of mixed AD-VaD, the lesions of which are responsible for at least 50% of the total brain damage. Jellinger estimated the relative percentages of AD, mixed AD and VaD [426] but claimed that additional cerebrovascular pathology in AD added little or no cognitive impairment to its progressive symptoms [431]. The ratio of mixed AD-VaD to pure

AD has been debated in several reviews (but not in follow-up control studies with neuropathology), as has been the issue of the clinical impact on dementia of the vascular components in AD, including claims that AD pathogenesis is actually vascular.

The vascular/degenerative dilemma

Dementia research has been heavily influenced by the distinction between vascular and degenerative diseases, probably limiting subclassification in both groups. Binswanger described a progressive subcortical vascular encephalopathy (PSVE) [53], and Alzheimer further developed the subclassification of VaD to include arteriosclerotic brain atrophy, PSVE, dementia apoplectica and perivascular gliosis [75]. Others have further contributed to the clinical and pathological description of PSVE [65,432–436], and the previous view that it is a rare form of dementia has changed as the result of improved diagnostic techniques [436–440]. There is little evidence that isolated hypertension or arteriosclerosis per se cause dementia other than in rare exceptions, although the probability of reduced reserve capacity due to subclinical brain lesions has been suggested. The term multiinfarct dementia (MID) was introduced to stress the relationship between this type of progressive dementia and multiple cerebral infarcts [441]. The clinical picture in MID is very similar to the early description of arteriosclerotic brain atrophy and PSVE [75], and the term was probably intended to cover the whole range of VaD. The ischemic score (IS) (Table 2.1) was developed as a clinical tool for the differential diagnosis among MID, AD and other primary degenerative dementias [345]. The IS was based on 13 items for the description of arteriosclerotic psychosis in the textbook of clinical psychiatry by Mayer-Gross et al [1]. Comparative clinicopathological studies and metaanalyses have shown the usefulness of the IS, as well as such limitations as a tendency to overdiagnose MID [357,442]. A large number of studies have analyzed [348,355,357,442] and modified [352] the Hachinski IS. The original version is still the most widely used diagnostic tool in both research and clinical practice [303,357,443,444].

Cognitive impairment was associated early with *etat lacunaire* and white matter ischemic lesions [445,446]. However, dementia is not an inevitable consequence of stroke [447,448]. It is related to the location and

severity of the ischemic lesions [449], as well as the possibility of multiple etiologies [440,448]. Supported by a series of clinical, pathological and imaging studies, interest in the role of WMD in VaD and AD increased greatly during the 1980s [119,450–454]. This trend was particularly facilitated by considerable advances in new imaging techniques and the appearance of more precise instruments, such as immunohistochemistry, in pathology. Descriptive terms, such as leukoaraiosis (LA – from the Greek words for white and rarefied) were introduced for these pathologies. The histopathological account of such changes in AD, also referred to as incomplete infarction, showed demyelination and rarefaction in deep hemispheric regions [119,452,455]. The current view is that the WMD is due to stenosing small vessel disease confined to the white matter arterioles, in combination with a central cerebral hypoperfusion, which can be induced in turn by cardiac insufficiency or other conditions [456–458]. Other vascular and biochemical factors have also been emphasized [459,460].

A strict dichotomy between vascular and degenerative forms of dementia has been questioned ever since the late 19th century. However, the terminology has not always managed to express the neuropathological and clinical findings of co-occurrence and the interplay among different pathological mechanisms, such as genetic factors, vascular autoregulation, amyloidosis, neurotransmitter failure and hyperhomocysteinemia [83,430,461–466]. Vascular pathologies of different types and severities have been reported in 40–90% of patients with AD [83,426,440]. Unspecified vascular pathologies that come into play include arteriosclerosis from the carotid arteries, basal cerebral vessels and the smallest intracerebral arterioles, as well as hypertensive vasculopathy and amyloid, plus diabetic angiopathy. Thus, the relative impact of neurodegenerative vs vascular-ischemic pathologies varies to form a continuous spectrum from AD through AD-VaD and VaD-AD to VaD. This type of multifaceted presentation of the most prevalent illnesses that lead to dementia has significant implications for therapeutic approaches [467].

Summary

From a clinical and neuropathological viewpoint, several subgroups are represented within the AD spectrum. In addition to the varying influence of genetic subtypes on the clinical and brain morphological pre-

sentation, AD occurs in morphologically varying forms, albeit with the same basic histopathological characteristics. These forms are the neurodegenerative hallmarks of SNPs, NFTs, neuronal degeneration and loss in the cortex and certain central and brain stem nuclei, microvacuolization, amyloid accumulation in parenchyma and meningocortical vessels, cortical atrophy in certain regions and white matter changes. These base characteristics coincide in various proportions, such as predominantly rich in plaques, predominantly gliotic or vacuolated, or degeneration to one extent or another of the basal nucleus of Meynert or the locus ceruleus.

Additional morphologic features that are consistent with the morphological picture without being an established part of it includes LBs (see Chapter 4 Dementia with Lewy Bodies).

A range of cerebrovascular alterations contribute a spectrum of changes, with everything from mild cerebrovascular atherosclerosis and mild hypertensive vessel changes that do not necessarily alter the main diagnosis of pure AD to the vast entity of AD-VaD consistent with pronounced vascular pathology and focal ischemic lesions.

A short overview of historical landmarks in the process of exploring dementia appears in Appendix 2.10.

Future issues in clinical and research dementia work

An obvious need exists for a global terminology in the field – a harmonization of terminologies regarding brain morphology and topography, as well as clinical symptomatology and diagnostic workup.

The more treatment comes into play as a realistic alternative, the more essential the introduction of a global terminology for differential diagnostics and evaluation scores.

Epidemiology must not be divorced from clinical disciplines.

There is a need for an improved multiaxial classification model in dementia diseases. This model should be open, flexible and amenable

to increased interaction, so as to create more opportunities for comparative clinical, pathological and epidemiological research.

If pathology is to maintain its position as the gold standard in diagnostics and nosology, there is an obvious need for the harmonization of diagnostic assessment techniques – the reconciliation of various working method strategies and coordination of histopathological assessments among centers.

There is also a need for greater transparency between the clinician and the pathologist when it comes to fundamental issues and working procedures.

A standard neuropathological assessment scheme should be recognized and applied in clinical diagnostics. A second assessment scheme should be recognized for research issues.

Figure 2.1 *Publications on major types of dementia in PubMed (Medline) 1960–2004.*

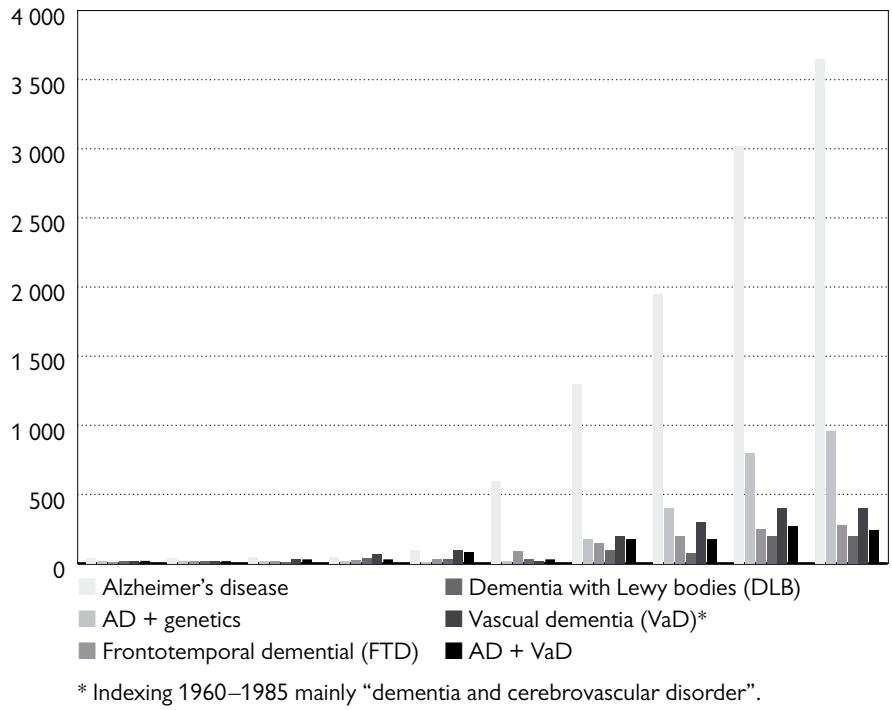

Table 2.1 *Ischemic Score [345].*

Symptom	**Score**
Abrupt onset	2
Stepwise progression	1
Fluctuating course	2
Nocturnal confusion	1
Relative preservation of personality	1
Depression	1
Somatic complaints	1
Emotional incontinence	1
History of hypertension	1
History of strokes	2
Evidence of associated atherosclerosis	1
Focal neurological symptoms	2
Focal neurological signs	2
Max score	**18**

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Appendices

Appendix 2.1 – Clinical features of frontotemporal dementia 1994 [67]

Core diagnostic features

Behavioral disorder

- Insidious onset and slow progression
- Early loss of personal awareness (neglect of personal hygiene and grooming)
- Early loss of social awareness (lack of social tact, misdemeanors such as shoplifting)
- Early loss of disinhibition (such as unrestrained sexuality, violent behavior, inappropriate jocularity, restless pacing)
- Mental rigidity and inflexibility
- Hyperorality (oral/dietary changes, over-eating, food fads, excessive smoking and alcohol consumption, oral exploration of objects)
- Stereotyped and perseverative behavior (wandering, mannerisms such as clapping, singing, dancing, ritualistic preoccupation such as hoarding, toileting, and dressing)
- Utilization behavior (unrestrained exploration of objects in the environment)
- Distractibility, impulsivity, and impersistence
- Early loss of insight into the fact that the altered condition is due to a pathological change of own mental state.

Affective symptoms

- Depression, anxiety, excessive sentimentality, suicidal and fixed ideation, delusion (early and evanescent)
- Hyperchondriasis, bizarre somatic preoccupation (early and evanescent)
- Emotional unconcern (emotional indifference and remoteness, lack of empathy and sympathy, apathy)
- Amimia (inertia, aspontaneity)

Speech disorder

- Progressive reduction of speech (aspontaneity and economy of utterance)
- Stereotypy of speech (repetition of limited repertoire of words, or themes)
- Echolalia and perseveration
- Late mutism.

Spatial orientation and praxis preserved (intact abilities to negotiate the environment).

Physical signs

- Early primitive reflexes
- Early incontinence
- Late akinesia, rigidity, tremor
- Low and labile blood pressure.

Investigations

- Normal EEG despite clinically evident dementia
- Brain imaging (structural or functional, or both): predominant frontal or anterior temporal abnormality, or both
- Neuropsychology (profound failure on "frontal lobe" tests in the absence of severe amnesia, aphasia, or perceptual spatial disorder).

Supportive diagnostic features

- Onset before 65
- Positive family history of similar disorder in a first degree relative
- Bulbar palsy, muscular weakness and wasting, fasciculations (motor neuron disease).

Diagnostic exclusion features

- Abrupt onset with ictal events
- Head trauma related to onset

- Early severe amnesia
- Early spatial disorientation, lost in surrounding, defective localization of objects
- Early severe apraxia
- Logoclonic speech with rapid loss of train of thought
- Myoclonus
- Cortical bulbar and spinal deficits
- Cerebellar ataxia
- Choreo-athetosis
- Early, severe, pathological EEG
- Brain imaging (predominant post-central structural or functional deficit). Multifocal cerebral lesions on CT or MRI)
- Laboratory tests indicating brain involvement or inflammatory disorder (such as multiple sclerosis, syphilis, AIDS and herpes simplex encephalitis).

Relative diagnostic exclusion features

- Typical history of chronic alcoholism
- Sustained hypertension
- History of vascular disease (such as angina, claudication).

Appendix 2.2 – Diagnostic criteria for dementia of the Alzheimer type DSM-IV, 1994 [32]

A. The development of multiple cognitive deficits manifested by both
   1) memory impairment (impaired ability to learn new information or to recall previously learned information)
   2) one (or more) of the following cognitive disturbances:
      a) aphasia (language disturbance)
      b) apraxia (impaired ability to carry out motor activities despite intact motor function)
      c) agnosia (failure to recognize or identify objects despite intact sensory function)
      d) disturbance in executive functioning (ie, planning, organizing, sequencing, abstracting).

B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

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

D. The cognitive deficits in A1 and A2 are not due to any of the following:
   1) other central nervous system conditions that cause progressive deficits in memory and cognition (eg, cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor)
   2) systemic conditions that are known to cause dementia (eg, hypothyroidism, vitamin B_{12} or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV infection)
   3) substance-induced conditions.

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

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

Code based on type of onset and predominant features:
With Early Onset: if onset is at age 65 years or below
290.11 With Delirium: if delirium is superimposed on the dementia
290.12 With Delusions: if delusions are the predominant feature
290.13 With Depressed Mood: if depressed mood (including presentations that meet full symptom criteria for a Major Depressive Episode) is the predominant feature. A separate diagnosis of Mood Disorder Due to a General Medical Condition is not given.
290.10 Uncomplicated: if none of the above predominates in the current clinical presentation

With Late Onset: if onset is after age 65 years
290.3 With Delirium: if delirium is superimposed on the dementia
290.20 With Delusions: if delusions are the predominant feature

290.21 With Depressed Mood: if depressed mood (including presentations that meet full symptom criteria for a Major Depressive Episode) is the predominant feature. A separate diagnosis of Mood Disorder Due to a General Medical Condition is not given.

290.0 Uncomplicated: if none of the above predominates in the current clinical presentation

Specify if:

With Behavioral Disturbance

Coding note: Also code 331.0 Alzheimer's disease on Axis III.

Appendix 2.3 – Diagnostic criteria for 290.4x Vascular Dementia. DSM-IV, 1994 [32]

A. The development of multiple cognitive deficits manifested by both
   1) memory impairment (impaired ability to learn new information or to recall previously learned information)
   2) one (or more) of the following disturbances:
      a) aphasia (language disturbance)
      b) apraxia (impaired ability to carry out motor activities despite intact motor function)
      c) agnosia (failure to recognize or identify objects despite intact sensory function)
      d) disturbance on executive functioning (ie, planning, organizing, sequencing, abstracting).

B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

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

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

Code based on predominant features:

290.41 With Delirium: if delirium is superimposed on the dementia

290.42 With Delusions: if delusions are the predominant feature

290.43 With Depressed Mood: if depressed mood (including presentations that meet full symptom criteria for Major Depressive Episode) is the dominant feature. A separate diagnosis of Mood Disorder Due to a General Medical Condition is not given.

290.40 Uncomplicated: if none of the above predominates in the current clinical presentation

Specify if:

With Behavioral Disturbance

Coding note: Also code cerebrovascular condition on Axis III.

Appendix 2.4 – World Health Organization, ICD-10, 1992 [6]

F00 Dementia in Alzheimer's disease

Alzheimer's disease (AD) is a primary degenerative cerebral disease of unknown etiology, with characteristic neuropathological and neurochemical features. It is usually insidious in onset and develops slowly but steadily over a period of years. This period can be as short as 2 or 3 years, but can occasionally be considerably longer. The onset can be in middle adult life or even earlier (AD with early onset), but the incidence is higher in later life (AD with late onset). In cases with onset before the age of 65–70, there is the likelihood of a family history of a similar dementia, a more rapid course, and prominence of features of temporal and parietal lobe damage, including dysphasia or dyspraxia. In cases with a later onset, the course tends to be slower and to be characterized by more general impairment of higher cortical functions. Patients with Down's syndrome are at high risk of developing AD.

There are characteristic changes in the brain: a pronounced reduction in the population of neurons, particularly in the hippocampus, substantia innominata, locus ceruleus, and temporoparietal and frontal cortex; appearance of neurofibrillary tangles made of paired helical filaments: neuritic (argentophil) plaques, which consist largely of amyloid and show a definite progression in their development (although plaques without amyloid are also known to exist); and granulovacuolar bodies. Neurochemical changes have also been found, including a pronounced reduction in the enzyme choline acetyltransferase, in acetylcholine itself, an in other neurotransmitters and neuromodulators.

As originally described, the clinical features are accompanied by the above brain changes. However, it now appears that the two do not always progress in parallel: one may be indisputably present with only minimal evidence of the other. Nevertheless, the clinical features of AD are such that it is often possible to make a presumptive diagnosis on clinical grounds alone.

Dementia in AD is at present irreversible.

Diagnostic guidelines

The following features are essential for a definite diagnosis:

a) Presence of a dementia as described above.
b) Insidious onset with slow deterioration. While the onset usually seems difficult to pinpoint in time, realization by others that the defects exist may come suddenly. An apparent plateau may occur in the progression.
c) Absence of clinical evidence, or findings from special investigations, to suggest that the mental state may be due to other systemic or brain disease which can induce a dementia (eg hypothyroidism, hypercalcemia, vitamin B_{12} deficiency, niacin deficiency, neurosyphilis, normal pressure hydrocephalus, or subdural hematoma).

d) Absence of a sudden, apoplectic onset, or of neurological signs of focal damage such as hemiparesis, sensory loss, visual field defects, and incoordination occurring early in the illness (although these phenomena may be superimposed later).

In a certain proportion of cases, the features of AD and vascular dementia may both be present. In such cases, double diagnosis (and coding) should be made. When the vascular dementia precedes the AD, it may be impossible to diagnose the latter on clinical grounds.

Includes: primary degenerative dementia of Alzheimer's type.

Differential diagnosis. Consider: a depressive disorder (F30–F39); delirium (F05.–); organic amnesic syndrome (F04); other primary dementias, such as in Pick's, Creutzfeldt-Jakob or Huntington's disease (F02.–); secondary dementias associated with a variety of physical disease, toxic states, etc (F02.8); mild, moderate or severe mental retardation (F70–F72).

Dementia in AD may coexist with VaD (to be coded F00.2), as when cerebrovascular episodes (multi-infarct phenomena) are superimposed on a clinical picture and history suggesting AD. Such episodes may result in sudden exacerbations of the manifestations of dementia. According to post-mortem findings, both types may coexist in as many as 10–15% of all dementia cases.

F00.0 Dementia in AD with early onset

Dementia in AD beginning before the age of 65. There is relatively rapid deterioration, with pronounced multiple disorders of the higher cortical functions. Aphasia, agraphia, alexia, and apraxia occur relatively early in the course of the dementia in most cases.

Diagnostic guidelines

As for dementia, described above, with onset before the age of 65 years, and usually with rapid progression of symptoms. Family history of AD is a contributory but not necessary factor for the diagnosis, as is a family history of Down's syndrome or of lymphoma.

Includes: AD, type 2
Presenile dementia, Alzheimer's type

F00.1 Dementia in AD with late onset

Dementia in AD where the clinically observable onset as after the age of 65 years and usually in the late 70s or thereafter, with a slow progression, and usually with memory impairment as the principal feature.

Diagnostic guidelines

As for dementia, described above, with attention to the presence or absence of features differentiating the disorder from the early-onset subtype (F00.0).

Includes: AD, type 1
Senile dementia, Alzheimer's type

F00.2 Dementia in AD, atypical or mixed type

Dementias that do not fit the descriptions and guidelines for either F00.0 or F00.1 should be classified here; mixed Alzheimer's and VaDs are also included here.

F00.9 Dementia in AD, unspecified

Appendix 2.5 – World Health Organization, ICD-10, 1992 [6]

F01 Vascular dementia

Vascular (formerly arteriosclerotic) dementia, which includes multi-infarct dementia, is distinguished from dementia in AD by its history of onset, clinical features, and subsequent course. Typically, there is a history of transient ischemic attacks with brief impairment of consciousness, fleeting pareses, or visual loss. The dementia may also follow a succession of acute cerebrovascular accidents or, less commonly, a single major stroke. Some impairment of memory and thinking then becomes apparent. Onset, which is usually in later life, can be abrupt, following one particular ischemic episode, or there may be more gradual emergence. The dementia is usually the result of infarction of the brain due to vascular diseases, including hypertensive cerebrovascular disease. The infarcts are usually small but cumulative in their effect.

Diagnostic guidelines

The diagnosis presupposes the presence of a dementia as described above. Impairment of cognitive function is commonly uneven, so that there may be memory loss, intellectual impairment, and focal neurological signs. Insight and judgment may be relatively well preserved. An abrupt onset or a stepwise deterioration, as well as the presence of focal neurological signs and symptoms, increases the probability of the diagnosis; in some cases, confirmation can be provided only by computerized axial tomography or, ultimately, neuropathological examination.

Associated features are: hypertension, carotid bruit, emotional lability with transient depressive mood, weeping or explosive laughter, and transient episodes of clouded consciousness or delirium, often provoked by further infarction. Personality is believed to be relatively well preserved, but personality changes may be evident in a proportion of cases with apathy, disinhibition, or

accentuation of previous traits such as egocentricity, paranoid attitudes, or irritability.

Includes: arteriosclerotic dementia.

Differential diagnosis. Consider: delirium (F05.–); other dementia, particularly in AD (F00.–); mood [affective] disorders (F30–F39); mild or moderate mental retardation (F70–F71); subdural hemorrhage (traumatic (S06.5), nontraumatic (I62.0)).

Vascular dementia may coexist with dementia in AD (to be coded F00.2), as when evidence of a vascular episode is superimposed on a clinical picture and history suggesting AD.

F01.0 Vascular dementia of acute onset

Usually develops rapidly after a succession of strokes from cerebrovascular thrombosis, embolism, or hemorrhage. In rare cases, a single large infarction may be the cause.

F01.1 Multi-infarct dementia

This is more gradual in onset than the acute form, following a number of minor ischemic episodes that produce an accumulation of infarcts in the cerebral parenchyma.

Includes: predominantly cortical dementia.

F01.2 Subcortical vascular dementia

There may be a history of hypertension and foci of ischemic destruction in the deep white matter of the cerebral hemispheres, which can be suspected on clinical grounds and demonstrated on computerized axial tomography scans. The cerebral cortex is usually preserved and this contrasts with the clinical picture, which may closely resemble that of dementia in AD. (Where diffuse demyelination of white matter can be demonstrated, the term "Binswanger's encephalopathy" may be used.)

F01.3 Mixed cortical and subcortical vascular dementia

Mixed cortical and subcortical components of the VaD may be suspected from the clinical features, the results of investigations (including autopsy), or both.

F01.8 Other vascular dementia

F01.9 Vascular dementia, unspecified

Appendix 2.6 – Vascular dementia; Diagnostic Criteria for Research Studies Report on the NINDS-AIREN International Workshop, 1993 [81]

I. The criteria for the clinical diagnosis of *probable* VaD include *all* of the following:

   1) *Dementia* defined by cognitive decline from a previously higher level of functioning and manifested by impairment of memory and of two or more cognitive domains (orientation, attention, language, visuospatial functions, executive functions, motor control, and praxis), preferably established by clinical examination and documented by neuropsychological testing; deficits should be severe enough to interfere with activities of daily living due to physical effects of stroke alone.

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

   2) *Cerebrovascular disease*, defined by the presence of focal signs on neurological examination, such as hemiparesis, lower facial weakness, Babinski sign, sensory deficit, hemianopia, and dysarthria consistent with stroke (with or without history of stroke), and

evidence of no relevant CVD by brain imaging (CT or MRI) including *multiple large vessel infarcts or a single strategically placed infarct* (angular gyrus, thalamus, basal forebrain, or PCA or ACA territories), *as well as multiple basal ganglia* and *white matter lacunes*, or *extensive* periventricular *white matter lesions*, or combinations thereof.

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

II. Clinical features consistent with the diagnosis of *probable* VaD include the following: (a) early presence of gait disturbance (small-step gait or marche a petits pas, or magnetic, apraxic-ataxic or parkinsonian gait); (b) history of unsteadiness and frequent, unprovoked falls; (c) early urinary frequency, urgency, and other urinary symptoms not explained by urologic disease; (d) pseudobulbar palsy; and (e) personality and mood changes, abulbia, depression, emotional incontinence, or other subcortical deficits including psychomotor retardation and abnormal executive function.

III. Features that make the diagnosis of VaD uncertain or unlikely include (a) early onset of memory deficit and progressive worsening of memory deficit and progressive worsening of memory and other cognitive functions such as language (transcortical sensory aphasia), motor skills (apraxia), and perception (agnosia), in the absence of corresponding focal lesions of brain imaging; (b) absence of focal neurological signs, other than cognitive disturbance; and (c) absence of cerebrovascular lesions on brain CT or MRI.

IV. Clinical diagnosis of *possible* VaD may be made in the presence of dementia (section I-1) with focal neurological signs in patients in whom brain imaging studies to confirm definite CVD are missing; or in the absence of clear temporal relationship between dementia and stroke; or in patients with subtle onset and variable course (pla-

teau or improvement) of cognitive deficits and evidence of relevant CVD.

V. Criteria for diagnosis of *definite* VaD are (a) clinical criteria for *probable* VaD; (b) histopathological evidence of CVD obtained from biopsy or autopsy; (c) absence of neurofibrillary tangles and neuritic plaques exceeding those expected for age; and (d) absence of other clinical or pathological disorder capable of producing dementia.

VI. Classification of VaD for research purposes may be made on the basis of clinical, radiological, and neuropathological features, for subcategories or defined conditions such as cortical VaD, subcortical VaD, BD, and thalamic dementia. The term "AD *with* CVD" should be reserved to classify patients fulfilling the clinical criteria for possible AD and who also present clinical or brain imaging evidence of relevant CVD. Traditionally, these patients have been included with VaD in epidemiologic studies. The term "mixed dementia", used hitherto, should be avoided.

Appendix 2.7 – Clinical diagnosis of AD: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease, 1984 [106]

I. The criteria for the clinical diagnosis of "probable Alzheimer disease" include:

- Dementia established by clinical examination and documented by the Mini-Mental Test, Blessed Dementia Scale (to be exact, the Dementia Test Score), or some similar examination, and confirmed by neuropsychological tests.
- Deficits in two or more areas of cognition.
- Progressive worsening of memory and other cognitive functions.
- No disturbance of consciousness.
- Onset between ages 40 and 90, most often after age 65.

- Absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

II. The diagnosis of "probable Alzheimer disease" is supported by:

- Progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia).
- Impaired activities of daily living and altered patterns of behavior.
- Family history of similar disorders, particularly if confirmed neuropathologically.
- Laboratory results of:
  - Normal lumbar puncture as evaluated by standard techniques.
  - Normal pattern or non-specific changes in EEG, such as increased slow-wave activity.
- Evidence of cerebral atrophy on CT with progression documented by serial observation.

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

- Plateaus in the course of progression of the illness.
- Associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss.
- Other neurological abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder.
- Seizures in advanced disease.
- CT normal for age.

IV. Features that make the diagnosis of "probable Alzheimer disease" uncertain or unlikely include:

- Sudden apoplectic onset.
- Focal neurological findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness.
- Seizures or gait disturbances at the onset or very early in the course of the illness.

V. Clinical diagnosis of "possible Alzheimer disease":

- May be made on the basis of the dementia syndrome, in the absence of other neurological, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the course.
- May be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia.
- Should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

VI. Criteria for diagnosis of "definite" Alzheimer's disease are:

- The clinical criteria for probable Alzheimer's disease and histopathologic evidence obtained from a biopsy or autopsy.

VII. Classification of Alzheimer's disease for research purposes should specify features that may differentiate subtypes of the disorder such as:

- Familial occurence;
- Onset before age of 65;
- Presence of trisomy-21; and
- Coexistence of other relevant conditions such as Parkinson's disease.

Appendix 2.8 – Consensus criteria for the clinical diagnosis of probable and possible DLB, 1996 [111]

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

2. **Two** of the following core features are **essential** for a diagnosis of *probable* DLB, **one** is essential for *possible* DLB.
   a) Fluctuating cognition with pronounced variations in attention and alertness.
   b) Recurrent visual hallucinations that are typically well formed and detailed.
   c) Spontaneous motor features of Parkinsonism.

3. Features **supportive** for the diagnosis
   a) Repeated falls
   b) Syncope
   c) Transient loss of consciousness
   d) Neuroleptic sensitivity
   e) Systematized delusions
   f) Hallucinations in other modalities.

4. A diagnosis of DLB is **less likely** in the presence of
   a) Stroke disease evident as focal neurological signs or on brain imaging
   b) Evidence on physical examination and investigation of any clinical illness, or other brain disorder, sufficient to account for the clinical picture.

Appendix 2.9 – The neuropathological assessment – proposal for investigation standard (minimum requirements)

1. **Macroscopical evaluation**
   Focal and regional discoloring or softenings are noted. Gyral atrophy/sulcal widening, meningeal changes and vascular appearance are noted, as well as the brain weight. Cerebellar size and surface are evaluated.

2. **Sampling for microscopy**
   At least 13 different cerebral regions are sampled for analysis, the number varying according to the clinical diagnosis:
   The frontal cortex and white matter, the precentral (motor) cortex, the parietal cortex and white matter, the temporal cortex, the hippocampus and amygdala, the occipital cortex and white matter, the frontal and occipital periventricular white matter, regions covering the superior arterial border zones, and the basal ganglia covering the caudate nucleus, the putamen and globus pallidus. The cerebellum, the mesencephalon with substantia nigra and the spinal cord should be sampled as well.

   Coronal whole brain sections cover several of the listed areas and are preferred for regional and topographic assessment with conventional stainings, along with selected small samples for immunohistochemistry.

3. **Stainings for microscopy**
   Stainings include hematoxylin-eosin and myelin staining, as well as silver stainings, stainings for beta-amyloid, tau protein and alfa-synuclein. Ubiquitin is used in selected cases, as well as prion protein staining.

Appendix 2.10 – Historical landmarks in the process of exploring dementia – overview of some important contributions

1822	First description of dementia paralytica [468]
1880	Depressive pseudodementia [24]
1881	Apoplectic dementia [469]
1892	Pick's disease, lobar atrophy [54]
1893	Dementia preaecox [4]
1894	Presenile dementia, Binswanger's disease [53]
1906	First report on Auguste D (by A Alzheimer) [94]
1907	First publication of Alzheimer's disease [95]
1910	Alzheimer's disease (AD) [52] Pathology of AD [97]
1911	Pathology of Pick's disease [56]
1912	Lewy body [470]
1913	Treponema pallidum in GPI [471]
1917	Treatment of GPI (Wagner-Jauregg)
1923	Dementia in Parkinson's disease [472]
1927	Stageing of Pick's disease [59]
1929	Down syndrome dementia [319]
1933	Normal ageing (N Gellerstedt) [473]
1938	Congophilic angiopathy [474]
1952	The three stage model of AD [61]
1961	Pseudodementia [23]
1962	Benign senescent forgetfulness [37]
1963	Paired helical filaments [375,475]
1965	Normal pressure hydrocephalus [89]
1969	CIBA-foundation: AD [100] Brain imaging [476]

The table continues on the next page

Appendix 2.10 continued

1974	Multiinfarct dementia [441]
1975	Ischemic Score [345], MMSE [107]
1976	Cholinergic deficiency in AD [477,478]
1978	Aluminum and other metals in AD [313]
1981	White Matter Disease (WMD) in AD [479]
1982	Reversible dementia [15] NbM in AD [480]
1983	Treatable dementia [14]
1984	Amyloid in AD and DSD [386]
1985	Tau protein [481,482] Vascular degenerative overlap [83,119,452]
1986	Age associated memory impairment [39] Cholinergic treatment
1987	Ubiquitin in NFT and plaque [483] Leukoaraiosis [484] APP characterization, mutations, markers [485,486]
1988	Strategic infarct dementia [78]
1991	Dementia with Lewy bodies [152,153]
1992	Semantic dementia [148] Amyloid cascade hypothesis [487] Swedish mutation [488]
1993	Apolipoprotein E [489]
1994	Frontotemporal dementia [67]
1996	CADASIL [490]
1998	Frontotemporal lobar degeneration [68]
1999	Mild Cognitive Impairment (MCI) [21]
2008	SBU-project: Dementia

3. **Vascular Dementia Nosology – Concepts and Evidence**

Introduction

Vascular dementia (VaD) has a somewhat unusual history. Once considered to be the obvious and most common type of dementia, it now plays a less prominent role. The change during the 1990s is attributable more to new attitudes than fresh evidence [1]. Epidemiology and brain imaging studies have identified cerebrovascular disease as an important factor in cognitive disturbances and the development of dementia [2–4]. The perception that VaD is underdiagnosed [5] is becoming more widespread, although one author disagrees [6]. Although knowledge is increasing in the fields of pathology, genetics, and clinical science, its applicability to clinical practice has not been sufficiently promoted.

Historical overview

The modern history of dementia began in 1910 when Emil Kraepelin's influential textbook *Psychiatrie* differentiated between "arteriosclerotic dementia" and "senile/presenile dementia" [7,8]. His work was based on clinical pathology studies by Otto Binswanger and Alois Alzheimer, who wanted to differentiate between syphilitic and other forms of dementia. Arteriosclerotic dementia was viewed as a spectrum of diseases from the very start. The brain lesions that were assumed to be responsible for dementia consisted of arteriosclerotic brain atrophy (characterized by multiple lacunar strokes and *état criblé* – dilated perivascular spaces – associated with arteriosclerosis of small and large blood vessels), senile cortical atrophy (granular atrophy and laminar necrosis), periventricular white matter atrophy (Binswanger's disease), perivascular gliosis (wedge-shaped lesions resulting from severe stenosis of a large vessel), arteriosclerotic hemispheric foci (predisposing for "dementia postapoplexiam") and the combined forms of dementia.

In practice, arteriosclerotic dementia was synonymous with senile dementia. Successively impaired blood flow was thought to lead to neuron death. In the mid 1970s, AD was first regarded as the main cause of brain atrophy and dementia. Now the pendulum has swung back in the other direction. Vascular lesions in patients with dementia are receiving growing attention. Vascular-related damage of the white matter has been found in more than half of patients with AD. It is becoming increasingly apparent that vascular morbidity is not a secondary finding in patients with AD but that it actively contributes to the development of dementia. The subclassification of VaD that appeared just over a century ago has sparked renewed interest. Stroke-related dementia is increasingly in the spotlight, as is subcortical VaD with white matter damage and lacunae, regarded by some as the most common form of VaD [9,10].

Aim

This review of the literature aims to present the approaches to, and knowledge about, VaD that has been published in recent decades. What approaches to VaD have been considered during this time? What are the current approaches? What is regarded as the characteristic clinical profile in VaD? What systems have been developed to diagnose VaD? What pathological conditions underlie the occurrence of VaD? What more do we need to know?

Methods

A Medline search was performed for literature relating to humans and published in English from January 1, 1970 to June 1, 2003. The following search items were used: dementia, vascular AND (criteria OR subgroups OR subtypes OR classification). We found 671 references.

Original papers, reviews, and editorials were all considered. The selection process did not include papers that focused specifically on treatment, epidemiology, and the diagnostic process. Papers dealing with neuropathology and brain imaging were considered if they fell within the scope of the present review. About 230 papers were initially selected.

After a brief inspection of the offprints, the number was reduced to about 190 and subjected to review. Approximately 100 additional articles relevant to the project (including those published after June 1, 2003) attracted our attention in the course of the review process and were also included. All in all, about 300 articles, approximately half of which were original papers, were reviewed.

Although the selection of articles was systematic, biases may have occurred. For instance, certain articles on cognitive impairment associated with stroke may not have been evaluated, given that stroke was not used as a search term.

The results of the review appear in five different sections: 1) the evolution of concepts; 2) disease manifestations; 3) clinical diagnostic systems and disease classification; 4) neuropathology; and 5) conclusions and recommendations. "Evolution of concepts" appears first because our approaches to diseases and syndromes largely shape our assumptions about what can be observed in a patient. The section covers the concept of multi-infarction dementia (MID) and its shortcomings, VaD as a heterogeneous disease group, the emergence of the mixed-type dementia concept, and the shift in focus to the mild cognitive impairment phases in cerebrovascular disease. Section 2, the most extensive, addresses disease manifestations. It focuses on manifestations in a clinical context, since that is where medical science becomes concrete for patients and physicians alike. First, we describe the symptom profile of VaD. Next, we present several views concerning the importance of stroke in the development of dementia. Before the manifestations of white matter disease (WMD) are discussed and accorded the prominent place that they deserve, we briefly address the importance of anatomical brain imaging in identifying vascular lesions, particularly in terms of white matter changes. Finally, we discuss the potential importance of various cerebrospinal fluid markers on understanding VaD, and we describe a genetic model disease for subcortical VaD. Section 3 takes up diagnostic criteria systems and condensed descriptions of disease manifestations, ie, how well the criteria system captures that which is characteristic of VaD. We present the various characteristics of the systems and look at how well the systems agree in terms of identifying patients with VaD. Section 4

examines various vascular lesions (vascular and tissue changes) that can be identified using neuropathological methods. The section also presents studies that compare clinical findings with neuropathological changes. Section 5 summarizes the most important conclusions and offers recommendations for the future.

Evolution of concepts

The rise and fall of the MID concept

Impaired blood flow resulting from partial blockage of the vessels that supply the brain dominated our concepts about the cause of dementia for decades. During the 1970s, when Alzheimer's lesions were identified as common changes in patients with dementia, the notion of chronic brain ischemia as an explanation of dementia was abandoned. The claim was that vascular disease could lead to cognitive disorders, by means not of bloodflow-related energy deficiency but of repeated stroke episodes resulting in cerebral tissue damage. A conceptually central 1974 work by Hachinski entitled "Multi-infarct dementia – a cause of mental deterioration in the elderly" [11] drew the following conclusion:

"The typical insidious slowly progressive dementia of old age is not due to atherosclerosis. Most cases show Alzheimer-like degeneration of the brain at necropsy. There is no relationship between these parenchymal degenerations and arterial disease. Progressive involvement of cerebral arteries by atherosclerosis does not critically stenose them and does not produce mental impairment; hence the term "cerebral atherosclerosis" as applied to mental deterioration in the elderly is misleading and inaccurate and should not be used in this context. When vascular disease is responsible for dementia it is through the occurrence of multiple small or large cerebral infarcts (multi-infarct dementia). This represents a relatively small group of patients and is most often associated with hypertension (état lacunaire) and/or extracranial vascular disease."

The results of thorough neuropathological studies by Tomlinson et al offered the strongest support for associating cerebral infarction and dementia [12,13]. Because the importance of lesion size and location

has not been clarified, other types of vascular and neurodegenerative lesions occur concurrently, and the symptom profile varies, multi-infarction dementia as a disease entity has been called into question [14]. It has also been claimed that the requisite injury volume for development of dementia according to Tomlinson's own studies was 50–200 ml, ie, multiple infarcts of lower volume were not calculated. The concept of multi-infarction dementia (MID) as a commonly occurring entity has garnered only limited neuropathological support since being introduced in the 1970s [15].

Nevertheless, the diagnosis of MID grew popular and was applied to a larger group of patients than originally proposed. People who had cerebrovascular disease and dementia without signs of sufficiently extensive cerebral infarction also received a diagnosis of MID. In other words, the MID concept was watered down.

Heterogeneity of VaD

The demonstration of vascular-related white substance damage (Binswanger's disease) contributed to the questioning multiple infarctions as the primary cause of VaD [16]. The increased percentage of elderly in the general population, along with changes in the cerebrovascular disease panorama in terms of reduced stroke mortality, has led to reevaluation and renewal in this area [17]. Instead of using simplified disease categories, the assertion was that vascular mechanisms leading to cognitive impairment should form the basis of disease classification [2,9,17,18]. Because several such mechanisms exist [19,20] (Table 3.1), there are also several types of VaD [9,21–24] (Table 3.2). Particular attention has been paid over the past decade to post-stroke dementia (cognitive impairment following an identified stroke) and subcortical VaD (a more insidious course). In that respect, post-stroke dementia has been regarded as a model for large vessel (thromboembolic) and subcortical VaD for small vessel (hypoperfusive) VaD. Less common types, such as CADASIL, also exist (see section on genetics below).

In other words, the disease panorama has expanded to cover several conditions.

Mixed-type dementia

It wasn't so long ago that the occurrence of vascular risk factors and diseases were regarded as exclusion criteria for the diagnosis of AD. However, longitudinal epidemiological studies have shown that hypertension, diabetes, atrial fibrillation, and smoking are risk factors for AD as well as VaD [25–29]. Ischemic processes have proven not only to co-exist with AD, but to potentiate its development. The "Nun study" was the first modern research able to demonstrate the potentiation effect [30]. Only 57% of deceased elderly nuns diagnosed with AD based on a neuropathological examination turned out to have dementia. Seventy-five percent of those who had been diagnosed with AD based on neuropathological methods and cortical infarctions had dementia and 93% of those who had AD and lacunae in subcortical brain regions had dementia. Other studies have also shown that vascular lesions potentiate the effect of AD (and vice versa). The OPTIMA (Oxford Programme to Investigate Memory and Ageing) project showed that cerebrovascular disease impaired cognitive performance in early phases of AD but not later in the course of the disease [31]. At the same grade of dementia, fewer Alzheimer's lesions were required in patients who had cerebrovascular damage [32,33]. Another study reported that the combination of Alzheimer's and vascular pathology was common in patients with cognitive impairment [34]. However, no threshold effects for the various changes could be found.

Ischemia via vasoactive effects of amyloid, impaired blood flow, reduced metabolism, inflammatory mechanisms and changes in the blood-brain barrier are among the factors that have been regarded as the genesis of vascular tissue damage in AD. Some authors have even claimed that AD is primarily microvascular, for which degeneration of the capillaries in the hippocampus and other brain regions, including secondary neuronal hypometabolism, is the central pathophysiological chain of events [35,36].

Identifying patients with AD and concurrent cerebrovascular disease is not easy when the patient lacks markers for AD. That may be one reason for the rate of mixed dementia having been underestimated [37]. According to a relatively current review of clinical neuropathological studies, mixed dementia accounts for 20–40% of dementia cases [38].

Vascular mild cognitive impairment

Since the mid-1990s, the focus has shifted to the earlier stages of VaD, ie, the milder symptomatic phase before the dementia syndrome has developed [39–46]. In one study, 50% of patients with vascular mild cognitive impairment developed dementia after 5 years [47]. Thus, the condition is potentially serious.

The usual definition of dementia implies difficulties with work, social interaction and other daily activities. In other words, cognitive problems are so pronounced that the meaningfulness of using preventive interventions aimed at averting the onset of the disease is called into question. Moreover, the cognitive symptom profile in VaD is defined the same way as for AD – impaired memory is the required cardinal symptom. That has proven to be false. Rather, the characteristic cognitive symptom profile for VaD is executive dysfunction (see section on symptom profile), even though memory disorders also occur. As a result, the concept of dementia is increasingly regarded as a misleading approach to describing cognitive disorder in cerebrovascular disease.

To create the proper conditions for prevention and treatment, the entire scope of vascular cognitive disorders must be recognized – from subtle, mild impairment to the fully developed dementia syndrome. In particular, it is important to measure executive dysfunction early in the course of the disease. The earliest phases offer the greatest opportunity to prevent the development of dementia in various risk groups. Among such patients are those with stroke, hypertension, diabetes mellitus, ischemic heart disease, smoking, hypercholesterolemia, heart failure or a history of cardiac bypass or other major surgical interventions.

Disease manifestations – a clinical perspective

Symptom profile

Although dementia leads to global disturbance of cognitive ability, some cognitive functions are usually more affected than others. The pattern of functional impairment largely reflects the nature of the dementia disease and the distribution of pathological changes in the brain. To put it simply, there are two types of cognitive functional disorders (cognitive syndromes). The first syndrome is characterized by impaired memory, recognition ability and ability to understand speech, carry out practical tasks and interpret sensory (mainly visual) impressions. The ability to plan and implement may also be impaired but only in parity with the receptive problems. The (posterior brain) syndrome originates from primary lesions in the posterior cortical association regions. The second syndrome is characterized by mental slowness, as well as impaired ability to initiate, plan and implement (ie, executive functions), and personality changes. Memory disorders also appear but are not as pronounced as in posterior brain syndrome. Recognition and interpretation capabilities remain relatively intact. Gait pattern is often slower, similar to that found in Parkinson's disease. The (anterior brain) syndrome originates from primary lesions in the frontal subcortical regions of the brain.

Posterior brain syndrome, characterized by impaired memory and difficulty in interpreting sensory impressions, is typical of AD. The ICD and DSM manuals for the diagnosis of dementia diseases define AD as a posterior brain syndrome. Dementia syndrome, regardless of genesis, is defined in the same way. In other words, it is largely influenced by what we know about the symptom profile of AD. That is noteworthy, given that other dementia diseases primarily affect the regions of the brain that lead to other symptom profiles. That is particularly true of VaD.

VaD is a more heterogeneous disease group with symptoms that vary according to the type of tissue damage, location, size and number of lesions. Anterior brain syndrome with executive [48] or intentional [49] dysfunction is the characteristic symptom profile, even though other cognitive disorders such as speech disorders, neglect phenomena, impaired memory and global cognitive impairment may occur. Anterior brain

syndrome appears in large vessel disease that leads to the formation of cortical infarction within the a. cerebri posteriors, *arteria cerebri* anteriors and *arteria cerebri basilaris* regions. It also appears in subcortical cerebrovascular disease with lacunae and white matter damage (small vessel disease) [48].

Selected original publications show that executive dysfunction was the key factor underlying functional impairment [50]. Disturbances in frontal lobe functions were found to be more pronounced in patients with VaD than AD [51,52]. Memory disturbances proved to be less pronounced early in the course of the disease than for AD. However, once the disease had progressed to a moderately severe level, the disturbances were just as pronounced as in AD [53]. Executive dysfunction may also appear in AD patients, but it more resembles attention deficit disorder. In VaD, executive function more involves a fundamental inability to work out strategies and carry out tasks [54]. Groves et al found few differences between AD and VaD, but they did identify a tendency toward greater functional impairment, more depression and less pronounced cognitive reduction in patients with VaD than AD [55]. To obtain a greater understanding of the clinical manifestations, Groves et al recommended a subtype classification of VaD in agreement with that proposed by others [21,22,24,56].

