Risk of dementia

The Rotterdam Study

Acknowledgments

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Risk of dementia
The Rotterdam Study

Risico op dementie
Het Erasmus Rotterdam Gezondheid en Ouderen (ERGO) onderzoek

Proefschrift

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Overige leden: Dr M.M.B. Breteler (tevens co-promotor)
                Prof. Dr H. van Crevel
                Prof. R. Doll, CH, FRS, FRCP
                Prof. Dr J.P. Mackenbach

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Manuscripts based on the studies described in this thesis

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Ott A, Breteler MMB, van Harskamp F, Claus JJ, van der Cammen TJM, Grobbee DE, Hofman A. Prevalence of Alzheimer's disease and vascular dementia: association with education. The Rotterdam Study. *BMJ* 1995;310:970-3.

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Smoking and the risk of dementia and Alzheimer's disease in a population-based cohort study: the Rotterdam Study. Ott A, Slooter AJC, Hofman A, van Harskamp F, Witteman JCM, Van Broeckhoven C, van Duijn CM, Breteler MMB. Submitted.

Chapter 1

Introduction

Dementia is a frequent disorder in the elderly. It is also a distressing condition both for the patient and caregiver. Dementia puts a high claim on health care costs. In the Netherlands about one tenth of the yearly health budget is spent on nursing homes. Dementia is the main diagnosis in 40% of nursing home patients and coexisting dementia may be the underlying motive for admittance to a nursing home in patients with other diseases.[1,2] The need for dementia care will probably grow since the elderly population is increasing both in percentage and in absolute number.[3,4]

Reliable estimates of the frequency of dementia are important. Prevalence figures are used by health planners to determine the demand for disease-specific services. The incidence rate is more informative when etiologic questions are addressed. For assessment of prevalence and incidence of dementia one cannot rely on medical registers; the disease is rarely reported on death certificates and usually mild cases are not recognised. Therefore we studied the prevalence (chapter 2.1) and incidence (chapter 2.2) of dementia in a population-based study by active screening of participants. This study formed part of the Rotterdam Study, a prospective cohort study on medical disorders in the elderly.[5]

Previous epidemiologic studies suggested that not all social layers are equally affected by dementia.[6] Especially lower educated people might be more susceptible. Therefore, we examined the association between education and prevalent dementia (chapter 2.1) and also assessed if lower educated were at higher risk of incident dementia (chapter 2.3).

The lack of knowledge on causes of dementia, especially Alzheimer's disease, motivated the second part of this thesis.[7] We mainly studied associations with other common disorders of old age that have vascular implications. This choice followed the notion that vascular disorders may play a role in cognitive decline and may be more important in Alzheimer's disease than previously thought.[8] Chapters 3.1 and 3.2 describe studies on the relation between diabetes mellitus and dementia, both in prevalent and incident cases. In chapter 4.1 the association between atrial fibrillation and dementia is described. Also, several measures of atherosclerosis were studied in relation to dementia (chapter 4.2). Smoking is a major risk factor of cardio- and cerebrovascular disease.[9] However, previous studies found an inverse association between smoking and Alzheimer's disease.[10] Therefore we studied the risk of incident

dementia in relation to smoking habits (chapter 4.3). In the last chapter of this thesis, I integrate and discuss all findings, with special reference to prevalence-incidence bias, and make suggestions for future research (chapter 5).

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Chapter 2.1

The prevalence of dementia, Alzheimer's disease, and vascular dementia: the association with education

Abstract

Objective: To estimate the prevalence of dementia and its subtypes in the general population and to study the relation with education. *Design:* Population-based, cross-sectional study. *Setting:* Ommoord, a suburb of Rotterdam, the Netherlands. *Subjects:* 7528 participants of the Rotterdam Study, aged 55 to 106 years. *Results:* The prevalence of dementia was 6.3%, ranging from 0.4% in subjects aged 55-59 years to 43.2% in those aged 95 years and over. Alzheimer's disease was the major subdiagnosis (72%); it also was the main cause of the strong increase of dementia with age. The relative proportion of vascular dementia (16%), Parkinson's disease dementia (6%) and other dementias (5%) decreased with age. A significantly higher prevalence of dementia was found in subjects with a low level of education. The association with education was not due to confounding by cardiovascular disease. *Conclusions:* The prevalence of dementia increases exponentially with age. About one-third of the population of 85 years and over suffers from dementia. Three-quarters of all dementia is due to Alzheimer's disease. In this study an inverse dose-response association was found between education and dementia, in particular Alzheimer's disease.

Introduction

In many populations the proportion of elderly people is growing steadily. Owing to shifts in the population pyramid and increasing life expectancy the number of people aged 75 and older in the Netherlands has increased by 65% in the past 20 years.[1] Similar increases have occurred in other countries and will have a major impact on future health care costs.[2] Dementing disorders are common in elderly and especially very old people.[3] Studies of their prevalence rates and determinants are of medical and social importance.

We studied the prevalence of dementia and its subtypes among 7528 subjects in the population based Rotterdam Study, with special reference to its association with level of education.

Population and Methods

The Rotterdam Study is a prospective population based study of several important groups of diseases of old age[4,5] -namely, neurological, cardiovascular, locomotor and ophthalmological. Between 1990 and 1993 all participants were subjected to detailed interview and examination in order to collect baseline data and to ascertain their health status. In a substudy the prevalence of dementia was assessed by a three phase approach. Firstly all participants were screened with a brief cognitive test. Screen positive subjects then underwent additional testing, and those whose results suggested a possibility of dementia were either subjected to detailed examinion or had their medical records used to confirm the diagnosis and establish the type of dementia.

STUDY POPULATION

All residents of the Rotterdam suburb of Ommoord aged 55 years and over (including those living in institutions) were invited to participate in the Rotterdam Study. Of the 10275 eligible subjects, 7983 (78%) accepted. Of the eligible subjects, 7528 (73%) were screened for cognition in the dementia study, the remaining subjects being lost through deaths or refusal.

MEASUREMENTS

The brief cognitive test for dementia comprised a combined minimental state examination[6] and geriatric mental state schedule (GMS-A, organic level).[7] The test was administered by trained research assistants. Screen positive subjects had a minimental state examination score of 25 or less or a geriatric mental state score of 1 or more. Screen positive subjects were subsequently examined by a physician with the CAMDEX (Cambridge examination for mental disorders .of the elderly) diagnostic interview,[8] which included an interview with an informant. Participants who scored less than 80 on the CAMDEX cognitive test or who had higher scores but were suspected of dementia clinically were asked to participate in a third, extensive examination. In this diagnostic phase they were examined by a neurologist, had a brain scan (by magnetic resonance imaging), and were tested by a neuropsychologist.

Of screen positive subjects, 92% underwent the CAMDEX diagnostic interview. Many subjects with dementia were resident in six homes for elderly people, which were included in the study. These homes had psychogeriatric departments. Often subjects were already known to be demented. Of these subjects and of 8% of the screen positive subjects who refused the CAMDEX interview or could not be examined, diagnostic information was obtained from the general practitioner, physicians in the homes, neurologists or the Rotterdam Regional Institute for Outpatient Mental Health Care.

During the initial interview the attained level of education was assessed according to the standard classification of education,[9] comparable to the international standard classification of education (UNESCO, Paris, 1976). In the standard classification of education seven levels are recognised. In our analysis we combined the 4 highest levels into one reference category, thus obtaining 4 levels: (1) primary education, this applied to 26% of the participants, (2) low level vocational training (20%), (3) medium level secondary education (15%), (4) medium level vocational training to university level (39%).

Three indicators of cardiovascular disease (stroke, myocardial infarction and periferal arteriosclerotic disease), as described in detail elsewhere,[10] were examined as possible confounders in the relation between education and dementia. A history of stroke was determined through interview or informant interview in dementia patients. Confirmation of the stroke by a treating physician was required. A previous myocardial infarction was assessed on an electrocardiogram. Suspected abnormalities according to preset criteria were all reviewed by a cardiologist. The presence of peripheral atherosclerotic disease was assumed if the ankle-arm index (ratio between tibial and brachial systolic blood pressure), measured in supine position, was less than 0.9 on at least one side.

DIAGNOSIS OF DEMENTIA

For the diagnosis of dementia DSM-III-R criteria were used.[11] The subdiagnosis of Alzheimer's disease was based on NINCDS-ADRDA criteria.[12] Both possible and probable Alzheimer cases were grouped in this category. For the subdiagnosis of vascular dementia the DSM-III-R definition of multi-infarct dementia was used.

The dementia type at the onset of the disease was ascertained. Some Alzheimer patients develop symptoms of vascular dementia in the course of the disease, usually following a stroke, which may result in a sudden worsening of dementia.[13] We classified these patients as Alzheimer's type with cerebrovascular disease. Parkinson's disease dementia was diagnosed when the dementia started after the onset of idiopathic parkinsonism. The three most important other dementias were alcohol-related dementia, tumour-related dementia and dementia associated with normal pressure hydrocephalus. In five patients insufficient information was available to make a subdiagnosis.

On the basis of the Clinical Dementia Rating scale (CDR)[14] and the MMSE score a division was made between severely impaired (CDR above 2 or MMSE below 15, hereafter referred to as 'severe dementia') and mild to moderately impaired. In the overall prevalence figures all dementia cases, from mild to severe, are included.

DATA ANALYSIS

The prevalence of dementia and its subtypes was calculated as the percentage of dementia by gender and 5 year age strata. Multivariate logistic regression was used to analyze the association between educational status and dementia. The odds ratio as estimated from the logistic model was used as our measure of association, and referred to as "relative risk". With dementia or one of the subtypes of dementia as outcome variable we compared the levels of education, adjusted for age (numerical variable) and gender. The highest education level (category 4) was used as reference. The trend in the relative risk for dementia by education was tested with level of education as a linear trend variable in the logistic regression analysis.

By adding either stroke history, myocardial infarction or peripheral atherosclerotic disease as covariates in the logistic regression model we checked if these cardiovascular indicators caused substantial changes in the relative risks, associated with the various levels of education.

Results

In Table 1 the number of participants in the dementia study is presented, as well as their distribution according to age and living conditions. Of the 7528 study participants 474 were demented (6.3% in total, 3.8% of the men and 7.9% of the women). Age and gender specific prevalences of dementia are given in Table 2 and visualised in Figure 1. With the exception of the age-category of 80-89 years there were no major differences in prevalence between men and women. In those aged 80-89 women had a higher prevalence then men. About one third of all demented persons had severe dementia; this applied to both men and women.

TABLE 1. Characteristics of the study population.

	Women	Men	Total
Number eligible	6325	3950	10275
Participants in the Rotterdam Study	4878 (77%)	3105 (79%)	7983 (78%)
Included in the dementia prevalence study	4589 (73%)	2939 (74%)	7528 (73%)
Age range (median)	55-106 (70)	55-97 (68)	55-106 (69)
Percentage living in institutions	15%	6%	12%

TABLE 2. Prevalence of dementia per age category.

Age category	Women %	(Numbers)	Men %	(Numbers)	Total %	(Numbers)
55 - 59 years	0.6	(4/688)	0.2	(1/493)	0.4	(5/1181)
60 - 64	0.4	(3/807)	0.5	(3/625)	0.4	(6/1432)
65 - 69	1.0	(7/735)	0.8	(5/624)	0.9	(12/1359)
70 - 74	2.1	(15/712)	2.0	(10/492)	2.1	(25/1204)
75 - 79	6.2	(37/597)	6.0	(22/365)	6.1	(59/962)
80 - 84	19.3	(92/477)	13.7	(28/204)	17.6	(120/681)
85 - 89	32.7	(118/361)	28.4	(29/102)	31.7	(147/463)
90 +	40.6	(86/212)	41.2	(14/34)	40.7	(100/246)
Total	7.9	(362/4589)	3.8	(112/2939)	6.3	(474/7528)

Prevalences of Alzheimer's disease, vascular dementia, Parkinson's disease dementia and other dementias are given in Figure 2. Overall, 72% of the dementias were of the Alzheimer's disease type, 16% were vascular dementia, 6% were Parkinson's disease dementia and 5% were other dementias. Table 3 shows the gender specific prevalence and number of cases of the types of dementia in 10-year age strata. There were no substantial differences between men and women in proportions of dementia types.
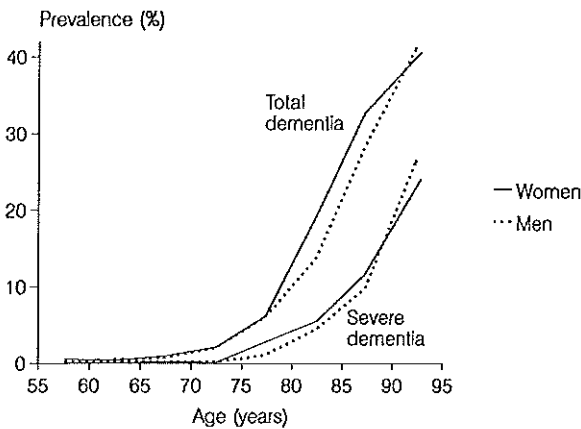

Figure 1. Prevalence of total dementia and severe dementia plotted at the mean age of each five year age category.

TABLE 3. Prevalence of Alzheimer's disease, vascular dementia, Parkinson's disease dementia and other dementias.[*]

	Age category	Women % (N)	Men % (N)	Total % (N)
Alzheimer's disease	55-64	0.1 (2)	0.2 (2)	0.2 (4)
	65-74	1.0 (15)	0.8 (9)	0.9 (24)
	75-84	8.4 (90)	5.4 (31)	7.4 (121)
	85+	27.2 (156)	25.0 (34)	26.8 (190)
	Total	*5.8 (263)*	*2.6 (76)*	*4.5 (339)*
Vascular dementia	55-64	0.2 (3)	0.2 (2)	0.2 (5)
	65-74	0.2 (3)	0.3 (3)	0.2 (6)
	75-84	2.0 (22)	2.1 (12)	2.1 (34)
	85+	4.9 (28)	2.2 (3)	4.4 (31)
	Total	*1.2 (56)*	*0.7 (20)*	*1.0 (76)*
Parkinson's disease dementia	55-64	0.1 (1)	(0)	0.04 (1)
	65-74	0.1 (2)	0.1 (1)	0.1 (3)
	75-84	1.0 (11)	0.4 (2)	0.8 (13)
	85+	1.7 (10)	2.2 (3)	1.8 (13)
	Total	*0.5 (24)*	*0.2 (6)*	*0.4 (30)*
Other dementias	55-64	0.1 (1)	(0)	0.04 (1)
	65-74	0.1 (2)	0.2 (2)	0.2 (4)
	75-84	0.6 (6)	0.9 (5)	0.7 (11)
	85+	0.9 (5)	2.2 (3)	1.1 (8)
	Total	*0.3 (14)*	*0.4 (10)*	*0.3 (24)*

[*] 5 undetermined cases are excluded from these figures

The level of education was related to dementia. As shown in Figure 3 the relative risks (adjusted for age and gender) decreased with increasing educational status. Among people with the two lowest levels of education significantly more dementia was diagnosed than among those with the highest level of education (relative risks: 3.2 (95% CI: 2.2-4.6) and 2.0 (1.3-3.2), respectively). Similarly for Alzheimer's disease the two lowest educational levels had increased relative risks: 4.0 (2.5-6.2) and 2.3 (1.3-4.1), respectively. For vascular dementia only the lowest educated were at significantly
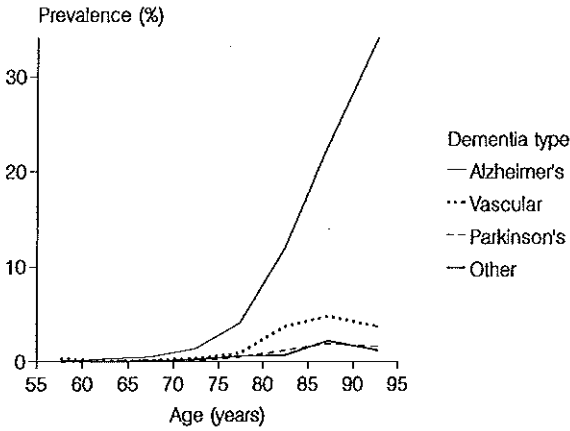
Figure 2. Prevalences of Alzheimer's disease, vascular dementia, Parkinson's disease dementia and other dementia's plotted at the mean age of each five year age category.
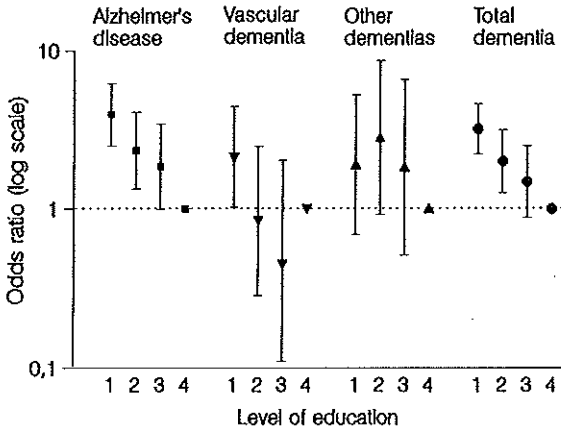
Figure 3. Association of level of education with subtypes of dementia (adjusted for age and sex) expressed as odds ratios and 95% confidence intervals (bars). Level 4 is the reference level.

increased risk: 2.1 (1.0-4.5). Other dementias, including Parkinson's disease dementia, were not significantly associated with education. The trend of higher dementia prevalences with less education was highly significant (p<0.0001). Similar trends were observed for Alzheimer's disease and vascular dementia (p<0.0001 and p=0.01, respectively).

Adding either one or a combination of the indicators of cardiovascular disease did not decrease the inverse relation between educational status and dementia, suggesting that the presence of cardiovascular disease does not explain the association between dementia and education.

Discussion

We presented detailed age specific prevalences of dementia and dementia subtypes, indicating Alzheimer's disease as the main contribution to the exponential increase of dementia with age. Our data also showed the consistent trend of a higher risk of dementia with lower education. This effect of educational status could not be explained by a confounding effect of cardiovascular disease.

All recent population-based studies on the prevalence of dementia with standardised diagnostic criteria show an exponential increase with age and a predominance of Alzheimer's disease as the cause of the dementia. However, age specific prevalences still vary considerably between studies. This may be due to the study design, the population sampling method or real geographic variations. The present study is the largest European study of its kind, thereby allowing more precise estimates of prevalence. Compared with a pooled reanalysis of 12 European studies,[3] we found slightly lower prevalences below the age of 75 years and slightly higher prevalences above the age of 80 years. Differences in the screening properties and the type of population are the most likely causes. A high sensitivity and specificity of the diagnostic procedure was ensured by the three phase comprehensive diagnostic work-up.[15] A major concern in prevalence studies is non-participation. The Rotterdam Study, of which the dementia study was only a part, had a relatively high participation rate (almost 80%). However the non-response may have been selective. If non-response has distorted the study results, it probably produced an underestimate of the prevalence of dementia. We consider it not very likely that the non-response has influenced the relative proportions of subtypes of dementia.

Without autopsy confirmation, subtyping dementia remains uncertain. Also, the current diagnostic criteria that we used have a limited accuracy, a fact which all large population based dementia studies have to face, even if we could base the subdiagnoses on a great number of reliable data. Alzheimer's disease was the main contributor to the steep increase of dementia prevalence with age. In fact, we observed only little increase with age in vascular dementia and even less in Parkinson's disease dementia and other dementias. We classified primary Alzheimer's disease complicated with cerebro-vascular disease, as Alzheimer's disease. This may be why we a found a somewhat higher prevalence of Alzheimer's disease than other European studies.[16]

This study shows, as others did, a higher prevalence of dementia in groups with less education.[17-21] It has been suggested that the education effect could be due to a diagnosis bias. There is indeed a possibility that an early dementia in a highly educated person has been missed, although we do not think it likely that this has happened often because the combined MMSE/GMS screening test is very sensitive.[15] The finding that

the education effect also applies to vascular dementia, led us to consider whether the association of education with dementia may be due to confounding by cardiovascular disease. This is possible since cardiovascular disease is associated with both education and dementia: particularly vascular dementia, but also Alzheimer's disease, are correlated with cardiovascular disease,[13,22,23] and cardiovascular pathology is more prevalent in people with less education.[24,25] However, control for possible confounding by cardiovascular disease did not substantially decrease the magnitude of the association of education with dementia; nor with subtypes of dementia.

In conclusion, this large population-based study suggests that the prevalence of Alzheimer's disease strongly increases with age and that dementia, in particular Alzheimer's disease, is inversely related with educational status.

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Chapter 2.2

The incidence and risk of dementia

Abstract

To assess age-, sex-, and subtype-specific incidence rates of dementia and to calculate the risk of dementia, the authors performed a large community-based, prospective cohort study on dementia, as part of the Rotterdam Study. Participants were recruited among residents of a suburb of Rotterdam, aged 55 years and older. Baseline examinations took place between 1990 and 1993. The average follow-up was 2.1 years. Screening for dementia followed a three stage protocol. Medical records were evaluated of subjects who had died or could not be examined in person. Of 7,046 subjects who were non-demented at baseline, 162 developed dementia, during 15,135 person-years of follow-up, resulting in an overall incidence rate of 10.7 per 1000 person-years. From the youngest to the oldest 5-year age-category the incidence rate increased from 0.6 to 97.2 per 1000 person-years. Only in men the increase levelled off after age 85. Overall, the incidence rate per 1000 person-years was 7.7 for Alzheimer's disease and 1.5 for vascular dementia. Dementia incidence rates and dementia-free Kaplan-Meier survival tables were used to calculate age- and sex-specific cumulative risks of dementia. Although the incidence rates of men and women up to age 85 were similar, the lifetime risk of dementia for 55 year old women was twice as high as for men (0.33 versus 0.16), reflecting both higher life-expectancy of women and a higher dementia risk at very old age.

Introduction

Dementia is a major disabling disease in elderly people. Besides personal suffering of patients the disease may induce immense distress among family and care-givers. Many elderly people fear imminent dementia, yet few can imagine the actual risk of the disease. Most studies on the occurrence of dementia in the general population were cross-sectional studies leading to prevalence figures, which are influenced by disease duration. Reliable figures of the age- and sex-specific incidence rates of dementia are still scarce.[1] Incidence rates reflect the probability of getting dementia conditional on being alive. These rates are based on the experience of a population. Of more interest on the individual level is a person's absolute (unconditional) risk to develop dementia

in the next few years, or in the rest of his or her life. To calculate these absolute risks, the competing risk of dying should be taken into account.

We performed a large prospective study on the incidence of dementia in the community, which enabled us to calculate period and lifetime risks to develop dementia.

Materials and methods

STUDY DESIGN

The Rotterdam Study is a community based prospective cohort study in which several chronic diseases of the elderly are investigated.[2] The study focuses on neurological, cardiovascular, locomotor and ophthalmologic diseases. The study was approved by the Medical Ethics Committee of Erasmus University/Academic Hospital Rotterdam. Informed consent and permission to retrieve information from treating physicians was obtained of all participants.

Between 1990 and 1993 participants were interviewed at their homes and thereafter, during two sessions, examined at the research center, in order to ascertain their health status and to collect baseline data. Follow-up examinations took place from mid 1993 to the end of 1994.

