COGNITIVE DECLINE

IN THE ELDERLY

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Cognitive decline in the elderly

Epidemiologic studies on cognitive function and dementia

Cognitieve achteruitgang bij ouderen

Epidemiologische studies naar cognitieve functie en dementie

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Publications and manuscripts based on the studies described in this thesis

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Breteler MMB, Claus JJ, van Duijn CM, Launer LJ, Hofman A. Epidemiology of Alzheimer's disease. Epidemiologic Reviews 1992;14:59-82.

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Breteler MMB, van den Ouweland FA, Grobbee DE, Hofman A. A community-based study of dementia: The Rotterdam Elderly Study. Neuroepidemiology 1992;11S1:23-8.

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Breteler MMB, Claus JJ, Grobbee DE, Hofman A. Cardiovascular disease and the distribution of cognitive function in an elderly population. The Rotterdam Study. (submitted)

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Breteler MMB, van Duijn CM, Chandra V, Fratiglioni L, Graves AB, Heyman A, Jorm AF, Kokmen E, Kondo K, Mortimer JA, Rocca WA, Shalat SL, Soininen H, Hofman A. Medical history and the risk of Alzheimer's disease: A collaborative re-analysis of case-control studies. Int J Epidemiol 1991;20(Suppl 2):S36-42.

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Breteler MMB, de Groot RRM, van Romunde LKJ, Hofman A. Risk of dementia in patients with Parkinson's disease, epilepsy and severe head trauma: a register-based follow-up study. (submitted)

Chapter 1

Introduction

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Introduction

In the last decades, the awareness has grown among the public, as well as among health politicians, that dementia is highly prevalent in older age, that it causes much distress to patients and their families, and that it poses a large burden on public health care resources.[1,2] Initially, research focused chiefly on Alzheimer's disease, the most frequent type of dementia. In recent years, there is also increasing interest in vascular dementia. The reasons for this are that vascular dementia may be more prevalent than previously recognized, that vascular causes may be involved in the clinical picture of other dementia syndromes as well, and, perhaps most importantly, that vascular causes of cognitive decline can potentially be influenced by available measures of intervention.[3]

In studies of the frequency and etiology of dementia, much emphasis has been put on differentiating demented subjects from cognitively unimpaired individuals. However, there is little evidence to support the idea of a sharp distinction between demented and non-demented persons. Cognitive impairment is a quantitative rather than a qualitative characteristic, and consequently its distribution in the population shows a continuum of severity.[4,5] The fact that cognitive dysfunction is common in old age does not imply that it is intrinsic to aging; it may be normal in the sense of usual, not in the sense of natural.[6]

This thesis focuses on epidemiologic studies on cognitive function and dementia. The main part is devoted to investigations of the relation between vascular risk factors and cognitive function; in these studies cognitive function was evaluated as a continuously distributed variable. In the other studies in this thesis, risk factors for dementia were investigated with dementia as a dichotomous outcome variable.

In chapter 2 the current epidemiological knowledge on Alzheimer's disease is reviewed. The next two chapters are based on the Rotterdam Study, a population-based study of subjects aged 55 years and over.[7] Chapter 3 starts with a brief description of the Rotterdam Study, and deals then with the distribution and vascular correlates of cognitive function in this elderly population. The relation between vascular disease and cognitive performance was evaluated from two different angles: first, the influence of the presence of atherosclerotic disease on the localization and shape of the population

distribution of cognitive function relative to that among subjects without atherosclerotic disease was assessed. Second, the association of various indicators of vascular disease, and of classical and putative risk factors for stroke, with level of cognitive performance was investigated. In chapter 4, the results are described from a study conducted on a subsample of the Rotterdam Study cohort in which the relation between vascular risk factors and cognitive function is assessed in more detail, by focusing on cerebral white matter changes, the presumed anatomical substrate of vascular causes of mental impairment. The basic research questions in this study regarded the prevalence of these lesions, their relation with vascular risk factors, and their relation with cognitive function. In chapter 5, two separate studies are described that both assess the risk of dementia in specific medical conditions. In chapter 5.1 the results are presented of a meta-analysis of case-control studies, in which several medical conditions were investigated as putative risk factors for Alzheimer's disease. Chapter 5.2 addresses the risk of dementia among patients with Parkinson's disease, patients with epilepsy, and among subjects who suffered a severe head trauma. Methodological issues related to the investigations based on the Rotterdam Study are discussed in chapter 6, together with a review of the results of these studies and some suggestions for further research.

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Chapter 2

Epidemiology of Alzheimer's disease

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Epidemiology of Alzheimer's disease

Dementia is emerging as a major health problem. It is an important cause of disability, in particular in the elderly. Dementia is a syndrome that can be caused by many conditions, but Alzheimer's disease is numerically the most important. Etiologic research and intervention studies have therefore mainly concentrated on Alzheimer's disease. In this article we will review current epidemiologic knowledge about this disease. We will focus on results of recent investigations, generally conducted since 1980, because these studies largely conform to contemporary standards of diagnosis. We will successively discuss diagnosis, prevalence, incidence, risk factors, prognosis and therapy of Alzheimer's disease.

DIAGNOSIS

Diagnostic criteria

The diagnosis of Alzheimer's disease is hampered by insufficient knowledge of its pathogenesis, the lack of biologic markers and the absence of unique clinical or morphologic features. High clinical and neuropathologic diagnostic accuracy and valid and standardized criteria are needed for the comparison of results in various studies. For a clinical diagnosis of Alzheimer's disease the majority of recent epidemiologic studies conform to the criteria for progressive degenerative dementia formulated in the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III),[1] to the essentially similar criteria for progressive degenerative dementia of the Alzheimer type in the third revised edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R),[2] or to the criteria for possible and probable Alzheimer's disease as developed by a work group of the National Institute for Neurological and Communicative Disorders and Stroke, and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA).[3] According to all sets of criteria the clinical diagnosis of Alzheimer's disease is more or less a diagnosis by exclusion of other specific causes of dementia. An important difference, however, is that DSM-III and DSM-III-R criteria preclude a diagnosis of Alzheimer's disease

when the intellectual decline does not interfere with everyday life, while according to NINCDS-ADRDA criteria impairment in daily life is supportive of a diagnosis of Alzheimer's disease, but not required for it. In addition, the NINCDS-ADRDA work group recommended for research purposes to identify a single, gradually progressive severe cognitive deficit as possible Alzheimer's disease.[3]

The diagnosis of definite Alzheimer's disease requires neuropathologic confirmation according to NINCDS-ADRDA criteria.[3] However, the neuropathologic hallmarks of neuritic plaques and neurofibrillary tangles are not pathognomonic for Alzheimer's disease. At present, there is no universally accepted set of criteria for a pathologic diagnosis of the disorder. Tierney et al. found that depending on the set of neuropathologic criteria, the percentage of subjects with a clinical diagnosis of probable Alzheimer's disease that was confirmed pathologically ranged from 64 to 86 percent.[4] The development of uniform criteria permitting consistent neuropathologic assessment of Alzheimer's disease is mandatory.[5,6]

The performance of current clinical criteria has been studied by various researchers. The agreement between several raters applying the same set of diagnostic criteria depends on the specific set of criteria used.[7] For DSM-III and NINCDS-ADRDA criteria the interrater reliability among physicians of Alzheimer's disease diagnosis was found to be comparable, and moderate.[7,8] Kukull et al. found NINCDS-ADRDA and DSM-III-R criteria for Alzheimer's disease to have similar overall accuracy, yet NINCDS-ADRDA was more sensitive and DSM-III-R more specific.[9] Several prospective clinicopathologic studies investigated the accuracy of a clinical diagnosis of probable Alzheimer's disease according to NINCDS-ADRDA or equivalent criteria, and reported percentages of diagnoses that were confirmed at autopsy to range from 85 to 100 percent,[10-12] but lower rates have been reported in patients with onset before the age of 65.[13] Although theoretically this high positive predictive value may have come at the cost of a low sensitivity, in the study by Wade et al. it was compatible with a sensitivity of 87 percent.[12]

The spectrum of disease severity is an important consideration when making a clinical diagnosis of Alzheimer's disease. Especially in the early stages of the disease, characterized by an insidious onset and gradual decline, Alzheimer's disease presents itself as a continuum with normal aging. While the extremes of the distribution are easily recognized, the diagnosis of Alzheimer's disease may be arbitrary in mild cases,[14,15] as evidenced by the wide range in prevalence estimates of mild dementia.[14,16] Although this difficulty is unlikely to be resolved without objective markers, further

operationalization of diagnostic criteria could limit the room for varying interpretations.[17]

Differential diagnosis

The diagnosis of Alzheimer's disease requires the exclusion of other specific causes of dementia. In particular the distinction between Alzheimer's disease and vascular dementia poses difficulty. The question how and when vascular disease and infarcts cause dementia is still a matter of debate.[18,19] The characteristics of vascular dementia itself are not unique and may be qualitatively indistinguishable from those seen in Alzheimer's disease.[20,21] The concept of vascular dementia is in fact a confusing one, since it encompasses a diversity of vascular mechanisms, as atherosclerosis, cerebral blood flow regulation and amyloid angiopathy, that alone or in combination may contribute to cognitive impairment.[22] Furthermore, Alzheimer's disease itself may have an important vascular component.[21] In today's epidemiologic practice, vascular dementia is still simply interpreted as atherosclerotic or multi-infarct dementia, and its diagnosis is largely based on the likelihood that a person has ischemic cerebrovascular disease. The scale that has gained most use for that purpose is the Hachinski Ischemic Score.[23] Although its reliability and validity to establish a diagnosis of multi-infarct dementia have been questioned, it tends to rule out possible atherosclerotic causes of dementia and is therefore useful in the diagnosis of Alzheimer's disease by exclusion.[12,24,25]

Vascular causes as well as Alzheimer's disease may contribute independently to dementia in the same patient. This gives rise to a diagnostic paradox,[26] since it requires the presence of cerebrovascular disease considered etiologically related to the dementia, along with a diagnosis of Alzheimer's disease for which cerebrovascular disease has to be excluded. As a pragmatic solution, epidemiologic studies on Alzheimer's disease tend to exclude both mixed and multi-infarct cases. In populations with a high vascular background risk the diagnostic practice regarding multi-infarct dementia might give a relative underestimation of Alzheimer's disease. For etiologic or intervention studies where homogeneity of patient groups is of prime importance, this need not be a problem. However, it may bias comparisons of the frequency of Alzheimer's disease across different populations.

There is considerable variation in the proportion of all types of dementia that is contributed to Alzheimer's disease across different regions.[27] On average, two out of three demented patients are diagnosed as having Alzheimer's disease in Europe and North America,[28,29] while in Japan and China only one out of three dementia patients gets the diagnosis of dementia of the Alzheimer type.[27]

PREVALENCE

The relevance of prevalence studies of dementia lies primarily in providing data for local health services planning. Furthermore, comparison of prevalence figures of specific dementing disorders from different populations or at different times might yield etiologic clues to the diseases. In reviews of earlier studies it was recognized that the large variation in prevalence estimates across studies could be possibly due to differences in methodology.[30,31] In this review we will limit ourselves to community based studies that used currently accepted diagnostic criteria (DSM-III, DSM-III-R, NINCDS-ADRDA, or equivalent)[1-3] for the diagnosis of Alzheimer's disease. We will disregard studies that only reported the overall prevalence of Alzheimer's disease for the population above a certain age,[32-35] since these figures are strongly dependent upon the underlying age- and gender-distributions and for that reason not suitable for comparison with other studies.

Comparison of studies from Europe, the United States and Japan

Studies that presented age-specific prevalence figures for Alzheimer's disease have been conducted in Europe, the United States and Japan (tables 1, 2).

Europe. All European studies on the prevalence of dementia conducted or published after 1980 were recently collaboratively re-analyzed under the auspices of Eurodem.[28] Using a specified set of criteria developed to enhance validity and comparability, six studies[36-41] were selected that allowed the calculation of age-specific prevalence figures of Alzheimer's disease.[29] One of these studies was restricted to women.[36] Results were very similar across studies (figure 1). The overall prevalence estimates from the Eurodem re-analysis for the age groups 60 to 69 years, 70 to 79 years, and 80 to 89 years, were 0.4, 3.6 and 11.2 percent for women, and 0.3, 2.5 and 10.0 percent for men, respectively.

United States. Four studies from the United States have reported age-specific prevalence estimates for Alzheimer's disease (figure 2). The Rochester study reported figures which were similar to those from the European studies.[42] Although the Rochester study is a register-based study, the coverage of the register permits to consider it community based. The estimates from the East Baltimore study were somewhat lower.[43] The highest prevalence figures reported to date were found in the East Boston study.[44] The study conducted in California by Pfeffer et al. rated cases according to severity ranging from questionable to severe.[45] When subjects with a diagnosis of "questionable"

Table 1. Population based prevalence studies of Alzheimer's disease.

Site (reference)	Diagnostic criteria	Sample size	Institutions	Response rate (%)	Number of cases	Proportion Alzheimer's disease (%)
Europe						
Finland, total country (39)	DSM-III, NINCDS-ADRDA	8,000 (aged ≥30 years)	Included	95	67	50
Italy, Appignano (38)	DSM-III, NINCDS-ADRDA	778	Included	95	19	41
Spain, Zaragoza (41)	DSM-III, NINCDS-ADRDA	334	Included	84	13	78
Sweden, Lundby (40)	DSM-III-R	3,563	Included	Not reported	13	*
UK, Cambridge (37)	DSM-III, NINCDS-ADRDA	2,311	Included	74	174	75
United States						
East Baltimore, MD (43)	DSM-III	1,230 (aged ≥65 years)	Not included	40	12	44
East Boston, MA (44)	DSM-III-R, NINCDS-ADRDA (excluding functional impairment)	4,485	Not included	53	300	84†
California (45)	NINCDS-ADRDA	1,367	Not included	60	162 (including questionable)	87
Rochester, MN (42)	DSM-III, NINCDS-ADRDA	23,000 (aged ≥30 years)	Included	Not applicable	206 (aged ≥65 years)	72 (all ages)
Japan						
Kanagawa (47)	DSM-III	1,800	Not included	80	17	24
Miki Town (46)	DSM-III-R	3,754	Not included	Not reported	59	39

DSM-III = Diagnostic and Statistical Manual of Mental Disorders, 3rd ed; DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, 3rd ed revised; NINCDS-ADRDA = National Institute for Neurological and Communicative Disorders and Stroke, and the Alzheimer's Disease and Related Disorders Association.
* No prevalence figures for all types of dementia reported. Alzheimer's disease more frequent than multi-infarct dementia among women, vice versa among men.
† Only the relative proportion of Alzheimer's disease among moderate/severe cases was reported.

Table 2. Age-specific prevalence (%) of Alzheimer's disease.

	Age class (years)						
	60-64	65-69	70-74	75-79	80-84	85-89	≥90
Europe							
Finland, total country*	— 0.3 —		2.5	5.1	— 11.9 —		
Italy, Appignano*	— 0.6 —		— 2.0 —		— 10.2 —		
Spain, Zaragoza*		0.0	— 2.8 —		— 12.1 —		
Sweden, Lundby*	— 0.3 —		— 2.5 —		— 10.9 —		
UK, Cambridge*				2.3	8.1	15.7	28.0
United States							
East Baltimore, MD		— 0.3 —		— 3.7 —		— 8.2 —	
East Boston, MA		— 3.0 —		— 18.7 —		— 47.2 —	
California†		0.8	1.2	3.7	8.2	— 31.7 —	
Rochester, MN		0.4	1.1	3.8	7.0	— 12.7 —	
Japan							
Kanagawa		0.2	0.5	0.8	4.0	— 8.3 —	
Miki Town		0.2	0.6	1.5	3.9	— 7.1 —	

* Prevalence calculated as a weighted average from the gender-specific figures in the Eurodem reanalysis (table 4 of reference 29).

† Prevalence calculated as a weighted average from the gender-specific figures (tables 2 and 6 of reference 45), excluding questionable dementia.

dementia were excluded, the prevalence estimates from this study were very similar to the figures reported from Rochester and the European studies, except for the highest age group.

Japan. The two Japanese studies reported the lowest age-specific prevalence figures of Alzheimer's disease.[46,47] Estimates from both studies were very similar (figure 2).

The majority of studies reported a higher prevalence of Alzheimer's disease for women as compared to men.[37-39,42,43] One study found similar figures[40] while in two other studies men had a higher prevalence.[41,45] The higher prevalence among men in the Californian study was due to male excess in the number of very early cases.[45]

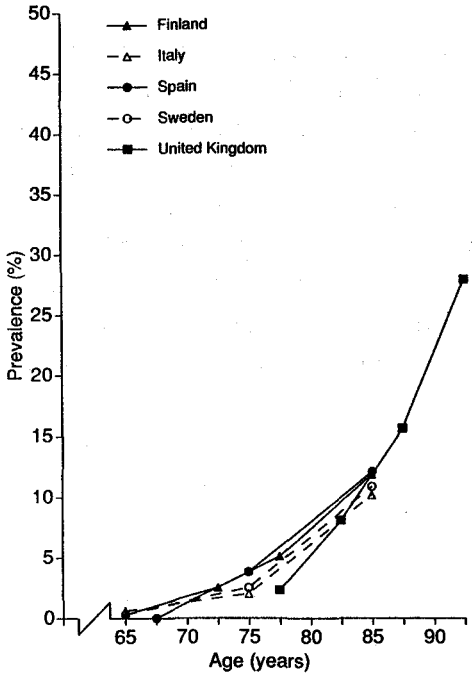

Figure 1. Comparison of age-specific prevalence of Alzheimer's disease in the EURODEM studies (37-41).

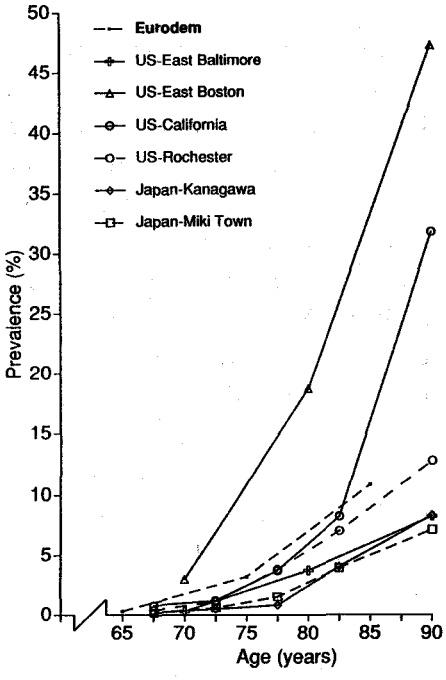

Figure 2. Comparison of age-specific prevalence of Alzheimer's disease in the EURODEM reanalysis, and the studies from the United States and Japan (29, 42-47).

Methodologic considerations

Despite the apparent similarity in diagnostic inclusion criteria across the recently reported studies, there are still important methodologic differences which hamper direct comparison of prevalence studies of Alzheimer's disease (table 1). Assessment procedures differed substantially between studies. Most surveys used a two phase design, with a cognitive screening in the first phase and in depth clinical examination in the second phase. However, various screening instruments were used, with presumably different sensitivities. Although the magnitude of the variation introduced by the use of different instruments is hard to assess, it may have been substantial.[15] Some studies included in the second stage a sample of the persons that had scored above the cut-off in the first phase to be able to correct for false-negatives, but others did not. Pfeffer et al. used a composite screening-instrument, and found that 80 percent of the persons

that were considered at least questionably demented in the end had scores above the often used cut-off point of 23/24 on the Mini Mental State Examination.[45] The thoroughness of case ascertainment also varied. Although neurologic examination and informant interview were part of the work-up in all studies, this was not the case for laboratory investigations, and neuro-imaging was performed in only a few studies.

In the studies under consideration, reported prevalence figures of Alzheimer's disease tended to increase with an increasing proportion of total dementia contributed to Alzheimer's disease (tables 1, 2). The variation in relative frequency of Alzheimer's disease was considerable across studies. Although this may be real, the possibility that it was due to different application of diagnostic criteria or varying background risk of vascular disease can not be excluded. Both Japanese studies found a predominance of vascular dementia. This is in agreement with results from earlier studies from Japan and China that fairly consistently reported a higher prevalence of vascular compared to Alzheimer's dementia.[48] Interesting in this respect is a study conducted in Shanghai, China, where participating psychiatrists were rigorously trained in the United States or by persons from the United States in the use of standard diagnostic criteria for case identification.[49] The Shanghai study reported the highest prevalence estimates of dementia to date from Japan or China. Furthermore, 64.7 percent of all dementia patients were classified as Alzheimer's disease, while only 26.8 percent were diagnosed as having vascular dementia, including mixed dementia.[49] The authors suggested that differences in application of diagnostic criteria may have contributed to the low figures of Alzheimer's disease reported from earlier surveys in Japan and China.[49]

The results from the East Boston study draw attention to differences in the interpretation and operationalization of criteria for Alzheimer's disease. In this study the diagnosis was based primarily on psychometric testing,[44,50,51] and functional impairment in everyday life was not required. Interestingly, the study by Pfeffer et al. also relied mainly on cognitive tests, and yielded more or less similar prevalence estimates when subjects with a diagnosis of "questionable" dementia were included (in percent by five years age group from 65 to 85 years, then 85 years and over: 0.8, 2.9, 11.9, 27.7, 47.3).[45] However, as mentioned above, the prevalence figures for mild to severe dementia in this study were very similar to those reported by others.[29,42,45]

The percentage of persons with Alzheimer's disease living in institutions varies widely from place to place,[52] but may exceed half of all cases with severe Alzheimer's disease.[34,39] Exclusion of institutionalized persons can therefore result in an

underestimation of prevalence rates, and this may have contributed to the relative low rates reported in the East Baltimore study and the Japanese studies.[43,46,47] All other studies included institutionalized persons, except for the East Boston and the California study.[44,45] A possible underestimation in the latter studies has possibly been outweighed by the high numbers of persons with a diagnosis of "questionable" dementia.

The reported differences in prevalence rates between men and women are difficult to interpret. Survival corrected for expectation has been reported to be worse for men than for women with Alzheimer's disease,[53-56] and this might at least partly explain the differences in prevalence between the genders.

A final issue that merits consideration is the response rate. Total sample attrition ranged from five to 60 percent among these studies. This is clearly an important source of potential bias. It is not likely that response was unaffected by cognitive status. However, it is hard to guess in what direction prevalence estimates may have been biased, because non-response can cause over- as well as underestimation.

Although all studies showed the well-known pattern of prevalence increasing with age, the actual estimates differed across studies. Part of the variation is likely to be a reflection of the small sample size in some of the studies. Several other methodologic differences may be underlying the variation, as discussed. It is remarkable that studies that were methodologically most comparable, yielded the most similar results.[29,42] This stresses the importance of the universal adaptation of comparable methods of case-ascertainment in well-defined populations for epidemiologic research on Alzheimer's disease.

INCIDENCE

Comparison of incidence rates is of etiologic interest, since these are theoretically not affected by differences in survival rates. A limited number of studies have reported age-specific incidence figures of Alzheimer's disease to date.[40,57-64] To enhance comparability, we will concentrate here on community surveys based on random or total samples of geographically defined populations.[40,59,63,64] As with the prevalence studies, we include the register based studies from Rochester,[57,58] because these can be considered community based.

Table 3. Population based incidence studies of Alzheimer's disease.

Site (reference)	Sample size	Length of study (years)	Incidence interval (years)	Free of disease	Disease onset	Non response information
Europe						
France, Bordeaux (64)*	4,134	8	2	Absence of dementia by DSM-III-R criteria	Diagnosis	General practitioner; informant
Sweden, Gothenburg (59)	652	10	5 and 4	Absence of dementia by DSM-III-R criteria	Diagnosis	Medical records searched for deceased and lost to follow up
Sweden, Lundby (40)	3,563	≥53	15	Clinical interview	Diagnosis	Medical record information
UK, Liverpool (63)*	1,070	6	3	GMS-AGECAT ≤ 2	First symptoms	Demographic information; informant
United States						
Rochester,MN 1960-1964 (58)	18,991 (aged ≥30 years)	5	Not applicable	Documented evidence of previously normal function	First symptoms	Mayo Clinic records-linkage system
Rochester,MN 1965-1974 (57)	22,976 (aged ≥30 years)	10	Not applicable	Documented evidence of previously normal function	First symptoms	Mayo Clinic records-linkage system

DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, 3rd ed revised; GMS-AGECAT = Geriatric Mental State - Automated Geriatric Examination for Computer Assisted Taxonomy.
* Ongoing study.

Comparison of studies from Europe and the United States

Four studies from Europe and two from the United States, based on the same population but covering different time-periods, reported age-specific incidence rates for Alzheimer's disease (tables 3, 4). All studies showed an exponential increase in the incidence rate with age (figure 3). Several studies found that the proportion of incident dementia patients attributable to Alzheimer's disease increased with age. In the Rochester study over the period 1965 to 1974 47 percent of all dementia patients were due to Alzheimer's disease among patients aged 60 to 69 years, 66 percent among patients aged 70 to 79 years and 80 percent among patients aged 80 years or over.[57] The data from France and the United Kingdom showed the same trend: for the age group 65 to 74 years, 75 to 85 years, and 85 years and over the proportion of Alzheimer's disease was 14, 86 and 86 percent in Bordeaux, France (J.-F. Dartigues, INSERM U330, Université de Bordeaux II, personal communication, 1991), and 50, 70 and 80 percent in Liverpool, UK (J.R.M. Copeland, University of Liverpool, personal communication, 1991), respectively.

Differences between men and women were minor within studies and inconsistent across studies. Two studies suggested that women have a greater risk for Alzheimer's disease then men,[40,57] while two other studies reported higher risks among men in most age categories.[58,59]

Table 4. Age-specific incidence of Alzheimer's disease (per 100,000 person-years).

Site	Age class (years)					
	60-64	65-69	70-74	75-79	80-84	≥85
Europe						
France, Bordeaux		— 106 —		— 868 —		3333
Sweden, Gothenburg			358	1326		
Sweden, Lundby, 1957-1972*	— 115 —		— 600 —		— 2230 —	
UK, Liverpool		— 187 —		— 824 —		2424
United States						
Rochester, MN 1960-1964	— 96 —		— 530 —		— 1432 —	
Rochester, MN, 1965-1974	— 66 —		— 409 —		— 1480 —	

* Incidence rate calculated as a weighted average from the gender-specific rates.

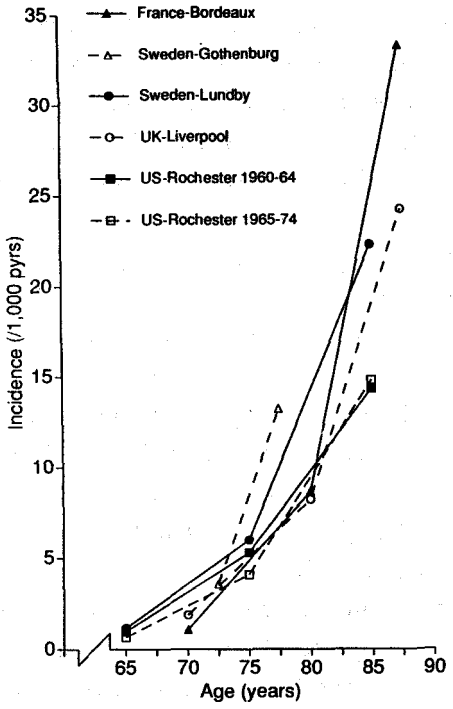

Figure 3. Comparison of age-specific incidence of Alzheimer's disease in community-based studies (41, 57-59, 63, 64).

Methodologic considerations

In addition to several of the methodologic problems already discussed under the heading of prevalence, there are some issues that pertain in particular to incidence studies.

In a cohort study there is inevitably loss to follow up. Since it can not be assumed that this occurs randomly, the intensity of follow-up and the documentation of and adjustment for non-responders, persons who died and those who withdrew from the cohort will affect the observed incidence rates. Most studies reviewed here sought medical records or information from general practitioners for deceased and lost persons (table 3).

The insidious onset of Alzheimer's disease makes it difficult to specify a specific point in time of disease occurrence. Definition of the time of disease onset influences the calculation of person-years of follow up. The length of the follow up interval can

also affect the results. Studies with an interval shorter than the longest lead time gained by the first screening will have a lower apparent rate than a study with a longer interval.[65]

The reported estimates of the incidence density of Alzheimer's disease do not permit conclusions on differences across populations that have been studied thus far. Estimates were derived from a small number of studies with a restricted geographical spread. Furthermore, some of these studies have only recently been started and follow up time is therefore limited. A new generation of incidence studies of Alzheimer's disease in Europe and North America is likely to provide us with ample data in the near future.[66]

RISK FACTORS

Methodologic issues

Given the high frequency of Alzheimer's disease, remarkably little epidemiologic research has focused on the etiology of the disease. A number of relatively small case-control studies has been performed[57,67-77] and these studies had little statistical power individually.[78] Moreover, the validity of these studies has been limited. First, all studies comprised a mixture of prevalent and incident Alzheimer patients. It is well known that, if prevalent cases are studied, selection bias may result from mortality and migration related to the disease. Second, there has been substantial opportunity for information bias in most epidemiologic studies of Alzheimer's disease, with the exception of one follow-up study[57] which was based on medical records. An important source of non-differential bias may have been the use of surrogate informants in the retrospective studies based on interviews. Differential misclassification in exposure status between cases and controls may have resulted from the possibility of recall bias, as exposures may have occurred decades before the onset of disease and informants of cases may be more willing to recollect such historical data than informants of controls. Therefore, the risk factors that emerged in the various case-control studies, as discussed below, remain to be confirmed in studies of incident cases in which the exposure status is measured before the onset of disease.

The putative risk factors of Alzheimer's disease that will be discussed are family history of dementia, Down's syndrome, Parkinson's disease, parental age, head trauma, medical history, smoking, aluminum and education. Many of these risk factors have

Table 5. Risk factors for Alzheimer's disease. Results from the Eurodem reanalysis on case-control studies of Alzheimer's disease.

Risk factor	Definition of exposure	Studies included (reference)	RR*	95% CI	Exposure frequency	
					cases	controls
Family history of dementia	Dementia of any kind in at least one first degree relative	68, 70-75	3.5†	2.6 - 4.6	305/814	140/894
Family history of Parkinson's disease	Parkinson's disease in at least one first degree relative	70, 73	2.4†	1.0 - 5.8	20/312	8/294
Family history of Down's syndrome	Down's syndrome/mental retardation in at least one first degree relative	68, 70, 71, 73, 75	2.7†	1.2 - 5.7	20/588	7/615
Head trauma	Head trauma with loss of consciousness ≥1 year before onset of Alzheimer's disease	57, 69-71, 73-75	1.8‡	1.3 - 2.7	87/1059	50/1059
Hypothyroidism	History of hypothyroidism ≥1 year before onset of Alzheimer's disease	57, 72, 75	2.3	1.0 - 5.4	17/655	8/732
Depression	Medically-treated depression that occurred ≥1 year before onset of Alzheimer's disease	57, 69, 72, 75	1.8	1.2 - 2.9	55/743	34/818
Smoking	Ever smoked	68-75	0.8	0.6 - 1.0	477/899	563/955

RR = relative risk; 95% CI = 95% confidence interval.
* Estimated using conditional logistic regression analysis, taking into account matching on age and gender.
† Adjusted for number of siblings.
‡ Adjusted for family history of dementia, education and alcohol consumption.

recently been collaboratively re-analyzed by the Eurodem Risk Factors Research Group.[79] The main overall results of this re-analysis are presented in table 5.

Family history of dementia

Although the cause of Alzheimer's disease is still unknown, genetic factors seem to play an important role in its etiology.[80-84] Together with age, a positive family history of dementia is one of the few established risk factors for Alzheimer's disease.[27] In a number of families the disease is apparently inherited as an autosomal dominant disorder.[81] Some studies of the genetics of the disease have suggested that all cases of Alzheimer's disease may be due to autosomal dominant inheritance.[80,85-88] Other studies have suggested a more complex mechanism, in which genetic as well as environmental factors may be implicated.[81,89-91] There is some evidence from genetic studies that the strength of familial aggregation of Alzheimer's disease may vary with age of onset and that familial aggregation may be specific to early-onset Alzheimer's disease.[71,92-96] However, modification of the association between Alzheimer's disease and family history of dementia by onset age was not observed in other studies.[97-99]

Family history of dementia has been studied in a variety of case-control studies.[67,68,70-77] Nine out of 10 studies reported a significantly higher risk of Alzheimer's disease for relatives of patients with dementia. The only study that failed to show an association was of late-onset Alzheimer's disease.[71] A re-analysis of all formal case-control studies of Alzheimer's disease[68,70-75] showed an association between family history of dementia and early-onset as well as late-onset Alzheimer's disease (table 5).[100] Although the risk decreased with increasing onset age, among patients with an onset of disease after 80 years there were significantly more subjects with one or more first degree relatives with dementia as compared to controls[100]

Down's syndrome

There is much evidence for a link between Alzheimer's disease and Down's syndrome. The Alzheimer type neuropathologic changes occur in patients with Down's syndrome,[101-103] and Down's syndrome may be considered a risk factor for Alzheimer's disease.[27] In addition, family history of Down's syndrome has been associated with Alzheimer's disease, suggesting a genetic link between these disorders. Family history of Down's syndrome has been studied in 10 studies.[68,70,71,75,85,86,92,96,99,104] Although seven studies observed more patients with a positive family history of Down's syndrome as compared to controls,[68,70,71,75,92,96,99] a significant association was established in only three studies.[68,75,92] It can be argued that the negative findings of the other studies may be explained by the low rate of occurrence of Down's syndrome (1 in 700 in the general population). A significant increase in risk of Alzheimer's disease for those with a first degree relative with Down's syndrome was shown in a re-analysis of case-control studies (table 5).[68,70,71,73,75,100] A genetic link between Alzheimer's disease and Down's syndrome will predict that familial aggregation of Alzheimer's disease with Down's syndrome is found in familial cases specifically. Indeed, the risk of Alzheimer's disease for those with a family history of Down's syndrome tended to be higher for those with a positive family history of dementia when pooling the data of all case-control studies.[100] However, familial aggregation of Down's syndrome and Alzheimer's disease was observed also in the absence of a first degree relative with dementia.[100]

Parkinson's disease

Alzheimer's disease and Parkinson's disease share several neuropathologic characteristics.[105] Lewy bodies, one of the hallmarks of Parkinson's disease, are frequently observed in Alzheimer's disease, while the Alzheimer type pathology is

found more often in patients with advanced idiopathic Parkinson's disease than in the general population.[105,106] These findings have led to the hypothesis that Alzheimer's disease and Parkinson's disease may have a common etiology.[107] Two case-control studies of Alzheimer's disease have investigated family history of Parkinson's disease.[70,73] In both studies there were more Alzheimer patients with a first degree relative with Parkinson's disease as compared to age- and sex-matched population controls (table 5). In the largest study a significant association to family history of Parkinson's disease was observed.[73] These findings support the view that Alzheimer's disease and Parkinson's disease may have a common pathogenesis, which is perhaps genetically determined.

Parental age

The role of parental age in Alzheimer's disease is subject to debate. To date, 13 studies have reported on this issue yielding contradicting results.[70,104,108-118] Five studies have reported a significant association to late maternal age,[70,104,108,114,118] while two studies reported a significant increase in risk for young maternal age as well as young paternal age.[112,117] Of the latter studies, the most recent one showed that the association with young maternal age disappeared when adjusting for paternal age, while the association with paternal age was specific for late-onset Alzheimer's disease.[117] As a corollary of these contradicting findings, there are two competing hypotheses on the underlying mechanism. For late maternal age, the association has been explained by the link with Down's syndrome. This hypothesis predicts that the risk of Alzheimer's disease follows the risk of Down's syndrome, which increases slowly with increasing maternal age until age 30 years and rapidly thereafter.[118] According to the second hypothesis, the association of late-onset Alzheimer's disease with young paternal age may be explained by genetic imprinting, i.e., patients have inherited an increased predisposition to the disease through a particular parent.[117] These two potential mechanisms may outbalance each other and therefore it is conceivable that their effects can only be shown at both extremes of the parental age distribution, which in most studies comprised only a limited number of subjects.

Head trauma

Repeated head trauma in boxers has been linked to dementia pugilistica (punch drunk syndrome).[119] In patients with this syndrome neurofibrillary tangles, indistinguishable from those seen in Alzheimer's disease, are found.[120] These findings have led to the hypothesis that head trauma may be implicated in Alzheimer's disease.