Subcortical VaD is the most homogeneous, and probably most common, subtype [57]. Changes found by magnetic resonance imaging (MRI) in the subcortical area of patients with VaD (see sections below on anatomic brain imaging and white matter lesions) showed an association with impairment of executive and psychomotor, but not global cognitive, capacity [58,59]. Patients with subcortical VaD had more pronounced impairment than those with AD in their ability to deal with complex information, formulate strategies and exercise self-control. The executive dysfunction of AD patients was mainly associated with attention deficit disorder and impaired working memory [54]. However, another study found that attention deficit disorder was more pronounced in the subcortical group [60]. Patients with subcortical VaD have shown less pronounced episodic memory impairment, but more depressive symptomatology and greater variability in progress speed, than those with

AD [61]. It has been suggested that patients with subcortical microvascular disease are the ones who later develop dementia that shows signs of mild cognitive impairment in the early phases of the disease [62].

The executive control function (for goal-oriented behavior) coordinates cognitive functions such as planning, attention, working memory, abstraction capacity, flexibility and the ability to take action. It ensures that mental and physical activities lead toward the intended goals. A disturbance in the executive control function leads to global impairment of the ability to engage in everyday social activities and work, as well as the development of dementia. In addition to being a characteristic disturbance in VaD, there is much to suggest that executive dysfunction is the determining component in the dementia syndrome itself. A study by Pohjasvaara et al found executive dysfunction in 40% of patients with ischemic stroke 3 months after the stroke episode [63]. Executive dysfunction was associated with ADL difficulties and impairment in MMSE, but not with depression. That has not been taken into consideration when designing diagnostic manuals and treatment studies. The DSM-IV criteria for Alzheimer's disease (AD), VaD and other dementia diseases, for example, mentions executive dysfunction, but its potentially important role has not been clarified. One reason may be that executive dysfunction is more difficult to identify and measure than memory impairment and receptive inability.

- Although several questions remain unanswered [64], the cardinal disturbance in VaD is clearly anterior brain syndrome with executive dysfunction.

Stroke

One way to obtain more specific information about VaD is to study cognitive ability in the course of the disease following an established stroke episode. Several studies of this type have been conducted since the 1990s. What are their findings? What role does cerebral infarction play in the development of cognitive dysfunction and dementia?

Several studies have shown an increased prevalence of dementia among stroke survivors. Three months after a stroke episode, the prevalence

of dementia (post-stroke dementia) ranged from 18% to 30% [65–68] depending on the composition of the patient group and the choice of criteria for the dementia syndrome. Barbas's study showed progressive cognitive dysfunction following stroke episodes among only 1 in 10 patients, suggesting that cognitive disorders are a residual syndrome, ie, not a sign of dementia in the strict sense of the word. At 3-year follow-up in a group of stroke patients, new dementia was reported in 29% of the cases [69]. Most of the patients developed dementia syndrome within the first six months, also suggesting that it is a residual syndrome. In a follow-up study of younger stroke patients (below age 65), 3 out of 52 cases showed progressive cognitive dysfunction with the development of mild dementia after 4 years. That is higher than would be expected in the normal population [70].

Approximately 10% of stroke patients who were followed up for cognitive ability showed signs of dementia even prior to the stroke episode [68,71,72]. In investigating patients during the acute phase, Henon et al found signs of pre-stroke dementia in 15% of the cases [73].

Stroke type, lesion location, total volume of infarcted tissue and incomplete impairment of tissue function are presumably the essential factors underlying the development of dementia [74]. As regards lesion location, the profile diverges. Multivariate analyses have shown that frontal lesions and left-sided hemispheric lesions, as well as infarctions in the arteria cerebri anterior, media, and posterior, play an independent role in the development of post-stroke dementia [66,67]. Another study found that location lacked significance [65]. Further studies are needed to clarify the importance of lesion location, as well as the influence of white matter changes, associated Alzheimer's pathology and silent infarctions.

Strategic infarction dementia is sometimes characterized as a special variety of post-stroke dementia. Isolated bilateral infarctions in the hippocampus can lead to dementia, but milder cognitive disturbances are more common. Bilateral thalamic, unilateral thalamic and basal frontal infarctions, as well as infarctions in the angular gyrus, non-dominant parietotemporal region and dominant hemisphere, are other strategically localized infarctions that reportedly cause dementia [75–81]. In addition

to memory impairment, bilateral thalamic lesions yield apathy, attention deficit, and disturbances in wakefulness. In other words, the symptomatology suggests more extensive brain damage. Thus, involvement of the thalamus and bordering brain areas is often found. The condition is called paramedial diencephalon syndrome. Effects on the extensive reciprocal thalamus-frontal and frontal reticular nerve connections may explain the discrepancy between the relatively limited lesions and the extensive symptomatology. Strategic infarction dementia has been called into question as a disease entity, given that the influence of other lesions is generally ignored. For instance, studies (often case descriptions) that address strategic infarction dementia do not always investigate white matter damage [78].

Although several questions are yet unanswered, it is more or less apparent that a causal association exists between stroke and dementia under certain conditions: 1) in young patients for whom there is small probability of concurrent AD; 2) when cognitive ability that was normal prior to the stroke episode was impaired immediately after stroke and cognitive dysfunction deteriorated with time; 3) when a well-defined vasculopathy leading to dementia is demonstrated. These conditions presumably apply to only a limited number of patients.

The situation is more complex for most patients with post-stroke dementia. The variation in cognitive status prior to the stroke episode and the development of cognitive dysfunction after stroke, as well as the variation of stroke-related and lesion-related characteristics that contribute to the development of dementia, suggest that post-stroke dementia is a heterogeneous condition for which factors other than the infarction formation itself are of importance.

- In order for us to become more knowledgeable about post-stroke dementia, the study groups must be redefined. The post-stroke dementia studies presented above have given only limited consideration to the categories of major and minor stroke. Patients with a major stroke, including hemiparesis or other deficit, probably represent a less urgent group for study, given that the condition has already been well-investigated in relation to risk factors, diagnostics and

treatment, not to mention primary and secondary prevention [39]. Likewise, patients with post-stroke, cognitive residual syndrome but no cognitive dysfunction prior to the stroke episode are probably not an essential group to study in terms of clarifying the cognitive effects of stroke. The most essential group of patients to study are presumably those with progressive post-stroke dementia in conjunction with minor stroke. Because minor stroke is usually an expression of lesions in the subcortical brain regions, where partial white matter damage is common [82], the coordination of research on minor stroke and white matter damage would be a reasonable way to go.

Anatomical brain imaging

Anatomical brain imaging – mainly computed tomography (CT) and MRI – is frequently used to examine suspected cognitive failure and dementia. It is also one reason for the renewed and more palpable interest in the association between vascular disease and dementia. Brain imaging is no longer a tool for simply ruling out various intracranial processes, such as brain tumors and subdural hematomas, but to demonstrate – or at least support – the existence of cerebrovascular disease as a probable cause of cognitive dysfunction and dementia. Anatomical brain imaging also helps determine the subtypes of VaD (hemorrhage vs ischemia, cortical vs subcortical, strategic infarction vs multi-infarction, large vessel disease vs small vessel disease) and thereby enhances our knowledge of vascular disease processes.

Anatomical brain imaging has played a particularly large role in demonstrating small vessel-related white matter changes.

However, several questions remain unanswered [83]. How pronounced must a vascular change be in order to cause cognitive dysfunction and dementia? How significant is location? What is the relative importance of different types of vascular lesions (infarctions, lacunae, white matter damage)? What role do atrophy and its association with vascular lesions play?

An association has been reported in patients with cerebrovascular disease between dementia and the degree of white matter damage, the degree of cerebral atrophy, left-sided lesions, bilateral lesions, and strategic localization [84,85]. An association between executive cognitive dysfunction and white matter damage has also been demonstrated [57,86]. Evidence also exists that white matter lesions progress over time [87] – see the section on white matter lesions below.

Anatomical brain imaging cannot be used to show neurodegenerative changes characteristic of AD, such as senile plaque and neurofibrillary tangles, but atrophy distribution can be measured. Because the interaction between degenerative and vascular pathology plays a role in the development of dementia, it is probable that the same interaction is present in brain imaging changes. One study showed that the concurrent presence of hippocampus and cortical atrophy explained the development of dementia in patients with subcortical VaD [88].

- Due in part to the role played by the results of brain imaging studies, the modern criteria-based definitions of VaD have enhanced our understanding of the association between vascular disease and dementia [89,90]. However, one result has been that what clinicians assume they can observe is often accepted without closer examination of the specific diagnostic and pathophysiological importance of particular vascular lesions. Further studies on the role of particular vascular lesions are needed.

White matter lesions

A series of common and uncommon diseases and disease processes – including multiple sclerosis, AIDS dementia, vasculitis, CADASIL, and mitochondrial disorders – can result in damage to the white matter of the brain. Moreover, some white matter lesions are not clearly associated with a specific disease. CT or MRI can detect and measure white matter lesions or leuco-araiosis [91]. They commonly occur in elderly people, particularly those with signs of vascular risk factors, cerebrovascular disease or cognitive impairment. Pathogenesis and clinical correlates to age-related white matter lesions are increasingly subject to investi-

gation. Some of the uncertainties stem from the lack of agreement among various definitions and ways of classifying the lesions.

In particular, we know that white matter lesions can be the most important pathological lesions in patients with vascular disease and progressive cognitive impairment or dementia [92–96]. It has also been shown that white matter lesions are associated with cognitive impairment [86,97,98], while anterior symptom profile is associated with impaired attentiveness, mental speed, gait and ability to plan and carry out tasks, as well as urinary incontinence [9,57,86], plus impaired global functioning [99].

We also know that other vascular lesions, particularly lacunae (mainly multiple ones), coexist with white matter lesions [100] in conjunction with cognitive impairment [101,102]. The latter association has been interpreted as evidence of the improbability that white matter lesions are important per se. The implication is rather that lacunae are decisive to the onset of symptoms. Others suggest that lacunae are the extreme manifestation, the tip of the iceberg, of the process that leads to white matter lesions. Since lacunae and white matter lesions are the result of the same ischemic process [9,82], the latter explanation appears to be the most reasonable. The white matter lesions, which are generally more widespread, probably play a greater role than the limited lacunae in generating symptoms.

It has also been demonstrated that the confluent white matter lesions of neuropsychiatrically healthy patients show progression over a 6-year period [103]. Other shorter studies have also found that white matter lesions progress over time [104–107]. The results of the progression studies suggest that white matter lesions are manifestations of a distinctive, ongoing disease process. MRI measurements of progression in white substance lesions have been proposed as an appropriate surrogate marker for small vessel disease in pharmacological studies [87].

Many of the controversies surrounding white matter lesions are attributable to disagreement among various rating scales of the radiological profile. Because the emphasis varies from scale to scale, the same radio-

graphic image can spawn different interpretations [103,108,109]. Such considerations directly impact the perception of what constitutes the clinical manifestations of white matter lesions.

Although white matter lesions have a relatively similar, homogeneous appearance in CT and MRI, they are associated with different types of pathological lesions [110]. For instance, periventricular white matter lesions (those limited to the area near the ventricle wall) correlate with reduced myelin content and fewer axons. On the other hand, the histological correlates of deep white matter lesions (those in the central part of the white matter area) are perivascularly widened areas, lacunae, demyelinization, vacuolation, and astrogliosis. Thickening of the small vessel walls (arteriosclerosis) usually appears in the cerebral areas in which the white matter lesions are located.

White matter lesions may lead to functional disruption in the connections between the cortical and subcortical areas of the brain. Disturbances in the connections between the thalamus and cortex are viewed as particularly important to the onset of cognitive impairment [48]. White matter lesions may also be due to circulatory disorders – damage to the vessel walls, as well as blood flow problems of an ischemic or hypoxic nature. Support for such an hypothesis has been gleaned from positron emission tomography (PET) studies that show impaired autoregulatory reserve capacity [111,112] and increased extraction of oxygen [113] in patients with white matter diseases. However, some studies tend to gainsay such an association [114]. Experimental studies have also demonstrated that white matter components (oligodendrocytes and myelinized axons) are vulnerable to ischemia [115,116] and that myelin damage appears even earlier and independently of neuronal damage [115,116]. Furthermore, postmortem studies have shown a more pronounced loss of myelin lipids than axonal membrane components in patients with VaD and AD [117].

Small vessel disease presumably plays an important pathogenic role in the appearance of white matter lesions [118]. The basal mechanism probably involves damage to the arterioles as a result of aging and hypertension, as well as other factors such as diabetes and genetic vulnerability.

The pathological vascular wall process (arteriolosclerosis) is characterized by replacement of the smooth muscle cells in the tunica media by lipid, hyaline and fibrotic material. That leads to lumen constriction, impaired ability to change lumen diameter according to metabolic needs and possible ischemic-hypoxic tissue damage in the vulnerable vascular architectural terminal areas of the long penetrating arteries (border zone areas). Structural and physiological changes in the branches of the arterioles (penetrating arteries) can also lead to degradation of the blood-brain barrier. Disturbances in fluid circulation have been advanced at times as an important factor in the onset of white matter lesions [119,120]. One study showed that carotid stenosis is unimportant to the onset of white matter lesions [121], while another study presented contrary results [122].

- In summary, the research of recent years suggests that age-related white matter lesions are a sign of small vessel disease that can lead to cognitive failure and impaired functional capacity. This disease entity has been dubbed subcortical VaD, with the alternative designations of subcortical ischemic VaD and subcortical white matter dementia.

Further study is needed on the white matter lesion threshold values for cognitive dysfunction, the importance of location, the association with atrophy changes and minor stroke, quantification, characteristics based on new brain imaging methods, the association with biomarkers, neuropathological correlates, prediction in longitudinal studies and specific pathogenesis, particularly the role of hereditary and acquired factors.

Neurochemical markers

There are several logical reasons for establishing the number of various neurochemical markers in the cerebral spinal fluid (CSF) of patients with VaD and other dementia diseases. In the first place, cerebrospinal fluid is in direct contact with the extracellular cerebral area. Thus, the CSF presumably reflects biochemical changes in the brain. One example is the change in tau protein levels after acute ischemic stroke. The CSF tau level is normal for 1 or 2 days, after which it palpably increases and peaks after 2–3 weeks. The effect then subsides, and the values normalize after 3–4 months [123]. The increase probably indicates leakage of

tau from the damaged neurons in the CSF, suggesting that biochemical analyses of the CSF reflect the pathological processes that take place in the brain. In the second place, CSF analyses enable us to study pathological processes as they occur. That includes not only cerebrovascular events, but the slower, stealthier course that characterizes subcortical VaD, AD, etc. Although there are similarities among these diseases, they presumably differ in terms of the basic etiological mechanisms. By identifying the biochemical markers of both vascular and primary degenerative disease processes (both of which are probably fundamental), we can acquire direct knowledge of their relative contributions. In the third place, lumbar puncture is a simple method of obtaining cerebrospinal fluid for biochemical analysis. The rate of postpunction headache in patients referred for examination of memory disorders and dementia is low, although somewhat higher among younger patients.

The integrity of the blood brain barrier (BBB) can be measured by determining the CSF/serum ratio for albumin. Impaired BBB function occurs in patients with VaD [124,125], particularly subcortical VaD [126]. The impaired function probably reflects disorders in the arterioles, although the capillary level may also be compromised.

Sulphatide, a glycosphingolipid that accumulates in myelin, is regarded as a marker for ongoing demyelinization. Two studies have noted elevated spinal fluid levels in patients with subcortical VaD [127,128].

Tau is a cytoskeletal protein that contributes to stabilizing the microtubules in nerve cells. An elevated CSF concentration of tau indicates ongoing neuronal or axonal degeneration. Several studies have shown elevated tau levels in patients with AD [129–131]. The same results emerged in studies of patients with VaD, while the levels were normal in patients with subcortical VaD [132]. Possible explanations for the elevated tau levels in some patients with VaD are the concurrent presence of Alzheimer's pathology or acute axonal damage from stroke. Tau levels that are normal in patients with subcortical VaD suggest that it differs pathogenetically from AD.

In AD, phosphorylated tau is less able to bind to microtubules in axons, thereby destabilizing the axons and affecting nerve cell function. Phosphorylated tau also has a tendency to aggregate to paired-helical filaments, which then form the major protein aggregates that build neurofibrillary tangles. Several studies have shown a significant increase of phosphorylated tau in the fluid of AD patients, while the levels are normal in VaD patients [129,130]. That suggests that the two diseases are characterized by different pathogenic processes.

Neurofilament, another cytoskeletal component, is concentrated in large myelinized neurons. Neurofilament consists of three proteins with different molecular weights. It has proven possible to measure neurofilament light subunit (NFL) in the CSF. The greatly increased concentration of CSF-NFL that has been found in patients with subcortical VaD [133] has been associated with the presence of white matter changes [134]. CSF-NFL has been shown to be normal in patients with pure AD who have no signs of vascular disease. That suggests that the increase in NFL among patients with subcortical VaD is not an indication of Alzheimer's pathology, but rather the axonal damage characteristic of VaD.

Beta amyloid 1–42 (A-beta 42) is another protein that has been primarily associated with AD. A-beta 42 accumulates in senile plaque, leading to changes in the CSF concentration of the protein. Several studies have shown a reduction in the concentration of A-beta 42 [129]. One study showed its concentration to be lower in patients with subcortical VaD, suggesting that the metabolism of beta amyloid is also disrupted in patients with VaD [135]. It is possible that patients with subcortical VaD have both vascular-related and amyloid-related brain lesions. Experimental ischemia studies have supported such a hypothesis. The studies found that amyloid precursor protein (APP) accumulated in white matter during ischemia [136]. Another possibility is that the patients also had Alzheimer's lesions.

- Knowledge of neurochemical markers for disease processes in the brain can provide clues to pathophysiological understanding of VaD and its subtypes [137]. The studies, which are considerably fewer than those on patients with AD, that have been conducted so far suggest

that patients with subcortical VaD have lower BBB function, signs of ongoing demyelinization (at least late in the course of the disease), axonal degeneration of a non-Alzheimer's type and impaired amyloid metabolism. These results support the argument that subcortical VaD is a homogeneous entity pathophysiologically distinct from AD.

Knowledge of neurochemical markers may also be important to understanding mixed dementia. For instance, the characteristic Alzheimer's profile of elevated tau and phosphotau levels and reduced beta-amyloid levels in the spinal fluid of a patient with a characteristic clinical profile of AD who shows concurrent signs of vascular lesions based on brain imaging and clinical vascular influence – such as sudden onset of symptoms, gradual disease course and medical history indicating stroke or focal neurology [138] –would suggest a diagnosis of mixed dementia [9].

Genetics

This section provides a brief overview of the topic. We know that the apolipoprotein E (apoE4) ε4 allele is a risk factor for AD [139,140]. Some studies have shown that the apoE4 allele is also a risk factor for VaD [141,142], while others tend to discourage such an association [143–147]. ApoE4 allele is a well-known risk factor for VaD [148]. Further research is needed to sort out the relevance of these disparate findings. Is there, as suggested by some of the results, a common genetic denominator between AD and VaD?

For just over a century, we have known that microvascular disease can lead to cognitive and other mental disorders. Sourander and Walinder described hereditary, multi-infarct dementia [149]. Several reports were published from 1977 to the mid-1990s about a new autosomal dominant disease that leads to stroke and dementia. The disease has now been recognized under the acronym CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy). The first known form of VaD with an identified genetic deviation [150–153], CADASIL, is caused by a point mutation in the Notch3 gene on the short arm of chromosome 19. The gene defect leads either to loss or increase of the cysteine amino acid. The function of Notch 3 genes is not

fully understood, but they clearly play a role in the early development of the tissue and codes of a transmembrane protein found in several cells.

Most people with CADASIL experience initial symptoms in their early 40s or 50s. Migraine with aura is a debut symptom in one-third of the cases. TIA/stroke is the most common onset symptom. The stroke symptoms that recur are usually of lacunar type and affect subcortical areas. Cognitive disorders (an anterior brain syndrome) follow, including attention deficit, mental slowness, apathy and impaired planning ability. Memory impairment appears later in the course of the disease. Other common symptoms include gait disorders, depression, irritability and personality changes. The dementia profile appears in 10–15% of the cases without being preceded by TIA/stroke. Approximately 80% of CADASIL patients have dementia at age 65.

MRI studies show increased signal density in the basal ganglia and white subcortical matter in nearly everyone with the disease. In asymptomatic carriers, MRI changes can often be observed long before other signs of the disease appear.

Neuropathological investigation shows multiple deep infarctions and diffuse white matter damage, as well as thickening of the walls in the meningeal and long perforated cerebral arteries. The vascular changes consist of an accumulation of a granular osmiophilic material between the degenerated smooth muscle cells. These changes occur not only in the cerebral arteries, but in nearly all organs of the body, including the kidneys, heart, muscles and skin. Learning more about the way in which the Notch3 gene leads to arteriopathy and how to treat the disease represents a major research challenge. CADASIL is also a model disease for subcortical VaD. Greater knowledge of the disease may contribute to our understanding of the association between white matter lesions and cognitive dysfunction in the large group of patients with dementia diseases.

Among additional hereditary microvascular diseases are mutations of the amyloid-beta precursor protein or presenilin-1 genes, as well as other amyloid protein-related mutations. They are all involved in amyloid deposition in the vessel walls of the central nervous system,

a manifestation known as cerebral amyloid angiopathy, the clinical picture of which includes cerebral hemorrhage, ischemic lesions and dementia [154,155].

Clinical diagnostic systems – condensed nosology

Presentation of diagnostic symptoms

A set of criteria for a disease is a type of condensed nosological description of it. Two principal sets of criteria apply to VaD [39]. The first set consists of two general diagnostic tools: the International Classification of Diseases, tenth revision (ICD-10) [156], and the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) [157]. The second set consists of operationalized refinements of the general criteria of the State of California Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC) [89], the National Institute of Neurological Disorders and Stroke, and Association Internationale pour la Rechereche et L'Enseignement en Neurosciences (NINDS-AIREN) [90]. In addition, the Ischemic Score [158] rating scale (IS) is a widely used checklist (rather than a set of criteria) that covers selected vascular risk factors, symptoms, and signs that are common in dementia associated with cerebrovascular disease. All of them are umbrella criteria for VaD, regardless of the underlying vascular mechanisms – with the possible exception of the AIREN criteria, which are regarded as having primarily post-stroke application.

The characteristics of the five diagnostic systems (IS, ICD-10, DSM-IV, ADDTC, NINDS-AIREN) described below generally agree with those presented earlier [39].

IS

The IS [158] (Table 3.3) has been developed and validated to differentiate between AD and VaD [39,159]. If, as is not uncommon, it is used as a basic tool to identify VaD, there is a risk of overdiagnosis. Patients with cerebrovascular diseases and stroke receive high ratings on the scale, regardless of whether the disease is associated with the dementia

profile. Because sudden onset and fluctuating disease course have not been operationalized [160], they are difficult to identify in practice [161]. A fluctuating disease course has not yet been identified as a characteristic of VaD [77,97].

ICD-10

The criteria for VaD based on ICD-10 [156] are listed in Chapter 2. Although not specified, the descriptions presented are relatively multifaceted and inclusive of subtypes. Memory disorders are accorded a prominent role, although other symptoms such as executive dysfunction dominate. The table does not specify what constitutes significant cerebrovascular disease in the genesis of the dementia profile.

DSM-IV

The criteria for VaD based on DSM-IV [157] are listed in Chapter 2. Aside from cerebrovascular disease, the table and DSM-IV are in full agreement. Memory disorders are assigned a prominent role, as is the case with ICD-10, although other symptoms dominate. How the symptoms and signs "are deemed to be etiology related to the disturbance" is not specified. The table affords the individual evaluator wide latitude to determine whether or not VaD is present.

ADDTC

The criteria of the State of California Alzheimer's Disease Diagnostic and Treatment Centers [89] are more detailed (Table 3.6). The definition does not include brain damage following cerebral hemorrhage or anoxia. Memory disorders have no special status, whereas the various cognitive symptoms have equal status. The clinical assessment of symptoms and their degree of severity plays a decisive role. Two or more ischemic stroke episodes based on anamnesis, a status examination or brain imaging are required for the criteria to be met. In rare cases, a stroke episode is allowed if the time between infarct formation and the development of dementia are clearly related. In contrast to the other sets of criteria, there are no requirements for a clear, temporal association between infarction formation and the development of dementia. The

reason is that vascular disease processes can advance gradually without the presence of clearly observable events, and it may be difficult to show a time relationship between events and cognitive deterioration.

NINDS-AIREN

The NINDS-AIREN criteria, which are more detailed, were primarily developed for use in epidemiological studies [90,162]. In practice, other types of studies have used them as well. The definition of VaD includes brain damage following cerebral hemorrhage or anoxia. As shown in Table 3.7, memory impairment is the cardinal symptom. Memory impairment and at least two other cognitive symptoms based on neuropsychological examination are required for a diagnosis of dementia. In order to meet the NINDS-AIREN criteria, a clear temporal association must exist between stroke and the onset of dementia. The cognitive disorder must develop within 3 months after stroke. Brain imaging is mandatory. VaD is ruled out if either MRI or CT fails to reveal vascular lesions. Recommendations for which vascular lesions are to be included, as well as their degree of severity, are specified. The criteria have been questioned by virtue of presumed limitations in our knowledge of cognitive disturbances following cerebrovascular disease with regard to which tissue lesions lead to dementia and how the corresponding brain imaging findings are expressed [163]. Generally speaking, the AIREN criteria are more rigid than the ADDTC criteria [164].

Other criteria

Bennett et al [165], Erkinjuntti et al [166] (Table 3.8), and Roman et al [9] have formulated criteria for subcortical VaD. Although subcortical VaD is more homogeneous etiologically than VaD, clinical and pharmacological studies have had only limited success in identifying it. Classifications of dementia diseases, among them VaD, that consider brain localization – including the anterior and subcortical/frontal subcortical variety – represent the focus of the Swedish Consensus of Dementia Diseases [167].

Lack of agreement among diagnostic systems

One study examined 167 patients who had been referred to the hospital for suspected dementia in order to determine the accuracy of various clinical definitions [168]. The study found that VaD was present in 27% of the patients according to DSM-IV, 14% according to ADDTC, 13% according to ICD-10 and 7% according to NINDS-AIREN. Another study in which 25 patients with manifest dementia were examined came up with similar figures: 26% according to DSM-IV, 21% according to ADDTC and 6% according to NINDS-AIREN [169]. Ischemic Score identified VaD in 14% of the patients. Thus, DSM-IV has the most inclusive criteria, a noteworthy finding given that the symptom profile corresponds to that which characterizes AD. As demonstrated by a third study as well, NINDS-AIREN has the most restrictive criteria [170]. That is not particularly remarkable, considering that the AIREN criteria are alone in including specific requirements for a temporal association between stroke episode and the development of dementia, as well as the presence of clear brain imaging signs of vascular-related tissue damage. As a result of these obligatory specifications, the AIREN criteria identify patients with post-stroke dementia if used correctly. Neither vascular-related dementia diseases whose course is more gradual nor stroke episodes that are not observable by MRI or CT are identified. The ADDTC criteria, which accord equal importance to the various cognitive symptoms (including executive dysfunction), have greater clinical validity than the AIREN criteria, which are more rigid about making memory impairment a required symptom [164]. ADDTC is preferable to AIREN when seeking to understand the magnitude of VaD.

A group of patients with dementia syndrome based on DSM-III three months after ischemic stroke (n = 107) was studied to determine how well the various diagnostic criteria identified the vascular genesis of the dementia profile [171]. DSM-IV identified vascular genesis in 92% of the patients, ADDTC in 87%, ICD-10 in 36% and AIREN in 33%. The pattern agrees with that which emerged in dementia patients independent of dementia type (see above [169]). That AIREN, which contains post-stroke dementia criteria, identified vascular genesis in only one-third of the post-stroke patients is rather remarkable. That suggests

that post-stroke dementia is not caused by infarction only. An alternative interpretation is that the criteria are not fully able to identify dementia caused by infarction.

- In summary, the studies point to a lack of agreement among different diagnostic systems for VaD. Despite certain similarities, the various criteria systems identify different patients and patient groups. Furthermore, the heterogeneous aspects of VaD are ignored. The lack of comparability, and the view of VaD as a single disease, erect barriers to research and patient care. Not only do the differences influence estimates of prevalence and incidence, but clinical management becomes more capricious.

Neuropathology

Table 3.9 lists the tissue changes that occur in VaD. The list largely concurs with the one that was composed a century ago (see Historical Overview). It is presented in the AIREN criteria [90], but without the magnitude of changes, location or a more detailed definition. Other classification systems for pathological lesions, in addition to tissue changes, in VaD also include extra and intracranial vascular changes [172] (Table 3.10). A review of clinical neuropathological studies published in recent years on patients with dementia or VaD indicates that the classification of vascular lesions varies from study to study and is generally simpler than Tables 3.9 and 3.10 [173]. That is presumably one of the reasons that the frequency of VaD varies between 0.3% and 58% according to an overview of certain autopsy studies in 1962–2001 [174].

Studies that deal primarily with AD, dementia without clinical subtyping and VaD are discussed below. The presentation and concepts agree with those offered by Pantoni et al in 2002 [173].

Several clinical neuropathological studies focused primarily on examining the frequency of degenerative and vascular changes in patients with a clinical AD diagnosis [175–178]. None of the studies considered white matter changes, including partial breakdown of the myelinized tissue and expanded perivascular areas, as signs of vascular lesions. As

a result, they presumably underestimated the vascular contribution to the dementia profile. The study by Galaskos sought to establish clearer rules for infarction-related neuropathological diagnosis. Bowler retested the pathological AD diagnosis by excluding AD cases with supratentorial infarctions and hippocampal sclerosis. That reduced the predicted value for clinical AD diagnosis by half. Nolan's study found signs of unspecified vascular lesions beyond the neurodegenerative changes in one-third of the cases. In none of the cases was there neuropathological evidence of pure VaD.

Another group of studies that examined vascular lesions in patients with dementia was able to establish the dementia diagnosis without clinical, ethnological type diagnostics [34,179–183]. Boller's study found multiple cerebral infarctions in 7% of the patients, but no pathological criteria were provided [179]. The Ince study identified cerebral infarctions in 19% of the cases, but only 6% were clinically significant (>100 ml) [182]. Hulette's study detected multiple cerebral infarctions without signs of neurodegenerative Alzheimer's changes in only 6 of 1 929 brain-examined dementia cases [181]. Both studies defined vascular lesions as infarcted brain tissue of large vessel type. Other vascular lesions were neither examined nor counted. Brun conducted one of the few studies that looked at the entire range of cerebrovascular lesions in patients with dementia [180]. Of 175 subjects, 34% showed cerebrovascular lesions (large vessel diseases, small vessel diseases, large vessel and small vessel diseases, selective incomplete white matter infarction, border-zone infarction and anoxia encephalopathy) without any signs of other diseases. Half of them showed signs of pure subcortical disease in the form of small vessel disease or selective incomplete white matter infarction. Thirty-six percent of the patients had a mixed picture of both cerebrovascular lesions and Alzheimer's changes, while only 16% exhibited Alzheimer's changes without signs of other brain diseases. The remaining 14% showed neuropathological grounds for a more unusual dementia diagnosis. According to Brun's pioneering study, vascular lesions contribute to the development of dementia in over two-thirds of dementia cases, while pure AD is equally common as subcortical VaD (one-sixth of the cases). Others who have examined the full range of cerebrovascular lesions include Jellinger et al [184], whose neuropathological study of

675 dementia cases showed significant cerebrovascular changes in 16%, and Alexianu et al [185], who found significant cerebrovascular lesions in 50% of the dementia cases.

Seno's study in Japan showed that the diagnosis of AD and VaD were just about as common; approximately one-third of the total group showed neuropathological grounds for each of the diseases [183]. Amyloid angiopathy was found to be associated with the degree of dementia severity, but no association of that type was demonstrated for neurofibrillary tangles and senile plaque. The study raises questions about the nature of AD. One study, though uncorroborated by others [93,186–189], was able to associate amyloid angiopathy with white matter lesions in AD patients [190]. If it is found that amyloid angiopathy leads to cognitive deterioration in patients with AD, that would support the hypothesis that AD is a vascular disease, at least in part [35].

The MRC-CFAS group conducted a neuropathological population study of older people. Of 209 subjects, 100 had a clinical diagnosis of dementia. Cerebrovascular (78%) and Alzheimer's (70%) pathology were the most common findings. The vascular lesions consisted of cortical infarctions, lacunae, and white matter lesions. Vascular lesions occurred to the same extent in the dementia and non-dementia groups, but multiple vascular lesions were more common in the dementia group (46%) than in the non-dementia group (33%). MR also studied the formalin-fixated cerebral material. White matter lesions occurred in 94% of the cases. Multivariate data analysis found the lesions to comprise an independent risk factor for dementia [191]. A neuropathological study of deceased subjects in an epidemiological, longitudinal study of the elderly in Cambridge detected pathological changes that overlapped between the dementia and non-dementia groups [192]. The changes that increased the risk of dementia consisted of white matter lesions, amyloid angiopathy, neuritic plaque, neurofibrillary tangles and Lewy bodies. Large or small infarctions did not increase the risk of dementia.

Neuropathological changes in a third group of patients with VaD were examined [193–196]. Esiri's neuropathological study compared the occurrence of microvascular and macrovascular lesions in dementia

patients with cerebrovascular disease who showed no signs of other cerebral disorders to corresponding changes in non-dementia patients both with and without cerebrovascular disease [195]. Microvascular disease (but not microscopic infarction) was found to be the most important factor underlying VaD. A method to semi-quantify small vessel disease was also presented. Ballard's study showed microinfarctions and white matter disease to form the basis of the clinical profile in patients with dementia and cerebrovascular disease [193]. Vinter's study, which investigated patients with suspected subcortical ischemic VaD, found that lacunae infarctions and microinfarctions in various cerebral regions were the reason for VaD and were associated with more extensive vascular damage [196]. Crystal et al identified 20 dementia cases that did not meet the pathological criteria for AD or Lewy body dementia and called them dementia of unknown etiology (DUE) [194]. Hippocampal sclerosis and white matter lesions were more common in the DUE group than the non-dementia groups. The difference was significant for hippocampal sclerosis. The findings suggest that hippocampal sclerosis is associated with VaD. That is important, given that the disorder may be difficult to distinguish from the MR finding of medial temporal lobe atrophy, a change that is usually regarded as indicating AD nowadays.

Because the summaries of various studies used different sets of ordinarily selected pathological criteria for VaD, the results are difficult to compare and often misleading. Some studies did not present the pathological criteria for VaD. The few studies that attempted to consider the full range of cerebrovascular lesions showed that cerebrovascular lesions are common – particularly in terms of subcortical small vessel diseases and white matter damage, which increasingly appear to be among the key etiological factors in VaD. Further studies are needed to clarify themost important pathological changes in the disease. Thus, neuropathological criteria and examination methods need to be specified and standardized [173]. A relatively new study showing a lack of consensus among the assessments of different neuropathologists regarding the occurrence of small vessel disease suggests that the task is urgent [197].

Conclusions

The time has come to give serious consideration to the data we have on vascular-related cognitive disorders. That is necessary in order to prevent the onset and reduce the consequences of cognitive disorders resulting from cerebrovascular disease. Both the heterogeneity of the disease group and the entire range of disorders – from subtle, mild-impairment to fully developed dementia syndrome – must be recognized. The disease panorama has widened from a focus on multi-infarct dementia to include post-stroke dementia, subcortical VaD, CADASIL, etc, as well as mixed dementia (AD + cerebrovascular diseases). VaD is a heterogeneous disease group in which the various categories may overlap at times.

This systematic review of the literature has generated the following specific conclusions.

The dominant view in the literature is that the *symptom profile* for VaD differs from that of AD. VaD is characterized by the following: mental slowness; impaired initiative, planning, and implementation ability (ie, executive function impairment); personality changes; and gait disorders (anterior brain syndrome). However, that has not received sufficient attention in different clinical and research contexts, such as when designing diagnostic manuals and pharmacological studies. If the field is to develop further, the symptom profile must be appropriately described and analyzed. There is also a great need for methodological advances aimed at identifying and measuring the severity of the cardinal symptoms of mental slowness and executive dysfunction.

Several articles demonstrate that *stroke* can lead to cognitive impairment (post-stroke dementia). However, there is a risk of overdiagnosis, given that some patients show signs of dementia even before a stroke episode. Worth noting is that the extent to which cognitive disturbance is progressive or nonprogressive has not been studied. Corroboration that it is progressive would suggest that the stroke episode initiates a process for development of dementia. Establishing that it is nonprogressive would support the assumption that the episode leads to a cognitive residual

syndrome. Finding out the extent to which stroke initiates a dementia process requires studies on refined patient groups that consider the occurrence of both major and minor stroke. Patients who have minor stroke with hemipareses or other loss are presumably the group that presents nonprogressive cognitive dysfunction. The damage that occurs is conceivably so extensive and/or clearly defined that there is little chance of progressive cognitive dysfunction. However, progressive cognitive dysfunction might be expected in patients with minor stroke, which is often a manifestation of lesions in the subcortical brain region, where concurrent, progressive white matter damage is common. Thus, there is good reason to coordinate research on minor stroke and white matter damage.

Now that vascular lesions can be imaged using *anatomical brain imaging technology*, we understand more about the association between vascular disease and dementia. However, what clinicians assume they can observe is often accepted without more thoroughly investigating the specific diagnostic and pathophysiological importance of particular vascular lesions. Anatomic brain imaging is a good deal more reliable in helping to identify vascular lesions than Alzheimer's lesions (senile plaque, neurofibrillary tangles), which cannot be identified by these methods. However, further studies are needed to investigate the importance of particular vascular lesions in cognitive impairment. From a routine clinical point of view, it is also essential to attract more interest among neuroradiologists and other neuroradiological professionals to the association between vascular lesions and cognition-impairing diseases.

The research of recent years has shown age-related *white matter lesions* to be signs of *small vessel disease* that leads to cognitive failure and impaired functional capacity. The disease profile that emerges is usually characterized by *subcortical VaD*. Although criteria exist for subcortical VaD, and although it is the most homogeneous and presumably the most common form of VaD, pharmacological and epidemiological studies have addressed it to a surprisingly limited extent. It has also been clinically underdiagnosed. The most important step toward providing more professional dementia care and gaining a greater understanding of subcortical VaD is to accept the disease as a distinct entity, as has been the case with AD. The second step is to conduct a closer investigation of white matter-lesi-

on threshold values for cognitive dysfunction, the importance of location, the association with atrophy changes, quantification, characteristics based on new brain imaging methods, the association with biomarkers, neuropathological correlates, prediction in longitudinal studies and specific pathogenesis – particularly in terms of hereditary and acquired factors.

Information on disease processes in the brain obtained from the determination of *neurochemical markers in the cerebrospinal fluid* has yielded clues for understanding VaD and its subtypes. Though substantially fewer than those on patients with AD, studies to date suggest that subcortical VaD differs pathophysiologically from AD. However, this field of research is relatively new. More studies are needed to clarify the neurochemical effects of cognitive impairment in conjunction with cerebrovascular disease.

The common *clinical criteria* (ICD-10, DSM-IV, ADDTC, NINDS-AIREN) for VaD are umbrella systems in that they do not consider the specific situation. Comparative studies show a lack of agreement among the systems. Despite similarities, they identify different patients and patient groups. Inadequate comparability erects a barrier to both research and patient care. Not only do these differences affect prevalence and incidence estimates, but clinical management becomes more capricious. In order to promote the development of more effective pharmacological treatments and other improvements, the criteria systems need to be modified and made more specific. Thus, greater attention should be paid to vascular mechanisms and subtypes. More extensive use of existing criteria for subcortical VaD would be a step in the right direction.

A review of *clinical neuropathological studies* on patients with VaD indicates that the configurations of ordinarily selected pathological criteria have varied from study to study. For that reason, the results are difficult to compare and are often misleading. The few studies that have attempted to consider the full range of cerebrovascular lesions have found them to be common, particularly the subcortical, small vessel disease and white matter damage that increasingly appears to be among the key fac-

tors underlying the origin of VaD. Further studies are needed to identify the pathological changes that are most important in the disease. As a result, neuropathological criteria and examination methods need to be specified and standardized.

Table 3.1 *Vascular mechanisms.*

Thromboembolism
Vessel wall damage (see also Table 3.10)
• Atherosclerosis
• Hyalinosis
• Amyloid angiopathy
Cerebrovascular insufficiency
• Disturbance of systemic circulation
• Vascular anatomy of the brain
• Disturbed regulation of cerebral blood flow
Hyperviscosity
Bleeding

Table 3.2 *Clinicopathological classification of vascular dementia [9]. Permission for publication granted.*

Large-vessel vascular dementia
Multi-infarct dementia – multiple large complete infarcts, cortical or subcortical in location, usually with perifocal incomplete infarction involving the white matter
Strategic infarct dementia – a single infarct in functionally critical areas of the brain (angular gyrus, thalamus, basal forebrain, or territory of the posterior cerebral artery or anterior cerebral artery)
Small-vessel vascular dementia
SIVD
Binswanger's disease
Lacunar dementia or lacunar state (état lacunaire)
Multiple lacunae with extensive perifocal incomplete infarctions
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL)
Cortical-subcortical
Hypertensive and arteriolosclerotic angiopathy
Cerebral amyloid angiopathies (including familial British dementia)
Other hereditary forms
Collagen-vascular disease with dementia
Venous occlusions
Ischaemic-hypoperfusive vascular dementia
Diffuse anoxic-ischaemic encephalopathy
Restricted injury due to selective vulnerability
Incomplete white-matter infarction

The table continues on the next page

Table 3.2 *continued*

Border-zone infarction
Haemorrhagic vascular dementia
Traumatic subdural haematoma
Subarachnoid haemorrhage
Cerebral haemorrhage
Modified with permission from the Taylor and Francis Group

Table 3.3 *Ischemic score [158].*

Symptom	**Score**
Abrupt onset	2
Stepwise deterioration	1
Fluctuating course	2
Nocturnal confusion	1
Relative preservation of personality	1
Depression	1
Somatic complaints	1
Emotional incontinence	1
History of strokes	2
Evidence of associated atherosclerosis	1
Focal neurological symptoms	2
Focal neurological signs	2
Max score	**18**

Table 3.4 *Vascular dementia: ICD-10 [156].*
See Chapter 2, Appendix 2.4.

Table 3.5 *Vascular dementia: DSM-IV [157].*
See Chapter 2, Appendix 2.3.

Table 3.6 *Vascular dementia: ADDTC [89].*
The criteria for the clinical diagnosis of probable ischemic vascular dementia (IVD) include all of the following:

1. Dementia.
2. Evidence of two or more ischemic strokes by history, neurologic signs, and/or neuroimaging studies (CT or T1-weighted MRI), or occurrence of a single stroke with a clearly documented temporal relationship to the onset of dementia.
3. Evidence of at least one infarct outside the cerebellum by CT or T1-weighted MRI.

The diagnosis of probable IVD is supported by the following.

1. Evidence of multiple infarcts in brain regions known to affect cognition.
2. A history of multiple transient ischemic attacks.
3. History of vascular risk factors (eg, hypertension, heart disease, diabetes mellitus).
4. Elevated Hachinski Ischemia Scale (original or modified version).

Clinical features that are thought to be associated with IVD, but await further research, include:

1. Relatively early appearance of gait disturbance and urinary incontinence.
2. Periventricular and deep white matter changes on T2-weighted MRI that are excessive for age.

3. Focal changes in electrophysiologic studies (eg, EEG, evoked potentials) or physiological neuroimaging studies (eg, SPECT, PET, NMR spectroscopy).

Other clinical features that do not constitute strong evidence either for or against a diagnsosis of probable IVD include:

1. Periods of slowly progressive symptoms.
2. Illusions, psychosis, hallucinations, delusions.
3. Seizures.

Clinical features that cast doubt on a diagnosis of probable IVD include:

1. Transcortical sensory aphasia in the absence of corresponding focal lesions on neuroimaging studies.
2. Absence of central neurological symptoms/signs, other than cognitive disturbances.

Table 3.7 *Vascular dementia: NINDS-AIREN [90,162].*

I. Topography Radiological lesions associated with dementia include ANY of the following or combinations thereof: 1. Large-vessel strokes in the following territories: Bilateral anterior cerebral artery Posterior cerebral artery, including paramedian Thalamic infarctions, inferior medial temporal lobe lesions Association areas: parietotemporal, temporooccipital territories (including angular gyrus) Watershed carotid territories: superior frontal, parietal regions 2. Small-vessel disease: Basal ganglia and frontal white matter lacunae Extensive periventricular white matter lesions Bilateral thalamic lesions
II. Severity In addition to the above relevant radiological lesions associated with dementia include: Large-vessel lesions of the dominant hemisphere Bilateral large-vessel hemispheric strokes Leukoencephalopathy involving at least ¼ of the total white matter Although volume of lesion is weakly related to dementia, an additive effect may be present. White matter changes observed only on T2 MRI but on T1 MRI or CT may not be significant. Absence of vascular lesions on brain CT/MRI rules out probable vascular dementia

Table 3.8 *Subcortical vascular dementia [166].*

I. The criteria for the clinical diagnosis of subcortical vascular dementia include all of the following :

   a. Cognitive syndrome including both
   Dysexecutive syndrome: Impairment in goal formulation, initiation, planning, organizing, sequencing, executing, set-shifting and –maintenance, abstracting, and Memory deficit (may be mild): Impaired recall, relative intact recognition, less severe forgetting, benefit from cues.
   Which indicate deterioration from a previous higher level of functioning, and are interfering with complex (executive) occupational and social activities not due to physical effects of cerebrovascular disease alone.

   b. Cerebrovascular disease including both
   Evidence of relevant cerebrovascular disease by brain imaging and
   Presence or a history of neurologic signs as evidence for cerebrovascular disease such as hemiparesis, lower facial weakness, Babinski sign, sensory deficit, dysarthria, gait disorder, extrapyramidal signs consistent with subcortical brain lesion(s).