STUDY POPULATION

The study was conducted in Ommoord, a suburb of the city of Rotterdam, the Netherlands. At baseline, all inhabitants of this suburb aged 55 years and older, including those living in institutions, were invited to participate. Of 10,275 eligible subjects, 7,983 (78%) agreed to take part in the study and 7,528 (73%) were screened and examined for dementia.[3] Of these, 474 subjects were diagnosed to be demented. Eight persons whose dementia status at baseline was uncertain were excluded from the follow-up analyses. This resulted in a cohort of 7,046 subjects at risk for dementia. At follow-up, 5,571 (79%) participants were re-screened for dementia, 476 (7%) subjects had died before screening, and in 999 (14%) subjects information was obtained through general practitioners and medical records.

DEMENTIA CASE-FINDING

Dementia screening and diagnosis at baseline and follow-up followed the same three step protocol. Firstly, with a combined Mini Mental State Examination (MMSE)[4] and Geriatric Mental State schedule (GMS-A, organic level),[5] the population was screened

for dementia. This test was administered by trained research assistants. Secondly, subjects scoring below 26 on the MMSE or more than 0 on the GMS were considered screen-positive and were subsequently examined by one of four study physicians with the CAMDEX diagnostic interview,[6] which includes an informant interview. Finally, participants who were judged to be demented or suspected of dementia after the CAMDEX were examined by a neurologist, were tested by a neuropsychologist and had a brain nuclear magnetic resonance imaging scan made. Of participants whose dementia work-up was not complete, additional information was obtained from medical files.

In addition to the dementia screening, the total cohort was continuously being monitored for detection of interval cases of dementia through linkage of the general practitioner's automated medical record system to the data base of the Rotterdam Study. All reports of incident events including onset of memory problems or dementia were regularly evaluated by the study physicians. Of non-respondents to the follow-up examination who were reported with memory problems or dementia, information was obtained from informants and medical files in order to make a diagnosis of dementia. Also, the regional institute for outpatient mental health care (RIAGG), covering the entire study population, provided information. This psychiatric service can both directly and by referral be consulted for social and psychiatric problems and is responsible for nursing home or other dementia-care-facility indications. Their diagnoses are based on (informant) interviews, neurologic and neuropsychologic examination, and relevant blood biochemistry and serology. From this service, once a year information was obtained on newly diagnosed dementia or amnestic syndrome in study participants. Surveillance of the population through the general practitioners and RIAGG reports continued up to the end of 1994.

The study diagnosis of dementia was made by a panel that reviewed all existing information. A diagnosis of Alzheimer's disease was based on *National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association* criteria.[7] According to those criteria a subdivision into possible and probable Alzheimer's disease was made. Vascular dementia was diagnosed in accordance with *National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences* criteria.[8] As proposed in the latter criteria we also categorized a subgroup of Alzheimer's disease with cerebrovascular disease. For other dementias, the *Diagnostic and Statistical Manual of mental disorders (3rd ed., revised)* dementia criteria were used.[9]

The highest achieved level of education was assessed during the initial home interview. To adjust for education we categorized educational level into six grades.

DATA ANALYSIS

The age-specific incidence was obtained per 5-year age-band by dividing the number of cases by the number of person-years, calculated by adding up each participant's contribution of follow-up time per age-band. The follow-up period ended either at the second screening, at age at onset of dementia, or at death. For both screened and reported cases, the age at onset of dementia was taken to be the midpoint between baseline age and age at diagnosis. Of subjects without a second screening, follow-up through the reports from treating physicians continued up till the end of 1994. Incidence figures were estimated by gender, by dementia subtype and response status. Poisson standard errors and 95% confidence intervals (95% CI) were calculated from the number of incident cases per follow-up period. The difference in incidence between groups of subjects was expressed as a rate ratio, which was calculated with proportional hazards regression, adjusting for age and if applicable other variables.

To calculate the risk to develop dementia over time, competing risk of death was taken into account. Using incident dementia and mortality data from the study cohort, we first made dementia-free survival functions with the Kaplan-Meier method.[10] Age at baseline was used as entry time variable, age at follow-up, dementia onset, or death as exit time, and both incident dementia or death as failures. Next, the cumulative absolute risk of dementia over a period was composed as the integrated product of the age-specific dementia incidence times the dementia free survival (reference 10, formula 7.10, page 169). These risks to develop dementia were calculated separately for men and women at ages of 55, 65, 75, and 85 years.

Results

In table 1 several characteristics of the study population are summarized. Of the total cohort (n=7,046) at risk to develop dementia, 79% was screened in person for dementia. Of those who were not examined at follow-up and of whom information on dementia was solely obtained through general practitioners and the RIAGG, 476 had died and 999 refused the screening tests. The proportion of subjects who were not examined in person increased with age from 9% in the youngest to 45% in the oldest age-category and was in all age-groups somewhat higher in women than in men. Mortality was higher among men.

Overall, after an average follow-up period of 26 months, 162 new cases of dementia were identified, 109 in the group examined in person and 53 through the general practitioner and RIAGG monitoring. The age- and sex-specific incidence is given in table 2. With a total of 15,135 follow-up years the overall incidence was

TABLE 1. Characteristics of participants in the study on dementia incidence. This study was conducted in a population-based sample, aged 55 years and over, as part of the Rotterdam Study, 1990-1994.

	Total cohort		Examined in person		No in person examination during follow-up *		Adjusted difference (95% CI) †	Died before follow-up examination *		Adjusted difference (95% CI) †
Number (% of total)	7046		5571	(79.1)	999	(14.2)		476	(6.8)	
Women (%)	59.9		58.8		68.9			54.6		
Baseline age (SD)	69.5	(9.1)	68.1	(8.3)	72.6	(9.7)		79.9	(9.0)	
Primary education or less (%)	24.1		20.6 .		36.8		9.0 (5.8 to 12.4)	41.5		4.4 (0.2 to 9.0)
Baseline MMSE score (SD)	27.6	(1.9)	27.8	(1.8)	27.0	(2.2)	-0.6 (-0.7 to -0.4)	26.5	(2.7)	-0.6 (-0.8 to -0.4)

* Information through general practitioners, the regional institute for outpatient mental health care and medical files.
† To adjust for age, sex, and education (in case of the MMSE), both groups were included in a logistic (for education) or linear (MMSE) regression model. The adjusted difference (and 95% CI) between both groups was calculated from the group coefficient (and standard error).
CI: confidence interval, MMSE: minimental state examination, SD: standard deviation.

TABLE 2. Age- and sex-specific number of person-years at risk (Pyrs), number of dementia cases (N) and incidence rates (per 1000 person-years, with 95% confidence interval) in a Dutch general population, the Rotterdam Study, 1990-1994.

Age category	Women				Men			
(years)	Pyrs	N	Rate	95% CI	Pyrs	N	Rate	95% CI
55 - 59	988	0	0.0	0.0 - 3.0	707	1	1.4	0.2 - 10.0
60 - 64	1611	2	1.2	0.3 - 5.0	1142	1	0.9	0.1 - 6.2
65 - 69	1591	3	1.9	0.6 - 5.8	1269	1	0.8	0.1 - 5.6
70 - 74	1683	6	3.6	1.6 - 7.9	1110	5	4.5	1.9 - 10.8
75 - 79	1404	25	17.8	12.0 - 26.3	813	12	14.8	8.4 - 26.0
80 - 84	1031	26	25.2	17.2 - 37.0	479	12	25.1	14.2 - 44.1
85 - 89	695	35	50.4	36.2 - 70.2	210	6	28.6	12.9 - 63.7
90 - 94	263	18	68.3	43.1 - 108.5	67	2	29.6	7.4 - 118.5
≥ 95	63	7	111.5	53.1 - 233.8	9	0	0.0	0.0 - 333.0
Total	9329	122	13.1	11.0 - 15.6	5806	40	6.9	5.1 - 9.4

CI: confidence interval
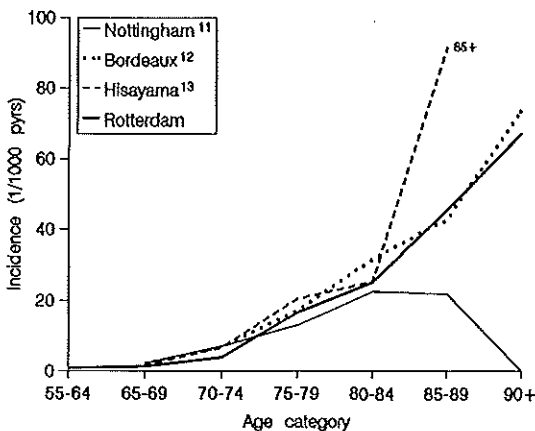
Figure 1. Age specific dementia incidence of other studies compared to results from the present Rotterdam Study, conducted in a Dutch general population of 55 years and older, between 1990 and 1994.

10.7 per 1000 person-years. The incidence increased strongly with age. Though the overall incidence was higher in women than men (13.1 versus 6.9 per 1000 person-years), age-specific incidence rates were very similar up to the age of 85 years. From that age onwards the incidence in men seemed to level off whereas in women it

continued to rise. However, in the highest age-categories in men, incidence estimates were based on small numbers of cases and person-years of follow-up and the 95% confidence intervals overlapped those for women of the same ages. Figure 1 shows the age-specific incidence among the total cohort compared with other incidence studies.[11-13] In this figure only studies are included which were relatively large, used similar procedures to diagnose dementia at baseline and follow-up and calculated 5-year age-specific incidence rates of total dementia.

Comparison of the incidence between the in-person screened and those whose information on dementia status came from informants and medical files, revealed that there was no major difference up till the age of 85. Above age 85 more demented persons were identified by personal examination than by evaluation of reported possible patients (76.1 per 1000 person-years versus 31.3 per 1000, respectively, with age and sex adjusted ratio of 0.5 (95% CI: 0.3-0.8). The difference in incidence between men and women could not be explained by differences in screening method.

A dementia subtype was determined in 158 cases (98%). Alzheimer's disease was diagnosed in 116 (73%); 69 of those had probable Alzheimer's disease and 47 possible Alzheimer's disease of whom 19 with cerebrovascular disease. Vascular dementia was detected in 22 (14%) and other dementias in 20 (13%). Proportions of dementia subtypes differed between men and women: of male cases, 58% was diagnosed as Alzheimer's disease and 23% as vascular dementia; of female cases these proportions were 79% and 11%. Overall incidence rates for Alzheimer's disease and vascular dementia in men were 4.0 and 1.6, and in women 10.0 and 1.4 per 1000 person-years, respectively. Though age-adjusted rates of total dementia did not differ
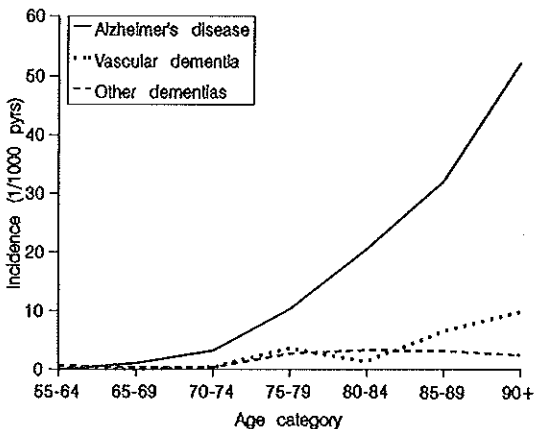

Figure 2. Age specific incidence of Alzheimer's disease, vascular dementia and other dementias in a Dutch general population (≥ 55 years), the Rotterdam Study, 1990 - 1994. Four cases whose dementia subtype could not be defined are excluded.
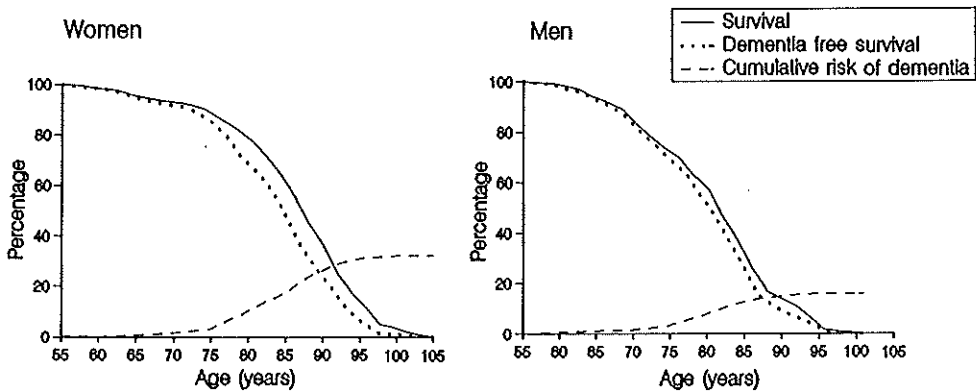
Figure 3. Kaplan-Meier survival with and without dementia, and the cumulative risk of dementia (competing risk of death taken into account) of 55 year old women and men, as observed in the Rotterdam Study, 1990 - 1994.

significantly between men and women, women were more often diagnosed with Alzheimer's disease than men (rate ratio: 1.7, 95% CI: 1.0-2.6). Men more often developed vascular dementia than women, though this difference did not reach significance (rate ratio: 1.6, 95% CI: 0.6-3.8). Figure 2 shows the age-specific incidence of subtypes of dementia for both sexes combined. The Alzheimer's disease incidence increased strongest with age. The incidence of vascular dementia also increased up to the oldest age categories, whereas the incidence of other dementias remained relatively stable with age.

Figure 3 shows survival and dementia-free survival as observed in the total study cohort. The area between these curves represents the average time people live while demented. This area is clearly larger in women than in men, suggesting that overall women suffer more life-years from dementia than men. According to these data, we estimated that fifty-five year old women on average will be demented during the last 2.5 years of their life. For men of this age the life expectancy with dementia is 1.2 years. Figure 3 also includes the cumulative absolute risk for dementia of 55 year old men and women. Table 3 gives 5 to 40 year period as well as lifetime risks of dementia. This table shows, for example, that 55-year old non-demented women have a 9.9% risk to become demented within a period of 25 years, and a 32.6% lifetime risk. For men, who are at much higher risk of dying, the corresponding figures are 7.7% and 15.9%.

TABLE 3. Period and lifetime risk (percent) of dementia (competing risk of death taken into account) for 55, 65, 75 and 85 year old women and men. These risks were estimated using Kaplan-Meier product limit estimators of dementia free survival and age-specific incidence as observed in a Dutch general population, the Rotterdam Study, 1990 - 1994.

Age	Period risk (%)								Lifetime risk (%)
	5 yrs	10 yrs	15 yrs	20 yrs	25 yrs	30 yrs	35 yrs	40 yrs	
Women									
55	0.0	0.6	1.5	3.1	9.9	17.5	26.3	31.0	32.6
65	0.9	2.6	9.9	17.8	27.2	32.2	34.0	34.4	34.5
75	8.1	16.9	27.3	32.7	34.8	35.3	35.4		35.4
85	18.3	28.2	31.7	32.5	32.7				32.7
Men									
55	0.7	1.1	1.5	3.2	7.7	12.7	15.0	15.9	15.9
65	0.4	2.2	7.1	12.5	14.9	16.0			16.0
75	6.4	13.4	16.6	18.0					18.0
85	8.7	12.3							12.3

Discussion

For an average 2.1 years, we prospectively followed a large cohort from the general population, which was initially free of dementia. New cases of dementia were detected through in-person examination and a reporting system of possible new cases, for those who could not be re-examined. Age-specific dementia incidence rates and mortality as observed in the study cohort, were used to estimate period risks of dementia, with competing risk of death taken into account.

The strength of our study is threefold. First, high sensitivity and specificity of the in-person screening was ensured by a three phase comprehensive diagnostic work-up,[14] which was similar at baseline and follow-up. Also, diagnoses were made by the same diagnostic panel. Second, through the reports from the general practitioners and RIAGG we had a complete follow-up of all members of the cohort, including those who died, which reduces the potential bias due to selective secondary refusal or death. Age-specific incidence rates were quite similar for the in-person screened subjects and those whose medical files were studied after being reported with possible dementia,

though we may have missed very mild cases in the latter group, particularly in the highest age-bands. A third advantage of the study is its size, which resulted in stable age-, gender- and subtype-specific estimates of dementia incidence in the community, despite the relatively short duration of follow-up.

We found the incidence of dementia for women to continuously increase with age, whereas there appeared to be a levelling off above age 85 for men. This pattern is consistent with reports from other studies.[11,15,16] A possible explanation is selective survival of men at lower risks for dementia. Also our finding of a higher incidence of Alzheimer's disease in women and tendency to higher incidence of vascular dementia in men is in agreement with previous studies.[12,13,16]

Whereas incidence rates reflect the actual experience of a cohort, predictions of how much disease a population may expect inherently require risk estimates. For estimating risks of dementia, a disorder which is particularly frequent at oldest age, the considerable competing risk of death cannot be ignored. We approximated cumulative risks of dementia, taking competing mortality into account. The period risk of dementia should be interpreted as the probability of becoming demented within a certain period. The lifetime risk, calculated at several ages, reflects the probability that a person of that age would at some time in his or her life suffer from dementia. This lifetime risk is determined by both individual risk and the population's longevity. To our knowledge, only in the Framingham Study lifetime risks of dementia have been assessed previously.[17] The Framingham estimates of dementia lifetime risks of 75 year old men (18.4%) and women (31.8%) were remarkably similar to ours (18.0% for men and 35.4% for women). Although in our study cohort, the age-specific incidence rates of dementia were similar for men and women below age 85, the 30-year risk of 55 year old women to become demented was 1.4 times higher than the risk of men, which reflects the higher life expectancy of women. The combination of higher life expectancy and higher incidence in women than men over age 85 resulted in a much higher lifetime dementia risk of around 1 in 3 for women and 1 in 6 for men. Estimates of lifetime risks at different ages were quite similar. Having survived without dementia up to high age appears not to reduce a person's risk to develop dementia.

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Chapter 2.3

Education and the risk of dementia

Abstract

We assessed the risk of dementia by educational level in a prospective population-based study. In the Rotterdam Study 6827 non-demented participants with known level of education were followed-up on average for 2.1 years. During this period 137 new cases of dementia occurred. Relative risks by educational level were calculated with proportional hazards regression analysis, adjusting for age and, if applicable, sex. Low education was associated with higher dementia risk in women but not in men, suggesting that the association is modified by gender. Our data suggest that cross-sectional studies may overrate the association between education and risk of dementia.

Introduction

Many studies examined the relation between dementia and educational background.[1] Studies reporting an inverse association between education and dementia have been criticized for possible methodologic flaws like selection or diagnostic bias.[2] Meanwhile, plausible hypotheses were formulated to explain the relation: higher brain reserve capacity of educated persons could postpone the onset of dementia;[3] educated elderly may get more brain stimulation ('use it or loose it');[3,4] and factors related to education, like lifestyle, occupational exposure, morbidity, and health care, may be responsible for the association with dementia.[2,4] Most studies on the relation between education and dementia were cross-sectional.[1] We examined whether education influences the risk of dementia in a large prospective study.

Methods

STUDY DESIGN

The Rotterdam Study is a community-based cohort study among 7983 persons aged 55 years and over (response rate 78%).[5] Baseline examinations took place from 1990 to 1993. After 2 to 3 years, participants were re-examined. Similar procedures were used for baseline and follow-up dementia screening.[6] In brief, dementia was diagnosed through a three-step protocol including screening, cognitive testing, informant

interviews, and a clinical dementia work-up. At baseline 6827 subjects with data on educational level were non-demented and thus at risk for incident dementia. Of subjects who died before follow-up (7.5%) or were not re-examined in person (12.4%) information was obtained from informants and general practitioners to complete follow-up. Diagnoses were made according to current clinical criteria (DSM-III-R, NINCDS-ADRDA, NINDR-AIREN) by a panel that reviewed all existing information.

DATA ANALYSIS

Educational level was grouped in three categories: (1) primary education or less; (2) lower vocational or intermediate general education; (3) intermediate vocational to university level.[7] Relative risk of dementia was assessed with a proportional hazards model, adjusting for age (linear and squared) and gender. The highest level of education was used as reference. We examined if the association was different for Alzheimer's disease and other dementias. Analyses were performed on all subjects and for men and women separately.

Results

In table 1 characteristics of the study population are summarized. After a mean 2.1 years of follow-up 137 incident dementia patients had been diagnosed. The incidence rate was higher in women than men because of a different age distribution. Age-specific incidence rates were almost similar in men and women. Table 2 shows that the lower educated had a non-significant increased risk of dementia when compared with the higher educated (relative risk: 1.4, 95% CI 0.9 to 2.1). In men we observed no difference in dementia risk by education. Low educated women were at significantly

TABLE 1. Characteristics of the study population.

	Men		Women		All	
Number (% of total population)	2767	(40.5)	4060	(59.5)	6827	
Mean baseline age (SD)	68.2	(8.1)	70.0	(9.4)	69.2	(9.0)
Primary education or less (%)	730	(26.4)	1871	(46.1)	2601	(38.1)
Medium level education (%)	637	(23.0)	1203	(29.6)	1840	(27.0)
Higher education (%)	1400	(50.6)	986	(24.3)	2386	(34.9)
Incident dementia (/1000 person-years)	39	(6.9)	98	(11.1)	137	(9.5)

TABLE 2. Adjusted relative risk and 95% confidence interval of incident dementia by level of education.

Level of education	Men [*]	Women [*]	All [†]
Primary education or less	0.7 (0.3 to 1.5)	2.1 (1.1 to 3.9)	1.4 (0.9 to 2.1)
Medium level education	1.0 (0.5 to 2.1)	1.6 (0.8 to 3.2)	1.2 (0.7 to 1.9)
Higher education	1 (reference)	1 (reference)	1 (reference)
Trend	p = 0.390	p = 0.018	p = 0.147

[*] Relative risks adjusted for age
[†] Relative risks adjusted for age and gender

increased risk of dementia (2.1, 95% CI 1.1 to 3.9). Analyses by subtype of dementia did not reveal a major difference between Alzheimer's disease and other dementias.

Discussion

This prospective study has several advantages over others which examined the association between education and dementia. The study is population-based with a high response rate. We also pursued complete follow-up of all subjects at risk. Therefore, there is little room for selection bias. As opposed to register-based studies we actively screened for dementia, which prevented bias by differences in health-care-utilisation. The study was prospective and we assessed educational level before onset of dementia, thereby minimising recall bias.

Studies on the relation between education and dementia are potentially affected by diagnostic bias.[1,4] In cross-sectional studies subjects with life-long low cognitive abilities may erroneously be diagnosed demented. This bias is unlikely in the present study as those subjects should have been diagnosed as prevalent cases and were thus not at risk of incident dementia. We cannot completely exclude that the screening tests are more sensitive to pick up cognitive deficits associated with early dementia in the lower than in the higher educated, which could have resulted in an underestimation of the risk of dementia in higher educated.

We previously described the association between education and prevalent dementia.[6] The age and sex adjusted odds ratio of low education and dementia,

obtained in this cross-sectional study (2.7, 95% CI 1.9 to 4.0), suggested a greater association with education than our present results. In the prevalence study however, we could not avoid all above biases. Disproportionately few higher educated dementia patients may have been included in the cross-sectional analyses. There is evidence that highly educated dementia patients have a shorter survival than the lower educated because their dementia remains unrecognized untill a more progressed stage.[8] The higher educated could thus be underrepresented in prevalent case series but not be at lower risk of dementia. Cross-sectional studies, which mostly reported strong associations,[1] may have overrated the association of education with dementia risk.