In four case-control studies a significant increase in risk of Alzheimer's disease was observed for those with a history of head trauma.[68,77,121,122] With the exception of two small studies,[67,76] each of the case-control studies reported an excess of head trauma in patients with Alzheimer's disease, although no significant association could be established.[69-72,75,123-125] Pooling of the data from all formal case-control studies of head trauma with loss of consciousness[69-71,75,121-123,125] showed a significant association (table 5).[126] Although the association was strongest for head trauma that occurred within 10 years before disease onset, a significant elevation in risk was also observed for head trauma that occurred more than 10 years before the onset of disease.[126] In this re-analysis the association between Alzheimer's disease and head trauma could only be established in men.[126]

Despite the apparently consistent findings of epidemiologic studies, there are some reasons to challenge the interpretation of a causal relationship. The only prospective follow-up study based on data obtained from medical records of the Rochester register[123] showed only a slight non-significant elevation in risk. In case-control studies, there is considerable scope for recall bias for events that occurred long before the disease onset. For head trauma occurring close to the disease onset, we can not exclude the possibility that the head trauma may be a consequence of an early stage of the dementia. Finally, there is as yet no biologic explanation for the effect modification by gender.

Medical history

A great variety of disorders has been linked with Alzheimer's disease, but many of these associations appeared in one or two studies and were not replicated in others.[127] Caution is warranted when interpreting these studies since exposures were usually rare and the precision in assessing the disease history or previous treatment was generally low.

There is some evidence for an association between Alzheimer's disease and history of thyroid disease. In the Rochester study,[57] an increase in risk was observed for history of hypothyroidism, albeit non-significant. However, exposure frequency was low in cases and controls. When re-analyzing the data of all formal case-control studies,[57,72,75] a significant association could be shown (table 5).[127] Although the association between Alzheimer's disease and hypothyroidism may be of interest because of the direct and indirect role of the thyroid hormone on the nervous system,[127-130] there are several arguments pleading for cautious interpretation: 1) earlier studies yielded contradicting results; 2) the classification for type of thyroid disorder may be criticized because

it was based on functional status as reported by informants, who, with the exception of the Rochester study, were not medically trained; 3) although an association could be shown with hypothyroidism, from a statistical point of view scepticism on this relationship results from the lack of an association with all thyroid diseases combined; and 4) hypothyroidism can be a cause of secondary dementia and cases may not have been recognized as such.[127]

In a re-analysis of case-control studies[57,69,72,75] history of medically-treated depression emerged as a risk factor for Alzheimer's disease, in particular for the late-onset form (table 5).[131] There were two findings that overruled concern of bias with regard to this relationship. First, the association was present in the Rochester follow-up study.[57] Since this study was based on medical records, there was no recall bias. Second, a significant association was observed for episodes of depression that occurred more than 10 years before the disease onset, suggesting a causal relationship rather than the depression being an early symptom of Alzheimer's disease. There are several possible explanations for an association between history of depression and Alzheimer's disease.[131] First, anti-depressant treatment may alter neurotransmitter functioning. Another explanation may be a joint etiology of both disorders, i.e., systems disrupted in depression may also be involved in Alzheimer's disease. It is also conceivable that, as patients with depression may already have subtle cognitive deficits, they may reach more quickly the threshold for the diagnosis of Alzheimer's disease.

Smoking

There is some evidence from clinical trials that nicotine may improve information processing and attention in Alzheimer patients and this would predict a protective effect of smoking for Alzheimer's disease.[132,133] The mechanism underlying this association may be related to the decreased nicotinic receptor binding, which has been linked to the Alzheimer type pathology.[134,135] Nicotine has been reported to increase the density of nicotinic receptors in the brain.[136] It has been suggested that nicotine from cigarette smoke may compensate the loss of nicotinic receptors in Alzheimer's disease and may thus delay the progression of Alzheimer's disease.[137] Indirectly, this hypothesis derives support from the fact that a decrease in nicotinic receptor binding has also been observed in patients with Parkinson's disease, while the majority of studies of Parkinson's disease have reported a protective effect of smoking.[138]

Epidemiologic studies of the association between Alzheimer's disease and smoking have yielded equivocal results.[69-72,75,76,137,139-144] In two studies, a significant positive association between smoking and Alzheimer's disease was reported,[72,143] but in four studies a significant inverse relationship was suggested.[76,137,139,142] Pooling of the data of all formal case-control studies,[68-72,74,75,137] however, resulted in a significant inverse association (table 5).[144] An inverse relationship between smoking and Alzheimer's disease could only be shown among patients with a positive family history of dementia in the Dutch case-control study[137] and in the re-analysis of case-control studies,[144] suggesting that smoking may interact with a genetically determined process. The main problem in the interpretation of these finding is that all studies were based on a mixture of prevalent and incident cases. Thus, it cannot be excluded that selection bias has occurred due to smoking related mortality and the findings remain to be confirmed in a follow-up study.

Aluminum

Aluminumsilicates are found in the cores of senile plaques and in neurons containing neurofibrillary tangles.[145] However, it remains to be established if the presence of aluminum is a cause, a consequence, or an epiphenomenon of the disease. Case reports of subjects exposed to high doses of aluminum leading to high concentrations in the brain suggest that the exposure does not lead to pathologic changes specific for Alzheimer's disease.[146-148] Yet, several studies reported an association between aluminum intake through drinking water and the risk of Alzheimer's disease, despite the fact that water contributes only a small percentage of aluminum intake.[149-151] However, there is considerable scope for bias in these observational studies. In the earliest study, dementia was assessed by death certificates,[149] a method that has been shown to be unreliable.[152,153] The study by Martyn et al. can be criticized because the diagnosis of Alzheimer's disease was based on CT-scan readings without clinical examination of the patients.[150] Furthermore, the association was mainly due to an increase in risk for the highest exposure category, without showing convincing evidence for a dose-response relationship. Finally, the findings of a relationship in the most recent study could not be replicated after re-measurement of the aluminum content of the drinking water.[151]

A role of aluminum in Alzheimer's disease was supported by the finding of a higher risk of Alzheimer's disease for miners who were treated with aluminum powder, albeit that the diagnosis was based on informant reports and was not clinically confirmed

for all cases.[154] Also, a case-control study based on informant interviews reported an increase in risk of Alzheimer's disease for subjects using aluminum containing antiperspirants.[155] On the other hand three case-control studies that investigated the role of aluminum containing antacids failed to show an association.[68,70,75] One can therefore not escape the conclusion that the etiologic significance of these findings remains to be proven.

Education

Education has been linked to cognitive decline and dementia in several studies.[27,49,156] However, the interpretation of these findings has been hampered by the possibility of assessment bias.[27,156] When the ascertainment of patients is accomplished through screening for cognitive impairment, an association with education may result from the fact that the scores of those screening tests may in part be determined by the subject's level of education. To date, only one study, conducted in Shanghai, China, showed an association between education and Alzheimer's disease specifically.[49] The interpretation of this finding is not straightforward as education-dependent cut-off points for the screening instrument were used.

Education may be related to Alzheimer's disease through several mechanisms.[27] It is conceivable that highly educated subjects have greater cognitive or neuronal reserves than poorly educated subjects and therefore can lose more neurons due to Alzheimer's disease before showing symptoms of the disease. It is also possible that the highly educated practice their cognitive skills more intensively during their lives than those with a low education and it has been suggested that lack of intellectual stimulation may lead to an increased risk of neuronal loss and Alzheimer's disease.[157] Another possibility is that low education may merely be related to socioeconomic status and that lifestyle and occupational exposures may be underlying an association with Alzheimer's disease.

Interaction between genetic and environmental risk factors

Little is known about the interaction between genetic and environmental risk factors for Alzheimer's disease. Several models can be hypothesized that describe the relationships between genetic and environmental effects.[158] Genetic factors and environmental risk factors may increase the risk of Alzheimer's disease independently.[158] It is also conceivable that a genetic factor exacerbates the effect of an environmental risk factor (or vice versa), or that the presence of both a genetic and an environmental

risk factor are required to increase the risk of disease.[158] In the Eurodem re-analysis of case-control studies, the interaction among genetic and other putative risk factors was studied using family history of dementia in first degree relatives as an indicator for genetic susceptibility.[79,159] Seven case-control studies had examined family history of dementia and other risk factors for Alzheimer's disease.[68,70-75] For family history of Down's syndrome and Parkinson's disease, late maternal age, history of head trauma and history of depression, an association with Alzheimer's disease was observed regardless of the presence or absence of a first degree relative with dementia.[159] Family history of dementia remained strongly associated with Alzheimer's disease in the absence of these other risk factors.[159] These findings suggest that genetic and environmental risk factors may independently increase the risk for Alzheimer's disease. As to the interaction between history of cigarette smoking and family history of dementia, an inverse association between Alzheimer's disease and smoking was only found in subjects with a positive family history of dementia. The risk for family history of dementia tended to be lower in smokers as compared to non-smokers. This effect was most pronounced in subjects with two or more affected relatives, suggesting that smoking may interact specifically with a genetically determined process.[159]

PROGNOSIS

Survival

There is much evidence for reduced life expectancy of patients with Alzheimer's disease as compared to the life expectancy in the general population.[57,60,160-162] Studies based on hospital-based case-series or on prevalent cases are difficult to interpret as there may have been large differences in study populations, in particular in severity of disease. Two studies were based on incident population-based cases, even though in both investigations the case-series were register-based.[57,60] Treves et al. studied survival in 71 patients with early-onset Alzheimer's disease (onset before the age of 60 years).[60] Patients were derived from the Israeli National Neurologic Disease Register. Survival was significantly reduced as compared to the expected survival in the general population of Israel, when adjusted for age and gender. The median survival in the cases with early-onset Alzheimer's disease was 8.1 years.[60] Kokmen et al. studied survival in Alzheimer patients derived from the Rochester register.[57] In this study of 296 Alzheimer patients with primarily late-onset of disease there was

evidence for reduced survival after the diagnosis of disease, as compared to the expected survival. The median survival was 6 years in men and 5 years in women. In these studies, survival from the moment of diagnosis or hospitalization was studied. Although these data may be of interest for health care planning, survival from the age of onset would give more insight in the course of the disease. Such studies have not been conducted to date on a community basis.

Up to now, no specific treatment is available that can positively alter the clinical course of Alzheimer's disease. Advances in understanding the pathophysiology of Alzheimer's disease may eventually lead to interventions that slow the progression of Alzheimer's disease, as will be discussed hereafter. The most common cause of death in patients with Alzheimer's disease are respiratory disease[163] and bronchopneumonia.[160] It has been argued that survival in dementia has increased due to improvement of treatment of infections.[164] There is some evidence for an improvement in prognosis in the Lundby study, a population-based study of incidence of dementing disorders that covered the period from 1947-1972.[40,162] Survival was worse in the period until 1962 when compared to survival thereafter, however, the difference was not significant.

Predictors of survival

There is a wide variation in the number of years of survival following a diagnosis of Alzheimer's disease. As expected, the prognosis is associated with the severity of the dementia at diagnosis.[161,162] Better survival has been reported for women with Alzheimer's disease as compared to men, when adjusted for the higher mortality among men in the general population.[53-56] The gender difference in survival may explain the predominance of women among prevalent cases with Alzheimer's disease that has been observed in a number of studies. It has been suggested that patients with early-onset Alzheimer's disease have a worse prognosis than patients with a late-onset of disease.[165] Again, these figures are to be adjusted for differences in life expectancy. Although crude survival rates suggest a worse survival in late-onset Alzheimer's disease,[53,55,60,166] the figures that are adjusted for age-related differences in life-expectancy show a worse survival in early-onset Alzheimer's disease.[54,55,166,167] To date, there is no evidence for ethnic differences in survival.[60] A number of clinical features, i.e., extrapyramidal signs, aphasia, psychosis, seizures and tremors, have been associated with a poor prognosis.[166,168]

INTERVENTION

There is a clear need for treatment of the symptoms related to Alzheimer's disease. However, the poor understanding of the pathogenetic mechanisms involved in the disease have impeded the development of effective treatment. Endeavors to develop therapies for Alzheimer's disease have largely focused on alleviation of symptoms by neurotransmitter substitution or by stimulation of neuronal metabolism. Recent advancements in molecular neuroscience have generated several hypotheses about mechanisms of neuronal death. Although at this stage these hypotheses remain highly speculative, they lead one to expect that specific interventions, that can modify the natural history of the disease by directly approaching the causative abnormality, may become available in the foreseeable future. We will briefly review palliative therapeutic strategies and then delineate the areas of current research that hold promise for potentially causal therapies.

Symptomatic therapy

Acetylcholine. The most widely employed strategy to symptomatic treatment of Alzheimer's disease dementia is the replacement of neurotransmitters found to be deficient in clinical and neuropathologic examinations. In the last decade, the cholinergic hypothesis of cognitive functioning in Alzheimer's disease has attracted most attention in the attempt to improve symptoms. This hypothesis is based on the consistent finding that cholinergic projections from the nucleus basalis of Meynert and other brain stem nuclei are lost and that this deficiency appears to be related to cognitive decline.[169] Three conceptually different approaches are used to improve cholinergic function: metabolic precursor therapy to stimulate acetylcholine synthesis,[170,171] inhibition of the enzyme acetylcholinesterase that metabolizes acetylcholine,[172-178] and receptor agonists to directly stimulate postsynaptic cholinergic receptors.[179-181] None of these strategies has shown to convert symptomatic benefit to Alzheimer patients.

Monoamines. Deficiencies in noradrenergic, serotonergic, and possibly dopaminergic central indices have been documented in Alzheimer's disease.[182] Although noradrenalin and serotonin have a well established role in memory and learning in preclinical studies, their relation to cognitive functions in Alzheimer's disease is less clear. Therapy with the antihypertensive drug clonidine, an alpha-2 adrenergic receptor agonist, yielded no improvement in a trial with Alzheimer's disease patients.[183] Serotonergic therapy, through blockade of synaptic uptake has no effect on cognitive functions or mood.[184,185]

Adverse effects were even reported for a serotonergic receptor agonist.[186] Replacement with L-dopa has no effect on Alzheimer's disease symptoms,[187] but short-term treatment with deprenyl (selegeline), a selective inhibitor of monoamine oxidase-B, showed some improvement in memory and attention.[188,189]

Neuropeptides. Changes in several central neuropeptides have been reported in Alzheimer's disease.[190,191] These neuropeptides have been implicated in learning and memory in preclinical models of dementia. Treatment with various neuropeptides, including synthetic vasopressin related peptides,[192] adrenocorticotropin-related compounds[193] and a synthetic somatostatin analogon[194] were not successful. Endorphins and enkephalins may have a deleterious effect on memory functions, but trials with opiate antagonists were without clinical benefit.[195,196]

Metabolic enhancers. In clinical dementia trials a multitude of efforts has been directed towards the evaluation of metabolic enhancers, compounds with mostly unknown mechanisms of action that are believed to stimulate neuronal metabolism. Dihydroergotoxine (hydergine), for example, has been widely investigated but without consistent positive results. Indeed, a recent study concluded that hydergine is ineffective for the treatment of Alzheimer's disease.[197] Nootropics are a group of psychotropic drugs of which piracetam was first discovered as derivative of gamma-aminobutyric acid. In animal models for dementia these drugs are effective in the reversal of amnesia induced by scopolamine or hypoxia. Although piracetam enhances cerebral metabolism in Alzheimer's disease patients,[198] the therapeutic effect is minimal[199] or absent.[200] The same disappointing results were found with other nootropics.[201,202]

New areas of intervention research

There are several new areas of intervention research that are based on recent pathophysiologic insights. We will briefly mention four of these research fields: amyloid deposition, excitotoxic mediated neurotoxicity, oxidative stress and growth factors.

Amyloid metabolism. The inhibition of abnormal protein deposition in the brains of Alzheimer's disease patients as a potentially therapeutic strategy is currently under study. It remains unknown whether the formation of neurofibrillary tangles and senile plaques arises as a consequence of a primary degenerative process, or as a byproduct of some other underlying mechanism of the disease. In the senile plaques the β-amyloid protein is found, which is probably released through abnormal cleavage by protease activity from the amyloid precursor protein. One of the proteins found in the intracellular accumulated neurofibrillary tangles is tau.[203] Abnormal phosphorylation

of tau may contribute to the formation of neurofibrillary tangles, but the precise mechanisms remain elusive. Further biochemical understanding of the complex cascade of events leading to senile plaques and neurofibrillary tangles may yield specific intervention strategies in the future.

Excitotoxin hypothesis. Excitotoxic amino-acids including glutamate and aspartate are neurotransmitters of pyramidal neurons in cerebral cortex and hippocampus and have a function in learning and memory.[204] These neurons are specifically involved in the neuropathology of Alzheimer's disease and form neurofibrillary tangles.[205] Excitotoxic amino-acids can act as neurotoxins by overactivation of postsynaptic glutamergic receptors and it is hypothesized that this process plays a role in the neurodegeneration in Alzheimer's disease.[206] Some evidence that excitatory amino acid antagonists may offer neuroprotection is derived from the ability of these drugs to inhibit neuronal death resulting from ischemia or hypoglycemia.[207] Several antagonists are available now but these agents have limited clinical use because of their potential toxicity.

Oxidative stress. Under normal conditions the cell produces free oxy-radicals, superoxides and peroxides. Several scavenger systems including superoxide dismutase act to protect against their potential toxicity. A defect in these scavenger systems or an intracerebral excess of oxy-radicals may result in cell membrane damage. The hypothesis that oxidative stress plays a role in the neuronal degeneration of Alzheimer's disease is currently under evaluation by the long-term administration of deprenyl.[208] Several other compounds that could afford neuroprotection according to this mechanism are being developed.

Growth factors. Neurotrophic factors have a function in neuronal regeneration and survival, and several studies suggested that nerve growth factor has a trophic function for cholinergic neurons in the basal forebrain.[209-211] Administration of nerve growth factor in an early phase of Alzheimer's disease could possibly prevent neuronal cell loss.[212] Other growth stimulating compounds are currently investigated but without definitive results.[213]

CONCLUSION

Alzheimer's disease is the most important cause of dementia. It is emerging as a major problem, for the patients and their families, as well as in terms of public

health. We have reviewed the main epidemiologic findings of Alzheimer's disease concerning its frequency, risk factors, prognosis and treatment.

In most recent epidemiologic studies the diagnosis of Alzheimer's disease has been based on sets of criteria like those of DSM-III, DSM-III-R and NINCDS-ADRDA. It remains essentially a clinical diagnosis, in the majority of population studies arrived at through a multi-stage approach.

Prevalence estimates of Alzheimer's disease rise exponentially with age. Typical estimates are about 0.5 percent in those aged 65 years, 3 percent in those aged 75 years, and 10 percent in those aged 85 years. On the basis of currently available figures there is little evidence to suggest that other than methodologic factors contribute importantly to the variation in Alzheimer prevalence. This applies to incidence estimates as well. A recent generation of incidence studies has been initiated and the evidence of these studies combined with earlier ones suggest until now relatively similar incidence rates of Alzheimer's disease across populations.

Risk factors for Alzheimer's disease have been investigated in a number of generally small case-control studies. Recently all formal case-control studies have been re-analyzed collaboratively and except for age and a positive family history of dementia no definite risk factors for Alzheimer's disease have been established as yet. There is, however, interesting evidence to suggest that a positive family history of Parkinson's disease or Down's syndrome, a history of depression, severe head trauma and smoking may be associated with Alzheimer's disease.

There is general agreement that the prognosis of Alzheimer patients in terms of life expectancy is compromised, although there is a wide variation in survival time among patients. Survival is worse in early-onset cases and in men, and it appears to be related to the initial severity of the disease. Improvement of prognosis through intervention has been unsuccessful until now. This applies to both symptomatic and potentially causal treatment.

New epidemiologic approaches to Alzheimer's disease will focus on studies of the incidence of the condition in prospective follow-up studies that have recently been initiated in Europe and North-America. These investigations will enable nested case-control studies of risk factors, and they are likely to emphasize gene-environment interaction in the etiology of Alzheimer's disease. As to prevention and treatment of the disease, new pathophysiologic leads in concert with epidemiologic evidence will in the near future hopefully result in improvement in the prognosis of Alzheimer patients.

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Chapter 3

Cognitive function

in the general elderly population

Chapter 3.1

A community-based study of dementia: The Rotterdam Study

The Rotterdam Study is a community-based prospective follow-up study, conducted by the department of Epidemiology and Biostatistics of Erasmus University Medical School, Rotterdam, The Netherlands. The general objective of the study is to investigate prevalence, incidence and determinants of diseases in the elderly in order to detect preventable causes of these illnesses. In addition, specific intervention studies are conducted. The four main fields of interest in which specific research projects are being performed are: neurogeriatric disorders, cardiovascular diseases, loco-motor diseases and ophthalmologic diseases. The research questions in neurogeriatrics relate to dementia, in particular Alzheimer's disease and vascular dementia, Parkinson's disease and epilepsy.

STUDY DESIGN

All participants in the Rotterdam Study will undergo at least two examinations. At enrollment health status is ascertained and baseline data are collected. This cross-sectional survey will yield prevalence estimates of the disorders of interest. In the second survey 3 years after the initial examination, all participants are re-examined using identical procedures. Endpoints in the study are cause-specific mortality, incident morbidity, and changes in determinants taking place during the follow-up interval. Moreover, the study base offers the possibility to conduct nested case-control studies to investigate determinants of various disorders.

Study cohort

The study area is Ommoord, a city district located in the north eastern part of Rotterdam with a total population of almost 30,000. This area has a relatively stable population, with few people moving out or into the area. Over 90% of the population is cared for by 12 GPs, who are supportive of the study and willing to collaborate. The study population is a fixed cohort defined by all inhabitants aged 55 years and

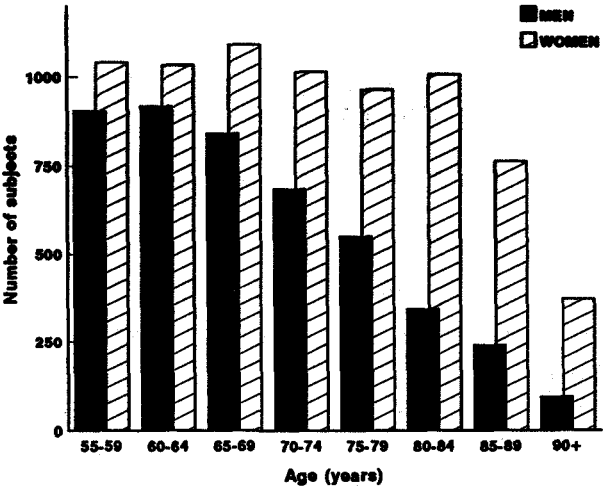

Figure 1. The age and gender distribution of the study population.

over who have lived for at least 1 year in the district at prevalence day, and who agree to participate. During the first survey, prevalence dates will shift every 6 months. Potential participants are invited in random clusters. Names and addresses are drawn from the municipal register which is reliable, complete and kept up to date weekly. The age and gender distribution of the study population is given in figure 1. The total number of eligible persons amounts to 11,850. This number is sufficient to study the incidence and determinants of the disorders of interest. As there are several homes for the elderly and one nursing home in this district, institutionalized persons will be included, constituting 11% of the study population. The percentage of institutionalized persons increases sharply with age, from 0% for those aged 55 to 59 years, to almost 80% for those over 90 years of age. For all age categories the percentage of women that are institutionalized is higher than that of men.

General examination schedule

In the cross sectional study a two stage design is used. Potential participants are informed by letter about the study before they are contacted in person. In the first stage the participants are visited at their home by trained research assistants who, after informed consent is obtained, conduct a computerized interview that takes about 1½ hour to administer. The issues that are covered in the questionnaire are listed in table 1. At the end of the interview an appointment is made with the subject to visit the research centre for the second stage of the study. At this field centre, which

Table 1. Information collected in home interview.

Medical history	Level of education
Current medical status	Occupation history
Cognitive screening test	Full pedigree information first degree relatives
Screening Parkinson's disease	Family history of specified disorders
Medication (prescriptions, actual use)	Instrumental activities of daily living
Socio-economic status	

is located centrally in the district, all study participants undergo an extensive set of investigations, ranging from simple anthropometry and blood pressure recordings, to more sophisticated examinations as bone densitometry and duplex scanning of the carotid arteries. The examination is split in two parts and applied in two successive weeks directly following the interview at home. This offers the opportunity to integrate part of the clinical workup that is needed for subjects that are selected on the basis of various screening procedures, with the core survey.

Non-responders

In the prevalence phase of the study information regarding age, gender and marital status of non-responders is available from the municipal register. All non-responders are asked about their reason for refusal, and consent is requested to obtain medical information from their general practitioner.

For the prospective study the same sources of information are used to keep track of subjects that otherwise might become lost to follow-up. The municipal register records all deaths and changes of address and passes the mutations. All collaborating general practitioners have automated practices and notify all mortality and intermediate morbidity of interest directly to the study.

Time schedule

From June to November 1989 a pilot study was conducted. In January 1990 the actual study was initiated, but full participant recruitment and complete data acquisition started in June 1990. The cross-sectional survey will take 3 years and will be directly followed by the second survey. First incidence figures are to be expected by the end of 1993.

Casefinding and diagnostic procedures for dementia

The screening for dementia follows the general design as outlined. Included in the home interview are cognitive screening tests, namely the Mini Mental State Examination (MMSE) and questions required to reach a Geriatric Mental Schedule (GMS) organic level score using the AGECAT algorithm.[1,2] Following EURODEM recommendations those who score positive on either or both of these tests, using the cut-off of 25/26 for the MMSE and 0/1 for the GMS, are defined screen-positive.[3] In addition to the routine examinations, screenpositives are seen during their first visit to the field centre by a trained physician who will administer the second phase of the dementia screening, consisting of a structured psychiatric diagnostic interview (CAMDEX), and more extensive neuropsychological testing (CAMCOG).[4] This physician also conducts an interview with an informant. The physician classifies the subject as 'not demented' or 'suspected of dementia' using DSM-III-R criteria[5] irrespective of the score on the CAMCOG. In addition the presence of depressive symptomatology is assessed using the Hamilton Depression Rating Scale.[6] All subjects that have a score below 80 on the CAMCOG, as well as subjects with a score of 80 or higher on the CAMCOG but who were labeled as 'suspected of dementia', are examined by a neurologist during their second visit to the research centre. The neurologist administers the Short Blessed Test[7] and carries out a complete neurological examination. Presence and severity of extrapyramidal symptoms is recorded separately using the

Table 2. Neuropsychological testbattery.

Intelligence	Groninger Intelligence Test
Attention	Digit Span
	Word Fluency
Memory	River Mead
	Word List Learning
	Biber Figure
Language	Modified Boston Naming Test
Construction	Circle, parallelogram, overlapping rectangles, cube, clock face
Visuo spatial	Line orientation
Reasoning, planning, sequencing	Stroop
	Trail Making Test

motor examination part of the Unified Parkinson's Disease Rating Scale.[8] Based on all information available and using DSM-III-R criteria the neurologist assesses whether a dementia syndrome is present. All subjects with a dementia syndrome are referred to the university clinic for neuroimaging (MRI and SPECT) and neuropsychological testing (table 2). Other subjects are also referred in case of doubt. The final diagnosis is made by a diagnostic panel consisting of the neurologist, the neuropsychologist and two physicians of the Rotterdam Study. This panel reviews the diagnosis of dementia syndrome using DSM-III-R criteria, and makes a subdiagnosis. Alzheimer's disease is diagnosed using DSM-III-R criteria as well as NINCDS-ADRDA criteria.[9] For the diagnosis of multi-infarct dementia DSM-III-R criteria are used which permit the consideration of neuroimaging information. For all subjects an Ischemic Score

Table 3. Interview derived information for the study of risk factors for dementia.

FAMILY HISTORY
Full pedigree information 1st degree relatives
Family history of dementia, Parkinson's disease, Down's syndrome, epilepsy, stroke, psychiatric history
MEDICAL HISTORY
Vascular determinants
Hypertension, angina, intermittent claudication, myocardial infarction, diabetes, stroke, TIA
Head trauma with loss of consciousness
Thyroid disease
Psychiatric history
Epilepsy
Parkinson's disease
Migraine
SOCIO-ECONOMIC STATUS
Family income
Education
TOXICOLOGICAL/DIETARY DETERMINANTS
Occupational exposures
Smoking habits
Alcohol consumption
Food frequency questionnaire
INSTRUMENTAL ACTIVITIES OF DAILY LIVING

Table 4. Investigations at research centre relevant to the investigation of risk factors for cognitive decline and dementia.

Blood pressure	Glucose tolerance test
ECG	Neurologic examination
Doppler peripheral arteries	Laboratory tests
Duplex scanning carotid arteries	Storage of serum and cells

according to Hachinski is calculated.[10] Severity is rated on both the Clinical Dementia Rating Scale[11] and the Global Deterioration Scale.[12]

Assessment of risk factors for dementia

Risk factors for dementia are assessed both by interview and by clinical measurements. Branching questionnaires are used to assess determinants for which subject given information is required. Most of this information is obtained in the home interview. For medical conditions that can not be reliably assessed by medically naive interviewers only highly sensitive questions are included in the home interview. If answered positively, a physician will take a more detailed history during the first visit to the research centre. Possibly delicate topics such as previous psychiatric history are only investigated by the physician. The most important risk factors that are evaluated by interview are summarized in table 3. The clinical measurements at baseline are mainly of interest to study the relation of cardiovascular determinants with cognitive decline and dementia (table 4).

FIRST RESULTS

From June until November 1989 a pilot study was conducted. Examinations were completed for 222 independently living persons aged 65 and over, as well as for 150 persons residing in an elderly home. The response rate was 80% for the home interview, while the overall response was 75%. To obtain age specific estimates of the prevalence of dementia the number of cases per number of screened subjects was recalculated to reflect the distribution of institutionalised persons in the population. The prevalence estimates of total dementia for the age groups 65 to 74 years, 75 to 84 years and 85 years and over, were 1.5%, 6.9% and 40.8%, respectively. Results of this pilot study

were contributed to the EURODEM Prevalence study, a pooled analysis of estimates of the prevalence of dementia in several European countries.[13]

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Chapter 3.2

Cardiovascular disease and the distribution of cognitive function in an elderly population

The frequency and severity of cognitive impairment and dementia strongly increase with age. Dementia is often labelled an age-related disorder, with the implicit suggestion that the decline in cognitive function may be intrinsic to aging itself. However, many aged individuals show no mental decline at all.[1] And in those instances where cognitive decline does occur, in general it develops insidiously and asymptomatically before it reaches the clinical threshold at which it becomes manifest and is referred to as dementia. The division of populations into diseased versus normal tends to neglect this heterogeneity.[2,3] It has therefore been suggested that research in degenerative disorders should focus not only on disease but also on the total distribution of health states.[4] In this paper we present data on the distribution of cognitive function, and on the impact of clinical manifestations of atherosclerotic disease on this distribution, in a geographically defined sample of 4,971 subjects aged 55 to 94 years.

MATERIAL AND METHODS

Study population

The Rotterdam Study is a single center prospective follow-up study for which the total population aged 55 years or over, including institutionalized persons, of the suburb of Ommoord in Rotterdam, The Netherlands, is invited. The study has been approved by the Medical Ethics Committee of Erasmus University. Written informed consent is obtained from all participants. Rationale and design of the Rotterdam Study have been described elsewhere.[5] In short, the objective of the study is to investigate determinants of chronic and disabling cardiovascular, neurodegenerative, locomotor and ophthalmologic diseases. Independently living participants are extensively interviewed at home, and are subsequently clinically examined during two visits at a research center. For institutionalized persons, all examinations were performed in their institute. Enrollment in the study started June 1990 and was based on random selection procedures. By December 31, 1992, 7,120 residents of Ommoord had been

invited and 5,673 subjects had actually participated. The overall participation rate was 80 percent, similar for men and women. To guarantee adequate numbers for both gender and all ages, we confined our sample for this analysis to individuals aged 55 to 94 years, which left 5,523 subjects. Of these, for 4,971 persons (90%) cognitive test data were available and these persons were included in the present analyses.

Measurements

As part of the screening protocol for dementia, cognitive function of all participants was tested with the Mini Mental State Examination (MMSE) during the first visit to the research center.[6] The MMSE contains 18 items and yields a maximum score of 30 points.[7] The test was administered by specially trained research assistants.

Attained level of education was assessed by classifying formal schooling according to the Standard Classification of Education (SOI) used by the Netherlands Central Bureau of Statistics, which is comparable with the International Standard Classification of Education (UNESCO, Paris, 1976).[8] For the present analyses subjects were grouped in those with at most primary education, those with junior vocational training, and those with senior vocational or academic training.

A history of stroke was assessed by direct questioning and considered positive if this diagnosis had been made by a treating physician. Presence of abnormalities diagnostic of previous myocardial infarction was assessed on a 12 leads electrocardiogram (ECG) by study physicians according to preset criteria, with any suspected abnormality reviewed by a cardiologist. Atherosclerosis of the arteries of the lower extremities and of the carotid arteries was non-invasively assessed with the use of doppler and ultrasound. The ratio of the ankle to brachial systolic blood pressure (ankle-brachial index) is thought to reflect the presence of atherosclerotic vessel wall abnormalities of the arteries of the lower extremities and has been shown to be a good indicator of generalized atherosclerosis.[9] Ankle systolic blood pressure was determined with the subject in supine position at both right and left posterior tibial arteries with a Doppler ultrasound transducer using a random-zero sphygmomanometer (cuff-size 38 x 14 cm). Lower extremity arterial disease was considered present when left or right ankle-brachial index was less than 0.90. Ultrasonography of both carotid arteries was performed with a 7.5 MHz linear-array transducer and a duplex scanner (ATL UltraMark IV, Advanced Technology Laboratories, Bethel, WA). Presence of atherosclerotic lesions, defined as a focal widening relative to adjacent segments with protrusion into the lumen, was assessed in the internal carotid arteries.

Analysis

The total distribution of cognitive function in the population is presented graphically according to age, level of education, gender, vascular events, and indicators of atherosclerosis. For each variable of interest, the distribution among subjects with the characteristic relative to that among subjects without the characteristic was obtained by creating dummy variables for each MMSE score, and subsequently calculating the difference in the total proportion attributable to that characteristic by including it in a linear regression model with the dummy variable for that MMSE score as the outcome variable. If applicable, age and gender were included as covariates to adjust for differences in these variables. For each determinant, the mean score on the MMSE was calculated among subjects in the reference group (i.e. age 55 to 64 years; men; lowest educational level; no vascular disease). For other levels of the determinants, adjusted mean scores were obtained by subtracting the differences as estimated by multiple linear regression from the reference means. Because the distributions of MMSE scores are highly skewed to the left, they were further characterized by calculating percentile scores (5th, 25th, 50th, 75th, 95th). The clinical relevance was substantiated by calculating the proportion of individuals that scored below a certain cutoff (MMSE scores of 24 and 26).

RESULTS

In table 1, the age- and gender distribution of the study population is presented, as well as the age-specific participation rates and proportions of participants for which cognitive test data were available. Total non-response increased with age, as did the number of subjects who completed the interview but did not come to the research center. Of the 4,971 subjects of which MMSE scores were available, 39% had primary school or less, 34% had junior vocational training, and 27% had senior vocational training or academic training. The prevalence of previous stroke in this group was 5%, of previous myocardial infarction according to ECG readings 7%, of peripheral arterial disease 21%, and of plaques in the internal carotid arteries on either or both sides 36%.

Figure 1 depicts the population distribution of MMSE scores according to age, gender, and level of education. In the upper panel it can be seen that with increasing age, the distributions shifted toward lower values while their skewness increased, reflecting increasing variability. The distributions for men and women overlapped

Table 1. Age-specific participation rates and age- and gender distribution of study participants.

Age	Participation rate (%)	Number of subjects included in study			Availability of MMSE scores (%)
		Men	Women	Total	
55 - 59	85	260	413	673	95
60 - 64	85	392	555	947	95
65 - 69	83	440	582	1022	93
70 - 74	83	378	591	969	91
75 - 79	76	296	494	790	89
80 - 84	72	175	406	581	86
85 - 89	70	84	292	376	74
90 - 94	76	25	144	169	69
Total	80	2050	3477	5527	90

almost completely, in particular when the level of education was taken into account (figure 1, middle panel). The distributions by level of education are shown in the lower panel. Subjects with higher levels of education performed better, as evidenced by a total shift of their distributions towards higher scores, and with less variability.