II. Clinical features supporting the diagnosis of subcortical vascular dementia include the following:

   a. Episodes of mild upper motor neuron involvement such as drift, reflex asymmetry, incordination.

   b. Early presence of a gait disturbance (small-step gait or marche a petits-pas, magnetic, apraxic-ataxic or Parkinsonian gait).

   c. History of unsteadiness and frequent, unprovoked falls.

   d. Early urinary frequency, urgency, and other urinary symptoms not explained by urologic disease.

   e. Dysarthria, dysphagia, extrapyramidal signs (hypokinesia, rigidity).

   f. Behavioral and psychological symptoms such as depression, personality change, emotional incontinence, psychomotor retardation.

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

   a. Early onset of memory deficit and progressive worsening of memory and other cognitive functions such as a language (transcortical sensory aphasia), motor skills (apraxia), and perception (agnosia), in the absence of corresponding focal lesions on brain imaging.

   b. Absence of relevant cerebrovascular disease lesions on brain CT or MRI.

Table 3.9 *Neuropathological tissue lesions associated with vascular dementia according to the NINDS-AIREN criteria [90].*

- Arterial territorial infarction
- Watershed infarctions
- Lacunae
- Laminar necrosis
- Granular atrophy
- Subcortical leukoencephalopathy
- Gliosis or incomplete ischemic necrosis (including hippocampal sclerosis)

Table 3.10 *Neuropathological vessel lesions associated with vascular dementia [172].*

Extracerebral vessel lesions
- Atherosclerosis
- Arterial thrombosis
- Thrombo-embolism
- Fibromuscular dysplasia
- Collagen-vascular disease
- Arteritis

Intracerebral vessel lesions
- Arteriolosclerosis
- Hyalinosis
- Hypertensive angiopathy
- Angiopathy in hereditary forms of vascular dementia
- Amyloid angiopathy

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4. Dementia with Lewy Bodies

Background

Dementia with Lewy bodies (DLB) is a neurodegenerative disorder initially described in neuropathological settings, as well as in 1996 on the basis of clinical consensus criteria. DLB shares clinical, neuropathological and neurochemical features of both Parkinson's disease (PD) and AD. An ongoing debate concerns whether DLB is a disease entity of its own, a variant of AD or equivalent to Parkinson's disease with dementia (PDD). The current view of most researchers is that both PDD and DLB belong on a continuum of Lewy body (LB) disease.

Identifying a clinical phenotype is the principal means of disease diagnosis. Neurodegenerative diseases are increasingly recognized as involving abnormalities in protein metabolism that create different proteotypes, most commonly involving ß-amyloid (AD, IDLB), α-synuclein (PD, DLB, multisystem atrophy (MSA)) and tau (frontotemporal lobar degeneration (FLD), progressive supranuclear palsy (PSP), cortico basal degeneration (CBD) and AD). The various protein-related disease groups are associated with distinctive clinical phenomena. Synucleinopathies are characterized by hallucinations, delusions and rapid eye movement (REM) sleep behavior disorder. Dopaminergic neurons are selectively vulnerable to the toxic effects of α-synuclein accumulation. Dopamine metabolism generates free oxygen radicals, leading to lipid peroxidation, membrane disruption and cell death. It is possible that α-synuclein causes defective sequestration of dopamine into protective vesicles, resulting in unmitigated oxidative injury [1].

Objective

The objective was to summarize current evidence of the relationship between DLB and AD/PDD on a clinicopathological and etiological level.

Questions

1. What clinical criteria should be used in DLB?
2. How accurate is the clinical DLB diagnosis (sensitivity, specificity)?
3. How is DLB classified and distinguished from other degenerative diseases by means of etiological/pathophysiological factors?

Methods

Inclusion

Papers published in 1966–2004 were included, with the exception of updated consensus criteria for DLB 2005 [2]. Only original articles published in English were considered. The database source was PubMed (Medline). The search used the MeSH term "Lewy body diseases" and keywords "classification, etiology, genetics, pathology and physiopathology".

The search yielded 408 articles. Based on a review of the abstracts, 260 articles were found to be potentially relevant to the topic. Studies were selected with the aim of identifying clinicopathological and biochemical descriptions. Those that focused on neuropathology, symptoms and diagnostic methods only were excluded.

The abstracts were classified according to their content and sorted into 3 main groups:

1. Etiology/pathophysiology (152)
   - Genetics (48)
   - Neurochemistry (Ach, DA, 5 HT) (33)
   - Morphology – LBs and their content (38)
   - Factors associated with oxidative stress, inflammatory processes and apoptosis (19)
2. Criteria (7)

3. Clinicopathological validation – clinical criteria, symptoms or diagnoses (101)
   - Clinical criteria (6)
   - Symptoms: parkinsonism (3), psychosis (6), cognition (21)
   - Diagnoses: AD (35), LB diseases (PD, Diffuse Lewy body disease (DLBD)) (21), Creuzfeldts-Jacobs disease (6), PSP/MSA (2), CBD (1).

Results

Background data

The neuropathology of DLB

The LB is the central histopathological feature of both PD and DLB. LBs are located in both the brainstem and cortex. The degree of LB pathology does not differentiate DLB from PD or PDD, although its location is more temporal in DLB [3] and more limbic/frontal in PDD [4,5].

Atrophy is more limited in DLB and PDD than other dementias. In particular, the medial temporal lobe and hippocampus appear to be spared more than in AD [6,7]. AD-type pathology in the form of Aß-positive plaques is a common feature of DLB, exhibiting a density that is equivalent to AD but less than PDD [8]. Tangle density is less in DLB than AD, sometimes giving rise to a "plaque only" picture [9].

Below are the percentage of cases with LBs (brainstem, limbic, cortical) in more general autopsy series (Table 4.1) and populations with dementia (Table 4.2).

Table 4.1 *Percentage of cases with LBs in autopsy series.*

Author Year Reference	n	Patients	Age at death LB patients
Lennox et al 1989 [10]	216	Referrals to dept of pathology from all clinics	77
Ince et al 1995 [11]	92	Community, nursing homes	85
Lindboe et al 1998 [12]	284	Referrals to dept of pathology from all clinics	78
Akatsu et al 2002 [13]	239	Patients who died at a geriatric hospital	78
Wakisaka et al 2003 [14]	102	Community, prospective	88

α-sy = α-synuclein; DLB = Dementia with Lewy body; HE = Hematoxylin Eosin; LB = Lewy body; NA = Not applicable; ubiq = Ubiquitin

Remarks: LB frequency in autopsy series may be estimated at 20%. An early study by Gibb et al addressed the question of LBs in an aging phenomenon (see Chapter 2, reference 413). A pattern of increasing LB frequency with age was found in both AD (13–15% above age 60) and control brains (4–13% in age 50–89). One difficulty in interpreting these percentages is to determine whether or not LB pathology is directly related to dementia.

	Stain	% LB	Concomitant AD
	Ubiq	7	Plaques 100% Tangles 27%
	Ubiq	20	77%
	Ubiq	8	Plaques 45% Tangles 95%
	Ubiq α-sy	18	NA Only 1 "pure" DLB
	α-sy	22	58%

Table 4.2 *Percentage of cases with LBs in clinical series.*

Author Year Reference	**n**	**Patients**	**Age at death LB patients**
Bergeron et al 1989 [15]	150	Brainbank	75
Leech et al 2001 [16]	98	Brainbank	?
Barker et al 2002 [17]	382	Brainbank	F: 24%/M: 38% <70 F: 19%/M: 25% >70
Xuereb et al 2002 [18]	52	Community, prospective epidem study	All dementia patients >85
Wakisaka et al 2003 [14]	29	Community, prospective	88

α-sy = α-synuclein; AD = Alzheimer's disease; HE = Hematoxylin Eosin; LB = Lewy body; ubiq = Ubiquitin

Remarks: LB frequency varies from study to study but appears to increase along with more sensitive staining methods (α-sy >ubiq >HE) and be highest in studies with the highest representativity (community-based). To a certain extent, the staining method limits the ability to detect LBs, especially cortical.

Type of dementia	Clinical data	% LB	Stain	Concomitant AD
Clinical dementia, pathological AD	No	25	HE	100%
All kind of dementia	No	13	Ubiq	100%
All kind of dementia	Clinical diagn	26	α-sy	66%
All kind of dementia	Clinical criteria for dementia	23	Ubiq	?
All kind of dementia	Clinical criteria for dementia	41	α-sy	58%

What criteria should be used in DLB?

Since the first publication of three cases with dementia and diffusely spread LBs in the brainstem and cortex [19], several sets of clinicopathological criteria have emerged under such titles as senile dementia of Lewy body type (SDLT), diffuse Lewy body disease (DLBD) and Lewy body variant of Alzheimer's disease (LBV). The first consensus criteria were published 1996. Consensus was reached to use the name dementia with Lewy bodies (Table 4.3).

Table 4.3 *Chronology.*

Author Year Reference	Name		Characteristics	Focus
Kosaka 1978 [20]	Diffuse Lewy body disease, common and pure	DLBD		Neuropathological
Hansen et al 1990 [21]	Lewy body variant of Alzheimer's disease	LBV	Deficits in attention, fluency and visuospatial processing Parkinsonism	Clinicopathological evaluation
Byrne et al 1990 [22]	Diffuse Lewy body disease	DLBD	Parkinsonism, dementia and fluctuations	Clinicopathological evaluation Clinical criteria – Nottingham
McKeith et al 1992 [23]	Senile dementia of Lewy body type	SDLT	Fluctuations + visual hallucinations/ Parkinsonism/falls	Clinicopathological Clinical criteria – Newcastle
McKeith et al 1996 [24]	Consensus criteria	DLB	Dementia + fluctuations, visual hallucinations, Parkinsonism	Clinicopathological criteria
McKeith et al 2005 [25]	Updated consensus criteria	DLB/PDD Lewy body disease	Dementia + fluctuations, visual hallucinations, Parkinsonism REM sleep disorder Neuroleptic sensitivity	Clinicopathological criteria

DLBD = Diffuse Lewy body disease; LBV = Lewy body variant of Alzheimer's disease; PDD = Parkinson's disease with dementia; SDLT = Senile dementia of Lewy body type

Figure 4.1 *Present criteria from workshop on DLB/PDD 2003 [25].*

1. ***Central feature*** Progressive cognitive decline of sufficient magnitude to interfere with normal social and occupational function. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits of tests of attention, executive function and visuospatial ability may be especially prominent.

2. ***Core features*** (*two* core features essential for a diagnosis of probable, one for possible DLB).
   Fluctuating cognition with pronounced variations in attention and alertness.
   Recurrent visual hallucinations that are typically well formed and detailed.
   Spontaneous features of parkinsonism.

3. ***Suggestive features*** (one or more present in addition to one or more core features is sufficient for a diagnosis of probable DLB, and in the absence of any core features is sufficient for possible DLB).
   REM sleep behavior disorder (which may precede onset of dementia by several years).
   Severe neuroleptic sensitivity.
   Abnormal (low uptake) in basal ganglia on SPECT dopamine transporter scan.

4. ***Supportive features*** (commonly present but lacking diagnostic specificity).
   Repeated falls and syncope.
   Transient, unexplained loss of consciousness.
   Severe autonomic dysfunction that may occur early in disease eg orthostatic hypotension, urinary incontinence.
   Systematized delusions.
   Hallucinations in other modalities.
   Depression.
   Relative preservation of medial temporal lobe structures on CT/MRI scan.

Generalized low uptake on SPECT/PET perfusion scan with reduced occipital activity.
Prominent slow wave activity on EEG with temporal lobe transient sharp waves.
Abnormal (low uptake) MIBG myocardial scintigraphy.

5. ***A diagnosis of DLB is less likely in the presence of*** cerebrovascular disease evident as focal neurological signs or on brain imaging, or any other physical illness or brain disorder sufficient to account in part or in total for the clinical picture [25].

6. ***Temporal sequence of symptoms***
   DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism (if present). PDD should be used to describe dementia that occurs in the context of well-established PD. In practice setting generic terms such as Lewy body disease is often helpful. In research studies the one-year rule between the onset of the dementia and parkinsonism continues to be recommended. In research settings that may include clinicopathological studies and clinical trials, both clinical phenotypes may be considered collectively under categories such as Lewy body disease or synucleinopathy.

Accuracy of diagnostic criteria

The imperfect fit between clinical and neuropathological features in dementia is a generally accepted fact. The best that is hoped for at present is an assessment of the likelihood that the neuropathological findings will account for dementia [26]. Such an assessment brings out the difficulties associated with separate neuropathological and clinical entities and the search for a perfect overlap. However several studies identified by our search investigated the overlap in terms of sensitivity and specificity.

Table 4.4 *Accuracy of diagnostic criteria.*

Author Year Reference	Patients	n	Prospective diagnoses
McKeith et al 1994 [27]	Hospital based	n: 50 Autopsy SDLT: 20	Dementia
Papka et al 1998 [28]	Neuropath database Clinical data from ADRC study	n: 39 Autopsy LBD: 18	Dementia
Litvan et al 1998 [29]	Neuropath cases, case vignettes	n: 105 DLB: 14 PD: 15 Not PD/DLB: 76	Clinical diagnoses autopsy confirmed
Verghese et al 1999 [30]	Patients in an aging study	n: 94 Autopsy DLB: 18	Dementia
Luis et al 1999 [31]	Brainbank	n: 56 Autopsy DLBD: 23 AD + DLBD: 12	Dementia, AD, DLBD, Binswanger
McKeith et al 2000 [32]	Specialist outpatient clinic, old age psychiatry	n: 50 Clinical	26 DLB CC 19 AD 5 VaD
Del Ser et al 2001 [33]	Longterm dementia project with autopsy	n: 46 Pure DLB + AD/ LB: 29	Dementia
Lopez et al 2002 [34]	Multidiscipl research clinic ADRC	n: 46 DLB Autopsy DLB: 26	46 DLB CC

AD = Alzheimer's disease; ADRC = Alzheimer disease research center; DLB = Dementia with Lewy Body; DLBD = Diffuse Lewy body disease; DLB CC = DLB consensus criteria; PD = Parkinson's disease; SDLT = Senile dementia of lewy body type; VaD = Vascular dementia

	Retrospective criteria evaluation	Sensitivity/Specificity prob DLB	Type of study
	Nottingham Newcastle	0.65 0.85/0.97	Retrospective
	DLB CC Newcastle	0.89/0.29	Retrospective
	DLB CC	0.18–0.29/0.99–0.97 (first-last visit)	Retrospective
	DLB CC	0.61/0.84	Retrospective
	DLB CC DLB CERAD Newcastle	0.57/0.90	Retrospective
		0.83/0.95	Prospective evaluation of DLB consensus criteria
	DLB CC	0.48/0.88	
		0.31/1.0	Prospective evaluation of DLB consensus criteria

The question of representativity is relevant, given that almost all of these studies are retrospective and/or based on patients treated at hospitals or by specialists. The few prospective evaluations exhibit diverse sensitivity but good specificity, with the exception of one characterized by both good sensitivity and high specificity [32]. In the wake of the improved clinical criteria in 2005, a further prospective evaluation of their accuracy is of the utmost importance.

How is DLB classified and distinguished from other degenerative diseases by means of etiological factors?

Attempts to answer this question illustrate the search for disease mechanisms by analyzing the pathological hallmark: the LB; factors involved in neurodegeneration, such as inflammatory processes and oxidative stress; neurochemical disturbances and underlying genetic factors.

Biochemical composition of the LB

The search identified 43 articles as relating to the biochemical composition of the LB. Twentyseven addressed various aspects of alpha-synuclein, 4 of ubiquitin and 12 other aspects of LBs.

LBs are the neuropathological hallmark of PD [35]. The LB is an inclusion body consisting of cytoskeletal neurofilament protein, ubiquitin and alpha-synuclein. Alpha-synuclein is located throughout the brain, though more abundant in the brainstem, limbic and neocortical areas [36]. It is found in DLB, PD and MSA, linking them as synucleinopathies [37]. While the function of alpha-synuclein remains unclear, its overexpression may impair exocytosis of the neurotransmitters. Alpha-synuclein is thought to have a propensity – enhanced by factors such as mutations, hyperphosphorylation, nitration and oxidation – to form aggregates [38,39]. Protective elements, including the chaperones clusterin and torsin, have been identified in colocalization with alpha-synuclein [40,41].

The LB is described as undergoing various developmental or degrading processes that involve different structures, such as micro- and astroglia [42,43].

Immunohistochemical and protein chemical studies indicate that LBs and Lewy neurites (LNs) are pathological aggregations of alpha-synuclein. LBs and LNs are associated with intermediate filaments, chaperon proteins and elements of the ubiquitin-proteasome system, indicating that the aggresomal response plays a role. However, these features are not specific to LBs and are also found in other neuronal inclusions [44].

Oxidative stress and inflammation

The search yielded 19 articles, 4 with a clear focus on oxidative stress and 5 on inflammatory factors. All 4 articles discuss results that indicate oxidative stress processes in DLB. The processes are shared by PD in 3 articles and AD in 1 article. The 5 papers on inflammation investigated different factors. The results of only one study contrasted with those regarding AD.

Table 4.5 *Etiology/pathophysiology – oxidative stress.*

Author Year Reference	n total/DLB	Focus	Signs of oxidative stress in DLB
Aksenova et al 1999 [45]	81/13	Creatinkinase in frontal lobes	Yes and in AD
Castellani et al 2002 [46]	13/5	Lipidperoxidation	Yes and in PD
Fessel et al 2003 [47]	25/4	Isofuranes in SN	Yes and in PD
Power et al 2002 [48]	17/5	Nonselenium glutation peroxidas (antioxidant)	Yes and in PD

DLB = Dementia Lewy body; PD = Parkinson's disease; SN = Substantia nigra

Table 4.6 *Etiology/pathophysiology – inflammation.*

Author Year Reference	**n total/ DLB**	**Focus**	**Signs of inflammatory mechanisms in DLB**
Shepherd et al 2000 [49]	29/8	HLA-DR reactive glia	No Less than in AD
Katsuse et al 2003 [50]	15/5	IL-1 α, TNF α (cytokines) iNOS (free radical)	Yes and in AD
Mackenzie 2000 [51]	20/5	Activated microglia	Yes and in AD
Rozemuller et al 2000 [52]	25/15	Activated glia and relation to LB bearing neurons	No
Gomez-Tortosa et al 2003 [53]	104/25	CSF interleukin 1ß and 6	No neither in AD, controls

AD = Alzheimer's disease; CSF = Cerebrospinal fluid; DLB = Dementia with Lewy body; HLA-DR = Human leukocyte antigen; IL-1 = The protein interleukin; iNOS = Inductible nitric oxide synthase; TNF = Tumor necrosis factor

Neurochemistry and DLB

The search yielded 33 articles on neurochemistry and DLB. All subjects in cholinergic studies were neuropathologically verified. Loss of cholinergic neurons in the basal forebrain was found in DLB, PDD and PD. A pronounced and significant neuronal loss in nucleus basalis of Meynert and the septal forebrain areas was found in PD and DLB [54,55]. Eleven of the papers investigated cholinacetyl transferase (ChAT) levels, a marker of cortical cholinergic activity, although five were from the same material [56–62]. However, all papers showed a reduction of ChAT activity in both AD and DLB – as well as PD, which was investigated in three papers. The cholinergic deficiency was sometimes even more pronounced in DLB than AD. Eight studies found nicotinic receptor loss in DLB and AD [63–69]. Four papers investigated muscarinic receptors and obtained differing results: a reduction in DLB and PDD in 1 paper, a reduction in DLB and AD in 1 paper, and an increase in PD and DLB in 2 papers (same material) [65,70,71].

Caudate nucleus dopamine loss is pronounced in both DLB and PD. The degree of cell loss in the dopaminergic substantia nigra suggests a similar pattern in DLB, PDD and PD, as well as correlating with disease duration [72]. Eight studies, 4 neuropathological and 4 based on clinical material, found consistent loss of DA in PD and DLB but not in AD. That confirmed a nigrostriatal dopaminergic dysfunction in DLB [57,58,73–79].

Few articles dealt with other neurotransmitters. Three focused on serotonin (5-HT), while all of them described preservation of 5-HT receptors in DLB as associated with hallucinations and depression [58,80,81].

One article highlighted the noradrenergic system, showing upregulation of postsynaptic A2 receptors as a response to loss of noradrenergic innervation in AD and DLB [82]. The only study yielded by this search found a decrease of glutamate receptors in the entorhinal cortex and hippocampus for both AD and DLB [83].

To sum up, neurochemical differences exist among the various neurodegenerative disorders but do not clearly distinguish DLB from AD, PDD and PD. AD, PDD and PD share the cholinergic deficiency, whereas the dopaminergic deficiency appears in DLB, PDD and PD. The consistent dopaminergic deficit is becoming a useful clinical imaging tool for differentiating DLB from AD and other dementia syndromes [84].

Genetics

Rare mutations of the alpha-synuclein gene on chromosome 4 cause PD [85,86]. However, only a minority of such people develop significant dementia [87]. Among the 48 articles on genetic factors, 9 investigated ApoE4 frequencies (Table 4.7), 5 focused on CYP2D6, 7 reported familial cases and 1 described a genetic epidemiological study.

Other topics included nitric oxide synthetas polymorphism (3 articles), mitochondrial DNA and RNA mutations (4 articles), polymorphism in NURR-1, DJ-1 and the transferrin gene.

ApoE epsilon 4 (ApoE4) allele is the most common identifiable genetic susceptibility factor for AD. Thus, ApoE4 frequency in DLB has been one justification for the argument that a genetic relationship to AD and DLB is a variant of AD. The cumulative evidence of the above studies (all performed on pathologically verified cases) is that ApoE4 in DLB is at the same level as, or just below, AD. However, the relation to LBs and vascular factors must also be taken into account. Knowledge is unable to distinguish between AD and DLB in terms of ApoE.

Table 4.7 *Etiology and genetics.*

Author Year Reference	Patients	ApoE4 frequency %	Increased ApoE4 in DLB
St Clair et al 1994 [88]	LBD: 39 AD: 68 Controls: 47	35 38 13	Yes
Galasko et al 1994 [89]	LBV: 40 AD: 74 DLBD: 8	29 40 6	Yes when coexisting AD
Betard et al 1994 [90]	Early AD: 21 Late AD: 70 LBV: 18 AD+VaD: 38 VaD: 19	40 36 47 51 8	Yes
Hardy et al 1994 [91]	AD: 13 PD: 24 LBD: 23 Controls: 11	43 10 25 10	Yes
Harrington et al 1994 [92]	AD: 67 SDLT: 26 PD: 51 VaD: 12 Hunt: 41 Controls: 50	33 36 10 25 17 15	Yes
Martinoli et al 1995 [93]	AD: 17 AD + cort LB: 10 DLBD: 4 PD + dem: 3 PD + AD: 9 AD + PD: 6 PD: 10	23 40 38 17 22 17 10	Yes
Morris et al 2003 [94]	Early AD: 17 Late AD: 64 LBD: 42 PD: 11 PD + dem: 12 Down: 28	33 46 38 18 21 29	Yes

The table continues on the next page

Table 4.7 *continued*

Author Year Reference	Patients	ApoE4 frequency %	Increased ApoE4 in DLB
Premkumar et al 1996 [95]	(AD with DLBD: 33) DLBD no CAA: 14 DLBD with CAA: 19 Controls: 16	27 4 45 15	Yes, but only in cases with CAA
St Clair 1997 [96]	LBD: 39 PD: 50 Early AD: 85 Late AD: 68 Controls: 47	35 19 41 38 13	Yes

AD = Alzheimer's disease; CAA = Congophil amyloid angiopathy; DLBD = Diffuse Lewy body dementia; Hunt = Huntington's disease; LBD = Lewy body dementia; LBV = Lewy body variant of Alzheimer's disease; PD = Parkinson's disease; SDLT = Senile dementia of Lewy body type; VaD = Vascular dementia

Remarks: Because the majority of the studies were published before 1996 (year of the consensus meeting and the adoption of the name DLB), many different disease labels are used.

Based on clinicopathological features, many molecular studies have examined hypotheses that DLB shares genetic etiologies with AD and/or PD. Particular attention has been devoted to cytochrome P450IID6 (debrisoquine 4-hydroxylase: CYP2D6). This enzyme plays an important role in catalyzing the metabolism of a number of drugs and inactivating biologic toxins. One mutant gene allele has been reported to be overrepresented in PD [97,98]. One early study of DLB showed results similar to those for PD [99], but others found no differences between AD and controls [100–103].

Familial cases of DLB have been reported. Our search identified 7 reports of families with at least one autopsy proven DLB case. Three of the reports were on AD families with autopsy proven AD and LB pathology. Two of the families had a mutation at codon 717 of the APP gene

on chromosome 21 [104,105]. LBs appeared in all but one case. One family member also had severe cerebrovascular disease combined with AD and LB. The ApoE genotype varied. The other study of 22 families established a linkage to chromosome 12 in 4 of them [106]. These genetic findings had previously been reported in familial AD. One family had a clinical presentation of FTD and 1 autopsy showing AD + LB, while 4 other members had clinical DLB [107].

One parkinsonian kindred of 6 generations found clinical phenotypes with pure parkinsonism, pure dementia or both. One autopsy showed LB pathology without AD [108]. A report on 2 families with DLB in 10 and 7 members respectively showed significant clinical heterogeneity with visual hallucinations in 1 family only, as well as parkinsonism – if present – late in the course of the disease. LBs appeared in all cases, along with AD in individual members of both families. All affected members carried at least one ApoE ε4 allele and no alterations in the synuclein or parkin genes [109]. A genetic epidemiology study of 191 patients with dementia indicated that familial clustering was strongest for patients with large onset AD or DLB [110]. The study found evidence of an association between alpha-2-macroglobulin (a gene located on chromosome 12) and DLB.

Among other genetic risk factors that have been proposed are 1) mitochondrial tRNAA4336G mutation, both for AD and PD [111], not AD; 2) the mtDNA haplotype H overrepresented in DLB [112]; 3) repeat variation in the NOS2A gene (in DLB, not AD) [113], not in AD or DLB [114]; and 4) polymorphism in the NURR1 gene (in PD and with borderline significance in DLB) [115].

Taken altogether, these studies do not reveal evidence that a particular candidate gene differentiates DLB from other degenerative disorders. However, additional studies are needed to determine the interaction between genetic predisposition and environmental factors.

CSF studies

Of the 4 CSF studies on DLB that were identified, 3 investigated Aß42 and tau levels as a reflection of plaques and tangles in the brain. Clark et al 2003 [116] correlated premortem CSF results with postmortem findings, concluding that CSF tau levels are associated with AD pathology. The studies of DLB cases showed levels of Aß42 that were similar (low) to AD, as well as normally low levels of tau in DLB, as opposed to elevated levels in AD [53,117].

More studies are needed for confirmation, although these studies all point to the plaque-dominated neuropathological findings described above. No methods are yet available for investigating alpha-synuclein.

Conclusions

DLB has a recognizable clinical phenotype that is differentiated from PDD on an operational basis only. In PDD, the parkinsonian symptoms clearly precede the dementia by at least one year. In DLB, the parkinsonism and dementia are more likely to start concurrently. A clear differentiation from AD is not possible based on our current knowledge of etiological factors. DLB probably exemplifies the convergence of various pathological processes (alpha-synuclein, ß-amyloid) shared by other neurodegenerative disorders as well. Identifying these processes in vivo is the challenge that lies ahead and the basis for treating these patients.

Finally, classification issues remain unresolved. As a result, further research is needed to determine whether DLB is best regarded as a separate disease entity or as on a continuum with LB and Alzheimer changes.

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5. **Disease Entity – Frontotemporal Dementia**

Background

Frontotemporal dementia (FTD) is regarded as one of the most common primary degenerative dementia disorders. It is usually distinguished from other dementia disorders, but the accumulated evidence that FTD is a separate disease entity with a specific etiology and homogenous clinical syndrome, as well as a corresponding macroscopic and microscopic pattern, has not been fully analyzed and summarized. Various subtypes of FTD have also been suggested, but the cumulative evidence that they are unique disease entities has not been presented. Below are the results of a literature search that was conducted for the purpose of identifying, analyzing and summarizing the evidence accumulated up until April 2005 for FTD as a unique disease entity.

Objectives and limits

The primary objective of the literature search was to identify, analyze (grade according to quality) and summarize the cumulative published evidence for FTD as a separate disease entity. The secondary objective was to identify, analyze and summarize the cumulative evidence for the suggested subtypes of FTD as separate disease entities. Early publications were included in the search, but the main focus was on more recent studies that applied multiple techniques to delineate FTD. Articles that mainly described other neurodegenerative disorders – such as neuroacanthocytosis, including body myositis associated with Paget's disease and schizophrenia – were excluded. Given that FTD may be on a spectrum of disorders, neurodegenerative disorders that were placed in the same context as FTD and identified with search terms such as corticobasal degeneration and progressive supranuclear palsy were included in the analysis.

Methods

Inclusion and exclusion criteria

1) *Time period*: 1966 to the present (September 1, 2003: updated search April 1, 2005).
2) *Language*: mainly English, as well as some early German publications.
3) *Type of article*: Originals, but also some reviews (articles describing diagnostic criteria were also included).
4) *Keywords*: a) Frontal lobe AND dementia, Frontotemporal, Pick disease of the brain, AND b) classification, subgroup, subtype, criteria, entity, etiology, cause and mutation.
5) *Database, sources*: PubMed (Medline), citations of available literature, personal knowledge.

Studies included

The search identified 1 374 articles, 483 of which were duplicates and thereby deleted. Of the remaining 891 articles, 158 were reviews and thereby deleted, while 24 dealt with non-human issues only and were also deleted (note that there was some overlap). After the remaining 722 abstracts and/or titles had been read through, 633 were excluded for one or more of the following reasons: was not relevant to the topic, included only neurodegenerative disorders other than FTD, included too few cases of FTD, was a review but not pertinent. The remaining 89 articles, along with 9 not found in PubMed but identified in the course of reading, were included. Fiftynine publications identified while reading these 98 articles were also deemed to be relevant to the objectives and thereby included. All 157 articles were analyzed and graded according to quality, after which relevant information gleaned from the reading was input into an Access database.

An updated search performed in April 2005 covering the period from September 2, 2003 to April 1, 2005 found 206 new articles, 10 of which were identified and thus included.

Quality assessment strategy

Based on the two objectives stated above, heavy emphasis was placed on studies that offered the following:

1. A coherent clinicopathological pattern in patients presenting a primary cortical neurodegenerative, non-Alzheimer, non-Lewy-body type of dementia disorder affecting frontotemporal brain regions.
2. Evidence for a specific cause (such as mutation) of the disorder described in Item 1. It should neither be a general cause of dementia nor lead to other types of dementia disorders, such as AD.

Checklist

The following quality grading variables were recorded: clinical symptomatology, neuropsychology, brain imaging, neurochemistry, pathology, genetic analyses, hypothesis-driven deductive or validating study, prospective longitudinal study, specified inclusion criteria, large groups included (defined as 20 or more patients in the FTD group), representativity (based on origin of the sample), dropouts recorded, clinicopathological study, blinded study, generalizability (based on representativity and the number of methods/dimensions used in the study). The sum (total variable) – a maximum of 15 points – was recorded (Table 5.1).

In addition, a summary variable (sum variable), based on three variables that were more important with regard to the specified aim of the review, was constructed from the checklist. The following three variables were included: 1) clinical symptomatology, with the optional inclusion of neuropsychology; 2) pathological description; and 3) genetic analyses (Table 5.2).

Summary of the available literature

All articles receiving a score of 3 on the sum variable were automatically selected for the review. For articles that scored 2 on the sum variable, a total variable of 6 was needed for inclusion. One hundred twenty of the 157 articles were found to be unacceptable and thus excluded from the final review, while 37 were included.

Of the 10 articles taken from the updated search in April 2005, three were unacceptable in accordance with the criteria and thereby excluded, while 7 were included. Thus, a total of 44 articles were ultimately included.

Results and discussion

Cumulative evidence that FTD is a unique disease entity

The evidence for FTD as a unique disorder has been most clearly described for FTD that is caused by mutations in the tau gene [1]. More than 70 original scientific papers have described tau mutations in patients with primary degenerative dementia disorders. Many of the papers contain data on neuropsychiatric features, neuropsychology, brain imaging, and pathology, including immunohistochemical characterization. According to current research, tau mutations do not give rise to either AD [2–4] or PD [5]. Thus, there is substantial evidence to support the hypothesis that FTD caused by mutations in the tau gene is a unique disorder. However, this disorder is not homogenous, given that there is clinical [6,7] and pathological [8] heterogeneity for one given cause (mutation) both within and among families. In other words, a specific mutation can give rise to two clinical or pathological manifestations or patterns [6,9], such as corticobasal degeneration and progressive supranuclear palsy. The source of this heterogeneity remains unclear, although environmental factors apparently interact. As of November 2005, at least 58 different mutations had been identified in the tau gene – including missense mutations in coding regions of different exons, mutations in alternatively spliced exon 10 and mutations in the exon 10 5' splice site – that give rise to phenotypical (clinical and pathological) variations in the FTD spectrum. Any overlap with other disorders is only minor.

FTD is also described in terms of a linkage to chromosome 9 (FTD-9) [10]. This type of FTD – which presents alone, as ALS alone or concomitantly with ALS – is neuropathologically characterized by the presence of ubiquitin inclusions. However, FTD caused by mutation in the tau gene may also lead to ALS or ALS-like clinical manifestations [11]. A third type is chromosome 3 linked FTD (FTD-3) [12]. A limited degree of tau pathology has been described in FTD-3 [13], but the

relation to FTD caused by mutations in the tau gene remains to be elucidated. The clinical manifestations of FTD-9 and FTD-3 are similar to FTD caused by mutation in the tau gene. As of September 2003, no mutated gene had been identified in FTD-9. However, a mutation in the charged multivesicular body protein 2B (CHMP2B) gene was recently described as causing FTD-3 [14].

Other mutations, such as a heterozygous mutation in the sterol 27-hydroxylase gene (CYP27), may occasionally generate a clinical picture similar to FTD. This mutation usually causes cerebrotendinous xanthomatosis and abnormal cholesterol metabolism but may also give rise to clinical FTD [15]. A mutation in the gene coding for the cholesterol binding protein HE1 (NPC2), causing slowly progressive Niemann-Pick disease type C (NPC) but absent the typical lysosomal storage in bone marrow and viscera, may also occasion clinical FTD that presents neuropathological changes of combined NPC and tauopathy. A large pedigree with multisystem myotonic nondystrophic myotonia 1 (non-DM1) – non-DM2 disorder with clinical features of FTD – was recently described. FTD developed after the onset of dystrophic myotonia, and a linkage to chromosome 15q21–24 was described [16]. Furthermore, mutations in the valosin-containing protein gene on chromosome 9p 13–p12 have been found to cause autosomal dominant inclusion body myopathy associated with both Paget's disease of the bone and FTD [17].

Mutations in the presenilin 1 gene (L113P mutation and an arginine insertion at codon 352) have also been found to lead to clinical FTD [18,19]. The fact that mutations typically leading to AD may also give rise to clinical FTD calls into question the uniqueness of the clinical manifestation of FTD.

The most extensive cumulative evidence that FTD is a separate disease entity has been found for the subtypes caused by mutations in the tau gene. The subtypes of FTD presented in this category include neuropathologically defined Pick's disease [20,21], clinical and neuropathological corticobasal degeneration [8,9], progressive supranuclear palsy [6,22,23], and ALS [11]. The heterogeneity of FTD caused by tau mutations also includes clinical manifestations such as a purely aphasic

disorder. However, no single cause or unique histopathological pattern associated with the proposed FTD subtypes of progressive nonfluent aphasia and semantic dementia has been identified. Nor has any single cause of dementia lacking distinctive histological features (DLDH) been found. These phenotypical patterns seem to be on the FTD spectrum of clinical expressions instead, though less distinct than corticobasal degeneration, etc. Thus, the current cumulative evidence that these putative subtypes are separate disorders remains weak.

Following are the best-known diagnostic criteria for FTD:

- The Lund-Manchester Research criteria [24]
- Frontotemporal lobar degeneration: Consensus criteria [25]
- Clinical and pathological diagnosis of frontotemporal dementia [26]
- Clinical characteristics as described by McKhann et al [26] (See Fact Box 5.1)
- Recommendations for classification of FTD according to McKhann et al [26] (See Fact Box 5.2).

Possible methodological errors

Other approaches to this literature exercise may possibly have yielded different results. For example, the terms FTD, frontal lobe, dementia and Pick's disease of the brain might not have allowed for the inclusion of all relevant disorders linkable to the disease entity that we are calling FTD. Furthermore, PubMed/Medline does not include all published articles that may have been relevant to this study, and some disorders that were excluded from the very start could indeed have been pertinent. Moreover, our criteria for a unique disease entity may have been over-inclusive or excessively narrow.

Conclusions

There is a large body of evidence that FTD is a unique primary degenerative dementia disorder (ie, no association with AD or dementia associated with PD) when caused by mutation in the tau gene. FTD with linkage to chromosomes 3 and 9 constitutes other putatively unique disorders, but the genes underlying these forms remain to be identified.

The clinical manifestation of FTD is not unique and may be caused by mutations that usually lead to other primary degenerative dementia disorders. Among such mutations may be those in the presenilin 1 gene that usually cause AD or those that usually lead to cerebrotendinous xanthomatosis, Niemann-Pick C, etc. Furthermore, there is vast clinical and neuropathological heterogeneity within FTD caused by tau mutations. That buttresses the argument for using "syndromes" as a term to describe clinical manifestations such as clinical FTD, corticobasal degeneration, PSP, semantic dementia and progressive nonfluent aphasia. In addition, the current cumulative evidence that the proposed FTD subtypes of progressive nonfluent aphasia and semantic dementia are unique neurodegenerative disorders remains weak.

We have also concluded that the clinical and pathological heterogeneity of one particular mutation brings out the influence of environmental factors on the phenotype. Such heterogeneity also implies that mutations in certain genes lead to dementia rather than to a specific phenotypic expression, thereby supporting the use of the term "dementia (causing) genes". The presenilin 1 gene has been proposed as one such dementia gene.

Given that genotyping is possible, we suggest that a future revision of ICD-10 include a category for FTD caused by mutations in the tau gene and enable classification of FTD.

Recommended areas for future research

- Mutations that underlie FTD with linkage to chromosome 9
- Other mutations that may cause FTD
- Other environmental factors that may influence the phenotypical expression of FTD.

Table 5.1 *Sample checklist for FTD articles.*

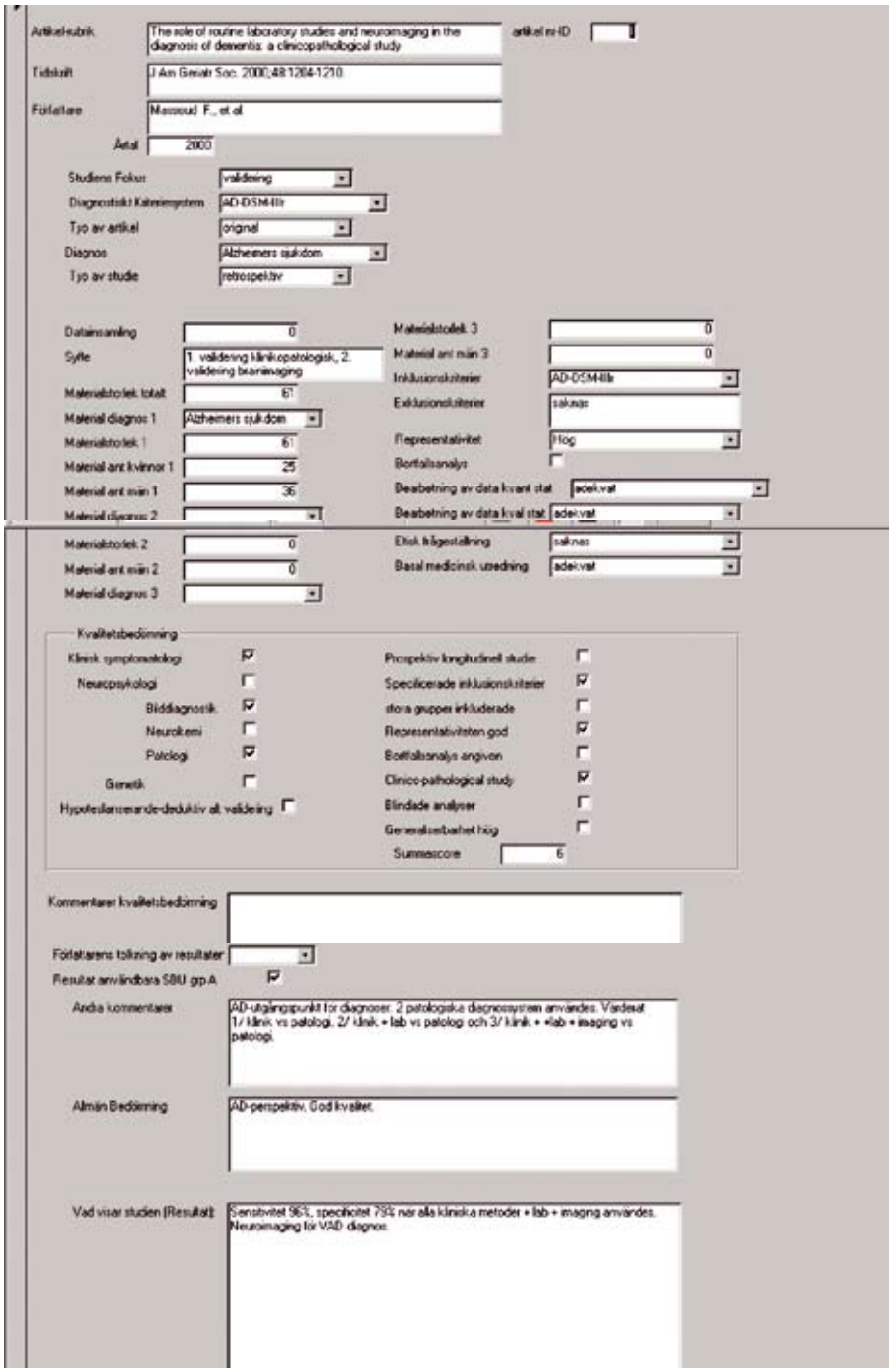
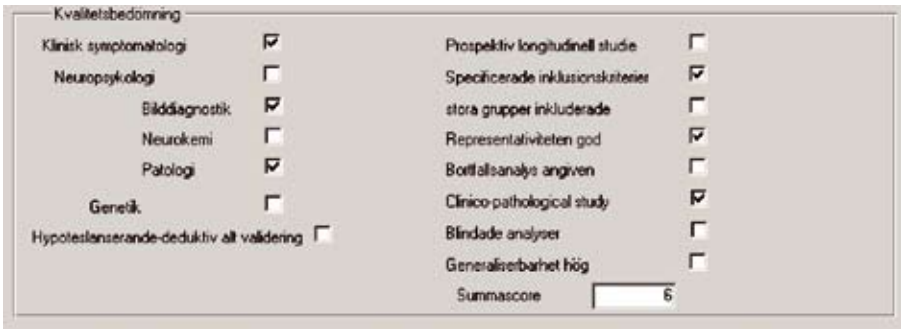


Table 5.2 *Sample quality grading scale for articles on FTD.*



Fact Box 5.1 *Clinical criteria for FTD according to McKhann et al 2001 [26].*

1. The development of behavioral or cognitive deficits manifested by either
   a) early and progressive change in personality, characterized by difficulty in modulating behavior, often resulting in inappropriate responses or activities or
   b) early and progressive change in language, characterized by problems with expression of language or severe naming difficulty and problems with word meaning.

2. The deficits outlined in 1a or 1b cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

3. The course is characterized by a gradual onset and continuing decline in function.

4. The deficits outlined in 1a or 1b are not due to other nervous system conditions (eg, cerebrovascular disease), systemic conditions (eg, hypothyroidism), or substance-induced conditions.

5. The deficits do not occur exclusively during a delirium.

6. The disturbance is not better accounted for by a psychiatric diagnosis (eg, depression).

Fact Box 5.2 *Recommendations for Classification of FTD based on neuropathological and immunohistochemical findings according to McKhann et al 2001 [26].*

1. When the predominant neuropathological abnormalities are tau-positive inclusions (with associated neuron loss and gliosis) and insoluble tau has a predominance of tau with 3 microtubule-binding repeats, the most likely diagnoses are
   a) Pick's disease
   b) frontotemporal dementia with parkinsonism linked to chromosome 17, or
   c) other as yet unidentified familial and sporadic frontotemporal disorders.

2. When the predominant neuropathological abnormalities are tau-positive inclusions (with associated neuron loss and gliosis) and insoluble tau has a predominance of 4 microtubule-binding repeats, the most likely diagnoses are
   a) corticobasal degeneration,
   b) progressive supranuclear palsy,
   c) frontotemporal dementia with parkinsonism linked to chromosome 17, or
   d) other as yet unidentified familial and sporadic frontotemporal disorders.

3. When the predominant neuropathological abnormalities are tau-positive inclusions (with associated neuron loss and gliosis) and insoluble tau has a predominance of 3 and 4 microtubule-binding repeats, the most likely diagnoses are
   a) neurofibrillary tangle dementia,
   b) frontotemporal dementia with parkinsonism linked to chromosome 17, or
   c) other as yet unidentified familial and sporadic frontotemporal disorders.

4. When the predominant neuropathological abnormalities are frontotemporal neuronal loss and gliosis without tau- or ubiquitin-positive inclusions and without detectable amounts of insoluble tau, the most likely diagnoses are
   a) frontotemporal lobar degeneration (also known as dementia lacking distinct histopathological features) or
   b) other as yet unidentified familial and sporadic frontotemporal disorders.

5. When the predominant neuropathological abnormalities are frontotemporal neuronal loss and gliosis with ubiquitin-positive, tau-negative inclusions and without detectable amounts of insoluble tau, with MND or without MND but with MND-type inclusions, the most likely diagnoses are
   a) frontotemporal lobar degeneration with MND,
   b) frontotemporal lobar degeneration with MND-type inclusions but without MND, or
   c) other as yet unidentified familial and sporadic frontotemporal disorders.