The present results suggest that the association between education and dementia may be modified by gender. A difference in the association by gender has not been described before. Re-analysis of our cross-sectional data affirmed also a difference (odds ratio in women, 4.7; in men, 1.8). This may be a direct effect of educational level; however, it may also be the result of interaction between education and gender with respect to dementia prognosis or risk factor profile.[8]

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Chapter 3.1

Cross-sectional association of diabetes mellitus and dementia

Abstract

Dementia and non-insulin-dependent diabetes mellitus are highly prevalent disorders in the elderly. Diabetes mellitus has repeatedly been reported to affect cognition, but its relation with dementia is uncertain. We therefore studied the association between diabetes and dementia in the Rotterdam Study, a large population-based study in the elderly. Of 6330 participants, aged 55 to 99 years old, complete information on diabetes and presence of dementia was available. Diabetes mellitus was diagnosed as use of anti-diabetes medication or random or post-load serum glucose over 11 mmol/l. Dementia was diagnosed through a stepped approach, including a sensitive screening of all participants and a comprehensive diagnostic work-up.

Diabetes mellitus was present in 724 (11.4%) subjects. Of the 265 dementia patients 59 (22.3%) had diabetes. Multiple logistic regression analyses, adjusting for age and sex differences, revealed a positive association between diabetes and dementia (odds ratio: 1.3, 95% CI: 1.0-1.9). In particular, strong associations were found between dementia and diabetes treated with insulin (odds ratio: 3.2, 95% CI: 1.4-7.5). The relation was strongest with vascular dementia, but was also observed with Alzheimer's disease. These associations were independent of educational attainment, smoking, body mass index, atherosclerosis, blood pressure and antihypertensive drug treatment, and and could not be explained by clinical cerebral infarctions.

The results suggest that non-insulin-dependent diabetes mellitus is associated with dementia. Alzheimer's disease may be more frequent in elderly diabetes patients treated with insulin.

Introduction

Non-insulin-dependent diabetes mellitus (NIDDM) is a well known risk factor for cardiovascular disease and stroke.[1-3] Apart from the obvious lesions caused by strokes, also subtle neurochemical, electrophysiologic and structural changes have been found in brains of patients with NIDDM.[3-5] Neuropsychologic test profiles of NIDDM patients, compared to those of healthy or hospital controls, showed decreased cognitive functions.[6-9] Several authors suggested that, analogous to its association with cerebral

infarction, NIDDM is related to vascular dementia.[10,11] However, the extend to which NIDDM is associated with other dementia subtypes, in particular Alzheimer's disease (AD), is unclear.[12-15] We examined the association between NIDDM and prevalent dementia in a large population based study.

SUBJECTS

The Rotterdam Study is a population-based prospective follow-up study in which several important diseases of the elderly are investigated.[16] The study focuses on four groups of diseases: neurological, cardiovascular, locomotor and ophthalmologic diseases. All inhabitants of Ommoord, a suburb of Rotterdam, aged 55 years and older, including those living in institutions, were invited to participate in the study. Of the 10275 eligible subjects, 7983 participated in the Rotterdam Study. Between 1990 and 1993 participants were extensively interviewed at their homes and examined at the research centre in order to collect baseline data and to ascertain their health status. Dementia status was missing in 455 (6%) subjects, mainly because they refused the cognitive screening test. Blood glucose measurements started in July 1990, after the pilot phase in which 544 randomly choosen participants had been examined. Of the 7439 subjects who were examined since then, blood glucose measurements were absent in 821 (11%), mainly due to logistic or technical problems. In the present analyses 6330 participants (85%), with complete information on drug use, blood glucose measurements and the presence of dementia were included. Dementia and diabetes assessments took place completely independent of each other without prior knowledge to the study physicians of which associations would later be tested.

EXAMINATIONS

The prevalence of dementia was assessed using a three phase approach.[17] With a brief cognitive test, the combined Mini Mental State Examination (MMSE)[18] and Geriatric Mental State schedule (GMS-A, organic level),[19] the population was screened for dementia. This test was administered by trained research assistants. Screen positive subjects (Mini Mental State Examination score below 26 or Geriatric Mental State score above 0) were subsequently examined by a physician with the Cambridge Examination for Mental Disorders of the Elderly diagnostic interview.[20] Participants who were suspected of dementia after this interview underwent an extensive examination which included examinations by a neurologist, a neuropsychologist and brain magnetic resonance imaging. Based on all available information a diagnosis of dementia was then made according to DSM-III-R criteria,[21] with a subdiagnosis of AD based on NINCDS-ADRDA criteria[22] and of vascular dementia in accordance with NINDS-AIREN criteria.[23]

Current drug use was assessed during the initial home interview. Participants were asked to show all medication they were using. Of institutionalised participants, medication was reported by the medical staff. From all participants blood was drawn by venipuncture and allowed to coagulate for 30 minutes. Subjects without anti-diabetic medication subsequently received a glucose drink of 200 ml which contained 75 g of glucose. Two hours later a second blood sample was obtained. Random and post-load glucose levels were measured by the glucose hexokinase method. Diabetes mellitus was defined as the use of anti-diabetic medication or at least one glucose value greater than 11 mmol/l.

Level of education was assessed during the initial interview and grouped in four levels, from primary school only to college and higher. Smoking habits were assessed during interview and categorised as never, former or current smoking. The body mass index was calculated by dividing weight through the square of height and expressed as kg/m^2. Systolic blood pressure was measured with a random zero sphygmomanometer. The ankle-to-brachial index (the ratio of the systolic blood pressure measured at the ankle and the upper arm) was used as a measure of peripheral atherosclerosis: a ratio of 0.9 or below was considered positive.[24] Resting ECG's were analysed by the Modular ECG Analysis System (MEANS) computer program.[25] This program contains modules for rhythm classification, contour analyses and Minnesota coding and was shown to give very accurate ECG diagnoses.[26] The presence of coronary artery disease, was approximated by the program's diagnosis of probable or definite myocardial infarction, which was used as a second measure of atherosclerosis. A history of stroke was determined through interview or in dementia patients through informant interview, and verified with medical records.

STATISTICAL ANALYSIS

The association between NIDDM and dementia was examined by calculating odds ratios (OR) by multivariate logistic regression with dementia as the dependent, and NIDDM, age and sex as independent variables in the model. In all regression models age was treated as a continuous variable. To assess whether this relation was different across levels of severity of NIDDM, we performed subanalyses in which we compared patients without anti-diabetes medication, patients using oral anti-diabetes medication and patients treated with insulin, to non-diabetic subjects. In addition to age and sex, we included educational level, smoking, body mass index, atherosclerosis, systolic blood pressure level and antihypertensive drug treatment to the regression model in order to adjust for confounding by these variables. To examine whether the association could be explained by an increased stroke risk in diabetes patients, the analyses were repeated in subjects without stroke history.

Results

Of the 6330 subjects in this study, 265 (4.2%) were diagnosed with dementia (table 1). In 194 the dementia was of the Alzheimer disease (AD) type (73%), 44 subjects had a vascular dementia (17%), and 27 had other dementias (10%). Of the AD patients 32 (16%) had cerebrovascular disease, based on a history of stroke or cerebral magnetic resonance imaging findings, that was considered not directly etiologically related to the dementia. Ages ranged from 55 to 99 years old. Dementia prevalence increased sharply with age: from 0.3% in the age group of 55-64 to 30% in subjects of 85 and older. Since the older age groups had higher proportions of women, there were relatively more women with dementia. The prevalence of NIDDM also increased with age: from 6% in the age group of 55-64 to 22% in subjects of 85 and older. NIDDM was diagnosed in 11% of the non-demented participants and in 22% of the dementia patients. Among AD, vascular and other dementia patients, 21%, 30% and 19% had NIDDM, respectively. Of the NIDDM patients 34% was using oral medication and 10% got insulin treatment. These proportions were similar among the dementia patients. After adjustment for age and sex differences, dementia patients had a significantly higher serum glucose level, a lower body mass index and systolic blood pressure, more frequent history of stroke and a lower educational status than subjects without dementia.

Table 2 shows the association between diabetes and dementia for the total population and for men and women separately. In women a significant association with dementia was observed (OR: 1.5, 95% CI: 1.0-2.2). However, NIDDM treated with insulin was strongly correlated to dementia in both men and women (OR: 3.2, 95% CI: 1.4-7.5, for both sexes combined). Additional adjustments for possible confounders did only marginally alter the associations.

Both NIDDM and dementia patients had more often stroke histories than participants without diabetes or dementia. Excluding subjects with a history of stroke however, did not change the association between diabetes and dementia (OR: 1.3, 95% CI: 0.9-1.9 for overall NIDDM and OR: 3.0, 95% CI: 1.1-7.8 for NIDDM treated with insulin).

In table 3 the associations between diabetes and dementia subtypes are given. The association of insulin treated NIDDM to dementia was observed for all subtypes, but was strongest for vascular dementia. Diabetes treated with oral medication was significantly associated with vascular dementia. Again additional adjustments for confounders resulted in essentially similar associations.

TABLE 1. Characteristics of the total study population, of demented and non-demented subjects.

	Total population	Non-demented subjects	Demented subjects	Adjusted difference[‡] (95%CI)	
Population size	6330	6065	265		
Women (%)	59.4	58.9	71.3		
Age (years) [*]	69.3 (9.1)	68.7 (8.7)	83.3 (7.8)		
Random serum glucose (mmol/l) [*]	6.9 (2.7)	6.9 (2.6)	7.9 (3.9)	0.5	(0.1 - 0.8)
NIDDM (%)	11.4	11.0	22.3	3.2	(-0.4 - 7.8)
no drug treatment (% of NIDDM)	55.9	56.1	54.2		
oral medication (% of NIDDM)	33.7	33.8	32.2		
insulin treatment (% of NIDDM)	10.4	10.1	13.6		
Only primary education or less (%)	24.2	22.6	64.8	20.2	(13.0 - 27.8)
Ever smoking (%)	64.3	65.0	47.2	-4.8	(-12.5 - 2.3)
Body mass index (kg/m^2) [*]	26.3 (3.7)	26.3 (3.7)	25.3 (3.9)	-1.2	(-1.8 - -0.7)
Peripheral atherosclerosis (%)	18.4	17.1	47.8	4.2	(-0.5 - 9.9)
ECG myocardial infarction (%)	9.2	8.9	17.2	2.4	(-0.8 - 6.7)
Systolic blood pressure (mmHg) [*]	139.5 (22.6)	139.4 (22.5)	141.5 (24.6)	-7.6	(-10.6 - -4.7)
Treated with antihypertensives (%) [†]	32.5	32.0	44.9	-4.0	(-9.0 - 1.7)
Stroke history (%)	3.3	2.8	15.5	4.7	(2.3 - 8.2)

[*] Mean (standard deviation),

[†] Including all beta-blocker and diuretic drug use,

[‡] Difference between non-demented and demented subjects adjusted for age and sex.

NIDDM = non-insulin-dependent diabetes mellitus; 95%CI = 95 % confidence interval.

TABLE 2. Association of non-insulin-dependent diabetes mellitus (NIDDM) with dementia.

	Total	Men	Women
Adjusted for age, sex			
NIDDM overall	1.3 (1.0 - 1.9) [*]	0.9 (0.5 - 1.8)	1.5 (1.0 - 2.2)
no drug treatment	1.2 (0.8 - 1.9)	1.0 (0.4 - 2.2)	1.4 (0.8 - 2.3)
oral medication	1.2 (0.7 - 2.1)	0.5 (0.1 - 2.2)	1.5 (0.8 - 2.6)
insulin treatment	3.2 (1.4 - 7.5)	3.2 (0.7 - 16.0)	3.2 (1.2 - 8.7)
Additional adjustments [†]			
NIDDM overall	1.2 (0.9 - 1.8)	0.7 (0.3 - 1.5)	1.5 (1.0 - 2.3)
no drug treatment	1.2 (0.8 - 1.9)	0.8 (0.3 - 2.0)	1.4 (0.8 - 2.5)
oral medication	1.0 (0.6 - 1.8)	0.3 (0.1 - 1.5)	1.3 (0.7 - 2.5)
insulin treatment	2.6 (1.1 - 6.2)	2.1 (0.4 - 11.5)	2.8 (1.0 - 7.6)

[*] Odds ratio, 95% confidence interval

[†] Adjusted for education, smoking, body mass index, atherosclerosis, systolic blood pressure and antihypertensive drug treatment

TABLE 3. Association between non-insulin-dependent diabetes mellitus (NIDDM) and subtypes of dementia, adjusted for age and sex.

	Alzheimer's disease N = 194	Vascular dementia N = 44	Other dementias N = 27
NIDDM overall	1.3 (0.9 - 1.9) [*]	2.1 (1.1 - 4.0)	1.1 (0.4 - 2.9)
no drug treatment	1.3 (0.8 - 2.0)	1.1 (0.4 - 3.2)	1.5 (0.5 - 4.4)
oral medication	1.3 (0.6 - 2.0)	3.2 (1.4 - 7.4)	no cases
insulin treatment	2.8 (1.0 - 8.0)	5.4 (1.2 - 23.8)	3.5 (0.4 - 27.0)

	AD without CVD N = 162	AD with CVD N = 32	
NIDDM overall	1.3 (0.9 - 2.0)	1.1 (0.4 - 2.7)	
no drug treatment	1.3 (0.8 - 2.2)	0.9 (0.3 - 3.1)	
oral medication	0.9 (0.5 - 2.0)	1.6 (0.5 - 5.5)	
insulin treatment	3.5 (1.2 - 9.8)	no cases	

[*] Odds ratio, 95% confidence interval

AD = Alzheimer's disease; CVD = cerebrovascular disease

Discussion

In this study we investigated the relation between non-insulin-dependent diabetes mellitus and dementia. NIDDM treated with insulin was strongly associated with dementia and this was independent of level of education, smoking, body mass index, presence of atherosclerosis, systolic blood pressure and antihypertensive medication. The association could not be explained by an increased prevalence of clinical strokes. The association was found with vascular dementia and Alzheimer's disease (AD). In vascular dementia the relation tended to be stronger with more severe NIDDM, whereas in AD an association was mainly found with NIDDM treated with insulin.

Three possible biases need to be discussed. Firstly, we did not obtain a 100% response. We do know that non-responders were on average older than the study participants. Dementia patients more often had to be excluded due to incomplete diabetes or risk-factor information. This, however, would only invalidate our results if the relation between NIDDM and dementia was different among non-responders as compared to participants, which we consider unlikely. Secondly, because we studied the relation between diabetes and dementia cross-sectionally, bias could have occurred due to survival effects.[27] This could have resulted in an overestimation of the relation if the relative decrease in survival due to diabetes would be greater in nondemented than demented subjects or in an underestimation if the combination of NIDDM and dementia in a patient would interact and lead to increased mortality. If anything, we consider the latter more likely. Thirdly, subtyping dementia, even if based on generally accepted diagnostic criteria, remains difficult and some misclassification cannot be excluded. Furthermore, although the criteria for vascular dementia are appropriate for identifying multi-infarct dementia, they may fail to identify subjects in whom other vascular mechanisms played an important etiological role, and vascular factors may be involved in AD as well.[11,23,28,29] In the present study AD was associated with NIDDM, particularly diabetes treated with insulin, even after exclusion of patients with cerebrovascular disease from the AD group.

The relation of NIDDM with dementia was similar between men and women only for NIDDM treated with insulin. In untreated and tablet treated NIDDM a relation with dementia also seemed present in women but not in men. We do not know if this is simply due to the low number of men with both NIDDM and dementia, resulting in an unstable odds ratio with wide confidence intervals or whether this reflects a greater impact of NIDDM on women. The latter was suggested in a report from the Framingham Heart Study, in which relatively more cardiovascular disease was found in diabetic women than men.[30]

Our results indicated that atherosclerosis had only limited influence on the

association between NIDDM and dementia. We cannot though completely exclude atherosclerosis as an etiologic factor. In order to investigate the relative contribution of strokes we investigated the association in a subgroup without history of stroke. Though the association was also found in subjects without a history of stroke it remains possible that silent infarctions due to NIDDM pathology may underly the excess of dementia in diabetic subjects.

Our finding of an increased prevalence of vascular dementia in diabetes patients is in line with results from a study in which 175 multi-infarct dementia patients were compared with 125 age-matched neurologically normal controls.[31] Diabetes was 2.8 times more prevalent in cases than in controls. And in a recent Japanese community based study on the incidence of dementia, it was shown that NIDDM patients had an increased risk to develop vascular dementia (age adjusted relative risk: 2.8).[15] Furthermore, Tatemichi et al. showed that in stroke patients, diabetes was associated with a higher rate of dementia 3 months after the stroke (OR: 2.6).[32]

Our findings of a relation between insulin treated NIDDM and AD contrasts with results of studies which suggested that diabetes mellitus is less frequent among AD patients than controls.[12-14] These studies were relatively small, used selected clinical AD cases, and geriatric clinic patients,[12] vascular dementia[13] or population controls.[14] Our results are in accordance with the Japanese Hisayama Study which reported that NIDDM patients had an increased risk to develop AD after 7 years of follow-up (relative risk: 2.2, 95% CI: 1.0-4.9).[15]

The relation between NIDDM and AD may be explained by diabetic vasculopathy and its sequelae. The common coincidence of AD with cerebral infarctions and subcortical white matter lesions[11,33,34] suggest that vascular factors may be important in AD. However, other and more direct mechanisms could be involved. Recently, increased glycation of proteins and advanced glycation end products (AGE), which may be involved in the etiology of diabetes complications, were found in plaques and tangles of AD patients.[35,36] AGE epitopes were even detected in the earliest states of Alzheimer brain lesions and do promote known plaque and tangle properties. Progressive glycation augments the deposition of proteins by crosslinking, it induces macrophages to secrete acute phase reactants, thereby stimulating immune-cell response and it might contribute to nerve-cell death by the formation of free radicals.[37,38] Alternatively, NIDDM effects on neurotransmitter metabolism could contribute to AD. In chronic diabetes, a considerable decline in the blood-brain barrier transport of choline, a precursor of acetylcholine, is found.[3] Changes in brain glucose utilisation or insulin induced hypoglycemias might contribute to a reduced acetylcholine synthesis.[5,39] Blocking of acetylcholine muscarinic receptors is known to disrupt higher cognitive functions and AD severity is correlated to the loss of brain cholinergic activity.[38,39]

Finally, we found that the correlation between NIDDM and AD was strongest in NIDDM patients treated with insulin. Most likely these patients had a more serious and long-standing diabetes. It is however conceivable that exogenous insulin itself or hypoglycemias which frequently complicate insulin therapy[40] increase the risk of dementia and AD. A direct correlation has been reported between increased endogenous insulin level and impaired cognitive function.[41]

In conclusion, we found that NIDDM, particularly when treated with insulin, is associated with dementia, both vascular dementia and AD. It is as yet unclear which pathophysiologic mechanisms could explain this association.

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Chapter 3.2

Diabetes mellitus and the risk of dementia

Abstract

Objective: To determine whether diabetes mellitus and measures of glucose metabolism are associated with increased risk of dementia and Alzheimer's disease.
Design: Population-based prospective cohort study.
Setting: A district of Rotterdam, the Netherlands.
Participants: 6370 non-demented residents, aged 55 years and older.
Measurements: Non-insulin-dependent diabetes mellitus was diagnosed at baseline if random or two hour post-load serum glucose was over 11 mmol/l or if antidiabetes medication was used. At baseline, also serum fructosamine and post-load insulin levels were assessed. Incident dementia was diagnosed, after a mean 2.1 years of follow-up, using a three step approach, including a sensitive screening and comprehensive diagnostic work-up. Of subjects who could not be re-examined, medical files were studied to diagnose dementia. Relative risks were estimated with proportional hazard regression, adjusting for age and sex.
Results: At baseline 692 (10.9%) participants had diabetes. During the follow-up period 126 subjects became demented, of whom 89 had Alzheimer's disease. The relative risk of diabetes patients to develop dementia was 1.9 (95% CI 1.3 to 2.8), and to develop Alzheimer's disease 1.9 (95% CI 1.2 to 3.1). Diabetes patients treated with insulin were at highest risk of dementia (relative risk 4.3, 95% CI 1.7 to 10.5). Levels of serum glucose, fructosamine, post-load insulin, and insulin resistance were not associated with increased risk of dementia. In this population the attributable risk of diabetes mellitus for dementia was 8.8%.
Conclusions: Diabetes mellitus almost doubled the risk of dementia. Diabetes mellitus could underlie a substantial proportion of all dementia.

Introduction

Both dementia and non-insulin-dependent diabetes mellitus (NIDDM) are frequent disorders in elderly people and major causes of disability. Little is known about their relationship. As NIDDM is a risk factor for stroke,[1,2] it is supposed to be linked with vascular (mainly multi-infarct) dementia.[3,4] Some studies found higher than expected

prevalence rates of diabetes in patients with multi-infarct dementia[5-7] and persons who had suffered from a stroke appeared at greater risk of subsequent dementia if they had diabetes.[8] Previous case-control studies reported decreased rates of diabetes mellitus in Alzheimer patients.[6,7,9-11] However, we found a positive association in a population-based prevalence study.[12] Recently, advanced glycation end-products (AGE) and increased AGE receptor expression were discovered in brains of patients with Alzheimer's disease.[13,14] As AGE's are thought to be involved in NIDDM complications[15] these findings warrant further investigation into the relation of diabetes mellitus with dementia and Alzheimer's disease.

We studied the risk of dementia by diabetes in a population-based prospective cohort study. In addition we assessed the association between measures of glucose metabolism and incident dementia.

Methods

STUDY POPULATION

The Rotterdam Study is a community-based prospective cohort study in which chronic disorders of the elderly are investigated.[16] The study was approved by the Medical Ethics Committee of Erasmus University. Participants gave written informed consent and permission to retrieve information from treating physicians.

The study was carried out in a suburb of the city of Rotterdam, the Netherlands. Baseline examinations were performed from 1990 to mid 1993. The eligible population (n=10275) consisted of all persons aged 55 years and older living in this suburb, and included people living in institutions. Of those, 7983 took part in the baseline examinations of the study (response rate 78%). During baseline 7528 (94%) were screened and examined for dementia.[17] Exclusion of prevalent dementia patients resulted in a cohort of 7046 subjects at risk for dementia. Diabetes examinations were not performed during the pilot phase of the baseline study (n=433) and measurements were incomplete due to logistic reasons in 243 subjects. This left 6370 persons to be included in the present prospective study. Follow-up examinations took place from September 1993 to the end of 1994. During this second round of the study 5232 (82%) participants were re-examined for dementia; 330 (5%) had died before follow-up and 808 (13%) refused examinations or were too ill. Of the 1138 subjects who were not re-examined information on dementia status was obtained through general practitioners and medical records.

DEMENTIA CASE-FINDING

Both at baseline and follow-up dementia was diagnosed with a three step protocol, consisting of a brief cognitive screening (Mini Mental State Examination[18] and the Geriatric Mental State schedule,[19] organic level) and an extensive diagnostic work-up.[17]

In addition to the follow-up examinations, the study cohort was monitored through linkage with the general practitioner's automated medical record system and close cooperation with the regional institute for outpatient mental health care (RIAGG) which is responsible for dementia-care-facilities and nursing home indications. Of interval cases reported with memory problems or dementia, and of subjects who could not be re-examined, information was obtained from medical files. Through this surveillance system we were able to obtain a complete follow-up of the population at risk.