In table 2 these distributions are further quantified. The differences in mean MMSE score across levels of age, education, and between men and women, reflect the average shift of the distributions relative to that of their reference group. For subjects aged 85 to 94 years compared to subjects aged 55 to 64 years it was 5.0 points, for highly educated persons compared to persons with at most primary school it was 1.7 points, and for women compared to men it was 0.2 points. The variability in the distributions is reflected in the range between the 5th and the 95th percentile: the larger this range, the more inter-individual variation exists. In all instances, a shift of the distribution towards lower values was accompanied by an increase in the variability, and the combined effect thereof was a considerable increase in the proportion of people scoring below the cutoffs.

In figure 2 the cognitive performance among subjects with and without a previous vascular event is compared. Both a history of stroke and ECG evidence of a previous myocardial infarction were associated with a shift of the population distribution of MMSE scores toward lower values. A similar pattern was observed for presence versus absence of atherosclerotic disease, either localized in the carotid arteries or in the

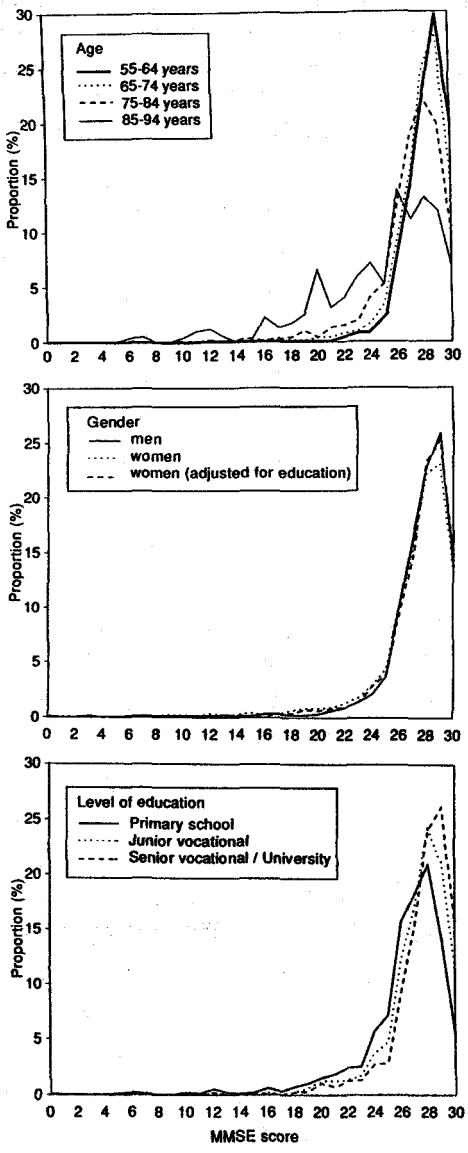

Figure 1. The distribution of cognitive function as measured by the MMSE among subjects aged 55 to 94 years, according to age, educational level and gender. The distributions for subjects aged 65 to 94 years are adjusted for gender and level of education to that for subjects aged 55 to 64 years; the distributions for higher levels of education are age- and gender adjusted to that for subjects with at most primary school; the distribution for women is adjusted for age and level of education to that for men.

Table 2. Characteristics of the distribution of cognitive function among subjects aged 55 to 94 years, according to age, gender, and level of education.

	Mean	Percentiles of the distribution of MMSE scores					Proportion below cutoff (%)	
		5th	25th	50th	75th	95th	<24	<26
Age								
55 - 64	28.1	25	27	28	29	30	1.8	5.2
65 - 74*	27.8	25	27	28	29	30	3.0	8.1
75 - 84*	26.6	22	26	28	29	30	7.8	17.1
85 - 94*	23.1	16	22	26	28	30	31.1	43.4
Level of education								
Primary school	26.3	20	25	27	28	30	12.5	25.4
Junior vocational training†	27.6	23	26	28	29	30	5.2	13.6
Senior vocational training/University†	28.0	24	27	28	29	30	3.7	9.2
Gender								
Men	27.5	23	27	28	29	30	5.2	11.0
Women‡	27.3	22	27	28	29	30	7.9	14.5

* Adjusted for gender and level of education to distribution among subjects aged 55 to 64 years.
† Adjusted for age and gender to distribution among subjects with at most primary school.
‡ Adjusted for age and level of education to distribution among men.

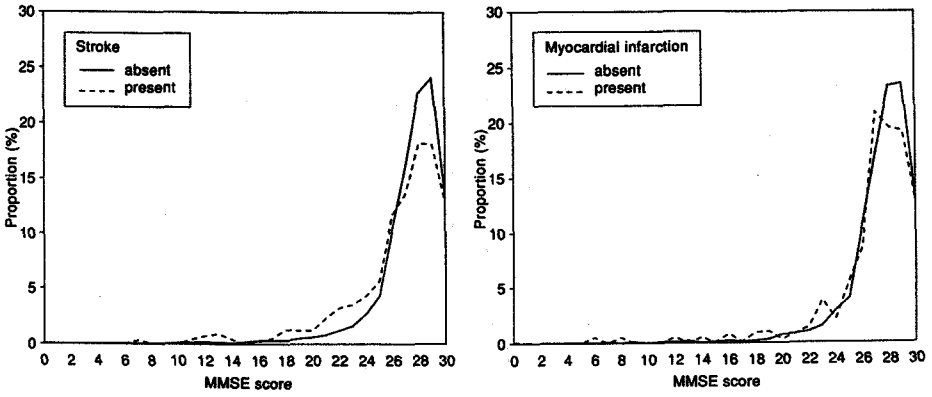

Figure 2. The distribution of cognitive function as measured by the MMSE among subjects aged 55 to 94 years, according to previous vascular event (stroke or myocardial infarction). The distributions for subjects with a previous vascular event are age- and gender adjusted to those for subjects without.

Table 3. Characteristics of the distribution of cognitive function among subjects aged 55 to 94 years, according to presence or absence of vascular disease, adjusted for age, gender, and level of education.

	Mean	Percentiles of the distribution of MMSE scores					Proportion below cutoff (%)	
		5th	25th	50th	75th	95th	<24	<26
History of stroke								
No	27.4	23	27	28	29	30	6.5	13.5
Yes	26.5	19	25	27	29	30	15.5	25.6
ECG evidence of myocardial infarction								
No	27.4	23	27	28	29	30	5.6	12.5
Yes	26.7	20	26	28	29	30	11.3	19.0
Peripheral arterial disease								
No	27.6	24	27	28	29	30	5.0	11.1
Yes	26.8	20	26	28	29	30	10.4	17.5
Plaques in the internal carotid arteries								
No	27.7	24	27	28	29	30	4.5	10.4
Yes	27.3	22	26	28	29	30	7.3	14.6

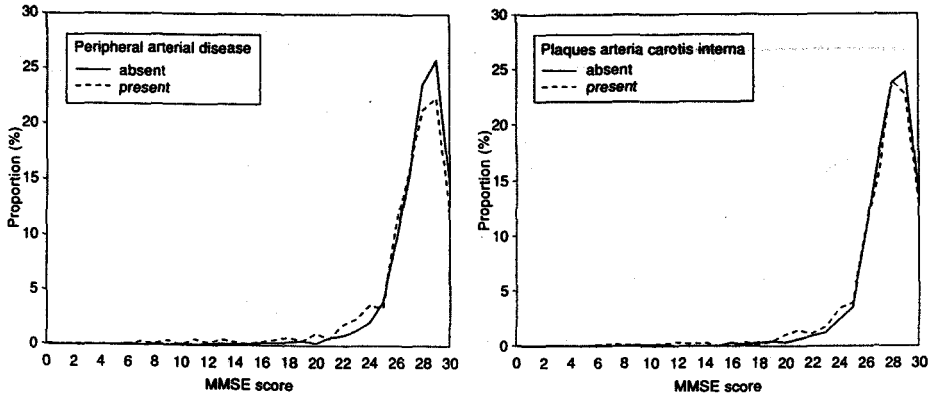

Figure 3. The distribution of cognitive function as measured by the MMSE among subjects aged 55 to 94 years, according to presence or absence of atherosclerotic disease (peripheral arteries, carotid arteries). The distributions for subjects with atherosclerosis are age- and gender adjusted to those for subjects without.

large vessels of the lower extremities (figure 3). The quantitative data regarding these distributions are given in table 3. As can be seen from the range between the 5th and 95th percentile of the distributions, shifts of the total distribution towards lower values were again accompanied by an increase in variability. Correspondingly, the proportion of subjects scoring below the cutoffs of 24 or 26 on the MMSE increased.

DISCUSSION

We presented the distributions of cognitive function in a geographically defined population of subjects aged 55 to 94 years according to age, gender, and level of education, and the influence of clinical manifestations of atherosclerotic disease on these distributions. We found that for subjects with higher age, lower educational level, and presence of vascular and atherosclerotic disease, the distributions were shifted toward lower values and the variability was increased, while gender had almost no effect on the localization or shape of the distribution.

Before discussing our findings, we must consider whether non-response may have influenced our results. The overall participation rate in our study was high (80%), and so was the overall availability of cognitive test results (90%). Furthermore, institutionalized persons were included in our study and the participation rate among them was high (83%). Although high response rates diminish the possibility of serious distortion of the study results, among independently living persons non-response increased with age and part of this non-response was probably selective and related to physical or mental morbidity. The direction of the associations that we observed among older subjects were, however, similar to those among younger subjects, for who response rates were highest. The most plausible pattern of selective non-response is, in our view, that non-response increased with increasing impairment, and particularly so when there was a combination of physical and mental handicaps. Therefore, we consider it most likely that, if selective non-response has biased our findings, this resulted in an underestimation of the strength of the relations that we investigated.

The inverse associations between age and cognitive performance and between level of education and cognitive test performance are well-recognized.[10-12] Most previous studies have presented summary results. One study, including 365 persons, presented information on the total distribution of cognitive function, and concluded that with lower level of education the distribution was shifted downwards, but similarly shaped.[13,14] Our study confirmed the previous reports, but showed in addition that with a decrease

in average performance, the shape of the distributions changes due to increased variability among individuals. With regard to age, an explanation for this finding could be that cognitive decline is not intrinsic to aging, but rather that age is a proxy for accumulated life-time exposures affecting cognitive function.

One putative risk factor for cognitive decline is vascular disease, in particular atherosclerosis.[15,16] We found that previous vascular events and presence of atherosclerosis were associated with a shift of the population distribution towards lower levels. However, the mean difference was less than one point on the MMSE which raises the question whether this is clinically relevant. The answer is not to be found on the individual level, but rather on the population level. The mean difference reflects the aggregate experience of people with a large decline and of those with no decline at all. This study does not indicate which individuals suffered cognitive impairment as a result from vascular disease. It does suggest however, that on a population level, atherosclerotic disease can account for considerable cognitive impairment, as reflected by the shifts and changes in shape of the distribution and the increasing proportion of subjects scoring below a specified cutoff. In the majority of cases, vascular events as stroke and myocardial infarction reflect a near-end stage of atherosclerotic disease. Therefore, it is not surprising that these were associated with a larger population shift in cognitive performance than mere presence of atherosclerosis. It should be noted, however, that, whereas stroke and myocardial infarction were present in 5% and 7% of the population respectively, one fifth to one third of the population had evidence for atherosclerosis in the peripheral or carotid arteries. This suggests that the total impact of atherosclerosis on the amount of cognitive impairment in the population at large may be much greater than that attributable to severe atherosclerosis resulting in clinically overt disease.

A question that remains to be answered is whether the prevention of atherosclerosis would result in the otherwise affected subjects to assume the distribution of the now unaffected individuals. If yes, this could mean a major health benefit. Although the average gain per individual would be small, the population gain might be substantial.[4] It seems timely to conduct a study to investigate whether intervention on risk factors for atherosclerosis can prevent cognitive decline on a population level.

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Chapter 3.3

Atherogenic and hemostatic factors and cognitive function in the elderly

There is an increasing interest in vascular dementia. An important reason for this is that it seems not only a common form of dementia, but also one that may be amenable to intervention.[1] If one wants to study vascular risk factors for dementia, "vascular dementia" is not the appropriate outcome measure, since the presence of these risk factors are part of the diagnostic criteria. The problems arising in defining vascular dementia can be avoided by directly investigating the association of interest, namely that between vascular risk factors and cognitive impairment.

The Rotterdam Study is a population based study of the elderly, that aims to investigate determinants of cardiovascular and neurodegenerative disorders, including cognitive impairment and dementia. This offers the opportunity to examine the relation between a broad range of cardiovascular determinants and cognitive function in a large, unselected, population. In this paper we report on the relation between clinically manifest vascular disease, non-invasive indicators of atherosclerotic disease, atherogenic and hemostatic risk factors, and cognitive function in 4,971 subjects aged 55 to 94 years.

MATERIAL AND METHODS

Study population

The Rotterdam Study is a single center prospective follow-up study of the total population aged 55 years or over, of the suburb of Ommoord in Rotterdam, The Netherlands. Institutionalized persons are included in the sample. The study has been approved by the Medical Ethics Committee of Erasmus University. Written informed consent is obtained from all participants. Rationale and design of the Rotterdam Study have been described elsewhere.[2] In short, the objective of the study is to investigate determinants of chronic and disabling cardiovascular, neurodegenerative, locomotor and ophthalmologic diseases. All participants are extensively interviewed at home, and are subsequently clinically examined during two visits at a research

center. Enrollment in the study started June 1990 and was based on random selection procedures. By December 31, 1992, 7,120 residents of Ommoord had been invited and 5,673 subjects had actually participated. The overall participation rate was 80 percent, similar for men and women. To guarantee adequate numbers for both gender and all ages, we confined our sample for this analysis to individuals aged 55 to 94 years, which left 5,523 subjects (participation rate among those aged 55 to 64 years, 65 to 74 years, 75 to 84 years and 85 to 94 years, was 85%, 83%, 74%, and 72%, respectively). Of these, for 4,971 persons (90%) cognitive test data were available and these persons were included in the present analyses.

Measurements

We assessed the following determinants as potential vascular correlates of cognitive function: clinical cardiovascular disease (previous stroke or previous myocardial infarction); presence of atherosclerosis (of the large vessels of the lower extremities and of the carotid arteries); risk factors for cardiovascular disease (diabetes mellitus, atrial fibrillation, smoking, hypertension, hypercholesterolemia and low high-density lipoprotein (HDL) cholesterol level); and hemostatic factors (levels of fibrinogen, factor VIIc, factor VIIIc). The results for hypertension will be briefly presented, but a detailed analysis of the relation between blood pressure and cognitive function will be reported separately.[3]

A history of stroke or myocardial infarction was assessed by direct questioning and considered positive when this diagnosis had been made by a treating physician. The presence of atherosclerosis of the arteries of the lower extremities and of the carotid arteries was non-invasively assessed with the use of ultrasound. The ratio of the ankle to brachial systolic blood pressure (ankle-brachial index) reflects the presence of atherosclerotic vessel wall abnormalities of the arteries of the lower extremities and has been shown to be a good indicator of generalized atherosclerosis.[4] Ankle systolic blood pressure was determined with the subject in supine position at both right and left posterior tibial arteries by Doppler ultrasound transducer using a random-zero sphygmomanometer (cuff-size 38 x 14 cm). The average of the left and the right ankle-brachial index was used in the present analyses. Lower extremity arterial disease was considered present when left or right ankle-brachial index was less than 0.90.[5] Ultrasonography of both carotid arteries was performed with a 7.5 MHz linear-array transducer and a duplex scanner (ATL UltraMark IV, Advanced Technology Laboratories, Bethel, WA). Presence of atherosclerotic lesions, defined as a focal widening relative to adjacent segments with protrusion into the lumen, was assessed

in the common carotid arteries, the bifurcations and the internal carotid arteries, as described previously.[6] Blood pressure was measured in the sitting position at the right upper arm with a random-zero sphygmomanometer. The average of two measurements, separated by a count of the pulse rate, was used in the analyses.[7] Hypertension was defined as a systolic blood pressure of 160 mmHg or over, or a diastolic blood pressure of 95 mmHg or over, or the use of antihypertensive medication. Medication was classified according to the Anatomical Therapeutic Chemical (ATC) classification index.[8] Diabetes mellitus was considered present if the subject was taking oral antidiabetics or insulin (ATC-code A10) or if the random serum glucose level was higher than 11.1 mmol/l.[9] In subjects without drug-treated diabetes mellitus, non-fasting glucose tolerance was assessed by measuring serum glucose levels two hours after an oral glucose load of 75 grams. Presence of atrial fibrillation, and of abnormalities diagnostic of previous myocardial infarction, were assessed on a 12-lead rest electrocardiogram (ECG). All ECG recordings were coded according to the Minnesota Code (version 1982) by trained physicians, with any suspected abnormality reviewed by a cardiologist.[10] With respect to smoking behavior, subjects were categorized in groups of current smokers, former smokers and those who had never smoked. Serum total cholesterol was determined with an automated enzymatic procedure.[11] High density lipoprotein cholesterol level was measured similarly, after precipitation of the non HDL fraction with phosphotungstate-magnesium. Plasma fibrinogen level was assessed according to the Clauss method (Diamed AG, Switzerland).[12] Factor VIIc and factor VIIIc were assayed by means of Automatic Coagulation Laboratory (ACL) (Instrumentation Laboratory, IJsselstein, The Netherlands), with the aid of factor VII and factor VIII deficient plasma (Ortho Diagnostic System, Beerse, Belgium) with Thromborel S (Behringwerke, Germany) and Thrombosil I (Ortho Diagnostic Systems, Beerse, Belgium) as reagents, respectively. Plasma obtained from 40 healthy men was pooled and served as reference for the measurements of factor VIIc and factor VIIIc. Factor VIIc and factor VIIIc levels of the donors were all within normal range and no differences between reference pools could be detected.

Global cognitive function was assessed at the research center by the Mini Mental State Examination (MMSE),[13] which was administered by specially trained research assistants. The MMSE is a brief cognitive test that covers several cognitive functions, takes about 8 minutes to complete, contains 18 items, and yields a maximum best score of 30 points.

Attained level of education, a potential confounder of the relation between vascular disease and cognitive function, was assessed by classifying formal schooling according

to the Standard Classification of Education (SOI) used by the Netherlands Central Bureau of Statistics that is comparable with the International Standard Classification of Education (UNESCO, Paris, 1976).[14]

Due to cost and time considerations, several measurements were only conducted, or completely analyzed, in a random sample of the total study population. This concerned the assessment of the presence of plaques in the carotid arteries (availability 48%), ECG readings (availability 60%), and the assessment of the hemostatic factors (availability of fibrinogen, factor VIIc and factor VIIIc, 57%, 36%, and 34%, respectively).

Analysis

The relation between the various vascular determinants and cognitive performance as measured by the MMSE was assessed by multiple linear regression analysis, with adjustment for the confounding effect of age. The regression coefficients of change in MMSE score are presented with a 95% confidence interval (95% CI) based on the maximum likelihood estimates of the standard error provided by the regression model. To assess whether the magnitude of the associations changed over age, additional analyses were performed in two 20-years age strata (55 to 74 years; 75 to 94 years), with adjustment for residual confounding by age within these strata. Confounding or effect modification by gender, history of stroke, and level of education was assessed by including these variables as covariates in the model, as well as by stratified analyses. If no reliable information could be obtained from a participant regarding the medical history, this person was discarded from the analyses that required interview information. All reported differences are adjusted for age and, if applicable, gender.

RESULTS

Table 1 shows the age- and gender distribution of the study population, together with the age-specific prevalences or age-specific mean values and standard deviations of the variables of interest. The total sample for which MMSE-scores and information on at least some of the other variables was available, comprised 4,971 subjects. Thirty-eight percent of the subjects were men, their proportion decreased with age. As expected, the prevalence of most of the indicators of vascular disease increased with age.

Clinical cardiovascular disease. The relation of clinical cardiovascular disease and of atherosclerosis with MMSE score is given in table 2. A previous stroke and a previous

Table 1. Characteristics of study population (the values are means with standard deviations in parentheses or percentages).

Characteristic	Age group (years)				Total
	55 - 64	65 - 74	75 - 84	85 - 94	
Number of subjects	1536	1838	1202	395	4971
Men (%)	40.4	41.8	34.8	21.5	38.0
MMSE	28.1 (1.8)	27.7 (2.0)	26.2 (4.0)	22.4 (6.0)	27.1 (3.4)
Clinical cardiovascular disease					
Previous stroke (%)*	2.0	4.3	7.9	8.5	4.6
Previous MI (%)*	5.9	11.0	13.8	14.8	10.1
Indicators of atherosclerosis					
Ankle-brachial index	1.17 (0.17)	1.14 (0.19)	1.03 (0.25)	0.89 (0.29)	1.11 (0.22)
Peripheral arterial disease (%)	11.2	15.3	32.8	58.9	21.1
Atherosclerotic plaques int. carotid artery, one-sided (%)	14.4	21.7	24.8	31.7	20.4
Atherosclerotic plaques int. carotid artery, two-sided (%)	9.1	16.1	21.9	28.9	15.6
Cardiovascular risk factors					
Hypertension (%)	13.0	20.8	25.9	31.6	20.3
Diabetes mellitus (%)	1.8	5.3	6.5	6.6	4.6
Glucose level, 2h (mmol/l)†	6.4 (2.3)	7.1 (3.3)	7.4 (3.3)	8.5 (3.8)	7.0 (3.1)
Atrial fibrillation (%)	0.6	1.6	4.8	12.2	2.6
Current smokers (%)	32.1	22.2	16.9	12.1	23.4
Total cholesterol (mmol/l)	6.76 (1.18)	6.71 (1.24)	6.43 (1.25)	6.10 (1.22)	6.62 (1.24)
HDL - cholesterol (mmol/l)	1.35 (0.37)	1.33 (0.38)	1.31 (0.37)	1.30 (0.32)	1.33 (0.37)
Hemostatic risk factors					
Fibrinogen (g/l)	2.61 (0.62)	2.78 (0.66)	3.00 (0.74)	3.30 (0.78)	2.82 (0.70)
Factor VIIc (IU/ml)	1.06 (0.24)	1.06 (0.26)	1.04 (0.28)	1.03 (0.28)	1.05 (0.26)
Factor VIIIc (IU/ml)	1.86 (0.74)	1.97 (0.80)	2.03 (0.74)	2.04 (0.89)	1.96 (0.78)

MMSE = Mini Mental State Examination; MI = myocardial infarction.

* Subjects in whom no reliable medical history could be obtained were excluded.

† Subjects with drug-treated diabetes were excluded.

Table 2. Clinical cardiovascular disease and atherosclerosis and cognitive function. Mean difference in MMSE score between subjects classified according to presence or absence of clinical cardiovascular disease and atherosclerosis, adjusted for age and gender.

	55 - 74 years (95% CI)	75 - 94 years (95% CI)	Total population (95% CI)
Previous stroke*	-0.75 (-1.12;-0.38)	-1.05 (-1.68;-0.42)	-0.88 (-1.21;-0.55)
Previous MI by history†	-0.31 (-0.60;-0.02)	-0.65 (-1.32;0.02)	-0.42 (-0.71;-0.13)
Previous MI on ECG	-0.32 (-0.67;0.03)	-1.02 (-1.90;-0.14)	-0.67 (-1.04;-0.30)
Peripheral arterial disease	-0.41 (-0.61;-0.21)	-0.55 (-1.02;-0.08)	-0.72 (-0.94;-0.50)
Atherosclerotic plaques internal carotid artery, one-sided‡	-0.10 (-0.32;0.12)	-0.92 (-1.61;-0.23)	-0.35 (-0.60;-0.10)
Atherosclerotic plaques internal carotid artery, two-sided‡	-0.24 (-0.53;0.05)	-0.92 (-1.65;-0.19)	-0.51 (-0.80;-0.22)

95% CI = 95% confidence interval; MI = myocardial infarction.

* Subjects from whom no reliable information regarding their medical history could be obtained, were excluded.

† For reasons of comparability, only subjects for who ECG-readings were available were included in the analysis.

‡ As compared to subjects without plaques in both internal carotid arteries.

myocardial infarction were significantly related to worse performance on the MMSE.

Atherosclerosis. Subjects with peripheral arterial disease performed significantly worse on the MMSE than did subjects without (table 2). A decrease of 0.1 mmHg/mmHg in ankle-brachial index was associated with an average decline in MMSE score of 0.10 (95% CI 0.02;0.18). Presence of atherosclerotic plaques in the internal carotid arteries was associated with lower MMSE scores. The differences were larger for subjects with lesions on both sides, than for subjects who had only plaques in one internal carotid artery (table 2). Presence of plaques in the carotid bifurcation or in the common carotid arteries was also inversely related to cognitive performance, without, however, reaching statistical significance. Adjustment for history of stroke or for level of education did not essentially alter any of these results.

Cardiovascular risk factors. The presence of hypertension seemed to be associated with better performance on the MMSE when assessed for the whole population (table 3). This was due to the strong positive relation between presence of hypertension and cognitive function among subjects aged 75 to 94 years. No differences were found in the cognitive performance of persons with diabetes mellitus as compared to that of persons without. Glucose intolerance in non-diabetic subjects seemed however

Table 3. Cardiovascular risk factors and cognitive function. Mean difference in MMSE score between subjects classified according to presence or absence of, or per unit increase in, cardiovascular risk factors, adjusted for age and gender.

	55 - 74 years (95% CI)	75 - 94 years (95% CI)	Total population (95% CI)
Hypertension	-0.06 (-0.22;0.10)	0.80 (0.37;1.23)	0.33 (0.15;0.51)
Diabetes mellitus	0.09 (-0.15;0.33)	-0.04 (-0.57;0.49)	0.07 (-0.18;0.32)
Glucose level 2 hours after glucose load (per mmol/l)	-0.03 (-0.05;-0.01)	-0.03 (-0.09;0.03)	-0.03 (-0.05;-0.01)
Atrial fibrillation	-0.88 (-1.68;-0.08)	-0.16 (-1.18;0.86)	-0.73 (-1.32;-0.14)
Former cigarette smokers (vs never smokers)*	0.03 (-0.15;0.21)	0.37 (-0.12;0.86)	0.20 (0.00;0.40)
Current cigarette smokers (vs never smokers)*	-0.22 (-0.44;0.00)	-0.36 (-1.05;0.33)	-0.24 (-0.48;0.00)
Total cholesterol (per mmol/l)	-0.01 (-0.07;0.05)	0.12 (-0.04;0.28)	0.05 (-0.01;0.11)
HDL - cholesterol (per mmol/l)	0.17 (-0.01;0.35)	0.43 (-0.08;0.94)	0.28 (0.08;0.48)

* Pipe and cigar smokers excluded.

related to cognitive function: the level of serum glucose measured two hours after an oral glucose load was inversely associated with cognitive test score. This relation was similar across strata of age and gender. Overall, atrial fibrillation was associated with lower scores on the MMSE (table 3). Stratification according to gender showed that this was due to a significant inverse relation in women (difference -1.11, 95% CI -1.93;-0.29), while no relation was found in men (difference 0.10, 95% CI -0.70;0.90). Cigarette smoking was related to worse performance when current smokers were compared to never smokers (difference -0.24, 95% CI -0.48;0.00); however, former smokers performed better when compared to never smokers (difference 0.20, 95% CI 0.00;0.40) (table 3). After additional adjustment for level of education the strength of these relations slightly decreased, and they were no longer statistically significant (current smokers versus never smokers: difference -0.15, 95% CI -0.39;0.09; former smokers versus never smokers: difference 0.19, 95% CI -0.01;0.39). Total serum cholesterol was not related to cognitive function. The level of HDL-cholesterol was

Table 4. Hemostatic factors and cognitive function. Mean difference in MMSE score per unit increase in hemostatic factors, adjusted for age and gender.

	55 - 74 years (95% CI)	75 - 94 years (95% CI)	Total population (95% CI)
Fibrinogen (per g/l)*	0.00 (-0.14;0.14)	-0.13 (-0.42;0.16)	-0.06 (-0.20;0.08)
Factor VIIc (per 0.1 IU/ml)†	0.03 (-0.03;0.09)	0.05 (-0.09;0.19)	0.04 (-0.02;0.10)
Factor VIIIc (per IU/ml)†	-0.04 (-0.18;0.10)	0.26 (-0.13;0.65)	0.08 (-0.08;0.24)

* Adjusted for current smoking.
† Subjects taking antithrombotic agents (ATC-code B01) excluded.

positively related to cognitive function (table 3), particularly among women (difference for women: 0.36 per mmol/l, 95% CI 0.12;0.60; difference for men: 0.07 per mmol/l, 95% CI -0.26;0.40).

Hemostatic factors. Fibrinogen, factor VIIc and factor VIIIc, appeared not to be related to cognitive function when all subjects were included in the analyses (table 4). Stratified analysis according to smoking status (for fibrinogen), and according to previous clinical vascular event (stroke or myocardial infarction; for fibrinogen, factor VIIc, factor VIIIc) showed no associations between any of these factors and MMSE score.

DISCUSSION

We investigated whether clinical vascular disease, atherosclerosis, cardiovascular risk factors and hemostatic factors were related to cognitive performance in the general elderly population. We found that clinical vascular disease and atherosclerosis were inversely associated with cognitive performance. Hypertension seemed not related with cognitive function among subjects below 75 years of age, but was positively associated with cognitive function among persons aged 75 years or over. Of the cardiovascular risk factors impaired glucose tolerance and current smoking were related to poorer cognitive function in both men and women, whereas atrial fibrillation and HDL-cholesterol were related to cognitive function in women only. Diabetes mellitus, total serum cholesterol, fibrinogen level, factor VIIc and factor VIIIc, appeared not to be associated with cognitive performance.

This is a cross-sectional study and caution is needed in the interpretation of our findings, particularly regarding possible causality. Besides, we have to consider whether non-response may have influenced our findings. It is likely that at least some of the non-response was related to physical or mental morbidity, that non-response increased with increasing impairment, and that it was highest among subjects with a combination of both physical and mental handicaps. The overall participation rate in our study was high, which diminishes the possibility of serious bias. To the extent that selective non-response has influenced our findings, it probably resulted in an underestimation of existing relations.

The association we found between previous stroke and cognitive function is not surprising since stroke is the crucial and causative event in multi-infarct dementia. Several studies reported cognitive impairment and increased risk of dementia after cerebral infarcts.[15,16] The strong relation we found with a history of myocardial infarction is of interest. In the Bronx Aging Study an association was found between myocardial infarction and the development of dementia in women, but not in men.[17]

We found that atrial fibrillation was associated with poorer cognitive performance in women, but not in men, independent of a history of stroke. We know of no other studies that investigated the relation between atrial fibrillation and cognitive function per se. A postmortem study on a selected group of demented patients reported that 47% of patients with cerebral infarctions, had had atrial fibrillation.[18] Atrial fibrillation is associated with a high risk of symptomatic as well as silent cerebral infarction,[19-21] and it is likely that this might take a subtle, but cumulative toll on cognition in the elderly.[22] Although we have no explanation for it, our finding of a different effect among women as compared to men seems to fit with results from the Framingham Study and the Copenhagen City Heart Study. Both studies found that the risk of stroke associated with atrial fibrillation was higher in women than in men.[23,24]

Diabetes mellitus is a well-recognized risk factor for stroke.[25] In the Framingham study glucose intolerance, including subjects with manifest diabetes mellitus, was the only significant correlate of imaged but clinically silent lesions in patients with first stroke.[26] It is conceivable that unrecognized lacunar strokes can contribute to poorer cognitive performance of diabetic patients. Several studies reported a negative association between non-insulin dependent diabetes mellitus and cognitive function.[27-30] In the East Boston Study on the other hand, like in our study, no association was found between cognitive performance and diabetes mellitus among 3,682 persons aged 65 years or over.[31] A possible explanation, that needs further investigation, for our finding of a negative relation between elevated glucose levels and cognitive function

could be that cognitive impairment is associated with hyperglycemia and related to glycemic control.[32]

Our results on the influence of smoking status are in concordance with those reported by Hill who found no differences in cognitive function between nonsmokers and ex-smokers, but worse performance for current smokers.[33] This matches the observation that ex-smokers rapidly assume similar risks of stroke and of coronary heart disease as nonsmokers, and is in agreement with the current notion that cigarette smoking does not act chiefly to promote atherosclerosis, but exerts its deleterious effect on the vasculature primarily through a direct and reversible effect on other factors, presumably fibrinogen.[34,35]

An elevated fibrinogen level is a major cardiovascular risk factor and associated with an increased risk of stroke as well as of myocardial infarction.[36-38] We found no relation between fibrinogen and cognitive function, nor between factor VIIc and factor VIIIc levels and cognitive performance. These negative results must be regarded tentative, because the number of subjects for which data were available was relatively small.

A problem in epidemiological studies of vascular causes of cognitive impairment and dementia remains how to define vascular dementia. The distinction between vascular dementia and other dementias is not always clear, and vascular causes may be involved in the clinical picture of other dementia syndromes, like Alzheimer's disease. Recently, sets of diagnostic criteria for ischemic vascular dementia and for vascular dementia have been proposed,[39,40] but they hardly solve the problem.[41] The circularity in the definition of vascular dementia limits the potential to investigate cardiovascular risk factors of cognitive impairment. We bypassed that problem by directly investigating the relations of interest, namely those between vascular risk factors and cognitive function.

On an individual level, the clinical relevance of a difference in MMSE score of less than half a point is negligible. It should be realized, however, that the differences that we estimated do not reflect individual changes, but rather the average population experience. Even a small shift downwards of the total population distribution of cognitive function, implies a relatively large increase in the proportion of demented subjects.[42] We found that clinical manifestations and risk factors of atherosclerosis were associated with lower cognitive performance in the population, irrespective of actual history of stroke. Although we can make no causal inferences, our results suggest that prevention of atherosclerosis might possibly defer cognitive deterioration in the population.

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Chapter 3.4

Blood pressure, hypertension, orthostatic hypotension, and cognitive function in the elderly

The relation between blood pressure and cognitive function remains ambiguous. Longstanding elevated blood pressure is considered to be etiologically involved in Binswanger's disease, or subcortical atherosclerotic encephalopathy, a dementing disorder.[1,2] Furthermore, hypertension is one of the main risk factors for stroke and thereby for multi infarct dementia. On the other hand, it has been suggested that in susceptible individuals low blood pressure can also be a risk factor for cognitive decline, when the pressure becomes to low to guarantee adequate cerebral blood flow.[2,3] Although several studies showed worse performance on different measures of cognitive function among hypertensive patients as compared with normotensive individuals, population-based studies that investigated the relation between blood pressure level and cognitive function found little evidence for a major role of blood pressure level as a determinant of cognitive performance.[4-7] In this paper we report on the relation between blood pressure, hypertension and orthostatic hypotension on the one hand, and cognitive function on the other hand in a population-based study of 4,971 Dutch subjects, aged 55 to 94 years.

MATERIAL AND METHODS

Study population

The Rotterdam Study is a single center prospective follow-up study of the total population aged 55 years or over, including institutionalized persons, of the suburb of Ommoord in Rotterdam, The Netherlands. The study has been approved by the Medical Ethics Committee of Erasmus University. Written informed consent is obtained from all participants. Rationale and design of the Rotterdam Study have been described elsewhere.[8] In short, the objective of the study is to investigate determinants of chronic and disabling cardiovascular, neurodegenerative, locomotor and ophthalmologic diseases. All participants are extensively interviewed at home, and are subsequently clinically examined during two visits at a research center. Enrollment in the study started June

1990 and was based on random selection procedures. By December 31, 1992, 7,120 residents of Ommoord had been invited and 5,673 subjects had actually participated. The overall participation rate was 80 percent, similar for men and women (participation rate among those aged 55 to 64 years, 65 to 74 years, 75 to 84 years and 85 to 94 years, was 85%, 83%, 74%, and 72%, respectively). To guarantee adequate numbers for both gender and all ages, we confined our sample for this analysis to individuals aged 55 to 94 years, which left 5,523 subjects. Of these, for 4,971 persons (90%) cognitive test data were available and these persons were included in the present analyses.

Measurements

In the initial interview at the participant's home, information on current health status, medical history, drug prescriptions and actual use, and lifetime formal schooling was obtained by means of a computerized questionnaire. Several blood pressure measurements as well as the assessment of cognitive function were done in the Rotterdam Study research center.