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6. Nosology and Epidemiology – Occurrence

This chapter summarizes our current knowledge about the occurrence of dementia based on a systematic, scientific review of published studies. Occurrence is expressed as either prevalence (the proportion of people with dementia in a defined population at a given point in time) or incidence (the rate of new dementia cases that develop in a defined population during a specified time interval). Whereas prevalence estimates the probability that a person will have dementia at a certain point in time, incidence estimates the probability of developing the disease.

Prevalence

Searching for literature

Inclusion criteria

Time period: January 1, 1986 through June 30, 2004. Language: English. Type of article: Reviews. *Keywords:* dementia AND prevalence; Alzheimer's disease AND prevalence; Vascular dementia AND prevalence; Frontotemporal dementia AND prevalence; Lewy Body dementia AND prevalence. Search methods: Medline, Medlineplus, PubMed, citations of available literature (ie, references in review articles), personal knowledge.

Search results

A total of 321 review articles were found by means of a screening search, as follows: a) Medline, citations, personal knowledge: 176 titles; b) PubMed: 208 titles; c) When adding together those two files in EndNote library, 63 duplicates were found, resulting in a total of 321 articles. After reading through the abstracts, another 275 papers were excluded as not true review articles or relevant to the topic. The articles concerned risk factors, treatment, clinical factors, autopsy reports and caregiving con-

siderations. A complete hardcopy version was obtained for each of the remaining 46 articles; d) The 46 articles were read through, and 32 more were excluded for the following reasons: methodological issues (n = 18); other topics, risk factors, autopsy, etc (n = 14); e) The remaining 14 papers were deemed suitable for inclusion and data input.

Summary of reviews and articles included

Most previous knowledge of dementia occurrence was based on prevalence rather than incidence data. Several reviews on the prevalence of dementia, Alzheimer's disease (AD) and Vascular dementia (VaD) in the world have already been reported on. Due to the large number of prevalence studies, we are reporting on the results of 6 meta-analyses in which data from several studies were pooled in order to obtain more precise estimates. We made an exception for Frontotemporal dementia (FTD) and dementia with Lewy Bodies (DLB), including non-review articles for a total of 14 studies. The studies were graded according to predefined criteria (Table 6.1). For quality grading of the studies, see Table 6.2. Tables 6.3 and 6.4 present summaries of the included studies. Only studies that employed internationally recognized diagnostic criteria were included.

Conclusions

Age

The relationship between age and the prevalence of dementia was found to be consistent throughout the studies, while the estimates culled from the 6 meta-analyses were very similar (Figure 6.1). The prevalence of dementia is very low before age 60, increasing exponentially after that. Prevalence is approximately 1% at ages 60–64, 1.5% at 65–69, 3% at 70–74, 6% at 75–79, 13% at 80–84, 24% at 85–89, 34% at 90–94 and 45% at 95 and up.

Type of dementia

Of the total prevalence of dementia in Europe, North America and Africa 60–70% is attributable to AD and 10–20% to VaD (Figure 6.2). The Asian figure for VaD approaches 40%. If only the more recent

studies are taken into account [1,2,3], the Asian findings are more consistent with those reported in Europe, ie, 61% for AD and 31% for VaD. Three population-based studies – in the Netherlands [4], the United Kingdom [5] and Sweden [6] – reported prevalence figures for FTD. The Dutch study found the prevalence of FTD per 100 000 to be 3.6 at ages 50–59, 9.4 at 60–69, and 3.8 at 70–79. The mean age at onset was 58. In the UK, the prevalence per 100 000 was 15.7 at ages 45–64 and the mean age at onset was 52.8. The Swedish study included a sample of 85-year-olds with a prevalence of 3%. A recent study by Rahkonen et al showed the prevalence of DLB in a Finnish population aged 75 and up at 5% [7]. The corresponding prevalence for a Japanese population aged 65 and up was 4.9% [8].

Gender

Three of the six reviews reported gender-specific figures for dementia, all showing a higher prevalence in women (Figure 6.3), mainly due to the more frequent occurrence of AD.

One study reported gender-specific prevalence figures for FTD [5]. For this population of 45–65 year olds in Cambridgeshire, United Kingdom, FTD was more common in men (27.3 per 100 000) than women (2.8 per 100 000). Two studies reported gender-specific prevalence for DLB, both showing higher figures for women than men: 5.8% vs 2.6% [7] and 7.8% vs 2.0% [8] respectively.

Geographic variations

With the exception of lower figures for Africa, no geographic differences have been reported regarding the prevalence of dementia (see Figure 6.4). The African findings are based on only one study, so that they need to be replicated and confirmed [9]. While lower survival rates or methodological differences may explain this discrepancy, ethnic factors cannot be ruled out.

Ethics

Excluding the reviews on the prevalence of dementia, all 3 prevalence studies on FTD reported having obtained the approval of ethics committees, while 2 out of the 5 prevalence studies on DLB reported having obtained such approval.

Incidence

Searching for literature

Inclusion criteria

Time period: January 1, 1986 through June 30, 2004. Language: English only. Type of articles: Originals (editorial and review papers not covered). *Keywords:* dementia AND incidence; Alzheimer's disease AND incidence; Vascular dementia AND incidence; Lewy Body dementia AND incidence; Frontotemporal dementia AND incidence.

Search methods

Medline, Medlineplus, PubMed, citations of available literature (ie, references in review articles), personal knowledge.

Search results

A total of 1 095 articles were found by means of a screening search, as follows a) Medline, citations, personal knowledge: 979 titles; b) PubMed: 576 titles; c) When adding together those two files in EndNote library, 460 duplicates were found, for a total of 1 095 articles. After reading through the abstracts another 951 articles were excluded as not relevant to the topic. The articles concerned risk factors, treatment, clinical factors, sleeping problems, caregiving, mortality or other diseases such as Parkinson's and Creutzfeldt-Jakob. A complete hardcopy version was obtained for each of the remaining 144 articles; d) All of the articles were read through, after which another 83 were excluded for the following reasons: Methodological issues (n = 16); Prevalence articles (n = 21); Descriptive of the disease (n = 19); Survival, mortality (n = 2); Reviews,

overviews or comparisons (n = 14); Others (n = 11); e) The remaining 61 articles were identified as suitable for inclusion and data input.

Summary of articles included

The 61 articles were graded according to predefined criteria (Table 6.1). Twelve were deemed unacceptable (Tables 6.5 and 6.6), mostly due to high (or unspecified) dropout rates, voluntary sample, the absence of consensus diagnostic criteria or the presence of bias with the potential to affect the results. Thus, 49 articles were included in the final analysis (Table 6.7). Of those studies, 39 (79.6%) used DSM criteria, 8 (16.3%) used either CAMDEX or CAMCOG, and 2 (4.1%) used ICD-10.

Conclusions

Age

The incidence of dementia increase steeply with age, even at the most advanced ages, in all regions (see Figure 6.5). Incidence rates are very similar in the younger age groups, whereas a wider variation appears in the older age groups (80 and up). The incidence rates of dementia per 1 000 person-years is approximately 1 at ages 60–64, 3–5 at 65–69, 8–10 at 70–74, 11–18 at 75–79, 20–40 at 80–84, 30–60 at 85–89 and 50–120 at 90 and up. Whether there is a leveling off at ages 90 and up remains to be seen, as little data is as yet available.

Type of dementia

AD is more common than VaD in all regions (Figures 6.6 and 6.7). AD presents the same pattern as dementia overall, showing increased incidence with age, whereas the incidence of VaD seems to decrease after 80. However, a study of 4 US communities found higher rates of VaD than reported in other studies. The results may have been influenced by the inclusion of mixed dementia (with or without AD) in the VaD estimates [10].

Only one study was identified that reported on FTD and incidence [11]. Conducted in a clinical setting of northern Sweden, the study included everyone living in the area age 42 and up who had memory impairment

that interfered with normal activities. The annual incidence of FTD was 0.11 per 1 000 person-years. The incidence of FTD was 0.22 at ages 65–69, 0.20 at 70–74, 0.39 at 75–79, 0.67 at 80–84, and 0.23 at 85 and up. According to a review by Papka et al, DLB is the second most common cause of dementia in the elderly based on clinical and autopsy studies [12]. Nevertheless, accurate clinical diagnosis remains elusive and epidemiological studies are lacking. As of June 2004, no population-based incidence studies on DLB had been reported.

Gender

Forty of the 49 incidence studies provided gender-specific rates, and 14 reported higher rates for women (see Table 6.7). The gender effect seems to be confined to AD – women are at significantly higher risk, whereas men peak after ages 80–85.

Geographic variations

Incidence rates for dementia are similar around the world, and no geographic differences have been reported (Figures 6.5–6.7).

Ethics

Of the 49 incidence studies included, 20 (40.8%) reported having obtained the approval of ethics committees, 5 (10.2%) had obtained a consensus agreement from their participants and 24 (49.0%) were silent about the issue.

Recommendations for future research

Given high prevalence and incidence rates, dementia is one of the most common diseases in the elderly and has emerged as a major public health problem faced by both developed and developing countries. More incidence studies with comparable methodology are needed in order to improve our understanding of how dementia occurs around

the world, as well as its breakdown by age and gender. We still do not know whether the occurrence of dementia shows a different age distribution in women and men or whether the correlation between occurrence and age varies from one type of the disease to another.

Table 6.1 *Criteria* for quality grading of studies on occurrence of dementia, Alzheimer's disease, Vascular dementia, Frontotemporal dementia and dementia with Lewy bodies.*

Quality grading	**0 = not acceptable**	**1 = low**
Population	Voluntary sample Institutions	Clinical settings
Drop-outs		
Cross-sectional (only refusal)	>40%	30–40%
Follow-up	>30%	20–30%
Design	Clinical observation (eg case report)	Ecological (correlation study)
Case ascertainment	Only screening/ psychological testing Only hospital records	
Diagnosis	Only screening instruments (eg MMSE <20; "diagnosed" to have dementia)	Screening computing system
Exposure	Differential exposure for cases and controls. Unreliable objective measurement	Unbalanced information. Self-report for controls and proxy for cases
Confounders	No control	Partial control (eg only demographics; gender, age, education)
Presence of bias	Yes might affect the results	Some, but not discussed
Statistical power		Cases (<100)
	0 = not acceptable	**1 = insufficient**
Conclusions	At least one not acceptable	> half are low

* The criteria was compiled by von Strauss E, Kivipelto M, Qiu Z, Agüero H and Fratiglioni L.

	2 = medium	**3 = high**
	Community based patients in institutions not included	Community based. Special exposure cohort
	10–29%	<10%
	10–19%	<10%
	Follow-up; exclude subjects lost at follow-up. Case-referent; hospital or non-random from general population. Cross-sectional	Follow-up (all included). Case-referent; random from general population. Randomised clinical trial. Community intervention
	Two phase study design	Clinical examination and psychological evaluation for all
	Clinical examination	Clinical examination and neuroimaging or -pathology
	Semi-reliable objective measurement (eg BP). Reports from subjects and informants	Reliable objective measurement. Report from subjects before cognitive impairment
	Reasonable control (related variables; eg smoking when analyzing the effect of alcohol)	Controlled for all known (all putative risk factors)
	Some but maybe not relevant	No
	Sample (500–1 000)	Sample (>1 000)
	2 = acceptable	**3 = appropriate**
	Half are high or medium	All are high or medium

Table 6.2 *Quality grading of studies on dementia prevalence, from 1986 to 2004 (6 reviews on dementia, Alzheimer's disease and vascular dementia, 3 studies on frontotemporal dementia, and 5 studies on dementia with Lewy bodies).*

Author Year, reference	Population	Drop-outs	Design
Dementia, Alzheimer's disease and vascular dementia reviews			
Jorm et al 1987 [13]	3	2	2
Hofman et al 1991 [14]	3	2	2
Ritchie et al 1995 [15]	3	2	3
Fratiglioni et al 1999 [16]	3	2	2
Mangone et al 1999 [17]	2	1	2
Lobo et al 2000 [18]	3	2	2
Frontotemporal dementia			
Ratnavalli et al 2002 [5]	3	2	2
Gislason et al 2003 [6]	3	3	2
Rosso et al 2003 [4]	3	2	2

	Diagnosis	Case ascertainment	Presence of bias	Statistical power	Conclusions
	2	2	2	3	3
	2	2	2	3	3
	2	2	2	3	3
	2	2	2	3	3
	2	2	1	3	2
	2	2	2	3	3
	2	3	2	2	3
	3	2	2	2	3
	3	3	2	2	3

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Table 6.2 *continued*

Author Year, reference	Population	Drop-outs	Design
Dementia with Lewy bodies			
Xuereb et al 2000* [19]	1	2	3
Yamada et al 2001 [20]	3	2	2
Chan et al 2002 [21]	1	3	2
Rahkonen et al 2003 [7]	3	2	2
Wakisaka et al 2003* [8]	1	1	3

* Autopsy studies.

	Diagnosis	Case ascertainment	Presence of bias	Statistical power	Conclusions
	2	2	1	1	2
	2	2	1	3	2
	2	3	0	1	0
	3	3	2	2	3
	2	3	1	2	2

Table 6.3 *Included reviews on dementia prevalence (n = 6).*

Author Year, reference	Year of studies	Place	Age
Dementia, Alzheimer's disease and vascular dementia reviews			
Jorm et al 1987 [13]	1945–1985	22 studies in: Asia (3), Canada (1), Europe (12), Oceania (2) and United States (4)	60+
Hofman et al 1991 [14]	1980–1990	12 studies in 8 European countries: Finland (1), Germany (1), Italy (1), The Netherlands (2), Norway (1), Spain (1) Sweden (1) and United Kingdom (4)	60+
Ritchie et al 1995 [15]	1985–1990	9 studies in: Canada (1), Japan (1) and Europe (7)	65+
Fratiglioni et al 1999 [16]	1957–1995	36 studies: Africa (1), Asia (6), Canada (1) Europe (25) and United States (3)	30+
Mangone et al 1999 [17]	1994–1996	3 studies in Latin America (Brazil, Chile and Uruguay)	65+
Lobo et al 2000 [18]	1988–1992	11 studies in 8 European countries: Denmark (1), Finland (1), France (1), Italy (1), The Netherlands (1), Spain (3), Sweden (1), United Kingdom (2)	65+

AD = Alzheimer's disease; VaD = Vascular dementia

	Type	Increased in age	Prevalence in women
	Dementia, AD, VaD	Yes	Yes, for AD
	Dementia	Yes	After 75
	Dementia	Up to 84	–
	Dementia, AD, VaD	Yes	–
	Dementia	Yes	–
	Dementia, AD, VaD	Yes	Yes

Table 6.4. *Included studies on prevalence of frontotemporal dementia and dementia with Lewy bodies, 1986 to 2004 (n = 7).*

Author Year, reference	Year of study	Place	Population
Frontotemporal dementia			
Ratnavalli et al 2002 [5]	2000	Cambridgeshire, United Kingdom	Community-based
Gislason et al 2003 [6]	1986	Gothenburg, Sweden	Community-based
Rosso et al 2003 [4]	1998	Zuid-Holland, The Netherlands	Community-based
Dementia with Lewy bodies			
Xuereb et al 2000 [19]	1990–1992	Cambridge, United Kingdom	Community-based Autopsy
Yamada et al 2001 [20]	1998	Amino-cho, Kyoto area, Japan	Door-to-door
Rahkonen et al 2003 [7]	1998	Kuopio, Finland	Community-based
Wakisaka et al 2003 [8]	1998–2001	Hisayama, Japan	Community-based Autopsy

CERAD = Consortium to establish a registry for Alzheimer's disease

Study population	Age	Diagnostic	Increased in age	Prevalence in women
125	45–64	Lund-Manchester criteria	–	Higher in men
451	85	Lund-Manchester criteria	–	–
245	30–79	Lund-Manchester criteria	Up to 70	–
101	75+	CERAD	–	–
170	65–99	Consensus criteria of McKeith et al, 1996 (see Chapter 4, reference 23)	–	–
601	75+	Consensus criteria of McKeith et al, 1996 (see Chapter 4, reference 23)	–	Yes
102	65+	Consensus criteria of McKeith et al, 1996 (see Chapter 4, reference 23)	–	Yes

Table 6.5 *Quality grading of incidence dementia studies, from 1986 to 2004 (n = 61).*

Author Year, reference	Population	Drop-outs	Design
Africa			
Hendrie et al 1995 [9]	2	2	3
Asia & Oceania			
Li et al 1991 [22]	3	1	3
Shen et al 1994 [23]	3	2	3
Fujishima et al 2002 [24]	3	3	3
Yoshitake et al 1995 [25]	3	3	3
Chandra et al 2001 [26]	3	2	3
Liu et al 1998 [27]	3	2	2
Fukunishi et al 1991 [28]	2	0	2
Zhang et al 1998 [29]	3	0	2
Waite et al 2001 [30]	2	3	3

	Diagnosis	Case ascertainment	Presence of bias	Statistical power	Con-clusions
	3	3	1	2	2
	2	3	2	2	2
	2	3	1	2	2
	3	3	2	2	3
	3	3	2	2	3
	3	2	1	1	2
	2	3	2	3	3
	2	3	0	1	0
	3	3	0	0	0
	2	3	1	2	2

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Table 6.5 *continued*

Author Year, reference	Population	Drop-outs	Design
Europe			
Andersen et al 1999 [31]	3	1	2
Riedel-Heller et al 2001 [32]	3	1	3
Bickel et al 1994 [33]	3	3	3
Fichter et al 1996 [34]	3	0	2
Letenneur et al 1994 [35]	2	1	2
Letenneur et al 1999 [36]	2	1	2
Magnusson et al 1989 [37]	3	0	3
Di Carlo et al 2002 [38]	3	1	3
Gussekloo et al 1995 [39]	3	1	3
Ruitenberg et al 2001 [40]	3	1	3
Breteler et al 1998 [41]	3	1	3
Ott et al 1998 [42]	3	1	3
Paykel et al 1994 [43]	3	2	3

	Diagnosis	Case ascertainment	Presence of bias	Statistical power	Con-clusions
	3	3	1	3	2
	2	3	1	2	2
	2	3	1	1	2
	2	2	0	1	0
	3	2	1	2	2
	2	3	1	2	2
	2	2	2	2	0
	2	3	2	3	2
	1	3	2	2	2
	3	3	2	3	2
	3	2	2	3	2
	3	3	2	3	2
	2	3	2	2	3

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Table 6.5 *continued*

Author Year, reference	Population	Drop-outs	Design
Brayne et al 1995 [44]	3	2	3
Paykel et al 1998 [45]	3	2	3
Brayne et al 1997 [46]	3	1	2
Copeland et al 1992 [47]	3	2	2
Copeland et al 1999 [48]	3	2	2
Boothby et al 1994 [49]	2	2	2
Morgan et al 1993 [50]	2	1	3
Clarke et al 1996 [51]	2	2	3
Andreasen et al 1999 [11]	1	3	3
Fratiglioni et al 1997 [52]	3	2	3
Aevarsson et al 1996 [53]	3	3	3
Rorsman et al 1986 [54]	3	3	3
Hagnell et al 1992 [55]	3	3	3

	Diagnosis	Case ascertainment	Presence of bias	Statistical power	Con-clusions
	2	3	2	2	3
	2	3	2	2	3
	2	3	1	1	2
	1	2	2	2	2
	1	3	1	3	2
	1	3	1	2	2
	2	2	1	2	2
	2	3	1	2	2
	3	3	1	2	2
	2	3	2	3	3
	3	2	2	2	3
	2	3	1	1	2
	2	3	1	1	2

The table continues on the next page

Table 6.5 *continued*

Author Year, reference	Population	Drop-outs	Design
Hagnell et al 1992 [56]	3	3	3
Johansson et al 1995 [57]	3	2	2
United States & Canada			
Sayetta 1986 [58]	0	0	2
Kawas et al 2000 [59]	0	0	2
Hebert et al 1995 [60]	2	0	2
Katzman et al 1989 [61]	0	3	3
Aronson et al 1991 [62]	0	3	3
Miech et al 2002 [63]	3	2	3
Evans et al 2003 [64]	3	2	2
Bachman et al 1993 [65]	3	0	2
Perkins et al 1997 [66]	3	0	3
Hendrie et al 2001 [67]	2	1	3
Gurland et al 1999 [68]	3	1	2

	Diagnosis	Case ascertainment	Presence of bias	Statistical power	Con-clusions
	2	3	1	1	2
	1	2	1	1	2
	3	3	1	1	0
	3	3	1	1	0
	2	3	1	1	0
	2	3	0	0	0
	2	2	0	2	0
	3	3	2	3	3
	2	2	1	1	2
	2	3	1	1	0
	3	3	0	0	0
	3	3	1	2	2
	1	2	1	2	2

The table continues on the next page

Table 6.5 *continued*

Author Year, reference	Population	Drop-outs	Design
Tang et al 2001 [69]	2	3	3
Fillenbaum et al 1998 [70]	2	3	3
Ganguli et al 2000 [71]	2	0	2
Schoenberg et al 1987 [72]	3	3	3
Kokmen et al 1993 [73]	3	3	3
Rocca et al 1998 [74]	3	3	3
Knopman et al 2002 [75]	3	3	3
Edland et al 2002 [76]	3	3	3
Kukull et al 2002 [77]	2	3	2
Hebert et al 2000 [78]	3	2	3
Anonymous et al 2000 [79]	3	1	3
Fitzpatrick et al 2004 [10]	3	2	3

Diagnosis	Case ascertainment	Presence of bias	Statistical power	Con-clusions
2	3	1	2	2
1	2	1	3	2
0	2	0	1	0
2	3	2	2	3
3	3	2	3	3
3	2	2	2	3
2	3	2	2	3
2	3	2	2	3
2	2	1	3	2
3	3	2	2	3
3	3	2	2	2
2	2	2	3	3

Table 6.6 *Summary of the quality grading on studies concerning dementia incidence (n = 61).*

Quality of a study	**Unacceptable**	**Low**
Population	4	1
Dropouts	10	15
Study design	0	0
Diagnosis	1	7
Case ascertainment	0	0
Presence of bias	7	29
Statistical power	3	15
Conclusions	12	0

Medium	High	Total
14	42	61
17	19	61
20	41	61
32	21	61
17	44	61
25	0	61
30	13	61
33	16	61

Table 6.7 *Incidence dementia, included studies, from 1986 to 2004 (n = 49).*

Author Year, reference	Year of study	Place	Population community based	Population at risk
Africa				
Hendrie et al 2001 [67]	1994–1998	Ibadan, Nigeria	Inst not incl	2 459
Asia & Oceania				
Li et al 1991 [22]	1989	Beijing, China	Yes	1 090
Shen et al 1994 [23]	1993	Beijing, China	Yes	1 076
Fujishima et al 2002 [24]	1992	Hisayama Town, Japan	Yes	828
Yoshitake et al 1995 [25]	1992	Hisayama Town, Japan	Yes	828
Chandra et al 2001 [26]	1999	Ballabgarh, India	Yes	490
Liu et al 1998 [27]	1995	Kaokaoping, Taiwan	Yes	2 807
Waite et al 2001 [30]	1994–1997	Sydney, Australia	Inst not incl	383

Follow-up time (months)	Age	Type (diagnostics)	Increased in age	Incidence in female
61	65+	Dementia, AD (b, e, f, g)	Yes	–
36	60+	Dementia (a)	Yes	No
36	60+	Dementia (a)	Yes	–
84	65+	Dementia (b, g, h)	Yes	No
84	65+	Dementia, AD, VaD (b, g, h)	Yes	No
24	55+	AD (c, g)	Yes	No
24	65+	Dementia, AD, VaD (e, g, h)	Yes	No
38	75+	Dementia, AD, VaD (b, c, g)	Yes	No

The table continues on the next page

Table 6.7 *continued*

Author Year, reference	Year of study	Place	Population community based	Population at risk
Europe				
Andersen et al 1999 [31]	1992	Odense, Denmark	Yes	3 086
Riedel-Heller et al 2001 [32]	1998–1999	Leipzig, Germany	Yes	1 124
Bickel et al 1994 [33]	1986	Mannheim, Germany	Yes	585
Letenneur et al 1994 [35]	1990	Bordeaux, France	Inst not incl	2 726
Letenneur et al 1999 [36]	1993	Bordeaux, France	Inst not incl	3 675
Di Carlo et al 2002 [38]	1995	8 municipal, Italy	Yes	3 208
Gussekloo et al 1995 [39]	1992	Leiden, The Netherlands	Yes	321
Ruitenberg et al 2001 [40]	1990–1999	Rotterdam, The Netherlands	Yes	7 046
Breteler et al 1998 [41]	1993–1994	Rotterdam, The Netherlands	Yes	7 046
Ott et al 1998 [42]	1993–1994	Rotterdam, The Netherlands	Yes	7 046
Paykel et al 1994 [43]	1988–1990	Cambridge, United Kingdom	Yes	1 778
Brayne et al 1995 [44]	1988–1990	Cambridge, United Kingdom	Yes	1 778
Paykel et al 1998 [45]	1988–1990	Cambridge, United Kingdom	Yes	1 778

Follow-up time (months)	Age	Type (diagnostics)	Increased in age	Incidence in female
24	65–84	Dementia, AD (b, f, g)	Yes	No
18	75+	Dementia (b, e)	Yes	No
84	65+	Dementia, AD, VaD (d, f)	Yes	Yes
36	65+	Dementia, AD, VaD (b)	Yes	No
60	65+	Dementia, AD (b, g)	Yes	After 80
45	65–84	Dementia, AD, VaD (b, f, g)	Yes	Up to 80
48	85+	Dementia (a)	–	Yes
67	55+	Dementia, AD, VaD (b, f, g, h)	Yes	After 90
26	55+	Dementia (e, g, h)	Yes	After 85
26	55+	Dementia (b, f, g, h)	Yes	Yes
29	75+	Dementia (f)	Yes	No
29	75+	AD, VaD (f)	Yes	No
29	75+	Dementia, AD, VaD (f)	Yes	No

The table continues on the next page

Table 6.7 *continued*

Author Year, reference	Year of study	Place	Population community based	Population at risk
Brayne et al 1997 [46]	1985–1990	Cambridgeshire, United Kingdom	Yes, women	336
Copeland et al 1992 [47]	1985	Liverpool, United Kingdom	Yes	690
Copeland et al 1999 [48]	1995	Liverpool, United Kingdom	Yes	4 140
Boothby et al 1994 [49]	1987–1990	London, United Kingdom	Inst not incl	656
Morgan et al 1993 [50]	1985–1989	Nottingham, United Kingdom	Inst not incl	970
Clarke et al 1996 [51]	1985–1993	Nottingham, United Kingdom	Inst not incl	970
Andreasen et al 1999 [11]	1990–1995	Piteå, Sweden	Clinical sett	29 357
Fratiglioni et al 1997 [52]	1990–1992	Stockholm, Sweden	Yes	1 473
Aevarsson et al 1996 [53]	1989–1990	Gothenburg, Sweden	Yes	347
Johansson et al 1995 [57]	1991–1992	Jönköping, Sweden	Yes	218
Rorsman et al 1986 [54]	1957–1972	Lundby, Sweden	Yes	2 612
Hagnell et al 1992 [55]	1957–1972	Lundby, Sweden	Yes	2 612
Hagnell et al 1992 [56]	1947–1972	Lundby, Sweden	Yes	2 550

Follow-up time (months)	Age	Type (diagnostics)	Increased in age	Incidence in female
60	70–79	Dementia (f)	–	–
36	65+	Dementia, AD, VaD (i)	Yes	–
72	65+	Dementia, AD, VaD (e, f)	Yes	No
36	65+	Dementia (f, g, i)	Yes	–
48	65+	Dementia (b)	Up to 84	Yes
96	65+	Dementia (b)	Up to 84	Yes
60	42–92	AD, VaD, FTD (b, g, h, j)	Yes	–
36	75+	Dementia, AD, VaD (b)	Yes	Yes
36	85–88	Dementia (b, g)	–	Yes
48	84+	Dementia (b)	Yes	No
180	60+	Dementia, VaD (a)	–	No
180	50+	VaD (b)	For men	No
300	50+	AD, VaD (b)	Up to 90	No

The table continues on the next page

Table 6.7 *continued*

Author Year, reference	Year of study	Place	Population community based	Population at risk
United States & Canada				
Miech et al 2002 [63]	1998–1999	Cache County, Utah, United States	Yes	4 614
Evans et al 2003 [64]	–	Chicago, United States	Yes	1 125
Hendrie et al 2001 [67]	1994–1998	Indianapolis, United States	Inst not incl	2 147
Gurland et al 1999 [68]	1989–1991	Manhattan, NY, United States	Yes	1 868
Tang et al 2001 [69]	1990–1997	New York, United States	Inst not incl	1 788
Fillenbaum et al 1998 [70]	1990	North Carolina, United States	Inst not incl	5 221
Schoenberg et al 1987 [72]	1960–1964	Rochester, United States	Yes	18 991
Kokmen et al 1993 [73]	1960–1984	Rochester, United States	Yes	–
Rocca et al 1998 [74]	1975–1984	Rochester, United States	Yes	–
Knopman et al 2002 [75]	1985–1989	Rochester, United States	Yes	2 809
Edland et al 2002 [76]	1985–1989	Rochester, United States	Yes	2 809

	Follow-up time (months)	Age	Type (diagnostics)	Increased in age	Incidence in female
	36	65+	Dementia, AD (b, g)	Yes	Yes
	49	65+	AD (g, h)	Yes	No
	56	65+	Dementia, AD (b, e, f, g)	Yes	–
	18	65+	Dementia (b)	–	–
	52	65+	AD (g, h)		Yes
	36	65+	Dementia (c, g)	No	No
	48	30+	Dementia, AD (a)	Yes	No
	300	45+	Dementia, AD (b, g)	Yes	No
	120	50–99	Dementia, AD (b, g)	Yes	No
	48	50–99	VaD (c, e, h)	Yes	Yes
	48	50–99	Dementia, AD (c, e)	Yes	Yes

The table continues on the next page

***Table 6.7** continued*

Author Year, reference	Year of study	Place	Population community based	Population at risk
Kukull et al 2002 [77]	1994–1996	Seattle, United States	Inst not incl	2 581
Fitzpatrick et al 2004 [10]	1992–1994	4 US communities	Yes	2 867
Hebert et al 2000 [78]	1996–1997	10 provinces in Canada	Yes	8 623
Anonymous et al 2000 [79]	1996	10 provinces in Canada	Yes	9 131

(1) Diagnostic Criteria and Instruments:
(a) DSM-III; (b) DSM-III-R; (c) DSM-IV; (d) ICD-9; (e) ICD-10; (f) CAMDEX or CAMCOG; (g) NINCDS-ADRDA; (h) NINDS-AIREN; (i) AGECAT; (j) Lund-Manchester criteria

AD = Alzheimer's disease; FTD = Frontotemporal dementia; VaD = Vascular dementia

	Follow-up time (months)	Age	Type (diagnostics)	Increased in age	Incidence in female
	24	65+	Dementia, AD (c, g)	Yes	No
	65	75+	Dementia, AD, VaD (c, g, h)	Yes	No
	60	65+	VaD (b, e, f)	Yes	No
	60	65+	Dementia, AD (b, e, f, g)	Yes	No

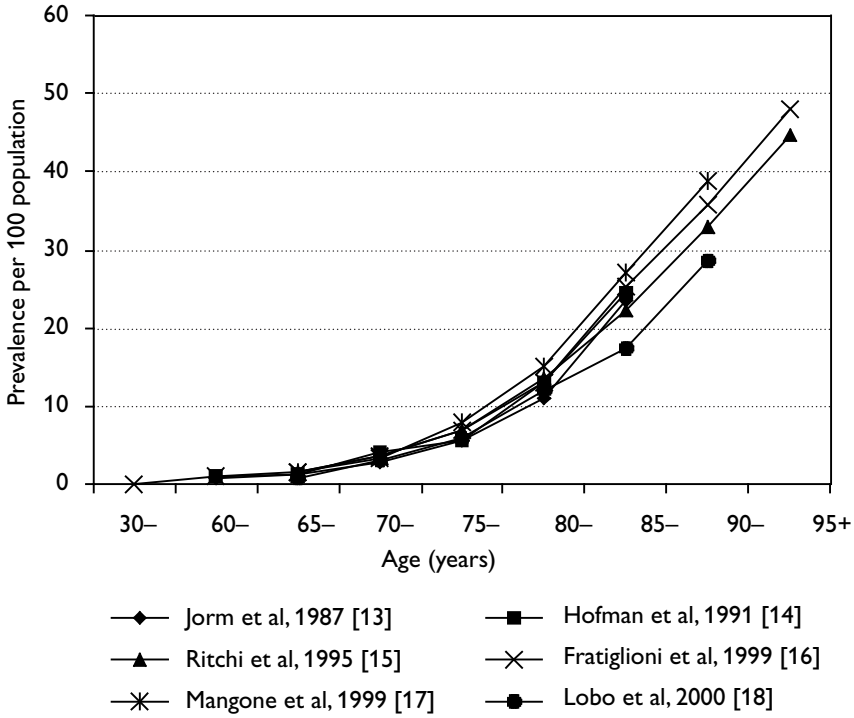

Figure 6.1 *Age-specific prevalence of dementia (per 100 population) comparing six meta-analyses [13,14,15,16,17,18].*

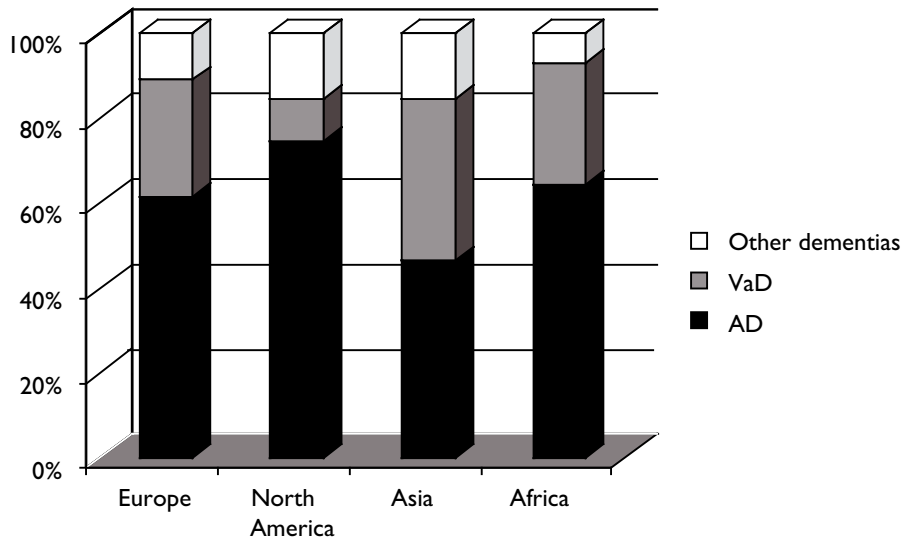

Figure 6.2 *Proportion (%) of dementing disorders in different geographic regions Prevalent cases are reported for Alzheimer´s disease (AD), vascular dementia (VaD) and other dementias deriving from pooled analysis of Jorm et al, 1987; Fratiglioni et al, 1999; and Lobo et al, 2000 [13,16,18].*

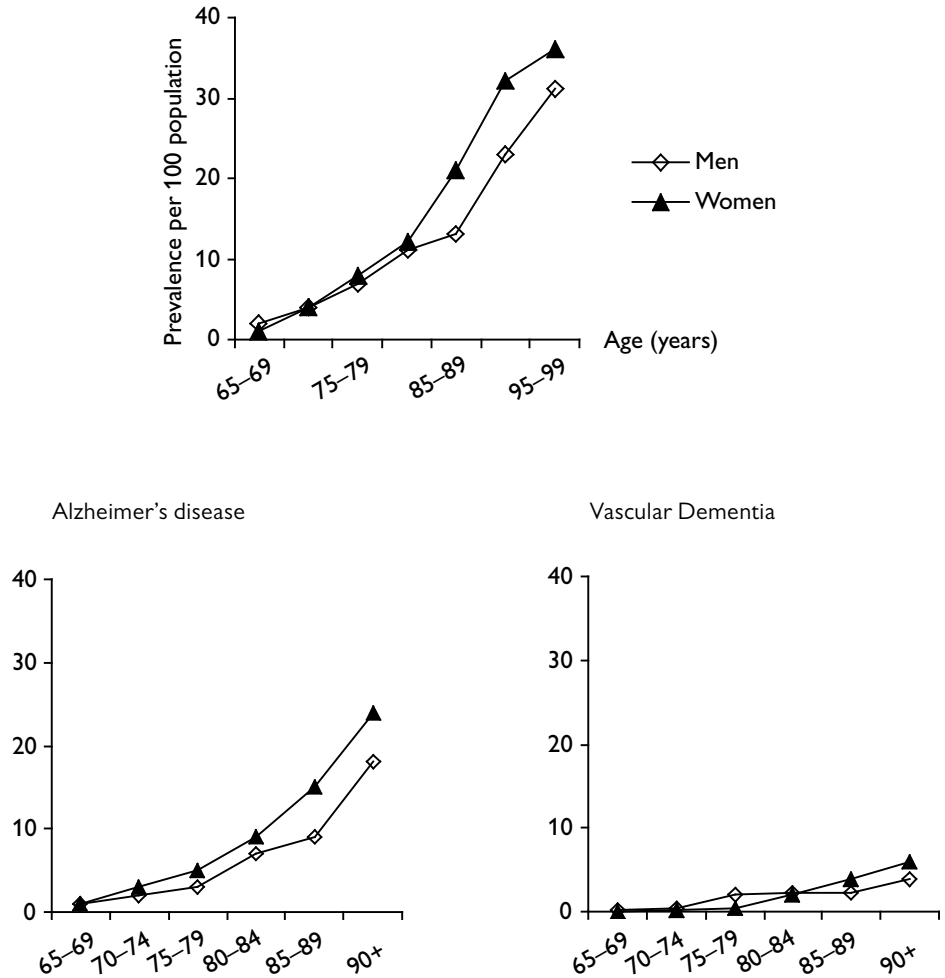

Figure 6.3 *Prevalence (per 100 population) of dementia, Alzheimer's disease and vascular dementia, divided by gender Data deriving from pooled analysis of Jorm et al, 1987; Hofman et al, 1991; and Lobo et al, 2000 [13,14,18].*

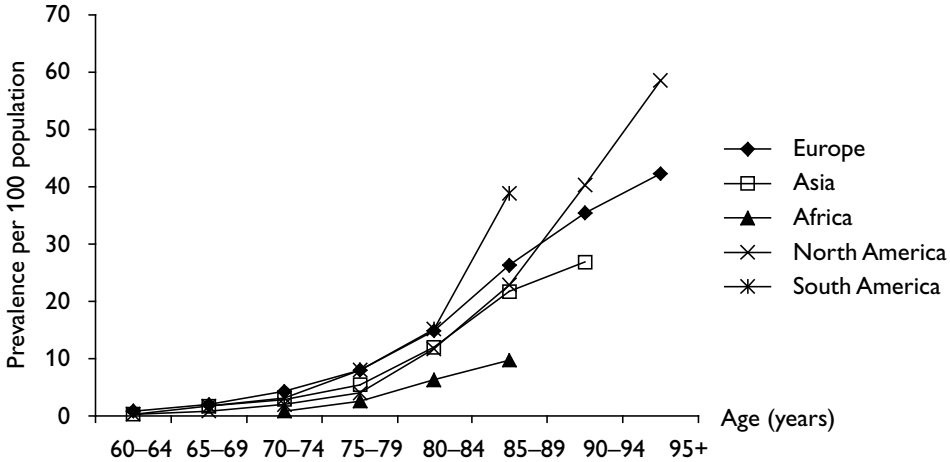

Figure 6.4 *Prevalence of dementia (per 100 population), in different continents (Europe, Asia, Africa, North America and South America) Data deriving from pooled analysis of Hofman et al, 1991; Ritchie et al, 1995; Fratiglioni et al, 1999; Mangone et al, 1999; and Lobo et al, 2000 [14,15,16,17,18].*

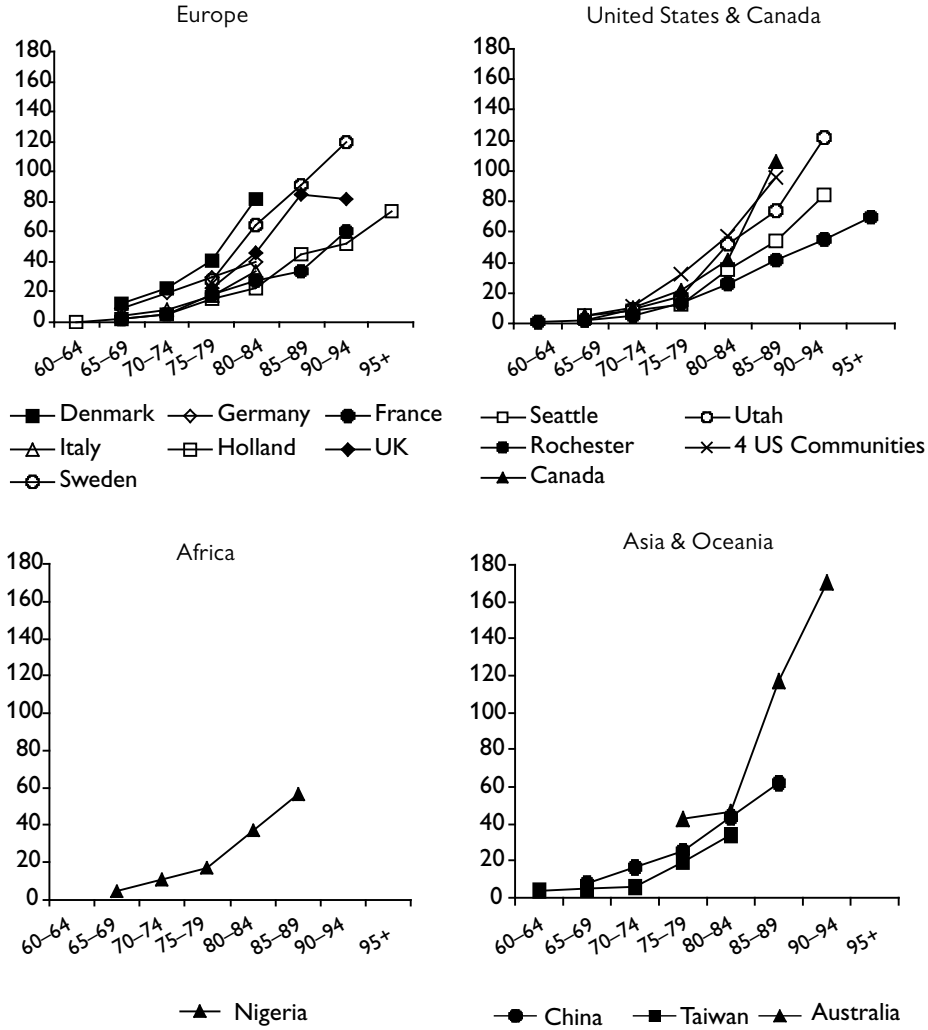

Figure 6.5 *Incidence rates of dementia per 1 000 person-years in various regions in the world Distribution by age.*

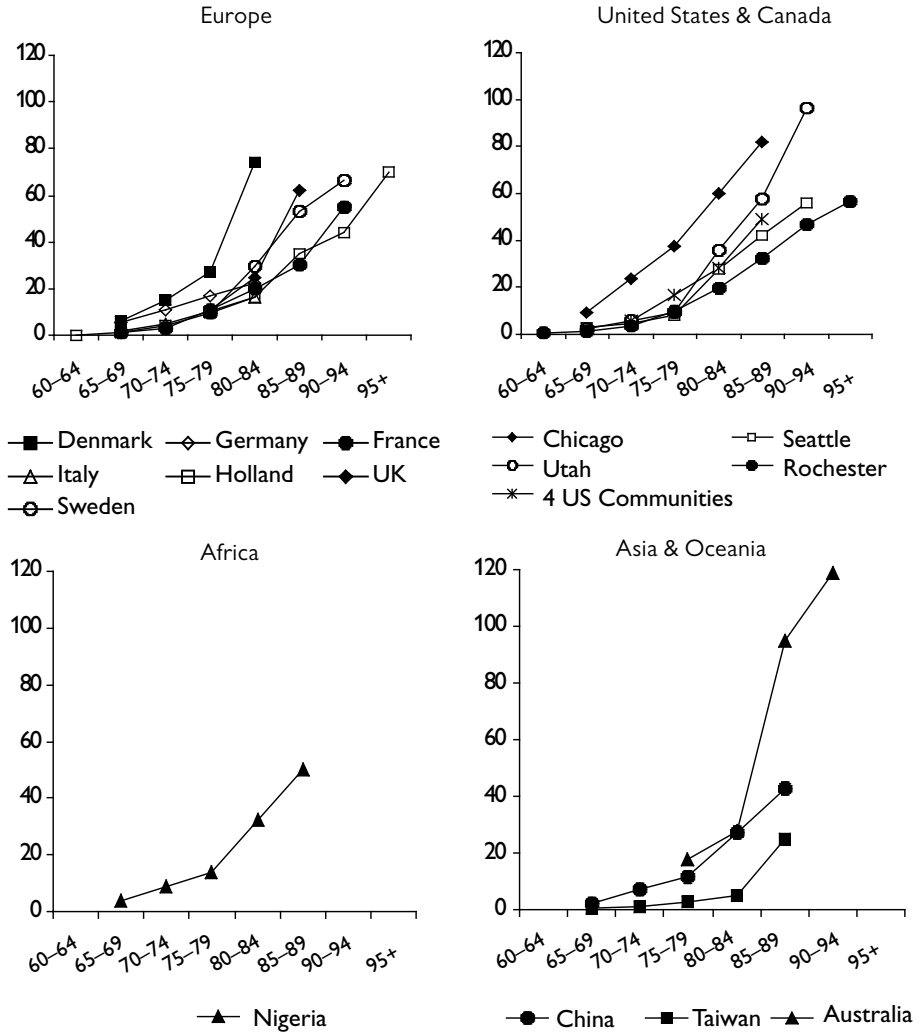

Figure 6.6 *Incidence rates of Alzheimer's disease per 1 000 person-years in various regions in the world distribution by age.*

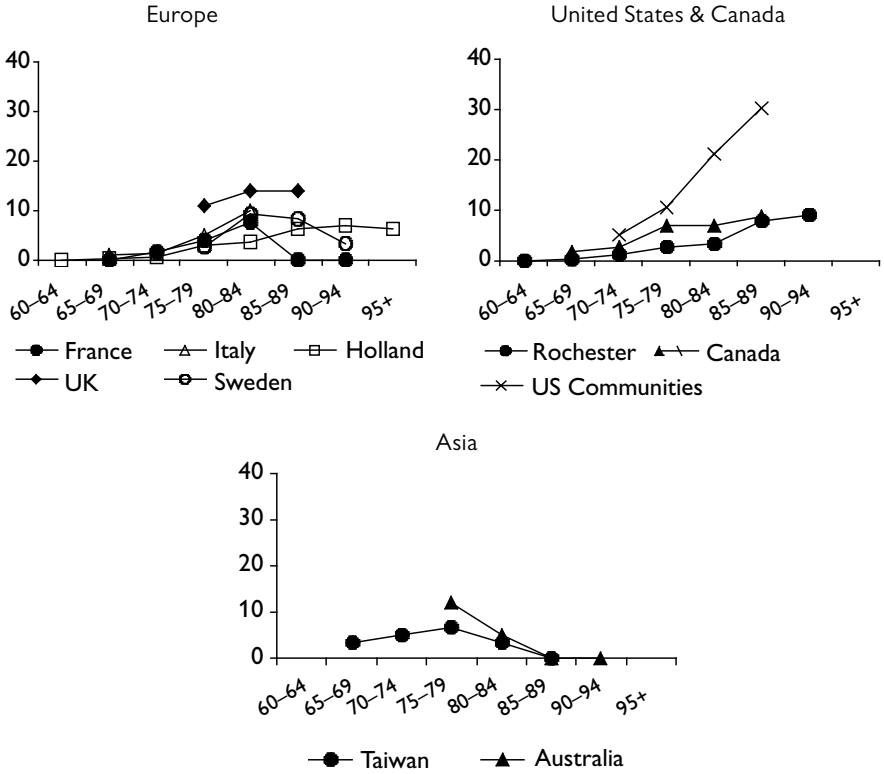

Figure 6.7 *Incidence rates of vascular dementia per 1 000 person-years in various regions in the world Distribution by age.*

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7. Nosology and Epidemiology – Consequences

Due to the dramatic increase in the size of the elderly population and the high occurrence of dementia in old age, the disease has a profound impact at both the individual and societal level. Following is a summary of our review and evaluation of the literature concerning the repercussions of dementia in terms of mortality and institutionalization.