Both baseline and follow-up diagnoses of dementia were made by a panel consisting of a neurologist, neuro-psychologist, and the study physician, who reviewed all existing information. A diagnosis of Alzheimer's disease was based on *National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association* criteria.[20] Vascular dementia was diagnosed in accordance with *National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences* criteria.[21] As proposed in the latter criteria we recognised a subgroup of Alzheimer's disease with cerebrovascular disease. For other dementias, the criteria from the *Diagnostic and Statistical Manual of mental disorders (3rd ed., revised)* were used.[22]

DIABETES AND OTHER BASELINE MEASUREMENTS

During the initial home interview current drug use was assessed by asking participants to show all medication they were using. Of institutionalised participants, medication was reported by the medical staff. Blood was drawn by venipuncture to assess non-fasting glucose and fructosamine levels. Participants who did not use antidiabetes medication received a glucose drink of 75 grams in 200 ml water. Two hours later a second blood sample was obtained to measure post-load serum glucose and insulin (by radioimmunoassay, Medgenix diagnostics, Brussels, Belgium). Diabetes mellitus was defined according to WHO criteria for epidemiologic studies of diabetes as the use of antidiabetes medication or at least one glucose value greater than 11 mmol/l.[23] As a measure of insulin resistance we used the ratio of post-load insulin over post-load glucose. which provides a good estimate in subjects without diabetes mellitus.[24]

The following variables were measured and tested as possible confounders or intermediates. Level of education was assessed during the initial interview and for the

analyses dichotomised in less than 7 years of education or more. Weight and height (measured with indoor clothing and no shoes) were used to calculate body mass index, expressed in kg/m^2. The ratio between waist circumference (measured midway between lower rib and iliac crest) and hip circumference (at the greater trochanter) was used as measure of body fat distribution. Smoking habits at baseline were categorised as never, past, and current smoking. Alcohol consumption was assessed as part of a semi-quantitative food frequency questionnaire and expressed as the intake in grams of pure alcohol per day. Systolic blood pressure was measured in supine position with a random zero sphygmomanometer. Hypertension was defined as a systolic blood pressure of 160 or above, a diastolic blood pressure of 95 or above, or the use of antihypertensive drugs. Ankle-to-brachial index, used as a measure of peripheral atherosclerosis,[25] was calculated as the ratio of the systolic blood pressure measured at the ankle over that measured at the upper arm. The presence of atrial fibrillation was assessed on resting ECG by computer software.[26] A computer diagnosis of probable or definite myocardial infarction was used as another measure of atherosclerosis. A history of stroke was assessed during the baseline interview and verified with medical records by a neurologist.

DATA ANALYSIS

Means and proportions of baseline characteristics were compared for subjects with and without diabetes mellitus. Also, means of glucose metabolism measures at baseline were compared for subjects with incident dementia and those who remained non-demented. Age and sex adjusted differences were calculated with logistic regression analyses for dichotomous variables and with linear regression for continuous variables.

Relative risks of dementia by diabetes were calculated with a Cox proportional hazard regression model, in which the covariates describe the risk of dementia as a function of follow-up time. To adjust for age, both linear and squared age were entered in the models. Gender was added to the model in analyses which included men and women. We examined if gender or age modified the relation by calculating relative risks for men and women separately, and in strata of age (below 75, 75 to 85, and of 85 years and older). To check if associations could be attributed to confounding, analyses were repeated with possible confounders added to the models. Similarly, we checked if the association remained, independent of possible intermediates.

We assessed which proportion of incident dementia was attributable to diabetes or to factors associated with diabetes as described by Levin.[27] This population attributable risk (PAR) was calculated using the adjusted relative risk (RR), the population fraction with diabetes (PF), and the formula:

$$PAR = [(RR - 1)PF] / [1 + (RR - 1)PF].$$

Finally, we assessed the influence of random serum glucose, fructosamine, post load insulin, and insulin resistance on the risk for dementia. This was done by adding these glucose metabolism measures both as continuous or as categorical (quintiles) variables to the proportional hazard regression model. We examined whether the influence of these measures on dementia risk was different for subjects without or with diabetes mellitus.

Results

At baseline, of the 6370 subjects in this study, 692 (10.9%) had diabetes mellitus, of whom 390 (56.4%) used no antidiabetes medication or were newly diagnosed, 232 (33.5%) used oral medication, and 70 (10.1%) were treated with insulin. Among those using insulin therapy, there were no cases with insulin-dependent diabetes mellitus.[28] Diabetes prevalence increased with age. After age-adjustment there was no difference in diabetes rates between men and women. Of the possible confounders or intermediates only the rates of low education and atrial fibrillation were not significantly different between subjects with and without diabetes mellitus (table 1).

TABLE 1. Baseline characteristics and selected variables of study participants, with and without non-insulin dependent diabetes mellitus (NIDDM). *

	NIDDM (n = 692)		No NIDDM (n = 5678)		Adjusted difference (95% CI) [†]		P-value [†]
Age (years)	72.6	(8.8)	68.4	(8.6)			
Women (%)	60.0		59.1				
Less than 7 years of education (%)	27.2		22.4		-0.8	(-3.9 to 2.6)	0.63
Body mass index (kg/m^2)	26.8	(4.2)	26.2	(3.7)	0.6	(0.2 to 0.9)	< 0.001
Waist to hip ratio	0.93	(0.09)	0.90	(0.09)	0.02	(0.02 to 0.03)	< 0.001
Current smoking (%)	23.1		22.9		3.6	(0.0 to 7.6)	0.05
Alcohol intake (g/day)	11.1	(18.6)	10.3	(14.9)	1.3	(0.0 to 2.6)	0.05
Systolic blood pressure (mmHg)	147.9	(24.2)	138.3	(22.0)	6.9	(5.1 to 8.6)	< 0.001
Hypertension (%)	50.8		31.8		14.6	(3.7 to 26.3)	< 0.001
Ankle to brachial blood pressure index	0.97	(0.3)	1.07	(0.2)	-0.07	(-0.09 to -0.05)	< 0.001
ECG myocardial infarction (%)	13.5		8.3		3.5	(1.1 to 6.3)	0.002
Atrial fibrillation (%)	4.0		2.3		0.5	(-0.5 to 2.0)	0.33
Stroke history (%)	5.9		2.4		2.2	(0.8 to 4.1)	< 0.001

* Values are proportions or means (SD)

† Adjusted for age and gender.

TABLE 2. Baseline glucose metabolism and dementia status after 2.1 years of follow-up. [*]

	Dementia at follow-up (n = 126)		No dementia at follow-up (n = 6244)		Adjusted difference (95% CI) [†]		P-value [†]
Age (years)	80.6	(7.7)	68.6	(8.6)			
Women (%)	73.8		58.9				
Random serum glucose (mmol/l)	7.7	(3.0)	6.9	(2.6)	0.1	(-0.2 to 0.5)	0.43
Fructosamine (μmol/l)	310.2	(68.8)	309.0	(51.3)	-5.0	(-15.1 to 5.1)	0.33
Post load insulin (mU/l) [‡]	77.8	(61.0)	61.6	(52.0)	4.7	(-6.0 to 15.4)	0.39
Insulin resistance (mU/mmol) [‡]	10.3	(6.9)	8.8	(6.4)	0.6	(-0.6 to 2.0)	0.35
Diabetes mellitus (%)	27.0		10.5		7.7	(1.9 to 15.0)	0.005

[*] Values are proportions or means (SD)

[†] Adjusted for age and gender.

[‡] Not assessed in subjects who used antidiabetes medication.

During a mean 2.1 years of follow-up, 126 (2.0%) participants became demented. Of those 89 (70.6%) were diagnosed as Alzheimer's disease (76 without and 13 with cerebrovascular disease), 18 (14.3%) had a vascular dementia, and 19 (15.1%) another type of dementia. Dementia patients were significantly older than those who were non-demented. There was no age adjusted difference in dementia risk by gender. The prevalence of diabetes was 10.5% in those who did not develop dementia, and 27.0% in subjects who developed dementia (table 2). This difference was significant, also after adjustment for age and sex. Incident dementia patients did not differ significantly from non-demented participants with respect to other measures of glucose metabolism (table 2).

NIDDM almost doubled the risk of dementia (age and sex adjusted relative risk 1.9, 95% CI 1.3 to 2.8, table 3), similarly for men (1.8, 95% CI 0.8 to 4.1) and women (1.9, 95% CI 1.2 to 3.0). When analyzed in strata of age no clear modification in diabetes related dementia risk was observed: For those below 75, 75 to 84, and of 85 years and older relative risks were 2.0, 2.2, and 1.4, respectively. The relative risk did not differ between those examined in person and the group in whom a diagnosis was made after reviewing medical files. The risk of incident dementia was clearly modified by type of treatment (table 3), with the lowest relative risk in diabetes patients not using antidiabetes medication (1.3, 95% CI 0.7 to 2.3) and the highest relative risk among those treated with insulin (4.3, 95% CI 1.7 to 10.5). Additional adjustment for

TABLE 3. Adjusted relative risk for dementia of non-insulin dependent diabetes mellitus and of three treatment categories of diabetes. Subjects without diabetes mellitus served as reference. [*]

	Total population Relative Risk (95% CI)		Men Relative Risk (95% CI)		Women Relative Risk (95% CI)	
All diabetes mellitus	1.9	(1.3 to 2.8)	1.8	(0.8 to 4.1)	1.9	(1.2 to 3.0)
no drug treatment	1.3	(0.7 to 2.3)	1.4	(0.5 to 4.0)	1.3	(0.7 to 2.6)
oral medication	2.4	(1.4 to 4.1)	2.2	(0.7 to 7.4)	2.4	(1.3 to 4.4)
insulin treatment	4.3	(1.7 to 10.5)	3.9	(0.5 to 29.5)	4.3	(1.6 to 11.8)

[*] Adjusted for age and gender (total population) or age (men, women).

TABLE 4. Relative risk for dementia by diabetes mellitus with, in addition to age and sex, adjustment for possible confounders or intermediates.

Confounder or intermediate	Relative Risk (95% CI)	
Low education	1.8	(1.2 to 2.7)
Body mass index	1.9	(1.3 to 2.8)
Waist to hip ratio	1.9	(1.2 to 2.8)
Smoking	1.9	(1.3 to 2.8)
Alcohol intake	1.7	(1.2 to 2.6)
Systolic blood pressure	1.9	(1.3 to 2.9)
Hypertension	2.0	(1.3 to 2.9)
Ankle to brachial blood pressure index	1.8	(1.2 to 2.7)
ECG myocardial infarction	1.8	(1.2 to 2.7)
Atrial fibrillation	1.8	(1.2 to 2.7)
Stroke history	1.9	(1.3 to 2.8)
Education, body mass index, waist hip ratio, smoking, and alcohol intake	1.7	(1.1 to 2.5)
Systolic blood pressure, hypertension, ankle to brachial index,		
ECG myocardial infarction, atrial fibrillation, and stroke history	1.8	(1.2 to 2.7)

TABLE 5. Age and gender adjusted relative risk for dementia subtypes of diabetes mellitus. Subjects without diabetes mellitus served as reference.

Dementia subtype	Relative Risk (95% CI)
Total Alzheimer's disease	1.9 (1.2 to 3.1)
without cerebrovascular disease	1.8 (1.1 to 3.0)
with cerebrovascular disease	3.0 (1.0 to 9.3)
Vascular dementia	2.0 (0.7 to 5.6)
Other dementias	1.6 (0.5 to 5.0)

possible confounders or intermediates hardly influenced these results (table 4). Diabetes increased the risk of all types of dementia, including Alzheimer's disease (table 5). Additional adjustments for possible confounders again did not result in substantial changes of the estimates.

In this population, the fraction of incident dementia attributable to diabetes mellitus was 8.8%. This population attributable fraction was 8.1% in men and 9.2% in women.

We found no significant influence on dementia risk by serum glucose, fructosamine, post load insulin, and insulin resistance (table 6), neither did we detect significant relative risks among subjects with values in the highest or lowest as compared to the median quintile of these glucose metabolism markers.

TABLE 6. Age and gender adjusted influence on the risk for dementia of glucose metabolism measures, assessed for the total population, and for subjects without and with diabetes mellitus. The relative risk for dementia is given per standard deviation increase of value. [*]

	Total population Relative Risk (95% CI)	Without diabetes Relative Risk (95% CI)	With diabetes Relative Risk (95% CI)
Random serum glucose	1.07 (0.92 to 1.24)	0.77 (0.51 to 1.16)	1.00 (0.81 to 1.25)
Fructosamine	0.95 (0.79 to 1.14)	0.79 (0.62 to 1.02)	0.95 (0.72 to 1.25)
Post load insulin [†]	1.04 (0.89 to 1.21)	1.08 (0.91 to 1.27)	0.87 (0.58 to 1.31)
Insulin resistance [†]	1.04 (0.89 to 1.22)	1.07 (0.92 to 1.25)	0.89 (0.52 to 1.52)

[*] One standard deviation (assessed in the total population) of random serum glucose: 2.6 mmol/l; fructosamine: 51.8 μmol/l; post load insulin: 52.2 mU/l; and insulin resistance: 6.4 mU/mmol.

[†] Insulin and insulin resistance were not assessed in subjects who used antidiabetes medication.

Discussion

In this large prospective study of dementia, subjects with NIDDM were at significantly increased risk of dementia, in particular if they were treated with insulin. NIDDM increased the risk of all types of dementia including Alzheimer's disease. Baseline serum glucose level, fructosamine, post-load insulin, and insulin resistance, did not influence the risk of dementia. These results confirmed our previous cross-sectional findings of an association of NIDDM with dementia and Alzheimer's disease.[12] Based on the results in this study we estimated that 8.8% of all dementia in the population could be attributable to NIDDM.

Major advantages of the Rotterdam Study to investigate risk factors of dementia are the size of the study, the longitudinal and population-based design, and the fact that exposure and disease status were defined by thorough in-person examination. Diabetes status was assessed before onset of dementia which minimised ascertainment bias. Selection bias was minimised because the study was population-based and because follow-up of the population at risk of dementia was complete.

A limitation of the present study is that brain imaging could not be obtained of all dementia patients and we may have underestimated the amount of cerebrovascular pathology of the demented subjects. We, however, consider it unlikely that the relation between diabetes and Alzheimer's disease is due to misclassification. The clinical Alzheimer's disease criteria that we used proved to be reliable.[29] Compared to the results shown in table 5, NIDDM patients had a similar increased risk of Alzheimer's disease when we restricted our analyses to patients who had undergone brain imaging.

Previous cross-sectional studies have shown positive associations of diabetes with vascular dementia, but a negative (inverse) relation with Alzheimer's disease.[6,7,9-11] These studies were based on selected patients and controls. The presence of diabetes was assessed from medical records and not actually screened for. Furthermore, in these studies, patients with indicators of vascular or cerebrovascular disease were more or less rigorously excluded from the Alzheimer group, thereby eliminating the possibility to study these factors in relation to Alzheimer's disease. Only two prior longitudinal studies on the risk for dementia by NIDDM have been published. A recent historical cohort study (Rochester, MN, USA) found among diabetes patients an increased risk of dementia (relative risk 1.7, 95% CI 1.3 to 2.1) and Alzheimer's disease (more pronounced in men (2.3, 95% CI 1.6 to 3.3) than women (1.4, 95% CI 0.9 to 2.0)).[30] Since this study was retrospective and register-based, disease ascertainment may have been selective and incomplete. A prospective population-based study (Hisayama, Japan), reported an increased risk among NIDDM patients of both Alzheimer's disease (relative risk 2.2, 95% CI 1.0 to 4.9) and vascular dementia (2.8, 95% CI 2.6 to 3.0).[31] This

study among 828 elderly with a follow-up of seven years, pursued complete ascertainment of incident dementia. The results of these studies are in line with our findings.

The relation between diabetes mellitus and dementia could either be explained through vascular disease or by non-vascular side-effects of diabetes. Diabetes mellitus is notorious for micro- and macrovascular complications.[32] It is a well-known risk factor for strokes,[1,2] which, if they accumulate or strike vital brain segments may cause dementia.[21,33] An increased risk of vascular (or multi-infarct) dementia by diabetes is to be expected. In case of Alzheimer's disease vascular mechanisms are less obvious. We cannot entirely exclude the possibility that we misdiagnosed some subjects with dementia due to vascular causes as Alzheimer's disease. However, the notion of vascular involvement in the pathogenesis of Alzheimer's disease is growing.[21,34,35] Also, small silent cerebral infarcts may have uncovered imminent Alzheimer's disease. The strong relative risk of Alzheimer's disease with cerebrovascular disease suggest vascular disease is often involved in diabetes-related dementia.

There are several arguments to consider other than vascular factors as a cause of dementia in diabetes patients. The limited effect of adjustment for vascular risk indicators suggests a non-vascular pathway. Moreover, previous studies have reported non-vascular functional and structural changes in the central nervous system of diabetes patients.[36-38] And NIDDM patients without clinical cerebrovascular disease [39-41]were found to perform significantly poorer on cognitive tests than healthy controls. Recently, advanced glycation end-products (AGE), which are the result of nonenzymatic glycosylation of proteins,[42] were found in plaques and tangles of Alzheimer brains, even in early stages of disease.[13] Excessive AGE formation by chronic hyperglycaemia may play a role in long-term diabetic complications.[15] In brains of Alzheimer patients the receptor for AGE appears overexpressed,[14] and this receptor is activated by β-Amyloid which is involved in Alzheimer pathology. If activated, oxidant stress is generated and cellular functions may disrupt.[43,34] Likewise, diabetes-induced AGE's could cause brain dysfunction.

Direct or indirect effects of insulin could contribute to the risk of dementia. In both this and our previous study we found that the highest risk was found for subjects on insulin treatment, suggesting that the risk is related to severity of NIDDM. Hypoglycaemic episodes frequently complicate insulin treatment,[44] and contrary to hyperglycaemia, hypoglycaemia can cause irreversible brain damage.[36,38] It cannot be excluded though that insulin itself may harm brain function. Though we did not find a relation of serum post-load insulin with dementia, high insulin levels have been associated with decreased cognition.[45]

We reported an increased risk of dementia in patients with diabetes mellitus. Non-insulin-dependent diabetes mellitus is a common disease in the elderly. For such common disorder, a 1.9 times increased risk of dementia as we found, implicates that a considerable proportion (8.8%) of all dementia could be attributed to diabetes. This high population attributable fraction ranges diabetes mellitus among the most important risk factors of dementia and Alzheimer's disease.

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Chapter 4.1

Atherosclerosis, apolipoprotein E, and the prevalence of dementia and Alzheimer's disease in a population based study

Abstract

Background: Vascular disorders have been implicated in dementia, but whether atherosclerosis is related to the most frequent type of dementia, Alzheimer's disease, is not known. The apolipoprotein-E genotype has been associated with Alzheimer's disease, and we postulated that it plays a part, together with atherosclerosis, in the aetiology of Alzheimer's disease. We investigated the frequency of dementia and its subtypes in relation to atherosclerosis and apolipoprotein E.

Methods: We did a population-based study of 284 dementia patients, 207 of whom had Alzheimer's disease, and 1698 individuals who were not demented. Indicators of atherosclerosis included wall-thickness and plaques of the carotid arteries, as assessed by ultrasonography, and systolic blood pressure ankle-to-brachial index, as a measure of generalized atherosclerosis. From these indicators a score of atherosclerosis ranging from 0 (no atherosclerosis) to 3 (severe atherosclerosis), was constructed. Apolipoprotein-E polymorphisms were assessed in 246 patients and in 928 reference subjects.

Findings: All indicators of atherosclerosis were associated with dementia (odds ratios ranging from 1.3 to 1.9), and its major subtypes, Alzheimer's disease (odds ratios 1.3 to 1.8) and vascular dementia (odds ratios 1.9 to 3.2). The prevalence of all dementia, Alzheimer's disease and vascular dementia, increased with the degree of atherosclerosis. The odds ratio for Alzheimer's disease in those with severe atherosclerosis was 3.0 (95% confidence interval 1.5-6.0; p = 0.001) as compared to those without atherosclerosis. In subjects with the apolipoprotein-E ε4 genotype and an atherosclerosis score of 2 or 3 the odds ratio for all dementia was 4.5 (95% confidence interval 2.0-10.1; p < 0.001). For Alzheimer's disease this odds ratio was 3.9 (1.6-9.6; p = 0.002), and for vascular dementia it was 19.8 (4.1-95.0; p < 0.001).

Interpretation: These findings suggest that dementia, and its two major subtypes, Alzheimer's disease and vascular dementia, is associated with atherosclerosis. This study also suggests an interaction between apolipoprotein E and atherosclerosis in the aetiology of Alzheimer's disease.

Introduction

Dementia is emerging as a major health problem.[1] It is an important cause of disability, in particular in the elderly. The most important subtype of dementia is Alzheimer's disease, which accounts for at least half of all dementia cases.[2] The causes of dementia and Alzheimer's disease are largely unknown, although recently important progress has been made in uncovering genetic factors that play a part in the aetiology of Alzheimer's disease. In particular, an association has been reported of the apolipoprotein-E ε4 allele with Alzheimer's disease.[3-5] Atherosclerosis has been implicated in dementia since long, but except for a relatively small group of patients labelled as vascular dementia, no evidence for a role of atherosclerosis in dementia at large and Alzheimer's disease in particular, has been presented.[6] The recently available non-invasive techniques to assess atherosclerosis provide the opportunity to study atherosclerosis and its putative sequelae in large populations.

We report here a population-based cross-sectional study of atherosclerosis, the apolipoprotein-E genotype, and the prevalence of dementia and its subtypes in 284 dementia patients and 1698 non-demented reference subjects.

Patients and methods

STUDY POPULATION

This study was carried out as part of the Rotterdam Study, a single-centre prospective follow-up study for which all residents aged 55 years or over of the suburb of Ommoord in Rotterdam, the Netherlands were invited. The study has been approved by the Medical Ethics Committee of Erasmus University, and written informed consent has been obtained from all participants. The objective of the study is to investigate determinants of chronic and disabling cardio-vascular, neuro-degenerative, locomotor and ophthalmologic diseases, as described in detail elsewhere.[7] Independently living participants were interviewed at home and subsequently clinically examined during two visits at a research centre. For institutionalized persons the examinations were performed in their institute. The base-line examination of the Rotterdam Study, on which the present report is based, was conducted between March 1990 and July 1993. Of the 10275 eligible subjects, 7983 participated (78%), ranging in age from 55 to 106 years. Of those who participated, 7528 (94%) underwent an extensive screening for dementia, and information on cardiovascular risk factors, indicators for atherosclerosis and apolipoprotein-E genotype was obtained. The other 455 subjects where lost through refusal of the cognitive examination or death. Indicators for atherosclerosis were compared between 284 dementia patients and 1698 non-demented reference subjects.

DEMENTIA CASES

Dementia was assessed by a three phase approach.[8] Firstly, all participants were screened with a brief cognitive test. Secondly, screen-positive subjects underwent additional cognitive and neurological testing. Thirdly, those whose results suggested a possibility of dementia were either subjected to a detailed examination or had their medical records used to confirm the diagnosis and establish the type of dementia.

The brief cognitive test for dementia in the first phase comprised a combined Mini-Mental State Examination (MMSE)[9] and Geriatric Mental State (GMS-A organic level).[10] The test was administered by trained research assistants. Screen-positive subjects had a MMSE score of 25 or less, or a GMS-A score of 1 or over. In the second phase, screen-positive subjects were examined by a Rotterdam Study physician with the CAMDEX (Cambridge examination for mental disorders of the elderly) diagnostic interview,[11] which included an interview with an informant. Participants who scored less than 80 on the CAMDEX cognitive test or who had higher scores but were suspected of dementia clinically were asked to participate in the third examination phase. In this diagnostic phase they were examined by a neurologist, had a brain scan (by magnetic resonance imaging), and were tested by a neuropsychologist.