Blood pressure was measured in the sitting position at the right upper arm with a random-zero sphygmomanometer. The average of two measurements, separated by a count of the pulse rate, was used in the analysis.[9] Hypertension was defined as a systolic blood pressure of 160 mmHg or over or a diastolic blood pressure of 95 mmHg or over, or as the use of antihypertensive drugs. Isolated systolic hypertension was defined as a systolic blood pressure of at least 160 mmHg with a diastolic blood pressure below 90 mmHg, with the exclusion of subjects taking antihypertensive medication.[9,10]

The presence of orthostatic hypotension was assessed with a Dinamap automatic blood pressure recorder (cuff size 32 x 17 cm). After five minutes rest in the supine position blood pressure was read twice at the right upper arm and the average value was taken as the baseline blood pressure level. Then the subject rose quickly and blood pressure was recorded at one-minute intervals for five minutes. Pulse rate was simultaneously recorded during each measurement, and occurrence of subjective symptoms, such as dizziness, tinnitus, profuse sweating and palpitations, was noted. No uniform criteria for orthostatic hypotension exist.[11-13] We defined as systolic orthostatic hypotension a drop in systolic blood pressure of at least 20 mmHg, and as diastolic orthostatic hypotension a drop in diastolic blood pressure of at least 10 mmHg, for at least one reading within five minutes upon standing. Orthostatic hypotension was defined as a systolic decline of at least 20 mmHg with a concomitant

diastolic decline of at least 10 mmHg for at least one reading within five minutes upon standing.[11]

Cognitive function was assessed at the research center by means of the Mini Mental State Examination (MMSE).[14] The MMSE is a brief cognitive test that was originally developed as a screening instrument for dementia. It takes about 8 minutes to complete, contains 18 items, and yields a maximum score of 30 points. The test was administered by specially trained research assistants.

As potential confounders or effect modifiers we considered presence of clinical vascular disease (previous stroke, previous myocardial infarction, generalized atherosclerosis) and level of education. A history of stroke and a history of myocardial infarction were assessed by direct questioning and considered positive if this diagnosis had been made by a physician. The ratio of the ankle to brachial systolic blood pressure (ankle-brachial index) reflects the presence of atherosclerotic vessel wall abnormalities of the arteries of the lower extremities and has been shown to be a good indicator of generalized atherosclerosis.[15] Ankle systolic blood pressure was determined with the subject in supine position at both right and left posterior tibial arteries by Doppler ultrasound transducer using a random-zero sphygmomanometer (cuff-size 38 x 14 cm). Lower extremity arterial disease was considered present when left or right ankle-brachial index was less than 0.90.[16] Attained level of education was assessed by classifying formal schooling according to the Standard Classification of Education (SOI) used by the Netherlands Central Bureau of Statistics, which is comparable with the International Standard Classification of Education (UNESCO, Paris, 1976).[17] For the present analyses subjects were grouped in those with at most primary education, those with junior vocational training, and those with senior vocational or academic training.

Analysis

The relation between blood pressure level and cognitive performance as measured by the MMSE, was assessed by multiple linear regression analysis. Since there was evidence for effect modification by age of the relation between blood pressure and MMSE, the analyses were done in 10-years age strata, with age as a continuous variable included in the model to correct for residual confounding. Potential confounding by gender, level of education, and previous vascular event (stroke, myocardial infarction) was assessed by including these variables as covariates in the model as well as by stratified analyses. The association of orthostatic hypotension, and of symptoms presumably associated with postural cerebral hypoperfusion, with cognitive function

was also evaluated through multiple linear regression analysis. To investigate whether the association between blood pressure and cognitive function differed among subjects with and without generalized atherosclerosis, stratified analyses were conducted for persons with and without peripheral arterial disease. All regression coefficients of change in MMSE score are presented with a 95% confidence interval (95% CI) based on the maximum likelihood estimates of the standard error provided by the regression model.

RESULTS

Table 1 presents some characteristics of the study population. As expected, the average MMSE score declined with age. The mean systolic blood pressure, the prevalence of isolated systolic hypertension, and the prevalence of orthostatic hypotension increased with age, as did the proportion of subjects who experienced symptoms upon standing. Mean diastolic blood pressure decreased with age.

The relation by 10-years age group between mean MMSE score and level of systolic

Table 1. Characteristics of study population.

Characteristic	Age group (years)				Total
	55 - 64	65 - 74	75 - 84	85 - 94	
Number of subjects	1536	1838	1202	395	4971
Men (%)	40.4	41.8	34.8	21.5	38.0
MMSE mean (sd)	28.1 (1.8)	27.7 (2.0)	26.2 (4.0)	22.4 (6.0)	27.1 (3.4)
Mean SBP (mmHg) (se)	131.4 (0.6)	140.4 (0.5)	144.5 (0.7)	146.1 (1.3)	138.9 (0.3)
Mean DBP (mmHg) (se)	74.2 (0.3)	73.6 (0.3)	71.3 (0.4)	70.7 (0.7)	73.1 (0.2)
ISH* (%)	4.8	10.9	16.1	21.5	10.8
Orthostatic hypotension† (%)	1.8	3.5	5.2	9.2	3.7
Orthostatic symptoms (%)	8.8	14.5	18.2	20.4	13.9

MMSE = Mini Mental State Examination; SBP = systolic blood pressure; DBP = diastolic blood pressure; ISH = isolated systolic hypertension.

* SBP ≥ 160 mmHg, DBP < 90 mmHg, subjects taking cardiovascular medication excluded.

† Fall in SBP ≥ 20 mmHg with concomitant fall in DBP ≥ 10 mmHg within five minutes upon standing.

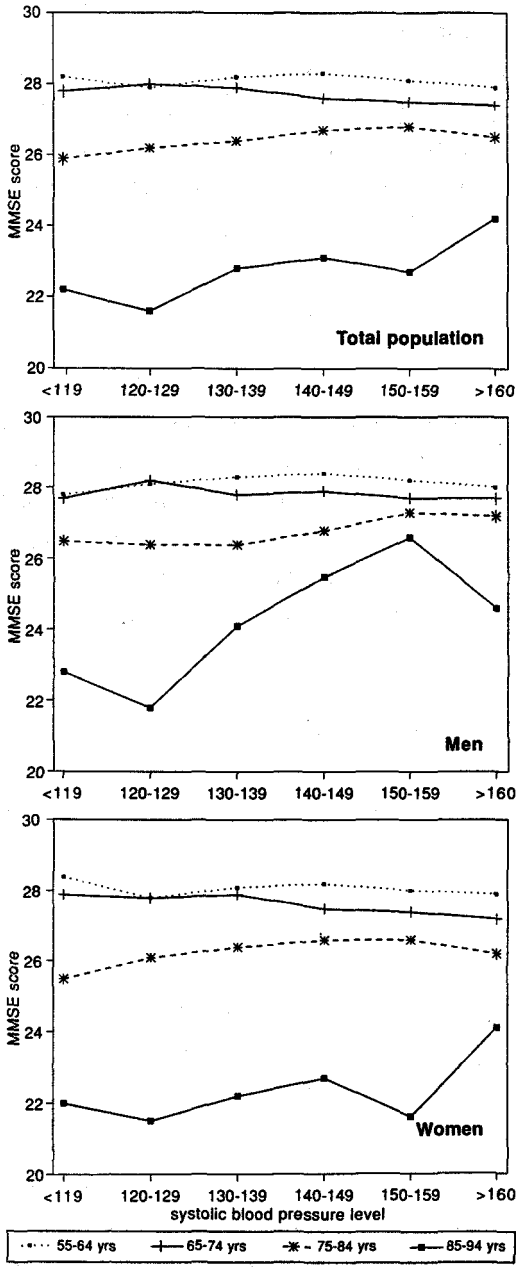

Figure 1. Average MMSE-score by level of systolic blood pressure and by age for the total study population (upper panel), and for men (middle panel) and women (lower panel).

Table 2. Mean change in MMSE score per 10 mmHg increase in systolic and diastolic blood pressure.

	55-64 years (95% CI)	65-74 years (95% CI)	75-84 years (95% CI)	85-94 years (95% CI)	Total (95% CI)
SBP (per 10 mmHg)					
Total population*	-0.03 (-0.07;0.01)	-0.08 (-0.12;-0.04)	0.10 (0.00;0.20)	0.30 (0.05;0.55)	0.04 (0.00;0.08)
Men†	0.04 (-0.04;0.12)	-0.05 (-0.11;0.01)	0.12 (-0.04;0.28)	0.33 (-0.16;0.82)	0.06 (0.00;0.12)
Women†	-0.08 (-0.14;-0.02)	-0.11 (-0.17;-0.05)	0.10 (-0.02;0.22)	0.29 (0.00;0.58)	0.04 (-0.02;0.10)
DBP (per 10 mmHg)					
Total population*	-0.01 (-0.09;0.07)	-0.16 (-0.24;-0.08)	0.11 (-0.07;0.29)	-0.01 (-0.46;0.44)	-0.04 (-0.12;0.04)
Men†	0.04 (-0.12;0.20)	-0.11 (-0.23;0.01)	0.05 (-0.24;0.34)	-0.51 (-1.35;0.33)	-0.06 (-0.16;0.04)
Women†	-0.04 (-0.14;0.06)	-0.20 (-0.32;-0.08)	0.13 (-0.09;0.35)	0.18 (-0.37;0.73)	-0.01 (-0.11;0.09)

* Adjusted for age and gender.
† Adjusted for age.

blood pressure, for the total population as well as for men and women separately, is depicted in figure 1. In the younger age groups no association between systolic blood pressure and MMSE score is discernible. If any, the mean MMSE score seems to decrease slightly with increasing systolic blood pressure. In those aged 75 to 94 years, however, increasing systolic blood pressure was associated with increasing cognitive performance. Examination of the gender-specific curves shows that this effect is present among women as well as men.

These observations were further quantified by multiple linear regression analysis (table 2). Systolic blood pressure was inversely associated with MMSE score among subjects below age 75 years. Above this age, systolic blood pressure was positively associated with cognitive performance, in particular for subjects aged 85 to 94 years. Analyses by gender revealed that the overall pattern of the relation between systolic blood pressure and cognitive function was similar for men and women (table 2). Diastolic blood pressure appeared not related to cognitive function, and there was no effect modification by age (table 2). Adjustment for level of education, and for previous vascular event (stroke or myocardial infarction) left the results virtually unchanged.

Table 3. Mean change in MMSE score per 10 mmHg increase in systolic and diastolic blood pressure according to presence or absence of peripheral arterial disease, adjusted for age and gender.

	55-64 years (95% CI)	65-74 years (95% CI)	75-84 years (95% CI)	85-94 years (95% CI)	Total (95% CI)
SBP (per 10 mmHg)					
Peripheral arterial disease absent	-0.03 (-0.07;0.01)	-0.09 (-0.15;-0.03)	0.05 (-0.07;0.17)	0.12 (-0.23;0.47)	0.00 (-0.39;0.39)
Peripheral arterial disease present	-0.03 (-0.23;0.17)	-0.03 (-0.17;0.11)	0.20 (0.04;0.36)	0.40 (0.07;0.73)	0.21 (0.09;0.33)
DBP (per 10 mmHg)					
Peripheral arterial disease absent	-0.05 (-0.13;0.03)	-0.16 (-0.26;-0.06)	-0.05 (-0.29;0.19)	0.10 (-0.57;0.77)	-0.08 (-0.16;0.00)
Peripheral arterial disease present	0.16 (-0.21;0.53)	-0.16 (-0.40;0.08)	0.27 (-0.06;0.60)	-0.06 (-0.67;0.55)	0.03 (-0.19;0.25)

SBP = systolic blood pressure; DBP = diastolic blood pressure.

Table 4. Mean difference in MMSE score between subjects classified according to presence or absence of hypertension.

	55-64 years (95% CI)	65-74 years (95% CI)	75-84 years (95% CI)	85-94 years (95% CI)	Total (95% CI)
Hypertension					
Total population*	-0.01 (-0.23;0.21)	-0.08 (-0.28;0.12)	0.51 (0.10;0.92)	1.65 (0.45;2.85)	0.33 (0.15;0.51)
Men†	0.08 (-0.33;0.49)	-0.09 (-0.40;0.22)	0.38 (-0.36;1.12)	0.07 (-2.32;2.46)	0.12 (-0.15;0.39)
Women†	-0.08 (-0.33;0.17)	-0.08 (-0.33;0.17)	0.58 (0.07;1.09)	2.15 (0.76;3.54)	0.47 (0.23;0.71)
Isolated systolic hypertension					
Total population*	-0.15 (-0.62;0.32)	-0.29 (-0.64;0.06)	0.06 (-0.59;0.71)	2.34 (0.79;3.89)	0.24 (-0.05;0.53)
Men†	0.11 (-0.77;0.99)	-0.18 (-0.67;0.31)	0.26 (-0.80;1.32)	2.48 (-0.73;5.69)	0.30 (-0.15;0.75)
Women†	-0.32 (-0.85;0.21)	-0.37 (-0.84;0.10)	-0.03 (-0.85;0.79)	2.31 (0.55;4.07)	0.24 (-0.15;0.63)

* Adjusted for age and gender.
† Adjusted for age.

Stratification according to presence of peripheral arterial disease suggested that the direct relation that was observed between increasing systolic blood pressure and cognitive function in the highest age groups, was mainly confined to subjects with evidence for peripheral arterial disease (table 3). For diastolic blood pressure, the association with MMSE score was absent irrespective of presence or absence of peripheral arterial disease (table 3).

When we dichotomized our population according to presence or absence of hypertension, or according to presence or absence of isolated systolic hypertension, the age-specific analyses reflected what was already apparent from the analyses where systolic blood pressure was included as a continuous variable: below the age of 75 years, subjects with hypertension performed worse than subjects without hypertension, whereas the opposite was true for persons older than 75 years (table 4).

Table 5 shows the results of the analyses regarding the relation between orthostatic hypertension and cognitive function. Orthostatic hypotension, defined as a concurrent decline in systolic and diastolic blood pressure, seemed not to be associated with cognitive function, and neither was systolic hypotension. Diastolic orthostatic hypotension was significantly associated with poorer performance on the MMSE. The occurrence of symptoms upon standing was also related to worse cognitive performance. The association between symptoms and cognitive test results was independent of the actual drop in blood pressure. The results were similar for subjects with and without presence of generalized atherosclerosis as indicated by presence of peripheral arterial disease.

Table 5. Mean difference in MMSE score between subjects classified according to presence or absence of orthostatic hypotension and symptoms, adjusted for age and gender.

	55-64 years (95% CI)	65-74 years (95% CI)	75-84 years (95% CI)	85-94 years (95% CI)	Total (95% CI)
Orthostatic hypotension	-0.92 (-1.61;-0.23)	0.36 (-0.15;0.87)	-0.23 (-1.13;0.67)	0.02 (-2.14;2.18)	-0.11 (-0.52;0.30)
Systolic orthostatic hypotension	0.03 (-0.24;0.30)	0.00 (-0.24;0.24)	0.20 (-0.25;0.65)	-0.19 (-1.56;1.18)	0.10 (-0.10;0.30)
Diastolic orthostatic hypotension	-1.03 (-1.46;-0.60)	-0.11 (-0.42;0.20)	0.09 (-0.50;0.68)	-0.73 (-2.26;0.80)	-0.31 (-0.58;-0.04)
Symptoms upon standing	0.16 (-0.17;0.49)	-0.05 (-0.32;0.22)	-0.66 (-1.17;-0.15)	-1.20 (-2.75;0.35)	-0.27 (-0.51;-0.03)

DISCUSSION

We assessed the relations of blood pressure level and orthostatic hypotension with cognitive function in a population based sample of 4,971 persons. We found that the relation between blood pressure and cognitive function was dependent on age. Among subjects younger than 75 years increasing systolic blood pressure was associated with poorer performance, whereas subjects older than 75 years performed better when they had higher systolic pressures. The relation of hypertension, and of isolated systolic hypertension, with cognitive function was in agreement with the relation for systolic blood pressure as a continuous variable and cognitive function. These relations could not be explained by differences in educational level. The positive relation between systolic blood pressure and cognitive function was especially present in subjects with generalized atherosclerosis. For orthostatic hypotension we found that a decline in diastolic blood pressure upon standing was inversely associated with cognitive function. Subjective symptoms were associated with poorer performance on the MMSE, irrespective of the actual change in blood pressure.

This study was based on cross-sectional data, which demands cautious interpretation. There are two ways in which selection could possibly have contributed to the relations we found, selective non-response and selective survival, and these deserve some discussion. Selective non-response may effect the validity of the study itself. Our study was based on a geographically defined elderly population without any exclusions. Although it is likely that at least some of the non-response was related to physical or mental morbidity, it is difficult to see how this could have resulted in the relations we found. For that would have required selective non-response of subjects with low blood pressures and high cognitive performance, or of subjects with high blood pressures and low cognitive performance among the oldest age groups, whereas opposite self-selection mechanisms should have occurred among younger subjects. We can not exclude the possibility of some non-response bias in our data, but we consider it unlikely to account for our findings. Selective survival pertains not so much to the validity of our study, but to the inference we can draw from it. If subjects with high blood pressure and concurrent poor cognitive performance would die prematurely as compared to individuals without any or both of these characteristics, a positive relation between blood pressure and cognitive function will result in the surviving population. On the other hand, our findings fit with results from mortality studies that found that in the very elderly higher diastolic blood pressure was associated with better survival,[18,19] and it has been suggested that in older subjects, because of more advanced

atherosclerosis, higher blood pressures may be needed to guarantee adequate blood flow.[20] Perhaps, for this age group, the concept of "essential" hypertension should be revised.

We used the Mini Mental State Examination as an indicator for cognitive function. The MMSE focuses mainly on cortical functions, whereas clinical studies have suggested that patients with hypertension as compared with normotensive controls perform in particular worse on tests assessing subcortical functions, such as mental speed and vigilance.[21] Furthermore, the MMSE was originally developed as a brief screening instrument for dementia and it may well be that the test is rather insensitive to minor disturbances in cognitive function. Both considerations suggest that cognitive impairment detected by the MMSE may be a conservative estimate of the actual loss of cognitive function. Although on an individual level the MMSE is probably not a very precise test to assess cognitive function, on a population level it adequately reflects the distribution of cognitive function.[22]

Most studies that reported on relations between blood pressure and cognitive function were based on samples of hypertensive patients, or middle-aged subjects. Population-based studies in the elderly reported thus far have shown conflicting results. Wallace et al. found that, among 2,433 subjects aged 65 years and over, persons with diastolic hypertension performed worse on a test of free-recall memory as compared to normotensive subjects, but they found no effect of isolated systolic hypertension.[6] In the Framingham Study, 2,032 individuals of 55 years or older were examined with a cognitive test battery. The authors concluded that there seemed no consistent relation between blood pressure and cognitive performance.[4] In the East-Boston Study four brief cognitive tests were administered to 3,627 persons aged 65 years and over. No consistent relations were found between diastolic or systolic blood pressure and cognitive function test scores, and the authors concluded that there was little evidence for a relation between blood pressure level and cognitive function among older persons.[7] The fact that we found systolic blood pressure and hypertension to be significantly associated with cognitive function, whereas others did not, is possibly owed to the larger size of our study population, which allowed for stratified analyses by age, and our sampling of a total population. By the stratification we could evaluate, and confirm, the modifying effect of age on the relation between blood pressure and cognitive function; an effect that has already been hinted at by Farmer et al.[4]

The appropriate way to analyse and interpret the data depends on how one views the pathophysiologic mechanisms that relate blood pressure, atherosclerosis, and cognitive function. Two basic possibilities may be postulated (figure 2). First, it may

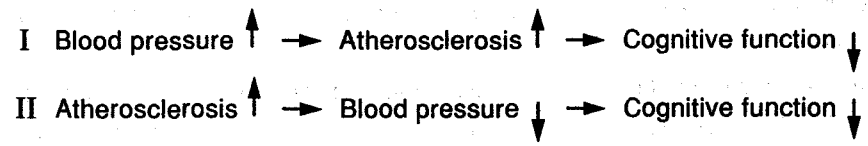

Figure 2. Scheme of different ways in which blood pressure, atherosclerosis, and cognitive function might be related.

be that elevated blood pressure causes atherosclerosis, which leads to clinically manifest or silent cerebral infarctions, resulting in loss of cognitive function. In that case, atherosclerosis and stroke would be intermediate on the causal pathway and should not be adjusted for when investigating the relation between blood pressure and cognitive function.[23] A second possibility is that atherosclerosis itself may alter the relation between blood pressure and cognitive function (mechanism I in figure 2). Atherosclerosis may result in narrowing of the cerebral arteries, which may require increasing blood pressure to guarantee adequate flow, and in impaired cerebral autoregulation of blood flow, and thereby in an increased vulnerability of the cerebral white matter to hypoperfusion. If this were the case, it would predict different associations to exist between blood pressure and cognitive function among subjects with and without atherosclerosis, dictating stratified analyses. It is conceivable that both proposed mechanisms coexist and that the question becomes rather which one predominates in which individuals. Our data are compatible with the view that among younger individuals (below age 75 years) the first mechanism is the most important one and that elevated blood pressure levels may have a deleterious effect on cognitive function, presumably by enhancing atherosclerosis and thereby increasing the loss of cerebral tissue due to clinically manifest or silent ischemic infarctions. Many of the persons who develop severe atherosclerotic disease will die prematurely. Among people who survive until ages above age 75 years, the situation differs according to presence or absence of atherosclerosis. The group without demonstrable atherosclerosis, may consist of subjects who have no atherosclerosis because they have blood pressures in the normal range, and of subjects with high blood pressures that constitute a selected group of survivors who are relatively resistant to the destructive effects of elevated blood pressure levels. In both instances, in the absence of atherosclerosis, blood pressure will seem unrelated to cognitive function. On the other hand, among persons who survive until older age while gradually accumulating atherosclerotic lesions, increasing

blood pressure may be required to maintain adequate cerebral blood flow. In that situation, low blood pressures can result in chronic hypoperfusion which then could lead to cognitive decline (mechanism II in figure 2).

When orthostatic hypotension is present, and cerebral autoregulation fails, the blood pressure may intermittently drop below the level that is required to guarantee cerebral perfusion. We know of no other population-based studies that investigated the relation between orthostatic hypotension and cognitive function. Researchers in vascular dementia have suggested that intermittent cerebral hypoperfusion might damage the cerebral white matter in the watershed zones that are particularly vulnerable to ischemia.[24] Our finding that orthostatic decrease in diastolic blood pressure was associated with poorer cognitive function may lend some support to this hypothesis. We found little overlap between orthostatic symptoms and actual change in blood pressure. Blood pressure change does not always reflect similar changes in cerebral perfusion and postural hypotension need not be similar to postural cerebral hypoperfusion.[25] Cerebral blood flow may fail in subjects with impaired cerebral autoregulation, resulting in subjective symptoms of cerebral hypoperfusion, even without a significant change in blood pressure.[12,13] We do not know whether reported orthostatic symptoms indeed occurred as a result of diminished cerebral perfusion, or merely reflected a frail physical status in the concerning persons. Given the significant association we found between these symptoms and cognitive function, it might be worthwhile to investigate the underlying pathophysiological mechanism.

Although this study does not allow us to draw conclusions regarding causality, the results are compatible with the view that intermittent or chronic hypotension in elderly subjects is associated with lower cognitive performance, particularly in the very old.

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Chapter 4

Vascular determinants of cognitive function

Chapter 4.1

Cerebral white matter lesions, vascular risk factors and cognitive function in a population-based study

Magnetic resonance imaging (MRI) brain scans of elderly persons frequently show lesions of the cerebral white matter. The frequency of these lesions reportedly increases with age,[1-7] and with the presence of cardiovascular risk factors.[1,2,6-10] Pathological correlates of white matter lesions support the hypothesis that arteriolosclerosis has an important role in their pathogenesis.[11-13] Although it has been suggested that these lesions represent the anatomical substrate of vascular dementia,[14,15] their clinical significance remains controversial. Some studies found a relation between white matter lesions and cognitive function,[10,16,17] but this was not confirmed by others.[3,4,18,19] Another issue is the type of white matter lesions on MRI. Several studies reported that periventricular hyperintensities were more prevalent in demented patients than in age-matched controls.[16,18,20]

Most studies on white matter lesions were based on retrospectively selected hospital series or small samples of volunteers. We studied the frequency of white matter lesions in a population-based sample and assessed whether white matter lesions were related to cardiovascular risk factors, and whether they were associated with impairment in cognitive function. We investigated coagulation factors along with classical vascular risk factors, because thrombogenesis has been recognised in recent years as an important determinant of cardiovascular disease.[21]

METHODS

Subjects

Subjects of the ages 65 to 84 years were randomly selected, stratified by gender and 5-year age-groups, from the list of participants of the Rotterdam Study. The Rotterdam Study is a single center prospective follow-up study of the total population aged 55 years or over, of the suburb of Ommoord in Rotterdam,

The Netherlands. The study has been approved by the Medical Ethics Committee of Erasmus University. Written informed consent is obtained from all participants. Rationale and design of the Rotterdam Study have been described elsewhere.[22] In short, the objective of the study is to investigate determinants of chronic and disabling cardiovascular, neurogeriatric, locomotor and ophthalmologic diseases. All participants are extensively interviewed at home, and subsequently undergo physical examination during two visits at a research center. The total eligible population comprises 11,854 persons, with 6,494 persons between the ages of 65 and 85 years. Enrollment in the study started in 1990 and was based on random selection procedures. By December 31, 1991, 3,352 residents of Ommoord had participated, including 1,994 subjects aged 65 to 84 years. The refusal rate in those aged 65 to 84 years was 18 per cent, similar for men and women. Subjects were invited to participate in the additional MRI study directly after they had finished the standard study protocol. Of the 134 individuals initially selected at random, three persons were excluded because they had a pacemaker or metal prostheses or clips, one because he was suffering from a major psychiatric disorder, and two persons who were wheelchair-bound. Persons residing in homes for the elderly were included. Of the 128 subjects that were actually invited to take part in the additional MRI study 111 (87%) consented to participate.

Measurements

Information on current health status, medical history, drug prescriptions and actual use, smoking behavior and level of education was obtained by means of a computerized questionnaire. Prevalent coronary heart disease was assessed by means of a Dutch version of the Rose cardiovascular questionnaire.[23] The history of cerebrovascular events or myocardial infarction was assessed by direct questioning and considered positive when the diagnosis had been confirmed by a physician. With respect to smoking behavior, subjects were categorized in groups of current smokers, former smokers and those who had never smoked. During the two visits at the research center several cardiovascular risk factors were measured. Blood pressure was measured in the sitting position at the right upper arm with a random-zero sphygmomanometer. The average of two measurements, separated by a count of the pulse rate, was used in the analysis.[24] Hypertension was defined as a systolic blood pressure of 160 mmHg or over and/or a diastolic blood pressure of 95 mmHg or over, or as the use of antihypertensive drugs.[24]

Isolated systolic hypertension was defined as a systolic blood pressure of at least 160 mmHg with a diastolic blood pressure below 95 mmHg, with the exclusion of subjects on antihypertensive medication.[25]

A venipuncture was performed, with minimal stasis, through a 21 gauge butterfly needle with tube (Surflo winged infusion set, Terumo, Belgium). Blood samples were collected into siliconized Vacutainer tubes (Becton & Dickinson, France) containing clotting activator and separator for serum, or 0.129 M sodium citrate for plasma. Serum was separated by a one-stage centrifugation for 10 min at 1,600 g. From the citrate tubes platelet poor plasma was prepared by a two-stage centrifugation; first for 10 min at 1,600 g at 4 ^{0}C and subsequently for 10 minutes at 10,000 g at 4 ^{0}C. All samples were quickly frozen in liquid nitrogen and then stored at -80 ^{0}C before assay. Serum total cholesterol was determined with an automated enzymatic procedure.[26] High density lipoprotein cholesterol level was measured similarly, after precipitation of the non HDL fraction with phosphotungstate-magnesium. Plasma fibrinogen level was assessed according to the Clauss method (Diamed AG, Switzerland).[27] Factor VIIc and factor VIIIc were assayed by means of Automatic Coagulation Laboratory (ACL) (Instrumentation Laboratory, IJsselstein, The Netherlands), with the aid of factor VII and factor VIII deficient plasma (Ortho Diagnostic System, Beerse, Belgium) with Thromborel S (Behringwerke, Germany) and Thrombosil I (Ortho Diagnostic Systems, Beerse, Belgium) as reagents, respectively. Plasma obtained from 40 healthy men was pooled and served as reference for the measurements of factor VIIc and factor VIIIc. Factor VIIc and factor VIIIc levels of the donors were all within normal range and no differences between reference pools could be detected.

Subjective impairment of memory was assessed as part of the home interview and was defined as the participant reporting to have memory problems that interfered with daily life, and that had developed during adult life. The CAMCOG, the neuropsychological test from the Cambridge Examination for Mental disorders of the Elderly (CAMDEX) was administered to all subjects that participated in the MRI study as an objective measure of cognitive function.[28,29] The CAMCOG is a composite cognitive test that consists of 60 items, has a maximum score of 107, and allows the calculation of 11 subscores (orientation, language comprehension, language expression, recent memory, remote memory, learning memory, attention, praxis, calculation, abstract thinking, perception).

Magnetic resonance imaging scans of the brain were obtained with a 1.5 T Philips Gyroscan. Multiple slice spin-echo sequences were performed with a repetition time of 2000 msec and an echotime of 50 and 100 msec, producing a T2-weighted image. Images were obtained in the axial plane with a slice thickness of 7 mm and a slice increment of 1.4 mm. The MRI scans were analyzed with the assessors blinded to any clinical information. No universally accepted scale exists to date for rating white matter lesions on MRI. We have previously used a rating system that distinguished only between no lesions, punctate lesions and confluent lesions; the reliability of this method was satisfactory.[30] For the present study, the presence of punctate lesions was dichotomized at less than five and five or more lesions.[18] Infarcts on MRI were recorded, but not included in the rating of the white matter lesions. In addition, we distinguished between white matter lesions directly adjacent to the ventricles (periventricular lesions), and punctate or confluent lesions at some distance from the ventricles (focal lesions), in accordance with several other authors.[2,18,20,31,32] Small caps on the horns of the lateral ventricles and pencil-thin lining around the ventricles were considered normal.[9,18,19,33] On the basis of these criteria the overall severity of white matter lesions was graded as follows (method developed by Dr. L.R. Caplan and Dr. J.C. van Swieten): grade 0 scans showed no or slight periventricular hyperintensity, less than 5 punctate lesions and no confluent lesions; grade 1 scans showed moderate periventricular hyperintensity or more than 5 punctate lesions, or both, but no confluent lesions; scans with severe periventricular hyperintensity or confluent lesions were graded as 2, regardless of the presence of punctate lesions.

Analysis

The prevalence of white matter lesions was calculated by 5 years age category for men and women separately. Since age was significantly associated with the prevalence of white matter lesions, and gender tended to be, the relations between all other variables and white matter lesions were evaluated with adjustment for both age and gender. Odds ratios (with 95 per cent confidence interval) were calculated as a measure of the strength of the association between the putative determinants in subjects with white matter lesions (grade 1 or 2) as compared to that in subjects without white matter lesions (grade 0), by means of multiple logistic regression analysis. For the analyses of factor VIIc activity, subjects currently taking anticoagulant drugs were excluded. Subjects taking

antihypertensive medication were excluded from the analyses of isolated systolic hypertension. Continuous variables were evaluated continuously as well as classified in quartiles of their distribution. When both analyses yielded the same information, only the results from the first analyses are reported.

The relation between the presence of white matter lesions and subjective memory impairment was assessed also by means of logistic regression, with the presence of complaints about memory as the dependent variable. Mean scores and 95 per cent confidence intervals were calculated for the CAMCOG, for each of the three levels of severity of white matter lesions. The relation between severity of white matter lesions and performance on the CAMCOG was evaluated after logarithmic transformation with multiple linear regression. In order to examine the relation between white matter lesions and cognitive function as restrictedly as possible, we performed a separate analysis excluding five subjects with a diagnosis of probable Alzheimer's disease, according to the criteria of the National Institute on Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association,[34] since in those individuals the Alzheimer dementia probably accounted for most of the cognitive impairment.

RESULTS

The distribution of the vascular risk factors in the 111 subjects in whom a MRI scan was made was very similar to that in all 65 to 84 year old subjects examined in the Rotterdam Study. White matter lesions were seen in 27 per cent of subjects, with severe lesions in 10 per cent. The prevalence of white matter lesions increased with age, from 11 per cent in persons aged 65 to 69 years to 54 per cent in persons aged 80 to 84 years (table 1). The severity of the lesions also increased with age; whereas severe lesions constituted 25 per cent of all lesions in subjects aged 65 to 69 years, the corresponding figure was 50 per cent for subjects of 80 to 84 years of age. In each age category the observed prevalence and severity of white matter lesions was higher among women than among men, but this difference failed to reach significance (odds ratio (OR) 2.1; 95 per cent confidence interval (95% CI) 0.9 - 4.9). The female predominance was independent of a history of stroke or myocardial infarction.

Table 1. Prevalence of cerebral white matter lesions by age and gender.

	Age (years)	Number of subjects	White matter lesions (% in age group)		
			No/slight*	Moderate†	Severe‡
Men	65 - 69	17	94	6	0
	70 - 74	12	83	17	0
	75 - 79	11	73	27	0
	80 - 84	11	64	27	9
	Total	51	80	18	2
Women	65 - 69	19	84	11	5
	70 - 74	11	73	18	9
	75 - 79	15	74	13	13
	80 - 84	15	33	27	40
	Total	60	67	17	17
Total	65 - 69	36	89	8	3
	70 - 74	23	78	17	4
	75 - 79	26	73	19	8
	80 - 84	26	46	27	27
	Total	111	73	17	10

* < 5 focal lesions, no/slight periventricular hyperintensities and no confluent lesions.
† < 5 focal lesions, moderate periventricular hyperintensities and no confluent lesions; or ≥ 5 focal lesions and no/slight/moderate periventricular hyperintensities but no confluent lesions.
‡ Confluent lesions and/or severe periventricular hyperintensities.

A history of a major cardiovascular event was present more often in subjects with white matter lesions, with an OR of 4.4 and a 95% CI of 1.4 - 13.7 (table 2). With increasing blood pressure there was only a slight and non-significant increase in risk of white matter lesions for all subjects combined (table 2). However, systolic blood pressure and diastolic blood pressure were significantly associated with white matter lesions in subjects aged 65 to 74 years, and not in those above the age of 75 years. These relations did not change when subjects on antihypertensive medication were excluded (table 2). The OR for systolic blood pressure in the younger group was 1.6 per 10 mmHg (95% CI 1.1 - 2.5), and for diastolic blood pressure 5.7 per 10 mmHg (95% CI 1.6 - 20.1). For the dichotomised definition of hypertension or isolated systolic hypertension the

Table 2. Positive history of cardiovascular events and blood pressure in relation to presence of white matter lesions, adjusted for age and gender.

	Subjects (events)	65-75 years	75-84 years	All ages
		OR (95% CI)	OR (95% CI)	OR (95% CI)
Stroke*	110 (10)	2.0 (0.1;28.6)	5.8 (0.8;41.7)	3.4 (0.8;14.8)
Myocardial infarction*	110 (14)	5.2 (0.5;50.3)	3.6 (0.7;17.8)	3.9 (1.1;14.1)
Stroke or myocardial infarction*	110 (20)	3.0 (0.4;23.1)	6.5 (1.4;30.8)	4.4 (1.4;13.7)
SBP (per 10 mmHg)	111	1.6 (1.1;2.5)	0.9 (0.6;1.2)	1.2 (0.9;1.5)
excl subjects on antihypertensive drugs	85	2.9 (1.2;7.0)	0.8 (0.6;1.2)	1.1 (0.8;1.5)
DBP (per 10 mmHg)	111	5.7 (1.6;20.1)	0.6 (0.3;1.3)	1.3 (0.8;2.1)
Hypertension†	111	8.2 (1.4;49.5)	0.7 (0.2;2.6)	1.8 (0.7;4.9)
ISH‡	85	45.5 (2.5;825.1)	0.8 (0.1;6.5)	4.0 (0.8;19.3)

OR = odds ratio; 95% CI = 95% confidence interval; SBP = systolic blood pressure; DBP = diastolic blood pressure; ISH = isolated systolic hypertension.

* Interview information was missing for one subject, due to accidental deletion from the database.

† Defined as systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 95 mmHg, or use of antihypertensive medication (n=35 with hypertension).

‡ Defined as systolic blood pressure ≥ 160 mmHg and diastolic blood pressure < 95 mmHg. Subjects currently on antihypertensive medication excluded (n=9 with isolated systolic hypertension).

same pattern was observed. The observed relations persisted after adjustment for a previous stroke or myocardial infarction.