Searching the literature

The inclusion criteria were similar for mortality and institutionalization. We examined PubMed for all publications in English from 1986 to 2004. The *keywords* for mortality were mortality, survival and death in combination with dementia or Alzheimer's disease. The *keywords* for institutionalization were: institution and institutionalization in combination with dementia or Alzheimer's disease.

Mortality and survival

Studies that use death certificates do not often report dementia as the main cause of death, which is usually attributed to events that occur in the terminal stages of the illness that leads to dementia [1,2]. As the result of such underreporting, dementia has been neglected as a fatal condition.

Search results

The search for literature led to 2 171 references from PubMed and 41 from personal files. All abstracts were revised. Non-relevant articles (those that dealt with cognitive impairment, psychiatric diseases in the elderly, autopsy reports, clinical studies, etc) were eliminated. Ninety-five articles remained after this first selection. Some articles were then

excluded because they focused on the survival or mortality rates of dementia patients living in institutions (n = 26), specific prognostic factors (n = 21), clinical trials (n = 5), national registers (n = 4) or special groups of subjects with dementia (those with terminal dementia, dementia after ischemic stroke, pre-senile dementia, etc) (n = 9).

Thirty articles were evaluated on the basis of the same criteria and score system employed in the studies that evaluated risk factors (see Chapter 8). The results of the evaluation are reported in Appendix 7.1, Table A.

Summary of articles included

Among the 30 articles evaluated, 22 used prevalent cases. The use of prevalent cases introduces a relevant bias, given that a relatively greater proportion of people with severe dementia or in latter stages of the disease are included, while people who die soon after a dementia diagnosis are excluded. The survival bias is especially important when survival and/or mortality are the outcomes. For that reason, not all 22 studies were accepted for making the final conclusions. Only 8 studies used incident cases to examine dementia mortality. Two incident studies examined voluntary samples and were also excluded. Thus, the summary of the main findings is based on 6 articles (Table 7.1).

Conclusions

These studies confirm that, independent of co-existing diseases, dementia is a major cause of death in the elderly. Elderly subjects with dementia face approximately double the risk of dying than those without dementia. Any type of dementia increases the risk of death. The prognosis for VaD tends to be less favorable than for AD.

Most studies calculated the median length of survival from the initial diagnosis of AD. Only one study estimated the time of survival from the onset of the disease. Similar figures were reported – approximately

4.5 years. Even though there was no difference in the reported survival time from onset or diagnosis, men (particularly younger ones) did not live as long as women.

Numerous factors have been associated with shorter survival times in AD patients. The findings suggest that male gender, more advanced age, disability, vascular diseases, neurological symptoms and poorer cognitive status reduce the survival period.

Institutionalization

People with dementia generally deteriorate progressively over several years from onset until death. Patients affected by a mild form of dementia usually live in the community with the assistance of family members. As the disease progresses into its later stages, many patients require institutional care. Demand for such care is expected to increase as the elderly population increases. Greater demand raises concerns about the nature and extent of services that this group requires. Several studies have investigated institutionalization and the factors that affect its role in treating dementia.

Search results

In PubMed 423 references were found and 38 in personal files. All abstracts were revised. Articles that were not relevant to the topic (those that dealt with cognitive impairment, psychiatric diseases in the elderly, cost evaluation, health service utilization, etc) were eliminated. Some articles were excluded because they focused on patients living in institutions (n = 13), specific prognostic factors (n = 18) or specific programs for nursing homes residents (n = 5). In the present evaluation 26 articles were included.

Summary of articles included

Appendix 7.2 reports on the evaluation of the 26 studies. Seventeen were accepted for inclusion in the summary (Tables 7.2.A,B,C). Due chiefly to differences in dementia care among various countries, the results of the various studies are not consistent. Most studies included AD patients from clinical settings that may underestimate the frequency and rate of institutionalization. Moreover, studies investigated both long-term and short-term institutional placement. In an attempt to ensure a straightforward summary, articles were broken down by length of follow-up.

Conclusions

The cumulative incidence of institutionalization during the first year was about 22% for patients diagnosed by memory clinics and about 33% for dementia outpatients.

When longer (2.5–3 years) follow-ups are considered, community-based studies indicate that approximately 49% of patients with dementia move to institutions. Studies carried out in clinical settings indicate that 50% of the advanced cases and 40–44% of the milder cases move to institutions after 3 years. No consistent findings have been identified when longer follow-up periods were reported.

Prognostic factors for institutionalization depend on the characteristics of both caregivers and patients. Caregiver-related factors include relationship (spouse, other relative or partner) and distress. Patient-related factors include advanced age, poorer cognitive and functional status, behavioral disturbances and other concomitant diseases.

Table 7.1 *Community-based studies reporting risk of death based on incident cases Relative risk (RR) and 95% confidence interval (95% CI) and size of the population (N) are also reported.*

Author Year Reference	Country	Population no	Cases	Age	Follow-up years
Bowen et al 1996 [3]	Seattle, United States		327	60+	3.3
Agüero-Torres et al 1999 [4]	Stockholm, Sweden	1 474	199	77+	5
Helmer et al 2001 [5]	Bordeaux, France	2 923	281	65+	8
Eaker et al 2002 [6]	Wisconsin, United States	811	448	Mean 82.8	5
Knopman et al 2003 [7]	Minnesota, United States	958	479	50+	12
Larson et al 2004 [8]	Washington, United States		521	60+	14

AD = Alzheimer's disease; Dem = Dementia; M = Men; RR = Relative risk; VaD = Vascular dementia; W = Women

RR (95% CI) of death	Commentary	Principal findings
AD (SMR) = 2.1	Standardized Mortality Ratio. Generalizable to patients who seek medical attention, not general population	Factors associated with decreased survival: disability, vascular diseases and worse cognitive status
Dem = 2.2 (1.7–2.8) AD = 2.0 (1.5–2.7) VaD = 3.3 (2.0–5.3)	Generalizable to very old subjects	Tendency of worse prognosis in VaD than AD subjects. Dementia is major cause of death in the elderly independent of comorbid conditions
Dem = 1.8 AD = 1.7	20% of the participants were never re-evaluated (lost follow-up). Dementia onset was estimated	The median survival time from disease onset: 4.5 years. Men had worse survival. Education did not modify survival
AD = 1.9 (1.4–2.7) Non-AD = 2.3 (1.6–3.2)	Population based study but cases were diagnosed in clinical/hospital settings	Dementia is major cause of death in the elderly independent of comorbid conditions
Dem = 1.8 (1.6–2.1) AD = 1,4 (1.2–1.7) VaD = 2.7 (1.9–3.9)	Mortality of VaD patients depends on the set of diagnostic criteria used	Worse prognosis stroke related dementia than dementia with just neuroimaging findings. Median survival from diagnosis: 4.1 years for VaD and 4.6 years for AD
W 70 y = 1.96 M 70 y = 2.82 M 75 y = 2.05 W 75 y = 2.07 W 80 y = 1.62 M 80 y = 1.86	Comparison of life expectancy of United States population	Median survival from diagnosis: 4.2 for men and 5.7 years for women with AD. Worse prognosis for men and elderly. Predictors of mortality: worse cognitive status, frontal lobe release signs, extrapyramidal signs, gait disturbances, history of falls, congestive heart failure, ischemic heart disease and diabetes

Table 7.2 *Studies reporting institutionalization and dementia (cumulative incidence).*

A. Institutionalization and dementia – short-term (12 months).

Author Year Reference	Country	Demented cases	Setting
Lieberman et al 1991 [9]	California, United States	321	Dementia patients living in the community recruited by dementia centers
Haupt et al 1993 [10]	Germany	66	AD outpatients with mild to moderate disease
Bianchetti et al 1995 [11]	Brescia, Italy	86	Dementia unit outpatients (clinical setting)
Hope et al 1998 [12]	Oxfordshire, United Kingdom	100	Dementia patients living in the community recruited by clinical practitioners
Pot et al 2001 [13]	Amsterdam, The Netherlands	138	Demented outpatients living in the community detected via caregiver

ADL = Activities of daily living; IADL = Intrumental activities of daily living

Follow-up (months)	Instutiona-lization rate (%)	Prognostic factors	Non associated factors
12	22	Type of caregiver arrangement. Caregiver distress	Cognitive level. Psychiatric symptoms and neurological problems
12	33	Older age, global cognitive decline, incontinence, aggression, depression and caregiver's wish to leave the care to someone else	
12	34	Older age, insomnia, non-relative caregiver, no home help services and lower cognition	Comorbidity, ADL and IADL functions
12	25	Female caregiver, more time away from the caregiver in a week, and behaviour-related physical stress for the caregiver	Aggressive behavior
12	33	Non-spouse caregiver	Cognitive or functional impairment, caregiver psychopathology

B. Institutionalization and dementia – longer follow-up (20–59 months).

Author Year Reference	Country	Demented cases	Setting
Knopman et al 1988 [14]	Minnesota, United States	101	Dementia clinic
Severson et al 1994 [15]	Minnesota, United States	145	Mayo Clinic community based register (AD)
Lopez et al 1999 [16]	Pittsburgh, United States	174	AD patients from a multi-disciplinary dementia research study
Agüero-Torres 2001 [17]	Stockholm, Sweden	225	Demented subjects from the community
Yaffe et al 2002 [18]	Medicare AD (multicenter, 8 sites), United States	5 788	Randomized clinical trial for patients with dementia (severe cases)
Gaugler et al 2003 [19]	Multiregional sample from 8 catchment areas, United States	3 944	Medicare AD (pre-senile and senile dementia)
Courtney et al 2004 [20]	Multicenter, United Kingdom	565	Randomized clinical trial. Mild and moderate AD patients

AD = Alzheimer´s disease; VaD = Vascular dementia

	Follow-up (months)	Instutiona-lization rate	Prognostic factors	Not associated factors
	24	Mild cases 35% Severe cases 62%	Initial ADL score, behavioral disturbances	Age, sex, caregiver relationship
	30	50%	Marital status, global cognitive function, and functional status	Age, gender, number of caregivers, dementia aetiology
	48 (mean)	41%	Psychotic symptoms	
	33.3	49%	VaD worse than AD	
	36	In 1 year: 22% In 2 years: 40% In 3 years: 52%	Patient and caregiver characteristics together	
	36	43%	Male gender, older age, living alone, functional status, cognitive status, less service utilization, caregivers characteristics	
	36	42% donepezil 44% placebo		Donepezil and placebo group had no significant difference

C. Institutionalization and dementia – longest follow-up (60+ months).

Author Year Reference	Country	Demented cases	Setting
Heyman et al 1987 [21]	Multicenter study CERAD, United States	727 AD cases	Clinical setting
Smith et al 2000 [22]	Minnesota, United States	220	Mayo Clinic community based register
Hebert et al 2001 [23]	The Canadian Study of Health and Aging (CSHA)	326	Demented subjects from the community
Smith et al 2001 [24]	Minnesota, United States	512 (dementia or MCI)	Mayo Clinic community based prospective register (AD = 228, VaD = 57, OD = 57, MCI = 170)
Geldmacher 2003 [25]	Multicenter, United States	763	AD patients from clinical trials with donepezil

AD = Alzheimer´s disease; CDR = Clinical dementia rating scale; CERAD = Consortium to establish a registry for Alzheimer's disease; EPS = Extrapyramidal signs; MCI = Mild cognitive impairment; MMSE = Mini-mental state examination

Follow-up	Instutiona-lization rate	Prognostic factors	Not associated factors
60 months	30%	Worse CDR, worse ADL, worse MMSE, older age, unmarried men	Education, gender marital status
15 years	In 5 years: 20% In 10 years: 90%	Lower education, age at onset, being single, sheltered accomodation, comorbidity and functional dependence	
60 months	50.9%	Disability, AD type, living place, and caregiver characteristics (age, relation, burden)	
12 years	Median time from diagnosis to institutionalization = 5.3 years. 10% per year in dem patients within 5 years from diagnosis	Gender (male > female), enrolment year, functional status and cognitive score	Disease duration, EPS, disruptive behavior, and comorbidity
63 months (max)	Delay in nursing home placement in donepezil users = 21.4 months	Use of donepezil delay institutionalization in patients with AD	

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Appendices

Appendix 7.1 *Evaluation of the epidemiological studies examining mortality and dementia/Alzheimer's disease and/or vascular dementia.*

A. Mortality and dementia – prevalent cases (excluded from further evaluation due to survivor bias).

Author Year, reference	Population	Drop-outs	Design	Diagnosis/ exposure
Barclay et al 1985 [26]	1	3	1	2
Walsh et al 1990 [27]	1	1	2	3
Martin et al 1987 [28]	1	2	1	3
Evans et al 1991 [29]	3	3	2	2
Jorm et al 1991 [30]	2		2	1
Li et al 1991 [31]	3	1	2	2
Heeren et al 1992 [32]	3	3	3	2
Skoog et al 1993 [33]	3	2	2	3
Katzman et al 1994 [34]	2		3	2
Bracco et al 1994 [35]	1	2	1	3
Jagger et al 1995 [36]	3		3	2

Cases ascertainment	Confounders	Bias	Statistical power	Conclusion
1	2	0	2	0
1	3	0	2	0
1	2	0	1	0
2	2	0	2	0
0	1	0	1	0
2	1	0	3	0
2	2	0	3	0
3	2	0	2	0
2	2	0	3	0
1	2	0	1	0
2	2	0	2	0

The table continues on the next page

A. continued

Author Year, reference	Population	Drop-outs	Design	Diagnosis/ exposure
Molsa et al 1995 [37]	2	3	2	3
Engedal et al 1996 [38]	2	2	3	2
Aevarsson et al 1998 [39]	2		2	3
Saz et al 1999 [40]	2	3	2	2
Baldereschi et al 1999 [41]	2	2	3	2
Witthaus et al 1999 [42]	2	2	2	3
Ostbye et al 1999 [43]	3	3	3	2
Wolfson et al 2001 [44]	3	2	2	2
Perkins et al 2002 [45]	3		2	2
Hui et al 2003 [46]	2	2	2	2
Tschanz et al 2004 [47]	3	3	2	2

Cases ascertainment	Confounders	Bias	Statistical power	Conclusion
2	2	0	2	0
3	2	0	2	0
3	2	0	2	0
2	2	0	3	0
2	2	0	3	0
2	2	0	2	0
2	2	0	3	0
2	2	0	3	0
2	2	0	3	0
1	2	0	1	0
2	2	0	2	0

B. Mortality and dementia – incident cases.

Author Year, reference	Population	Drop-outs	Design	Diagnosis/ exposure
Aronson et al 1991 [48]	0	3	2	2
Bowen et al 1996 [3]	1	2	3	2
Agüero-Torres et al 1999 [4]	3	3	3	2
Helmer et al 2001 [5]	2	3	3	2
Eaker et al 2002 [6]	1		2	1
Brookmeyer et al 2002 [49]	0	2	3	2
Knopman et al 2003 [7]	3	3	3	3
Larson et al 2004 [8]	3	3	3	2

	Cases ascertainment	Confounders	Bias	Statistical power	Conclusion
	2	2	2	1	0
	3	2	2	2	2
	3	2	2	3	3
	2	2	2	3	2
	2	2	2	2	2
	3	2	2	3	0
	3	2	2	3	3
	1	2	2	2	2

Appendix 7.2 *Evaluation of the epidemiological studies examining institutionalization and dementia (AD, VaD).*

A. Institutionalization and dementia – short term (12 months).

Author Year, reference	**Population**	**Drop-outs**	**Design**	**Diagnosis/ exposure**
Lieberman et al 1991 [9]	1	2	1	2
Haupt et al 1993 [10]	1		2	2
Bianchetti et al 1995 [11]	1		2	3
Vernooij-Dassen et al 1997 [50]	1		2	0
Scott et al 1997 [51]	0		2	
Hope et al 1998 [12]	1		2	3
Pot et al 2001 [13]	3	2	2	2
Spruytte et al 2001 [52]	0		2	0
Banerjee et al 2003 [53]	1	0	2	2

	Cases ascertainment	Confounders	Bias	Statistical power	Conclusion
	1	1	1	1	1
	1	2	1	1	1
	1	2	1	1	1
	1	2	1	1	0
		1	1	2	0
	1	2	1	1	1
	2	2	2	2	2
	1	2	1	1	0
	0	2	0	1	0

B. Institutionalization and dementia – longer follow-up (20–59 months).

Author Year, reference	Population	Drop-outs	Design	Diagnosis/ exposure
Drachman et al 1990 [54]	1	1	1	2
Severson et al 1994 [15]	1	3	1	2
Knopman et al 1988 [14]	1	3	2	3
Lopez et al 1999 [16]	1	3	2	3
Agüero-Torres 2001 [17]	3	2	3	2
Yaffe et al 2002 [18]	3	3	3	2
Gaugler et al 2003 [19]	1	2	3	2
Courtney et al 2004 [20]	2	2	3	3

Cases ascertainment	Confounders	Bias	Statistical power	Conclusion
1	2	0	1	0
1	1	1	2	1
3	1	1	2	2
1	2	1	2	2
2	2	3	3	2
1	2	1	3	3
3	2	1	3	2
1	2	2	3	2

C. Institutionalization and dementia – longest follow-up (60+ months).

Author Year, reference	Population	Drop-outs	Design	Diagnosis/ exposure
Heyman et al 1987 [21]	1	3	2	3
Drachman et al 1990 [54]	1	1	2	2
Heyman et al 1997 [55]	2	1	2	
Smith et al 2000 [22]	3		2	3
Hebert et al 2001 [23]	3		2	2
Smith et al 2001 [24]	3		2	
Eaker et al 2002 [56]	2		2	
Phillips et al 2003 [57]	1		2	0
Geldmacher et al 2003 [25]	2	2	3	3

Cases ascertainment	Confounders	Bias	Statistical power	Conclusion
1	1	0	1	0
1	2	1	1	1
3	2	2	3	2
3	1	1	2	2
3	2	2	3	2
3	1	1	2	2
0	2	1	2	0
0	1	1	2	0
1	2	1	2	2

8. **Nosology and Epidemiology – Risk Factors**

Introduction

This chapter deals with the prevention of dementia and various disorders that lead to dementia. Prevention is traditionally broken down into primary, secondary, and tertiary. Primary prevention aims to reduce the incidence of dementia by eliminating or treating specific risk factors that may avert or delay onset. Secondary prevention aims to reduce the progression of the disease from its initial phase to a complete clinical picture. Tertiary prevention aims to minimize the long-term impact of complications and disabilities.

Most researchers agree that dementia syndrome develops over a long period of time characterized by progression from normal cognition through a transition phase of cognitive impairment (sometimes defined as Mild Cognitive Impairment) to full-scale dementia (Table 8.1). Preventive strategies can be implemented before the onset of the process of dementia by eliminating or treating risk factors, as well as promoting protective factors (primary prevention). Secondary prevention relies on the identification of clinical or biological markers for disorders that lead to dementia in order to detect subjects early who will develop dementia within a few years. Tertiary prevention includes the identification of prognostic factors and the evaluation of the care provided to patients with dementia by comparing different care strategies in terms of specific individual and family outcomes.

This chapter addresses primary prevention only. For each risk or protective factor, we systematically reviewed the literature in order to summarize the evidence for the specific association and its interpretation in relation to the etiology of dementia. We adopted the same search methods and inclusion criteria for all risk factors. We did not consider risk factors that have been investigated only sporadically.

Searching for literature

Search methods

Medline; MedlinePlus; Citations of available literature; Available abstract books of workshops and conference proceedings.

Inclusion criteria

Time period: 1985 through December 2004; Language: English only; Type of article: Originals only (review articles were not covered); *Key-words:* specific to each risk factor.

Quality grading of the studies

All suitable articles were evaluated on the basis of their internal validity and three classical causal criteria. The different characteristics of each study were summarized on an electronic form. A program was created in "Access to automatically quantify the quality of each study based on predefined criteria". The form and the criteria took account of similar evaluation standards that had been applied to other diseases, as well as specific aspects of the dementias.

A final quality index was calculated for each study in accordance with a 4-step procedure:

1. The internal validity of the article was scored on the basis of a 4-point scale that separately considered population type, dropout rate, case ascertainment, diagnostic procedure, exposure assessment, confounding control, presence of bias and statistical power. Table 8.2 reports on the scoring criteria for each item.

2. Three specific causal criteria (strength of the association, temporality and biological gradient) were examined for each article and their quality was graded. Table 8.3 reports on the scoring criteria.

3. The single items for both internal validity and the causal criteria were summarized in a score that included 4 categories: unacceptable,

insufficient, acceptable and appropriate. Table 8.4 reports on the scoring criteria.

4. Internal validity and the causal criteria were integrated in a final quality index of unacceptable, low, medium and high. Table 8.4 reports on the scoring criteria.

Summary of the evidence

The evidence from the literature for each specific putative risk or protective factor has been summarized by looking at both the quality and quantity of the reports.

Quantity was categorized as follows:

- Score of 0 = Insufficient: less than 4 studies reported an association, and the percentage of studies reporting an association was less than double that of those not reporting an association.

- Score of 1 = Limited: fewer than 4 studies reported an association, but the percentage of studies reporting an association was at least double that of those not reporting an association.

- Score of 3 = Moderate: more than 4 studies reported an association, but the percentage of studies reporting an association was less than double that of those not reporting an association.

- Score of 4 = Substantial: more than 4 studies reported an association, and the proportion of studies reporting an association was double that of those not reporting an association.

Only studies with a final quality score above 0 (unacceptable) were included in order to evaluate the evidence for the putative risk factor examined. The evidence was assigned one of four grades: insufficient, limited, moderate or strong. Table 8.5 reports on the criteria.

Table 8.1 *Potential preventive strategies for dementing disorders at different phases of disease development.*

Prevention	Phase in dementia process	Epidemiological research	Actions
Primary	Normal cognition	Detection of risk and protective factors	Treatment of risk factors/promotion of protective factors
Secondary	Mild cognitive impairment	Identification of clinical and biological markers	Treatment of pre-clinical cases
Tertiary	Dementia	Detection of prognostic factors	Differential care strategies

Table 8.2 *Internal validity: quality grading and evaluation criteria for each item.*

			Score	
Items	**0/Not acceptable**	**1/Low**	**2/Medium**	**3/High**
Population	Voluntary sample Institutions	Clinical setting Case-control from hospitals	Community-based, but subjects in institutions not included	Community-based Specific exposure cohort
Dropouts (only refusals)				
Cross-sectional studies	>40%	30–40%	10–29%	<10%
Follow-up studies	>30%	20–30%	10–19%	<10%
Design	Clinical observation (eg case report)	Ecological (correlation study) Case-control study with very selected controls	Follow-up, but only analysis of survivors Case-control: controls from hospital or non-random from general population Cross-sectional	Follow-up (whole population analysed) Case-control: cases from community Randomised clinical trial Community intervention
Case ascertainment	Only screening or psychological testing Only hospital records	Case-control studies: cases from hospital	Two-phase design	Clinical examination and psychological evaluation
Diagnosis	Only screening instruments (eg MMSE <20)	Screening + computing system	Clinical examination	Clinical examination and neuroimaging or -pathology

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***Table 8.2** continued*

			Score	
Items	**0/Not acceptable**	**1/Low**	**2/Medium**	**3/High**
Confounders	No control	Partial control (eg only demographics; age, gender, education)	Reasonable control (related variables; eg smoking when analysing alcohol)	Controlled for all known potential confounders
Presence of bias	Yes, results might be affected (differential misclassification	Some, but not discussed	Some but maybe not relevant	No
Statistical power		Sample <500 Cases exposed <20	Sample 500–1 000	Sample >1 000

Table 8.3 *Causal criteria: quality grading and evaluation criteria for each item.*

			Score	
Items	**0/Not acceptable**	**1/Low**	**2/Medium**	**3/High**
Strength of the association		RR <1.5 RR >0.8	RR = 1.5–2.5 RR = 0.5–0.7	RR >2.5 RR <0.5
Temporality	Exposure after disease onset	Not stated	Exposure before disease onset	Exposure objectively measured before disease onset
Biological gradient (dose-response)	No grading. Register Yes/No			

Table 8.4 *Summary score for internal validity, causal criteria and final quality index: grading and evaluation criteria.*

			Score	
Items	**0/Not acceptable**	**1/Low**	**2/Medium**	**3/High**
Internal validity	At least one item graded as not acceptable	More than half of the items graded as low	Half or more of the items graded as high or medium	All items graded as high or medium
Causal criteria	Exposure after disease onset	Not stated	Exposure before disease onset	Exposure objectively measured before disease onset
Final quality index. Including internal validity and causal criteria	At least one aspect (internal validity or causal criteria) graded as not acceptable	At least one aspect (internal validity or causal criteria) graded as low	At least one aspect graded as medium and both aspects scored more than low	Both internal validity and causal criteria are graded as high

Table 8.5 *Criteria for grading the evidence based on both the final quality index and the quantity of the reports.*

Final quality index			
Quantity	**Low**	**Medium**	**High**
Insufficient	Insufficient	Limited	Limited
Limited	Insufficient	Limited	Moderate
Moderate	Insufficient	Moderate	Moderate
Substantial	Insufficient	Moderate	Strong

Risk and protective factors for dementia and AD

A number of hypotheses have been suggested for the etiology of AD and dementia. Each hypothesis is based on both experimental and observational findings. Table 8.6 shows the most widely discussed hypotheses, along with the corresponding factors that have been explored thus far.

The most significant risk factor for both dementia and AD is old age. Both the incidence and prevalence of disorders leading to dementia increase, almost exponentially, with age. Whether this correlation is due to the aging process itself remains a bone of contention. For more detailed information and a review of the literature, see Chapter 6. The same paragraph discusses the hypothesis that women run an extra risk of having dementia.

The period of life at exposure has also emerged as a relevant variable in recent years. Two major considerations are involved: 1) the risk for dementia is a result of combined exposure to risk and protective factors along the life course [1]; 2) some factors may be active in specific phases of life only [2].

Table 8.7 summarizes the evidence for all the factors that this review has taken into account. Due to the difficulties involved in differentiating AD from VaD, cerebrovascular disease was excluded.

Table 8.6 *Studied risk and protective factors for AD and dementia in accordance with various etiopathogentic hypotheses.*

Genetic hypothesis	**Vascular hypothesis**	**Inflammatory hypothesis**	**Toxic hypothesis**	**Oxidative hypothesis**	**Psychosocial hypothesis**
Familial aggregation ApoE ε4 allele	Smoking Alcohol consumption Blood pressure Diabetes mellitus Cholesterol/obesity Cardiovascular diseases/Ats Homocysteine Anti-hypertensive Statins HRT	NSAIDs Inflammation markers	Head trauma Aluminum Occupational exposure	Diet Folate/B_{12} deficiency	Depression Low education Socioeconomic status Leisure activities Social network Personality

HRT = Hormonal replacement therapy; NSAID = Non-steroidal anti-inflammatory drug

Table 8.7 *Examined risk and protective factors for dementia and AD. Grading of the scientific evidence (see next paragraph).*

Examined factor	Evaluated articles (No)	Accepted studies (No)	Evidence of a risk/protective effect on dementia	Evidence of a risk/protective effect on AD
Familial aggregation	24	20	Moderate	Moderate
ApoE ε4 allele	52	39	Moderate	Strong
Smoking	40	11	Insufficient	Insufficient
Moderate alcohol use (protective)	31	13	Limited	Limited
High blood pressure	36	19	At Midlife: moderate Late life: insufficient	At Midlife: moderate Late life: insufficient
Diabetes mellitus	32	11 dem/ 17 AD	Moderate	Insufficient
High cholesterol levels	11	8	–	Midlife: moderate-limited Late life: insufficient Insufficient
Obesity (high BMI)	3	3	Insufficient	Insufficient
High homo-cysteine levels	19	7	Insufficient	Insufficient
Cardiovascular diseases	3	1	Insufficient	Limited
Anti-hypertensive drugs (protective)	12	12	Strong	
Statins (protective)	7	7	Insufficient	Insufficient
HRT (protective)	13	9	Insufficient	Insufficient

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Table 8.7 *continued*

Examined factor	Evaluated articles (No)	Accepted studies (No)	Evidence of a risk/protective effect on dementia	Evidence of a risk/protective effect on AD
NSAIDs	16	12	Insufficient	Insufficient
Inflammation markers	2	2	Insufficient	Insufficient
Head trauma	22	13	Insufficient	Insufficient
Aluminum	13	6	Insufficient	Insufficient
Occupational exposure	24	6 dem/ 12 AD	Limited	Limited
Diet	20	15	Insufficient	Insufficient
Folate/B_{12} deficiency	16	3	Insufficient	Insufficient
Depression	14	8	Insufficient	Insufficient
Low education	16/23	16-dec	Moderate	Moderate
Low socio-economic status	7	5	Insufficient	Insufficient
Leisure activities (protective)	18	16	Moderate	Moderate
Social network (protective)	6	4	Insufficient	Insufficient
Personality type	8	1	Insufficient	Insufficient

Familial aggregation

Search results from the literature

Keywords: "Dementia" or "Alzheimer disease" and "familial history" or "familial aggregation" and "population study", with the delimiters of "human" and "English language".

A total of 79 articles were found by searching PubMed. After reading through the abstracts or titles, 55 were excluded due to non-originality, leaving 24 studies for evaluation. Table 8.9 reports on the results of the evaluation. An additional 4 studies were excluded due to non-representativeness of the study population, lack of estimates concerning the correlation or the existence of a secondary report on the same data. That left 20 studies for assessing the evidence.

Summary of articles included

Familial aggregation and Alzheimer's disease. A total of 20 studies were accepted for this analysis (Table 8.9). Table 8.8 summarizes the main conclusions drawn from these studies.

Familial aggregation and other forms of dementia. Very few well-designed studies have specifically addressed the familial aggregation of other forms of dementia, such as VaD.

Table 8.8 *Familial aggregation and AD: Number of studies by final quality index score.*

	Final quality index score		
	High	**Medium**	**Low**
Positive association	0	9	8
Inverse association	0	0	0
No association	0	1	2

A positive association means that familial aggregation is associated with increased risk of AD, and inverse association that familial aggregation is associated with reduced risk of AD.

Conclusions

Moderately strong evidence exists that first-degree relatives of AD or dementia patients run an increased risk for the development of AD, thereby indicating a clear familial aggregation (Evidence Grade 2).

The evidence is insufficient to draw any conclusions about the familial aggregation of other dementias, such as VaD.

Table 8.9 *Familial aggregation and AD: Description of the studies that received a final quality score over 0.*

Author Year Reference Country	**Study design**	**Study population (age at baseline, years)**
Breitner et al 1988 [3] United States	Follow-up study	379 first-degree relatives of 79 AD probands
Hofman et al 1989 [4] The Netherlands	Population case-control study	198 matched pairs of AD cases and controls, younger than 70
Graves et al 1990 [5] United States	Case-control study	Clinical settings, 130 matched pairs of AD and controls
Mayeux et al 1991 [6] United States	Follow-up study	Clinical settings
Fratiglioni et al 1993 [7] Sweden	Population case-control study	A community population, 98 AD, 216 controls (age 75+)
van Duijn et al 1991 [8] Europe	Pooling analysis on case-control studies	EURODEM project
Korten et al 1993 [9] Australia	Case-control study	99 cases and 116 controls

Risk/protective factor	Diagnostic criteria	Results
Familial aggregation	AD-like illness	No difference in AD risk among relatives of presenile- vs senile-onset probands
Family history of dementia	DSM-III-R, NINCDS-ADRDA	OR = 40.0
Dementia history in first-degree relatives	Clinically diagnosed	OR = 2.21 (95% CI 1.17–4.18)
Family history of dementia	DSM-III-R	OR for dementia = 6
Dementia history in first-degree relatives	DSM-III-R	OR = 3.2 (95% CI 1.8–5.7)
Dementia history of first-degree relatives	DSM-III, DSM-III-R, NINCDS-ADRDA	OR = 3.5 (95% CI 2.6–4.6)
Family history of AD	DSM-III-R	Family history of AD was confirmed to be risk factor for AD

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***Table 8.9** continued*

Author Year Reference Country	**Study design**	**Study population (age at baseline, years)**
Lindsay et al 1997 [10] Canada	Case-control study	258 prevalent AD cases, 535 controls (age 65+)
Li et al 1996 [11] United States	Case-control study	382 first-degree relatives of 77 AD probands, 848 of 198 non-demented aged 45+ years
Lautenschlager et al 1996 [12] United States	Follow-up study MIRAGE study	12 971 first-degree relatives of 1 694 AD probands
Payami et al 1997 [13] United States	Follow-up study	Community volunteers of 114 Caucasian, age 75+
Marder et al 1999 [14] United States	Follow-up study	146 non-demented Parkinson's disease (PD), 120 with PD and dementia, 903 normal controls
Launer et al 1999 [15] Europe	Pooled data of 4 European follow-up studies	528 dementia cases, 352 AD cases, aged 65+ years, 28 768 person-years of follow-up
Devi et al 2000 [16] United States	Follow-up study	Community residents (n = 5 529), aged 65+ years

Risk/protective factor	Diagnostic criteria	Results
Family history of mental retardation	DSM-III-R, NINCDS-ADRDA	OR = 3.23 (95% CI 0.98–10.6)
Dementia history of first-degree relatives	NINCDS-ADRDA	Cumulative AD risk was higher in relatives of AD probands than those of nondemented
Family history of dementia	DSM-III-R, NINCDS-ADRDA	Life-time risk of AD in first-degree relatives was 39.0%
Family history of dementia	NINCDS-ADRDA	RR = 3.80 (95% CI 0.87–16.50, p = 0.07)
Family history of PD and dementia	DSM-III-R	RR of AD for siblings of demented PD cases: 4.9 (95% CI 1.1–21.4)
Family history of dementia (ie, at least 2 relatives affected)	DSM-III-R, NINCDS-ADRDA	For AD: RR = 1.59 (95% CI 0.78–3.26) For dementia: RR = 1.42 (95% CI 0.75–2.68)
Family history of dementia	NINCDS-ADRDA	RR = 1.5 (95% CI 1.2–1.9)

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***Table 8.9** continued*

Author Year Reference Country	**Study design**	**Study population (age at baseline, years)**
Silverman et al 2000 [17] United States	Follow-up study	First-degree relatives of out-patients of memory disorder clinics, mean age 58 years, n = 6 039
Tyas et al 2001 [18] Canada	Nested case-control study	36 AD cases, 658 controls aged 65+ years
Lindsay et al 2002 [19] Canada	Nested case-control study	194 AD and 3 894 controls from national sample, aged 65+ years old
Demirovic et al 2003 [20] United States	Cross-sectional study	1 758 community residents, aged 65+ years old
Silverman et al 2003 [21] United States	Follow-up on clinical settings	Relatives of 3 proband groups of earlier-onset AD, very late-onset AD, and non-dementia
Huang et al 2004 [22] Sweden	Follow-up study	907 community residents aged 75+ years

AD = Alzheimer's disease; CI = Confidence interval; OR = Odds ratio; RR = Relative risk

Risk/protective factor	Diagnostic criteria	Results
Family history of AD	NINCDS-ADRDA, ICD-9	RR = 2.1 (95% CI 1.6–2.7)
Family history of dementia	NINCDS-ADRDA	No significant association with AD (OR = 0.60, 95% CI 0.13–2.66)
Family history of dementia	DSM-III-R, NINCDS-ADRDA	OR = 1.02 (95% CI 0.59–1.77)
Family history of AD	NINCDS-ADRDA	OR = 3.01 (95% CI 1.23–7.42)
AD history of first-degree relatives	NINCDS-ADRDA	Relatives of late-onset AD had lower AD risk than those of earlier-onset; family AD risk declined with increasing age
Dementia history of first-degree relatives	DSM-III-R	Familial history of dementia is related to AD (RR = 2.2, 95% CI 1.2–4.1) only in the presence of ApoE ε4 allele

Apoliproprotein E (ApoE)

Search results from the literature

The initial studies were published in 1993. We used the following *Keywords:* Apoliproprotein E and dementia or Alzheimer's disease or other types of dementia.

A total of 2 035 titles were found, and all relevant abstracts were read. We excluded clinic-based studies (in other words, we included population-based studies only) and studies with cognitive impairment as the major outcome. Initially 71 articles were selected. Of those 19 were excluded due to their having replicated the same study within the identical population. In this case, methodologically stronger articles were included and reported in the tables. The reference list also contains replicating studies. Ultimately we included 52 articles in the quality grading evaluation.

Summary of the articles included

Comments: Due to the nature (genetic) of the risk factor, the causal criteria index is always high by virtue of being essentially based on the temporal relation. In addition, the correlations are less likely to be affected by confounding. For that reason, the following criteria for confounders were applied in this particular case: 1) Low, if the results were not adjusted; 2) Medium, if the results were adjusted for age and gender; 3) High, if the results were also adjusted for vascular factors. Thirteen studies were excluded because they received a final quality index score of 0. Thirtynine studies were accepted for evaluating the evidence (Table 8.13). Tables 8.10–12 summarize the main conclusions of these studies for dementia, AD and VaD respectively.

Table 8.10 *ApoE and dementia: Number of studies by final quality index score.*

	Final quality index score		
	High	**Medium**	**Low**
Positive association	ε4: 3 ε24: 1	ε4: 6	ε4: 1
Inverse association	0	0	0
No association	0	ε4: 4 ε2: 2	0

A positive association means that ApoE is associated with increased risk of dementia, and an inverse association that ApoE4 is associated with reduced risk of dementia.

Table 8.11 *ApoE and AD: Number of studies by final quality index score.*

	Final quality index score		
	High	**Medium**	**Low**
Positive association	ε4: 11	ε4: 17	0
Inverse association	ε2: 1	0	0
No association	ε24: 1	ε4: 2 ε23: 1	0

A positive association means that ApoE is associated with increased risk of AD, and an inverse association that ApoE is associated with reduced risk of AD.

Table 8.12 *ApoE and Vascular dementia: Number of studies by final quality index score.*

Final quality index score			
	High	**Medium**	**Low**
Positive association	ε4: 2 ε24: 1	2: 1	0
Inverse association	0	0	0
No association	0	4: 6 ε22 23: 1	0

A positive association means that ApoE is associated with increased risk of VaD, and an inverse association that ApoE is associated with reduced risk of VaD.

Conclusions

Moderately strong evidence was found that ApoE ε4 is a risk factor for dementia (Evidence Grade 2).

Strong evidence was found that ApoE ε4 is a risk factor for AD (Evidence Grade 1).

The majority of the studies concerning VaD were inconclusive and often underpowered (limited evidence).

Only a few studies reported associations for ApoE ε2.