Dementia was diagnosed according to the American Psychiatric Association's criteria (DSM-III-R).[12] The subdiagnosis of Alzheimer's disease was based on criteria produced by a working group of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA).[13] For the subdiagnosis of vascular dementia the DSM-III-R definition of multi-infarct dementia was used. The dementia type at the onset of the disease was ascertained. Some patients with Alzheimer's disease develop symptoms of vascular dementia in the course of the disease, usually after a stroke, which may result in a sudden worsening of dementia.[14] We classified these patients as Alzheimer's type with cerebrovascular disease.

A total of 474 cases of dementia was identified.[7] The present analysis was restricted to 284 of those in whom the dementia onset was less than three years before they were examined as part of this study. This effectively restricted the analysis to mild and moderate cases of dementia in whom the disease is unlikely to have changed the atherosclerosis status. In 228 of the 284 dementia patients (80.3 %) the diagnosis was based on the CAMDEX and examination by the study neurologist; in 52 cases (18.3 %) it was based on MMSE and GMS data; and in 4 cases (1.4 %) the diagnosis was based on medical records only. Data on apolipoprotein E were available in 246 of the dementia cases.

REFERENCE SUBJECTS

A random sample of 1698 participants, ranging in age from 55 to 99 years, served as controls. They were selected from the group of participants of the Rotterdam study who were screen-negative for dementia. Data on cardiovascular risk factors and on indicators for atherosclerosis were available for all these control participants and data on apolipoprotein-E polymorphisms were available for 928 of them.

MEASUREMENTS

Presence of atherosclerosis of the carotid arteries (wall thickness and plaques as measured by ultra-sonography) and presence of atherosclerosis of the large vessels of the legs (assessed by the ratio of the ankle-to-brachial systolic blood pressure) were assessed as potential correlates of dementia.

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). Intima-media thickness was measured in the common carotid arteries as described previously.[15] Presence of atherosclerotic plaques, defined as a focal widening relative to adjacent segments with protrusion into the lumen, was assessed in the common carotid arteries, the bifurcation and the internal carotid arteries.[16] The presence of atherosclerosis of the lower extremities 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.[17,18] Ankle systolic blood pressure was determined with the subject in supine position at both right and left posterior tibial arteries using a Doppler ultrasound transducer with 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. Peripheral arterial disease was considered present when left or right ankle-brachial index was less than 0.90.

Genomic DNA was used for apolipoprotein-E typing.[19] The apolipoprotein-E gene was amplified using the primers and amplification conditions described by Wenham et al.[20] After amplification the PCR product was digested with the restriction enzyme HhaI and fragments were separated by electrophoresis on a 5% agarose gel. Apolipoprotein-E alleles were visualized by ethidium bromide staining.

Sitting blood pressure was measured at the right upper arm with a random zero sphygmomanometer. The average of two measurements obtained on one occasion, separated by a count of the pulse rate, was used. Serum total and high density lipoprotein (HDL) cholesterol concentrations were determined by an automated

enzymatic procedure.[21] Body mass index was determined as body weight (in kg) divided by height squared (in m^2).

STATISTICAL ANALYSIS

The associations between atherosclerosis, apolipoprotein E and dementia were analysed in four ways. First, the associations of indicators of atherosclerosis with dementia and its subtypes were estimated. To adjust for age and gender differences within the age strata, a multiple linear regression model was used, with age and gender added to the model. Because of the importance of age as a potential confounder, we added age as a continuous variable in years and months to the regression models, and in addition we added indicator variables for 5-year age bands to all regression models. The associations are presented as odds ratios with 95% confidence intervals.

Second, a composite measure of atherosclerosis was constructed: a point was added to the atherosclerosis score if the following characteristics were present: plaques in at least one of the common carotid arteries, average wall-thickness of common carotid arteries in the highest quartile of the distribution, and evidence of peripheral arterial disease, defined as ankle-to-brachial index less than 0.90. This score of atherosclerosis was analysed in four categories corresponding to score values of 0-3. With a logistic regression model, the odds ratio of each category of atherosclerosis for dementia and its subtypes was computed, with age and gender entered into the regression model, and with age in 5-year age bands.

Third, the association between the atherosclerosis score and dementia was assessed for subgroups of participants according to apolipoprotein-E polymorphisms; in this analysis subjects homozygous for apolipoprotein E3 (ε3/ε3 genotype) were compared with those with at least one apolipoprotein E4 allele (ε4/ε2, ε4/ε3 and ε4/ε4). The results of this analysis are presented as age- and gender-adjusted prevalence figures, both by apolipoprotein-E type and atherosclerosis score.

Fourth, in a further analysis of the interaction of atherosclerosis and apolipoprotein-E genotype, odds ratios are presented in a table with atherosclerosis score 2 or 3 and score 0 or 1 and genotype (homozygous ε3, or at least one ε4 allele). In addition, a regression analysis was performed on the full data set with the product term for apolipoprotein genotype (in two categories as above) and atherosclerosis (also in two categories as above), as assessed with a model which also included both terms separately, adjusted for age and gender. The coefficient of the interaction term was expressed as an odds ratio with a 95% confidence interval.

No major differences in the associations between atherosclerosis and dementia were observed between men and women, and therefore the estimates are presented for men and women combined.

Results

Of the 284 dementia cases, 82 were male and 202 were female. In 207 (73%) of all cases the subdiagnosis was Alzheimer's disease, in 50 (18%) vascular dementia, and in 27 (10%) other dementia's. Table 1 presents some characteristics of the demented and non-demented subjects.

All indicators of atherosclerosis were significantly associated with all dementia, with odds ratios ranging from 1.3 to 1.9 (table 2). All indicators of atherosclerosis were also associated with Alzheimer's disease, with odds ratios ranging from 1.3 to 1.8, and with vascular dementia with odds ratios ranging from 1.9 to 3.2 (table 2). When patients classified as Alzheimer's disease with cerebrovascular disease (n=31) were excluded from the Alzheimer's disease group, the estimates of the odds ratios remained virtually unchanged.

The apolipoprotein-E ε4 allele was associated with all dementia (odds ratio 1.8, 95% CI 1.2-2.7), Alzheimer's disease (odds ratio 1.7, 95% CI 1.0-2.7) and vascular dementia (odds ratio 2.3, 95% CI 1.1-4.8).

The odds ratio's of all dementia, Alzheimer's disease and vascular dementia increased by the score of atherosclerosis (table 2). As shown in the figure, the prevalence of all dementia, Alzheimer's disease and vascular dementia by atherosclerosis score showed a strong increase in those with the apolipoprotein-E ε4 genotype.

Table 1. Characteristics of the study subjects.

	Men		Women	
	Dementia (N = 82)	No dementia (N = 623)	Dementia (N=202)	No dementia (N=1075)
Age (yr)	81.2 (59-97)[*]	69.9 (55-94)	84.1 (59-98)	71.9 (55 - 99)
Systolic BP (mmHg)	137.7 (24.5)	138.1 (20.7)	143.2 (24.6)	138.9 (22.4)
Diastolic BP (mmHg)	74.0 (16.2)	72.8 (10.9)	71.1 (14.6)	71.2 (11.6)
Total cholesterol (mmol/L)	5.8 (1.1)	6.3 (1.2)	6.3 (1.2)	6.9 (1.3)
Body Mass Index (kg/m^2)	24.8 (3.2)	25.9 (3.2)	25.7 (4.1)	27.0 (4.3)

[*] Values are means and ranges for age, and means and standard deviations for other variables.

Table 2. Age-adjusted odds ratios of Alzheimer's disease, vascular dementia and other dementias with indicators of atherosclerosis.

	Alzheimer's disease (N = 207)	Vascular dementia (N = 50)	Other dementias (N = 27)	All dementia (N = 284)
Peripheral arterial disease	1.3 (0.9-1.8) [*]	2.5 (1.3-4.8)	1.0 (0.4-2.4)	1.5 (1.1-2.0)
Plaques common carotid arteries	1.8 (1.2-2.7)	3.2 (1.6-6.8)	1.6 (0.6-4.3)	1.9 (1.3-2.7)
Wall thickness common carotid arteries [†]	1.3 (1.0-1.6)	1.9 (1.3-2.8)	0.8 (0.4-1.5)	1.3 (1.1-1.6)
Atherosclerosis score				
0 (reference)	1.0	1.0	1.0	1.0
1	2.2 (1.2-3.9)	1.3 (0.4-4.7)	0.1 (0.0-1.0)	1.6 (1.0-2.7)
2	2.5 (1.3-4.6)	4.8 (1.6-14.2)	0.6 (0.2-2.4)	2.3 (1.4-3.9)
3	3.0 (1.5-6.0)	9.5 (3.0-30.0)	0.7 (0.1-3.4)	3.2 (1.8-5.7)
P-value for trend	$p < 0.001$	$p < 0.001$	$p = 0.392$	$p < 0.001$

[*] Adjusted for age and gender, with 95% confidence interval in parentheses.

[†] Odds ratio of one SD (0.20 mm) increase of wall thickness

Table 3. Age-adjusted odds ratios of Alzheimer's disease, vascular dementia and all dementia by atherosclerosis (− if score is 0 or 1; + if score is 2 or 3) and apolipoprotein genotype.

Genotype [*]	Alzheimer's disease Atherosclerosis		Vascular dementia Atherosclerosis		All dementia Atherosclerosis	
	−	+	−	+	−	+
ApoE 33	1.0 (reference)	1.4 (0.7-3.1)	1.0 (reference)	7.1 (1.5-34.3)	1.0 (reference)	1.6 (0.8-3.2)
ApoE 4+	1.3 (0.6-2.7)	3.9 (1.6-9.6)	3.6 (0.8-16.2)	19.8 (4.1-95.0)	1.4 (0.7-2.7)	4.5 (2.0-10.1)

[*] ApoE 33: apolipoprotein-E ε3/ε3 genotype; ApoE 4+: apolipoprotein-E ε2/ε4, ε3/ε4, or ε4/ε4.

Figure. The prevalence of all dementia, Alzheimer's disease and vascular dementia, adjusted for age and gender, by apolipoprotein-E genotype and atherosclerosis score.
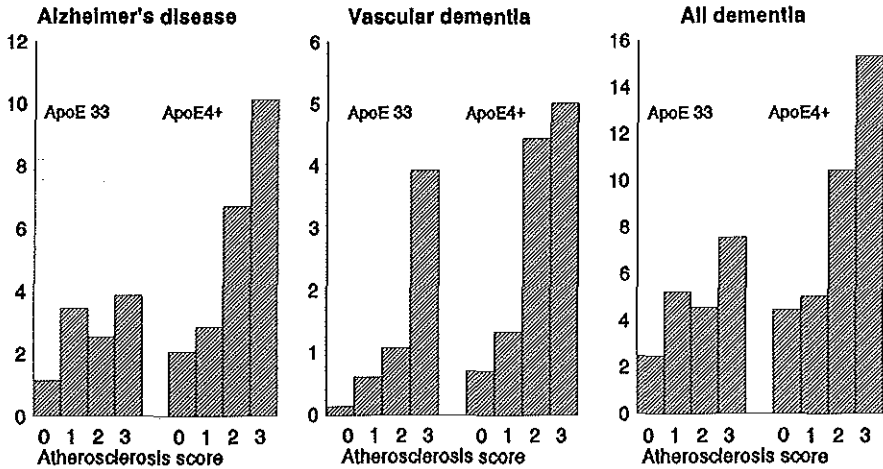
Subjects with evidence for atherosclerosis (score 2 or 3) and the apolipoprotein-E ε4 genotype had an increased odds for all dementia (odds ratio 4.5; 95% confidence interval 2.0-10.1), for Alzheimer's disease (3.9; 1.6-9.6), and for vascular dementia (19.8; 4.1-95.0) (table 3). The odds ratio of the interaction term of atherosclerosis and apolipoprotein genotype was 2.0 (95% confidence interval 0.7-5.9) for all dementia, and 2.4 (0.9-7.6) for Alzheimer's disease.

The observed associations of atherosclerosis and apolipoprotein-E genotype with dementia, Alzheimer's disease and vascular dementia were virtually not altered after adjustment for blood pressure, total cholesterol and body mass index.

Discussion

The main findings in this study are that indicators of atherosclerosis measured at different sites are all associated with the presence of dementia, and both of its subtypes, Alzheimer's disease and vascular dementia, and that the association between atherosclerosis and dementia and its subtypes appears to be particularly strong in those with the apolipoprotein-E ε4 genotype. Before we can accept these findings some methodologic issues have to be addressed.

This is a cross-sectional study and it is conceivable that changes in the

atherosclerotic status have occurred as a consequence of dementia. Although we consider this unlikely, we further reduced this possibility by restricting our study to patients who were recently diagnosed with dementia. Another concern is the measurement of atherosclerosis. We used ultrasonographic indicators of atherosclerosis, but increased common carotid intima media thickness may not necessarily reflect atherosclerosis. It may merely reflect an adaptive response of the vessel wall to changes in the sheer stress and tensile stress. However, ultrasonographically determined increased wall thickness of the common carotid artery has been associated with cardiovascular risk factors.[22-24] In addition, progression of wall thickness has been associated with risk factors for atherosclerosis.[25] This supports the view that non-invasively assessed intima media thickness of the common carotid artery may be regarded as an indicator of atherosclerosis.

It is likely that some error has occurred in the measurement of atherosclerosis indicators. This may have led to misclassification which tends to underestimate any true association between atherosclerosis and dementia, provided that the measurement error has occurred to the same extent among the dementia patients and the reference subjects.

A strength of our study is that it was population-based and had a relatively high response rate. We consider it therefore unlikely that a selection bias may be responsible for our findings. However, the diagnosis of dementia and in particular its subtypes is of concern. A high sensitivity and specificity of the diagnostic procedure was ensured by the three phase comprehensive diagnostic work-up.[7,8,26,27] Without confirmation at necropsy, however, subtyping dementia remains uncertain. Also, the diagnostic criteria that were used are of limited accuracy, which complicates all large population-based dementia studies. A major concern in the present study is the classification of dementia patients with cerebrovascular disease. In our main analysis, we classified primary Alzheimer's disease complicated by cerebrovascular disease as Alzheimer's disease. However, the additional analysis in which cerebrovascular patients were excluded from the Alzheimer's group yielded virtually the same results as the main analysis. Although we fully cannot exclude diagnostic misclassification enen in this additional analysis, we feel that it supports the view that atherosclerosis is associated with Alzheimer's disease per se.

Our findings suggest that atherosclerosis is not only associated with a small subgroup of vascular, or multi infarct dementia, but also with the major subtype of dementia, Alzheimer's disease. The findings are in agreement with a recent report that suggested a role of β-amyloid peptides in vascular endothelial damage.[28] The large difference in the prevalence in dementia and Alzheimer's disease between those with the apolipoprotein-E ε4 allele compared to those with the apolipoprotein-E ε3/ε3

genotype by degree of atherosclerosis suggests an interplay between apolipoprotein E and atherosclerosis in the aetiology of Alzheimer's disease. Although addition of cardiovascular risk factors like blood pressure and serum lipids to our analysis did not change the association between indicators of atherosclerosis and dementia, this does not preclude a role of these risk factors in the occurrence of dementia.[29]

This population-based study confirms that the apolipoprotein-E genotype is associated with Alzheimer's disease.[3-5] Our data suggest an interaction between atherosclerosis and apolipoprotein E, to the effect that the increase of the prevalence of Alzheimer's disease with atherosclerosis is particularly marked in those with the apolipoprotein-E ε4 genotype.[30] Unfortunately, these cross-sectional data do not enable us to further investigate in which way apolipoprotein E and atherosclerosis interact.

In conclusion, our observations suggest that atherosclerosis may not only play a role in dementia at large, but also in its major subgroup, Alzheimer's disease. The association, which was observed with all measured indicators of atherosclerosis, was particularly marked in those with the apolipoprotein-E ε4 allele. Our findings suggest interaction between specific genetic factors and atherosclerosis in the aetiology of Alzheimer's disease.

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Chapter 4.2

Atrial fibrillation and the prevalence of dementia

Abstract

Background and Purpose: Atrial fibrillation is a frequent disorder in the elderly and a known risk factor of cerebrovascular strokes. We investigated the association of atrial fibrillation with dementia and cognitive impairment in a large cross-sectional, population-based study in the elderly.

Methods: Of 6584 participants of the Rotterdam Study, aged 55 to 106 years old, detailed information on dementia status and electrocardiographic (ECG) abnormalities was available. Dementia was diagnosed in three phases. Participants were first screened. Screenpositive subjects were further tested. Those suspected of dementia underwent an extensive diagnostic work-up. Dementia and dementia subtypes was diagnosed according to prevailing criteria. Cognitive impairment was defined as a Minimental State Examination test score of less than 26 points in a non-demented subject.

Results: Atrial fibrillation was diagnosed in 195, dementia in 276 and cognitive impairment in 635 subjects. We found significant positive associations of atrial fibrillation with both dementia and impaired cognitive function (age and sex adjusted odds ratios of 2.3 (95% CI: 1.4 - 3.7) and 1.7 (95% CI: 1.2 - 2.5), respectively). The strongest association was not found for vascular dementia but for patients diagnosed as Alzheimer's disease with cerebrovascular disease. The associations were stronger in women and the relation with dementia was more pronounced in the relatively younger elderly. A history of stroke in subjects with atrial fibrillation could not explain these associations.

Conclusions: Dementia and its subtypes Alzheimer's disease and vascular dementia may be related to atrial fibrillation even if no clinical stokes have occurred.

Introduction

Atrial fibrillation is a common finding in the elderly.[1] Patients with atrial fibrillation frequently develop cerebral infarctions, which often remain clinically silent.[2,3] The inefficient cardiac performance that accompanies atrial fibrillation may result in cerebral underperfusion which compromises the ageing brain.[4] Though already in 1977 it was suggested that cardiac dysrythmias could aggravate or even precipitate senile

dementia,[5] studies on cognitive performance in patients with atrial fibrillation are rare. An association with vascular dementia has been suggested but not well quantified. We studied the association of atrial fibrillation with dementia, its subtypes and cognitive function in a large community-based study.

SUBJECTS AND METHODS

The Rotterdam Study is a population-based prospective cohort study investigating the occurrence and progression of chronic diseases of the elderly.[6] The study focuses on neurological, cardiovascular, locomotor and ophthalmologic diseases. All inhabitants of Ommoord, a suburb of Rotterdam, aged 55 years and older, including those living in institutions, were invited to participate in the study. Of the 10275 eligible subjects, 7983 (78%) participated in the study. Between 1990 and 1993 all participants were extensively interviewed at their homes and examined at a specially equiped research centre in order to collect baseline data and to ascertain health status. Of 577 participants no data on cognitive function were available, mostly because of refusal. An additional 822 subjects had no ECG, usually due to technical or logistic problems. In the present analyses 6584 participants (82%) with completed ECG and dementia work-up were included.

EXAMINATIONS

At their homes participants were interviewed about their medical history. Subsequently they were examined at the research centre. Examinations in institutionalised subjects were performed in the institution. All participants underwent a short neurologic examination. Dementia was assessed using a three phase approach.[7] First, with a combined Mini Mental State Examination (MMSE)[8] and Geriatric Mental State schedule (GMS-A, organic level),[9] the population was screened for dementia. Secondly, screen positive subjects (MMSE score below 26 or GMS score above 0) were examined by a physician with the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX) diagnostic interview,[10] which includes an informant interview. Thirdly, all independently living, and some institutionalised participants suspected of dementia, were invited for examination by the study neurologist (FvH). Upon his indication participants were referred for a two hour neuropsychologic testing, and brain magnetic resonance imaging (MRI), which was obtained in half of the independently living patients. Of most institutionalised patients, who were on average older, had more physical constraints, and were more severely demented, and of other patients in whom the dementia work-up was limited additional information was obtained from medical records. A panel consisting of the neurologist, neuropsychologist and the study

physician reviewed all available data and made a diagnosis of dementia according to *Diagnostic and Statistical Manual of mental disorders*, edition 3, revised[11] criteria with a subdiagnosis of Alzheimer's disease based on *National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association*[12] criteria and of vascular dementia in accordance with *National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences*[13] criteria. Briefly, for the distinction between Alzheimer's disease and vascular. dementia, review of the data focused on cerebrovascular disorders as determined by neurologic exam or on MRI scan, their relation with the onset of dementia, the acuteness of onset and pattern of progression, and the distribution of cognitive defects over the distinct domains of cognition. If a cerebrovascular event occurred within 3 months before the onset of dementia, this strongly favoured a diagnosis of vascular dementia. The presence of cerebrovascular disorders did not prohibit a diagnosis of Alzheimer's disease. In accordance with above mentioned NINDS-AIREN criteria Alzheimer's disease patients were subdivided into a group without and with cerebrovascular disease. This subdivision was based on evidence of strokes or transient ischemic attacks in the medical history, or on cerebral MRI. In subjects with the clinical presentation of Alzheimer's disease, a history of stroke was considered not directly etiologically related to the dementia if the stroke had · occurred definitely before or after the onset of dementia.

We defined cognitive impairment as a MMSE score below 26 in subjects who were not demented.

The presence of atrial fibrillation was assessed in standard 12-lead ECG's, which were made at the research centre with an ACTA Gnosis IV ECG recorder (Esaote/Biomedica, Florence, Italy) and digitally stored. ECG's were analyzed by the Modular ECG Analysis System (MEANS) computer program.[14] The program contains a module for rhythm classification of the ECG, contour analysis and Minnesota coding. Its algorithm calculates ECG diagnoses, which have been shown to be highly reliable.[15] For this study the program's ECG diagnoses of atrial fibrillation and myocardial infarction were used. Myocardial infarction was graded at 4 different levels of certainty and was assumed present if the diagnosis was probable or definite.

Besides myocardial infarction the following possible confounders were measured: systolic and diastolic blood pressure, peripheral atherosclerosis, diabetes mellitus, education, antihypertensive, beta-blocker, digoxin, verapamil, anticoagulation and thyroid drug treatment. Systolic and diastolic blood pressure were measured with a random zero sphygmomanometer. The ankle-to-brachial index (the ratio of the systolic blood pressure measured at the ankle and the upper arm) was used as a measure of peripheral atherosclerosis: a ratio of 0.9 or below was considered evidence for

atherosclerosis.[16] Diabetes mellitus was defined as the use of anti-diabetic medication or a random or post-load serum glucose level above 11 mmol/l.[17] The level of education was assessed during the initial home interview and graded in four levels, from primary school only to college and higher. Also current drug use was assessed during the interview. Participants were asked to show all medication they were using. Of institutionalised subjects, medication was reported by the medical staff. We combined diuretics with the group of specific antihypertensive drugs.

Stroke was considered a possible intermediate in the relation between atrial fibrillation and cognitive deficits. We only had information on clinically overt strokes. This was determined by asking participants if they ever suffered from a stroke, which was diagnosed by a physician. In dementia patients this was asked in the informant interview. All histories of stroke were verified with medical records.

STATISTICAL ANALYSIS

In the analysis subjects with dementia and those with impaired cognitive function without being demented were treated as separate groups. The characteristics of subjects with dementia or cognitive impairment were compared to those with normal cognition. Because the age-distributions in demented and non-demented participants were very different we calculated age and sex adjusted differences with multivariate regression analysis.