Total cholesterol and high density lipoprotein cholesterol levels were not significantly associated with the presence of white matter lesions among all subjects combined. However, for subjects aged 65 to 74 years higher levels of total cholesterol tended to be associated with white matter lesions (table 3). Body mass index (weight in kilograms divided by height squared in meters) was not related to the presence of white matter lesions. We nevertheless evaluated the relation between lipoprotein levels and white matter lesions adjusting for body mass index, since the latter is a known risk factor for vascular disease and usually strongly related to lipoprotein levels. However, this only marginally influenced the results (table 3).

Table 3. Levels of plasmalipids and thrombogenic factors in relation to presence of white matter lesions, adjusted for age and gender.

	Subjects	65-75 years	75-84 years	All ages
		OR (95% CI)	OR (95% CI)	OR (95% CI)
Cholesterol (per mmol/l)	109	1.8 (0.9;3.6)	0.7 (0.4;1.2)	1.1 (0.7;1.5)
Adjusted for BMI	107	2.2 (1.0;4.7)	0.8 (0.5;1.4)	1.2 (0.8;1.7)
HDL (per 0.1 mmol/l)	108	0.1 (0.0;2.8)	0.6 (0.1;3.7)	0.4 (0.1;1.9)
Adjusted for BMI	106	0.2 (0.0;4.0)	0.4 (0.1;2.7)	0.3 (0.1;1.7)
Factor VIIc (per 0.1 IU/ml)*	94	1.3 (0.9;1.9)	1.2 (0.8;1.7)	1.2 (0.9;1.6)
Above vs below 75th percentile	94	5.1 (0.9;29.7)	5.3 (0.8;33.7)	4.7 (1.4;15.8)
Factor VIIIc (per 0.1 IU/ml)	100	1.1 (0.9;1.2)	1.0 (0.9;1.2)	1.1 (1.0;1.1)
Fibrinogen (per g/l)†	82	2.7 (0.3;25.3)	2.4 (0.9;6.8)	2.7 (1.1;6.8)

OR = odds ratio; 95% CI = 95% confidence interval; BMI = body mass index (weight(kg)/length(m)^2); HDL = high density lipoprotein cholesterol.

* Subjects currently taking anticoagulant drugs excluded.

† Current smokers excluded.

Of the hemostatic factors, factor VIIIc activity was not associated with white matter lesions (table 3). When analyzed continuously, factor VIIc activity showed a slight positive relation with white matter lesions, but this was not significant. More detailed analysis revealed a threshold effect, in that subjects with a high factor VIIc activity (above the 75th percentile of the distribution) had significantly more often white matter lesions than subjects with lower factor VIIc activity (below the 75th percentile) (OR 4.7, 95% CI 1.4 - 15.8). The odds ratio of plasma fibrinogen with the presence of lesions was 1.6 (95% CI 0.8 - 3.3). Since smoking increases fibrinogen levels, we subsequently excluded current smokers from the analyses. This increased the strength of the relation (OR 2.7, 95% CI 1.1 - 6.8) (table 3). No threshold effects were discerned. With regards to smoking itself, no relation was observed between white matter lesions and current or former smoking. When we adjusted for previous stroke or myocardial infarction our findings did not substantially change.

Table 4. Relation between white matter lesions and subjective memory impairment.

	Number of subjects		Crude		Adjusted*	
	Total	Memory complaints	OR	(95% CI)	OR	(95% CI)
All subjects						
Grade 0	81	11	1	—	1	—
Grade 1	19	5	2.3	(0.7;7.6)	2.1	(0.6;7.7)
Grade 2	10	4	4.2	(1.0;17.5)	4.1	(0.8;21.1)
Test for linear trend			p = 0.05		p = 0.02	
AD patients excluded						
Grade 0	77	9	1	—	1	—
Grade 1	17	3	1.6	(0.4;6.8)	1.6	(0.3;7.1)
Grade 2	10	4	5.0	(1.2;21.3)	5.1	(0.9;28.8)
Test for linear trend			p = 0.15		p = 0.16	

OR = odds ratio; 95% CI = 95% confidence interval; AD = Alzheimer's disease.
* Adjusted for age, gender, and previous stroke.

Table 5. Comparison of test scores on the CAMCOG test of cognitive function between subjects with and without white matter lesions.

	Overall	White matter lesions			Linear trend test (p)	
		Grade 0	Grade 1	Grade 2	Crude	Adjusted
All subjects						
CAMCOG mean (95% CI)	89.9 (87.5;92.2)	90.9 (88.3;93.5)	88.1 (83.2;93.0)	84.6 (69.6;99.5)	0.07	0.23
AD patients excluded						
CAMCOG mean (95% CI)	91.5 (89.5;93.4)	92.8 (91.0;94.6)	89.5 (85.4;93.7)	84.6 (69.6;99.5)	0.02	0.08

AD = Alzheimer's disease; 95% CI = 95 % confidence interval.

Subjective memory impairment was reported by 18 per cent of all subjects, and significantly more often by subjects with white matter lesions. There was a significant trend for more memory complaints to occur with increasing level of

severity of lesions. This relation did not change after we controlled for age, gender and a history of previous stroke; nor after the exclusion of Alzheimer patients (table 4).

The average score on the CAMCOG increased from 84.6 for individuals with severe white matter lesions to 90.9 for subjects without lesions; when Alzheimer patients were excluded the corresponding figures were 84.6 and 91.5, respectively. These differences were, however, partly confounded by age. After we controlled for age, lower scores still tended to be associated with increasing severity of lesions, but this was not significant at the five percent level (table 5). Analysis on the subtests of the CAMCOG did not reveal particular subtests to be more severely affected than others. The level of education on its own was highly correlated with cognitive test scores. However, when age had been controlled for, additional adjustment for the period of formal education (in three categories: 6 years or less; 7 to 13 years; 14 years and over) did not affect the results.

DISCUSSION

We studied the prevalence, risk factors and relation with cognitive function of cerebral white matter lesions in a sample from the general population of 65 years or over. The prevalence and severity of lesions both increased with age. The observations in this study suggest that a history of stroke or myocardial infarction, factor VIIc activity and fibrinogen level are independent risk factors for all subjects of 65 years or over; for subjects between 65 and 74 years the level of blood pressure and plasma cholesterol are additional independent risk factors. This study also provides some evidence for an association between white matter lesions and cognitive function, in particular subjective impairment of memory.

Most previous studies on the presence of white matter lesions were based on hospital series, and are therefore not representative for the occurrence of white matter lesions in the general population. A few studies addressed the presence of white matter lesions in smaller samples of healthy elderly volunteers, and reported prevalence estimates of moderate to severe lesions that were similar[3,4] or somewhat higher[18] than we found. Our study presents the first population-based estimates of the prevalence of white matter lesions. However, since the

response rate in our study was less than 100 per cent we have to face the possibility of selection bias. Although we have no actual information on those who refused to participate, in some instances refusal seemed related to physical or mental impairment and we consider it possible that our results slightly underestimate the true prevalence.

The increasing frequency of white matter lesions with age seems to have shifted by 5 years towards earlier ages in women as compared to men, resulting in a female predominance for the prevalence of these lesions. This finding is in contrast with the usually reported age-specific predominance of men in cardiovascular disease. No gender differences in prevalence of MRI lesions have been reported from other studies. In a study of patients with Alzheimer's disease Diaz et al. found white matter lesions on CT to be disproportionately common in female patients.[35] On the basis of our data we can not conclude whether the incidence of white matter lesions is actually higher in women, whether this higher prevalence is merely the result of unequal survival of women and men once they have developed the lesions, or whether it is a chance finding.

In accordance with other studies, we found previous cardiovascular events to be related with white matter lesions. Several explanations are possible for the age-dependent results regarding blood pressure and total cholesterol, which were associated with the presence of white matter lesions only in the age band 65 - 74 years. First, it could be the result of selection bias. However, subjects were randomly sampled and we have no indication that cerebral disorders or multiple vascular morbidity were directly related to refusal to undergo MRI-scanning. Furthermore, the relatively high response rates in both the overall study (82 per cent) and in the MRI study (87 per cent) make it unlikely that this can fully explain the difference between older and younger subjects. Second, the findings could be the result of selective survival. Most studies of cardiovascular risk factors in the elderly reported a decrease in relative importance of total cholesterol with age.[36] Analogously, in the very old the importance of an elevated blood pressure for the risk of vascular disease seems to diminish, or even to reverse.[37] Our findings in subjects aged 75 to 84 years fit these observations. Since cardiovascular risk factors are all associated with an increased mortality, very old persons with these risk factors may form a special group by natural selection. A third explanation can be that the relative importance of various atherogenic factors actually changes with age.

Several studies identified factors associated with coagulation and hemostasis as important risk factors for the initiation and progression of cardiovascular disease.[21] An elevated fibrinogen level is a major cardiovascular risk factor.[21,38,39] Schneider et al. found elevated fibrinogen levels and hyperviscosity in patients with subcortical arteriosclerotic encephalopathy (Binswanger's disease), the end stage of the white matter lesions under study, and also in patients with lacunar infarcts, compared with healthy control subjects without vascular risk factors. They suggested that plasma hyperviscosity together with arteriolosclerosis might lead to chronic hypoperfusion of the white matter.[40] However, there are many intermediate factors that alone or in combination might underlie the association of fibrinogen with ischemic vascular events, including fibrin formation, platelet aggregation, blood rheology and inflammation, and the precise pathophysiologic processes remain to be elucidated.[41] Increased levels of factor VIIc and factor VIIIc activity are associated with increased risk of coronary heart disease,[42] and raised levels of factor VIIc and factor VIIIc activity were recently observed in elderly subjects with atherosclerotic disease.[43] Similarly, it was found in the Rotterdam Study that these factors are elevated in subjects with atherosclerotic disease of the carotid artery.[44] The increased prevalence of white matter lesions with both fibrinogen and factor VIIc levels suggests involvement of the coagulation system in the pathogenesis of white matter lesions of the brain. The question remains, however, whether the increased fibrinogen and factor VII levels are causal factors in the pathogenesis of white matter lesions, or whether they merely reflect an increased production of coagulation factors in reaction to severe vascular disease. It will be important to asses their impact prospectively since these factors are potentially modifiable, e.g. through appropriate life-style changes, or drugs.[45]

In our study, moderate or severe lesions of the white matter were significantly associated with lower scores on tests of cognitive function when demented patients were excluded, and tended to be so after controlling for age and education. Leukoencephalopathy was furthermore significantly associated with subjective impairment of memory. It is unknown whether such subjective impressions are indicative of actual cognitive decline, but the lower scores on the CAMCOG suggest that this might be the case. A few other studies reported a relation between white matter lesions on MRI in non-demented elderly persons and cognitive impairment[10,17] although small lesions did not seem to have an effect on intellectual function.[3,4] However, since all these reports come from

cross-sectional surveys, inferences regarding a causal relationship between white matter lesions and cognitive function remain tentative.

In conclusion, we found that the presence of white matter lesions was associated with most known vascular risk factors, supporting the hypothesis that atherosclerosis underlies these lesions. Furthermore, we found that white matter lesions in non-demented subjects tended to be related to cognitive dysfunction. A potentially important finding is the relation we observed with thrombogenic factors. If their role in the pathogenesis of white matter lesions would be confirmed in follow-up studies, this might offer clues for preventive intervention.

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Chapter 4.2

Cerebral white matter lesions and atherosclerosis in a population-based study

Cerebral white matter lesions are frequently found on magnetic resonance images of brains of elderly subjects.[1-3] These lesions have been associated with a positive history of stroke and coronary heart disease and with elevated levels of established cardiovascular risk factors.[4-7] Recently, we reported a positive association between hemostatic factors and cerebral white matter lesions in an elderly population.[6] These findings may indicate that part of the cerebral white matter lesions in the elderly may be due to atherosclerosis, possibly mediated by cardiovascular risk factors.

With the availability of non-invasive techniques for assessing the presence and extent of atherosclerotic vessel wall abnormalities at different arterial sites, the association between cerebral white matter lesions and atherosclerosis can be studied more directly in populations at large. Non-invasive duplex ultrasonography, combined with Doppler spectral analysis, may be used to assess hemodynamically significant stenosis of the carotid artery.[8] Furthermore, with high resolution B-mode ultrasonography signs of early atherosclerosis of the carotid artery wall can be assessed non-invasively in an effective and accurate way.[9-13] The ratio of systolic blood pressure at the ankle to the systolic blood pressure at the arm (ankle-arm index) has been found to reflect the presence of atherosclerotic vessel wall abnormalities of the arteries of the lower extremities.[14,15] The presence of a myocardial infarction, confirmed by electrocardiography, may be used as an indicator of the presence of coronary atherosclerosis.[16]

In this paper we present findings on the association of cerebral white matter lesions and non-invasively assessed atherosclerosis among 111 participants of the Rotterdam Study.

METHODS

Population

The Rotterdam Study is a single centre prospective follow-up study of a cohort of elderly subjects, aged 55 years or over. Eventually the cohort will comprise close to 10.000 subjects. The study has been approved by the Medical Ethics Committee of Erasmus University and written informed consent is obtained from all participants. The rationale and design of the Rotterdam Study have been described elsewhere.[17] In short, all inhabitants, aged 55 years or over, living at a specific point in time in one district of Rotterdam (the suburb of Ommoord), The Netherlands were invited for participation. The cohort comprises all those who consented to participate and were enroled in the study. The objective of the Rotterdam Study is to investigate determinants of chronic disabling diseases in an ageing population. Incidence and risk factors of neurogeriatric diseases, locomotor diseases, ophthalmologic diseases and cardiovascular diseases are being studied. The study comprises an extensive home interview, followed by two visits at the Rotterdam Study research centre for clinical examinations. The participation rate of the cohort at the time of the present analysis was 80%.

Participants, aged 65 to 85 years, were invited to participate in an additional study on the presence and determinants of cerebral white matter lesions on magnetic resonance images directly after they had finished the baseline study protocol of the Rotterdam Study.[6] They were randomly selected, stratified by 5 years age-groups and gender. Of the 134 subjects initially selected, six were excluded: three because of a pacemaker or metal prostheses or clips, one because of a major psychiatric illness and two because they were wheelchair-bound and unable to walk. Of the 128 subjects that were eligible for magnetic resonance imaging, 111 (87%) consented to participate.

Measurements

Carotid arteries. Haemodynamically significant stenosis of the carotid artery was ultrasonographically assessed using a 7.5 MHz sector transducer in combination with a 5 MHz pulsed Doppler (ATL UltraMark IV, Advanced Technology Laboratories, Bethel, Washington, USA).[18] For reasons of feasibility, only the right carotid artery was measured. Interpretation of velocity profiles was done on-line according to standard criteria.[19] The right internal carotid artery was categorized as normal (0% reduction of lumen diameter), minimal lesions (1-15% reduction), moderate stenosis (16-49% reduction) or severe stenosis (≥ 50% reduction).

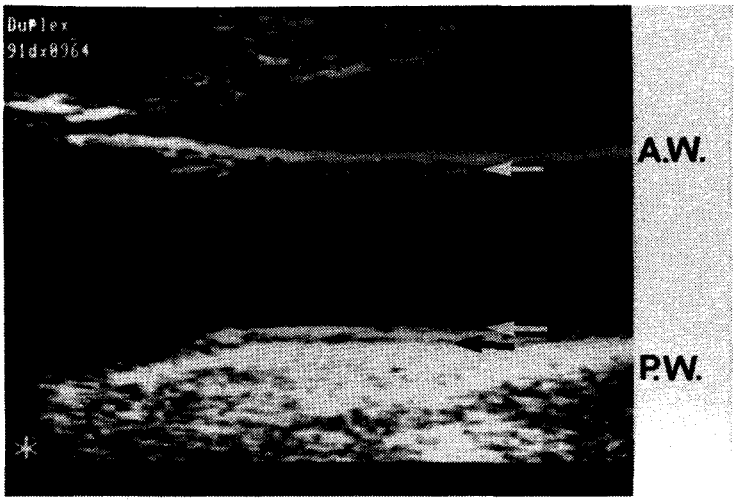

Figure 1. Characteristic longitudinal 2-D ultrasound image of the distal common carotid artery. AW = Anterior (near) wall of the carotid artery; PW = Posterior (far) wall of the carotid artery. Arrows from top to bottom indicate the leading edge of the intima-lumen interface at the near wall, the lumen-intima interfaces and the media-adventitia interface at the far wall, respectively.

To assess carotid intima-media wall thickness, ultrasonography of both carotid arteries was performed with a 7.5 MHz linear array transducer. On a longitudinal 2-dimensional ultrasound image of the carotid artery, the near and far wall of the carotid artery are displayed as two bright white lines separated by a hypo-echogenic space (figure 1).[20] The distance of the leading edge of the second bright line on the near wall (intima-lumen interface) to the leading edge of the first bright line on the far wall (lumen-intima interface) represents the lumen diameter. The distance between the lumen-intima-interface and the leading edge second bright line (media-adventitia interface) indicates the intima-media wall thickness.[20,21] Studies have indicated that the posterior (far) wall intima-media thickness as seen with ultrasound, truly reflects the anatomical intima-media layer.[20,21]

According to the Rotterdam Study scanning protocol, a careful search is performed for the intima-lumen interface on the near wall, the lumen-intima interface and the media-adventitia interface on the far wall of the distal common carotid artery.[13] When an optimal longitudinal image is obtained, it is frozen on the R wave of the electrocardiogram and stored on video tape. This procedure is repeated three times for both sides. Subsequently, the common carotid artery is on-line evaluated for the presence (yes/no) of atherosclerotic lesions, defined as a focal widening relative to

adjacent segments, with protrusion into the lumen either composed of only calcified deposits or a combination of calcifications and non-calcified material. The actual measurements of lumen diameter and intima-media wall thickness are performed off-line. From the video tape, the frozen images are digitized and displayed on the screen of a personal computer using additional dedicated software. This procedure has been described in detail previously.[13,21] In short, with a cursor the interfaces of the distal common carotid artery are marked over a length of 10 mm. The beginning of the dilatation of the distal common carotid artery serves as a reference point for the start of the measurement. This method permits the determination of mean values as well as maximal values for intima-media wall thickness and lumen diameter. The average of the lumen diameter and the intima-media wall thickness of each of the three frozen images is calculated. For each subject a mean lumen diameter and a mean intima-media wall thickness ((left + right)/2) is taken as a measure for current lumen diameter and wall thickness of the distal common carotid artery, respectively. With respect to focal lesions the presence or absence of calcifications and acoustic shadowing is noted. For all measurements, alternative choices are present as 'can not tell' and 'not recorded'. In this paper, only data from the intima-media wall thickness of the far wall of the common carotid artery were considered in the analysis.

In a separate reproducibility study, eighty participants of the Rotterdam Study underwent a second ultrasound scan of both carotid arteries within 3 months of the first scan. The replicate measurements involved the posterior intima-media wall thickness. Mean differences (SD) in intima-media wall thickness of the carotid artery between paired measurements of sonographers, readers and visits were -0.005 (0.09), 0.060 (0.05) and -0.033 mm (0.12), respectively.

Coronary arteries. A resting standard 12-lead electrocardiogram was obtained with an ACTA Gnosis IV (EsaoteBiomedica, Firenze, Italy). The electrocardiograms were read and coded according to the Minnesota code.[22] The assessment of a possible or definite myocardial infarction was based on the presence of major, moderate and minor Q/QS abnormalities and a clinical evaluation of the electrocardiogram by a cardiologist (Dr H.A.C.M Kruijssen). The presence of a possible or definite myocardial infarction on the electrocardiogram was used as an indicator of prevalent atherosclerotic coronary artery disease.[16]

Arteries of the lower extremities. The presence of atherosclerosis in the arteries of the lower extremities was evaluated by measuring the systolic blood pressure level of the posterior tibial artery at both left and right side by means of an 8 MHz continuous wave doppler probe (Huntleigh 500 D, Huntleigh Technology, Bedfordshire, UK)

and a random-zero sphygmomanometer.[14,15] For each side a single blood pressure reading was taken with the subject in supine position. The ratio of the systolic blood pressure at the ankle to the systolic blood pressure at the arm (ankle-arm index) was calculated for each leg. The lowest ankle-arm index in either leg was used in the analysis.[14] In agreement with the criteria proposed by Fowkes et al.,[15] and by Schroll and Munck,[23] an ankle-arm index level lower than 0.90 at at least one side was used to select a group with a high probability of having peripheral atherosclerosis. In the analysis this group was classified as 'peripheral arterial disease'.

Cardiovascular risk factors. Information on current health status, medical history, drug use, and smoking behaviour was obtained using a computerized questionnaire. With respect to smoking behaviour, subjects were categorized in groups of current smokers, former smokers and those who had never smoked. During two visits at the research centre several cardiovascular risk indicators were measured. Sitting blood pressure was measured at the right upper arm with a random-zero sphygmomanometer. The average of two measurements obtained at one occasion, separated by a count of the pulse rate, was used in the analysis. Hypertension was defined as a systolic blood pressure level of 160 mmHg or over and/or a diastolic blood pressure level of 95 mmHg or over and/or current use of antihypertensive drugs.

A venipuncture was performed, applying minimal stasis, using a 21 gauge Butterfly needle with tube (Surflo winged infusion set, Terumo, Belgium). Serum total cholesterol was determined by means of an automated enzymatic procedure.[24] High density lipoprotein (HDL) cholesterol was measured similarly, after precipitation of the non HDL fraction with phosphotungstate-magnesium.

Cerebral white matter lesions. Magnetic resonance imaging scans of the brain were obtained with a 1.5 T Philips Gyroscan. Multiple slice spin-echo sequences were performed with a repetition time of 2000 msec and an echotime of 50 and 100 msec, producing a T2-weighted image. Images were obtained in the axial plane with a slice thickness of 7 mm and a slice increment of 1.4 mm. The magnetic resonance imaging scans were analyzed with the assessors blinded to any clinical information and to the results of the other measurements. We distinguished between cerebral white matter lesions directly adjacent to the ventricles (periventricular lesions), and punctate or confluent lesions at some distance from the ventricles (focal lesions). The presence of punctate lesions was dichotomized at less than five and five or more lesions. Small caps on the horns of the lateral ventricles and pencil-thin lining around the ventricles were considered normal.[1,5,25] Infarcts on magnetic resonance imaging were recorded, but not included in the rating of the cerebral white matter lesions. On the basis of

these criteria the overall severity of cerebral white matter lesions was graded as follows (method developed by Dr. L.R. Caplan and Dr. J.C. van Swieten): grade 0 scans showed no or slight periventricular hyperintensity, less than 5 punctate lesions and no confluent lesions; grade 1 scans showed moderate periventricular hyperintensity or more than 5 punctate lesions, or both, but no confluent lesions; grade 2 scans had severe periventricular hyperintensity or confluent lesions, regardless of the presence of punctate lesions. In addition, for some analyses subjects were classified as having cerebral white matter lesions (grade 1 or 2) or as being without cerebral white matter lesions (grade 0).[6]

Analysis

In three subjects it was not possible to obtain reliable measurements of the internal carotid artery, mainly because of extreme tortuosity of the artery. Of five subjects, data on intima-media wall thickness were not available, because of technical failure of the equipment. Of four subjects measurement of vessel wall thickness could not be performed from the stored images because of poor visualization. Of 102 subjects (92%) measurements of posterior intima-media wall thickness were available, whereas data on presence of plaques in the common carotid artery and the bifurcation were obtained in 94% and 78% of the subjects, respectively. Data of the ankle-arm index were obtained from all subjects. Of 6 subjects no data were available with respect to the electrocardiogram.

Mean levels of common carotid artery intima-media wall thickness and of ankle-arm index were compared between subjects with and without cerebral white matter lesions. With respect to continuous distributed variables, multiple linear regression analysis was used for analysis of differences across groups, adjusted for age and gender. The differences are presented with a 95% confidence interval (95% CI). Analyses for trends across groups with increasing severity of cerebral white matter lesions were performed using a multiple linear regression analysis.

The risk of cerebral white matter lesions associated with binary variables, such as presence of plaques of the carotid artery, definite and possible myocardial infarction, and presence of peripheral arterial disease were assessed using logistic regression analysis, with presence of cerebral white matter lesions as the dependent variable. The odds ratios (OR), as measures of strength of the association, are presented with a 95% confidence interval. Since the prevalence of cerebral white matter lesions strongly increases with age and tends to be different across gender,[6] all associations between

other variables and cerebral white matter lesions were adjusted for differences in age and gender.

In a separate analysis, a multiple logistic regression model was used to assess whether the observed associations between common carotid intima-media wall thickness, myocardial infarction, ankle-arm index and cerebral white matter lesions, remained after adjustments for cardiovascular risk factors, including hypertension, total serum cholesterol, HDL cholesterol and current smoking.

RESULTS

In table 1 general characteristics of subjects with and without cerebral white matter lesions on the magnetic resonance imaging scan are presented. Compared to subjects without cerebral white matter lesions, those with cerebral white matter lesions were older and among them were more women.[6] In a separate paper, we have reported

Table 1. General characteristics of subjects with and without cerebral white matter lesions.

	White matter lesions	
	Absent (n=81)	Present (n=30)
Age (years)	72.4 (5.8)	77.7 (5.4)
Gender (women)	49%	67%
Body mass index (kg/m^2)	26.4 (3.6)	26.5 (3.0)
Smoking current	30%	10%
former	47%	52%
never	23%	38%
Systolic blood pressure (mmHg)*	132 (18)	141 (19)
Diastolic blood pressure (mmHg)*	69 (10)	70 (9)
Hypertension†	28.3%	41.4%
Total cholesterol (mmol/l)	6.56 (1.34)	6.83 (1.25)
HDL cholesterol (mmol/l)	1.29 (0.32)	1.24 (0.30)

Values are percentages and means with standard deviation in parentheses.

* Subjects on antihypertensive drugs excluded.

† Systolic blood pressure ≥ 160 mmHg and/or diastolic pressure ≥ 95 mmHg and/or the use of antihypertensive drugs.

Table 2. Indicators of atherosclerosis in subjects with and without cerebral white matter lesions.

		White matter lesions		*p* value*
		Absent	Present	
CAROTID ARTERIES				
Stenosis	0%	74%	45%	0.97
	1-16%	22%	21%	0.89
	≥ 16%	4%	4%	0.84
Intima-media wall thickness (mm)		0.81 (0.16)	0.96 (0.24)	0.01
Plaques†	common carotid artery	14%	11%	0.97
	carotid bifurcation	57%	83%	0.05
CORONARY ARTERIES‡				
Definite myocardial infarction		7%	19%	0.26
Possible myocardial infarction		3%	8%	0.12
Combined		10%	27%	0.07
PERIPHERAL ARTERIAL DISEASE§				
Ankle-arm index		1.13 (0.21)	1.03 (0.25)	0.04
Peripheral arterial disease		14%	30%	0.09

Values are percentages and means with standard deviation in parentheses.

* *p* value of the difference between groups, adjusted for age.

† Plaques located at the anterior or posterior wall of the common carotid artery or bifurcation, observed in at least one of the carotid arteries.

‡ Coronary atherosclerosis indicated by evidence of a definite or possible myocardial infarction on the electrocardiogram.

§ Measurements of the posterior tibial artery. Peripheral arterial disease defined as an ankle-arm index ≤ 0.90.

on the association between cerebral white matter lesions and cardiovascular risk factors.[6]

In table 2, vessel wall characteristics of the carotid artery, presence of myocardial infarction, and the systolic blood pressure readings of the posterior tibial artery are shown. Intima-media wall thickness of the common carotid artery was significantly higher in subjects with cerebral white matter lesion compared to those without lesions, with a for age and gender adjusted difference of 0.13 mm (95% CI 0.04;0.21). The results for the logistic regression analysis (table 3) indicated that an increase of 0.1 mm in common carotid intima-media wall thickness was associated with 50% increase in the probability of cerebral white matter lesions (OR 1.5, 95% CI 1.1;2.1). Furthermore, atherosclerotic plaques in the carotid bifurcation were significantly associated with the presence of cerebral white matter lesions. The odds ratio of cerebral white matter lesions associated with the presence of plaques in the carotid bifurcation

Table 3. The association of measures of atherosclerosis in subjects with and without cerebral white matter lesions.

		Odds ratio (95% CI) of presence of cerebral white matter lesions	
		Crude	Adjusted*
CAROTID ARTERIES			
Stenosis	0%	0.9 (0.3;2.2)	1.0 (0.3;2.7)
	1-16%	0.9 (0.3;2.5)	0.7 (0.2;2.1)
	≥ 16%	0.9 (0.1;9.2)	2.2 (0.2;6.7)
Intima-media wall thickness (per 0.1 mm increase)		1.5 (1.2;1.9)	1.5 (1.1;2.1)
Plaques†	common carotid artery	0.8 (0.2;3.2)	0.9 (0.2;4.1)
	carotid bifurcation	3.8 (1.1;12.5)	3.9 (1.0;14.5)
CORONARY ARTERIES‡			
Definite myocardial infarction		3.3 (0.9;12.8)	2.1 (0.5;9.2)
Possible myocardial infarction		3.0 (0.4;23.4)	6.9 (0.7;70.0)
Combined		3.6 (1.1;11.6)	3.1 (0.8;11.4)
PERIPHERAL ARTERIAL DISEASE§			
Ankle-arm index (per 0.1 decrease)		1.2 (1.0;1.5)	1.2 (1.0;1.5)
Peripheral arterial disease		2.7 (1.0;7.6)	2.4 (0.8;7.6)

* Adjusted for age and gender.
† Plaques located at the anterior or posterior wall of the common carotid artery or bifurcation, observed in at least one of the carotid arteries.
‡ Coronary atherosclerosis indicated by evidence of a definite or possible myocardial infarction on the electrocardiogram.
§ Measurements of the posterior tibial artery. Peripheral arterial disease defined as an ankle-arm index ≤ 0.90.

was 3.9 (95% CI 1.0;14.5). The prevalence of a minimal or moderate to severe haemodynamic stenosis of the right carotid artery did not differ across the two groups (table 2).

The ankle-arm index was significantly reduced in subjects with cerebral white matter lesions compared to subjects without lesions with a for age and gender adjusted difference -0.11 (95% CI -0.21;-0.01). A decrease of 0.1 in the ankle-arm index was associated with a 20% increase in probability of cerebral white matter lesions (odds ratio was 1.2 (95% CI 1.0;1.5)). Similar results were observed when the left or right carotid artery and the left or right ankle-arm index were used in the analysis. Peripheral arterial disease was found in 30% of the subjects with cerebral white matter lesions

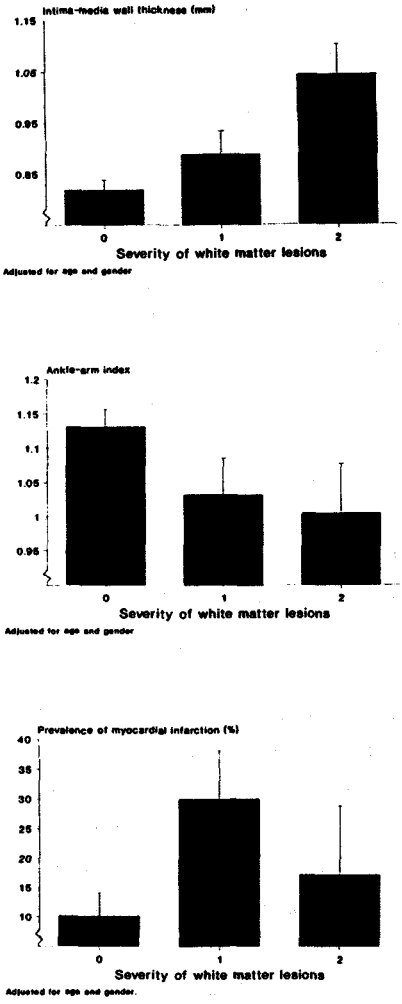

Figure 2. Measures of atherosclerosis across groups with increasing severity of cerebral white matter lesions. Top: Mean intima-media wall thickness (SE) of the common carotid arteries (mm). Test for linear trend across groups: $p < 0.01$. Middle: Mean ankle-arm index (SE) of the tibial posterior arteries. Test for linear trend across groups: $p = 0.05$. Bottom: Prevalence of combined definite and possible myocardial infarction (SE), diagnosed on the electrocardiogram. Test for linear trend across groups: $p = 0.19$.

compared to 14% in subjects without lesions. The odds ratio of cerebral white matter lesions associated with peripheral arterial disease was 2.4 (95% CI 0.8;7.6).

The prevalence of definite and possible myocardial infarction, based on the electrocardiogram, was 27% in subjects with cerebral white matter lesions compared

to 10% in those without lesions. The odds ratio for cerebral white matter lesions associated with myocardial infarction was 3.1 (95% CI 0.8;11.4). The observed associations for peripheral arterial disease and prevalence of myocardial infarction did, however, not reach conventional levels of statistical significance.

Across groups with increasing severity of cerebral white matter lesions, significant trends were found for carotid intima-media wall thickness (figure 2, top) and ankle-arm index (figure 2, middle). Although myocardial infarction was more common among subjects with grade 1 or grade 2 cerebral white matter lesions, a significant gradual increase in the prevalence of myocardial infarction with increasing severity of cerebral white matter lesions could not be demonstrated (figure 2, bottom).

For subjects aged 65 to 74 years the association between cerebral white matter lesions and carotid intima-media wall thickness was stronger than in subjects aged 75 to 84 years. Mean differences across groups were 0.16 mm (95% CI 0.03;0.27) and 0.09 mm (95% CI -0.04;0.22), respectively. Similar results were obtained for ankle-arm index. The strength of the association between myocardial infarction and cerebral white matter lesions, however, increased with age. For those aged 75 to 84 years an odds ratio of 5.1 (95% CI 0.8;31.5) was observed, compared to an odds ratio of 1.5 (95% CI 0.1;7.6) for subjects aged 65 to 74 years.

The magnitude of the association between cerebral white matter lesions and intima-media wall thickness did not differ between elderly men and women. With respect to the ankle-arm index, a difference in ankle-arm index of -0.14 (95% CI -0.03;-0.025) was observed between women with and without cerebral white matter lesions, whereas for men the difference was -0.04 (95% CI -0.24;0.20). For myocardial infarction, an opposite association was found with a stronger association in men as compared to women.

The results of additional multivariate adjustment of cardiovascular risk factors on the magnitude of the odds ratios of intima-media wall thickness, ankle-arm index and presence of possible or definite myocardial infarction between subjects for cerebral white matter lesions are presented in table 4. With respect to the carotid intima-media wall thickness, adjustment for differences in risk factors reduced the magnitude of the association without, however, changing the direction of the association between carotid atherosclerosis and cerebral white matter lesions. Similar results were found for the differences in ankle-arm index. No change was observed in the magnitude of the association between cerebral white matter lesions and myocardial infarction after additional adjustment of cardiovascular risk factors.

Table 4. Odds ratio (95% CI) of an increase in common carotid intima-media wall thickness, myocardial infarction, and a reduction in ankle-arm index, for presence or absence of cerebral white matter lesions, with and without adjustment for several cardiovascular risk factors.

Adjustment	Increase in intima-media wall thickness (per 0.1 mm)	Myocardial infarction*	Decrease in ankle-arm index (per 0.1)
No adjustment	1.5 (1.2;1.9)	3.6 (1.1;11.6)	1.2 (1.0;1.5)
Age and gender	1.5 (1.1;2.1)	3.1 (0.8;11.4)	1.2 (1.0;1.5)
Hypertension†	1.4 (1.1;2.1)	2.9 (0.8;10.9)	1.2 (1.0;1.5)
Total cholesterol†	1.5 (1.1;2.2)	3.0 (0.8;11.3)	1.2 (1.0;1.5)
HDL cholesterol†	1.5 (1.1;2.1)	2.8 (0.7;10.6)	1.2 (1.0;1.5)
Current smoking†	1.5 (1.1;2.2)	3.3 (0.9;12.5)	1.3 (1.0;1.6)
All‡	1.4 (1.0;2.1)	2.9 (0.7;11.6)	1.2 (0.9;1.6)

* Combined definite and possible myocardial infarction diagnosed on electrocardiogram.
† Results obtained by multivariate logistic regression. Each risk factor is entered separately in a model in which age and gender are included.
‡ All risk factors included in the logistic regression model.

DISCUSSION

Our findings, in a population-based study of magnetic resonance images of brains of elderly people, provide evidence that cerebral white matter lesions are associated with atherosclerosis as non-invasively demonstrated by increasing carotid intima-media wall thickness and a reduced ankle-arm index. Atherosclerotic plaques in the carotid bifurcation, evidence of myocardial infarction on the electrocardiogram and peripheral arterial disease are more common in subjects with cerebral white matter lesions compared to those without lesions. Trend analyses suggest that a gradual increase in severity of cerebral white matter lesions is associated with an increase of intima-media wall thickness and a decrease of the ankle-arm index. Haemodynamically stenosis of the right internal carotid artery was, however, not associated with cerebral white matter lesions.