Table 8.13 *ApoE and dementia, AD, and VaD: Description of the studies that received a final quality score over 0.*

Author Year, reference Country	**Study design**	**Study population (age at baseline, years)**
Anttila et al 2002 [23] Finland	Population-based cohort study	n = 1 449 (65–79)
Benedetti et al 2002 [24] Italy	Population-based cross-sectional study	n = 168 (75+)
Bennett et al 2003 [25] United States	Population-based cross-sectional study	n = 128 (mean age at death 85)
Borenstein Graves et al 2001 [26] United States	Population-based cohort study	n = 1 058 (65+)
Breitner et al 1998 [27] United States	Population-based case-control study	Cases = 37, control = 344 (62–73)
Breitner et al 1999 [28] United States	Population-based cross-sectional study	n = 4 932 (65+)
Chandak et al 2002 [29] India	Population-based cross-sectional study	n = 178 (40+)
Evans et al 1997 [30] United States	Population-based cohort study	n = 578 (65+)
Evans et al 2003 [31] United States	Population-based cohort study	n = 818 (65+)

Risk/ protective factor	Diagnostic criteria	Results
ApoE 4	DSM-IV, NINCDS-ADRDA	Dementia: no 4 (ref); one 4 OR 2.28 (1.39–3.75)
ApoE 4	DSM-III-R, NINCDS-ADRDA	Dementia: no 4 (ref); one 4 OR 1.6 (0.6–3.9) AD: no 4 (ref); one 4 OR 2.7 (0.9–7.7) VaD: no 4 (ref); one 4 OR 1.9 (0.4–8.8)
ApoE 4	NINCDS-ADRDA	AD: no 4 (ref); one 4 OR 3.46 (1.44–8.33)
ApoE 4	DSM-IV, NINCDS-ADRDA	AD: no 4 (ref); one 4 OR 4.84 (1.81–12.88)
ApoE 4	NINCDS-ADRDA	AD: 33 (ref); any 4 OR 3.50 (1.71–7.18)
ApoE 4	DSM-III-R, NINCDS-ADRDA	AD: no 4 (ref); one 4 OR 4.32 (3.19–5.86); 44 OR 11.85 (7.00–20.05)
ApoE 4	DSM-IV, NINCDS-ADRDA	AD: no 4 (ref); any 4 RR 2.59 (1.20–5.60)
ApoE 4	NINCDS-ADRDA	AD: 33 (ref); any 4 RR 2.27 (1.06–4.89)
ApoE 4	NINCDS-ADRDA	AD: In blacks: no 4 (ref); any 4 RR 1.02 (0.39–2.68). In whites: no 4 (ref); any 4 RR 2.73 (1.40–5.32)

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***Table 8.13** continued*

Author Year, reference Country	Study design	Study population (age at baseline, years)
Frikke-Schmidt et al 2001 [32] Denmark	Population-based cross-sectional study	n = 8 964 (65+)
Ganguli et al 2000 [33] United States/ India	Population-based cross-sectional study	n = 4 450/India; n = 886/United States (age: India 55+; United States 70+)
Gessner et al 1997 [34] Germany	Population-based cross-sectional study	n = 477 (aged 70–103)
Ging-Yuek et al 2004 [35] Canada	Population-based cohort study	n = 1 469 (age 65+)
Guo et al 2001 [36] Sweden	Population-based cohort study	n = 985 (age 75+)
Haan et al 2003 [37] United States	Population-based cross-sectional study	n = 1 614 (age 60+)
Havlik et al 2000 [38] United States	Population-based cohort study	n = 2 577 (age 71–93)
Heijmans et al 2002 [39] The Netherlands	Population-based cross-sectional study	n = 648 (age 85+)

Risk/ protective factor	Diagnostic criteria	Results
ApoE 4	NINCDS-ADRDA	AD: 33 (ref); 23 OR 0.9 (0.2–4.0); 43 OR 3.3 (1.4–8.0) (3.19–5.86); 44 OR 10.1 (2.5–41.0)
ApoE 4	DSM-III-R, NINCDS-ADRDA	Dementia: no 4 as ref. United States any 4: OR 2.10 (1.21–3.63). India any 4: 2.39 (1.04–5.52). AD: United States: any 4: 2.26 (1.29–3.95). India any 4: 2.62 (0.98–7.01)
ApoE 4	DSM-III-R, NINCDS-ADRDA	Dementia: Among 70–84 years, no significant association. Among 85–103 year olds: 33 (ref); 34 OR 2.16 (1.03–4.51)
ApoE 4	DSM-III-R, ICD-10, NINCDS-ADRDA	AD: no 4 (ref); any 4 RR 2.89 (1.96–4.28) VAD: 3.13 (1.76–5.55)
ApoE 4	DSM-III-R	Dementia: 33 (ref); any 4 RR 1.5 (1.1–2.1)
ApoE 4	NINCDS-ADRDA, CAD-DTC	Dementia: 33 (ref); 22: OR 1.02 (0.46–2.28); 23/24: 1.38 (0.47–4.09); 24/34: 1.02 (0.35–3.02); 44: 2.04 (0.88–4.72)
ApoE 4	DSM-III-R, CAD-DTC, NINCDS-ADRDA	Dementia: no 4 (ref); any 4 RR 1.50 (1.03–2.20) AD: 2.39 (1.07–5.31). VaD: 1.27 (0.33–4.83)
ApoE 4	DSM-III	Dementia: 33 (ref); 23/22 OR 0.7 (0.3–1.5); any 4 OR 4.1 (2.2–7.7)

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***Table 8.13** continued*

Author Year, reference Country	Study design	Study population (age at baseline, years)
Henderson et al 1995 [40] Australia	Population-based cohort study	n = 638 (age 70+)
Juva et al 2000 [41] Finland	Population-based cohort study	n = 187 (age 85+)
Katzman et al 1997 [42] China	Population-based case-control study	Cases = 65, controls = 363 (age 55+)
Kivipelto et al 2002 [43] Finland	Population-based cohort study	n = 1 291 (age 65–79)
Kukull et al 1996 [44] United States	Population-based case-control study	Cases = 234, controls = 304 (age 60+)
Kuller et al 2003 [45] United States	Population-based cohort study	n = 3 271 (age 65+)
Kuusisto et al 1997 [46] Finland	Population-based cross-sectional study	n = 980 (age 65–78)
Molero et al 2001 [47] Venezuela	Population-based cross-sectional study	n = 1 853 (age 65+)
Myers et al 1996 [48] United States	Population-based cohort study	n = 1 030 (age 71–100)

Risk/ protective factor	Diagnostic criteria	Results
ApoE 4	DSM-III-R, ICD-10	Increment of one ε4: Dementia (DSM-III-R): OR 1.9 (0.96–3.76). Dementia (ICD-10): OR 3.6 (1.39–8.04)
ApoE 4	DSM-III-R	Dementia: 33 (ref); any 4 OR 1.78 (0.88–3.60)
ApoE 4	DSM-III, NINCDS-ADRDA	AD: no 4 (ref); any 4 OR 4.10 (2.18–7.71)
ApoE 4	DSM-IV, NINCDS-ADRDA	AD: no 4 (ref); any 4 OR 2.1 (1.1–4.1)
ApoE 4	DSM-III-R	AD: no 4 (ref); one 4 OR 3.1 (2.1–4.5); 44 OR 34.3 (8.0–146.3)
ApoE 4	DSM-IV, NINCDS-ADRDA, NINDS-AIREN	Dementia: no 4 (ref); any 4 RR 2.1 (1.69–2.61) AD: any 4 RR 2.6 (2.05–3.43) VaD/AD+VaD: any 4 RR 1.5 (0.97–2.27)
ApoE 4	DSM-III-R, NINCDS-ADRDA	AD: no 4 (ref); any 4 OR 3.60 (1.91–6.79)
ApoE 4	NINCDS-ADRDA, CAD-DTC	AD: no 4 (ref). Women any 4: OR 3.43 (2.04–5.76). Men any 4: 1.38 (0.43–4.45). VaD: Women any 4: 0.92 (0.26–3.30). Men any 4: 0.49 (0.06–3.99)
ApoE 4	NINCDS-ADRDA	AD: 33 (ref); 34 RR 3.7 (1.9–7.5); 44 RR 30.6 (10.7–84.4); any 2 RR 0.25 (0.04–1.89)

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***Table 8.13** continued*

Author Year, reference Country	Study design	Study population (age at baseline, years)
Notkola et al 1998 [49] Finland	Population-based cohort study	n = 444 (age 40–59)
Polvikoski et al 2001 [50] Finland	Population-based cross-sectional study	n = 532 (age 85+)
Prince et al 2000 [51] United Kingdom	Population-based cross-sectional study	n = 370 (age 65–74)
Qiu et al 2004 [52] Sweden	Population-based cohort study	n = 985 (age 75+)
Quiroga et al 1999 [53] Chile	Population-based case-control study	Cases = 95, controls = 187 (age 65–97)
Sahota et al 1997 [54] United States	Population-based cross-sectional study	n = 288 (age 65+)
Skoog et al 1998 [55] Sweden	Population-based cohort study	n = 282 (age 85)
Slooter et al 1999 [56] The Netherlands	Population-based case-control study	Cases = 244 (176 AD; 42 VaD), controls = 1 002 (age 55+)

Risk/ protective factor	Diagnostic criteria	Results
ApoE 4	DSM-III-R	AD: no 4 (ref); any 4 OR 1.7 (0.7–3.9)
ApoE 4	DSM-III-R	AD: no 4 (ref); any 4 OR 2.5 (1.5–4.2)
ApoE 4	DSM-IV, NINCDS-ADRDA	Dementia: 33 (ref); any 4 OR 3.13 (1.40–7.02) AD: any 4 OR 4.81 (1.60–14.4)
ApoE 4	DSM-III-R	AD: 33 (ref); 34 RR 1.4 (1.0–2.0); 44 RR 3.1 (1.6–5.9); Among 85+: any 2 RR 0.4 (0.2–0.8)
ApoE 4	DSM-III-R, NINCDS-ADRDA	AD: 33 (ref); 34 OR 2.4 (1.3–4.5); 44 12.8 (3.9–47.6)
ApoE 4	DSM-III-R, ICD-10, NINCDS-ADRDA	AD: 33 (ref); 34 OR 1.20 (0.58–2.45); 44 OR 4.83 (1.71–13.64)
ApoE 4	DSM-III-R, NINCDS-ADRDA Erkinjuntti criteria	Dementia: no 4 (ref); any 4 RR 1.2 (0.7–2.1). AD: any 4 RR 6.2 (1.3–29.6). VaD: any 4 RR 0.5 (0.2–1.3); no 2 (ref); any 2 RR 2.5 (1.2–5.5)
ApoE 4	DSM-III-R, NINCDS-ADRDA, NINDS-AIREN	Dementia: 33 (ref); 24: OR 3.9 (1.2–12.6); 34: 1.7 (1.1–2.7); 44: 15.2 (5.9–39.4). AD: 24: 1.6 (0.4–7.0); 34: 1.5 (0.9–2.6); 44: 17.1 (6.1–48.4). VaD: 24: 16.9 (3.4–83.2); 34: 2.2 (1.0–5.1)

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***Table 8.13** continued*

Author Year, reference Country	Study design	Study population (age at baseline, years)
Stevens et al 1998 [57] The Netherlands	Population-based case-control study	Cases = 75, controls = 561 (age 37–73)
Tang et al 1998 [58] United States	Population-based cohort study	n = 1 079 (age 65+)
Tilvis et al 1998 [59] Finland	Population-based cross-sectional study	n = 550 (age 75–85)
van Duijn et al 1995 [60] The Netherlands	Population-based case-control study	Cases = 175, controls = 532 (age at onset below 65)
Zhu et al 2000 [61] Sweden	Population-based cohort study	n = 985 (age 75+)

33 = alleles ε3ε3; 34 = alleles ε3ε4 etc; AD = Alzheimer's disease; OR = Odds ratio; ref = Reference group; RR = Relative risk; VaD = Vascular dementia

Risk/ protective factor	Diagnostic criteria	Results
ApoE 4	Lund-Manchester	FTD: not 44 (ref); 44 OR 2.2 (0.6–8.9)
ApoE 4	DSM-III-R, NINCDS-ADRDA	RR: of any 4 for AD 33 (ref): Whites 2.5 (1.1–6.4); African Americans 1.0 (0.6–1.6); Hispanics 1.1 (0.7–1.6)
ApoE 4	DSM-III-R	AD: no 4 (ref); any 4 RR 3.24 (1.67–6.25)
ApoE 4	NINCDS-ADRDA	Early onset AD: 33 (ref); 34 OR 2.0 (1.3–3.1); 44 OR 16.6 (6.9–40.0)
ApoE 4	DSM-III-R	Dementia with stroke: 33 (ref); 22 or 23 RR 1.4 (0.6-3.3); any 4 RR 1.2 (0.6-2.4)

Smoking

Search results from the literature

Keywords: Smoking and dementia/risk of dementia/Alzheimer's disease.

After eliminating 30 duplicates, we found 141 articles. Sixteen articles were added to the list based on personal knowledge for a total of 157. After reading through the abstracts, we excluded 112 articles as irrelevant to this topic for one or more of the following reasons:

- The outcome was other than dementia (such as cognitive decline, mortality, depression, institutionalization, functional status, vascular risk factors, stroke or cognition; n = 45);
- The participants already had dementia (n = 12);
- The topic was treatment of, or caregiving in, dementia (n = 15);
- The focus was on other disorders leading to dementia that were not included in our review, such as PD, AIDS, Creuzfeldt-Jakob or Alcohol dementia (n = 40).

There were 45 articles identified as suitable for evaluation. After reading the articles, we eliminated 5 articles because they were part of the same study. That left 40 articles to be assessed.

Summary of articles included

Thirtyone of the forty articles were deemed unacceptable in accordance with our quality criteria. The primary shortcomings were high (or unreported) dropout rates, the use of non-standardized diagnostic criteria, the presence of bias that might affect the results and or incorrect directionality. That left 11 studies for inclusion in the final assessment (Table 8.19).

Table 8.14 *Smoking and AD: Number of studies by final quality index score.*

	Final quality index score		
	High	**Medium**	**Low**
Positive association		2	3
Inverse association	0	0	0
No association	1	2	3

A positive association means that smoking is associated with increased risk of dementia, and an inverse association that smoking is associated with reduced risk of dementia.

Conclusions

Our findings concerning the relationship between smoking and AD are largely inconsistent (Table 8.14). Six of the eleven studies that we included reported no association and three obtained a score of medium quality. Five studies reported a positive correlation between smoking and the risk for AD, but only two obtained a score of medium quality. In short, insufficient evidence exists that smoking is a risk factor for AD. None of the selected articles reported a protective effect.

Table 8.15 *Smoking and AD: Description of the studies that received a final quality score over 0.*

Author Year, reference Country	**Study design**	**Study population (age at baseline, years)**
Hebert et al 1992 [62] United States	4.7-year follow-up	513 community residents (aged 65+)
Broe et al 1998 [63] Australia	3-year follow-up	n = 327 (aged 75+)
Ott et al 1998 [64] The Netherlands	2.1-year follow-up	n = 5 479, aged 55+
Launer et al 1999 [15] Denmark, France, The Netherlands, United Kingdom	4-year follow-up	n = 16 334 (aged 65+)
Merchant et al 1999 [65] United States	Community-based longitudinal study over 2 years	n = 1 062
Wang et al 1999 [66] Sweden	Cross-sectional and 6-year follow-up	n = 636 for cross-sectional n = 343 for follow-up (aged 75+)
Maia et al 2002 [67] Portugal	Case-control	AD cases = 54, controls = 54 (age and sex matched)

Risk/protective factor	Diagnostic criteria	Results
Smoking: 1) Ever vs never; 2) Packs of cigarettes daily; 3) Number of years of smoking, and 4) Pack-years	NINDS-ADRDA	Smoking does not increase risk of AD
Smoking: Current and ex-smokers	DSM-IV, NINDS-ADRDA	No association was found with dementia and AD
Subjects were asked about their current and past smoking habits	DSM-III-R	Compared with never smokers, smokers had increased risks of dementia RR = 2.2 (1.3–3.6) and AD RR = 2.3 (1.3–4.1). Its stronger for AD in people without ApoE4. RR = 4.6 (1.5–4.1)
Smoking status was obtained at baseline from the participants	DSM-III-R, NINDS-ADRDA	Smoking did not protect against AD or dementias
At least one cigarette per day for a period of 1 year or more 2 years before diagnosis	CDR	The RR among smokers was 1.9 (1.2–3). Smokers without an ApoE 4 had the highest risk of AD, RR = 2.1 (2.1–3.7)
Smokers: 1. Current smoker, 2. Former who smoked >4 years or stopped after age 40, irrespective of dose, 3. Had been smoking >4 cigarettes daily	DSM-III-R	Smoking does not seem protective against AD or dementia, and the cross-sectional association might be due to differential mortality
Smoking information 20 year preceded diagnosis of AD: controls: from themselves, patients from accompanying people	NINDS-ADRDA	Smoking was not associated with AD

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***Table 8.15** continued*

Author Year, reference Country	Study design	Study population (age at baseline, years)
Lindsay et al 2002 [19] Canada	Case-control, 5-year retrospective	n = 4 615 (aged 65+)
Suh et al 2003 [68] Korean	3-months follow-up	n = 370 (aged 65+)
Tyas et al 2003 [69] United States	25–30 years follow-up	3 734 survivors with an initially age 65+ (25–30 years before)
Juan et al 2004 [70] China	Cohort study 2-year follow-up	n = 2 820 (age 65+)

AD = Alzheimer's disease; RR = Relative risk; VaD = Vascular dementia

Risk/protective factor	Diagnostic criteria	Results
No clear definition of smoking	DSM-IV, NINDS-ADRDA, NINDS-AIREN	No association was found for smoking and AD
Cigarette smoking in pack-years were obtained by face-to face interview 3 months before diagnosis	DSM-III-R, NINDS-ADRDA, NINDS-AIREN	Smoking for more than 30 pack-years increased the risk of VaD, RR = 11.5 (2.8–44.6)
Smoking history: never/former/ current smokers, & amount & duration of smoking 25–30 years before diagnosis	DSM-III-R, NINDS-ADRDA	Mid-life men smokers, the number of pack-years predicted dose-dependent risk of AD and AD+VaD assessed 25 years later
Smoking: past, current, never smokers. Status of smoking: light, medium, heavy, very heavy	DSM-III-R	Current smokers had an increased risk of AD and VaD. AD risk increased with medium-heavy pack-years, but not very heavy smoking

Alcohol

Search results from the literature

Keywords: Alcohol and dementia/Alzheimer's disease.

In the initial screening 837 titles were identified. All relevant abstracts were read, producing 31 articles to be evaluated. Thirteen studies were accepted, while eighteen were excluded because they had a final quality index score of 0.

Summary of articles included

Table 8.19 describes the 13 studies.

Remarks: Depending on the definition of exposure, 3 different kinds of studies can be identified:
1) Abuse or excessive use of alcohol;
2) Drinking vs non-drinking (dichotomous exposure);
3) Alcohol consumption based on quantity and/or frequency (several categories, the ability to evaluate moderate drinking).

Table 8.16 *Alcohol and dementia: Number of studies by final quality index score.*

Final quality index score			
	High	**Medium**	**Low**
Positive association	Frequent drinking (in ApoE4 group): 1	Beer monthly: 1	0
Inverse association	0	Wine monthly: 1 Moderate drinking: 3 Light–moderate wine (no ApoE4): 1	Moderate drinking: 1
No association	0	0	0

A positive association means that alcohol is associated with increased risk of dementia, and an inverse association that alcohol is associated with reduced risk of dementia.

Table 8.17 *Alcohol and AD: Number of studies by final quality index score.*

	Final quality index score		
	High	**Medium**	**Low**
Positive association	0	0	0
Inverse association	0	Moderate drinking: 3 Light–moderate wine (no ApoE4) : 1	Regular drinking: 1 Moderate drinking: 1
No association	0	0	Alcohol use (yes/no): 1 Regular drinking: 1 Quantity/frequency: 1

A positive association means that alcohol is associated with increased risk of AD, and an inverse association that alcohol is associated with reduced risk of AD.

Table 8.18 *Alcohol and VaD: Number of studies by final quality index score.*

	Final quality index score		
	High	**Medium**	**Low**
Positive association	0	0	Alcohol use (yes/no): 1 Alcohol abuse: 1
Inverse association	0	Moderate drinking: 1	0
No association	0	Moderate drinking: 1	Regular drinking: 1

A positive association means that alcohol is associated with increased risk of VaD, and an inverse association that alcohol is associated with reduced risk of VaD.

Conclusions

For both dementia and AD, there is limited evidence that moderate drinking reduces the risk of dementia. Only one study, albeit with a high quality score, showed an increased risk for dementia in frequent drinkers. The evidence is inconclusive with respect to VaD (Table 8.16, 8.17, 8.18).

Table 8.19 *Alcohol and dementia, AD, and VaD: Description of the studies that received a final quality score over 0.*

Author Year, reference Country	**Study design**	**Study population (age at baseline, years)**
Hebert et al 1992 [62] United States	Population-based cohort study	n = 513 (age 65+)
Yoshitake et al 1995 [71] Japan	Population-based cohort study	n = 828 (age 65+)
Lindsay et al 1997 [10] Canada	Population-based cross-sectional study	n = 664 (age 65+)
Orgogozo et al 1997 [72] France	Population-based cohort study	n = 2 273 (age 65+)
Hebert et al 2000 [73] Canada	Population-based cohort study	n = 904 (age 65+)
Tyas et al 2001 [18] Canada	Population-based cohort study	n = 694 (age 65+)
Huang et al 2002 [74] Sweden	Population-based cohort study	n = 402 (age 75+)
Lindsay et al 2002 [19] Canada	Population-based cohort study	n = 4 688 (age 65+)
Mukamal et al 2003 [75] United States	Population-based nested case-control study	Cases = 373, controls = 373 (age 65+)

Risk/protective factor	Diagnostic criteria	Results
Yes/no, ounces/day (cont-inuous and in 3 categories)	NINCDS-ADRDA	AD: ns
Alcohol drinking (yes/no)	DSM-III-R, NINDS-AIREN, NINCDS-ADRDA	Risk for VaD, not for AD
History of alcohol abuse (asked from proxies)	DSM-III-R, ICD-10, HIS	Alcohol abuse associated with increased risk of VaD
Drinks/day, in categories: none, mild, moderate (= 3–4 drinks/day), heavy	DSM-III-R, NINCDS-ADRDA	Moderate wine consumption protect dementia/AD
Alcohol (drunk beer/wine/ spirits at least once/week)	DSM-IV, NINDS-AIREN	VaD: ns
Regular drinker, beer, wine, spirits (at least once/week)	NINCDS-ADRDA	AD: ns
Non-drinker vs light-to-moderate (1–14 units/week females, 1–21 males)	DSM-III-R	Light to moderate drinking had protective effect for dementia and AD
Regular drinker, beer, wine, spirits (= at least once/week)	DSM-III-R, NINCDS-ADRDA	AD: Alcohol and wine consumption protective, but not in adjustment analyses
Drinks/week: <1, 1–6, 7–13, 14+	DSM-IV, NINDS-AIREN, NINCDS-ADRDA	U-shape for dementia and AD, tendency for VaD

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***Table 8.19** continued*

Author Year, reference Country	Study design	Study population (age at baseline, years)
Ruitenberg et al 2002 [76] The Netherlands	Population-based cohort study	n = 5 395 (age 55+)
Truelsen et al 2002 [77] Denmark	Population-based cohort study	n = 1 709 (age 65+)
Anttila et al 2004 [78] Finland	Population-based cohort study	n = 1 018 (65+)
Luchsinger et al 2004 [79] United States	Cohort study	n = 980 (65+)

AD = Alzheimer's disease; VaD = Vascular dementia

Risk/protective factor	Diagnostic criteria	Results
No, <1 drink/week, 1–7/week, 1–3/day, 4+/day	DSM-III-R, NINCDS-ADRDA, NINDS-AIREN	Light–moderate drinking (1–3/day) associated with lower risk of dementia and VaD. Similar for AD among ApoE4+. No difference between beverages
Never, monthly, weekly, daily intake of beer, wine and spirits	DSM-III-R, NINCDS-ADRDA, HIS	Monthly/weekly wine intake associated with decreased risk, monthly beer intake with increased risk of dementia
Never drank alcohol; infrequently; (< once a month); frequently (several times a month)	DSM-IV, NINCDS-ADRDA	Risk of dementia increased with increasing alcohol consumption only in individuals carrying ApoE ε4
Non drinkers, light and moderate drinkers, heavy drinkers	DSM-IV, CDR, NINCDS-ADRDA	Light to moderate wine drinking associated with a lower risk of AD in elderly without ApoE ε4

Blood pressure

Search results from the literature

Keywords: Dementia OR Alzheimer's disease AND blood pressure AND risk factor/dementia OR Alzheimer's disease AND blood pressure AND population study, with the delimiters of "human", "English language", and aged "65+".

A total of 126 papers were found by searching PubMed. After reading through the abstracts or titles, we excluded 90 due to non-originality, leaving 36 for final evaluation. Seventeen of them were not acceptable for etiological assessment due to cross-sectional surveys or retrospective case-control study design, leaving 19 for final analysis (Table 8.23).

Summary of articles included

Table 8.19 describes the 19 studies.

Blood pressure and dementia: Of the 16 studies that were evaluated, 5 received a quality score of 0 and 1 was deemed to be a secondary report on the same data. Thus, 10 studies were included in the final assessment.

Blood pressure and AD: Ten of the 22 studies that were evaluated received a quality score of 0, and one neuropathological study was excluded. Thus, 11 studies were included in the final assessment.

Blood pressure and VaD: Three of the eight studies that were evaluated received a quality score of 0, leaving five studies for the final assessment.

Table 8.20 *High blood pressure and dementia: Number of studies by final quality index score.*

	Final quality index score		
	High	**Medium**	**Low**
Positive association	At midlife: 1	At late life: 3	At late life: 1
Inverse association	0	At late life: 2	At late life: 2
No association	0	At midlife: 1 At late life: 1	0

A positive association means that blood pressure is associated with increased risk of dementia, and an inverse association that blood pressure is associated with reduced risk of dementia. One study showed that both high systolic pressure and low diastolic pressure were associated with increased risk of dementia.

Table 8.21 *High blood pressure and AD: Number of studies by final quality index score.*

	Final quality index score		
	High	**Medium**	**Low**
Positive association	At midlife: 1	At midlife: 1 At late life: 2	0
Inverse association	0	At late life: 1	At late life: 1
No association	0	At midlife: 1 At late life: 4	At late life: 1

A positive association means that blood pressure is associated with increased risk of AD, and an inverse association that blood pressure is associated with reduced risk of AD. One study showed that both high systolic pressure and low diastolic pressure were associated with increased risk of AD.

Table 8.22 *High blood pressure and VaD: Number of studies by final quality index score.*

	Final quality index score		
	High	**Medium**	**Low**
Positive association	1	4	0
Inverse association	0	0	0
No association	0	0	0

A positive association means that blood pressure is associated with increased risk of VaD, and an inverse association that blood pressure is associated with reduced risk of VaD.

Conclusions

There is moderately strong evidence that elevated blood pressure in midlife is a risk factor for dementia and probably for Alzheimer's type of dementia (Evidence Grade 2).

There is moderate to strong evidence that high blood pressure is a risk factor for VaD (Evidence Grade 2).

Among very old people (ages 75 and up), low blood pressure may be predictive of clinical dementia and AD as well (Evidence Grade 3).

Table 8.23 *Blood pressure and dementia, AD, and VaD: Description of the studies that received a final quality score over 0.*

Author Year, reference Country	Study design	Study population (age at baseline, years)
Dementia		
Launer et al 2000 [80] United States	Population-based follow-up study	Japanese-American men n = 3 703 (age 45–68)
Skoog et al 1996 [81] Sweden	Longitudinal study (9–15 year follow-up)	Community-based random sample n = 382 (age 70)
Brayne et al. 1998 [82] United Kingdom	Nested case-control study (2.4-year follow-up)	General practice based population (age 75+, 36 dementia, 340 controls)
Ruitenberg et al 2001 [83] The Netherlands, Sweden	Community-based cohort, 2.1-year follow-up	n = 6 985 (55+ years)
Verghese et al 2003 [84] United States	Follow-up study (1–21 year follow-up; mean 6.7 year)	Volunteers from the general population n = 406 (age 75+)
Guo et al 2001 [36] Sweden	3-year follow-up study	Community-based cohort n = 1 270 (age 75+)
Guo et al 1999 [85] Sweden	3-year follow-up study	Community-based random sample n = 304 (age 75+)
Qiu et al 2003 [86] Sweden	Follow-up study	Community-based cohort n = 1 270 (75+ years)
Yamada et al 2003 [87] Japan	6-year follow-up study	Community-based cohort n = 1 774 (age 35+)

Risk/protective factor	Diagnostic criteria	Results
High BP in midlife	DSM-III-R, CADDTC, NINCDS-ADRDA	Midlife high BP increases the risk of dementia in late life
High BP	DSM-III-R, NINCDS-ADRDA,	Previous high BP increases the risk of dementia
Hypertension	CAMDEX, ICD-10	No association with dementia (OR = 1.1, 95% CI 0.4–2.6)
Low BP	DSM-III-R, NINCDS-ADRDA	An inverse association between BP and dementia risk among old people on antihypertensive medication
Low DBP (<70 mm Hg)	DSM-III-R	Low DBP and consistent low BP were associated with higher risk of dementia
High SBP (>180 mm Hg)	DSM-III-R, HIS	Very high SBP was associated with high risk of dementia
Low SBP (≤140 mm Hg)	DSM-III-R, HIS	Low SBP is related to dementia dependent on initial cognitive function
High SBP (>180 mm Hg) and low DBP (<70)	DSM-III-R, HIS	Both high SBP (≥160) and low DBP (<70 mm Hg) were related to increased risk of dementia
High SBP in midlife	DSM-IV	OR/10 mm Hg increase for VaD was 1.3 (95% CI 1.1–1.6)

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Table 8.23 *continued*

Author Year, reference Country	Study design	Study population (age at baseline, years)
Kuller et al 2003 [45] United States	6-year follow-up study	A cohort of medicare receivers n = 3 608 (age 65+)
Alzheimer disease		
Brayne et al 1998 [82] United Kingdom	Nested case-control study (2.4-year follow-up)	18 cases and 340 control (age 75+). General practice based population
Yoshitake et al 1995 [71] Japan	Community-based 7-year follow-up study	n = 887 (age 65+)
Kivipelto et al 2001 [88] Finland	Community-based cohort follow-up study	n = 1 449 (age 45–68)
Morris et al 2001 [89] United States	Follow-up study (2–13 years observation)	n = 642 (age 65+). Random sample of a community population
Tyas et al 2001 [18] Canada	Nested case-control study (5-year follow-up)	36 AD, 658 controls (age 65+). Random sample
Guo et al 2001 [36] Sweden	3-year follow-up study	Community-based cohort, (75+ years)
Posner et al 2002 [90] United States	7-year follow-up study	Medicare recipients n = 1 259 (96+ years)
Lindsay et al 2002 [19] Canada	Nested case-control study (5-year follow-up)	Community-based cases = 194, controls = 3 894 (65+ years)

Risk/protective factor	Diagnostic criteria	Results
Hypertension	MRI	Hypertension led to OR of 1.2 (95% CI 0.99–1.41) for dementia
Hypertension	CAMDEX, ICD-10	No association with AD (OR = 0.8, 95% CI 0.3–2.9)
High SBP	DSM-III, DSM-III-R, NINCDS-ADRDA	High BP was not related to AD
High SBP (≥160 mm Hg) in midlife	DSM-IV, NINCDS-ADRDA	Raised SBP in midlife increases the risk of AD in late life (OR 2.8; 95% CI 1.1–7.2)
High BP	NINCDS-ADRDA	No association between BP and AD (OR/10 mm Hg 1.03, 95% CI 0.80–1.32)
High BP	NINCDS-ADRDA	AD: OR = 1.14 (95% CI 0.53–2.45)
High SBP (>180 mm Hg)	DSM-III-R, HIS	Very high SBP was associated with high risk of AD
Hypertension history	NINCDS-ADRDA	AD: OR = 0.9 (95% CI 0.7–1.3)
High BP	DSM-IV	AD: OR = 0.88 (95% CI 0.62–1.27)

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Table 8.23 *continued*

Author Year, reference Country	Study design	Study population (age at baseline, years)
Guo et al 1999 [85] Sweden	3-year follow-up study	Community-based random sample n = 304 (75+ years)
Wu et al 2003 [91] China	Case-control study	A rural population-based cases = 301, controls = 16 187 (50+ years)
Qiu et al 2003 [86] Sweden	6-year follow-up study	Community-based cohort n = 1 270 (75+ years)
Vascular dementia		
Yoshitake et al 1995 [71] Japan	7-year follow-up study	Community-based cohort n = 887 (65+ years)
Posner et al 2002 [90] United States	7-year follow-up study	Medicare recipients n = 1 259 (96+ years)
Ross et al 1999 [92] United States	Population-based case-control study	Japanese-American men, 68 VaD cases, 3 335 controls (age 65+)
Hebert et al 2000 [73] Canada	Population-based nested case-control study (5-year follow-up)	105 VaD cases, 802 controls, age 65+
Yamada et al 2003 [87] Japan	Community-based follow-up study	n = 1 774 (age 35+)

AD = Alzheimer's disease; CI = Confidence interval; DBP = Diastolic blood pressure; OR = Odds ratio; SBP = Systolic blood pressure; SD = Standard deviation; VaD = Vascular dementia

Risk/protective factor	Diagnostic criteria	Results
Low SBP (≤140 mm Hg)	DSM-III-R, HIS	Low SBP is related to AD risk dependent on initial cognitive function
High BP in midlife	DSM-IV	AD: OR = 2.0 (95% CI 1.1–3.5)
High SBP (>180 mm Hg) and low DBP (<70)	DSM-III-R, HIS	High SBP (≥160) and low DBP (<70 mm Hg) were related to increased risk of AD
High SBP	DSM-III, DSM-III-R, NINCDS-ADRDA	High BP was related to high risk of VaD (OR/1-SD increase 2.0, 95% CI 1.3–2.9)
Hypertension history	NINCDS-AIREN	VaD: OR = 1.8 (95% CI 1.1–3.5)
Midlife hypertension	DSM-III-R	VaD: Multi-adjusted OR = 1.92 (95% CI 0.96–3.82)
Hypertension	NINCDS-AIREN	VaD: For men, OR 0.9 (95% CI 0.4–1.8) For women, OR 2.1 (95% CI 1.2–3.5)
High SBP in midlife	DSM-IV	VaD: OR/10 mm Hg increase 1.3 (95% CI 1.1–1.6)

Diabetes mellitus

Search results from the literature

Keywords: Diabetes and dementia, diabetes and Alzheimer's disease (not including cognitive impairment or decline).

A total of 510 papers were found by searching PubMed. All titles and abstracts were read online. Most of these studies concerned issues (cognitive functions and impairment, diabetes care, genetic aspects, etc) other than the association between diabetes and dementia. Some of them were review articles and comments. Thirty-four of the articles were identified as suitable for inclusion, but 2 more studies were excluded because they did not have a control group without dementia, but rather compared AD with VaD patients (both studies found diabetes to be rare in AD) [93,94]. A total of 32 articles were evaluated.

Summary of included papers

Diabetes and dementia: Three of the studies that addressed the relation between diabetes and dementia were deemed unacceptable due to the non-representativeness of the study population or the fact of being a secondary report on the same project. Table 8.26 describes the included nine studies.

Diabetes and AD: Eleven of the 29 articles that investigated the association between diabetes and AD were not accepted due primarily to a selective population (institutions, voluntary sample), bias, lack of an estimate concerning the correlation or insufficient control for confounders. All but one of those articles found diabetes to be rare in AD. Two articles were derived from the same cohort – the better designed one was accepted. Table 8.27 describes the nine studies.

Table 8.24 *Diabetes and dementia: Number of studies by final quality index score.*

	Final quality index score		
	High	**Medium**	**Low**
Positive association	0	7	0
Inverse association	0	0	0
No association	0	4	0

A positive association means that diabetes is associated with increased risk of dementia, and an inverse association that diabetes is associated with reduced risk of dementia.

Table 8.25 *Diabetes and AD: Number of studies by final quality index score.*

	Final quality index score		
	High	**Medium**	**Low**
Positive association	0	9	0
Inverse association	0	0	0
No association	0	7	1

A positive association means that diabetes is associated with increased risk of AD, and an inverse association that diabetes is associated with reduced risk of AD.

Conclusions

Diabetes and dementia: The evidence linking diabetes to dementia is moderately strong. A total of seven studies with medium quality reported a positive correlation. Three of the four studies with medium quality that reported no association between diabetes and dementia nevertheless showed strong indications of a positive correlation, with the point estimations of the relative risk range at 1.3–2.6 and the lower level of the 95% confidence interval at 0.9 or above.

Diabetes and AD: We identified inconsistent results with respect to the relation between diabetes and AD. Nine positive studies with medium to high quality demonstrated a positive correlation, while seven studies with medium to high quality reported no significant association (although five showed definite indications). Thus, we concluded that there is insufficient evidence linking diabetes to AD.

Table 8.26 *Diabetes and dementia. Description of the studies that received a final quality score over 0.*

Author Year, reference Country	**Study design**	**Study population (age at baseline, years)**
Leibson et al 1997 [95] United States	Population-based, 15-year follow-up study	1 455 people from the Rochester diabetes register
Ott et al 1999 [96] The Netherlands	Population-based, 2.1-year follow-up study	6 370 people from the Rotterdam study (age 55+)
MacKnight et al 2002 [97] Canada	Population-based, 5-year follow-up study	5 574 people age from the Canadian Study of Health and Aging (65+ mean 74)
Peila et al 2002 [98] United States	Population-based, 2.9-year follow-up study	2 574 Japanese-American men Honolulu-Asia Aging Study (age 72–91)
Curb et al 1999 [99] United States	Population-based, 25-year follow-up study	3 774 Japanese-American men enrolled in the Honolulu-Asia Aging Study (age 45–68)
Brayne et al 1998 [82] United Kingdom	Case-control, 2.4-year follow-up study	376 people from selected general practices in Cambridge city (age 75+)
Xu et al 2004 [100] Sweden	Population-based, 6-year follow-up study	1 301 community dwellers age (75+ mean 81)
Schnaider Beeri et al 2004 [101] United States	35-year prospective historical study	1 892 participants (mean age 82)

Risk/protective factor	Diagnostic criteria	Results
Rochester diabetes mellitus cohort, data from complete community based medical records	DSM-III	Diabetes increased the risk of dementia, with RR 1.66 (1.34–2.05)
Diabetes was defined as use of an antidiabetic medication or a random or post load serum glucose >11 mol/l	DSM-III-R, NINCDS-ADRDA	Diabetes doubled dementia risk: RR = 1.9 (1.3–2.8); Patients treated with insulin were at highest risk: RR 4.3 (1.7–10.5)
Self-report, clinical interviews, medication list, and lab testing (glucose >11.1 mmol/l)	DSM-III-R, ICD-10, NINCDS-ADRDA, NINDS-AIREN	Diabetes was not significantly associated with dementia: RR 1.26 (0.9–1.76)
Self report of doctors' diagnose of diabetes, use of medication or fasting/post challenge glucose levels	DSM-III-R, NINCDS-ADRDA	Diabetes was associated with dementia; RR = 1.5 (1.01–2.2)
Self report of diagnose of diabetes, use of medication or fasting/post challenge glucose levels	DSM-III-R, NINCDS-ADRDA	RRs of dementia related to diabetes diagnosed 15 and 25 years ago were 1.37 (0.97–1.95) and 1.10 (0.69–1.76)
History of diabetes was asked from the informants of the incident dementia cases at the follow-up visit	ICD–10	Diabetes was associated with OR of 2.62 (0.89–7.75) for all dementias
Diabetes was defined based on medical records, antidiabetic drug use, or blood glucose >11 mol/l	DSM-III-R for dementia	Diabetes increases the risk of dementia, in particular VaD: HR for dementia 1.5 (1.0–2.1)
Diabetes was defined based on glucose level, use of oral hypoglycemic/insulin therapy, or history of diabetes	TICS-m based on the MMSE; DQ, GDQ, Hachinski Ischemic Scale, DSM-IV	Diabetes in mid-life was associated with dementia (82% were AD subtype), OR 2.83 (1.40–5.71)

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***Table 8.26** continued*

Author Year, reference Country	Study design	Study population (age at baseline, years)
Luchsinger et al 2004 [79] United States	5.4-year (3 691 person-years) longitudinal follow-up study	N = 683, 70.5% women (age >65, mean 76.2 ± 5.8)

AD = Alzheimer's disease; HR = Hazard ratio; OR = Odds ratio; RR = Relative risk; VaD = Vascular dementia

Risk/protective factor	Diagnostic criteria	Results
Diabetes was defined by self-report or use of diabetes medications	DSM-IV, NINCDS-ADRDA	HR relating hyperinsulinemia or diabetes to dementia: 2.2 (1.5, 3.1)

Table 8.27 *Diabetes and AD. Description of the studies that received a final quality score over 0.*

Author Year, reference Country	Study design	Study population (age at baseline, years)
Ott et al 1999 [96] The Netherlands	Population-based 2.1-year follow-up study	6 370 people from the Rotterdam study (age 55+)
Yoshitake et al 1995 [71] Japan	Population-based 7-year follow-up study	828 residents of Hisayama Town (age 65+)
Yamada et al 2003 [87] Japan	Population-based 25–30 years follow-up study	1 774 people from the Adult Health Study; midlife
Peila et al 2002 [98] United States	Population-based 2.9-year follow-up study	2 574 Japanese-American men. Honolulu-Asia Aging Study (age 72–91)
Curb et al 1999 [99] United States	Population-based 25-year follow-up study	3 774 Japanese-American men midlife enrolled in the Honolulu-Asia Aging Study (age 45–68)
Brayne et al 1998 [82] United Kingdom	Case-control study, mean 2.4-year follow-up	376 people from selected group general practices in Cambridge city (age 75+)
Posner et al 2002 [90] United States	Population-based 7-year follow-up study	1 259 people from Washington Heights-Inwood Columbia Aging Project (65+ years)
Kuusisto et al 1997 [46] Finland	Population-based 3.5-year follow-up	1 192 people from Kuopio (age 69–78)

Risk/protective factor	Diagnostic criteria	Results
Diabetes: use of antidiabetic medication or a random or post-load serum glucose >11 mol/l	DSM-III-R, NINCDS-ADRDA, NINDS-AIREN	Diabetes doubled the risk of AD: RR 1.9 (1.2–3.1). Patients treated with insulin were at highest risk for AD
Diabetes: interview based on comprehensive questionnaires	DSM-III-R, NINCDS-ADRDA, NINDS-AIREN	Diabetes was associated with AD: OR 2.18 (0.97–4.90) in the multivariate analysis
Diabetes: AHS physical examination; glucose tolerance test or a history of treatment	DSM-IV	Diabetes was associated with AD: OR 4.38 (p = 0.007); The effects were lost in multivariate model including other vascular factors
Self report of doctors' diagnose of diabetes, use of medication or fasting or postchallenge glucose	DSM-III, NINCDS-ADRDA, California criteria for VaD	Diabetes was associated with AD: RR 1.8 (1.1–2.9). The association was particularly strong among ApoE4 carriers. RR 5.5 (2.2–13.7)
Self report of diagnose of diabetes, use of medication/fasting or postchallenge glucose levels	DSM-III-R, NINCDS-ADRDA, California criteria	No association between midlife diabetes and late-life AD; RR 2.09 (0.91–4.81)
History of diabetes from the informants of the incident dementia at the follow-up visit	ICD–10	Diabetes was associated with AD, OR 1.4 (1.05–17.0). OR for all dementias 2.62 (0.89–7.75)
History of diabetes by standardized interview	DSM-IV, NINCDS-ADRDA, NINDS-AIREN	Diabetes was not associated with AD. OR 1.3 (0.7–2.6). Joint effect of diabetes and hypertension for AD; OR 1.6 (1.0–2.6)
Glucose tolerance test, fasting plasma glucose and insulin and 2 hours plasma glucose	DSM-III-R, NINCDS-ADRDA	AD: Fasting insulin OR 1.04 (1.01–1.08); abnormal glucose tolerance, fasting 1.11; 1.01–1.23 and 2 hours plasma glucose 1.08; 1.03–1.13

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Table 8.27 *continued*

Author Year, reference Country	Study design	Study population (age at baseline, years)
Luchsinger et al 2001 [102] United States	Population-based 4.3-year follow-up study	1 262 people from Washington Heights-Inwood Columbia Aging Project (age 65+)
MacKnight et al 2002 [97] Canada	Population-based study, 5-year follow-up	5 574 people from the Canadian Study of Health and Aging, (age 65+ mean 74)
Leibson et al 1997 [95] United States	Population-based 15-year follow-up study	1 455 people. Rochester diabetes mellitus cohort
Hassing et al 2002 [103] Sweden	Population-based 7-year follow-up study	702 people from the Swedish Twin Register (OCTO-Twin Study) (age 80+)
Amaducci et al 1986 [104] Italy	Clinic based case-control	322 people from 7 different centers: 119 cases, 116 hospital and 97 population controls (age 41–80)
Kokmen et al 1991 [105] United States	Population based case-control	830 people (415 cases and 415 controls) from Rochester Epidemiology Project
Xu et al 2004 [100] Sweden	Population-based 6-year follow-up study	1 301 community dwellers (aged 75+ mean age 81)
Luchsinger et al 2004 [79] United States	5.4-year (3 691 person-years) follow-up study	n = 683 (>65, mean age 76.2 ± 5.8, 70.5% women)
Arvanitakis et al 2004 [106] United States	9-year follow-up study	824 older Catholic nuns, priests, and brothers (age >55)

AD = Alzheimer's disease; HR = Hazard ratio; OR = Odds ratio; RR = Relative risk

Risk/protective factor	Diagnostic criteria	Results
Reported use of antidiabetic medications or a clinical history of diabetes	DSM-IV, NINCDS-ADRDA	Diabetes was not associated with AD: RR 1.3 (0.8–1.8)
Selfreport + informant/health records, medication list, and lab testing (glucose >11.1 mmol/l)	DSM-III-R, NINCDS-ADRDA	Diabetes was not associated with AD: RR 1.3 (0.83–2.03)
Data from the Rochester diabetes register followed through review complete medical records	DSM-III	Diabetes increased the risk of AD in men 2.27 (1.55–3.31) and in women 1.37 (1.94–2.01)
Diabetes diagnoses from medical records	DSM-III-R, NINCDS-ADRDA, NINDS-AIREN	Diabetes was not associated with AD: RR 0.83 (0.46–1.48)
Diabetes was based on a structured interview to the next of kin of cases and controls	NINCDS-ADRDA	Diabetes was not associated with AD: hospital controls OR 0.71, p = 0.54, populations controls OR 1.0, p = 1.0
Diabetes diagnoses from medical record linkage system	Consensus criteria	Diabetes was not associated with AD: OR 1.19 (0.79–1.84)
Diabetes based on medical records, antidiabetic drug use, or blood glucose >11 mol/l	DSM-III-R, Hachinski's ischemic scale	Diabetes did not significantly increase the risk of AD: RR 1.3 (0.9–2.1)
Diabetes: self-report or use of diabetes medications	DSM-IV, NINCDS-ADRDA	HR relating hyperinsulinemia or diabetes to AD was 2.2 (1.6–3.2)
Diabetes: took antidiabetic drugs or history of diabetes	NINCDS-ADRDA	Diabetes mellitus may be associated with an increased risk of AD, HR 1.65 (1.10–2.47)

Cholesterol

Search results from the literature

Keywords: Cholesterol and dementia/Alzheimer's disease (not including cognitive impairment or decline).

All the titles and relevant abstracts of the 502 identified articles were read online. Most of the articles were reviews, experimental studies or examinations of outcomes (cognition, cognitive impairment, stroke, etc) other than dementia. Cross-sectional studies were also excluded due to their inability to determine the cause/effect relationship between cholesterol and dementia. Eleven articles were ultimately chosen for a more thorough evaluation. Two studies concerning AD pathology were not evaluated but are nevertheless discussed below.

Summary of articles included

Nine of the studies that we evaluated were included in the final assessment of the scientific evidence (Table 8.29).

Two studies that addressed the relationship between midlife cholesterol and late-life AD found a positive correlation [43,49] – one of them identified a trend toward a risk for dementia [107]. The association between midlife cholesterol and late-life AD was corroborated by two autopsy studies. One study addressing the relationship between long-term cholesterol values and subsequent AD found no association [108]. Shorter-term follow-up studies (up to six years) reported either no association between baseline cholesterol values and subsequent AD [109] or an inverse association [46,110,111].

Table 8.28 *Cholesterol and AD: Number of studies by final quality index score.*

	Final quality index score		
	High	**Medium**	**Low**
Positive association	At midlife: 1	At midlife: 1	At midlife: 1 (trend)
Inverse association	0	0	Short follow-up: 3
No association	0	At midlife: 1 Long-term: 1	Short follow-up: 1

A positive association means that cholesterol is associated with increased risk of AD, and an inverse association that cholesterol is associated with reduced risk of AD.

Remarks: The Honolulu-Asia Aging Study (HAAS) evaluated the long-term association between clustered metabolic cardiovascular risk factors, including serum total cholesterol and triglycerides, and the risk of dementia at old age [107]. Higher triglycerides were associated with dementia, and a trend was identified for higher cholesterol values. The study concluded that the clustering of metabolic cardiovascular risk factors (high BMI, subscapular skinfold thickness, DBP, SBP, trigly, cholesterol and postload glucose) increased the risk for dementia. A subsequent autopsy study from HAAS evaluated the association of cholesterol to NPs and NFTs [112]. The study found that low midlife cholesterol was associated with fewer NPs and NFTs. A more recent autopsy evaluated the association between midlife cholesterol and amyloid depositions in the brain [113]. The study found that high cholesterol levels correlated with early amyloid depositions in the youngest subset (ages 40–55), suggesting that serum hypercholesterolemia may be an early risk factor for the development of AD amyloid pathology.

Conclusions

There is limited to moderately strong evidence that high cholesterol at midlife is a risk factor for AD later in life.

The role of cholesterol at late life is unclear. Some short-term follow-up studies have associated low cholesterol levels with an increased risk of AD. Reports of a decline in cholesterol values prior to the manifestation of dementia may explain these findings.

The total number of studies linking cholesterol to AD is limited, and many of them have suffered from methodological limitations. Thus, the evidence for an association between cholesterol levels and AD remains insufficient.