The association between atrial fibrillation and dementia or cognitive impairment was examined by calculating odds ratios by multivariate logistic regression analysis with dementia or cognitive impairment as the dependent, and atrial fibrillation, age and sex as independent variables in the model. In the analyses on dementia, subjects with cognitive impairment were excluded, and vice versa. We subsequently added myocardial infarction, systolic and diastolic blood pressure, peripheral atherosclerosis, diabetes mellitus, educational level, antihypertensive medication, beta-blocker, digoxin, verapamil, anticoagulation and thyroid drug treatment to the regression model to adjust for possible confounding. Missing values on the confounding variables were handled with the indicator method.[18]

We repeated the multiple regression analyses in subjects without a history of stroke to examine the association of atrial fibrillation with cognitive disorders in the absence of clinical strokes.

To assess whether women with atrial fibrillation had disproportionally more vascular comorbidity than men with atrial fibrillation, we performed logistic regression analyses with the various vascular determinants as the dependent and age, sex, atrial fibrillation and the product term of sex and atrial fibrillation as independent variables in the model.

Results

Of the 6584 participants (age range: 55 to 106 years) in this study, 635 (9.6%) had cognitive impairment without dementia, whereas 276 (4.2%) were diagnosed with dementia (table 1). In 206 subjects the dementia was of the Alzheimer disease type (75%), 41 subjects had vascular dementia (15%), and 29 had other dementias, including one undefined dementia (11%). Of the Alzheimer's disease patients, 40 (19%) had cerebrovascular disease that was considered not directly related to the dementia. Both cognitive impairment and dementia prevalence increased strongly with age.[7] Since the proportion of women was markedly higher in older age groups, there were relatively more women with cognitive disorders. Atrial fibrillation was found in 195 of the 6584 participants (3.0%) and more frequent in men (3.3%) than women (2.7%). The age-specific prevalence of atrial fibrillation in men increased from 55 years onward per 10 year: from 0.9%, 3.0%, 7.6% to 13.2% in those aged 85 and older. In women these prevalences were 0.3%, 1.8%, 5.2% and 10.6%. Table 1 gives the age and sex adjusted characteristics of subjects with and without cognitive disorders.

Dementia was more than twice as common in subjects with atrial fibrillation than in those without (table 2). We also found a significant positive association between cognitive impairment and atrial fibrillation, but this association was less strong. Stratification for gender showed that associations were restricted to women. Table 3 shows that the relation between dementia and atrial fibrillation was modified by age and that associations were stronger below 75 years of age in both men and women. No such age effect was found for cognitive impairment. Additional adjustments for myocardial infarction, blood pressure, peripheral atherosclerosis, diabetes melitus, education and various medication, did only slightly change the associations (tables 2,3). Only in subjects below 75 years of age the association between dementia and atrial fibrillation became smaller when subjects with a history of stroke were excluded.

Table 4 shows the relation between atrial fibrillation and subtypes of dementia. Positive associations were observed for both Alzheimer's disease and vascular dementia. In particular Alzheimer's disease with cerebrovascular disease was strongly associated with atrial fibrillation. Additional adjustment for possible confounders resulted in reduced odds ratios, but did not essentially change the relation.

We further explored the gender differences in the association of atrial fibrillation with cognitive disorders. If men and women with atrial fibrillation are treated differently this could result in variations in the occurrence of complications. Therefore we compared treatment regimens between men and women. Similar proportions of men and women with atrial fibrillation were treated with digoxin glycosides (38% and 42%, respectively) and verapamil (13% and 16%). A larger proportion of men than women

Table 1. Characteristics of the study population, dementia patients and subjects with mild cognitive impairment [*]

Characteristics	No cognitive impairment	Dementia	p-value [‡]	Cognitive impairment without dementia	p-value [‡]	Total population
Number	5673	276		635		6584
Age (mean ± sd)	67.9 ± 8.2	83.3 ± 7.3		74.4 ± 9.6		69.2 ± 9.1
Women (%)	57.7	71.7		67.6		59.2
Atrial fibrillation (%)	2.1	13.0	<0.01	6.0	0.01	3.0
ECG Myocardial infarction (%)	8.8	17.1	0.14	8.8	0.17	9.1
Systolic blood pressure (mmHg, mean ± sd)	138.3 ± 22.0	142.8 ± 24.4	<0.01	146.7 ± 24.0	<0.01	139.3 ± 22.5
Diastolic blood pressure (mmHg, mean ± sd)	73.6 ± 11.3	72.1 ± 15.0	0.50	74.9 ± 13.4	<0.01	73.7 ± 11.7
Peripheral atherosclerosis (%)	15.6	50.6	<0.01	26.8	0.35	18.3
Diabetes mellitus (%)	9.9	21.7	0.27	15.5	0.16	11.0
Only primary education (%)	19.4	66.0	<0.01	49.6	<0.01	24.0
Treated with antihypertensives [†] (%)	22.0	41.9	1.00	28.3	0.29	23.4
Treated with beta-blocking agents (%)	14.7	8.8	<0.01	15.6	0.84	14.6
Treated with digoxin glycosides (%)	3.0	17.7	<0.01	7.1	0.08	3.9
Treated with verapamil (%)	5.9	10.4	0.84	7.2	0.61	6.2
Treated with antithrombotic agents (%)	4.7	9.2	0.22	6.3	0.42	5.0
Treated with thyroid medication (%)	2.2	6.2	0.07	2.7	0.86	2.4
Stroke history (%)	2.3	14.9	<0.01	5.7	0.02	3.2

[*] cognitive impairment was defined as minimental state examination score below 26 points in non-demented subjects

[†] excludes beta-blocking agents, includes all diuretics, irrespective of the indication

[‡] sigificance of age and sex adjusted difference with non-impaired subjects

TABLE 2. Association of atrial fibrillation to dementia and cognitive impairment by gender. Subjects without cognitive impairment were used as the referent category.[*]

	Men OR (95%CI) [†]	Women OR (95%CI)	Total population OR (95%CI)
Dementia			
Age and (if applicable) sex adjusted	1.3 (0.5 - 3.1)	3.1 (1.7 - 5.5)	2.3 (1.4 - 3.7)
Additional adjustments [‡]	0.8 (0.3 - 2.4)	3.0 (1.5 - 5.9)	2.0 (1.2 - 3.4)
Subjects with stroke history excluded	1.2 (0.5 - 3.4)	3.0 (1.6 - 5.5)	2.3 (1.4 - 3.8)
Cognitive impairment without dementia [*]			
Age and (if applicable) sex adjusted	1.1 (0.6 - 2.2)	2.3 (1.4 - 3.8)	1.7 (1.2 - 2.5)
Additional adjustments [‡]	1.0 (0.5 - 2.1)	2.4 (1.4 - 4.3)	1.7 (1.1 - 2.6)
Subjects with stroke history excluded	0.9 (0.4 - 1.9)	2.2 (1.3 - 3.7)	1.6 (1.0 - 2.4)

[*] cognitive impairment was defined as minimental state examination score below 26 points in non-demented subjects

[†] odds ratio (95 % confidence interval)

[‡] additional adjustments for ECG myocardial infarction, systolic and diastolic blood pressure, peripheral atherosclerosis, diabetes mellitus, education, antihypertensive, beta-blocker, digoxin, verapamil, anticoagulation and thyroid drug treatment

used antithrombotic drugs (34% versus 20%). In both men and women without atrial fibrillation, 4% indicated to use treatment for irregular hartaction. Of these 28% of men and 36% of women used digoxin, 20% of both men and women used verapamil and 23% of men versus 4% of women used antithrombotic drugs. There was more vascular comorbitity in women than men with atrial fibrillation, and this difference was significant for diabetes mellitus, antihypertensive drug use and borderline significant for ECG myocardial infarction.

Discussion

In this study we found that atrial fibrillation is significantly associated with dementia. Particularly women and subjects below age 75 with atrial fibrillation have an increased prevalence of dementia. Atrial fibrillation appears to be associated with vascular dementia but also with Alzheimer's disease, particularly in cases with concomitant cerebrovascular disease.

TABLE 3. Association of atrial fibrillation with dementia. Subjects without cognitive impairment were used as the referent category.[*]

	Men OR (95%CI) [†]	Women OR (95%CI)	Total population OR (95%CI)
Age < 75 years			
Age and (if applicable) sex adjusted	1.9 (0.2 - 15.6)	9.2 (2.5 - 34.3)	4.9 (1.7 - 14.7)
Additional adjustments [‡]	4.6 (0.5 - 45.9)	7.1 (1.1 - 45.7)	4.4 (1.0 - 18.7)
Subjects with stroke history excluded	2.2 (0.3 - 18.2)	3.2 (0.4 - 25.4)	2.6 (0.6 - 11.4)
Age ≥ 75 years			
Age and (if applicable) sex adjusted	1.2 (0.5 - 3.1)	2.6 (1.4 - 4.8)	2.0 (1.2 - 3.4)
Additional adjustments [‡]	0.7 (0.2 - 2.2)	2.6 (1.3 - 5.3)	1.8 (1.0 - 3.2)
Subjects with stroke history excluded	1.1 (0.4 - 3.2)	2.9 (1.5 - 5.6)	2.2 (1.3 - 3.8)

[*] non-demented subjects with minimental state examination score of 26 points or higher

[†] odds ratio (95 % confidence interval)

[‡] additional adjustments for ECG myocardial infarction, systolic and diastolic blood pressure, peripheral atherosclerosis, diabetes mellitus, education, antihypertensive, beta-blocker, digoxin, verapamil, anticoagulation and thyroid drug treatment

TABLE 4. Association between atrial fibrillation and subtypes of dementia. Subjects without cognitive impairment were used as the referent category.[*]

	Alzheimer's disease without CVD [†] OR (95% CI) [‡]	Alzheimer's disease with CVD [†] OR (95% CI)	Vascular dementia OR (95% CI)
Age and sex adjusted	1.8 (1.0 - 3.3)	4.1 (1.7 - 9.7)	1.9 (0.6 - 5.5)
Additional adjustments [§]	1.8 (0.9 - 3.5)	2.9 (1.1 - 7.5)	1.5 (0.4 - 4.9)

[*] non-demented subjects with minimental state examination score of 26 points or higher

[†] cerebro vascular disease

[‡] odds ratio (95 % confidence interval)

[§] additional adjustments for ECG myocardial infarction, systolic and diastolic blood pressure, peripheral atherosclerosis, diabetes mellitus, education, antihypertensive, beta-blocker, digoxin, verapamil, anticoagulation and thyroid drug treatment

This is a cross-sectional study and there is some potential for bias. Firstly, 18% of the Rotterdam Study participants had to be excluded from these analyses due to incomplete data. An ECG was more often missing in (especially severely) demented participants and non-responders were on average older than those who could be included in the present study. However, we consider it unlikely that the association between atrial fibrillation and dementia among non-responders was opposite to what we found. Therefore we do not think that non-response has led to essential biases in our estimates. Secondly, since our analyses were cross-sectional there is a potential for survival effects. If coexisting atrial fibrillation and dementia reduces survival, the combination would be seen less and the association would be underestimated. Most likely this survival effect is stronger in more severe disease and could have attributed to a reduced association in men, in older age and vascular dementia. A third possible bias is due to misclassification. Since we used a very sensitive screening for dementia it is unlikely that many cases have been missed. Also, the thorough diagnostic work-up ensured minimal false positive diagnoses. However, misclassification may have occurred in dementia subtyping. Even though the criteria we used for the diagnosis Alzheimer's disease have a high sensitivity and specificity for the autopsy proven diagnosis,[19] subtyping dementia remains uncertain without post-mortem confirmation or additional brain imaging data. Besides, there is increasing evidence that Alzheimer's disease and vascular dementia are not as clear entities, nor can be distinguished as sharply, as suggested by the common use of these labels. Atrial fibrillation has undoubtedly been underdiagnosed. Since only one ECG was recorded, we did not detect all paroxysmal atrial fibrillation. In the Cardiovascular Heart Study, a population-based study in persons of 65 years and older, it was shown that a 10-second resting ECG (like we used) detected 74% of all subjects with atrial fibrillation on 24-hour ambulatory electrocardiography.[20] Other cardiac arrhythmias were in the present analyses also not taken into account. Both undetected atrial fibrillation and other arrhythmias may have diluted the association and thus lead to an underestimation of the true effect of atrial arrhythmias. Finally, in our definition of cognitive impairment we did not account for additional causes of decreased Minimental State Examination test scores, like depressive symptoms, sensory impairments and physical disabilities. We consider it however unlikely that this has confounded the association between cognitive impairment and atrial fibrillation.

With respect to the stronger association in women than men several hypotheses were considered. Antithrombotic drugs are more often prescribed for men and it is possible that complications due to atrial fibrillation are more adequately prevented in men than women. Women with atrial fibrillation had more coincident cardiovascular disorders than men with atrial fibrillation. Two prospective studies on atrial fibrillation

in the community showed similar gender differences: both in the Copenhagen City Heart Study and in the Framingham Study women with atrial fibrillation had higher relative risks of developing a stroke than men.[21,22] It is possible that the combination of atrial fibrillation and other cardiovascular disorders is more lethal in men than in women. A decreased survival reduces the probability to be detected as demented in a cross-sectional study and could explain the reduced association with dementia in the oldest group.

When studying atrial fibrillation as a correlate of cognition it should be kept in mind that atrial fibrillation is often a consequence of underlying cardiac disease. The leading causes in the elderly are ischaemic heart disease, hypertension and to a lesser extend thyrotoxicosis.[4] In less than 8% of the cases in a community-based study no causes were found.[1] Therefore the association with atrial fibrillation could in fact be due to the underlying disease. Our results show that adjustment for factors related to these diseases, did not weaken the association, and thus plead for an independent effect of atrial fibrillation on cognition. Atrial fibrillation results in heamodynamic disturbances that might be responsible for brain lesions: Ineffective atrial clearance promotes the formation of thrombi. The Framingham Heart Study in 1978 reported a 5 fold increased risk of stroke among patients with chronic non-rheumatic atrial fibrillation.[23] In our study the age and sex adjusted association of stroke history to atrial fibrillation was lower (odds ratio: 1.9, 95%CI: 1.1 - 3.1), though hypertension was often treated and 26% of the atrial fibrillation patients used antithrombotic medication. Two findings in our study indicate that clinical strokes were no major cause of the positive relation of atrial fibrillation with cognitive disorders: Excluding subjects with a history of stroke did not result in reduced associations and also vascular dementia was not particularly associated with atrial fibrillation. However, silent infarctions may underlie the relation between dementia and atrial fibrillation. In previous studies, silent infarctions were noticed in 15 - 26% of atrial fibrillation patients.[2,24] In a community based autopsy series, silent infarctions (13%) were associated with higher age, blood pressure and atrial fibrillation.[25] Silent infarctions tend to be small and located deep in the brain.[24,25] Multiple silent infarctions could very well resemble Alzheimer's disease since the few neurologic symptoms that may be found are nonspecific, especially in the very old, or alternatively, they could accelerate the conversion of subclinical Alzheimer's disease to a conclusive dementia.

Atrial fibrillation not only results in thromboembolism but also in a reduced cardiac output. This reduction is greater at fast ventricular rates and could lead to cerebral underperfusion.[26] This reduced capacity to maintain adequate brain perfusion, could be a second mechanism of brain damage and cognitive decline.[27,28] The association of white matter lesions to low blood pressure and atrial fibrillation[29]

suggests a heamodynamic etiology. White matter lesions were found correlated with reduced cognition[28,30] and are about 3 times more prevalent in Alzheimer's disease patients than in normal controls.[31,32] Subnormal cardiac output could be one of the probably many cerebral affronts that finally result in the common picture of plaques and neurofibrillary tangles.[5]

Since the present study was cross-sectional no conclusions can be drawn regarding causality. We think our results most likely indicate that atrial fibrillation patients have an increased risk of cognitive decline and dementia. Atrial fibrillation was been suggested as a risk factor for vascular dementia.[33,34] Adequate treatment of atrial fibrillation may help prevent multi-infarct dementia[33,35] but could also be beneficial for those predisposed to develop an Alzheimer's disease type dementia.

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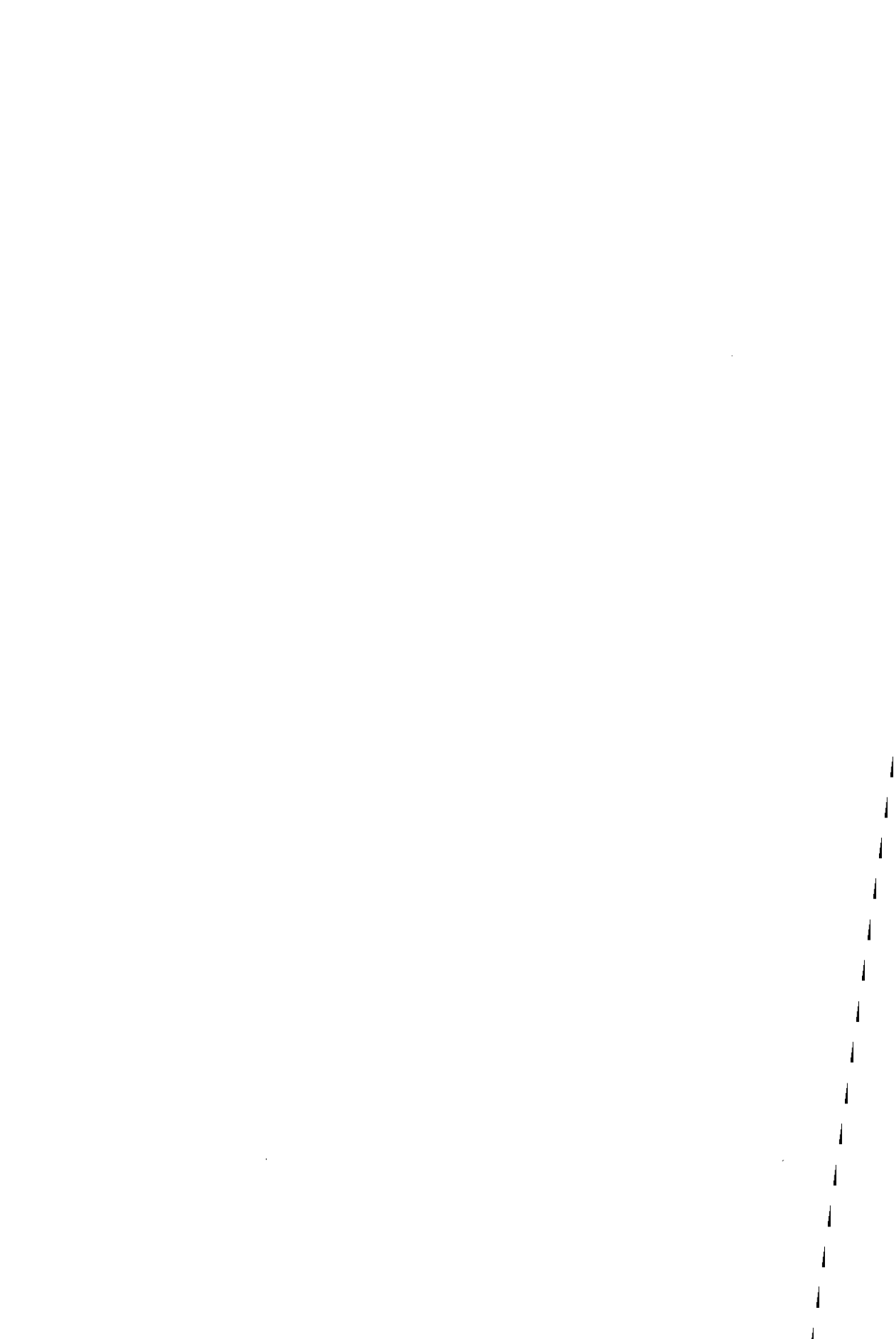
Chapter 4.3

Smoking and the risk of dementia and Alzheimer's disease

Abstract

Background: Previous studies suggested a protective effect of smoking on Alzheimer's disease. These studies were mostly case-control studies based on prevalent cases. Prospective studies on the risk of dementia associated with smoking are scarce and inconclusive.

Methods: We performed a population-based follow-up study of 6870 elderly who were initially free of dementia. Smoking history was obtained at baseline and subjects were classified as never smokers, former smokers, and current smokers. Complete ascertainment of cases with incident dementia was pursued. Using never smokers as the reference, relative risks were calculated with Cox proportional hazards regression, adjusting for age, sex, education, and alcohol intake. We examined modification by age, sex and apolipoprotein E genotype.

Findings: During an average follow-up of 2.1 years, 146 incident cases of dementia were detected, of whom 105 had Alzheimer's disease. Smokers had a more than twofold increased risk of dementia (relative risk 2.2, 95% CI 1.3 to 3.6), and Alzheimer's disease (relative risk 2.3, 95% CI 1.3 to 4.1). Smoking appeared a strong risk factor of Alzheimer's disease in those without the apolipoprotein E4 allele (relative risk 4.6, 95% CI 1.5 to 14.2), whereas no effect was observed in subjects with the E4 allele (relative risk 0.6, 95% CI 0.1 to 4.8).

Interpretation: This prospective study did not confirm results from previous studies, which suggested a general protective effect of smoking on dementia and Alzheimer's disease. Smoking was associated with a doubling of the risk of dementia and Alzheimer's disease. Carriers of the apolipoprotein E4 allele had no increased risk, suggesting interaction between smoking and apolipoprotein E4 genotype in the etiology of Alzheimer's disease.

Introduction

Dementia is a frequent disorder with immense impact on quality of life. Its prevalence increases exponentially with age to at least 30% in people aged 85 years and over.[1] Alzheimer's disease and vascular dementia are the major subtypes of dementia, and

account for about 90% of patients.[1] Smoking has both been related to vascular dementia and Alzheimer's disease. As an important risk factor for cardiovascular diseases,[2,3] smoking is expected to increase the risk of vascular dementia.[4] In contrast, an inverse association has been observed between smoking and Alzheimer's disease.[5] In a study on early onset Alzheimer's disease this possible protective effect of smoking was found to be limited to carriers of the apolipoprotein E4 allele.[6] Although there are several possible explanations for a protective effect of smoking on Alzheimer's disease,[5,6] it is also conceivable that findings in previous studies were the result of bias.[7] Also, smoking strongly increases mortality and smokers who survive till later age may be a more selected group than contemporaneous non-smokers.[8]

We performed a prospective population-based study of the association of cigarette smoking with dementia and Alzheimer's disease, while considering the effects of age, sex and the apolipoprotein E genotype.

Methods

STUDY DESIGN AND POPULATION

The Rotterdam Study is a community-based prospective cohort study among persons aged 55 years and over,[9] for which approval was given by the local Medical Ethics Committee. All 10275 residents of a suburb of Rotterdam over the age of 55 years were eligible and of those 7983 (78%) participated and gave informed consent and permission to obtain medical information from treating physicians. Baseline examinations took place from 1990 to 1993 and comprised a home interview and medical examinations at the study centre or, for institutionalized persons, at their institution. At baseline, 7528 persons (94%) were evaluated for dementia,[1] of whom 474 were diagnosed with dementia and excluded from the present study. Of those without dementia an additional 184 were excluded because of missing data on smoking history. The remaining 6870 subjects were followed-up for an average of 2.1 years (range 1.5-3.4), until the second round of examinations. During this follow-up period 429 participants (6.2%) died. Another 962 subjects (14.0%) were not re-examined because of refusal or severe illness. Follow-up of all subjects who were not examined in person was completed by evaluating their medical files.