Before these findings can be accepted some aspects of the study need to be considered. Firstly, increased common carotid intima-media wall thickness may not necessarily be atherosclerosis and is not per se a precursor of atherosclerosis. It may merely reflect an adaptive response of the vessel wall to changes in shear stress and

tensile stress.[26] Furthermore, atherosclerosis is viewed as a disorder which is restricted to the intima layer of the arterial vessel wall, and ultrasound imaging can not discriminate between the intima layer and the media layer of vessel wall. In several studies, ultrasonographically determined increased carotid intima-media wall thickness of the common carotid artery has been associated with elevated levels of cardiovascular risk factors.[10,13,27,28] In addition, progression of common carotid intima-media wall thickness over time has been associated with risk factors for atherosclerosis.[11] These results supports the view that non-invasively assessed intima-media wall thickness of the common carotid artery may be regarded as a measurement of atherosclerosis.

Secondly, the ankle-arm index was based on a single blood pressure reading performed on one occasion. Some misclassification may have occurred, which may have reduced the observed difference between the groups, provided a true association exists and misclassification occurred to the same extent among subjects with and without cerebral white matter lesions. Similarly, misclassification in the assessment of coronary atherosclerosis may have occurred, since the diagnosis was based on findings on the electrocardiogram only. This may have resulted in some dilution of the observed association.

In several studies cerebral white matter lesions have been found to be related to elevated levels of established cardiovascular risk factors.[1,4-6] In addition, elevated levels of hemostatic and rheological factors have been associated with cerebral white matter lesions.[6,7] Post-mortem neuropathological studies have indicated that cerebral white matter lesions seen on magnetic resonance imaging are associated with degenerative changes in arterioles which are related to the process of atherosclerosis.[29-31] Our observation of an association of cerebral white matter lesions and carotid-, coronary- and peripheral atherosclerosis in free living subjects supports these findings.

In the present study, the frequency of haemodynamic important stenosis of the right internal carotid artery among subjects with cerebral white matter lesions did not differ from those without lesions. This finding can probably not be explained by the fact that only the right carotid artery was evaluated for stenosis, since stenosis of the internal carotid artery appears to be randomly distributed across both left and right sides.[32] Our finding contrasts with the occurrence of uni- or bilateral stenosis in 8 of 53 volunteers with cerebral white matter lesions observed in a study of Fazekas.[33] Post-mortem neuropathological studies, however, have indicated that cerebral white matter lesions are predominantly associated with arteriolosclerosis, a type of small-artery disease. Furthermore, the findings of the present study with respect to stenosis are in accordance with findings from others, in which a relatively low prevalence of carotid

artery stenosis was observed in subjects with lacunar infarcts, another type of small-artery disease.[34,35] These results may indicate that the haemodynamic consequences of stenosis of the carotid artery may not be responsible for the development of cerebral white matter lesions, and rather support the view that cerebral white matter lesions represent generalized vascular disease.

In our study among elderly subjects, adjustment for differences in smoking, hypertension and elevated levels of serum lipids, had no appreciable effect on the observed associations between cerebral white matter lesions and carotid atherosclerosis, peripheral arterial atherosclerosis, and coronary atherosclerosis. These findings suggest that the association between cerebral white matter lesions and large vessel atherosclerosis can not be entirely attributed to confounding by common cardiovascular risk factors, but rather favours the hypothesis that cerebral white matter lesions are partly a direct consequence of atherosclerotic vessel wall disease, which in it self is related to elevated levels of cardiovascular risk factors. An alternative explanation is that, besides these factors, others factors, yet unknown, play a role in the development of atherosclerosis of the carotid arteries, coronary arteries and peripheral arteries and cerebral white matter lesions or that the effect of these risk factors on both atherosclerosis and cerebral white matter lesions may be different across different arterial sites. A time dependent relationship between cerebral white matter lesions and atherosclerosis can not be determined on the basis of these cross-sectional data.

Whether cerebral white matter lesions give rise to dementia is still debated. Conflicting results about the association between cognitive impairment and evidence of cerebral white matter lesions have been reported. In some studies cerebral white matter lesions were associated with impaired cognitive functioning,[4,36,37] whereas in others no such association could be observed.[2,3,25] The type of cerebral white matter lesions on magnetic resonance images may also be of importance. Periventricular hyperintensities were found more often in demented patients than in age-matched controls in most studies.[25,38] The extent and the location of cerebral white matter lesions may also partly explain some of the negative results.[39] In addition, differences between studies with regard to the association with dementia may have to be attributed to differences in selection of subjects, in sample sizes, in classification of presence or absence of cerebral white matter lesions, and in the assessment of cognitive functioning. Finally, since our findings and those of others, suggest that cerebral white matter lesions are clearly associated with atherosclerosis, differences in etiology of cerebral white matter lesions may also have contributed to the contrasting results.

In conclusion, we found that cerebral white matter lesions, as seen on magnetic resonance images of a population sample of elderly subjects showed a clear association with atherosclerotic abnormalities in the carotid artery, the coronary arteries and in the peripheral vessels.

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Chapter 4.3

Cognitive correlates of ventricular enlargement and cerebral white matter lesions on MRI

It is of practical importance to detect early stages of vascular dementia because potential measures of intervention are available.[1,2] Cerebral white matter lesions are frequently observed on magnetic resonance imaging (MRI) scans in elderly subjects and have been related to vascular dementia. Clinical, epidemiological and pathological studies consistently indicate a vascular cause for the majority of these lesions.[3-7] However, their clinical significance remains controversial. Most previous studies that investigated whether these lesions are related to cognitive impairment suffered from methodological drawbacks that limited the interpretation of their results; e.g. they mainly included demented patients,[8,9] were based on highly selective samples of volunteers, or had very small sample sizes.[10-12]

Another frequent finding in elderly persons that also has been related to cognitive decline is an increase in ventricular volume. It is generally assumed that this ventricular enlargement occurs, ex vacuo, by shrinkage of periventricular structures.[13] This view has also often been taken to explain the positive relation between ventricular size and occurrence of dementia in subjects with multiple infarcts,[14-17] although some studies suggested that the effects of ventricular enlargement and that of the size of the infarcted area on cognitive performance are partly independent.[15,16,18] Until now, few studies have investigated the relevance of ventricular volume per se for cognitive performance.

In this paper we present the results of a study conducted in a random sample from the general population, to investigate the associations between cerebral white matter lesions and ventricular size on the one hand and cognitive performance on the other.

SUBJECTS AND METHODS

Subjects

The Rotterdam Study is a single center prospective follow-up study of the total population aged 55 years or over of the suburb of Ommoord in Rotterdam, The

Netherlands, encompassing 11,854 subjects and including institutionalized persons. The study has been approved by the Medical Ethics Committee of Erasmus University. Written informed consent is obtained from all participants. Rationale and design of the Rotterdam Study have been described elsewhere.[19] To study the prevalence and determinants of cerebral white matter lesions on MRI, subjects of the ages 65 to 84 years were randomly selected, stratified by gender and 5-year age-groups, from the cohort of the Rotterdam Study. At the time of the MRI study the participation rate in the Rotterdam Study was 82 percent for those aged 65 to 84 years; 111 (87%) of the 128 subjects that were invited for the additional MRI study consented to participate.[7] To investigate the relations of cerebral white matter lesions as well as of ventricular enlargement with cognitive function, all participants in the MRI study were subsequently invited for additional neuropsychological testing, with the exception of 6 patients with a diagnosis of probable Alzheimer's disease, according to the criteria of the National Institute on Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association,[20] and of 2 patients with Parkinson's disease. Of the 103 eligible subjects 7 declined further examinations, leaving 96 persons in the present study.

Magnetic resonance imaging

T2 weighted axial magnetic resonance images of the brain were obtained by means of a 1.5 T Philips Gyroscan. Presence and severity of white matter lesions was graded as follows. Grade 0 scans showed no or slight periventricular hyperintensity, less than 5 punctate lesions and no confluent lesions. Grade 1 scans showed moderate periventricular hyperintensity or more than 5 punctate lesions, or both, but no confluent lesions. Scans with severe periventricular hyperintensity or confluent lesions were graded as 2, regardless of the presence of punctate lesions.[7] To measure ventricular volume we traced the MRI films on each axial slice on which the ventricles were present, with the use of a light table and transparent paper to identify the perimeter of the entire brain and of the ventricles. Subsequently, these areas were measured in pixel percents by means of an IBAS 2000 (Zeiss-Kontron, Ober-Kochen, Germany) and summed over all slices to arrive at total ventricular volumes and corresponding total brain volumes. To control for differences in individual head size and height, ventricular volume was expressed as the percentage of the total brain volume (ventricle-to-brain ratio).[14,21]

Assessment of cognitive function

The following neuropsychological tests were administered: Stroop test (parts I, II and III),[22] verbal fluency tests,[23] Trail Making Test A and B,[24] Digit Span forward and backward (WAIS),[25] Word List Learning (CERAD),[26] Mini Mental State Examination (MMSE),[27] CAMCOG[28,29] and a shortened version of the Groninger Intelligence Test (GIT), a Dutch intelligence test.[30] Verbal fluency was assessed as phonologic word fluency, in which test the subject was asked to produce as many words as possible within one minute that begin with a specified letter (letter B), and as semantic word fluency, which demands generating words that belong to a specific category (animals). The Stroop test, Trail Making Test, and verbal fluency tests are timed tasks that measure executive control functions (mental flexibility, vulnerability to interference, conceptual tracking), sustained attention and mental speed; these functions are regarded to be located principally in subcortical and frontal areas. Digit Span assesses auditory attentional span. The CAMCOG and the MMSE are global cognitive tests developed for use in dementia screening and appeal mainly to cortical functions. Word List Learning and GIT also address primarily cortical functions; respectively visual verbal memory, and verbal abstraction, calculation and mental visuospatial construction. The neuropsychological test battery was always administered after the MRI scans had been made, with a mean interval of 19 days. Information regarding the level of formal education was elicited in the home interview of the Rotterdam Study.

Analysis

Mean test scores were calculated for subjects with (grade 1 or 2) and without (grade 0) white matter lesions. Since age and gender were associated with test scores as well as with presence of white matter lesions, we used multiple linear regression to compute adjusted differences (with 95 % confidence intervals (95% CI)) between the groups with and without lesions. The relation between ventricle-to-brain ratio (as a continuous variable) and test scores was also examined through multiple linear regression analysis, with adjustment for age and gender. The potential confounding effect of education was investigated by inclusion of the level of education as an additional covariate in the model. Some persons were unable to complete the more difficult parts of the Stroop or the Trail Making Test. Rather than excluding these subjects from the analyses, we arbitrarily assigned them the worst score that was obtained among those who did complete the tests. To assess whether the relation between

MRI abnormalities and cognitive functioning was dependent on age, additional stratified analyses were performed in two 10-years age strata (65 to 74 years, 75 to 84 years).

Stroke patients pose a difficult problem. On the one hand the stroke itself may directly impair cognitive function. On the other hand, these subjects may well constitute the extreme end of the distribution of cerebrovascular disease that we wanted to investigate and excluding them would then reduce the possibility of finding a true relation. Therefore, we performed analyses including all subjects, as well as after exclusion of the 7 subjects who had either a history of stroke confirmed by a neurologist or evidence of stroke on the MRI scan.

To investigate whether white matter lesions and ventricular enlargement merely reflected the same pathological process or independently affected cognitive performance, we assessed the relation between white matter lesions and neuropsychological test scores while adjusting for ventricle-to-brain ratio, and vice versa.

RESULTS

In table 1 some characteristics of the study population are presented. Age was significantly associated with presence and severity of white matter lesions; female gender showed a similar but non-significant tendency that was independent of age.

Table 1. General characteristics of the study population, for all subjects and by level of severity of cerebral white matter lesions.

Characteristic	Total	White matter lesions		
		No/slight*	Moderate†	Severe‡
Number of subjects	103	75	17	11
Age (yrs) - mean (SD)	73.8 (6.2)	72.3 (5.8)	76.8 (5.7)	79.5 (5.0)
Gender (men/women)	46/57	37/38	8/9	1/10
Previous stroke (%)	7 (7%)	2 (3%)	2 (12%)	3 (27%)
Refusals (%)	7 (7%)	4 (5%)	1 (6%)	2 (18%)
Ventricle-to-brain ratio (%) - mean (SD)	7.8 (2.2)	7.2 (1.6)	8.7 (2.5)	10.1 (3.3)

* < 5 focal lesions, no/slight periventricular hyperintensities and no confluent lesions.
† < 5 focal lesions, moderate periventricular hyperintensities and no confluent lesions; or ≥ 5 focal lesions, no/slight/moderate periventricular hyperintensities and no confluent lesions.
‡ Confluent lesions and/or severe periventricular hyperintensities.

The proportion of subjects with a previous stroke increased with the severity of white matter lesions, as did the proportion of subjects who refused further neuropsychological testing. The severity of white matter lesions was positively associated with ventricle-to-brain ratio ($p < 0.01$; adjusted for age and gender).

Table 2 shows the results of the neuropsychological tests according to presence or absence of white matter lesions, and in relation to ventricular enlargement. Subjects with white matter lesions performed worse on all tests, except for the subtest of the Groninger Intelligence Test that assessed verbal abstraction (matrices). When age and gender were taken into account the direction of the differences did not change, but they remained significant only for the Trail Making Test (A and B), phonologic word fluency (letter 'b'), and delayed verbal recall (Word List Learning); the differences on several of the other tests approached statistical significance.

For the relation between ventricular size and cognitive function we found that the larger the ventricles (expressed as increasing ventricle-to-brain ratio), the poorer the performance on all neuropsychological tests. When adjusted for age and gender the associations were significant for the Stroop (part II), the Trail Making Test (B), the MMSE, direct and delayed verbal recall (Word List Learning), two of the three subtests of the GIT (matrices and calculation), and the summary scores on the GIT (total score, IQ) (table 2). Age-stratified analyses did not suggest the associations of white matter lesions and ventricle-to-brain ratio with cognitive performance for younger subjects (age 65 to 74 years) to differ from those for older subjects (age 75 to 84 years).

The exclusion of subjects with stroke did not affect the general picture of subjects with white matter lesions or larger ventricles performing worse, and all significant associations persisted. However, for white matter lesions the magnitude of the associations slightly decreased when stroke patients were omitted.

The level of education itself was highly correlated with test scores, even after adjustment for age and gender, but education was associated neither with ventricular enlargement nor with the presence of white matter lesions. Therefore, it appeared not to be a confounder for the relations that we investigated, and the adjusted differences did not change when level of education was included in the model as a covariate.

Finally, we found that the effects of white matter lesions and ventricular volume on cognitive performance were largely independent: when we entered ventricle-to-brain ratio and presence of white matter lesions simultaneously in the regression model,

Table 2. Association of white matter lesions and ventricular enlargement with performance on neuropsychological tests, adjusted for age and gender.

Test	Mean	White matter lesions			Ventricle-to-brain ratio		
		difference*	(95% CI)	*p*	difference†	(95% CI)	*p*
Stroop							
I (word reading)	49.45	3.39	(-0.90;7.68)	0.13	0.57	(-0.27;1.41)	0.18
II (color naming)	67.38	5.89	(-1.05;12.83)	0.10	1.40	(0.07;2.73)	0.04
III (color interference)‡	138.65	22.39	(-6.25;51.03)	0.13	4.03	(-1.60;9.66)	0.16
Wordfluency							
Animals	19.17	-2.52	(-5.30;0.26)	0.08	-0.43	(-1.04;0.18)	0.17
Letter 'b'	12.07	-4.11	(-6.78;-1.44)	<0.01	-0.29	(-0.90;0.32)	0.34
Trail Making							
Test A‡	57.48	20.61	(5.97;35.25)	0.01	2.92	(-0.76;6.60)	0.12
Test B‡	137.48	57.27	(25.17;89.37)	<0.01	13.06	(5.14;20.98)	<0.01
MMSE	28.00	-0.29	(-1.05;0.47)	0.45	-0.22	(-0.38;-0.06)	0.01
CAMCOG	91.35	-2.85	(-7.40;1.70)	0.22	-0.60	(-1.58;0.38)	0.24
Digit Span							
Forward	4.74	-0.36	(-1.03;0.31)	0.30	-0.04	(-0.20;0.12)	0.65
Backward	3.54	-0.53	(-0.60;0.06)	0.09	-0.06	(-0.20;0.08)	0.46
Word list learning							
Direct recall	18.46	-1.23	(-3.29;0.83)	0.24	-0.50	(-0.99;-0.01)	0.05
Delayed recall	6.39	-1.14	(-2.12;-0.16)	0.02	-0.29	(-0.53;-0.05)	0.02
Recognition	19.34	-0.13	(-0.72;0.46)	0.68	-0.09	(-0.23;0.05)	0.21
GIT							
Matrices	8.79	0.40	(-1.38;2.18)	0.66	-0.38	(-0.73;-0.03)	0.05
Calculation	11.52	-1.57	(-3.63;0.49)	0.14	-0.49	(-0.92;-0.06)	0.03
Perceptual puzzle	9.32	-0.09	(-1.89;1.71)	0.92	-0.14	(-0.51;0.23)	0.47
Total	29.80	-1.20	(-5.37;2.97)	0.58	-0.93	(-1.77;-0.09)	0.03
IQ	116.43	-3.05	(-11.20;5.10)	0.47	-1.95	(-3.60;-0.30)	0.02

* Difference in average test score between subjects with and without white matter lesions, adjusted for age and gender.
† Average change in test score when the ventricle-to-brain ratio increases with one unit of measurement (i.e. with 1%; mean ratio 7.8%, range 3.9-18.1%), adjusted for age and gender.
‡ Subjects who were unable to complete the test were included by assigning them the worst score.

together with age and gender, the magnitude and significance of all associations remained virtually unchanged.

DISCUSSION

We investigated the relation with cognitive function of cerebral white matter lesions and enlargement of the ventricular system in non-demented subjects that were randomly sampled from the general population. We found that the presence of either of these anatomical abnormalities was associated with worse performance on all tests of cognitive function. After adjustment for age and gender, individuals with white matter lesions performed significantly worse on tests addressing primarily subcortical and frontal functions (executive control functions, attentional abilities and mental speed). Ventricular enlargement was also significantly associated with poor performance on tests that assess executive control functions, but in addition with poor performance on tests that aim to assess cortical functions. The effects of white matter lesions and ventricular size were independent.

There are three important methodological issues that need to be mentioned and that distinguish our study from most previous investigations. In the first place, we randomly sampled subjects from the general population and excluded only subjects with non-vascular neurological diseases known to potentially impair cognitive function. Consequently, the only possible bias in our data is the one introduced by selective refusal. The participation rate in the initial MRI study was high, particularly in view of the age of the study population and the kind of investigation. However, subjects with MRI abnormalities more often refused further neuropsychological testing, which probably resulted in an underestimation of the deleterious effect of white matter lesions and ventricular enlargement. It is likely that in studies that were based on volunteers selective participation has led to an even larger depreciation of the importance of these MRI characteristics in the general population. Assuming that vascular lesions of the white matter can accumulate over time to result eventually in overt dementia, one would expect to find a continuous distribution of cognitive impairment related to such vascular lesions in the population. Most previous studies that investigated non-demented subjects did not show a clear relationship between white matter lesions on MRI and cognitive function. However, small sample sizes,[8,11,12] or restricted sampling of the population (including only subjects with cerebrovascular events,[10] or, conversely, excluding subjects with vascular risk factors,[11] or selecting

volunteers on the basis of good performance[9]) may have resulted in too little power to detect existing differences. We did not primarily exclude persons with a recognized previous stroke, on the assumption that these subjects might constitute the extreme end of the distribution of cerebrovascular lesions. Our finding that the effect of including stroke patients in the analyses merely strengthened the relations between white matter lesions and cognitive function that we observed in subjects without previous stroke, lends support to this hypothesis.

A second important methodological issue is age. Age is the strongest determinant of cognitive function in the elderly and needs to be taken into account when one is to assess the influence of other putative determinants. By limiting the overall age-span of subjects to be included in the study to 20 years and by age-stratified sampling within this range, we ensured adequate numbers in all age-groups to correct for the effect of age when studying the consequences of white matter lesions and ventricular enlargement.

A third matter concerns the sensitivity of the neuropsychological tests. The studies that have reported more or less convincing evidence for a relation between white matter lesions on MRI and cognitive impairment showed, as we did, primarily worse performance on tests of subcortical and frontal functions.[10,31,32] These findings are in accordance with the theory that multifocal white matter lesions collectively cause a disconnection syndrome.[33,34] Screening tests for dementia such as the MMSE or the more extended CAMCOG focus mainly on cortical functions, such as language and visuoperceptual abilities, and are less sensitive to subcortical functional decline which presents itself predominantly in slowing of mental speed and impairment of attentional abilities. That CT studies have shown a relation between white matter lesions and cognitive function in non-demented subjects[35] is compatible with the view that the most common neuropsychological tests are rather insensitive to subtle deficits from cerebrovascular damage, because CT detectable lesions are invariably rated as severe on MRI.[3]

We found ventricular enlargement to be related with cognitive performance, independent of age or presence of white matter hyperintensities. Few other studies investigated the relation between ventricular size and cognitive function in non-demented subjects. Kaye et al. found that, after adjustment for age, cerebral atrophy as measured by ventricular enlargement was not related to cognitive performance in non-demented persons.[21] However, they based their conclusions on a relatively small number of subjects that were extensively tested (n=39). Since that sample comprised a broad age range, their study may have had little power to detect a relation between ventricular size

and cognitive function once the confounding effect of age had been taken into account. Our population-based results fit well with the results from Pujol et al. in a selected group of vascular patients with leukoaraiosis. They found that ventricular enlargement was significantly associated with global deterioration of complex cognitive functions, and that this was complementary to the degree of leukoaraiosis. They suggested that ventricular enlargement had the greatest clinical significance.[18] Our results lend support to this latter proposition. The magnitude of the associations of ventricular size with various tests of cognitive function and the fact that these associations are not only with tests presumed to measure subcortico-frontal functions but also with tests addressing cortical functions, seem to indicate that ventricular enlargement is at least as important an MRI indicator of cognitive impairment as white matter hyperintensities are.

How should we interpret the relation between white matter lesions and cognition? It is tempting to conclude that white matter lesions on MRI are a morphological substrate of dementia related to vascular disease. However, all evidence until now has been based on cross-sectional studies. One study suggested that on follow-up subjects with white matter lesions had declined most, but the findings were based on very small groups and the subjects with lesions were older than those without.[36] Furthermore, not all lesions on MRI reflect ischemic changes. Population-based follow-up studies are needed to fully ascertain the relevance of cerebral white matter lesions.

With regard to ventricular size a question that remains to be answered is what factors contribute to cerebral atrophy resulting in ventricular enlargement. Vascular factors seem to be implicated in a substantial proportion of patients with dilatation of the ventricle system. Hypertension, the predominant risk factor for stroke and vascular dementia, is associated with brain atrophy even when subjects with severe periventricular hyperintensities are excluded.[37] In patients with multiple infarcts or with subcortical arteriosclerotic encephalopathy the accompanying dilatation of the ventricular system is thought to be secondary to the white matter changes resulting from ischemia.[14-17] However, this does not explain why several studies found, as we did, that the relation between ventricular enlargement and cognitive function, or subsequent development of dementia, was independent from the effect of white matter lesions and infarcts.[15,16,18] Degeneration of cortical neurones, from preclinical stages of Alzheimer's disease or from other causes, can also contribute to expansion of the ventricle volume and would explain that cortical functions seemed more impaired in individuals with enlarged ventricles than in those with white matter lesions. Given the negative relation between ventricular size and cognitive function, it needs to be clarified which elements of brain tissue have disappeared in patients with ventricular widening.

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Chapter 5

Medical conditions and risk of dementia

Chapter 5.1

Medical history and the risk of Alzheimer's disease

In this article we present the results of an analysis of several exposures from the medical history as putative risk factors for Alzheimer's disease (AD). Until now most studies failed to demonstrate any major premorbid clinical feature to be consistently associated with the risk of AD except for head trauma, which is discussed in another paper in this issue.[1] However, several disorders have been provisionally associated with AD because of positive findings in one or more studies, or based on theoretical considerations. In this analysis we focused on medical conditions that have previously been put forward as possibly related to AD, namely thyroid disorders, infections with neurotropic viruses, encephalitis and meningitis, blood transfusions, allergic conditions, arthritis, epilepsy, migraine and general anaesthesia.

An increased risk of AD in women with a history of thyroid disease was reported by Heyman.[2] Several investigators have sought to reproduce this finding without success.[3-9] Lopez and coworkers compared the prevalence of pathologically and clinically documented thyroid disorders between 31 patients with AD and 31 age-matched non-demented individuals. Except for carcinomas, all kinds of abnormality occurred in a higher percentage of the AD patients than of the controls, although none of the differences reached significance. They concluded that their results did not support a relationship between AD and thyroid abnormalities.[10]

The transmissibility of several spongiform encephalopathies like kuru, Creutzfeldt-Jakob disease and scrapie, raised the hypothesis of a possible infectious aetiology of other chronic degenerative diseases of the central nervous system, such as AD and Parkinson's disease. Although the failure to transmit AD to animals has long been interpreted as evidence against the role of an infectious agent,[11] the hypothesis of an unknown infective agent involved in the pathogenesis has never been completely abandoned. Manuelidis et al hypothesized that infectivity might occur only at early stages of AD and inoculated hamsters with buffy coats of relatives of patients with a positive family history of AD. They found an increase in spongiform encephalopathies among the hamsters.[12] If an infective agent should indeed be involved in the pathogenesis of AD, this might be transmitted by blood products causing recipients of blood transfusions to be at a higher risk of developing AD.

Other authors have suggested an alternative infection hypothesis, in which the involved pathogen could be an ubiquitous one, affecting genetically susceptible subjects by either vertical or horizontal transmission, or both.[13,14] The neurotropic viruses are among the potential candidates for obvious reasons. Bharucha et al drew attention to a possible role of herpes zoster. In a register based case-control study on AD they found this condition to be more prevalent in cases as compared to controls, although not significantly.[15] This finding has not been confirmed in other case-control studies.[2,5-9] Ball suggested that retrograde spread of herpes simplex virus type I from the trigeminal ganglion might be involved.[16] This hypothesis has been investigated in several neuropathological and neuroimmunological studies. Though initially several negative studies were reported,[17,18] a more recent study found evidence for increased presence of type I herpes simplex in the brains of AD patients as compared to controls.[19]

Several changes in immune function have been described in AD suggesting an activated immune system, but the mechanism of activation is still unknown.[20] In particular it is unclear whether the immunological changes are causally related to the disease, or merely a result of the degenerative processes.[21,22] It has also been suggested that they might reflect enhanced immunological suppression by a chronic viral infection, thus lending support to the infection hypothesis.[21] To date no convincing evidence exists for an association between any specific autoimmune disorder and AD. Allergic conditions may reflect a more generally overactive immune system. However, case-control studies that examined atopic conditions in relation to AD did not show any significant association.[5,7,8,23] Jenkinson et al reported on a lower prevalence of rheumatoid arthritis in AD patients as compared to non-demented subjects in a geriatric hospital based survey.[24] This finding has not been confirmed by others.

Seizures are known to develop in the clinical course of AD.[25] It is yet unknown whether this is simply the result of degeneration of brain tissue or of the involvement of other epileptogenic mechanisms. In the study of Hofman et al the risk of AD was increased in patients with epilepsy (unpublished data), suggesting that epilepsy itself might be a risk factor for AD as well.

Dewey et al pointed to the lower frequency of headaches in AD patients as compared to controls.[26] Similar results, though not significant, were reported in two other studies in which migraine and severe headaches before disease onset were investigated.[2,8] These findings are of interest in view of the literature on the pathogenesis of migraine. Although the pathogenetic mechanism in migraine is not completely clear, serotonin seems to play a role in it,[27] and also neuroexcitatory plasma amino acids are elevated

in migraine.[28] Serotonin can modulate learning and memory processes,[29] and serotonin receptors are decreased in AD.[30]

General anaesthesia has been considered in several case-control studies as a possible risk factor for AD,[2,7-9,31,32] but no associations have been reported to date.

METHODS

Data of 11 case-control studies were available for this collaborative re-analysis.[2,5-9,23,31-34] A descriptive overview of these studies and of the general strategy of analysis is given by van Duijn et al.[35] Eight studies were eligible for the investigation of exposures from the medical history.[2,5,7-9,23,31,32] One study, the study from Rochester, was completely register based. Medical records are likely to provide different information than can be obtained from an interview with an informant, and this might jeopardize comparability. Therefore, if applicable, all analyses were done both including and excluding the Rochester dataset. In case this considerably influenced the point estimate, results of both the analyses are presented.

With regard to the analyses on specific exposures inclusion was dependent upon data availability, specificity of the assessment within studies, and comparability of the investigated exposures across studies. An overview of the studies that contributed data to the analyses is presented in table 1. Only diseases that occurred at least one year before onset of AD were included. Although all studies investigated the occurrence of thyroid disorders at any time during a subject's life, two studies were excluded from the overall analysis of any kind of thyroid disease, one because only hypothyroidism had been asked for,[23] and the other because hypothyroidism was one of the exclusion criteria for entry into the study.[9] Specific types of thyroid disorders could be studied in five datasets, three of which allowed for a functional classification of hypothyroidism, hyperthyroidism, goitre and other.[5,8,9] In the Rochester dataset no specification of the functional status of patients with adenoma was given, so this study was excluded from the analyses of goitre and hyperthyroidism.

Six studies had collected data on atopy, either by separate questions regarding various allergic conditions[5,7,9,23,31] or by one question covering all manifestations of an allergic constitution.[8] For the analysis on atopic constitution the answers to the questions regarding hay fever, allergic rhinitis, food allergies, and allergic eczema were combined. Four studies explicitly ascertained hay fever.[7,9,23,31] For the investigation of epilepsy prior to onset of AD, studies that had not specified age of onset of the

Table 1. Medical conditions considered in the collaborative re-analysis and the individual studies that contributed data.

	Australia[9]	Italy[5]	Netherlands[31]	USA Bedford[23]	USA Durham[2]	USA Minneapolis[7]	USA Rochester[32]	USA Seattle[9]
Thyroid disease	X	X	X		X	X	X	
Hyperthyroidism	X	X						X
Hypothyroidism	X			X			X	
Goitre	X	X						X
Atopy	X	X	X			X		X
Hayfever			X	X		X		X
Rheumatoid arthritis			X					X
Osteoarthritis	X				X	X		
Poliomyelitis			X		X	X		X
Herpes simplex		X	X					
Shingles	X	X	X		X	X	X	X
Encephalitis/ meningitis	X	X	X	X	X	X	X	
Epilepsy	X		X	X			X	
Severe headaches/ migraine	X		X		X	X		
Blood transfusion	X	X	X		X	X		
General anaesthesia	X		X		X	X	X	X

epilepsy were excluded. As in one of the remaining studies none of the cases nor any of the controls reported epilepsy before onset of AD,[7] four studies effectively contributed data to examine this exposure.[8,23,31,32] Rheumatoid arthritis was only assessed in the study from Seattle, USA and in a subset of the Dutch study. Three other studies included a similar question, asking whether the subject had ever had arthritis.[2,7,8] The exposure thus measured is a mixed bag of all kind of joint related complaints, in this age group probably mainly osteoarthritis. Severe headaches and migraine were combined in most studies that investigated this.[2,7,8,31] Occurrence of herpes zoster, polio, herpes simplex, and encephalitis or meningitis, as well as exposure to general anaesthesia and blood transfusions, were assessed by direct questions that were much the same in the different studies. Four studies had collected information on the frequency of general anaesthesia.[7,9,31,32] To investigate a possible dose-response relationship the exposure was dichotomized into once and more than once.

Table 2. Thyroid disease as a risk factor for Alzheimer's disease.

	Exposure frequency		RR*	95% CI
	cases	controls		
THYROID DISEASE (ANY KIND)				
Australia	14/167	14/166	0.9	0.4 - 2.3
Italy	5/115	12/97	0.2	0.0 - 1.1
Netherlands	11/198	11/198	1.0	0.4 - 2.7
Durham, USA	7/44	5/91	3.2	1.0 - 10.9
Minneapolis, USA	5/78	0/47	∞	
Rochester, USA	68/392	73/392	0.9	0.6 - 1.4
Overall analysis	110/994	115/991	1.0	0.8 - 1.3
HYPERTHYROIDISM				
Australia	5/167	4/166	1.3	0.3 - 7.3
Italy	3/115	5/97	0.5	0.0 - 4.3
Seattle, USA	6/126	3/127	2.0	0.4 - 14.8
Overall analysis	14/408	12/390	1.2	0.5 - 2.6
HYPOTHYROIDISM				
Australia	4/167	1/166	4.0	0.5 - 35.8
Bedford, USA	3/96	1/174	5.2	0.5 - 50.3
Rochester, USA	10/392	6/392	1.7	0.6 - 4.6
Overall analysis	17/655	8/732	2.3	1.0 - 5.4
without Rochester, USA	7/263	2/340	4.5	0.9 - 22.1
GOITRE				
Australia	1/167	2/166	0.5	0.0 - 15.3
Italy	0/115	4/97	0.0	0.0 - 2.3
Seattle, USA	11/126	12/127	0.9	0.3 - 2.7
Overall analysis	12/408	18/390	0.6	0.3 - 1.4

RR = relative risk; 95% CI = 95% confidence interval.

RESULTS

The results of the analyses for thyroid disease are shown in table 2. The relative risk for any kind of thyroid disease prior to onset of AD was 1.0 (95% CI 0.8;1.3).

Table 3. Immune related disorders and osteoarthritis as risk factors for Alzheimer's disease.

Condition	Exposure frequency		RR*	95% CI
	cases	controls		
Atopy	172/670	190/684	0.9	0.6 - 1.2
Hay fever	31/445	38/454	0.8	0.5 - 1.2
Rheumatoid arthritis	10/200	10/200	1.0	0.4 - 2.9
Osteoarthritis	131/277	168/302	0.7	0.5 - 1.0

RR = relative risk; 95% CI = 95% confidence interval.
* Adjusted for age and gender.

There was no effect modification by age of onset, gender, or family history of dementia. For the different types of thyroid disorder no association was found with hyperthyroidism and goitre. The risk for hypothyroidism, however, was significantly increased, the relative risk being 2.3 with a 95% confidence interval of 1.0 to 5.4. This effect was consistent for the studies involved. The minimum interval between onset of hypothyroidism and onset of dementia was 6 years, with an average of 20 years for cases and 16 years for controls.

Table 3 shows the results of the evaluation of immune related disorders and of osteoarthritis. The odds ratios for atopy as well as for hay fever were not significantly different from 1. The relative risk for rheumatoid arthritis was 1.0. Osteoarthritis was significantly less common in cases than in controls, the relative risk being 0.7, with a 95% confidence interval of 0.5 to 1.0.

Results from pooling the data on several infections that had occurred at any time over a subject's life prior to onset of AD are presented in table 4. None of the neurotropic viruses, nor encephalitis or meningitis, was significantly associated with AD.

The overall relative risk for epilepsy was 1.6 (95% CI 0.7;3.5). All studies consistently showed a positive association (table 5). No differences were found between familial and sporadic cases, or between men and women. The risk seemed to be higher for cases with an early onset of AD, but this effect was mainly due to the high relative risk in the Dutch study. To investigate a possible relation between the age of onset of epilepsy and the onset of AD, separate analyses were conducted for epilepsy presenting up to 10 years and more than 10 years before onset of AD. The relative risk was 2.5 (95% CI 0.4;13.9) when the interval was less than 10 years, and 1.4 (95%

Table 4. Neurotropic viruses and encephalitis as risk factors for Alzheimer's disease.

Condition	Exposure frequency		RR*	95% CI
	cases	controls		
Poliomyelitis	5/451	7/467	0.8	0.3 - 2.7
Herpes zoster	100/1103	105/1110	0.9	0.6 - 1.2
Herpes simplex	94/314	78/295	1.2	0.8 - 1.8
Encephalitis/meningitis	7/1081	5/1167	1.6	0.5 - 5.3

RR = relative risk; 95% CI = 95% confidence interval.
* Adjusted for age and gender.

Table 5. Epilepsy as a risk factor for Alzheimer's disease.