Table 8.29 *Cholesterol and AD. Description of the studies that received a final quality score over 0.*

Author Year, reference Country	**Study design**	**Study population (age at baseline, years)**
Kuusisto et al 1997 [46] Finland	Population-based study	n = 980 (46 AD) (aged 66–75)
Notkola et al 1998 [49] Finland	Population-based study	n = 444 (47 dementia, 27 AD) of Finnish male cohort of the Seven Counties Study (age 40–59)
Moroney et al 1999 [114] United States	Community-based 2.1-year follow-up study	n = 6 435 (225 AD, 61 VaD) (mean age 73)
Romas et al 1999 [110] United States	Community-based 2.5-year follow-up study	n = 987 (126 AD) of white, African Americans, and Caribbean Hispanic elderly in New York (mean age 73)
Kalmijn et al 2000 [107] United States	Population-based study, 25-year follow-up	n = 3 734 (215 dementia) Honolulu-Asia Aging Study; Japanese-American male cohort (age 45–68 mean 52.7)
Slooter et al 2000 [109] The Netherlands	Population-based 5.8-year follow-up study	n = 6 435 (395 with dementia). Rotterdam Study
Kivipelto et al 2002 [43] Finland	Population-based 21-year follow-up study	n = 1 449 (61 dementia, 48 AD) CAIDE study (mean age 50.4)

Risk/protective factor	Diagnostic criteria	Results
Serum total cholesterol values	DSM-III-R	Increasing total cholesterol at baseline; OR 0.67 (0.50–0.87) for AD
Serum total cholesterol at midlife	DSM-III-R	AD associated with a high cholesterol value (>6.5 mmol/l) OR 3.1 (1.2–8.5)
Serum total and LDL cholesterol	NINCDS-ADRDA, NINDS-AIREN	High LDL cholesterol at baseline; RR 3.1 (1.5–6.1) for dementia with stroke, RR 0.77 (0.51–1.15) for AD
Serum total cholesterol values	NINCDS-ADRDA	Low total cholesterol at baseline; OR 1.6 (1.0–2.7) for incident AD
Cardiovascular risk factors at midlife: serum total cholesterol and triglycerides	DSM-III-R, NINCDS-ADRDA	Adjusted RR for dementia with 1-SD increase in cholesterol 1.10 (0.95–1.26); in triglycerides 1.26 (1.09–1.45)
Serum total cholesterol values	NINCDS-ADRDA	No association between cholesterol at baseline and incident AD; RR 0.99 (0.89–1.10)
Serum total cholesterol at midlife	DSM-IV, NINCDS-ADRDA	AD associated with a high cholesterol value (>6.5 mmol/l) OR 2.6 (1.2–6.0)

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***Table 8.29** continued*

Author Year, reference Country	Study design	Study population (age at baseline, years)
Tan et al 2003 [108] United States	Population-based 10-year follow-up study	n = 1 026 (77 AD). Framingham Study
Reitz et al 2004 [111] United States	Community-based 4.8-year follow-up study	n = 1 168 elderly (119 AD, 54 VaD) Medicare beneficiaries (mean age 78.4)

Moroney [114] and Reitz [115] from the same cohort, only Reitz, 2005 is included to the assessment of the evidence.

AD = Alzheimer's disease; HDL = High density lipoproteins, HR = Hazard ratio: LDL = Low density lipoproteins; OR = Odds ratio; RR = Relative risk; VaD = Vascular dementia

Risk/protective factor	Diagnostic criteria	Results
Life-long average cholesterol values and cholesterol values at age 76	DSM-IV	No association between long-term average cholesterol values and AD; RR 0.95 (0.87–1.04) or at age 76: 0.97 (0.90–1.05)
Serum total, LDL, and HDL cholesterol at baseline	DSM-III-R, NINCDS-ADRDA	AD due to higher total cholesterol: HR 0.48 (0.26–0.86). VaD risk with increasing non-HDL cholesterol quartile: HR 2.38 (1.05–5.37) and LDL: HR 2.45 (1.05–5.70)

Obesity

Search results from the literature

Keywords: Body-mass index/obesity and dementia/Alzheimer's disease.

All the titles and relevant abstracts of 133 articles were read online. Most of the articles were reviews or had outcomes other than dementia (cognition, cognitive impairment, stroke, etc), or focused on the body mass index (BMI) in patients with dementia. Cross-sectional studies were excluded because of their inability to determine the cause/effect relationship between BMI and dementia. Three articles were ultimately chosen for the evaluation (Table 8.31).

Summary of articles included

All the 3 evaluated studies were accepted (Table 8.31). All of them had follow-up of over 10 years. One study that addressed the relationship of midlife BMI to late-life dementia found a positive correlation [107], while another did not find any association [87]. One study indicated a positive correlation between late-life BMI and subsequent dementia.

Table 8.30 *Obesity and AD: Number of studies by final quality index score.*

	Final quality index score		
	High	**Medium**	**Low**
Positive association	0	At midlife: 1 Late-life: 1	0
Inverse association	0	0	0
No association	0	At midlife: 1	0

A positive association means that obesity is associated with increased risk of AD, and an inverse association means that obesity is associated with reduced risk of AD.

Conclusions

There is insufficient evidence to link high BMI to the risk of dementia or AD.

Remarks: Two studies were published in 2005: Rosengren et al from Sweden reported a J-shaped relationship between midlife BMI and the risk of hospital discharge or death certificate diagnosis of dementia (BMI less than 20 and an increasing BMI of 22.5 or greater were associated with a greater risk of dementia) [116].

An extended (26-year) follow-up of HAAS by Stewart et al did not find any significant association between midlife weight and dementia in late life [117]. An earlier study from the same cohort that focused on clustered metabolic cardiovascular risk factors indicated an association between increased BMI at midlife and subsequent development of dementia [107]. The study by Stewart et al reported that dementia-associated weight loss begins before the onset of the clinical syndrome and accelerates by the time of diagnosis.

Finally, Kivipelto et al reported that people diagnosed with dementia had significantly higher midlife BMI than those who maintained normal cognitive function [88]. No adjusted ORs were reported.

Our conclusion does not change even when these 2 recent studies are included.

Table 8.31 *BMI and dementia and AD. Description of the studies that received a final quality score over 0.*

Author Year, reference Country	Study design	Study population (age at baseline, years)
Gustafson et al 2003 [118] Sweden	Population-based study, 9–18 years follow-up	n = 382 age 70 (266 women – men were not included in analyses because of the low participation number)
Yamada et al 2003 [87] Japan	Population-based study, 25–30 years follow-up	n = 1 774 (114 dementia and 51 AD), age range 30s to 50s. Adult Health Study
Kalmijn et al 2000 [107] United States	Population-based study, 25-year follow-up	n = 3 734 (215 dementia), mean age 52.7. Honolulu-Asia Aging Study; Japanese-American male cohort

BMI was calculated as weight in kilograms divided by the square of height in meters. Weight and height were measured (at baseline).

AD = Alzheimer's disease; HR = Hazard ratio; OR = Odds ratio

Risk/protective factor	Diagnostic criteria	Results
BMI at the age of 70, 75 and 79 years, and dementia/AD at 79 to 88 years	DSM-III-R, NINCDS-ADRDA at ages 85 and 88. <85 years: severe disorientation and/or longstanding severe memory impairment	HR for dementia per 1 increase in BMI at age 70; 1.13 (1.04–1.24), 75; 1.13 (1.04–1.24); 79; 1.15 (1.05–1.26). AD: at age 70; 1.36 (1.16–1.59), 75; 1.35 (1.19–1.53), 79; 1.23 (1.10–1.37)
BMI at midlife	DSM-IV	No association between midlife BMI and incident AD; OR for BMI increments 1.1, p = 0.134
BMI at midlife	DSM-III-R, NINCDS-ADRDA	Dementia related to 1-SD increase in midlife BMI: RR 1.21 (1.05–1.40)

Homocysteine

Search results from the literature

Keywords: Homocysteine and dementia/Alzheimer's disease.

All the titles and relevant abstracts of the 192 identified articles were read online. For a more thorough evaluation 19 articles were chosen after excluding those concerning cognition or cognitive impairment and genetic factors (such as MTHFR gene), vitamin B supplementation studies, etc.

Summary of articles included

Of the 19 evaluated studies 7 were accepted for the final assessment of the evidence (Table 8.33).

One positive and one inverse study had medium to high quality, while three positive and two inverse studies had low to medium quality. Most of the studies were cross-sectional and clinic-based.

Table 8.32 *Homocysteine and AD: Number of studies by final quality index score.*

	Final quality index score		
	High	**Medium**	**Low**
Positive association	0	1	3
Inverse association	0	0	0
No association	0	1	2

A positive association means that homocysteine is associated with increased risk of AD, and an inverse association means that homocysteine is associated with reduced risk of AD.

Conclusion

There is insufficient evidence that homocysteine is a risk factor for dementia or AD.

Table 8.33 *Homocysteine and AD. Description of the studies that received a final quality score over 0.*

Author Year, reference Country	Study design	Study population (age at baseline, years)
Miller et al 1999 [119] United States	Clinic-based case-control study	43 AD and 37 controls, mean age 79 years for AD, 75 for controls
Clarke et al 1998 [120] England	Clinic-based case-control study	164 AD (mean age 73.2), 76 histologically confirmed AD (76.6), and 108 controls (72.8) age 55+
Seshadri et al 2002 [121] United States	Population-based study, 8-year follow-up	n = 1 092 (111 dementia, including 83 AD), mean age 76 years. Framingham study
McIlroy et al 2002 [122] Ireland	Clinic based based-control study	Cases (AD) = 83 (mean age 77.2 years), controls = 71 (74.3 years)
Mizrahi et al 2004 [123] Israel	Population-based cohort study among Arabs	Cases (AD) = 79, controls = 156
Quadri et al 2004 [124] Switzerland	Hospital-based case-control study	92 dementia, 74 AD, and 55 controls, mean age cases = 79.5, controls = 75.6
Luchsinger et al 2004 [79] United States	Population-based cohort study, 3.2 years follow-up	n = 679 (109 incident AD), mean age 77.2. Medicare recipients; Washington Heights-Inwood Columbia Aging Project

AD = Alzheimer's disease; OR = Odds ratio

Risk/protective factor	Diagnostic criteria	Results
Homocysteine levels	NINCDS-ADRDA	Non-significant association between elevated plasma homocysteine (>12 μmol/l) and AD: OR 2.2 (0.31–16.0)
Homocysteine levels in AD patients and controls	NINCDS-ADRDA, CERAD for histological diagnosis of AD	Histopathologically confirmed AD associated with homocysteine level (>14μmol/l) compared with bottom third: OR 4.5 (2.2–9.2), clinical AD: 2.0 (1.1–3.4)
Homocysteine levels	DSM-IV, NINCDS-ADRDA	RRs for each increase of 1 SD log-transformed homocyesteine, dementia: 1.4 (1.1–1.9), AD: 1.8 (1.3–2.5). homocysteine >14 μmol/l, dementia: 1.9 (1.3–2.8), AD: 1.9 (1.2–3.0)
Homocysteine levels	DSM-IV, NINCDS-ADRDA	Plasma Hcy (log-transformed) ≥13.3. 14 μmol/l, OR for AD 2.9 (1.0–8.1)
Homocysteine levels	DSM-IV	OR of AD for a Hcy level in the top third (>17.4 μmol/l) compared with the bottom third was 2.6 (0.9–7.7)
Homocysteine levels	NINCDS-ADRDA, CERAD	OR of dementia for a Hcy level (>14.6 μmol/l) compared with the bottom third: 4.3 (1.3–14.7) and AD: 3.7 (1.1–13.1)
Homocysteine levels	DSM-IV, NINCDS-ADRDA	OR of AD for the highest quartile of Hcy compared to the lowest was 1.4 (0.8–2.4)

Cardiovascular disease

Search results from the literature

Keywords: Cardiovascular diseases/myocardial infarct/heart infarct/ atrial fibrillation/heart failure and dementia/Alzheimer's disease.

All the titles and relevant abstracts were read online. Most of the articles were reviews or experimental studies or had an outcome other than dementia (cognition, cognitive impairment, stroke, etc).

Summary of articles included

One article (of 59), which concerned myocardial infarction and dementia, was ultimately selected for further evaluation [125]. The study was based on initially community-residing elderly without dementia and detected seventyfive incident dementia cases after seven years or less of follow-up. A history of MI was associated with dementia (OR approximately five among women, not significant among men).

One article from the Rotterdam study that concerned atrial fibrillation and dementia had a cross-sectional design and found a positive correlation [126].

No studies about heart failure and dementia were detected. An autopsy study linked coronary artery disease to senile plaques in the brain in autopsy material [127].

Conclusion

Only a few epidemiological studies have been conducted about cardiovascular diseases and the risk of dementia or AD. Thus, the evidence from epidemiological studies is insufficient to conclude whether or not cardiovascular disorders are risk factors for dementia and AD.

Antihypertensive drugs

Search results from the literature

Keywords: Dementia OR Alzheimer's disease AND antihypertensive treatment, with the delimiters of "human", "English language", and aged "65+".

A total of 145 papers were found by searching PubMed. After reading through the abstracts or titles, we excluded 133 due to non-originality or other reasons (dementia or AD was not an outcome, etc), leaving 12 for the evaluation. Table 8.35 shows the final analysis (including 6 population-based studies and 6 clinical trials).

Summary of articles included

Antihypertensive drug use, dementia and AD: We ultimately evaluated 12 studies (6 population-based studies and 6 clinical trials). Table 8.35 summarizes the 12 studies.

Antihypertensive drug use and VaD: One population-based (Rotterdam) study that specifically addressed the effect of antihypertensive drug use on VaD showed a strongly protective effect. One clinical (PROGRESS) trial conducted among patients with a history of cerebrovascular disease (including TIAs) showed that antihypertensive treatment (perindoprin alone or perindoprin plus indapamide) had a protective effect on "dementias with recurrent stroke" [128].

Table 8.34 *Antihypertensive drugs and dementia, AD, and VaD: Number of studies by final quality index score.*

	Final quality index score		
	High	**Medium**	**Low**
Positive association	Dementia: 1 AD: 1	Dementia: 5 AD: 4 VaD: 2	Dementia: 1 AD: 1
Inverse association	0	0	0
No association	0	Dementia: 2 AD: 1	0

A positive association means that antihypertensive is associated with increased risk of dementia/AD/VaD, and an inverse association that antihypertensive is associated with reduced risk of diseases.

Conclusions

Strong evidence from population-based studies and clinical trials suggests that the use of antihypertensive medications could prevent the elderly from developing dementia, especially VaD (Evidence Grade 1).

The evidence that antihypertensive treatment has a protective effect for AD in particular is more limited (Evidence Grade 3).

The biological mechanisms underlying the protective effect need further clarification.

Table 8.35 *Antihypertenisve drugs and dementia, AD, and VaD. Description of the studies that received a final quality score over 0.*

Author Year, reference Country	Study design	Study population (age at baseline, years)
Dementia		
The SHEP Group 1991 [129] United States	Randomised clinical trial	Isolated systolic hypertension patients n = 4 736 (age 60+)
Forette et al 1998 [130] Europe	Randomised clinical trial	Isolated systolic hypertension patients n = 2 418 (age 60+). Syst-Eur trial I
Richards et al 2000 [131] United States	Cross-sectional survey	A random sample of African-American adults n = 2 212 (age 65+)
in't Veld et al 2001 [132] The Netherlands	Follow-up study	Community-based cohort n = 6 416 (age 55+)
Forette et al 2002 [133] Europe	Randomised clinical trial	Extension of Syst-Eur trial I to 4 year follow-up. Syst-Eur trial II
Guo et al 1999 [85] Sweden	Cross-sectional & cohort study	Community-based, n = 1 810; cohort, n = 1 301 (age 75+ cross-sectional)
Qiu et al 2003 [86] Sweden	Follow-up study	Community-based cohort n = 1 270 (age 75+)
Lithell et al 2003 [134] Europe	Limit randomised clinical trial	Moderate hypertension patients n = 4 964 (age 60+). SCOPE trial
Lithell et al 2004 [135] Europe	Limit randomised clinical trial	Moderate hypertensive patients n = 2 098 (age 60+)

Risk/protective factor	Diagnostic criteria	Results
Antihypertensive drug: chlorthalidone+	Expert panel	Rates: active treated group 1.6% vs placebo 1.9%, p>0.05
Antihypertensive drug: nitredipine plus	DSM-III-R	Reduce risk of dementia by 50%: rates, treated group 3.8 vs placebo 7.7 per 1 000 person years, p = 0.05
Antihypertensive medications	DSM-III-R, NINCDS-ADRDA	OR = 0.73 (95% CI 0.37–1.45)
Antihypertensive drug use (mean follow-up 2.2 years)	DSM-III-R, NINCDS-ADRDA	RR = 0.67 (95% CI 0.45–1.00)
Antihypertensive drug: nitredipine plus	DSM-III-R	Dementia risk reduced by 55%: rates, treated group 3.3 vs placebo 7.7 per 1 000 person years
Antihypertensive drug use	DSM-III-R, HIS	Cross-sectional OR 0.4 (95% CI 0.3–0.6); 3-year follow-up RR 0.7 (95% CI 0.6–1.0, p = 0.03)
Antihypertensive drug use	DSM-III-R, HIS	RR = 0.8 (95% CI 0.6–1.0, p = 0.03)
Antihypertensive drug: candesartan	Modified ICD-10	Rates: active treated group 6.8 vs placebo 6.3 per 1 000 person years, p>0.20
Antihypertensive drug: candesartan	Modified ICD-10	Rates: active treated group 6.7 vs placebo 6.0 per 1 000 person years, p>0.20

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Table 8.35 *continued*

Author Year, reference Country	Study design	Study population (age at baseline, years)
Alzheimer´s disease		
Forette et al 1998 [130] Europe	Randomised clinical trial	Isolated systolic hypertension patients n = 2 418 (age 60+ years). Syst-Eur trial I
Richards et al 2000 [131] United States	Cross-sectional survey	A random sample of African- American adults n = 2 212 (age 65+)
in't Veld et al 2001 [136] The Netherlands	Follow-up study	Community-based cohort n = 6 416 (age 55+)
Forette et al 2002 [133] Europe	Randomised clinical trial	Extension of Syst-Eur trial I to 4 years follow-up. Syst-Eur trial II
Lindsay et al 2002 [19] Canada	Nested case-control, 5-year follow-up	Community-based cases = 194, controls = 3 894 (age 65+)
Qiu et al 2003 [86] Sweden	Follow-up study	Community-based cohort n = 1 270 (age 75+)
Khachaturian et al 2004 [137] United States	Follow-up study	Community-based cohort n = 3 308 (age 65+)
Vascular dementia		
in't Veld et al 2001 [136] The Netherlands	2.2-year follow-up study	Community-based cohort n = 6 416 (age 55+)

Risk/protective factor	Diagnostic criteria	Results
Antihypertensive drug: nitredipine plus	DSM-III-R	Reduced risk of dementia by 50%
Antihypertensive medications	DSM-III-R, NINCDS-ADRDA	OR = 0.62 (95% CI 0.27–1.43)
Antihypertensive drug use (mean 2.2-year follow-up)	DSM-III-R, NINCDS-ADRDA	RR = 0.77 (95% CI 0.49–1.24)
Antihypertensive drug: nitredipine plus	DSM-III-R	AD risk reduced by 62%: rates, treated group 1.9 vs placebo 5.0 per 1 000 person years
Antihypertensive agents	DSM-IV	OR = 0.91 (95% CI 0.64–1.30)
Antihypertensive drug	DSM-III-R, HIS	RR = 0.7 (95% CI 0.5–0.9)
Antihypertensive drug	DSM-III-R	RR = 0.64 (95% CI 0.41–0.98)
Antihypertensive drug	DSM-III-R, NINCDS-ADRDA	RR = 0.30 (95% CI 0.09–0.92)

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Table 8.35 *continued*

Author Year, reference Country	Study design	Study population (age at baseline, years)
Vascular dementia		
PROGRESS Group 2003 [128] World	Randomised clinical trial	Patients with history of CVD, n = 6 105 (mean age 64)

AD = Alzheimer's disease; CI = Confidence interval; CVD = Cerebrovascular disease; OR = Odds ratio; RR = Relative risk; VaD = Vascular dementia

	Risk/protective factor	Diagnostic criteria	Results
	Antihypertensive drug: perindopril plus	DSM-IV	For dementia with recurrent stroke: RR = 0.7 (95% CI 0.5–1.0), $p<0.05$

Statin drug use

Search results from the literature

Keywords: Statins and dementia/Alzheimer's disease.

All the titles and relevant abstracts of 134 articles were read online. Most of the articles were reviews or experimental studies or had outcomes other than dementia (cognition, cognitive impairment, stroke, etc). Ultimately, 7 articles were chosen for the evaluation (Table 8.37).

Summary of articles included

All the evaluated studies were accepted (Table 8.37). Four retrospective or case-control studies [138–141] and one prospective study [142] suggested an association between the use of statins and a lower risk of dementia or AD. On the other hand, some recent short-term prospective studies have not found any association [111,143].

Table 8.36 *Statin drugs and dementia and AD: Number of studies by final quality index score.*

	Final quality index score		
	High	**Medium**	**Low**
Positive association	0	0	0
Inverse association	0	1	4
No association	0	2	0

A positive association means that statin use is associated with increased risk of dementia/AD, and an inverse association means that statin use is associated with reduced risk of dementia/AD.

Conclusions

The evidence linking statin treatment to a lower risk for dementia or AD is insufficient.

Remarks: One paper published in 2005 from the Cache County Study reported that statin use was inversely associated with the prevalence of dementia (OR 0.44; 0.17–0.94) but not with the incidence of dementia (HR 1.19; 0.53–2.34) or AD (HR 1.19; 0.35–2.06) 3 years later [144].

The Heart Protection Study (HPS) was a randomized, placebo-controlled clinical trial of cholesterol lowering with simvastatin [145]. The study did not find any difference in the incidence of dementia during the five years of follow-up. However, the incidence of dementia was generally very low (0.3% based on epidemiological studies – the expected rate in this age group would have been at least 10 times higher), making the study underpowered with respect to detecting any difference in the incidence of dementia.

Table 8.37 *Statin use and dementia and AD. Description of the studies that received a final quality score over 0.*

Author Year, reference Country	Study design	Study population (age at baseline, years)
Wolozin et al 2000 [138] United States	Clinic-based cross-sectional study	N = 57 104. (age 60+) Computer database of 3 different hospitals in 1996–1998
Jick et al 2000 [139] United Kingdom	Nested case-control study	N = 284 dementia cases and 1 080 controls (age 50+). UK-based General Practice Research Database
Rockwood et al 2002 [142] Canada	Nested case-control based on a population cohort. 4–5 years follow-up	N = 492 incident dementia cases (326 AD); N = 823 controls (age 65+). Canadian Study of Health and Aging
Reitz et al 2004 [111] United States	Community-based 4.8–year follow-up study	N = 1 168 (119 AD, 54 VaD) (age 78.4). Medicare beneficiaries
Li et al 2004 [143] United States	Community-based study	N = 2 356 (312 incident dementia, 168 AD) (age 65+). Adult changes in thought
Zamrini et al 2004 [141] United States	Clinic-based nested case-control study	309 male AD patients, 3 088 controls. (Mean age: cases 72.9, controls 73)
Rodriguez et al 2002 [140] United States	Nested case-control study based on a population cohort	N = 845 (170 dementia cases) (mean age 80.5). Monongahela Valley Independent Elders Survey

AD = Alzheimer's disease; HR = Hazard ratio; LLA = Lipid-lowering agents; OR = Odds ratio

Risk/protective factor	Diagnostic criteria	Results
Statin treatment	ICD-9 for probable AD	AD prevalence in the cohort taking statins during the study interval 60–70% ($p<0.001$) lower than total patients or patients taking other medications
Treatment with LLAs	Clinical diagnosis (criteria not stated)	The risk of dementia lower in statins users, OR 0.29 (0.13–0.63) than those had no hyperlipidemia or those with untreated hyperlipidemia. Treatment with non-statin LLA; OR 0.96 (0.47–1.97)
Treatment with LLAs, and incident dementia	DSM-III-R, NINCDS-ADRDA	The use of statins and other LLAs was associated with a lower risk of dementia and AD in subjects younger than 80 years, OR 0.26; 0.08–0.88
Treatment with LLAs	DSM-III-R, NINCDS-ADRDA,	Treatment with LLA was not associated with incident AD (HR 0.88; 0.44–1.76). It was cross-sectional associated with AD (OR 0.45; 0.27–0.75)
Treatment with LLAs, patients were re-examined for cognition every 2 years	DSM-IV, NINCDS-ADRDA	HR of statin use for dementia 1.19 (0.82–1.75), AD 0.82 (0.46–1.46). For ApoE4 carriers who entered the study before age 80 years, HR 0.33 (0.10–1.04)
Statin use	ICD-9 CM (Clinical Modified)	Statin users had a lower risk for AD relative to nonusers; OR 0.61 (0.42–0.87)
LLA use based on a medication regimen	CERAD	LLA users were less likely to be demented than non-users; OR 0.39 (0.16–0.95)

Hormonal replacement therapy (HRT)

Search results from the literature

Keywords: Estrogen, Alzheimer's, dementia.

All the titles and abstracts of 474 articles were read online. In the initial selection 461 articles were excluded because they;

1) Did not focus on the topic (for instance, estrogen and cognition instead of estrogen and dementia)
2) Were not originals (editorials, reviews, etc)
3) Did not concern epidemiological studies (laboratory studies, case series, etc)
4) Duplicated papers from the same study group (for instance, the Women's Health Initiative Memory Study). Ultimately, 13 articles were chosen for the evaluation (Table 8.39).

Summary of articles included

Nine studies were included in the assessment of the scientific evidence (Table 8.39).

Table 8.38 *HRT and AD: Number of studies by final quality index score.*

	Final quality index score		
	High	**Medium**	**Low**
Positive association	0	1	0
Inverse association	0	1	4
No association	0	0	3

A positive association means that HRT is associated with increased risk of AD, and an inverse association means that HRT is associated with reduced risk of AD.

Conclusion

The evidence on the role of estrogen replacement therapy as a protective factor for the development of dementia is currently insufficient.

Table 8.39 *HRT and dementia and AD. Description of the studies that received a final quality score over 0.*

Author Year, reference Country	Study design	Study population (age at baseline, years)
Brenner et al 1994 [146] United States	Case-control study	107 AD cases from Patient Registry. 120 controls from pharmacy data
Tang et al 1996 [147] United States	Prospective study; mean follow-up time 1-5 years	1 124 community-dwelling non-demented women mean age 74.2 from the Manhattan Study of Aging
Kawas et al 1997 [148] United States	Prospective study; follow-up time up to 16 years	472 community dwelling women mean age 61.5 from the Baltimore Longitudinal Study of Aging
Baldereschi et al 1998 [149] Italy	Cross-sectional study	1 582 women age 65–84 from Italian Longitudinal Study of Aging
Slooter et al 1999 [56] The Netherlands	Case-control study	109 cases, 119 controls
Seshadri et al 2001 [150] United Kingdom	Population-based nested case-control study	59 cases age 66.7 and 221 controls age 65.2 from the UK General Practice Research Database
Lindsay et al 2002 [19] Canada	Population-based nested case-control study	194 cases age 81, 3 894 controls age 73 from the Canadian Study of Health and Aging
Zandi et al 2002 [151] United States	Prospective study; 3-year follow-up	1 889 women, mean age: 74.5 from the Cache County Study
Shumaker et al 2003 [152] United States	Multicentered randomized clinical trial; 4.2-year follow-up	4 381 post-menopausal women, 65+ years from 39 clinical centers (2 236, treatment, 2 236 placebo)

AD = Alzheimer's disease; CI = Confidence interval; HR = Hazard ratio; OR = Odds ratio

Risk/protective factor	Diagnostic criteria	Results
Ever use of any form of estrogen vs never use	NINCDS-ADRDA	No significant difference between the groups in the risk of developing dementia
Ever use of any form of estrogen vs never use	NINCDS-ADRDA	Estrogen use reduces the risk of dementia RR 0.40 (95% CI 0.22–0.85). There's also a dose-response trend
Ever use of any form of estrogen vs never use	DSM-III-R criteria	Oral or transdermal estrogens reduces the risk of dementia: RR 0.46 (95% CI 0.21–1.0)
Ever use of any form of estrogen vs never use	DSM-III-R, ICD-10, NINCDS-ADRDA	Estrogen use reduces the risk of dementia: OR 0.28 (95% CI 0.08–0.98)
Ever use of any form of estrogen vs never use	NINCDS-ADRDA	Estrogen use reduces the risk of early onset AD: OR 0.34 (95% CI 0.12–0.94)
Ever use of any form of estrogen vs never use	NINCDS-ADRDA	No significant difference between the groups in the risk of developing dementia
Ever use of any form of estrogen vs never use	DSM-III-R, NINCDS-ADRDA	No significant difference between the groups in the risk of developing dementia
Ever use of any form of estrogen vs never use	DSM-III-R	Prior estrogen use reduces dementia risk: HR 0.41 (95% CI 0.17–0.86). No effect of current estrogen use
Estrogen plus Progestin therapy: 1 daily tablet 0.625 mg conjugated equine estrogen + 2.5 mg medroxyprogesterone acetate or matching placebo	DSM-IV	Estrogen plus Progestin therapy increases the risk for probable dementia in postmenopausal women HR = 2.05 (CI = 1.21–3.48)

Non-steroidal anti-inflammatory drugs (NSAIDs)

Search results from the literature

Keywords: Non-steroidal anti-inflammatory drugs (NSAIDs), risk of Alzheimer's disease (AD), and dementia. Initially, 361 articles were identified. For the evaluation 77 abstracts and 16 studies were selected. Articles concerning the use of aspirin, cognitive impairment or cognitive decline only were excluded. Because VaD was scrutinized in just 2 articles, it was not included in the evaluation.

Four studies were excluded from the final assessment. The last study by Cornelius et al found that no one who used NSAIDs for three years had developed AD 3 years later and one person had developed VaD – the risk calculation was based on the group that included this person [162]. The risk was low (0.23), but the confidence interval was wide and included one subject.

Three studies [19,136,153] of moderately strong study quality showed that NSAIDs have a protective effect against AD, whereas two studies of AD [19,154] and one study of dementia [155] with a moderately strong study quality found no association. Five studies (inverse association = [156–159]; no association = [160]) showed insufficient evidence.

Summary of articles included

All studies [136,153,161,162] that examined the use of NSAIDs for more than 2 years showed an inverse association with the risk for AD or dementia, thereby supporting the hypothesis that anti-inflammatory drugs require a longer period of use before onset of the disease in order to have a protective effect.

Table 8.40 *NSAIDs and AD: Number of studies by final quality index score.*

	Final quality index score		
	High	**Medium**	**Low**
Positive association	0	0	0
Inverse association	0	4	4
No association	0	3	1

A positive association means that NSAIDs is associated with increased risk of AD, and an inverse association means that NSAIDs is associated with reduced risk of AD.

Conclusion

There is insufficient evidence that NSAIDs generally have a protective effect against AD or dementia. Any protective effect that exists is due to the long-term use of NSAIDs.

Table 8.41 *NSAIDs and dementia and AD. Description of the studies that received a final quality score over 0.*

Author Year, reference Country	**Study design**	**Study population (age at baseline, years)**
CSHA 1994 [156] Canada	Case-control	N = 258 cases/535 controls (age >64)
Breitner et al 1994 [160] United States	Case-control, twins	N = 50 cases/50 controls (mean age 69 and 75 years)
Andersen et al 1995 [157] The Netherlands	Cross-sectional cohort	N = 6 258 of 7 983 (age >54 years)
Breitner et al 1995 [158] United States	Siblings at high risk AD	N = 186 of 205
Henderson et al 1997 [155] Australia	3.6-year follow-up study	N = 588 of 709 (mean age 80 years)
Stewart et al 1997 [161] United States	Follow-up study, >2 years	N = 1 686 of 2 357 (age 54+)
Beard et al 1998 [154] United States	Case-control	N = 302 cases/302 controls (age 65+)
Anthony et al 2000 [159] United States	Case-control	N = 201 cases/4 425 controls (age 64+)
in't Veld et al 2001 [136] The Netherlands	6.8-year follow-up study	N = 6 989 of 7 046 (age 54+)
Lindsay et al 2002 [19] Canada	Case-control	N = 194 cases/3 894 controls (age 69+)

Risk/protective factor	Diagnostic criteria	Results
NSAIDs	3MS, DSM-III-R	0.55 (0.37–0.82)
NSAIDs ≥1 year	Dem questionnaire	0.50 (0.10–2.23)
NSAIDs	DSM-III-R, NINCDS-ADRDA	0.38 (0.15–0.95)
NSAIDs ≥1 year	NINCDS-ADRDA	0.07 (0.02–0.26)
NSAIDs	DSM-III-R	1.66 (0.64–4.32)
NSAIDs >2 years	DSM-III-R, NINCDS-ADRDA	0.46 (0.24–0.86)
NSAIDs	Similar to DSM-III-R	0.79 (0.45–1.38)
NSAIDs	DSM-III-R, NINCDS-ADRDA	0.47 (0.24–0.90)
NSAIDs	DSM-III-R, NINCDS-ADRDA	0.20 (0.05–0.83)
NSAIDs	DSM-III-R, NINCDS-ADRDA	0.62 (0.37–1.04)

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***Table 8.41** continued*

Author Year, reference Country	Study design	Study population (age at baseline, years)
Zandi et al 2002 [153] United States	3-year follow-up study	N = 3 227 of 3 411, age 65+
Cornelius et al 2004 [162] Sweden	6-year follow-up study	N = 1 301 of 1 473, age 65+

	Risk/protective factor	Diagnostic criteria	Results
	NSAIDs	DSM-III-R, NINCDS-ADRDA	0.45 (0.17–0.97)
	NSAIDs ≥3 years	DSM-III-R	0.23 (0.03–1.68)

Inflammatory markers

Search results from the literature

Keywords: Inflammation markers and dementia/Alzheimer's disease.

All the titles and relevant abstracts were read online. Most of the articles were experimental studies or genetic studies or had an outcome other than dementia (such as HIV).

Summary of articles included

Ultimately, 2 articles (of 18) concerning inflammation markers and dementia were selected for further evaluation. Of these 1 was a nested case-control study based on a random sample (n = 214 cases and 838 controls) of the Honolulu-Asia Aging study. High-sensitivity C-reactive protein concentrations were measured from serum taken at the second examination and checked 25 years later for dementia. High-sensitivity C-reactive protein has 3 times as much risk of all dementia, AD and VaD for men in the upper 3 quartiles as for men in the lowest quartile (<0.34 mg/L). For VaD, the risk became greater as the quartile increased. The researchers concluded that inflammatory markers may reflect not only peripheral disease, but cerebral disease mechanisms related to dementia, and that these processes are measurable long before clinical symptoms appear [163].

Another article on a case-cohort study within the Rotterdam study concerned inflammatory proteins in plasma and dementia. A random sub-cohort of 727 subjects and 188 cases who developed dementia at follow-up was taken from a baseline dementia-free cohort of 6 713 subjects. The researchers reported that high levels of α1-antichymotrypsin (rate ratio = 1.49, 95% CI 1.23–1.81), interleukin 6 (RR = 1.28, 95% CI 1.06–1.55) and C-reactive protein (RR = 1.12, 95% CI 0.99–1.25) were associated with an increased risk of dementia. Similar associations were found for AD, whereas the rate ratios for VaD were higher when it came to α1-antichymotrypsin and C-reactive protein [164].

Conclusions

Only a few epidemiological studies have been conducted on inflammation markers and the risk of dementia or AD. Thus, the evidence from epidemiological studies is insufficient to conclude whether or not inflammation markers are risk factors for dementia and AD.

Head trauma

Search results from the literature

Keywords: Craniocerebral trauma, head injury, head trauma, unconsciousness, Alzheimer's, dementia.

All the titles and abstracts of the 554 articles identified were read directly online. In the initial selection 14 were excluded because the studies were not epidemiological (laboratory studies, etc). Then 40 articles were read and 18 immediately excluded, as they were meta-analyses, reviews, letters containing inadequate information, papers with slightly different goals (for example, studies on time to onset of AD, rather than the risk of developing AD) or duplicate papers from the same study group. In the latter case, the best and most recent method was chosen (for instance, a paper with cross-sectional data from one study was excluded if there was a later paper with longitudinal data).

For the evaluation 22 articles remained (Table 8.43).

Summary of articles included

Thirteen studies were included in the assessment (Table 8.43).

Table 8.42 *Head Trauma and AD: Number of studies by final quality index score.*

	Final quality index score		
	High	**Medium**	**Low**
Positive association	0	1	5
Inverse association	0	0	0
No association	0	2	5

A positive association means that head trauma is associated with increased risk of AD, and an inverse association means that head trauma is associated with reduced risk of AD.

Conclusion

The evidence is currently insufficient.

Table 8.43 *Head trauma and dementia and AD. Description of the studies that received a final quality score over 0.*

Author Year, reference Country	Study design	Study population (age at baseline, years)
Amaducci et al 1986 [104] Italy	Case-control	116 AD/116 hospital controls/97 population-based controls (age 40–80). 7 neurological departments
Williams et al 1991 [165] United States	A cohort with medical documentation of head trauma	821 head injured subjects (age 40+). Community-based medical records linkage system
Li et al 1992 [166] China	Case-control	70 AD cases/140 controls (age 50+). Hospital cases, neighbourhood controls
van Duijn et al 1992 [167] The Netherlands	Case-control study within a population-based cohort	198 cases/198 controls (age 50+). Rotterdam study
Fratiglioni et al 1993 [7] Sweden	Case-control study	98 cases/216 controls (age 75+). Kungsholmen Project
Breteler et al 1995 [168] The Netherlands	Prospective 8-year follow-up	n = 91 740 (age 50–75). Dutch Nationwide Morbidity Registers
O'Meara et al 1997 [169] United States	Case-control	349 cases/342 controls (age 48–94). Cases from AD patient register, healthy controls from medical care cooperative

Risk/protective factor	Diagnostic criteria	Results
Relative informants reports. Head injury with loss of conciseness (LOC) at least 1 year before AD onset	NINDCS-ADRDA	No increased risk of AD. No analysis for severity, number or time of injury
Medical record documentation of: Concussion with LOC, post traumatic amnesia, neurological signs of brain injury. Head trauma with skull fracture	Clinical diagnosis of AD or dementia from the medical linkage records, and all patient records	No increased risk of AD for any severity or number or time of injury
Relative informants reports. Head injury with LOC	NINDCS-ADRDA, medical records were reviewed	No increased risk of AD. No analysis for severity, number or time of injury
Structured interview to informants. Head trauma with LOC, age at trauma, circumstances surrounding event, and medical treatment	NINDCS-ADRDA, two-stage case ascertainment	No AD risk for head trauma with LOC for all, men, or women. Risk only for traumas occurred 10 years before AD onset. < onset: 0.9 (0.4–2.2)
Severe head injury with LOC reported by informant proxy	DSM-III-R, 2-phase case ascertainment	No increased risk of AD. No analysis for severity, number or time of injury
Documentation of head trauma in medical records: ICD-9-CM codes 800–804, 850–854	Hospital discharge, institutionalisation, or admission to day care in a nursing home or psychiatric hospital with a diagnosis of dementia	No increased risk for dementia for any head injury in past 10 years or for traumas with explicit mention of intracranial injuries and LOC
Informant report of head injury that required medical care or caused LOC	DSM-III-R, NINDCS-ADRDA Three-stage case ascertainment	Crude OR for AD due to head injury. All: 2.1 (1.1–3.8). Men: 4.2 (1.5–11.5). Women: 1.1 (0.5–2.6)

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***Table 8.43** continued*

Author Year, reference Country	Study design	Study population (age at baseline, years)
Salib et al 1997 [170] United Kingdom	Case-control from clinical setting	198 AD cases/164 other dementias/ 176 nondemented controls from psychogeriatric unit (age 65+)
Schofield et al 1997 [171] United States	5-year longitudinal study from a community-based register	n = 271 (age 60+). Manhattan study
Mehta et al 1999 [172] The Netherlands	Community-based 2-year prospective study	n = 6 645 (age 55+). Rotterdam study
Guo et al 2000 [173] United States	Case-control	2 233 AD cases/14 668 controls first-degree family relatives. MIRAGE study. United States, Canada and Germany
Plassman et al 2000 [174] United States	Prospective cohort of World War II veterans (males)	n = 1 776 (mean age: 72.9). World War II US Navy or Marine Veterans
Lindsay et al 2002 [19] Canada	Community-based 5-year prospective study	n = 6 434 (age 65+). Canadian Study of Health and Aging

AD = Alzheimer's disease; LOC = Loss of consciousness; OR = Odds ratio

Risk/protective factor	Diagnostic criteria	Results
Informant reports of history of head injury at any time prior to onset of dementia, with or without LOC	NINDCS-ADRDA, Hachiniski score >7 or other identifiable dementia cause	Any head injury: AD vs no dementia: OR 2.4 (1.3–4.1). Other dementias vs no dementia: OR 2.4 (1.4–4.0)
Reported by subjects. Head injury with LOC or amnesia, duration of LOC, date of injury	NINDCS-ADRDA, Two-stage case ascertainment	AD: 4.1 (1.3–12.7). Result similar when stratifying for baseline cognition
Self-reported head injury at baseline: number, date, duration of trauma, LOC, posttraumatic amnesia	DSM-III-R, NINDCS-ADRDA	No increased risk of AD for any number or time of injury or duration of LOC. No interaction between ApoE and head trauma on risk of AD
Relative informants reports. Head injury requiring medical care or with LOC	AD: NINDCS-ADRDA	AD with LOC 9.9: 6.5–15.1. AD with no LOC 3.1: 2.3–4.0). Risk was greater in people not carrying ApoE ε4 allele
Head injury based on medical record. Mild: No skull fracture, <30 minutes LOC. Moderate: LOC 30 minutes–24 hours and/or a skull fracture. Severe: >24 hours LOC/ post traumatic amnesia	DSM-III-R, NINDCS-ADRDA, Three-stage case ascertainment	Mild head trauma: no increased risk of AD. Moderate: 2.3 (1.0–4.6). Severe: 4.5 (1.8–115)
Prior head injury with or without LOC from self-administered questionnaire at baseline in cognitive intact subjects	DSM-III-R, NINDCS-ADRDA	No increased risk of AD. No analysis for severity, number or time of injury

Aluminum

Search results from the literature

Keywords: Aluminum AND dementia.

All the titles and relevant abstracts of 273 articles were read online. For the evaluation 13 articles were chosen. Articles concerning cognition or cognitive impairment, or antacid or antiperspirant use, as the exposure were excluded.

Comment: Aluminum as a risk factor for dementia and AD may be broken down into 2 main lines of lines: 1) Aluminum in drinking water and 2) Occupational aluminum exposure.

Summary of articles included

Seven of the thirteen evaluated studies were not included.

Table 8.44 *Aluminum and AD: Number of studies by final quality index score.*

	Final quality index score		
	High	**Medium**	**Low**
Positive association	0	1	1
Inverse association	0	0	1
No association	0	1	2

A positive association means that aluminum is associated with increased risk of AD, and an inverse association means that aluminum is associated with reduced risk of AD.

Conclusion

The scientific evidence is insufficient to conclude whether or not aluminum is a risk factor for dementia and AD.

Table 8.45 *Head trauma and dementia and AD.*
Description of the studies that received a final quality score over 0.

Author Year, reference Country	**Study design**	**Study population (age at baseline, years)**
Forster et al 1995 [175] United Kingdom	Case-control study	Cases = 109, controls = 109 (age at diagnosis 58)
Salib et al 1996 [176] United Kingdom	Hospital-based case-control study	Cases = 198, controls = 340 (mean age cases = 77, controls = 73)
Gun et al 1997 [177] Australia	Hospital-based case-control study	Cases = 170, controls = 170 (age 52–96, mean 77)
Graves et al 1998 [178] United States	Population-based case-control study	Cases = 89, controls = 89 (mean age 77)
Gauthier et al 2000 [179] Canada	Population-based case-control study	Cases = 68, controls = 68 (age 70+)
Rondeau et al 2000 [180] France	Population-based cohort study	n = 2 698 (age 65+)

AD = Alzheimer's disease; OR = Odds ratio

Risk/protective factor	Diagnostic criteria	Results
Aluminum concentration in water in the area where subject had lived longest prior the onset	NINCDS-ADRDA and onset before 65	Non-significant AD risk was found. ORs ranging from 0.8 to 1.2, depending on the chosen cut-off
History of occupational aluminum exposure (yes/no)	NINCDS-ADRDA	OR 0.98 (0.53–1.75)
Lifetime occupational exposure (yes/no) to aluminum	NINCDS-ADRDA	OR 0.33 (0.01–4.16)
Lifetime occupational exposure to aluminum (yes/ no, duration, intensity, age at exposure)	NINCDS-ADRDA	Non-significant risk was found. ORs 0.76–4.52, depending on the model
Long term exposure (from 1945 up until the onset) of different aluminum forms in drinking water at residence	NINCDS-ADRDA	Non-significant association with 9 or the 10 different Al forms. For organic monomeric Al OR: 2.67 (1.04–6.90)
Aluminum concentration in drinking water in 70 water areas in previous 10 years (0.1 mg/l as cut-off)	DSM-III-R for dementia, NINCDS-ADRDA for AD	RR for incident dementia 1.99 (1.20–3.28). AD: 2.14 (1.21–3.80)

Occupation

Search results from the literature

Keywords: Occupation, occupational exposure, electromagnetic field, solvents, dementia, Alzheimer's disease.

The search in PubMed identified 134 articles. After exclusions due to irrelevant outcomes, 24 articles remained.

Summary of articles included

The number of studies included in the final assessment are as follows:
- for dementia: 4/5 (larger occupational categories), 2/3 (EMF), 0/1 (solvents).
- for AD: 6/8 (larger occupational categories), 4/11 (EMF), 2/3 (solvents).

Table 8.46 *Occupation and dementia: Number of studies by final quality index score.*

	Final quality index score		
	High	**Medium**	**Low**
Positive association	0	Work Categories: 2 EMF: 2	Categories: 1
Inverse association	0	0	0
No association	Categories: 1	0	0

A positive association means that occupation is associated with increased risk of dementia, and an inverse association means that occupation is associated with reduced risk of dementia.