DEMENTIA DIAGNOSIS AND MEASUREMENTS

For the assessment of dementia the same protocol was used at baseline and at follow-up, as described in more detail elsewhere.[1,10] Briefly, all subjects were screened with a brief test of cognition (Mini Mental State Examination[11] and the Geriatric Mental State

schedule, organic level[12]). Screen positives underwent further cognitive testing, and an informant was interviewed on daily functioning of the participant. Persons who were suspected of dementia, were examined by a behavioral neurologist, underwent neuropsychological testing, and if possible had a brain scan made by magnetic resonance imaging.[1,10] Of subjects who could not be re-examined in person, information was obtained from general practitioners and the regional institute for outpatient mental health care (RIAGG), which covers the entire study population. In the Netherlands, the RIAGG is responsible for dementia-care-facility indications. Examinations by the RIAGG include (informant) interviews, neurologic and neuropsychologic testing, blood biochemistry and syphilis serology.

The diagnosis of dementia was based on Diagnostic and Statistical Manual of mental disorders (DSM-III-R) criteria,[13] and made by a panel of study physicians, a neurologist and a neuropsychologist, which reviewed all existing information. A diagnosis of Alzheimer's disease and vascular dementia was based on criteria of the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA),[14] and of the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN).[15] Alzheimer patients were further classified into those with and without cerebrovascular disease.[14] For other dementias, DSM-III-R criteria were used.[13] Cerebrovascular disease was recognised by history of stroke or transient ischemic attack, or by evidence for cerebrovascular lesions on brain scans.

At baseline, participants were interviewed about the average amount of cigarettes smoked, the age at first smoking and, in former smokers, the age at quitting. Subjects were also interviewed about attained level of education and alcohol consumption.

Apolipoprotein E genotyping was performed on coded DNA samples without knowledge of the diagnosis. The polymerase chain reaction product was digested with the restriction enzyme *HhaI*, and fragments were separated by electrophoresis.[16]

DATA ANALYSIS

Cigarette smoking at baseline was categorised into never, former and current smoking. The number of pack-year exposure was calculated by the average daily number of cigarettes divided by 20 and multiplied with the number of years smoked. In all analyses never smokers were used as reference category. The relative risk of dementia by smoking was calculated with Cox proportional hazards regression, and presented with a 95% confidence interval (95% CI). Since age is a major determinant of dementia and age-distributions differed by smoking status, age was adjusted for by including linear and squared baseline age in the models. Sex, education and alcohol consumption

were judged to possibly confound the association and therefore added to all models. Education was dichotomized into primary school or less, and more than primary school. Daily alcohol intake, expressed in grammes of pure alcohol per day, was added as continuous variable.

We also investigated whether the smoking related risk of dementia was modified by the apolipoprotein E genotype. The apolipoprotein E genotype was available for 122 of those who developed dementia and a random sample of 1428 non-demented participants. Data were analyzed as a nested case-control study using logistic regression analysis. Corrections for age, sex, education and alcohol intake were made similarly to the above models. Besides, we added duration of follow-up as a continuous variable to the regression models.

Results

Table 1 summarizes characteristics of the study population. More than half of all women were never smokers, whereas more than half of the men had stopped smoking cigarettes ($p < 0.00005$). Smokers were on average younger than never smokers ($p < 0.00005$). Never smokers had more often primary education only ($p < 0.00005$). Average daily alcohol intake was higher among smokers than non-smokers ($p < 0.00005$).

The mean follow-up period was 2.1 years (range 1.5-3.4), and included 14761 person-years of observation. We detected 146 incident cases of dementia, of whom 105 (72%) had Alzheimer's disease and 19 (13%) vascular dementia. Table 2 shows that

TABLE 1. Baseline characteristics of the study population by smoking status.

	Cigarette smoking			Total
	Never	Former	Current	
Total studied (n=6870) (%)	39.1	40.1	20.7	
Women (n=4094) (%)	54.6	27.6	17.8	
Men (n=2776) (%)	16.4	58.6	25.0	
Age (years) (SD)	71.9 (9.9)	68.3 (8.0)	66.4 (7.6)	69.3 (9.0)
Primary education only (%)	31.5	20.2	23.5	25.3
Alcohol intake (g/day) (SD)	4.2 (8.8)	19.9 (14.6)	12.2 (18.8)	8.1 (14.1)

TABLE 2. Relative risk of dementia and dementia subtypes by baseline cigarette smoking.[*]

	Total dementia	Alzheimer's disease			Vascular dementia	Other dementias
		Total	Without CVD	With CVD		
	n=146	n=105	n=88	n=17	n=19	n=22
Never smokers	1.0 (reference)	1.0	1.0	1.0	1.0	1.0
Former smokers	1.4 (0.9 - 2.0)	1.3 (0.8 - 2.1)	1.4 (0.8 - 2.3)	1.2 (0.4 - 4.2)	1.4 (0.5 - 4.4)	1.5 (0.5 - 4.2)
Current smokers	2.2 (1.3 - 3.6)	2.3 (1.3 - 4.1)	2.1 (1.1 - 4.0)	3.9 (1.0 - 15.2)	2.2 (0.6 - 8.4)	2.1 (0.6 - 6.8)

[*] Relative risks with 95% confidence intervals, adjusted for age, sex, alcohol intake, and education.
CVD = Cerebrovascular disease.

smokers were at increased risk of dementia, Alzheimer's disease and vascular dementia. The relative risk of dementia for current smokers at baseline was somewhat higher in persons who died or were not re-examined than in participants who were re-examined in person: 2.7 (95% CI 1.2 to 6.0) versus 2.0 (95% CI 1.0 to 3.7). The mean age at onset of dementia for never smokers was 85.5 years. Both former and current smokers were on average younger at dementia onset than never smokers (respectively 4.1 years, 95% CI 1.7 to 6.6; and 8.6 years, 95% CI 5.2 to 12.1).

The total amount of pack-years smoked was available for 1368 (96%) of current smokers and for 2527 (92%) of former smokers. For current smokers at baseline, the relative risk of dementia was 2.5 (95% CI 1.1 to 5.5) for those who smoked less than 20 pack-years and 3.0 (95% CI 1.6 to 5.4) for those who smoked 20 pack-years or more. For former smokers these figures were 1.5 (95% CI 1.0 to 2.5) and 2.1 (95% CI 1.2 to 3.7), respectively.

The apolipoprotein E4 allele modified the association between smoking and dementia (table 3). In subjects without the apolipoprotein E4 allele, smoking increased the risk of dementia substantially (relative risk 3.2, 95% CI 1.2 to 8.5). However, among carriers of APOE*4, there appeared to be no association between smoking and dementia (relative risk 1.4, 95% CI 0.3 to 5.6). This effect modification was more outspoken in Alzheimer patients with an increased relative risk of 4.6 (95% CI 1.5 to 14.2) for subjects without APOE*4 and a non-significantly decreased relative risk of 0.6 (95% CI 0.1 to 4.8) in those with APOE*4.

TABLE 6. Relative risk of dementia and Alzheimer's disease by baseline cigarette smoking and apolipoprotein E4.[*]

	All dementia		Alzheimer's disease	
	Apolipoprotein E4 absent (n=73)	Apolipoprotein E4 present (n=49)	Apolipoprotein E4 absent (n=57)	Apolipoprotein E4 present (n=33)
Never smokers	1.0 (reference)	1.0	1.0	1.0
Former smokers	1.9 (0.8-4.6)	1.0 (0.3-3.3)	2.4 (0.9-6.5)	0.9 (0.2-3.6)
Current smokers	3.2 (1.2-8.5)	1.4 (0.3-5.6)	4.6 (1.5-14.2)	0.6 (0.1-4.8)

[*] Relative risks estimated as odds ratios with 95% confidence intervals, adjusted for age, sex, alcohol intake, education, and duration of follow-up.

Discussion

In this large prospective population-based study, people who smoked cigarettes were at increased risk of dementia and Alzheimer's disease. An elevated relative risk was particularly present for smokers without the apolipoprotein E4 allele.

The present investigation has several advantages over previous studies on smoking and dementia.[5] Selection bias was avoided because the study was prospective and population-based with a high response rate and complete follow-up. As smoking habits were assessed before onset of dementia, recall bias is not an issue. Survival bias was avoided by including subjects who deceased during follow-up. The somewhat higher relative risk of dementia in subjects who died or could not be re-examined illustrates that survival bias may indeed have diluted the association of smoking and dementia in previous, cross-sectional studies.

A limitation of the present study is the lack of autopsy confirmation of our Alzheimer's disease diagnoses. Another problem is that Alzheimer's disease pathology and cerebrovascular disease are often concurrently present and it may be difficult, both clinically and pathologically, to estimate their contribution to the development of dementia.[15] Although our clinical work-up was extensive and we adhered to commonly accepted and reliable criteria, we can not rule out that we misclassified the dementia subtype in some cases.

Most previous studies on smoking and dementia used prevalent cases and a case-control design.[5] As reviewed by Lee, 4 out of 17 studies reported a significant inverse

relation between smoking and Alzheimer's disease.[5] Some earlier results may differ from the present findings due to differing methods.[7] Of particular concern is the definition of Alzheimer's disease in the earlier studies. Patients with coexisting vascular disease may have been classified as 'mixed' dementia. By excluding these from the Alzheimer category, these studies may have selectively cleared cigarette smokers from the cases, as smokers are more prone to vascular diseases.[2,3] However, we found that smokers had also an increased risk of Alzheimer's disease without cerebrovascular disease. The few studies which estimated the relation with vascular dementia found, as we did, a positive association with smoking.[17,18] A few studies have used incident cases to assess the risk of Alzheimer's disease by smoking, with varying results.[19-22] However, none of these looked at a possible effect-modification by apolipoprotein E genotype.

Smoking is a risk factor for vascular disease, including atherosclerosis and thrombosis.[2,3] Reduction of cerebral perfusion is an acute effect of cigarette smoking, and this may be harmful in elderly with a compromised cerebral circulation.[23] In the pathogenesis of Alzheimer's disease, by far the most common dementing illness, vascular involvement is probably more important than previously thought.[24,25]

Van Duijn et al previously reported that the inverse association between smoking and Alzheimer's disease was limited to carriers of the apolipoprotein E4 allele.[6] In line with that observation we found that the increased risk of dementia and Alzheimer's disease associated with smoking was restricted to persons without this allele. If atherosclerosis is indeed the intermediate factor in the association between smoking and dementia, various explanations could be hypothesized for a modifying effect of apolipoprotein E4. Firstly, the presence of the apolipoprotein E4 allele might alter the association between smoking and atherosclerosis. However, this was not supported by our data (not shown). Secondly, the apolipoprotein E4 allele may inhibit the association between vascular damage and dementia. This is however in sharp contrast to the synergistic effect that we observed between apolipoprotein E4 and atherosclerosis on the risk of dementia.[25] Thirdly, smoking may exert different and opposite effects on the risk of Alzheimer's disease, being generally harmful through for example a vascular mechanism, but also partly beneficial in selected individuals, especially in those who carry an APOE*4 allele. This hypothesis may be supported by the observation that in Alzheimer patients carriers of apolipoprotein E4 have fewer nicotinic receptor binding sites and decreased activity of choline acetyltransferase, as compared to non-carriers of this allele.[26] Smoking could have some effects on the cholinergic system, which might counterbalance the selective impairment associated with apolipoprotein E4, including increasing the density of nicotine receptors or facilitating the release of acetylcholine.[6,20]

In conclusion, we found that for the majority of the population, namely those not carrying the apolipoprotein E4 allele, smoking increased the risk of dementia and Alzheimer's disease. For subjects with the apolipoprotein E4 allele, however, smoking was not associated with an increased risk of dementia.

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Chapter 5

General discussion

This thesis describes studies on the frequency of dementia in the general population and the association of dementia with various determinants or possible risk factors. All chapters are based on studies performed as part of the Rotterdam Study, a prospective cohort study of residents aged 55 or over, living in the suburb Ommoord of Rotterdam, the Netherlands.[1] The studies in this thesis can be grouped into prevalence (chapters 2.1; 3.1; 4.1; 4.2) and incidence studies (chapters 2.2; 2.3; 3.2; 4.3). The prevalence studies used data obtained at the baseline examinations. We assessed which persons had a dementia syndrome and cross-sectionally compared characteristics of dementia patients with those of non-demented participants. For the incidence studies, we monitored participants for the development of dementia after baseline. This enabled us to calculate the risk to become demented, and to study how this risk varied in relation to baseline characteristics of participants.

Major findings

PREVALENCE STUDIES

At baseline 7528 persons were evaluated for the presence of dementia (chapter 2.1). This number included 94% of the Rotterdam Study participants and 73% of the eligible Ommoord population. Dementia was diagnosed in 474 persons. Dementia prevalence increased exponentially with age from 0.4% in the youngest (55-59 years old) to more than 40% in the oldest (95+) age category. One-third of the patients had a mild dementia, another third was severely demented. Alzheimer's disease was diagnosed in 72% of all cases, vascular dementia in 16%. The prevalence of dementia appeared higher in persons with a low level of education as compared to higher educated.

Diabetes mellitus (chapter 3.1), measures of atherosclerosis (chapter 4.1), and atrial fibrillation (chapter 4.2) were significantly associated with dementia and Alzheimer's disease, independently of age and gender. Dementia prevalence increased with increasing severity of diabetes or atherosclerosis. Interestingly, the association of dementia with atherosclerosis seemed modified by the apolipoprotein-E genotype. The ε4 allele encoding for this protein is reportedly associated with greater risk for Alzheimer's disease. Our results suggest an interaction between apolipoprotein-E and atherosclerosis in the etiology of dementia.

INCIDENCE STUDIES

Of 7046 persons who were at risk for dementia, 162 developed a dementia syndrome during an average 2.1 years of follow-up, resulting in an overall incidence rate of almost 11 per 1000 person-years (chapter 2.2). Incidence rates increased strongly with age. Our results suggested that the increase continues up to high age in women but may level off in men around the age of 85. Although age-specific incidence rates were largely similar between men and women, due to considerable differences in longevity, the lifetime risk for dementia may be twice as high in women than men. According to our estimates 33% of 55 year old women will suffer from dementia at the end of their life versus 16% of 55 year old men. Low educated women were at double risk for dementia as compared to higher educated women (chapter 2.3). No difference in dementia risk by education was observed in men.

Persons with diabetes mellitus had an age and sex adjusted risk for dementia which was almost twice as high as the risk of those without diabetes (chapter 3.2). The relative risk (RR) was marginally increased in patients not using antidiabetes medication (RR = 1.3), intermediate in those on oral medication (RR = 2.4), and high in patients treated with insulin (RR = 4.3). Diabetes increased the risk of both vascular dementia and Alzheimer's disease.

Persons who smoked cigarettes were at significantly increased risk of dementia and Alzheimer's disease (chapter 4.3). This finding is important because case-control studies suggested that smoking might protect against Alzheimer's disease. Compared to persons who never smoked, people who smoked had a 2.2 times increased risk of dementia. The relative risk of ex smokers was 1.4.

Methodologic considerations

PREVALENCE STUDIES

Selection bias

The most important threat to the validity of our results in the prevalence studies is probably selective non-inclusion of subjects in the analyses. We were able to evaluate 73% of the eligible population for the presence of dementia, which is a good response proportion. Still, selective non-response may have biased the estimates based on prevalent cases of dementia.

With respect to the dementia prevalence figures (chapter 2.1) one can only speculate about the effect of non-response. In the AMSTEL study non-responders were interviewed by their general practitioner and they performed significantly poorer than

responders on a cognitive test.[2] Non-responders may more often than responders have a dementia syndrome and non-response may thus have caused an underestimate of dementia prevalence figures. In the study on prevalence of dementia the inclusion rate of elderly home residents (80.4%) was slightly higher than of persons living independently (72.4%), which was particularly the case for the oldest age groups. As cognitive problems are probably more common in institutionalised persons than in those living independently,[3] this difference in inclusion rate may have led to an overestimate of the prevalence in the oldest age-groups.

Biased association estimates can occur if non-response was disproportionate with respect to exposure or case status. If for instance an unevenly high proportion of exposed demented not responded to the study, the association between the exposure and dementia would be underestimated.

Associations with prevalent cases can lead to false conclusions because of differential survival.[4,5] Prevalent cases are survivors of previous incidence cohorts and cases with slower disease progression will be over-represented. Factors that are positively associated with prevalent cases may rather reflect determinants of a milder disease type or of better survival. The effect of selective survival has been demonstrated before by Ellenberg who showed that under- or overestimate of the odds ratio by differential survival equals the inverse odds ratio of the survival proportions.[5] If survival is disproportionately lower in the exposed demented group, the odds ratio between the exposure and dementia is underestimated. In our studies on prevalent cases of dementia, differential survival may therefore have influenced the association estimates.

Also selective missing of exposure data may have biased the cross-sectional associations. The reliability of interview data obtained from demented subjects can be questioned, besides, they were often missing. Other measurements (ECG, blood exam, etc.) were also more often missing in cases than in non-demented subjects. Missing data were more common among severely demented subjects than in cases of mild dementia. This may have introduced a bias, comparable to survival bias, if the determinants under investigation influenced the rate of progression of dementia.

Diagnostic accuracy

We used a sensitive screening test to enable detection of very mild (CDR 0.5)[6] cases of dementia, who may be important for etiologic, prognostic, and future therapeutic studies on dementia. Very mild dementia however is not without reason also referred to as dubious dementia.[6] Patients classified in this category may be wrongly diagnosed demented.[7] During follow-up, in 7 of the 74 very mild cases the dementia diagnosis appeared incorrect. Mostly, these persons suffered from depression or another

psychiatric disorder. On the other hand, with diagnostic information accumulating, we later judged that during the prevalence phase we had failed to detect very mild dementia in 15 persons. Reassuringly, the majority of mild cases turned out correctly diagnosed, as shown by progression of the dementia at follow-up. And our earlier prevalence estimates did not change substantially due to the few incorrect diagnoses.

Representativeness

Prevalence figures may be used by health care planners to determine the demand of specific services. For that purpose it is important to know if the prevalence figures can be extrapolated to the entire population. The participating Ommoord population was rather representative for the Dutch population but there were differences. The lowest and highest socioeconomic classes were slightly under-represented though this unlikely influenced the representativeness of the prevalence estimates. The slightly higher than average proportion of very old people in the study cohort is no problem when age-specific figures are used. Relevant for dementia prevalence estimates is the presence of institutionalised elderly in the study cohort. Elderly homes which had somatic and psychogeriatric nursing wards were well represented. However, the cohort did not include a psychogeriatric nursing home and therefore severe dementia may have been slightly under-represented.

INCIDENCE STUDIES

Selection bias

A possible threat to incidence studies is bias due to selective loss to follow-up. In our study this source of bias was largely avoided by obtaining complete follow-up and pursuing complete case-ascertainment. Only 20% of all subjects at risk of dementia could not be re-examined in person and had to be evaluated for incident dementia through their medical files, reports from general practitioners, and, in some cases, informant interviews. The incidence by age curve of re-examined subjects was slightly higher than of subjects who were not examined in person, which may suggest that we missed some mild cases of incident dementia in the latter group.

In the incidence studies some subjects had missing risk factor data. However, as these were obtained at baseline before onset of dementia missing data are a very unlikely source of bias in these studies.

Several studies on the incidence of dementia assessed incidence at follow-up among survivors only. Associations with these cases may be affected by differential survival. Because we included information on deceased subjects, survival bias is unlikely in our studies based on incident cases.

Diagnostic accuracy

As most incident cases of dementia had only mild or very mild disease, the potential for misdiagnosis seems greater in incident than prevalent cases. However, at follow-up most study subjects had repeated measurements of cognition, enabling detection of decline, which probably improved the diagnostic accuracy. Comparison of prevalence figures (chapter 2.1) and incidence rates (chapter 2.2), while accounting for differential mortality risk between demented and non-demented subjects, showed good agreement between both estimates, suggesting a comparable precision of the incidence rates to the prevalence figures. Above the age of 85 years however, for men the incidence rates levelled off, which was not the case for incidence rates in women, nor for the prevalence of dementia in men. As the number of very old men was small, a few undiagnosed cases in this group may already spuriously suggest a levelling off in dementia incidence. However, there is an alternative explanation: Similar prevalence at high age but lower incidence among very old men than women may result from a difference in mortality relative risk. With similar mortality rates for demented men and women, but higher overall mortality for men, the relative risk of dying with dementia can be lower in men than women. A lower mortality relative risk of very old demented men would explain the relatively high prevalence.

PREVALENCE - INCIDENCE BIAS

Education and diabetes mellitus were both studied in relation to prevalent and incident cases of dementia. For education we found a strong cross-sectional association with dementia in contrast with the minor influence of education on the risk of incident dementia (chapters 2.1 and 2.3). Diabetes mellitus was in both cross-sectional and longitudinal analyses significantly related to dementia, but the relative risk was substantially larger for incident dementia (chapters 3.1 and 3.2). This raises the question how these differences can be explained.

The relation between low education and dementia may have been overestimated by the cross-sectional analyses (chapter 2.1). Low educated dementia patients were shown to survive longer than higher educated,[8] and thus have a higher probability to be included in a study on prevalent dementia. Also our data suggested a trend of lower mortality relative risk of dementia patients with less education. The age and sex adjusted mortality relative risks, obtained with proportional hazards regression, were 2.0, 2.4, 2.8, and 3.8 respectively in subjects with primary school or less, lower vocational education, lower secondary education, and intermediate vocational education or higher. Longer survival of lower educated dementia patients is probably due to

earlier recognition of the disorder in low educated. Dementia diagnosis is thus postponed in higher educated, but their risk of dementia may not be reduced, as suggested by our longitudinal study (chapter 2.3). As data on educational level was missing in 35% of prevalent dementia patients versus 3% of non-demented subjects, selective absence of education data of higher educated dementia patients, who may have been in a more progressed dementia stage, could also account for part of the difference between the cross-sectional and longitudinal associations.

Our data suggest that the association between diabetes and dementia was underestimated by the cross-sectional analysis (chapter 3.1). Differential survival may have played a role, even though we did not find a difference between diabetes patients and subjects without diabetes in the relative mortality risk for dementia. In both groups dementia patients had a 2.4 times increased age and sex adjusted risk to die within the follow-up period. But among survivors we noticed a considerable difference between the two groups in the relative proportions of non-response to the follow-up examinations. Among survivors without diabetes the adjusted relative risk of non-response for demented subjects was 2.8 (95% CI 2.0-4.0), whereas among diabetes patients this relative risk was 5.4 (95% CI 2.8-10.3). A similar disproportionate non-response in the prevalence phase of the study could explain the weaker cross-sectional association between diabetes and dementia.

SUBTYPING DEMENTIA

In most previous chapters we discussed the possibility of misdiagnosed dementia subtype. As we found associations between Alzheimer's disease and all vascular determinants that we investigated, it is tempting to speculate that we misdiagnosed vascular dementia as Alzheimer's disease. Contrary to many previous studies we did not categorise patients as mixed dementia when both Alzheimer and vascular symptoms were present, but tried to determine which disorder was the first or main cause of the dementia. Therefore much attention was given to the medical history. Even though there are now well-considered and widely accepted criteria for dementia types,[9,10] subdiagnosing remains difficult, in particular if a brain scan, a reliable informant interview, or neurologic examination are missing. Several previous studies excluded patients with vascular disease from the "pure" Alzheimer's disease category, but this removes the possibility to study vascular determinants of the disease.[11] It is possible that Alzheimer brain pathology predisposes to vascular brain damage and inversely, vasculopathy and vascular insults could initiate or aggravate Alzheimer-type lesions.[12] In the general population and at high age, often a mixture of possible causes of dementia can be identified.[13] Therefore we can not exclude the possibility that we

wrongly subtyped some dementia patients. But we consider it very unlikely that the relation we found between vascular determinants and Alzheimer's disease can be fully explained by misclassification of dementia subtypes. Given diagnostic difficulties, epidemiologic research should not be restricted to Alzheimer's disease, but should include all subtypes of dementia.