	Exposure frequency		RR*	95% CI
	cases	controls		
Australia	6/163	4/166	1.5	0.4 - 5.3
Netherlands	4/198	1/198	4.0	0.4 - 36.0
Bedford, USA	1/98	1/174	3.5	0.2 - 55.7
Rochester, USA	6/392	5/392	1.2	0.4 - 3.9
Overall analysis	17/851	11/930	1.6	0.7 - 3.5
Overall analysis without Rochester, USA	11/459	6/538	2.2	0.8 - 5.9

RR = relative risk; 95% CI = 95% confidence interval.
* Adjusted for age and gender.

CI 0.6;3.4) when it was 10 years or more.

In table 6 the results for the analysis on severe headaches and migraine are given. The overall analysis yielded a relative risk of 0.7 with a 95% confidence interval of 0.5 to 1.0. All studies, except one that had only included men, gave point estimates below 1.0. Interaction between gender and headaches was significant at the 5% level. The number of subjects involved permitted separate analyses for men and women. Women had a consistently lower risk than men. The overall relative risk for men was 1.1 (95% CI 0.6;2.0), and for women 0.6 (95% CI 0.4;0.9). There were no significant interactions with age of onset or familial aggregation.

Table 6. Severe headaches/migraine as a risk factor for Alzheimer's disease.

	Exposure frequency		RR*	95% CI
	cases	controls		
All study subjects				
Australia	23/148	31/156	0.8	0.4 - 1.4
Netherlands	25/198	33/198	0.7	0.4 - 1.3
Durham, USA	9/45	30/88	0.5	0.2 - 1.1
Minneapolis, USA	11/72	7/48	1.3	0.5 - 3.8
Overall analysis	68/463	101/490	0.7	0.5 - 1.0
Men				
Australia	7/54	11/59	0.9	0.3 - 2.4
Netherlands	6/74	4/74	1.7	0.4 - 7.0
Durham, USA	4/14	8/30	1.0	0.3 - 3.5
Minneapolis, USA	11/72	7/48	1.3	0.5 - 3.8
Overall analysis	28/214	30/211	1.1	0.6 - 2.0
Women				
Australia	16/94	20/97	0.7	0.3 - 1.5
Netherlands	19/124	29/124	0.6	0.3 - 1.1
Durham, USA	5/31	22/58	0.3	0.1 - 1.0
Overall analysis	40/249	71/279	0.6	0.4 - 0.9

RR = relative risk; 95% CI = 95% confidence interval.
* Adjusted for age and gender.

Table 7. Blood transfusions and general anaesthesia as risk factors for Alzheimer's disease.

Condition	Exposure frequency		RR*	95% CI
	cases	controls		
Blood transfusions	71/523	112/562	0.6	0.4 - 0.9
General anaesthesia	827/1098	838/1114	1.0	0.8 - 1.3

RR = relative risk; 95% CI = 95% confidence interval.
* Adjusted for age and gender.

The medical treatments that were investigated are presented in table 7. The relative risk for blood transfusions was 0.6, and the 95% confidence interval was 0.4 to 0.9. General anaesthesia proved to be a very common exposure, one that was not associated with the risk of AD. Dichotomizing this exposure into once and more than once yielded no significant associations either.

DISCUSSION

The potential biases of most concern in this study are selection bias, including prevalence-incidence bias and referral bias, and information bias, including recall bias. As to prevalence-incidence bias, since the conditions under study have only a limited effect upon survival the results are unlikely to be seriously affected by the inclusion of prevalent cases. There are however three other possible sources of selection bias. Firstly, controls should be derived from the same population as the cases. In studies in which the cases originate from the general population, population based controls are preferred. Most of the studies used hospital based cases and it might be argued that hospital based controls would constitute a more reasonable reference group for these studies. However, this is only true if the controls are selected on the basis of another disease that is neither related to AD nor associated with the risk factors that are being investigated. Furthermore, the hospital's catchment area for this reference illness and for AD should be identical. When these strict conditions are not met, population based controls might be preferable to hospital based controls for the evaluation of medical conditions and exposures. The two studies that had used both hospital and population controls,[5,7] as well as the study that had only used hospital controls,[6] did not specify which reference illnesses were eligible. Therefore, we decided to include only population based controls in the analyses. Selection bias may also occur when AD patients with comorbidity have a higher chance to come to medical attention and to be subsequently selected into a hospital based or register based study. Whether this has indeed influenced the results can only be evaluated in population based studies. Finally, the incentive for AD patients and their relatives to participate in a study like the case-control studies included in this analysis is more obvious than for controls. This is reflected in higher response rates among cases than controls in most of the studies.[35] The willingness of controls to participate may depend upon their health and the importance they ascribe to health related issues. This may

have particularly affected the assessment of chronic, non-specific conditions like arthritis and headaches or exposures related to medical consumption, such as blood transfusions.

With regard to information bias, we tried to partly overcome this problem by only including studies in which data had been collected symmetrically through surrogate informants for controls as well as for cases. The type of surrogate respondent may also influence the quality of the data, and the ability of different types of informants to provide valid information varies by topic.[36] However, the effect of this source of bias, if any, would presumably be non-differential misclassification. Finally, selective recall bias may distort the evaluation of conditions which the informant suspects may be related to AD. The conditions most likely to be subjected to recall bias in the present analysis are headaches and epilepsy. For epilepsy we cannot rule out the possibility that this has indeed been the case. For headaches we found however an effect opposite to what one would expect if recall bias were the only explanatory factor.

All analyses were adjusted for age and gender. Separate analyses adjusting for familial history of dementia and education yielded similar results. As we are not aware of any other variables that are related to both AD and the conditions under study, confounding is unlikely to be a problem in these analyses.

Since multiple tests of significance are done on the same dataset, some of the significant findings may represent chance results. We tried to reduce this risk by only investigating factors about which we had at least some *a priori* hypothesis. Even with the pooling the statistical power may have been too low to detect factors with a moderately increased risk of AD but a low frequency.

One of the most interesting findings in this analysis is related to thyroid disease. We found an increased risk in patients with history of hypothyroidism. As most people are not aware of any relation between thyroid disease and AD, recall bias is not a plausible explanation. Hypothyroidism itself can cause disturbance of cognitive function. However, the greater frequency of hypothyroidism among cases as compared to controls was not related to disease onset and it is therefore unlikely that this effect was due to misdiagnosis of the dementia. We had no *a priori* hypothesis concerning an increased risk of AD in patients with hypothyroidism, so we are cautious in our inference as this may be a mere chance result. Besides, the classification we used for specific kinds of thyroid disorder was a rather crude one, based on functional status as reported by informants. This lack of aetiological precision and the small number of studies involved in these sub-analyses restrict the potential to draw firm conclusions. If the association we found is indeed a real effect, a possible explanation might focus on the role of thyroid hormone, which is known to have an influence on maturation of

the nervous system and on neuritic outgrowth.[37,38] Furthermore, thyroid hormone is functionally related to several other hormones and trophic factors that have been reported in relation to AD.[39] Unfortunately, we were not able to investigate the role of thyroid medication, as this was not measured in a comparable way among studies.

The finding of an increased risk of AD in patients with epilepsy, particularly if the epilepsy first presented in the 10 years directly preceding the onset of AD, suggests that epileptic seizures are among the first symptoms which AD can present with. However, recall bias on the part of the informants cannot be excluded as a possible explanation. As all studies showed a consistent trend, the lack of statistical significance may be due to the limited power to detect relative risks below 2.0, given the low exposure rate among controls (1%).

None of the viral exposures we investigated yielded an association with AD. For some of these exposures this may have been due to methodological limitations. For both poliomyelitis and encephalitis or meningitis the number of subjects that reported clinically manifest disease appeared to be too small to reliably assess an association with AD. For herpes simplex the clinical manifestation of the infection probably inadequately measures the real exposure of interest, which is retrograde spread of the virus from the trigeminal ganglion. It is not known which factors can mediate this process. Other research methods, e.g. virological and neuropathological studies, are required to investigate this question. For herpes zoster no relation was found either. Most individuals contract varicella during their lifetime and an exacerbation of herpes zoster often reflects an impaired immune system. Since the numbers of exposed subjects were sufficiently large to examine this condition, we feel that on the basis of this analysis herpes zoster can be excluded as related to AD.

The interpretation of the decreased risk in osteoarthritis and severe headaches is not directly clear. Although AD patients may have less morbidity before onset of dementia than age-matched controls, selection bias in the controls is a more plausible explanation for these findings. Recently, use of anti-inflammatory drugs has been reported to be possibly inversely associated with AD.[40] If this speculative theory were true it might be an other explanation for the lower frequency of osteoarthritis and headaches among AD patients, as prolonged use of non steroid anti-inflammatory drugs is often implied in these conditions. Apart from that, the findings for migraine and severe headaches are intriguing because of the involvement of serotonin and neuroexcitatory plasma amino acids in migraine, as mentioned before.[27,28] We have however no explanation for the different findings for men as compared to women.

Contrary to our a priori hypothesis, the risk of AD was lower in subjects who had received at least one blood transfusion. Probably this is also the result of selection bias. Unfortunately, the study that could be expected to have the most accurate data, namely those directly based on medical records, did not investigate this exposure.

CONCLUSIONS

A serious constraint of this re-analysis was the considerable potential for bias, inherent in the design of most of the studies included in the analysis. Besides, several exposures were assessed in a crude and inconsistent way across studies. None of the medical conditions we evaluated in this analysis was convincingly associated with AD. For some of the exposures the findings are regarded as tentative. This applies in particular to migraine. As selection and recall bias cannot be excluded, migraine needs further assessment. Our finding that hypothyroidism is positively associated with the risk of AD also warrants further evaluation of this disorder as a risk factor for AD. Allergies, herpes zoster, general anaesthesia and blood transfusions are unlikely to be risk factors for AD.

To overcome some of the limitations of retrospective case-control studies to assess medical conditions as possible risk factors for AD, these factors need to be evaluated prospectively, for example in case-control studies nested within follow-up studies. Rare exposures can be studied most efficiently in cohorts defined by exposure status. Much attention should be paid to a careful definition and standardized assessment of determinants, aimed to assess specific aetiological hypotheses.

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Chapter 5.2

Risk of dementia for patients with Parkinson's disease, epilepsy, and severe head trauma

Over 70 disorders have been suggested as potentially causing dementia.[1] Disorders in which the dementia syndrome is inherent to the disease, the so-called primary dementias such as Alzheimer's disease, are numerically the more important. However, evidence suggests that among people younger than 70 years of age at least half the cases of dementia may be attributable to other causes.[2] Most putative causes are associated with cerebrovascular disease or degenerative diseases of the central nervous system. In clinical practice it is important to know the likelihood of developing dementia in these neurological disorders for prognostic reasons. Besides, these secondary dementias are of theoretical interest in understanding the different pathophysiological processes that may lead to a dementia syndrome.

We conducted a follow-up study based on three Dutch morbidity registers over the period 1980 to 1989 to quantify the risk of developing dementia in patients with Parkinson's disease, epilepsy or major head trauma.

SUBJECTS AND METHODS

The data to be presented here were derived from the 1980 to 1989 records of three Dutch nationwide morbidity registers which were linked for the purpose of this study: (1) the Dutch Information System on Hospital Care and Day Nursing (LMR), a hospital discharge register; (2) the Dutch Nursing Homes Information System (SIVIS), a register for residential care and nursing homes; and (3) the Dutch Information System on Mental Hospital Care and Mentally Retarded Inpatient Care (PIGG), a register for psychiatric hospitals. The coverage of the registers is virtually complete for the Dutch general and psychiatric hospitals, and over 81 percent for the nursing homes. The total population of the Netherlands in 1988 amounted to 14.7 million people. In the LMR information is provided for each hospitalization on the patient's date of birth, gender, place of residence, admission and discharge dates, surgical treatments that were performed during the hospitalization period and the primary diagnosis and

up to nine secondary diagnoses at discharge. For SIVIS and PIGG the same information is recorded, except that the diagnoses are admission data instead of discharge data. Entries in the registers of SIVIS and PIGG include both subjects who become completely institutionalized and subjects who only use day-care facilities. During the study period in all three registers diseases were coded according to the 9th edition of the International Classification of Diseases, Clinical Modification (ICD-9-CM).[3] Surgical treatments were coded in the LMR according to the Hospital Adaptation of ICDA (H-ICDA).[4]

Subjects

The study cohort was defined as all subjects aged 50 to 75 years who entered the hospital discharge register during the period of January 1, 1980 to December 31, 1982, with one of the following diseases as a primary or secondary diagnosis: Parkinson's disease (ICD-9-CM code 332.0), epilepsy (ICD-9-CM codes 345, 333.2), or severe head trauma (ICD-9-CM codes 800, 801, 803, 804, 850-854). Persons who fell into more than one of these disease categories were excluded. In addition, a reference group was selected to estimate the risk in the general population consisting of all persons aged 50 to 75 years entering the hospital discharge register during this same period (January 1, 1980 to December 31, 1982) with one of the following diagnoses: chronic obstructive pulmonary disease (ICD-9-CM codes 490-496), osteoarthrosis (ICD-9-CM code 715, 721.9), appendectomy (H-ICDA code 49.1), or lumbar intervertebral disc disorders (ICD-9-CM codes 722.1, 722.5), but without any of the diseases of primary interest. Subjects with a diagnosis of dementia or amnesic syndrome made prior to or simultaneously with the diagnosis which made them eligible for the cohort were excluded (ICD-9-CM codes 290.0-290.4, 294.0, 294.1, 331.0, 331.1, 331.2), as were persons with other cerebral degenerations (ICD-9-CM codes 331.3-331.9) and patients with cerebrovascular disease (ICD-9-CM codes 430-438).

Follow-up

The follow-up period started directly after the first person had entered the cohort, and ended on December 31, 1989. Outcome was defined as hospital discharge, institutionalization, or admission to a day-care centre in a nursing home or psychiatric hospital with a diagnosis of dementia (ICD-9-CM codes 290.0-290.4, 294.0, 294.1, 331.0, 331.1, 331.2). First all subjects with this diagnosis during the period 1980 to 1989 were selected from the combined database of the three morbidity registers. Then they were linked to the subjects of the initial cohort, taking into account the date of entry into the cohort. Because no unique patient identifiers are available in the

registers, subjects were linked through the combination of date of birth, gender and place of residence.

Analysis

The follow up period lasted for an average of 8 years, ranging from 7 to nearly 9 years. Therefore, the risk of dementia was expressed as the 8-year cumulative incidence for each of the diseases of interest as well as for the reference group, and estimated by dividing the number of persons in a disease category that became demented during follow-up by the total number of persons with that diagnosis in the initial cohort. Relative risks were computed by taking the ratio of the 8-year cumulative incidence of dementia in the diseased to the 8-year cumulative incidence of dementia in the reference subjects; 95 percent confidence intervals (95% CI) were estimated using Woolf's approximation.[5] Because the risk of dementia in the general population increases strongly with age, the relative risk of dementia in the diseased will decrease with age when this disease carries an additional risk of dementia that is constant over age. Therefore, we also calculated risk differences to provide better insight in the excess absolute risk due to the diseases of interest. All measures were calculated age-specifically in 5-year age groups according to the age at entry in the cohort, and for both sexes separately. Pooled point estimates and approximated 95% confidence intervals over the various age-strata were calculated using the Mantel-Haenszel approach for relative risks, and direct weighting for risk differences.[5]

RESULTS

The age and gender distributions of the patients identified as members of the cohort are shown in table 1. In table 2 the 8 year risk of dementia among the reference group is presented, as well as the average annual incidence. Forty seven percent of the outcome diagnoses of dementia were made in the hospital register (LMR), with 37 percent in the nursing home register (SIVIS) and the remaining 16 percent in the register for the psychiatric hospitals (PIGG). These percentages were very similar for the various groups in the cohort. Table 3 shows the estimated relative risks and risk differences for dementia subsequent to a diagnosis of Parkinson's disease. The overall relative risk was 3.4 for men and 2.5 for women. The relative risk was particularly increased in younger age-groups and amounted to 13.3 (95% CI 6.2 to 28.6) in those aged 50 to 54 years, and to 5.9 (95% CI 3.4 to 10.3) in those age 55 to 59 years. The

Table 1. Number of subjects in the cohort at entry by age, gender and disease category.

Age at entry (years)	Parkinson's disease		Epilepsy		Head trauma		Reference group	
	Men	Women	Men	Women	Men	Women	Men	Women
50 - 54	98	89	576	450	1024	781	7196	6145
55 - 59	209	192	577	472	1085	878	8323	6693
60 - 64	342	373	486	401	1048	810	8901	7094
65 - 69	624	639	449	366	1085	918	10302	8264
70 - 74	899	977	404	324	1137	897	10250	8909
Total	2172	2270	2492	2013	5379	4284	44972	37105

Table 2. Age- and gender specific risks of dementia in reference subjects.

Age at entry (years)	8 year risk of dementia (%)			Incidence rate (per 1,000 personyears)*		
	Men	Women	Total	Men	Women	Total
50-54	0.29	0.36	0.32	0.37	0.47	0.42
55-59	0.61	0.66	0.63	0.79	0.91	0.84
60-64	1.09	1.59	1.31	1.43	2.14	1.75
65-69	2.68	3.51	3.05	3.55	4.77	4.10
70-74	4.13	7.25	5.58	5.51	9.80	7.50

* Age-specific adjustment was made for the incomplete coverage of the SIVIS register.

risk difference for Parkinson's disease was more or less constant over age and around 4.5 percent for 8 years of follow up, similarly for men and women. Table 4 shows the dementia risk for patients with epilepsy. The estimated risk of dementia in patients with epilepsy was higher than the risk among reference subjects (relative risk 1.5, 95% CI 1.4 to 1.7). Although the relative risks are highest in the younger age-groups, the excess absolute risk of epilepsy seems to rise slightly with age (age-specific risk-differences increased from 0.9 for subjects aged 50 to 54 years, to 2.8 for subjects aged 70 to 74 years). Table 5 shows the estimated risk of dementia in subjects with severe head trauma. Overall, severe head trauma did not bear an increased risk of

Table 3. Risk of dementia in patients with Parkinson's disease as compared to the risk in the reference group.

Age at entry (years)	Relative risk (95% confidence interval)			8-year risk difference (%) (95% confidence interval)		
	Men	Women	Total	Men	Women	Total
50-54	21.0 (8.3;53.2)	6.3 (1.5;27.1)	13.3 (6.2;28.6)	5.8 (1.0;10.6)	1.9 (-1.2;5.0)	4.0 (1.1;6.9)
55-59	6.3 (2.9;13.3)	5.6 (2.5;12.5)	5.9 (3.4;10.3)	3.2 (0.6;5.8)	3.0 (0.3;5.7)	3.1 (1.3;5.0)
60-64	6.2 (3.9;9.9)	3.7 (2.3;5.9)	4.8 (3.4;6.7)	5.6 (3.0;8.3)	4.3 (1.9;6.7)	5.0 (3.2;6.8)
65-69	3.0 (2.2;4.1)	3.2 (2.4;4.2)	3.1 (2.6;3.9)	5.3 (3.2;7.5)	7.6 (5.1;10.1)	6.5 (4.9;8.2)
70-74	2.0 (1.6;2.6)	1.4 (1.1;1.8)	1.7 (1.4;2.0)	4.2 (2.4;6.1)	3.0 (1.0;5.0)	3.8 (2.4;5.1)
Overall	3.4 (3.3;3.5)	2.5 (2.4;2.6)	3.0 (2.9;3.1)	4.7 (3.6;5.7)	4.0 (2.9;5.1)	4.5 (3.7;5.3)

Table 4. Risk of dementia in patients with epilepsy as compared to the risk in the reference group.

Age at entry	Relative risk (95% confidence interval)			8-year risk difference (%) (95% confidence interval)		
	Men	Women	Total	Men	Women	Total
50-54	3.6 (1.4;8.9)	3.7 (1.5;9.2)	3.6 (1.9;6.9)	0.8 (-0.1;1.6)	1.0 (-0.1;2.1)	0.9 (0.2;1.5)
55-59	2.8 (1.4;5.6)	2.6 (1.2;5.5)	2.7 (1.6;4.5)	1.1 (0.0;2.2)	1.0 (-0.1;2.2)	1.1 (0.3;1.9)
60-64	1.9 (1.0;3.6)	2.0 (1.1;3.7)	2.0 (1.3;3.1)	1.0 (-0.3;2.3)	1.7 (-0.1;3.4)	1.3 (0.2;2.3)
65-69	1.4 (0.9;2.3)	1.5 (0.9;2.4)	1.5 (1.0;2.0)	1.1 (-0.7;2.9)	1.7 (-0.6;4.0)	1.4 (-0.1;2.8)
70-74	1.4 (0.9;2.1)	1.6 (1.1;2.3)	1.5 (1.2;2.0)	1.6 (-0.7;3.9)	4.5 (0.9;8.0)	2.8 (0.8;4.8)
Overall	1.5 (1.4;1.7)	1.5 (1.4;1.6)	1.5 (1.4;1.7)	1.0 (0.4;1.5)	1.3 (0.6;2.0)	1.1 (0.7;1.5)

Table 5. Risk of dementia after severe head trauma as compared to the risk in the reference group.

Age at entry	Relative risk (95% confidence interval)			8-year risk difference (%) (95% confidence interval)		
	Men	Women	Total	Men	Women	Total
50-54	0.7 (0.2;2.9)	---	0.3 (0.1;1.4)	-0.1 (-0.4;0.2)	-0.4 (-0.5;-0.2)	-0.2 (-0.4;0.0)
55-59	2.0 (1.1;3.6)	0.4 (0.1;1.4)	1.2 (0.7;2.1)	0.6 (-0.1;1.3)	-0.4 (-0.8;-0.1)	0.1 (-0.3;0.5)
60-64	1.1 (0.6;2.0)	0.7 (0.4;1.4)	0.9 (0.6;1.4)	0.2 (-0.6;0.9)	-0.5 (-1.3;0.3)	-0.1 (-0.7;0.4)
65-69	0.7 (0.5;1.1)	0.9 (0.6;1.3)	0.8 (0.6;1.1)	-0.7 (-1.6;0.1)	-0.5 (-1.6;0.7)	-0.6 (-1.3;0.1)
70-74	1.3 (1.0;1.7)	1.3 (1.0;1.6)	1.3 (1.1;1.5)	1.2 (-0.2;2.5)	2.0 (0.0;4.0)	1.5 (0.3;2.6)
Overall	1.1 (0.9;1.2)	1.0 (0.9;1.1)	1.0 (0.9;1.1)	0.0 (-0.2;0.3)	-0.3 (-0.6;0.0)	0.0 (-0.2;0.2)

dementia in the subsequent 8 years (relative risk 1.0, 95% confidence interval 0.9 to 1.1). Limiting the analysis to traumas with explicit mentioning of intracranial injuries and loss of consciousness yielded similar results.

DISCUSSION

We conducted this register-based cohort study to ascertain and quantify the risk of dementia after Parkinson's disease, epilepsy and head trauma in persons aged 50 to 75 years. The 8-year risk after Parkinson's disease was three times as high as compared to the risk in the reference group, the relative risk after epilepsy was 1.5, but the risk after major head trauma was not increased.

Methodological issues

Before discussing these results, we want to make some comments on the design of this study, particularly in relation to its use of register data. The use of existing databases for this kind of research clearly has advantages, its major appeal and strength being the availability of a large amount of data, that would be very hard to collect otherwise. It enables the definition of large cohorts, as well as internal comparison

groups. Furthermore, the follow-up design eliminates the potential of recall bias. There are potential limitations, however, since the data were not specifically collected for this study. The first concerns have to do with the accuracy and completeness of coding of diagnoses in the database. Persons with very mild dementia who got hospitalized for some other reason may not have been recognized as having dementia. For serious morbidity, however, administrative databases tend to be complete and reliable,[6] and moderate or severe cases of dementia were probably properly recorded. Not all Dutch nursing homes contributed to the SIVIS register during the study period. This will have resulted in an underestimation of approximately seven percent of the number of subjects that became demented (37 percent of all dementia diagnoses were made in the SIVIS register that covered over 81 percent of the nursing homes). Since this small underreport is not related to the conditions under study, it will not have affected the validity of our study.

A second question that arises is whether it is indeed possible to identify and trace persons by means of these registers. We selected our reference group on the basis of disorders that are unrelated to the risk of dementia. On the assumption that the reference group was properly chosen to reflect the risk of dementia in the general population, we could check the validity of our method by comparing age-specific incidence rates in our reference group with available incidence estimates from other studies. The yearly age-specific incidence rates of dementia that we found (table 2) were in very close concordance with those reported from Rochester, Minnesota, for the years 1970 to 1974,[2] and with preliminary results from ongoing population based studies in Bordeaux and Liverpool.[7-9]

A third issue related to the use of register-data is the potential for ascertainment bias. If the chance of being hospitalized during the follow-up period were dependent on comorbidity, and therefore disproportionate for the various disease categories, this would be a serious concern. We could examine this potential bias to some degree in our reference group. Age-specific incidence rates of dementia were very similar in persons with chronic diseases (chronic obstructive pulmonary disease, osteoarthrosis) and persons suffering from temporary disorders (appendectomy or lumbar intervertebral disc disorders), suggesting that ascertainment bias was not a major threat to our results.

Finally, the privacy legislation that precluded person identifiable records also impeded linkage to mortality registers, so we could not directly measure incidence rates. For that reason, we treated our data in the analysis as cumulative incidence data which inherently assumes that there is no competing mortality. However, the diseases under study are all known to lower life expectancy. To the extent that this has influenced

the results, it will have given an underestimation of the risk of dementia in the groups with the increased mortality.

Parkinson's disease and the risk of dementia

In patients with Parkinson's disease we found the risk of dementia to be increased about three times, an estimate rather similar to the 3.7 that was reported by Rajput et al. from a cohort study based on medical records from Rochester, Minnesota.[10] The age-specific relative risk was highest in the youngest age-group and declined from 13.3 for those aged 50 to 54 years to 1.7 for those aged 70 to 74 years. This implies that among younger dementia patients a considerable proportion is due to Parkinson's disease. Mayeux et al. reviewed patient-records from a tertiary care centre and found that the incidence rates of dementia in patients with Parkinson's disease increased from 28.6 per 1,000 persons per year for those aged 30 to 59 years, to 136.5 per 1,000 persons per year for those over 80 years of age.[11] The increasing incidence figures with age have been interpreted as an age-disease interaction.[12] Since we had an internal comparison group in our study, we could calculate age-specific risk differences. The excess absolute risk of dementia for patients with Parkinson's disease was constant over age. This suggests that in Parkinson's disease patients the observed rise in the incidence of dementia with age does not result from an interaction between the disease and age but is rather due to the increasing background risk of dementia, and that the proportion of Parkinson's disease patients that develop dementia as an intrinsic characteristic of the disease is independent of age.

Epilepsy and the risk of dementia

The reason for an elevated risk of dementia in patients with epilepsy is unclear. Interestingly, in patients with Down's syndrome, who are at a highly increased risk of developing Alzheimer's disease, there is an increased prevalence of seizure disorders that precedes the onset of dementia.[13] In a reanalysis of case-control studies of Alzheimer's disease, epilepsy was more common among cases than controls, especially in the years directly preceding the onset of Alzheimer's disease, although the difference was not significant.[14] The results in our current study can only be interpreted tentatively, since it was impossible to subdivide epilepsy according to underlying cause. We feel however that the relation between epilepsy and subsequent dementia merits further investigation, in particular the hypothesis that epilepsy can be a first manifestation of Alzheimer-related changes in the brain.

Severe head trauma and the risk of dementia

The syndrome of dementia pugilistica is regarded as evidence that repeated head traumas, as occur in boxers, may cause neurofibrillary degeneration and subsequently dementia. Whether a single traumatic event can have the same effect is not clear. Case-control studies of Alzheimer's disease suggested that a severe head trauma might increase the risk of Alzheimer's disease, especially in men.[15] Overall, we did not find an increased risk of dementia within 8 years after severe head injury. Our results are in agreement with those from a register-based study from Rochester, Minnesota.[16] Although we can draw no conclusions on the long term effects of a major head trauma, the case-control studies suggested that the risk was particularly increased for head injuries that occurred within a period of 10 years before onset of dementia.[15,17] A possible explanation is that the results in the case-control studies have been due to recall bias. On the other hand, our focus on dementia instead of Alzheimer's disease may have obscured an existing relationship between head trauma and Alzheimer's disease. It is also conceivable that an increased mortality experience in cases with severe head trauma has biased estimates of relative risk downwards. Although our findings are not conclusive, they do not support the hypothesis that severe head trauma is an important risk factor for dementia in general.

CONCLUSIONS

The linked registers provided a reliable base to estimate the incidence of moderate or severe dementia in large cohorts of patients and compare these with appropriate reference groups. We found that Parkinson's disease strongly increases the incidence of dementia. Relative risks were in particular highly elevated in younger patients with Parkinson's disease due to the low population risk of dementia in younger subjects. The proportion of Parkinson patients that become demented as a direct result of the disease, however, remains constant over age. Epilepsy is also associated with an elevated risk of dementia, but the absolute excess risk increases with age. Our findings do not suggest that severe head trauma is related to the risk of dementia.

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Chapter 6

General discussion

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General discussion

In this thesis several studies, based on different populations and using different designs, are described. The overall and unifying aim was to further epidemiological knowledge on dementia and cognitive decline. The limitations and strengths of the various studies have been discussed in the previous chapters. This chapter will concentrate on aspects of the studies that were based on the Rotterdam Study. First, some of the methodological issues that were raised by these studies and that also apply to further studies on the topic, will be discussed. Next, the evidence from the various studies will be reviewed. Finally, suggestions will be given as to along which lines epidemiological research in this field could be continued.

METHODOLOGICAL ISSUES

Study design

The studies based on the Rotterdam Study presented in this thesis were observational and, more in particular, cross-sectional. Cross-sectional studies yield prevalence estimates, or, if the outcome is expressed on a quantitative scale, a distribution of the outcome variable among the investigated subjects, as opposed to longitudinal studies, that may provide incidence estimates, or, quantitatively, change distributions.[1] In the investigation of etiologic relationships, cross-sectional studies are commonly regarded as inferior to longitudinal studies. Although this applies in general to prevalence studies relative to incidence studies, in the context of quantitative health characteristics the study of cross-sectional status distribution need not be inferior to the study of change distributions.[1] To appreciate the possibilities as well as the limitations of cross-sectional studies for causal inference, two issues should be considered: the supposed time-relationship between the determinant and the outcome, and the natural course among subjects with different levels of the outcome. As to the first issue, the central question is here whether the exposure, notwithstanding the fact that it is assessed simultaneously with the outcome, can be conceptualized as having exerted its supposed effect in the period preceding the onset of the outcome.[2]

If the determinant is relatively stable and presumed to have a cumulative effect over time, the cross-sectional assessment may be as good as a longitudinal one, particularly so if the time-interval in a follow-up study would be short relative to that of the hypothesized antecedent causal process. On the other hand, if the exposure of interest is highly variable over time, or if the outcome, or some closely related pathophysiologic process, influences the level of the determinant, the interpretation of cross-sectional results is easily jeopardized by fallaciously mistaking correlation for causation. The second consideration, regarding the natural course among subjects with different levels of the outcome, bears upon what is called in the dichotomous situation of diseased versus non-diseased, prevalence-incidence bias. If the case-fatality rate differs across levels of the outcome, the determinant-outcome relation that can be assessed cross-sectionally may actually reflect determinants of survival given the outcome. Though this problem is most stringent in cross-sectional studies, it may play a role in longitudinal studies as well if information is missing regarding the outcome-status for people who die during the follow-up interval.

How do these considerations bear upon the results from the cross-sectional studies in this thesis (chapters 3 and 4)? We investigated the relation between various indicators of vascular disease and risk factors for cardiovascular disease, and cognitive function. We found that presence of atherosclerosis was associated with poorer cognitive performance. Since atherosclerosis is a relatively stable determinant, that is supposed to reflect life-time accumulation of vascular damage, we feel confident to conclude that atherosclerosis is etiologically related to cognitive impairment.

The nature of the relation between blood pressure level and cognitive function is less clear. The actual blood pressure measured at the time of the survey may not adequately reflect the level in the period in which it could have exerted its influence on cognitive status. Longstanding elevated blood pressure can result in atherosclerosis which in turn may lead to a paradoxical drop in blood pressure. If elevated blood pressure would negatively influence cognitive function through its effect on atherosclerosis, this could possibly result in a spurious association between low blood pressure and cognitive impairment on cross-sectional assessment. It should be noted that these reservations, though perhaps less extreme, will apply in prospective follow-up studies as well, to the extent that the blood pressure measured at baseline may not reflect the blood pressure level in the preceding, etiologically relevant, period.

For fibrinogen and the other hemostatic factors the time-occurrence relationship is even more difficult to interpret. The levels of these factors are highly variable. Although several studies have suggested that these factors are etiologically involved

in vascular disease, increased levels may result from existing vascular lesions as well. Therefore, these factors need to be evaluated prospectively.

Accuracy

Two separate issues pertain to the accuracy of estimates in epidemiologic research: validity and precision. As for validity, referring to the amount of bias or systematic error in a study, a useful distinction according to the source of error can be made: selection bias, information bias, and confounding.

Selection bias. Selection bias occurs if the relation between the determinant and the outcome is different for those who participate and those who are eligible but do not participate in a study. In the population-based study of correlates of cognitive function (chapter 3), non-response could occur at two occasions: first, individuals could entirely refuse participation in the study, and second, once the home-interview had been conducted, they could refuse to come to the research center for the additional examinations. Supposedly, at least part of the non-response was selective and related to poor physical or mental health, resulting in a respondent population that was biased both with respect to the determinants as well as to the outcome variable. As a consequence, the relation between the determinants and cognitive function may have been different among non-responders as compared to that among responders.[3] However, the overall response was high (80%) which limits the amount of possible bias. Moreover, to seriously affect the inferences that can be drawn from the study observations, the relations among non-responders should have been quite opposite to the ones among responders, which is unlikely.

In the MRI-study, which was based on a subsample of the participants of the Rotterdam Study, additional attrition occurred. Comparison of the subjects who underwent MRI scanning as well as the neuropsychological testing with those who were scanned but refused the testing, revealed that among the latter cerebral white matter lesions were more prevalent. Most likely, this resulted in an underestimation of the relations.

Information bias. For a meaningful investigation of the relation between a determinant and an outcome variable, information is needed on the determinant and the outcome as well as on potential confounders of that relationship. Incorrect information will lead to misclassification with respect to exposure, outcome or confounders. Since perfect assessment is in most instances only a theoretical possibility, the question is not whether misclassification occurred, but rather to what extent it occurred and whether it biased the results.

If the assessment of the exposure is independent on the outcome variable, misclassification of the exposure is non-differential. Non-differential misclassification tends to bias effect estimates toward the null value.[4] For continuously scaled variables this is referred to as regression-dilution bias, and this will occur in particular when intraindividual variability is high.[5] Dual measurement strategies have been advocated as a remedy, however, they are likely to remove only part, if any, of the effect attenuation due to non-differential exposure misclassification, because both measurements are usually not independent conditional on the true value.[6,7] If, on the other hand, the assessment of the exposure is dependent on the outcome variable, this will result in differential misclassification, and serious bias may occur which can result in either over- or underestimation of the true relation. In the Rotterdam Study, the physical examinations, the laboratory assessments, and the MRI scans, were objective measurements and measured blindly as to cognitive function status. Although differential misclassification is therefore not an obvious concern here, non-differential misclassification is, and primarily in those situations in which no effect was found. For instance, it is well possible that nondifferential misclassification has obscured an existing relation between hemostatic factors and cognitive function in the analyses based on the total cohort. With regard to the information that was elicited by the interview, differential misclassification could have occurred if cognitively impaired individuals provided less accurate accounts of their medical history. When subjects whose interviews were classified as "unreliable" were excluded from the analyses, the average difference in MMSE score between subjects with and without history of previous stroke, and between subjects with and without history of myocardial infarction, increased. This indirect evidence suggests that the differential misclassification of interview information may have resulted in an underestimation of these relationships.

The outcome in our studies, cognitive function, was assessed independently from the determinants and expressed as the mean of a continuous variable. Therefore, the assessment of the outcome was only subject to random error.[1] Though this error may bear upon precision (see below), it did not affect validity.