EMF = Electromagnetic fields

Table 8.47 *Occupation and AD: Number of studies by final quality index score.*

	Final quality index score		
	High	**Medium**	**Low**
Positive association	0	Categories: 4 EMF: 3 Solvents: 1	0
Inverse association	0	0	0
No association	Categories: 1	Categories: 1 Solvents: 1	EMF: 1

A positive association means that occupation is associated with increased risk of AD, and an inverse that occupation is associated with reduced risk of AD.

EMF = Electromagnetic fields

Conclusion

The scientific evidence for the risk factor of occupational exposure, which was broken down into three groups (larger occupational categories, occupational exposure to electromagnetic fields and occupational exposure to solvents), is limited for both dementia and AD (Evidence Grade 3).

Table 8.48 *Occupation, dementia and AD. Description of the studies that received a final quality score over 0.*

Author Year, reference Country	Study design	Study population (age at baseline, years)
Dementia		
Stern et al 1994 [181] United States	Follow-up study	850 individuals (age 60+)
Anttila et al 2002 [23] Finland	Follow-up	2 000 individuals (age 65+)
Helmer et al 2001 [182] France	Follow-up	3 675 individuals (age 65+)
Bonaiuto et al 1995 [183] Italy	Case-control	Cases = 48, controls = 96 (age 59+)
Qiu et al 2004 [52] Sweden	Follow-up	1 473 individuals (age 75+)
Feychting et al 1998 [184] Sweden	Case-control	Cases = 77 controls = 466 (age 57+)
Alzheimer's disease		
Helmer et al 2001 [182] France	Follow-up	3 675 individuals (age 65+)

Risk/protective factor	Diagnostic criteria	Results
Low (unskilled/semiskilled, skilled trade or craft, and clerical office workers) lifetime occupation	DSM-III-R	The risk of dementia was increased in subjects with low lifetime occupational attainment (RR = 2.25; 95% CI 1.32–3.84)
Physical occupation (farming, animal husbandry, cooking, factory or construction, and mining) as main occupation during life	NINCDS-ADRDA	Having an physical occupation mainly during life increased the risk for dementia (RR = 2.3; 95% CI 1.279–4.398)
Being a farmer	DSM-III-R	No association found between any occupational categories and risk of dementia
Principal lifetime occupation (farmer, factory worker, housewife and other)	DSM-III	Manual work (farming and factory) increased the risk of dementia RR = 2.9; 95% CI 1.2–7.4
Lifetime occupational exposure to ELF-MF (extremely-low-frequency magnetic field)	DSM-III-R	ELF-MF exposure ≥0.2 microtesla in lifetime job was related to dementia RR 2.0; 95% CI 1.1–3.7 for men. No association found in women
Occupational exposure to EMF (primary, last and highest exposed occupation)	DSM-III-R	For the last occupation and the highest exposure increased risk for dementia RR 3.8; 95% CI 1.4–10.2
Being a farmer	DSM-III-R, NINCDS-ADRDA	No association found between any occupational categories and risk of AD

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***Table 8.48** continued*

Author Year, reference Country	Study design	Study population (age at baseline, years)
Salib et al 1996 [176] England	Case-control	Cases = 198, controls = 340
Stern et al 1994 [181] United States	Follow-up study	850 individuals (age 60+)
Qiu et al 2003 [185] Sweden	Follow-up	913 individuals (age 75+)
Fratiglioni et al 1993 [7] Sweden	Case-control	Cases = 98, controls = 216 (age 75+)
Sobel et al 1996 [186] United States	Case-control	Cases = 326, controls = 152 (age 65+)
Feychting et al 1998 [184] Sweden	Case-control	Cases = 55, controls = 466 (age 57+)
Sobel et al 1996 [186] United States, Finland	Case-control	Cases = 387, controls = 475
Qiu et al 2004 [187a] Sweden	Follow-up	1 473 individuals (age 75+)
Gun et al 1997 [177] Australia	Case-control	Cases = 170, controls = 170 (age 52+)

Risk/protective factor	Diagnostic criteria	Results
Previous work in aluminum factory, and manual work	NINCDS-ADRDA	No association found between occupational aluminum exposure and AD or between manual work and AD
Low (unskilled/semiskilled, skilled trade or craft, and clerical office workers) lifetime occupation	DSM-III-R, NINCDS-ADRDA	The risk of AD was increased in subjects with low lifetime occupational attainment (RR 2.25; 95% CI 1.32–3.84)
Lifetime manual work, goods production	DSM-III-R	Working with goods production increased the risk of AD, RR 2.0; 95% CI 1.2–3.2
Blue-collar work as principal work during life	DSM-III-R	Blue collar work among men increased the risk of AD RR 5.3; 95% CI 1.1–25.5
Occupational exposure to EMF in the primary occupation during life	NINCDS-ADRDA	For high exp to EMF the odds ratio was 2.45; 95% CI 1.11–5.37
Occupational exposure to EMF (primary, last and highest exposed occupation)	DSM-III-R	For the last occupation and the highest exposure increased risk for AD RR 2.7; 95% CI 0.9–7.8
Medium to high exposed occupations	NINCDS-ADRDA	Odds ratios of 3.0 for the combined series 95% CI 1.6–5.4. Medium to high EMF exp are associated with AD
Lifetime occupational exposure to ELF-MF (extremely-low-frequency magnetic field)	DSM-III-R	ELF-MF exposure ≥0.2 microtesla in lifetime job was related to AD, RR 2.3; 95% CI 1.0–3.1 for men. No association found in women
Occupational exposure to solvent	NINCDS-ADRDA	No significant OR found

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***Table 8.48** continued*

Author Year, reference Country	Study design	Study population (age at baseline, years)
Kukull et al 1995 [187b] United States	Case-control	Cases = 193, control = 243 (age 59+)
Smyth et al 2004 [188] United States	Case-control	Cases = 122, control = 235

AD = Alzheimer's disease; CI = Confidence interval; ELF-MF = Electric fields-Magnetic fields; OR = Odds ratio; RR = Relative risk

Risk/protective factor	Diagnostic criteria	Results
Occupational exposure to solvent	DSM-III-R, NINCDS-ADRDA	History of exposure to one or more solvent groups: adj OR 2.3 95% CI 1.1–4.7
Occupational demands (mental, social, physical and motor)	NINCDS-ADRDA	Sign diff found in mental (protective) and physical (risk) occupational demands

Diet

Search results from the literature

Keywords: Diet, nutrition, fat, antioxidant, coffee, tea, vitamin, meat, fish, calorie, flavonoid.

Search 1: Diet and dementia. Limits: human studies published in English only, excluding reviews: 187 titles.
Search 2: Nutrition and dementia. Limits: as above, excluding all titles that had appeared in the previous search: 201 additional titles.
Searches 3–11: Using additional keywords (fat, antioxidant, coffee, tea, vitamin, meat, fish, calorie, flavonoid) based on the articles that were found during searches 1 and 2. Limits: as above: 884 additional titles.

All the titles and relevant abstracts were read. Twentytwo articles were chosen for a more thorough evaluation. Articles were excluded that:

- Had cognitive impairment as the outcome
- Compared nutritional status in patients with and without dementia (nutrition not a risk factor).

After the initial round of reading, two studies that replicated another study with the same population, exposure and outcome were also excluded. The study with the more precise design was included and reported in the tables. If the excluded study had findings inconsistent with the included study, it is reported in the summary section. The reference list also contains replicating studies. Twenty articles were chosen for the evaluation. Three of them were excluded because they had a final quality index score of zero. All of these studies looked at associations between "other dietary exposures" and dementia or AD. Two additional studies were not included because they replicated (same study population and exposure) other studies. One of them showed results contrary to the study that was included – ie, the earlier report of the Rotterdam study (Kalmijn et al [189] which was not included) found an association between fat consumption and dementia, whereas the later study (Engelhart et al [190] which was included), which had a longer follow-up period, found no such association.

Remarks: Diet was broken down into 4 different exposure groups:
1) Fat, fish and meat
2) Vitamins and antioxidants
3) Coffee and tea
4) Other.

Summary of articles included

Fifteen of the 20 articles were ultimately included in the final evaluation (Table 8.52).

Table 8.49 *Fat/fish/meat and dementia/AD: Number of studies by final quality index score.*

	Final quality index score		
	High	**Medium**	**Low**
Positive association	1	4	0
Inverse association	0	0	0
No association	0	0	0

A positive association means that polyunsaturated fatty acids and fish are associated with reduced risk of dementia, and the saturated and trans-unsaturated fatty acids, or meat with increased risk. An inverse association means the opposite: polyunsaturated fatty acids are increasing the risk whereas the saturated and trans-unsaturated fatty acids are decreasing it.

Table 8.50 *Vitamins/antioxidants and dementia/AD: Number of studies by final quality index score.*

	Final quality index score		
	High	**Medium**	**Low**
Positive association	1	3	0
Inverse association	0	0	0
No association	1	2	0

A positive association means that vitamins/antioxidants are associated with increased risk of dementia/AD.

Table 8.51 *Coffee/tea and dementia/AD: Number of studies by final quality index score.*

	Final quality index score		
	High	**Medium**	**Low**
Positive association	0	0	0
Inverse association	0	2	0
No association	0	0	2

A positive association means that coffee/tea consumption is associated with an increased risk of dementia/AD.

Conclusion

Only a few studies exist for each of the dietary factor groups. A major additional drawback is that most of the studies had relatively short follow-up period. Thus, the current epidemiological evidence for an association between diet and dementia is insufficient.

Table 8.52 *Diet, dementia and AD. Description of the studies that received a final quality score over 0.*

Author Year, reference Country	Study design	Study population (age at baseline, years)
Fat, Fish, Meat		
Barberger-Gateau et al 2002 [191] France	Population-based cohort study	n = 1 416 (68 years or older)
Engelhart et al 2002 [190] The Netherlands	Population-based cohort study	n = 5 395 (55 years or older)
Luchsinger et al 2002 [192] United States	Population-based cohort study	n = 980 (65 years or older)
Morris et al 2003 [193] United States	Population-based cohort study	n = 815 (65 years or older)
Morris et al 2003 [194] United States	Population-based cohort study	n = 815 (65 years or older)
Vitamins, Antioxidants		
Morris et al 1998 [195] United States	Population-based cohort study	n = 633 (age 65+ years)

Risk/protective factor	Diagnostic criteria	Results
Frequency (daily/weekly/ sometimes/never) of fish and meat consumption	DSM-III-R	Significant trend with increasing fish consumption associated with decreasing incidence of dementia. But trend is non-significant for AD. No association with meat
Dietary intake of total fat, saturated fat, trans fat, cholesterol, MUFA, PUFA, n-6 PUFA, n-3 PUFA	NINCDS-ADRDA, NINDS-AIREN	Decreased risk of AD per 1 SD increase in total fat, saturated fats, and trans fats. No associations between fats and dementia and VaD
Daily intake of calories divided into quartiles	NINCDS-ADRDA	Highest daily caloric intake compared to lowest had RR 1.5 (1.0–2.2) for AD
Intake of total fat, vegetable fat, animal fat, cholesterol, saturated fat, trans-unsaturated, n-6 and monounsaturated fat	NINCDS-ADRDA	High intake of saturated and trans-unsaturated fat associated with increased risk of AD. High intake of n-3 PUFA and monounsaturated fats associated with decreased risk
Frequency of fish eating, quantity of n-3, DHA, and EPA in the diet	NINCDS-ADRDA	At least weekly fish consumption compared to never consumption had RR 0.4 (0.2–0.9) for AD. Intake of total n-3, and DHA was associated with reduced risk of AD, but not EPA
Intake of supplemental vitamin C and E and multivitamins	NINCDS-ADRDA	None of those using vitamin E and C supplement became demented. Significant different for vitamin C, but not for E. No association for multivitamin use

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***Table 8.52** continued*

Author Year, reference Country	Study design	Study population (age at baseline, years)
Commenges et al 2000 [196] France	Population-based cohort study	n = 1 367 (age 65+ years)
Engelhart et al 2002 [197] The Netherlands	Population-based cohort study	n = 5 395 (55 years or older)
Laurin et al 2002 [198] United States	Population-based cohort study	n = 2 369
Morris et al 2002 [199] Chicago, United States	Population-based cohort study	n = 815 (age 65+ years)
Helmer et al 2003 [200] France	Population-based nested case-control study	Cases = 46, controls = 136 (age 65+ years)
Luchsinger et al 2003 [201] United States	Population-based cohort study	n = 980 (age 65+ years)
Coffee, Tea		
Broe et al 1990 [202] Australia	Clinic-based case-control study	Cases = 170, controls = 170 (52–96 years)

Risk/protective factor	Diagnostic criteria	Results
Dietary intake of flavonoids	DSM-III-R	RR for dementia in highest tertile of flavonoid intake compared to lowest tertile was 0.49 (0.26–0.92)
Dietary intake of vitamins C and E, beta carotene, and flavonoids	NINCDS-ADRDA	Risk of AD decreased per 1 SD increase in the intake of vitamin C and E. No significant association with beta carotene or flavonoids
Intake of supplemental vitamin E and C (long term or short term use of both or one only)	DSM-III-R, NINCDS-ADRDA, AD-DTC	No association between supplemental vitamin use and dementia/AD/VaD
Vitamin C, E and beta carotene intake from foods and supplements	NINCDS-ADRDA	Decreasing AD risk with increasing vitamin E intake from foods. No associations with total vitamin E, total or from foods intake of vitamin C or beta carotene
Plasma concentrations of vitamin E, A and MDA	DSM-III-R	Increased dementia OR in subjects at lowest vitamin E tertile. Similar trends for vitamin A and MDA and between AD and vitamins E and MDA, not A
Dietary and supplemental intake of vitamin C and E	NINCDS-ADRDA	No significant association (tendency for protective effect of vitamin C)
Drinking coffee and tea never or >4 cups/day sometimes in life. History of starvation	NINCDS-ADRDA	No significant associations

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Table 8.52 *continued*

Author Year, reference Country	Study design	Study population (age at baseline, years)
Forster et al 1995 [175] England	Clinic-based case-control study	Cases = 109, controls = 109. Cases under 65 at diagnosis
Lindsay et al 2002 [19] Canada	Population-based cohort study	n = 4 088 (age 65+ years)
Maia et al 2002 [67] Portugal	Clinic-based case-control study	Cases = 54, controls = 54 (mean age 71 years)
Other Dietary Exposures		
Ross et al 1999 [92] Honolulu, United States	Population-based cohort study	n = 3 403 (age 71–93 years)

AD = Alzheimer's disease; DHA = Docosahexaenoic acid (22:6n-3); EPA = Eicosapentaeoic acid (20:5n-3); MDA = Malondialdehyde; MUFA = Monounsaturated fatty acids; n-3 = n-3 polyunsaturated fatty acids; OR = Odds ratio; PUFA = Polyunsaturated fatty acids; RR = Relative risk; VaD = Vascular dementia

Risk/protective factor	Diagnostic criteria	Results
Drinking >4 cups of tea prior the onset of symptoms, asked from a proxy	NINCDS-ADRDA	No significant association
Regular (nearly every day) consumption of coffee or tea	DSM-IV	Regular coffee consumption had OR 0.69 (0.50–0.96) for AD
Average daily caffeine intake during life	NINCDS-ADRDA	Caffeine exposure was inversely associated with AD
Preference of Western vs Oriental diet	AD-DTC	Preference of Western vs Oriental diet was associated with decreased OR for VaD

Vitamin B_{12} and folate

Search results from the literature

Keywords: B_{12} vitamin/folate and dementia/Alzheimer's disease.

For vitamin B_{12} and dementia 158 articles were identified, and 99 for folate and dementia. Many studies overlapped, ie, they investigated both B_{12} and folate.

All of the titles and relevant abstracts were read online. Twenty articles concerning vitamin B_{12} deficiency and 15 concerning folate deficiency (partially overlapping) were chosen for the evaluation.

Summary of articles included

Three of the 16 evaluated studies were acceptable (conclusions 1 and 2 >0).

Table 8.53 *Vitamin B_{12} and folate and dementia/AD: Number of studies by final quality index score.*

	Final quality index score		
	High	**Medium**	**Low**
Positive association	0	1	1
Inverse association	0	0	0
No association	0	1	0

A positive association means that Vitamin B_{12} and folate are associated with increased risk of dementia/AD. An inverse association means that Vitamin B_{12} and folate are associated with reduced risk of dementia/AD.

Conclusion

One study with medium quality found a positive association when both vitamins were taken into account, while another study with medium/low quality found an association between both low B_{12} and low folate and AD. One study with medium quality reported a non-significant trend between low folate and AD. Thus, there is insufficient evidence to conclude that B_{12} or folate deficiency are risk factors for dementia or AD.

Table 8.54 *Vitamin B_{12} and folate and dementia and AD*
Description of the studies that received a final quality score over 0.

Author Year, reference Country	Study design	Study population (age at baseline, years)	Risk/protective factor
Clarke et al 1998 [120] United Kingdom	Clinic based case-control study (volunteers controls)	Cases = 164 AD, controls = 108 (age 55+; mean age: controls 72.8, AD 73.2, confirmed AD 76.6)	B_{12} and folate levels in AD patients and controls (cross-sectional)
Wang et al 2001 [203] Sweden	Population-based cohort study	n = 370 (60 dementia) (age 75+ years) (Kungsholmen Project)	B_{12} and folate values 3 years before the diagnosis of incident dementia
Maxwell et al 2002 [204] Canada	Population-based cohort study (Canadian Study of Health and Aging)	n = 369. Dementia based on n = 243, 66 dementia; AD based sample n = 226, 49 AD	Folate levels 5 years before the diagnosis of incident dementia

AD = Alzheimer's disease; OR = Odds ratio; VaD = Vascular dementia

Diagnostic criteria	Results
NINCDS-ADRDA, CERAD for AD diagnosis (76 cases with histologically confirmed AD)	Histopathologically confirmed AD: lower 3rd vs higher 3rd serum folate OR = 3.3 (1.8–6.3), B_{12} OR = 4.3 (2.1–8.8). Clinically diagnosed AD, folate OR = 2.3 (1.4–3.8), B_{12} 1.4 (0.8–2.5)
DSM-III-R	Subjects with low B_{12} (≤150 pmol/l)/folate (≤10 nmol/L) had an increased risk for AD; RR 2.1 (1.2–3.5)
DSM-III-R for dementia, NINCDS-ADRDA for AD, and ICD-10 for VaD	OR for the lowest folate quartile compared with the highest for dementia 2.19 (0.93–5.15) and for AD 2.17 (0.85–5.53)

Depression

Search results from the literature

Keywords: Depression and risk of dementia/depression and risk of Alzheimer's disease.

Threehundredthirtynine articles were identified. All of the titles and abstracts were read online. Fortyfive abstracts or articles were ultimately printed out for a more thorough evaluation. All articles concerning cognition, Parkinson's disease, depression as an (adverse) effect of treatment for dementia or AD, depression in elderly in nursing facilities, and depressive symptoms after the onset of dementia or AD were excluded.

Besides being a risk factor, depression can be regarded as an emotional reaction to the loss of control in the early dementia process. Depression may also be regarded as an early manifestation of AD. In addition, depression and dementia have been suggested as having overlapping biological backgrounds of APOE 4 or white matter hyperintensities. Only articles (14) concerning depression as a risk factor for dementia or AD were included.

Summary of articles included

Six of the fourteen articles were deemed unacceptable due to a final quality index score of zero. Table 8.56 below reports the quality score of the eight remaining (acceptable) articles. Four of those studies assessed depressive symptoms, while 4 investigated a history of depression as the risk factor/exposure.

Seven studies reported an association between depression and the risk of dementia or AD. The studies interpret those associations differently. Two of them talk about preclinical or early manifestations of dementia, while five studies discuss the possibility of depression as a risk factor for dementia. One study with moderately strong study quality found no association.

Table 8.55 *Depression and dementia/AD: Number of studies by final quality index score.*

	Final quality index score		
	High	**Medium**	**Low**
Positive association	0	1	6
Inverse association	0	0	0
No association	0	1	0

A positive association means that depression is associated with increased risk of dementia/AD. An inverse association means that depression is associated with reduced risk of dementia/AD.

Conclusion

A number of findings suggest that depression may be a risk factor for dementia, but the current scientific evidence is insufficient.

Table 8.56 *Depression and dementia and AD. Description of the studies that received a final quality score over 0.*

Author Year, reference Country	**Study design**	**Study population (age at baseline, years)**
Speck et al 1995 [205] United States	Case-control study	n = 594 (age 60+)
Devanand et al 1996 [206] United States	Follow-up, 12–60 months	n = 478 (age 60+)
Berger et al 1999 [207] Sweden	Follow-up, 36 months	n = 222 (age 75+)
Chen et al 1999 [208] United States	Follow-up, 24–96 months	n = 803 (age 65+)
Palsson et al 1999 [209] Sweden	Follow-up, 36 months	n = 267 (age 85)
Geerlings et al 2000 [210] The Netherlands	Follow-up, 38.4 months	n = 3 147 (age 65–84)
Wilson et al 2002 [211] United States	Follow-up, 84 months	n = 651 (age 75.4) SD 6.9

Risk/protective factor	Diagnostic criteria	Results
Informants provided data regarding history of depression	NINCDS-ADRDA, NINDS-AIREN	Restricting treated depression to exclude primary loss or grief reactions, a modest association with AD OR = 1.8; 95% CI = 0.9–3.5
Depressive symptoms were evaluated with the 17-item Hamilton Rating Scale for depression	DSM-III-R	Depressed mood moderately increased the risk of developing dementia, primarily AD
Depressive symptoms assessed by the Comprehensive Psychopathological Rating Scale	DSM-III-R	Depressive symptoms are elevated preclinically in AD, and this elevation is not merely a by-product of self-perceived cognitive difficulties
A "depression cluster" was identified by the presence of 5 or more depressive symptoms	DSM-III-R, NINCDS-ADRDA	Depressive symptoms did not confer a significantly increased RR of AD (1.28; 95% CI 0.51–3.20)
Depression diagnosis from the subjects themselves, medical records, general/psychiatric hospitals, and outpatient clinics	DSM-III-R	The higher incidence of dementia in those with early-onset major depression
Depression was assessed with the Geriatric Mental State Schedule	DSM-IV	Depression was associated with an increased risk of AD and cognitive decline, only in subjects with higher levels of education
Number of depressive symptoms was assessed with a modified 10-item Center for Epidemiologic Studies Depression Scale	NINCDS-ADRDA	For each depressive symptom, AD risk increased by 19%, and annual decline on a global cognitive measure increased by 24%

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Table 8.56 *continued*

Author Year, reference Country	Study design	Study population (age at baseline, years)
Green et al 2003 [212] United States	Case-control study	n = 4 046 (age 70.1) SD 10.6

AD = Alzheimer's disease; CI = Confidence interval; OR = Odds ratio;
SD = Standard deviation

Risk/protective factor	Diagnostic criteria	Results
A question about depression and age at the first episode were asked to subject or proxy	NINCDS-ADRDA	Depression symptoms before the onset of AD are associated with the development of AD, even in families where first depression symptoms occurred >25 years before the onset of AD

Education

Search results from the literature

Keywords: Dementia OR Alzheimer's disease AND education AND risk factor/dementia OR Alzheimer's disease AND education AND population study.

A total of 301 papers were found by searching Pub-Med. After reading through the abstracts or titles, we excluded 262 for the following reasons:

- Reviews/Pooled analyses of many populations/Guidelines = 14
- Studies performed on a population that is already cognitively impaired = 21
- Outcomes other than dementia or AD (Cognitive impairment, cognitive decline, cognitive functions, functional impairment, VaD, post-stroke dementia, Parkinson's disease, etc) = 144
- Education used only as a confounder to investigate other associations = 71
- Retrospective study design in clinical setting/volunteer = 11
- Full text not found in Karolinska Institute electronic library = 1.

That left 39 articles for the analysis. Of these 16 have all dementias as the outcome, and 23 have AD as the outcome.

Summary of articles included

Dementia: In the final assessment 12 of the 16 studies evaluated were included. Table 8.59 describes these studies.

Table 8.57 *Education and dementia: Number of studies by final quality index score.*

	Final quality index score		
	High	**Medium**	**Low**
Positive association	0	0	0
Inverse association	0	10*	0
No association	0	2#	0

* Here a positive association means that low education is associated with increased risk of dementia. An inverse association means that high education is associated with reduced risk of dementia. One of the 7 studies reported a positive association for both gender, 2 a positive association only in women, 1 only in men.

Both indicate a positive association when other types of dementia than AD are considered separately.

AD: In Table 8.59 16 of the 23 studies evaluated were included and summarized.

Table 8.58 *Education and AD: Number of studies by final quality index score.*

	Final quality index score		
	High	**Medium**	**Low**
Positive association	0	0	0
Inverse association	0	10	1
No association	0	3	2

A positive association means that low education is associated with increased risk of AD. An inverse association means that high education is associated with reduced risk of AD.

Conclusions

There is moderately strong evidence that low education is a risk factor for dementias and AD (Evidence Grade 2).

The likelihood that more poorly educated subjects will adopt unhealthy lifestyle behaviors has been suggested as an explanation for the stronger association found in subjects with types of dementia other than AD.

Issues have been raised regarding variations in age and stage of dementia at detection in subjects with different educational levels.

No conclusions can be drawn concerning gender differences in the association between education and dementia.

Table 8.59 *Education, dementia and AD Description of the studies that received a final quality score over 0.*

Author Year, reference Country	Study design	Study population (age at baseline, years)
Fratiglioni et al 1991 [213] Sweden	Population-based case-control study	n = 1 810 (age 75+)
Stern et al 1994 [181] United States	Cohort incidence study	n = 593 (age 12–48)
Bonaiuto et al 1995 [183] Italy	Population-based case-control study	n = 778 (age 59+)
Cobb et al 1995 [214] United States	Community-based cohort study	n = 3 330 (age 55–88)
Ott et al 1995 [215] The Netherlands	Population based cross sectional study	n = 7 528
Evans et al 1997 [30] United States	Follow-up study	n = 642 (age 65+)
Azzimondi et al 1998 [216] Italy	Comparative study on prevalence	n = 773 (age 74+)
De Ronchi et al 1998 [217] Italy	Prevalence study	n = 495 (age <60)

Risk/protective factor	Diagnostic criteria	Results
Elementary school vs high school/university	DSM-III-R, Clinical evaluation	Less educated subjects had a higher prevalence of all dementias but not of AD
Education: low (<8 years), and high (≥8 years)	DSM-III-R, NINCDS-ADRDA	More years of education (continuous variable) was associated with a reduced dementia risk (RR = 0.92; 95% CI 0.88–0.95). Lower education (<8 years) was associated with a higher RR (2.02; 95% CI 1.33–3.06)
Education	DSM-III-R, NINCDS-ADRDA	OR 15.7; 95% CI 4.3–57.1 of dementia for illiterates compared to over 4th grade education, and a consistent trend toward a decreasing risk with increasing education
Education: < grade school, < high school, and ≥ high school	DSM-III, NINCDS-ADRDA	Subjects with a grade school education or less compared with high school had a RR of AD 1.04 (0.62–1.74)
Education: primary; low vocational; medium secondary; medium vocational to university		The lower two levels of education significantly related to higher risk of dementia. RR 3.2 (2.2–4.6) and 2.0 (1.3–3.2)
Number of years of formal education	NINCDS-ADRDA	A 17% risk decrease of developing dementia for each years of education
Length of schooling: ≥2 years vs >2 years	DSM-II-R	Schooling ≤2 years was a strong independent predictor of dementia, OR 4.3 (2.8–6.7)
Education: no education, up to 3 years, >3 years	DSM-III-R	Comparing no education with any education, OR 4.7 (95% CI 2.3 to 9.6)

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***Table 8.59** continued*

Author Year, reference Country	Study design	Study population (age at baseline, years)
Lin et al 1998 [218] Taiwan	Prevalence study	n = 2 915 (age 65+)
Letenneur et al 1999 [219] France	Community based cohort study	n = 2 881 (age 65+)
Ganguli et al 2000 [220] United States	Prospective study	n = 1 298 (age 65+)
Hall et al 2000 [221] United States	Community prevalence study	n = 2 212 (age 65+)
Bowirrat et al 2001 [222] Israel	Door-to-door survey prevalence study	n = 821 (age 60+)
Qiu et al 2001 [223] Sweden	Community-based longitudinal study	n = 1 296 (mean age 33.6±12)
Lindsay et al 2002 [19] Canada	Population-based prospective study	n = 6 434 (age 65+)

Risk/protective factor	Diagnostic criteria	Results
Low education: <6 years	ICD-10, NINCDS-ADRDA	Age standardized prevalence rate of dementia for literate 1.8 (1.1–2.8) vs illiterate 3.1 (2.3–4.1) and of AD for literate 0.4 (0.1–0.9) vs illiterate 4.9 (3.9–6.1)
No schooling, primary school, secondary or university	DSM-III, NINCDS-ADRDA	Higher risk of developing dementia in subjects with no schooling (HR 1.93) and primary school (HR 1.49) compared with the highest
< high school vs > high school education	DSM-III-R, NINCDS-ADRDA	< high school education had an incidence rates 1.5 times higher than those with more education or dementia and AD
Low education ≤6 grade, and high education >6 grade	NINCDS-ADRDA	Low education (<7 years) and rural childhood residence related to AD (OR 6.5; 95% CI 2.6–16.7) compared to high education and urban group. Possessing one of them did not relate to high AD risk
Years of schooling	DSM-IV	Illiteracy (no formal schooling) was associated with a higher AD prevalence (27% vs 4%, OR 9; 95% CI 4.4–19)
Education: <8 years, 8–10 years, or ≥11 years	DSM-III-R	Low level of education (<8 years) was associated with an increased incidence of dementia (RR 2.1; 95% CI 1.3–3.5) and AD (RR 2.7; 95% CI 1.4–5.0)
Self-administered questionnaire	DSM-IV, NINDS-AIREN	Protective effect of education on AD. RR 0.92; 95% CI 0.88–0.97

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***Table 8.59** continued*

Author Year, reference Country	Study design	Study population (age at baseline, years)
Harmanci et al 2003 [224] Turkey	Population-based case-control study	n = 254 (age 70+)
Kahana et al 2003 [225] Israel	Population based prevalence study	n = 1 720 (age 75+)
Karp et al 2004 [226] Sweden	Community-based longitudinal study	n = 931 (age 75+)

AD = Alzheimer's disease; CI = Confidence interval; OR = Odds ratio; RR = Relative risk

Risk/protective factor	Diagnostic criteria	Results
		A university/college degree had a protective effect on AD risk. OR 0.10; 95% CI 0.02–0.50
Education: illiterates; 1–7 years; 8–1 years; ≥12 years	DSM-III-R	Low education in relation to dementia development completely explained the ethnic differences and partly the female predominance
Education: 0–7 years, >7 years	DSM-III-R	Less educated subjects had an adjusted RR of 3.4; 95% CI 2.0–6.0 of developing AD

Socioeconomic status (SES)

Search results from the literature

Keywords: Socioeconomic status and risk of Alzheimer's.

All the titles and abstracts of 35 articles were read online. Seven articles were chosen for a more thorough evaluation.

Remarks: Socioeconomic status as a risk factor for dementia and AD were broken down into 2 main lines of research: 1) Early life SES; 2) Adult life SES.

All seven articles originally evaluated were chosen on the grounds that they focused on socioeconomic status as a risk factor, as opposed to examining only education in itself as a risk factor for dementia and AD. Two of the evaluated studies concerned SES in early life, but only 1 was included in the final assessment [227]. Five of the seven studies were ultimately deemed acceptable (Table 8.61).

Summary of articles included

Three of the five acceptable articles showed a positive association between SES and dementia. However, one did not report statistically significant associations for occupation and income when education was included in the model [228]. Two studies did not show any association between SES and dementia.

Table 8.60 *SES and dementia/AD: Number of studies by final quality index score.*

	Final quality index score		
	High	**Medium**	**Low**
Positive association	0	3#	0
Inverse association	0	0	0
No association	0	2	0

One study concerns early life SES measured by father's SES and in another one study occupation-based SES and income were not significant when controlling for education and income.

A positive association means that low SES is associated with increased risk of dementia/AD. An inverse association means that high SES is associated with reduced risk of dementia/AD.

Conclusion

The evidence of a positive association between socioeconomic status in adult or early life and dementia is insufficient.

Table 8.61 *SES and dementia and AD. Description of the studies that received a final quality score over 0.*

Author Year, reference Country	Study design	Study population (age at baseline, years)
Stern et al 1995 [181] United States	Follow-up 12–48 months	n = 593 age (60–99)
Evans, et al 1997 [30] United States	Follow-up 51.6 months	n = 642 (age 65+)
Moceri et al 2001 [227] United States	Case-control study	n = 574 (age 75+)
Anttila et al 2002 [23] Finland	Follow-up 132–312 months	n = 1 449 (age 65–79)
Karp et al 2004 [226] Sweden	Follow-up 36 months	n = 1 473 (age 75+)

AD = Alzheimer's disease; CI = Confidence interval; OR = Odds ratio;
RR = Relative risk; SES = Socio Economic Standard

Risk/protective factor	Diagnostic criteria	Results
Occupation was classified based on US census categories: housewife, un/semi-skilled, skilled, clerical, manager, and professional	NINCDS-ADRDA, DSM-III-R	The risk of dementia was increased with low education (RR 2.02; 95% CI 1.33 to 3.06) or low lifetime occupational attainment (RR 2.25; 95% CI 1.32–3.84)
Education, income, and occupation (coded according to perceived prestige)	NINCDS-ADRDA	Fewer schooling, lower income, and lower occupational each predicted AD incidence. AD risk decreased by 17% education/per year. When all 3 measures were included in the model, only education remained significant
Father's occupation was coded into SES categories as defined by US Census Bureau in 1937	NINCDS-ADRDA	Subjects' fathers were unskilled manual workers or labourers were at higher risk for AD (OR 1.8; 95% CI 1.19–2.73). OR 2.35; 95% CI 1.07–5.16 among subjects with the ApoE ε4
Self-administered questionnaire. Occupation: sedentary, physical and no occupation	NINCDS-ADRDA	Reduction in income level during follow-up and low income level at old age might be the consequence of a dementing process rather than risk evolution of dementia
Occupation from informants and grouped according to the socio-economic classification system developed by Statistics Sweden	DSM-III-R	Less-educated subjects had an adjusted RR 3.4 (95% CI 2.0, 6.0) developing AD and lower SES RR 1.6 (95% CI 1.0, 2.5). When both of them were introduced into the model, only education remained significant

Leisure activities

Search results from the literature

Keywords: Physical activities and risk of dementia/Alzheimer's disease (AD) Cognitive/mental/intellectual/productive/cultural activities and risk of dementia/Alzheimer's disease. Leisure activities and risk of dementia/Alzheimer's disease.

After eliminating 93 duplicates, 225 articles were found in the database. In addition 6 articles were added to the list based on personal knowledge [19,71,87,229–231]. After reading through the abstracts, we excluded 213 articles. The remaining 18 were deemed suitable for inclusion and data input.

In the final analysis 16 of the 18 articles were included (Table 8.63).

Summary of articles included

Table 8.62 *Leisure activities and dementia: Number of studies by final quality index score.*

	Final quality index score		
	High	**Medium**	**Low**
Positive association	0	0	0
Inverse association	4	7	3
No association	0	1	1

A positive association means that leisure activities are associated with increased risk of dementia. An inverse association means that leisure activities are associated with reduced risk of dementia.

Conclusions

A large number of studies have looked at the association between leisure activities and the risk for dementia or AD. All the studies deemed appropriate for this project found a significant protective effect of cognitive activities, and the majority of studies reported a protective effects of social and leisure activities on the risk of dementia or AD. One study found no effect of leisure activities [232]. However, the results of studies on physical activities showed a less distinct pattern in relation to the risk of dementia or AD. To sum up, there is moderately strong evidence of an inverse association between leisure activities and dementia and AD.

Table 8.63 *Leisure activities, dementia and AD. Description of the studies that received a final quality score over 0.*

Author Year, reference Country	Study design	Study population (age at baseline, years)
Broe et al 1990 [202] Australia	Case-control study	Cases = 170, controls = 170 (age 52+)
Li et al 1991 [229] China	Population-based 3-year follow-up study	n = 825 (age 60+)
Fabrigoule et al 1995 [233] France	Population-based 3-year follow-up study	n = 2 040 (age 65+)
Yoshitake et al 1995 [71] Japan	Population-based 7-year follow-up study	n = 828 (age 65+)
Helmer et al 1999 [232] France	Population-based 5-year follow-up study	n = 3 675 (age 65+)
Laurin et al 2001 [230] Canada	Population-based 5-year follow-up study	n = 4 615 (age 65+)
Scarmeas et al 2001 [234] United States	Population-based 2.9-year follow-up study	n = 1 172 (age 65+)
Lindsay et al 2002 [19] Canada	Population-based 5-year follow-up study	n = 4 615 (age 65+)

Risk/protective factor	Diagnostic criteria	Results
The assessment of physically under active was not clear stated	NINCDS-ADRDA	Physically under active in previous 10 years (OR 6.25) and before 10 years ago (OR 3.5) were associated with significant risk of AD
Physical mobility. 3-year before diagnosis	DMS-III	RR 8.66 for indoor activity as compared with not limited activity
Subjects completed a questionnaire on social and leisure activities at baseline	DMS-III-R	Travelling (RR 0.48), odds job or knitting (RR 0.46), and gardening (RR 0.53) were associated with decreased risk of dementia
Physical activity was defined as daily exercise during the leisure period or moderate to severe physical activity at work	DMS-III-R, NINCDS-AIREN, NINCDS-ADRDA	Physical activity was a significant protective factor for AD (RR 0.18)
Structured interview on social and leisure activities: 1) marital status, 2) social network, 3) number of activities	DSM-III-R, NINCDS-ADRDA	Never married was associated with increased risk of dementia and AD. No association with social network and leisure activities
Level of physical activity was assessed 5-year before diagnosis by combining frequency and intensity of regular of physical activity	DMS-III-R, NINCDS-ADRDA, ICD-10	High level of physical activity were associated with reduced risks of AD, RR 0.5 (0.28–0.9) and dementia, RR 0.63 (0.4–0.98)
Self reported participation during the month preceding the interview in 13 predefined activities at baseline	DMS-III-R, NINCDS-ADRDA	The risk of dementia was decreased n subjects with high leisure activities (RR 0.62)
Participant were asked whether they engaged in regular exercise	DMS-IV, NINCDS-AIREN	Regular physical activity were associated with a reduced risk of AD, RR 0.69 (0.5–0.96)

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***Table 8.63** continued*

Author Year, reference Country	Study design	Study population (age at baseline, years)
Wang et al 2002 [235] Sweden	Population-based 6-year follow-up study	n = 732 (age 75+)
Wilson et al 2002 [236] United States	Population-based 4.5-year follow-up study	n = 740 (age 65+)
Wilson et al 2002 [237] United States	Population-based 4-year follow-up study	n = 842 (age 65+)
Abbott et al 2004 [238] United States	Prospective cohort study (6-year)	n = 2 257 (age 71–93
Crowe et al 2003 [239] Sweden	A prospective twins study (1.5-year)	n = 107 (age 75+)
Seidler et al 2003 [240] Germany	Case-control study	195 cases, 229 controls (age 65+)
Yamada et al 2003 [87] Japan	Prevalence study within a longitudinal cohort (27-year follow-up)	n = 1 774 (age 33+)
Verghese et al 2003 [241] United States	5-year prospective community cohort study	n = 469 (age 75+)

AD = Alzheimer's disease; CI = Confidence interval; OR = Odds ratio; RR = Relative risk; VaD = Vascular dementia

Risk/protective factor	Diagnostic criteria	Results
Regular engaged in any activities and the frequency of participating such activities were asked to participants	DMS-III-R	Frequent engagement in mental (RR 0.54), social (RR 0.58), and productive (RR 0.58) activities were associated with sig. reduced risk of dementia
Subjects were asked for time typically spent in 7 common activities that involving information processing as central component	NINCDS-ADRDA	Frequent participation in cognitively activities was associated with reduced risk of AD (RR 0.67; 95% CI 0.49–0.92)
Subjects were interviewed for current frequency of participation in 7 cognitive and 9 physical activities	NINCDS-ADRDA	A 1-point increase in cognitive activity score was associated with 33% reduction in risk of AD (RR 0.67; 95% CI 0.49–0.92). Physical activity: no association
Distance walked per day was assessed in physically capable men in the Honolulu-Asia Aging study	DSM-III-R	Men who walked the least (<0.25 mile/day) experienced a 1.8-fold excess risk of dementia compared with those who walked more than 2 mile/day
Structured questionnaire sent home about the frequency of participation in 11 leisure activities >20 years prior to clinical evaluation	DMS-III, NINCDS-ADRDA	Participant in greater overall number of leisure activities was associated with lower risk of both AD (RR 0.54) and dementia (RR 0.53)
Structured interview on marital status, living situation, social ties, leisure activities, smoking and alcohol	ICD-10	OR for subjects with high psychosocial or high social activities vs poor was 0.4 (0.04–0.5)
Physical activity index was calculated from occupational and leisure activities	DMS-III-R, DMS-IV	Physical activity did not show any significant effect of prevalence of VaD or AD
Subjects were interviewed for 6 predefined cognitive and 11 physical activities and the frequency of participating for each activities	DMS-III, DMS-III-R, NINCDS-ADRDA	Participation in leisure activities was associated with a reduced risk of AD and dementia, A 1-point increment in the cognitive-activity score was associated with risk of dementia, HR 0.93 (0.90–0.97)

Social network

Search results from the literature

Keywords: Social network and risk of dementia/Alzheimer's disease (AD). Social support and risk of dementia/Alzheimer's disease. Social integration and risk of dementia/Alzheimer's disease.

After eliminating 30 duplicates, 81 articles were found in the database. Based on personal knowledge 4 articles were added to the list [233,234,242,243]. After reading through the abstracts, 76 papers were excluded as not relevant. The remaining 6 articles were included in the evaluation.

Summary of articles included

Two of the six articles were deemed unacceptable in accordance with the predefined criteria (see Quality grading). Thus, four studies were included in the final analysis.

Table 8.64 *Social network and dementia: Number of studies by final quality index score.*

	Final quality index score		
	High	**Medium**	**Low**
Positive association	0	2	0
Inverse association	0	0	1
No association	0	1#	0

A positive association means that a poor social network is associated with increased risk of dementia. An inverse association means a rich social network is associated with reduced risk of dementia.

This study found that social network has no effect on dementia incidence but never married was associated with an increased risk of dementia.

Conclusion

Only a few studies have looked at the association between social network and the risk for dementia or AD. The evidence of a positive association between social network and dementia and AD is insufficient.

Table 8.65 *Social network, dementia and AD. Description of the studies that received a final quality score over 0.*

Author Year, reference Country	**Study design**	**Study population (age at baseline, years)**
Bickel et al 1994 [242] Germany	Community and long-stay care residents' based 7–8 and 5–6 years follow-up study	n = 422 (age 65+)
Helmer et al 1999 [232] France	Population-based 5-year follow-up study	n = 3 675 (age 65+)
Fratiglioni et al 2000 [244] Sweden	Population-based 3-year follow-up study	n = 1 203 (age 75+)
Seidler et al 2003 [240] Germany	Case-control study	195 cases, 229 controls (age 65+)

AD = Alzheimer's disease; OR = Odds ratio; RR = Relative risk

Risk/protective factor	Diagnostic criteria	Results
Social interview: social relations; social support; marital status	ICD-9	The group of single and divorced people combined had an increased incidence rate of dementia than married. RR 3.37 (1.2–9.5)
Structured interview on: 1) marital status, 2) social network, 3) number of activities	DSM-III-R, NINCDS-ADRDA	Never married was associated with increased risk of dementia (RR 1.91, $p = 0.018$) and AD (RR 2.68, $p<0.001$) than those married or cohabitants. No association with social network and leisure activities
Structured interview on marital status, living arrangement, parenthood and friendship. Social network index	DSM-III-R	Single, living alone, or no-satisfaction was associated with increased dementia. A poor or limited social network increases the risk of dementia RR 1.6 (1.2–2.1)
Structured interview on marital status, living situation, social ties, leisure activities	ICD-10	A protective effect of psychosocial network on dementia. Especially the number of confidants, sports, and cultural activities. High psychosocial social activities vs poor OR 0.4 (0.04–0.5)

Personality

Search results from the literature

Keywords: Personality and risk of dementia/Alzheimer's disease (AD). Personality traits and risk of dementia/Alzheimer's disease (AD). Personality types and risk of dementia/Alzheimer's disease (AD). Neuroticism and risk of dementia/Alzheimer's disease (AD). Extraversion and risk of dementia/Alzheimer's disease (AD).

After eliminating 42 duplicates, 71 articles were found in the database. Based on personal knowledge 2 articles were added to the list [245,246]. After reading through the abstracts, we excluded 66 articles as irrelevant. The remaining 8 articles were deemed suitable for inclusion and evaluation.

Summary of articles included

Seven of the eight articles were deemed unacceptable in accordance with the predefined criteria. Thus, only one study was included in the final analysis.

Conclusions

Only a few studies have looked at the association between personality and the risk of dementia or AD. All but one received a score of insufficient in our quality grading. The accepted study reported an association between distress proneness and AD. People with high distress proneness faced twice the risk of developing AD as those with low distress proneness.

Table 8.66 *Personality, dementia and AD. Description of the studies that received a final quality score over 0.*

Author Year, reference Country	**Study design**	**Study population (age at baseline, years)**
Wilson et al 2003 [247] United States	2.9-year follow-up study	n = 797, mean age 75.2. Catholic nuns, priests, and brothers

AD = Alzheimer's disease; HR = Hazard ratio

Risk/protective factor	Diagnostic criteria	Results
The Neuroticism Scale (NEO Five-Factor Inventory)	NINCDS-ADRDA, Medical history, Neurologic exam. Cognitive function testing, Scan	With each 1-point increase in distress proneness risk of AD increased. HR 1.06 (1.02, 1.09)

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