Suggestions for future epidemiologic research

The studies in this thesis indicate that vascular factors are important in the etiology of dementia and Alzheimer's disease. New studies on the mechanism how these factors cause dementia are needed. Strokes are well recognised as a vascular cause of dementia. The possible role of (silent) brain infarctions in Alzheimer's disease needs to be disclosed.[12] Brain hypoperfusion resulting from atherosclerosis, damage of capillaries, and abnormal haemodynamics could be a contributing factor to the Alzheimer's disease pathogenesis. To study this hypothesis it would be useful if measures of brain circulation and perfusion, suitable for population research, could be identified. They might prove important predictors of cognitive decline and dementia. Blood pressure disorders could besides inducing strokes also influence brain circulation. Blood pressure drop has been shown to be predictive of incident Alzheimer's disease.[14] Therefore, blood pressure and the use of antihypertensives should further be studied as determinants of dementia, both in relation to and independent of strokes. Major surgery (anaesthesia) may critically reduce brain circulation and should thus be studied as risk factor for incident cognitive decline and dementia. Other potentially important vascular determinants are haemostatic factors and haematocrit. Some indication that haemostasis may influence dementia risk came from our prospective study on atrial fibrillation, in which patients who used anticoagulant drugs had a lower risk of developing dementia than those without this medication.[15] NSAIDs, oestrogens, diet, and alcohol use, could influence the risk on Alzheimer's disease by a direct mechanism, but the possibility that these factors act indirectly, though their effects on vascular determinants, cannot be excluded and requires more attention.[16,17]

Other vascular and non-vascular variables that may be examined as possible determinants of dementia are medical and psychiatric history, the use of specific medication, and dietary intake. Associations between dementia and pulmonary disease could indicate that decreased blood oxygenation may affect the brain, which would provide another clue to the relation of dementia with smoking. In line with above remarks, one could speculate that persons with cardiac failure are at increased risk of dementia. We found a strong and significant association between digoxin use and

dementia, which needs further attention. A longer follow-up of the existing cohort and additional cases with incident dementia will enable the study of less frequent determinants like psychiatric disease history or specific medication use (like NSAIDs and oestrogens).[18] Some determinants assessed by interview, like family history, intake of anti-oxidants, free radicals or other food components,[17] can only validly been studied in relation to incident dementia.

New baseline variables could be collected. The association between dementia and diabetes mellitus and the recent findings on advanced glycation end-products in Alzheimer patients brains (chapter 3.2), prompts to measure these products in study participants. The intriguing relations between specific infectious agents and common disorders, which used to be thought of as non-infectious, such as peptic ulcer and atherosclerosis,[19,20] emphasize the need to keep an open mind to possible involvement of infectious agents in the etiology of Alzheimer's disease.

Mass screening for genetic markers of dementia is now possible. Besides the apolipoprotein-E gene other susceptibility genes are expected to be identified.[21] Most likely, the influence of such genetic risk indicators like the apolipoprotein-E ε4 allele can be modified by environmental factors (chapter 4.1). The study of gene-environment interaction in the etiology of dementia will become of much greater relevance.

There remains uncertainty with respect to subtypes of dementia. It would be particularly useful to have brain magnetic resonance imaging (MRI) scans of all dementia patients in the Rotterdam Study, to enable comparison of clinical observations with brain anatomy. This might help to understand the difference or resemblance between Alzheimer's disease and vascular dementia. Standardised measures of atrophy, white matter lesions and infarctions could be correlated to dementia symptoms, subtypes and severity. Attention should be paid to specific location of these lesions (hippocampal, medial temporal, (sub)cortical). Comparison of patient MRI scans with age matched non-impaired subjects could provide clues to dementia etiology.

A longer follow-up of study participants and dementia patients will permit studies on prognosis, which may both be of interest to treating physicians and serve public health purposes. The development of a risk function for dementia might be worthwhile for future intervention studies.

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Summary

This thesis contains studies on the risk of dementia, which were performed as part of the Rotterdam Study.

The Rotterdam Study is a large epidemiologic study on diseases in the elderly. The study focuses on chronic disabling diseases. It aims to assess the occurrence of these diseases in the general population, and to identify modifiable risk factors. The study is situated in Ommoord, a suburb of Rotterdam, the Netherlands. All 10,275 residents of Ommoord, aged 55 years or over, were invited to participate, and 7983 (78%) agreed to do so. Informed consent and permission to retrieve information from treating physicians was obtained of all participants. The study started in 1990 and is ongoing. With intervals of about 3 years participants are asked to come for examinations to the research centre. This thesis describes results from the first two rounds of examinations; a third round started in March 1997. During the baseline survey, which ended mid 1993, participants were extensively interviewed and examined. The first follow-up examinations took place from September 1993 to the end of 1994. From their entrance in the study onwards participants are being monitored for the development of various diseases. Through linkage of the general practitioner's automated medical record system with the Rotterdam Study data base, occurrence of specific diseases is notified to the researchers. All relevant incident disorders are verified with the participant's medical files.

During the baseline survey of the study, we evaluated 7528 persons for the presence of dementia (chapter 2.1). Participants got a short test of cognition. Those scoring below the threshold were asked to return for more detailed tests. Persons suspected of dementia were referred to a neurologist, and, on indication, underwent neuropsychologic testing, blood examination, and a brain scan. A diagnosis of dementia was made by a diagnostic panel according to international criteria. A total of 474 (6.3%) persons had a dementia syndrome. The proportion of persons with dementia, the prevalence, increased steeply with age from 0.4% of 60 years old persons up to 41% in persons aged 90 years and over. One third of the patients had a mild dementia syndrome whereas another third was severely demented. Alzheimer's disease was the major dementia subtype (72% of the patients), followed by vascular dementia, mostly due to strokes (16%), dementia in patients with Parkinson's disease (6%), and other types of dementia (5%). A higher prevalence of dementia was noticed among people with a low level of education. Persons with primary school only had a 3 times higher dementia prevalence than high educated persons.

Study participants without dementia at baseline were followed for, on average, 2.1 years. Of 7,046 subjects, 162 developed dementia during that period **(chapter 2.2)**. The rate at which new dementia develops (incidence) is expressed in cases per 1000 person-years (pyrs) of follow-up. The overall incidence rate per 1000 pyrs was 10.7 for all types of dementia, 7.7 for Alzheimer's disease, and 1.5 for vascular dementia. The incidence rate, which is a measure of dementia risk, increased from 0.5 per 1000 pyrs at the age of 60 years, to more than 60 per 1000 pyrs in persons of 90 years and over. Up to 85 years of age there was no difference in dementia incidence between men end women. Above that age the incidence of dementia appeared higher in women than men. Women tend to get older than men and are therefore on average during a longer time at risk to develop dementia. From our data, we estimated that during life 33% of all women suffer (to some degree) from dementia, versus 16% of all men.

Our analyses suggested a relatively strong relation between education and dementia prevalence. We therefore examined if lower educated are at increased risk of dementia **(chapter 2.3)**. We found no difference between low and high educated men, but women with primary school only had an increased risk of dementia as compared to higher educated women. The results from our longitudinal study suggest that previous cross-sectional studies may have overestimated the influence of education on dementia risk.

Recent studies showed a correlation between vascular disorders and decreased cognitive function. We examined if vascular factors are also related with dementia and Alzheimer's disease.

. We first studied relationships between diabetes mellitus and dementia **(chapter 3.1)**. Diabetes mellitus was diagnosed by blood glucose measurements or the usage of antidiabetes medication. We found a 1.3 times higher prevalence of dementia in diabetes patients. This figure (which is an odds ratio (OR)) was derived by comparing persons with and without diabetes for the presence of dementia, whilst adjusting for differences between the groups in age and gender distribution by multiple regression analysis. Diabetes mellitus was both associated with vascular dementia and, to a lesser degree, with Alzheimer's disease. The prevalence of dementia was particularly high (OR: 3.2) in diabetes patients who were treated with insulin.

Patients with diabetes and dementia have a relatively high mortality risk. Our cross-sectional study described in chapter 3.1 may therefore have lead to an underestimate of the risk diabetes patients run to develop dementia. In **chapter 3.2** we compared dementia incidence rates of persons with and without diabetes mellitus. In this study differences in survival do not influence the results. The risk of diabetes patients to get dementia appeared almost twice as high as of people without diabetes. The risk increased with severity of diabetes. Patients without antidiabetes medication

were at 1.3 times increased risk, those treated with oral antidiabetes medication at 2.4, and those on insulin at 4.3 times increased risk of dementia. Besides a positive relation with vascular dementia, we found a significant association of diabetes mellitus with Alzheimer's disease, suggesting that diabetes may be involved the etiology of the disease. We estimated that diabetes mellitus may play a contributing role in almost 9% of all dementia occurring in the population.

We cross-sectionally examined the relation between dementia and atherosclerotic disease (chapter 4.1). Peripheral atherosclerosis, plaques in the carotid artery, and thickening of the carotid artery vessel wall, were significantly related with dementia, particularly with vascular dementia, but also with Alzheimer's disease. Dementia prevalence increased with amount of atherosclerosis. Recently, the Apolipoprotein-E gene, which encodes for a protein involved in lipid metabolism, was found strongly related with Alzheimer's disease. People with the ε4 allele of this gene are at increased risk of dementia. The exact mechanism is as yet unknown. We found a stronger association of atherosclerosis to dementia in persons with the ε4 allele as compared to those without, which suggests an interplay between atherosclerosis and the Apolipoprotein-E genotype in the etiology of dementia and Alzheimer's disease.

We then studied the relation of atrial fibrillation to dementia (chapter 4.2). In patients with atrial fibrillation blood circulation is less efficient and a cardiac thrombus might form. From this thrombus fragments could come into circulation and cause strokes. We found a two fold increased prevalence of dementia in persons with atrial fibrillation. The relation existed with vascular dementia, but also with Alzheimer's disease, suggesting that atrial fibrillation may cause dementia through other mechanisms than clinical strokes.

We finally examined the risk of dementia in relation to cigarette smoking (chapter 4.3). Previous studies suggested that smoking may reduce the risk of Alzheimer's disease. Our study on the incidence of dementia offered good conditions to reliably investigate the effect of smoking on dementia. Compared to people who never smoked, smokers had twice the risk to develop dementia and Alzheimer's disease. Those who had quit smoking still were at a 1.4 times increased risk of dementia. Interestingly, we found a clear modifying effect of Apolipoprotein-E genotype. Smoking appeared a strong risk factor for dementia and Alzheimer's disease in those without the ε4 allele, whereas no effect of smoking was observed in subjects with the ε4 allele.

In chapter 5 we discussed the results of the studies presented in this thesis. We conclude that dementia is a frequent disorder, particularly at high age. Alzheimer's disease is the most important subtype, followed by vascular dementia. Various vascular disorders, of which most are common in the population, were significantly associated

with dementia. Without exception they were also related to Alzheimer's disease, suggesting that vascular factors may play a role in the etiology of Alzheimer's disease. Further studies should focus on possible mechanisms of how vascular disorders can lead to dementia in the absence of major strokes. Prevention of cardiovascular diseases may contribute to prevention of dementia and Alzheimer's disease.

Samenvatting

Dit proefschrift beschrijft onderzoek naar het risico op dementie. Het onderzoek werd verricht als onderdeel van het Erasmus Rotterdam Gezondheid en Ouderen (ERGO) onderzoek.

Het ERGO onderzoek is een groot epidemiologisch onderzoek naar chronische ziekten bij ouderen. Doel van het onderzoek is vast te stellen hoe vaak deze ziekten in de bevolking optreden en of ze gerelateerd zijn aan risicofactoren die zich lenen voor preventieve maatregelen. Het onderzoek vindt plaats in Ommoord, een buitenwijk van Rotterdam. Van alle 10.275 Ommoord bewoners ouder dan 54 jaar die uitgenodigd waren aan het onderzoek deel te nemen stemden 7983 (78%) daarmee in. Van alle deelnemers werd toestemming verkregen medische informatie van behandelend artsen op te vragen. Het onderzoek begon in 1990 en duurt nog voort. Ongeveer om de 3 jaar worden deelnemers uitgenodigd voor onderzoek naar het ERGO centrum te komen. Dit proefschrift bevat resultaten van de eerste twee onderzoeksrondes. Een derde ronde is in maart 1997 gestart. Gedurende het baseline onderzoek, dat in juli 1993 eindigde, werden deelnemers uitgebreid geïnterviewd en lichamelijk onderzocht. Een eerste follow-up onderzoek begon in september 1993 en duurde tot eind 1994. Vanaf het begin van de studie zijn deelnemers vervolgd en is het nieuw optreden van bepaalde aandoeningen bijgehouden. Dit vond onder andere plaats door koppeling van gegevensbestanden van geautomatiseerde huisartsen in Ommoord met het ERGO databestand. Relevante nieuw opgetreden aandoeningen bij deelnemers worden regelmatig in medische statussen geverifieerd.

Gedurende het baseline onderzoek zijn 7528 personen onderzocht op dementie (**hoofdstuk 2.1**). Deelnemers ondergingen eerst een korte test van de cognitie. Zij die onder de drempelwaarde scoorden werden verzocht terug te komen voor nauwkeuriger testen van denkvermogen en geheugen. Personen die na dit onderzoek verdacht werden van dementie werden verwezen naar een neuroloog. Op indicatie werd aanvullend neuropsychologisch onderzoek gedaan, werd bloed onderzocht en een hersenscan gemaakt. Een diagnostisch panel stelde de diagnose dementie en bepaalde tevens het subtype volgens internationale criteria. In totaal bleken 474 (6,3%) personen dementie te hebben. De proportie personen met dementie (prevalentie) nam sterk toe met de leeftijd van 0.4% bij personen van 60 jaar oud tot 41% bij 90-plussers. Ongeveer een derde van alle patiënten had een ernstige dementie, een derde leed slechts in geringe mate aan dementie. De ziekte van Alzheimer werd in 72% van de patiënten gediagnosticeerd, vasculaire dementie (meestal het gevolg van beroertes) in 16%, en

dementie bij de ziekte van Parkinson in 6%. We vonden een hogere prevalentie van dementie bij mensen met een laag opleidingsniveau. Bij personen die niet meer dan lager onderwijs hadden genoten werd 3 maal vaker dementie gevonden dan bij hoog opgeleiden.

Deelnemers aan de studie die niet dement waren werden gedurende gemiddeld 2,1 jaren gevolgd. Van deze 7046 personen ontwikkelden 162 een dementie syndroom **(hoofdstuk 2.2)**. De incidentie, ofwel het aantal nieuwe ziektegevallen gedurende een bepaalde tijd, wordt hierna uitgedrukt per 1000 persoonsjaren (incidentiecijfer). Het incidentiecijfer was 10,7 voor dementie; 7,7 voor de ziekte van Alzheimer en 1,5 voor vasculaire dementie. Het incidentiecijfer, wat een maat is voor het risico op dementie, nam toe van 0,5 bij 60-jarigen tot meer dan 60 bij 90-plussers. Tot 85-jarige leeftijd vonden we geen verschil tussen mannen en vrouwen; boven die leeftijd leek de incidentie van dementie bij vrouwen hoger dan bij mannen. Vrouwen worden gemiddeld ouder dan mannen en lopen daardoor gemiddeld ook langer risico om dement te worden. Met behulp van onze gegevens schatten we dat 33% van alle vrouwen gedurende hun laatste levensfase aan (enige mate van) dementie zal lijden, en 16% van alle mannen.

Het dwarsdoorsnede onderzoek beschreven in hoofdstuk 2.1 liet een relatief sterk verband zien tussen opleidingsniveau en de prevalentie van dementie. Daarom onderzochten we of lager opgeleiden inderdaad een verhoogd risico hebben op dementie. We vonden geen verschil tussen laag en hoog opgeleide mannen, maar vrouwen zonder vervolgonderwijs na de lagere school hadden meer kans dementie te ontwikkelen dan hoger opgeleide vrouwen **(hoofdstuk 2.3)**.

Recent onderzoek liet een verband zien tussen verminderde cognitie en aandoeningen van de bloedvaten. Daarom richtten wij ons onderzoek vervolgens op vasculaire risicofactoren voor dementie en de ziekte van Alzheimer.

We onderzochten eerst het verband tussen suikerziekte en dementie. Suikerziekte werd gediagnosticeerd aan de hand van bloedsuiker bepalingen en medicatie tegen suikerziekte. We vonden een 1,3 maal verhoogde dementie prevalentie bij suikerziekte patiënten **(hoofdstuk 3.1)**. Dit getal, een odds ratio (OR), werd verkregen door het voorkomen van dementie te vergelijken bij personen met en zonder suikerziekte. Bias door verschil in leeftijd en geslachtsverdeling tussen beide groepen werd voorkomen door correctie voor deze variabelen met multipele regressie analyse. Suikerziekte bleek geassocieerd met vasculaire dementie, maar ook, zij het in mindere mate, met de ziekte van Alzheimer. Vooral bij suikerziekte patiënten die behandeld werden met insuline was de prevalentie van dementie hoog (OR: 3,2).

Personen met suikerziekte en dementie hebben een relatief grote kans om te overlijden. Het risico dat suikerziekte patiënten lopen dementie te ontwikkelen kan

daardoor onderschat worden in een prevalentie onderzoek zoals beschreven in hoofdstuk 3.1. Daarom hebben we vervolgens het dementie incidentiecijfer vergeleken van de groep zonder en met suikerziekte **(hoofdstuk 3.2)**. Dit onderzoek geeft een beter inzicht in het effect van suikerziekte op het ontstaan van dementie. We vonden dat suikerziekte het risico op dementie bijna verdubbelt. Het risico nam toe met de ernst van de suikerziekte en was 1,3 keer verhoogd bij patiënten zonder medicatie, 2,4 bij patiënten met orale antidiabetes medicatie, en 4,3 bij patiënten behandeld met insuline. Afgezien van een positieve relatie met vasculaire dementie was suikerziekte significant geassocieerd met de ziekte van Alzheimer. Volgens onze schatting zou suikerziekte een rol kunnen spelen bij het ontstaan van 9% van alle dementie in de samenleving.

We onderzochten vervolgens het verband tussen slagaderverkalking en de prevalentie van dementie **(hoofdstuk 4.1)**. Aderverkalking van de beenslagaders, de halsslagaders en verdikking van de halsslagaderwand, waren significant gerelateerd met dementie, vooral met vasculaire dementie, maar ook met de ziekte van Alzheimer. Dementie kwam vaker voor bij toenemende mate van aderverkalking. Recent is gevonden dat het gen voor Apolipoproteïne-E, een eiwit betrokken bij de vetstofwisseling, een sterke relatie vertoont met de ziekte van Alzheimer. Mensen met het ε4 allel van dit gen hebben een verhoogd risico dement te worden. De oorzaak hiervan is vooralsnog onbekend. Wij vonden een sterker verband tussen slagaderverkalking en dementie bij personen met het ε4 allel dan bij personen zonder dat allel. Dit suggereert een wisselwerking tussen slagaderverkalking en het Apolipoproteïne-E genotype in het ontstaan van dementie en de ziekte van Alzheimer.

Vervolgens bestudeerden we de relatie tussen atrium fibrilleren en het voorkomen van dementie **(hoofdstuk 4.2)**. Ten gevolge van atrium fibrilleren is de bloedcirculatie minder efficiënt en kan een stolsel in het hart ontstaan. Fragmenten hiervan kunnen loslaten en een beroerte veroorzaken. Wij vonden dat personen met atrium fibrilleren twee keer zo vaak dement waren dan personen zonder die aandoening. Atrium fibrilleren was zowel gerelateerd met vasculaire dementie als met de ziekte van Alzheimer, hetgeen suggereert dat er andere mechanismen zijn waardoor atrium fibrilleren dementie veroorzaakt dan alleen door klinische beroertes.

Tenslotte onderzochten we de relatie tussen dementie en het roken van sigaretten **(hoofdstuk 4.3)**. Eerder onderzoek suggereerde dat roken beschermt tegen de ziekte van Alzheimer. Ons dementie incidentie onderzoek bood goede condities voor een betrouwbare analyse van het effect van roken op dementie. Vergeleken met mensen die nooit rookten hadden rokers een twee keer zo hoog risico op dementie en de ziekte van Alzheimer. Personen die gestopt waren met roken hadden nog een 1,4 keer verhoogd risico. Een interessante bevinding was dat het Apolipoproteïne-E genotype de relatie tussen roken en dementie leek te beïnvloeden. Roken bleek vooral een duidelijke

risicofactor voor dementie bij personen zonder het ε4 allel. Daarentegen ondervonden dragers van het ε4 allel geen effect van roken op het dementie risico.

In **hoofdstuk 5** zijn de resultaten van het onderzoek, beschreven in dit proefschrift, besproken. We concluderen dat dementie een veel voorkomende aandoening is, vooral op hoge leeftijd. De ziekte van Alzheimer is de meest voorkomende vorm van dementie, gevolgd door vasculaire dementie. Diverse vasculaire aandoeningen waren significant gerelateerd met dementie. Zonder uitzondering was dat ook het geval met de ziekte van Alzheimer, hetgeen suggereert dat vaataandoeningen een rol spelen bij het ontstaan van deze ziekte. Verder onderzoek is nodig om te verklaren hoe deze vasculaire aandoeningen tot dementie kunnen leiden bij afwezigheid van beroertes. Preventie van hart- en vaatziekten zou kunnen bijdragen aan het voorkómen van dementie en de ziekte van Alzheimer.

Dankwoord

Aan het eind van dit proefschrift wil ik graag een aantal mensen noemen die aan het onderzoek hebben bijgedragen.

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About the author

Alewijn Ott was born in Berkhout on Januari 17, 1960. He attended grammar school at the West-Fries Lyceum, Hoorn, and passed V.W.O. exams in 1978. The same year he started medical studies at the Free University of Amsterdam (FUA). In 1985 he cooperated in a study on rehabilitation of harddrug addicts (Stichting De Regenboog, Amsterdam). In 1987 he assisted in a research project on development of the murine immune system (department of Histology, FUA). After obtaining his medical degree he moved to Blantyre, Malawi, in May 1989. There he worked as clinical doctor in peadiatrics and internal medicin at the Queen Elizabeth Central Hospital (QECH). He got employed by DGIS (department of Dutch Ministery of Foreign Affairs) and attended a course in Tropical Medicine and Hygiene at the Royal Tropical Institute, Amsterdam. From March to December 1990 he worked in surgery and obstetrics at the QECH. Thereafter he was appointed as District Health Officer at the District Hospital, Mangochi, Malawi. In September 1992 he started the Master of Science in Epidemiology course at the Erasmus University Rotterdam. After graduating in June 1993, he became research fellow at the department of Epidemiology & Biostatistics of Erasmus University (Head Prof.Dr A. Hofman), studying dementia in the Rotterdam Study. In April 1997, he started specialist training in microbiology at the University Hospital Rotterdam, department of Bacteriology (head: Prof. Dr H.A. Verbrugh).
He is married to Annemieke Boot, paediatrician-in-training. They have a daughter called Susan.

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