Misclassification of a confounder leads to a partial loss of the ability to control confounding.[8] The use of a surrogate variable in place of a factor of more direct interest, will introduce misclassification and thereby impede control of confounding by that factor. The outstanding confounder in the relations that we investigated was age. It should be noted that, although calendar age can be measured very precisely, it is only a proxy for the more relevant measure of biological age, which in turn is a proxy for a whole array of life-time accumulated exposures.

Confounding. Confounding can occur when an extraneous factor is associated with the determinant under study as well as with the outcome variable. It is the actual relation between the potentially confounding variate and disease, not the relation observed in the data, that determines whether confounding can occur.[9] The most important confounders in the studies on cognitive function were age and, potentially, gender and level of education. The large numbers of subjects in the total population studies, and the stratified sampling in the MRI-study, enabled adequate control of their potential confounding influence in the analyses. Another issue is whether one should control for factors which are in part caused by the exposure under study and also correlated with the outcome under study. Even when such a factor is not intermediate on the causal pathway, adjusting for it may introduce bias. The factor can be looked upon as a partial surrogate for the outcome of interest, and correcting for it then implies that the outcome is to some extent represented on both sides of the model equation.[10] We faced this problem in the analyses on the relation between vascular risk factors and cognitive function. The true underlying causal mechanisms, which are largely unknown, should dictate which factors to treat as potential confounders or effect modifiers.

Precision. Precision corresponds to the amount of random error in a study, and is directly related to the statistical power of a study to detect existing relationships. Basically, there are two ways to increase precision: one is to reduce measurement error, and the other is to enlarge the size of the study. In the Rotterdam Study, the reproducibility of the assessment of several determinants could have been enhanced by dual measurements or by further standardization of the measurement procedures, e.g. fixed time of the day for blood sampling, only fasting levels of glucose and serum lipids. (It should be noted that, although in practice measurement error in the assessment of exposures bearing upon precision is closely related to that bearing upon validity, conceptually the two can be distinguished. With regard to precision, the reason for dual measurements is simply to have an estimate with less variability, whereas with regard to validity its rationale is to obtain a better estimate of the true value.) The random variation in the assessment of cognitive function, the outcome variable, could probably have been reduced by using a more extensive test than the MMSE. Increasing precision by reducing measurement error comes at considerable costs. The alternative is to increase the size of the study. In the studies based on the population distribution of cognitive function, the number of people that were included (4,971) seemed to ensure adequate power. However, the proportion of participants for which information was available differed across the various determinants, and for some of the hemostatic

factors it reached only 34 per cent. These missing data do not affect validity, since the decision whether to complete laboratory assessment or not was taken randomly. But, in combination with the large variability in the assessment of these variables, the resulting power may have been low. The MRI-study was based on 111 persons. Subjects with white matter lesions performed worse on all cognitive tests. The consistency across tests, together with the considerable size of the estimated differences, suggests that the failure of several differences to reach significance, may have been due to insufficient power.

Operationalization of the outcome

Of prime importance in the design of a study is the distinction between the conceptual entity one intends to assess and its operational counterpart.[1] Existing diagnostic criteria for dementia reveal the considerations for patient management that primarily instigated their formulation. In addition to a decline from an attained level of mental functioning, significant interference with work or other social activities is required.[11,12] Defined this way, dementia is a composite measure that reflects not only the cognitive decline of the individual, but also the coping abilities of the affected individual and that of his or her social environment, as well as the demands put upon this person. From a public health point of view this may well be the relevant measure for estimating the need for support. If the interest is in causes of cognitive decline the outcome measure should be as specific as possible, that is, actual cognitive performance.

Another issue involves the decision whether to dichotomize or categorize the outcome of interest, or evaluate it continuously. In previous studies of the frequency and etiology of dementia, much emphasis has been put on differentiating demented subjects from cognitively unimpaired individuals. However, there is little evidence to support the idea of a sharp distinction between demented and non-demented persons.[13] Cognitive impairment is a quantitative rather than a qualitative characteristic, and consequently its distribution in the population shows a continuum of severity.[14] If the determinants are continuously distributed in the population as well, and if there is a graded relationship between the determinants and cognitive function, collapsing the distribution of cognitive function in two categories, impaired versus unimpaired, will diminish the amount of information in the study.

Related to the imperative of defining relevant operationalizations is the question whether and how to subtype dementia. Here again, the crucial consideration concerns the reason for doing so. The most important distinction among degenerative dementias

is the one between Alzheimer disease and vascular dementia, and this classification is based on presumed different etiologies. The clinical diagnosis of Alzheimer's disease is a diagnosis by exclusion of other specific causes of dementia.[15] In etiologic studies of Alzheimer's disease, the notion of vascular dementia can be useful in obtaining a more homogeneous group of Alzheimer patients, by excluding subjects in which Alzheimer's disease can be doubted to be the only cause of the dementia. In recent years vascular dementia itself became a primary object of research. In analogy with those for Alzheimer's disease, sets of diagnostic criteria for ischemic vascular dementia and for vascular dementia have been proposed.[16,17] However, these overlook the problem that if one wants to study vascular risk factors for dementia, vascular dementia is not the appropriate outcome measure, since the presence of the risk factors forms part of the diagnostic criteria. The problems arising in defining vascular dementia can only be circumvented by directly investigating the relations of interest, namely those between vascular risk factors and cognitive impairment. If the primary interest is not in etiology but in the relative frequency of the different types of dementia, it may seem that there is merit in clear and unequivocal criteria for vascular dementia. However, any definition of vascular dementia implicitly assumes that vascular risk factors and dementia are causally related when they are both present in the same individual. This will invalidate the comparison of relative proportions of dementia subtypes across populations with different vascular background risks.

Data-analysis

In the studies on cognitive function the outcome measure was the score obtained on the MMSE (chapter 3) or on other tests of cognitive function (chapter 4). These testscores have highly skewed and truncated distributions. In principal this dictates the use of non-parametric methods in the analysis. However, available non-parametric methods (e.g. stratified Wilcoxon test) are well suited for significance testing, but yield no effect estimates. Since our primary interest was in intelligible measures of the strength of the relations, we choose to use multiple linear regression techniques without any transformations. The violation of the model assumption of normality was no problem because of the large numbers included in the studies and the point estimates of the effect are reliable.[18] Because homoscedasticity could not be assumed, the corresponding standard errors, and the confidence intervals based upon these, may be wrong. Calculation of robust confidence intervals learned that these differed only slightly from the confidence intervals based upon the standard errors derived from the linear regression models.[18]

MATERIAL ASPECTS

The basic research questions in the studies that were based on the Rotterdam Study and that are described in this thesis, referred to the distribution of cognitive function in an elderly population according to demographic variables (age, gender, level of education); to the relation between clinical vascular disease and vascular risk factors, and cognitive function; and to the meaning of cerebral white matter lesions in the context of vascular causes of cognitive impairment. The evidence from the various studies can be summarized as follows:

* Age is inversely associated with cognitive performance.
* There is no indication for a major difference in cognitive performance according to gender.
* Educational level is positively associated with cognitive performance.
* Presence of atherosclerotic disease is associated with poorer cognitive performance.
* In the very old, elevated blood pressure is associated with better cognitive performance.
* Presence of diastolic orthostatic hypotension is associated with poorer cognitive function.
* Atrial fibrillation is inversely related to cognitive function among women.
* HDL-cholesterol is positively associated with cognitive function.
* Hemostatic factors (fibrinogen, factor VIIc) are associated with cerebral white matter lesions.
* Atherosclerosis and vascular risk factors are associated with cerebral white matter lesions.
* Cerebral white matter lesions are associated with impaired cognitive function.
* A small average decline in cognitive function can result in a large increase in the proportion of severely impaired persons in the population.

Age

That, on average, cognitive function declines with age is well recognized. Consideration of the shift of the population distribution with age learns, however, that not all persons decline to the same extent, resulting in an increased heterogeneity with increasing age. This bears upon the concepts of usual versus successful aging,[19] and is compatible with the view that cognitive decline is not intrinsic to age.[20] The

major challenge for prospective studies on cognitive function is to identify factors that underlie the relation between age and cognitive function.

Gender

In prevalence studies of dementia in general women have been found to have somewhat higher prevalence rates than men. The question is whether this reflects a difference in risk, in detection, or in survival. Incidence data of dementia, though still scanty, seem to indicate little difference between gender. We found that the relation between gender and cognitive function was strongly confounded by education. It is possible that detection bias has contributed to the differences in prevalence rates of dementia for men and women.[21] Among Alzheimer patients survival is reportedly better for women than for men.[22] A follow-up study of cognitive function should seek answers to the following questions regarding potential gender differences: (1) Is the rate of cognitive decline different for men and women?, and (2) Do mortality rates, conditional on level of cognitive function and adjusted for overall life-expectancy, differ according to gender?

Education

The role of education in cognitive function and dementia remains controversial. Several studies found evidence for an association between lower educational levels and the prevalence of clinically diagnosed dementia.[23] It has been suggested that this is merely the result of detection bias.[21] On the other hand, there is some evidence that subjects with higher educational achievement may have indeed larger cognitive reserve capacities.[23,24] Our cross-sectional results confirmed the association between educational level and cognitive function, but can not distinguish between the possible explanations. Prospective epidemiologic studies could help resolve the dispute. If the differences were only the result from detection bias, this would predict cognitive decline to occur in similar proportions, and at similar rates, across educational levels. If, on the other hand, the proportion of subjects who show cognitive decline would be larger among the less-educated than among higher-educated persons, or if the less-educated would have accelerated rates of decline, this would suggest an etiologic role for education. Even then, however, the question remains what underlies this association. Educational achievement may serve as a proxy for determinants as different as early-childhood exposures, socioeconomic status, neocortical synaptic density, or continuing stimulation of neuronal regenerative processes.[23,25]

Atherosclerotic disease

Although the relation between atherosclerotic disease and cognitive impairment seems beyond doubt, the exact pathogenetic mechanisms remain largely unresolved. Most explanations for the relation between atherosclerotic disease and cognitive function have focused on the hemodynamic implications of atherosclerosis. It is also conceivable, however, that atherosclerosis, or the determinants of atherosclerosis, have an influence on cognitive function apart from the effect on cerebral perfusion, e.g. by impairing blood-brain barrier function as a result of cerebral vessel wall damage.[26] Epidemiologic methods seem not to be suited to disentangle the precise pathogenetic pathways. The role that epidemiology can play in this context, is to investigate whether cognitive decline can be prevented by intervention on factors contributing to atherosclerosis.[27]

Blood pressure

The relation between blood pressure and cognitive function remains ambiguous. Longstanding elevated blood pressure is considered to be etiologically involved in Binswanger's disease, as well as in multi-infarct dementia.[28,29] On the other hand, it has been suggested that in susceptible individuals low blood pressure can also be a risk factor for cognitive decline, when the pressure becomes too low to guarantee adequate cerebral blood flow.[26,29] We found evidence both in the study that was based on the total cohort of the Rotterdam Study, and in the MRI study, for the relation between blood pressure and cognitive function to be dependent on age. Among subjects younger than 75 years increasing blood pressure was associated with poorer performance on the MMSE, and with the presence of white matter lesions. In contrast, among subjects older than 75 years higher blood pressures were associated with better test performance, particular when atherosclerotic disease was present, and unrelated to white matter lesions. Several pathophysiologic mechanisms can be conceptualized that relate blood pressure, atherosclerosis, and cognitive function. Our findings could be explained if we assume that among younger persons elevated blood pressure causes atherosclerosis, which leads to clinically manifest or silent cerebral infarctions, resulting in loss of cognitive function. Many of them will die due to the complications of severe vascular disease, resulting in a selected group of older persons. Among people who survive until ages above age 75 years, the situation differs according to presence or absence of atherosclerosis. Subjects with high blood pressure, but without demonstrable atherosclerosis, may constitute a special group that is relatively resistant to the destructive effects of elevated blood pressure levels. In those individuals, blood pressure seems unrelated to cognitive function. On the other hand, among persons who survive

until older age while accumulating atherosclerotic lesions, low blood pressures may result in chronic hypoperfusion which then could lead to cognitive decline.

Atrial fibrillation

We found atrial fibrillation to be inversely associated with cognitive function among women but not among men. Stroke and transients ischemic attacks are thromboembolic complications of chronic atrial fibrillation. In the Framingham study, the risk of stroke associated with atrial fibrillation seemed larger for women than for men.[30] Several recent trials showed the efficacy of anticoagulant therapy in the prevention of cerebral infarcts in patients with atrial fibrillation.[31] When we compared the relation of atrial fibrillation with cognitive function between women with or without anticoagulant therapy, we found that the association was only present among women not using anticoagulant drugs. This comparison should be interpreted with caution, because the use of anticoagulant drugs is likely to be influenced by presumed intermediates (TIA, stroke) in the relation between atrial fibrillation and cognitive function. However, that would rather predict a stronger effect among women using anticoagulants. A possible explanation for the gender difference could be that cardiac disease is often underdiagnosed in women.[32]

Lipid levels

There is little consensus regarding the importance or mechanisms of lipids in the pathophysiology of stroke or dementia in elderly persons.[33] In the Bronx Aging Study the risk of dementia associated with serum lipids and lipoproteins was assessed prospectively, but no relation was found.[34] A study conducted among subjects over age 80 years in Southern Italy reported cognitive function to be positively associated with HDL-cholesterol levels, but not with total cholesterol.[35] In the Rotterdam Study, we found similar relations between lipid levels and cognitive function as in the Italian study. An important question, which can not be answered on the basis of our cross-sectional data, is whether increased levels of HDL-cholesterol are protective of cognitive decline, or rather that low levels of HDL-cholesterol reflect the poorer health state or lower physical activity of subjects with cognitive impairment.

Hemostatic factors

In recent years, several studies identified factors associated with coagulation and hemostasis as important risk factors for the initiation and progression of cardiovascular disease.[36-38] This raised the question whether hemostatic factors are risk factors for

for cognitive decline due to vascular lesions. We found no indication for an association between levels of fibrinogen, factor VIIc and factor VIIIc, and cognitive function in our study based on the total cohort of the Rotterdam Study. In the MRI study, on the other hand, both fibrinogen and factor VIIc levels were associated with the presence of white matter lesions. It is possible that in the first study, non-differential misclassification and lack of power obscured an existing relation, as discussed previously. However, it may as well be that the increased levels that we observed among subjects with white matter lesions, reflected the presence of those lesions, rather than any etiologic involvement. On the basis of these studies we can not conclude whether hemostatic factors are associated with cognitive function. Prospective studies are needed to answer this important question.

Cerebral white matter lesions

Cerebral white matter lesions are commonly found on magnetic resonance imaging (MRI) scans in the elderly and pathological studies have shown that these lesions reflect mainly vascular pathology.[39,40] In selected series of patients these lesions have been shown to be related to hypertension and several other vascular risk factors.[41,42] Although in demented patients the presence and severity of white matter lesions seem to correlate with dementia severity, their meaning in non-demented subjects has been questioned. In our study white matter lesions were associated both with vascular risk factors, and with cognitive function, particularly with subcortical or frontal functions. Our findings strongly support the idea that white matter lesions on MRI reflect vascular pathology contributing to cognitive impairment.

Clinical relevance

In our investigation of the relation between vascular risk factors and cognitive function the mean difference was usually less than half a point on the MMSE which raises the question whether this is clinically relevant. The answer to this is not to be found on the individual level, but rather on the population level. When the distribution of cognitive function is compared between subjects with or without vascular risk, it becomes clear that even a slight decrease in average performance, is associated with a downward shift and change in shape of the total distribution, resulting in a large increase of the proportion of subjects scoring below a specified cutoff. It is easy to see that for conditions that are associated with lower cognitive function, the more prevalent they are, the larger their population impact will be. The question remains to be answered whether prevention of such conditions would result in the otherwise

affected subjects to assume the distribution of the now unaffected individuals. If yes, this would mean a major health benefit. Although the average gain per individual would be small, the population gain might be substantial. These considerations provide a strong argument to investigate whether intervention on risk factors for atherosclerosis can prevent cognitive decline on a population level.

FUTURE RESEARCH

The major part of this thesis was devoted to cross-sectional correlates of cognitive function. An underlying assumption in the conduct of these studies was that, on average, lower levels of cognitive performance reflected a decline from a previous higher level. The relevance of these studies was derived from another, though closely related, assumption, namely, that the actual level of cognitive function is predictive for future change in cognitive function. Both these assumptions need further investigation in prospective follow-up studies.

Prospective follow-up studies would also provide a powerful and efficient way to investigate risk factors for cognitive decline, by enabling the conduct of nested case-control studies. Two areas seem of particular interest in etiologic research in dementia. One is the contribution of vascular risk factors to cognitive decline. Of particular potential interest in this regard is the role of hemostatic factors, since these may be intermediate in the relation of other risk factors with cardiovascular disease.[43] Most vascular risk factors are not stable over time. Moreover, the relevant exposure could be change in risk factor level rather than actual level. Therefore, prospective follow-up studies should investigate change in cognitive function as a function of both baseline assessment of vascular factors, as well as of change in vascular determinants, conditional on baseline level. Another promising lead is the studies of gene-environment interaction in the etiology of Alzheimer's disease,[44] and in the investigation of vascular causes of cognitive impairment.[45] Obviously, those studies need to be conducted in close collaboration with basic research.

Research on cognitive function and dementia is fundamentally motivated by the pursuit of ways to prevent cognitive decline. Even though the precise pathophysiologic mechanisms through which various vascular risk factors contribute to cognitive impairment remain to be elucidated, there is ample evidence that vascular risk factors and vascular disease are associated with cognitive decline. The widespread prevalence of these conditions in the population justifies an attempt to prevent cognitive decline

on a population level by intervention on vascular risk factors. In an intervention study, a quantitative outcome measure that can be objectively assessed is to be preferred. The cerebral white matter lesions that can be seen on MRI scans reflect primarily cerebral damage due to vascular causes. Change in their frequency and severity seems particularly apt as the primary outcome measure in an intervention study on vascular causes of cognitive decline. As a secondary outcome measure, change in cognitive function as measured by neuropsychological tests should be assessed, to obtain an indicator of clinical relevance. Such research would in addition offer the opportunity to further investigate the relation between cerebral white matter lesions and cognitive function.

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Chapter 7

Summary

Chapter 7.1

Summary

Dementia is emerging as a major health problem. It is an important cause of disability, particularly in the elderly, and imposes a severe burden on public health resources. For many people, growing old is strongly connected with the fear of "losing their mind". This thesis focuses on epidemiologic studies on cognitive function and dementia.

Alzheimer's disease is the most important cause of dementia. In chapter 2 the main epidemiologic findings of Alzheimer's disease concerning its frequency, risk factors, prognosis and treatment, are reviewed. The prevalence of Alzheimer's disease rises exponentially with age. Typical estimates are about 0.5 percent in those aged 65 years, 3 percent in those aged 75 years, and 10 percent in those aged 85 years. Currently available figures do not indicate important geographical or racial differences in the frequency of Alzheimer's disease. Except for age and a positive family history of dementia no definite risk factors for Alzheimer's disease have been established as yet. There is, however, interesting evidence to suggest that a positive family history of Parkinson's disease or Down's syndrome, a history of depression, severe head trauma and smoking may be associated with Alzheimer's disease. The prognosis of Alzheimer patients in terms of life expectancy is compromised, although there is a wide variation in survival time among patients. Survival is worse in early-onset as compared to late-onset cases and in men as compared to women, and appears related to the initial severity of the disease. Improvement of prognosis through intervention has been unsuccessful until now. This applies to both symptomatic and potentially causal treatment.

In chapter 3 the results are presented from a study on cognitive function in the general elderly population. The study was part of the Rotterdam Study, a single center prospective follow-up study of the total population aged 55 years or over, including institutionalized persons, of the suburb of Ommoord in Rotterdam, The Netherlands. After a general outline of the Rotterdam Study and a detailed description of its casefinding and diagnostic procedures for the study of cognitive function and dementia (chapter 3.1), the chapter deals with the distribution and vascular correlates of cognitive function among 4,971 subjects aged 55 to 94 years. Cognitive performance decreased with age, whereas the variation between individuals increased with age. Level of

education was positively related to cognitive function: the higher the educational level, the better the results on the cognitive test. Men and women performed very similar, when confounding by education was taken into account (chapter 3.2). Our data support the notion that cognitive decline is not inherent to aging per se, but is attributable to potentially identifiable causes. Vascular risk factors may be important in this respect. Clinical vascular disease and atherosclerosis were independently and negatively associated with cognitive performance. Of the cardiovascular risk factors impaired glucose tolerance, current smoking, and increased levels of fibrinogen were related to poorer cognitive function in both men and women, whereas atrial fibrillation and HDL-cholesterol were related to cognitive function in women only. Diabetes mellitus, total serum cholesterol, and several measured thrombogenic factors were not associated with cognitive performance (chapter 3.3). The relation between blood pressure and cognitive function was dependent on age (chapter 3.4): among subjects younger than 75 years increasing blood pressure was associated with poorer performance, whereas subjects older than 75 years performed better when they had higher blood pressures. For orthostatic hypotension, a decline in diastolic blood pressure was inversely related to cognitive function. Subjective symptoms upon standing were associated with poorer performance on the MMSE, irrespective of the actual change in blood pressure (chapter 3.4). These findings are compatible with the hypothesis that, in the very old, intermittent or chronic hypoperfusion is associated with impaired cognitive performance.

Cerebral white matter lesions are commonly found on magnetic resonance imaging (MRI) scans in the elderly and pathological studies showed that these lesions reflect mainly vascular pathology. In selected series of patients these lesions were related to hypertension and several other vascular risk factors. The frequency of cerebral white matter lesions, and their relation with cardiovascular risk factors, non-invasively assessed atherosclerosis, thrombogenic factors and cognitive function, were assessed in a subsample of the Rotterdam Study, that consisted of 111 subjects, aged 65 to 84 years (chapter 4). T2-weighted axial MRI scans of the brain were obtained for all participants, who were in addition tested with an extensive neuropsychological test battery. Overall, 27% of subjects had white matter lesions. The prevalence and severity of lesions increased with age. A history of stroke or myocardial infarction, factor VIIc activity, and fibrinogen level were each significantly and independently associated with the presence of white matter lesions. Significant relations with blood pressure level, with hypertension, and with plasma cholesterol were observed only for subjects aged 65 to 74 years (chapter 4.1). Atherosclerosis of the carotid arteries, of the coronary arteries, and of the peripheral arteries, was related to the presence

of cerebral white matter lesions (chapter 4.2). Presence of white matter lesions was associated with poorer performance on all tests. After adjustment for age and gender, the differences were significant for tests measuring primarily subcortico-frontal functions (executive control functions, attentional abilities, mental speed) (chapter 4.3). The size of the ventricles was measured on the same scans, and the relation between ventricular enlargement and cognitive function was assessed. Ventricular enlargement was significantly associated with worse scores on tests assessing subcortico-frontal as well as cortical functions (global cognitive function, memory, executive control functions). The associations of white matter lesions and of ventricular size with cognitive function, were largely independent (chapter 4.3).

In a re-analysis of eight case-control studies on Alzheimer's disease several medical conditions that had previously been suggested as possible risk factors for Alzheimer's disease, were explored (chapter 5.1). A history of hypothyroidism was increased in cases as compared to controls, whereas severe headaches and migraine were inversely related to Alzheimer's disease. Previous diseases caused by neurotropic viruses, allergic conditions, general anaesthesia and blood transfusions were not associated with Alzheimer's disease. Given the ample potential for bias in the assessment of the conditions under study, these results must be regarded tentative. Several neurological disorders have been suggested to bear an increased risk of dementia. The risk of developing dementia among persons aged 50 to 75 years who suffered from Parkinson's disease, epilepsy or severe head trauma as compared to the risk in a reference group, was assessed in a register based follow-up study over the years 1980 to 1989 (chapter 5.2). The overall relative risk of developing dementia within 8 years in patients with Parkinson's disease who were initially free of dementia was 3.0. The relative risk was especially increased in younger Parkinson's disease patients. For patients with epilepsy the overall relative risk was 1.5. Severe head trauma was not associated with an increased risk of dementia.

In chapter 6, some of the methodological issues involved in the studies based on the Rotterdam Study are discussed, and the findings of these studies are reviewed. Clinical vascular disease and vascular risk factors are associated with cognitive impairment and with detectable changes in the cerebral white matter, even among non-demented subjects. There is a clear need for further epidemiological studies in concert with basic research to elucidate the pathophysiology of vascular causes of cognitive decline. Besides, in view of the findings thus far and the availability of several measures for intervention on vascular risk factors, a sensible next step to take would be to start an intervention study on the prevention of cognitive decline related to vascular disease.

Chapter 7.2

Samenvatting

Dit proefschrift bevat een aantal epidemiologische studies naar cognitieve functie en dementie. De ziekte van Alzheimer is de meest voorkomende oorzaak van dementie, en tevens de meest onderzochte. In hoofdstuk 2 wordt een overzicht gegeven van de belangrijkste epidemiologische bevindingen betreffende de ziekte van Alzheimer tot dusver. Het voorkomen van de ziekte van Alzheimer stijgt exponentieel met de leeftijd. Van de 65-jarigen lijdt ongeveer 0.5 procent aan de ziekte, van de 75-jarigen ongeveer 3 procent, en van de 85-jarigen ruim 10 procent. Op grond van de tot op heden uitgevoerde studies zijn er geen aanwijzingen voor belangrijke geografische of raciale verschillen in het voorkomen van de ziekte. De belangrijkste risicofactoren voor de ziekte van Alzheimer zijn leeftijd en een positieve familie anamnese. Daarnaast bestaan er indicaties voor een verhoogd risico op de ziekte van Alzheimer bij personen die eerstegraads familieleden hebben met de ziekte van Parkinson of het syndroom van Down. Mogelijk zijn ook een doorgemaakte depressie, een ernstig hoofdtrauma, en roken, geassocieerd met het risico op de ziekte van Alzheimer. Patiënten met de ziekte van Alzheimer hebben een verkorte levensverwachting, hoewel de overlevingsduur van patiënt tot patiënt sterk verschilt. De beperking van de levensverwachting is relatief groter voor patiënten die de ziekte op jonge leeftijd krijgen dan voor mensen bij wie het zich op latere leeftijd manifesteert, en groter voor mannen dan voor vrouwen. De overlevingsduur is gerelateerd aan de ernst waarmee de ziekte zich bij aanvang openbaart. Op dit moment bestaat er nog geen adequate therapie voor de ziekte van Alzheimer.

Hoofdstuk 3 is gewijd aan een onderzoek naar het mentaal functioneren van ouderen. De gegevens werden verkregen uit het ERGO onderzoek (Erasmus Rotterdam Gezondheid en Ouderen), een bevolkingsonderzoek dat momenteel uitgevoerd wordt onder de inwoners van Ommoord, een wijk in Rotterdam, die 55 jaar of ouder zijn. Na een beschrijving van de opzet van het ERGO onderzoek en van het onderzoek naar cognitieve functie daarin (hoofdstuk 3.1) worden de bevindingen in deze bevolkingsgroep gepresenteerd. Hierbij werd mentaal functioneren als een continue uitkomstmaat gehanteerd. Het bleek dat gemiddeld het functioneren sterk afnam met de leeftijd, terwijl de variatie toenam met de leeftijd. Een soortgelijk verband werd gevonden voor opleidingsniveau: naarmate het opleidingsniveau hoger was, was

de gemiddelde score op de test hoger en de variatie geringer. Er bestond vrijwel geen verschil in prestatie tussen mannen en vrouwen, wanneer met het opleidingsniveau rekening werd gehouden (hoofdstuk 3.2). Deze bevindingen zijn in overeenstemming met het idee dat cognitieve achteruitgang niet inherent is aan het ouder worden, maar dat het is toe te schrijven aan identificeerbare oorzaken. Vasculaire factoren spelen hierbij mogelijk een belangrijke rol. Cognitieve functie vertoonde een duidelijk verband met diverse indicatoren van en risicofactoren voor hart- en vaatziekten. Dit bleek met name het geval te zijn voor factoren die gerelateerd zijn aan atherosclerose. Van de risicofactoren voor hart- en vaatziekten waren een gestoorde glucose tolerantie, roken, en een hoog fibrinogeengehalte gerelateerd aan een slechtere cognitieve functie voor zowel mannen als vrouwen. Atrium fibrilleren en HDL-cholesterolgehalte gaven daarentegen alleen een verband te zien met cognitieve functie bij vrouwen. Geen verband met cognitieve functie werd gevonden voor diabetes mellitus, voor het totale serum cholesterolgehalte, en voor diverse thrombogene factoren (hoofdstuk 3.3). Het verband tussen de bloeddruk en cognitieve functie was afhankelijk van de leeftijd: op jongere leeftijd (jonger dan 75 jaar) was een hogere bloeddruk gecorreleerd met slechtere resultaten op de cognitieve test, terwijl oudere personen (75 jaar of ouder) het juist beter deden wanneer ze een hogere bloeddruk hadden. Deze bevindingen rijmen met de hypothese dat een verminderde cerebrale perfusie kan leiden tot cognitieve achteruitgang (hoofdstuk 3.4).

Op hersenscans gemaakt met behulp van nucleaire magnetische resonantie (MRI) worden bij oudere personen vaak afwijkingen in de witte stof van de hersenen gezien. Postmortem studies hebben aangetoond dat deze laesies doorgaans vasculaire pathologie weerspiegelen. In geselecteerde groepen van patiënten bleken deze laesies geassocieerd te zijn met hypertensie en diverse andere vasculaire risicofactoren. Wij onderzochten het voorkomen van deze afwijkingen, en de relatie van deze afwijkingen met zowel vasculaire risicofactoren als cognitieve functie, in een onderzoek dat bij 111 personen in de leeftijd van 65 tot 84 jaar uit het ERGO cohort werd uitgevoerd (hoofdstuk 4). Bij alle personen werd een T2-gewogen axiale MRI scan gemaakt en werd een uitgebreid neuropsychologisch onderzoek verricht. Witte stof afwijkingen werden gevonden bij 27% van de deelnemers. De prevalentie en ernst van de laesies namen sterk toe met de leeftijd. Het hebben doorgemaakt van een CVA of een myocardinfarct, hoge activiteit van stollingsfactor VII en een hoog fibrinogeengehalte, waren onafhankelijk van elkaar geassocieerd met het voorkomen van witte stof afwijkingen. Voor personen van 65 tot 74 jaar werd tevens een significant verband gevonden tussen het voorkomen van witte stof afwijkingen en het niveau van de bloeddruk, hypertensie

en het plasma cholesterol gehalte (hoofdstuk 4.1). Atherosclerose van de carotiden, van de coronair-arteriën, en van de perifere bloedvaten, was geassocieerd met de aanwezigheid van witte stof afwijkingen (hoofdstuk 4.2). Personen met witte stof afwijkingen scoorden slechter op alle afgenomen cognitieve tests. Na correctie voor verschillen in leeftijd waren de verschillen significant voor tests die geacht worden met name subcorticale en frontale functies te meten (uitvoerend-controlerende functies, aandacht, psychomotorische snelheid). De grootte van de ventrikels werd gemeten op dezelfde scans. Ventrikelgrootte was significant geassocieerd met zowel subcorticale en frontale testscores, als met de scores op tests die gericht zijn op het meten van corticale functies. De relaties tussen witte stof afwijkingen en cognitieve functie, en tussen ventrikelgrootte en cognitieve functie, waren grotendeels onafhankelijk (hoofdstuk 4.3).

In hoofdstuk 5 worden twee studies beschreven die als gemeenschappelijk kenmerk hebben dat ze het risico op dementie bestuderen in personen met bepaalde medische aandoeningen. Hoofdstuk 5.1 beschrijft een heranalyse van de oorspronkelijke gegevens van 8 patiënt-controle onderzoeken, betreffende factoren uit de medische voorgeschiedenis als mogelijke risicofactoren voor de ziekte van Alzheimer. Patiënten hadden vaker aan hypothyreoïdie geleden, maar minder vaak aan ernstige hoofdpijn of migraine, dan controlepersonen. Voor neurotrope virussen, allergische aandoeningen, totale anesthesie, en bloedtransfusies werd geen verband gevonden met de ziekte van Alzheimer. Gezien de methodologische beperkingen van de verschillende studies is voorzichtigheid bij de interpretatie van deze resultaten geboden. In hoofdstuk 5.2 worden de resultaten weergegeven van een retrospectief vervolgonderzoek dat werd uitgevoerd met behulp van de gekoppelde morbiditeitsregisters van de Stichting Informatievoorziening Gezondheidszorg, Utrecht, over de jaren 1980 tot 1989. In dit onderzoek werd, voor 50- tot 75-jarigen, het risico op dementie voor personen met de ziekte van Parkinson, personen met epilepsie en personen die een ernstig hersentrauma hadden doorgemaakt, vergeleken met het risico in een referentiegroep. Het risico dementie te krijgen binnen 8 jaar, was 3 maal hoger voor patiënten met de ziekte van Parkinson dan voor controlepersonen. Het relatieve risico was met name verhoogd onder jongere patiënten. Patiënten met epilepsie hadden een anderhalf maal verhoogd risico. In deze studie werd geen verband gevonden tussen hoofdtrauma en dementie.

Het proefschrift wordt besloten met een hoofdstuk waarin een aantal formele en inhoudelijke aspecten van de op het ERGO onderzoek gebaseerde studies wordt besproken. Zowel klinisch manifeste hart- en vaatziekten als risicofactoren voor hart-

en vaatziekten zijn geassocieerd met cognitieve functie en met waarneembare afwijkingen in de witte stof van de hersenen, ook in niet-demente personen. Verder onderzoek naar de pathofysiologie van vasculaire oorzaken van cognitieve dysfunctie is van groot belang en zou idealiter moeten geschieden in nauwe samenwerking tussen basiswetenschappers en epidemiologen. Daarnaast zou, gezien de omvang van het probleem en de beschikbare therapeutische middelen, een onderzoek uitgevoerd dienen te worden naar de mogelijkheden van preventieve interventie op cognitieve achteruitgang ten gevolge van vasculaire aandoeningen.

Nawoord

Dit proefschrift is het resultaat van ruim 4 jaar werken op de afdeling Epidemiologie en Biostatistiek van de Erasmus Universiteit. Vele mensen hebben, direct en indirect, bijgedragen aan de totstandkoming ervan, en ik wil hen hier graag noemen.

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De MRI-studies werden opgezet en uitgevoerd in samenwerking met de afdeling neurologie van het Academisch Ziekenhuis Utrecht. De expertise van John van Swieten betreffende MRI onderzoek naar cerebrale witte stof afwijkingen was daarbij van groot belang. Het kritische commentaar van professor J. van Gijn op de diverse manuscripten heb ik bijzonder gewaardeerd.

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De kern van dit proefschrift wordt gevormd door de binnen het ERGO onderzoek uitgevoerde studies. ERGO zou niet kunnen bestaan zonder de voortdurende inspanningen van zijn onderzoeksleiders Bert Hofman, Rick Grobbee, Huib Pols en Paulus de Jong. Daarnaast ben ik hen erkentelijk voor hun kritische aandacht voor de resultaten van het onderzoek. Frank van den Ouweland verzette veel werk in de beginfase van ERGO. De screening op cognitieve functie binnen ERGO werd voor het leeuwedeel verricht door Henriëtte Ensing, Els van Helden, Eline Herfst, en Marjon Huuksloot. Ik wil hen bijzonder danken voor de inzet en het geduld waarmee ze dag in dag uit naar bekende wegen bleven vragen. Janny van Gastel en Anneke

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En Frans.

Curriculum vitae

Monique Breteler was born on January 26, 1961 in Nijmegen, the Netherlands. She passed secondary school in 1978 at the "Canisius College" in Nijmegen. In the same year, she started her medical studies at the University of Nijmegen. She obtained her medical degree in 1987. During her studies she worked for 6 months in primary health care projects in the outskirts of La Paz and on the Altiplano, Bolivia. In 1988 she worked at the department of Biostatistics (head: professor R. van Strik), Erasmus University Rotterdam, on a study of quality of life in cancer patients. In 1989, she started her training in epidemiology at the department of Epidemiology & Biostatistics (head: professor Dr A. Hofman), Erasmus University Rotterdam. She participated in the subprojects on prevalence, incidence and risk factors of the 1989-1991 EURODEM EC Concerted Action on the Epidemiology and Prevention of Dementia, and in the 1990-1991 EC Preparatory Activity for the Concerted Action 'Study of Risk Factors for Parkinson's Disease'. She is member of the Project Management Group of EUROPARKINSON, the 1993-1995 EC Concerted Action on Incidence and Risk Factors for Parkinson's Disease, and member of the steering committee of the Dutch Study on Vascular Factors in Dementia.