Vascular factors in dementia.

Observations in the Rotterdam Study.

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Vascular factors in dementia.
Observations in the Rotterdam Study.

Vasculaire factoren bij dementie.
Observaties uit het Erasmus Rotterdam Gezondheid en Ouderen (ERGO) onderzoek.

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1

INTRODUCTION

1

Introduction

One of the earliest known written reports on senile dementia is attributed to Pythagoras in the 7th century B.C, who described old age as a period of decline and decay of the human body and regression of mental capacities.[1] In 1907, it was Alois Alzheimer who first described the finding of neurofibrillary tangles in a middle-aged woman with a clinically unusual dementia.[2-4] He considered that a rare condition. Nowadays Alzheimer's disease is regarded the most frequent cause of senile dementia, with prevalence ranging from less than 1% for those aged 55-64 years to over 25% for those aged 85 years and over.[5]

Although numerous studies have been done to identify risk factors for dementia and Alzheimer's disease, the aetiology is still largely unknown. Over the last decade, epidemiological evidence has mounted that vascular factors and indicators of vascular disease are associated with the risk of Alzheimer's disease.[6-8] However, most evidence came from cross-sectional studies and studies with a short follow-up.[9-11] Since the underlying neuropathology may start long before dementia can be clinically recognised, we need studies with a longer follow-up to unravel cause and consequence in the association between vascular factors and dementia.

The aim of the research described in this thesis was to further quantify the role of vascular factors in the aetiology of dementia and Alzheimer's disease and to identify possible underlying mechanisms. We studied the association between vascular risk factors and dementia in the Rotterdam Study, a large population-based cohort study on 7,983 persons of 55 years and older living in a suburb of Rotterdam, the Netherlands, that started in 1990. Since the start of the study we tried to identify all new cases of dementia, and distinguish them according to subtype (Alzheimer's disease and vascular dementia) (chapter 2).

It has been suggested that hypertension is an important risk factor for vascular dementia.[12] Also, a recent trial suggested that in elderly people treatment of isolated systolic hypertension reduced the risk of dementia.[13] We explored the possible association between blood pressure level, antihypertensive treatment and dementia, Alzheimer's disease and vascular dementia (chapter 3).

Most vascular risk factors are not stable over time and change in vascular risk factor level may be more important than actual level. Therefore, we studied both the short-term (chapter 3.1) and long-term effects of elevated blood pressure (chapter 3.2). In addition we examined the association between change in blood pressure level and risk of dementia (chapter 3.2).

In an earlier report from the Rotterdam Study we found that the frequencies of dementia, Alzheimer's disease, and vascular dementia increased with the degree of atherosclerosis. These findings were based on prevalent dementia cases. Because cross-sectional studies are prone to selection- and survival bias, we now investigated this association prospectively based on incident cases of dementia (chapter 4.1). We investigated cerebral functional status as assessed with Transcranial Doppler sonography in relation to occurrence of dementia and cognitive dysfunction (chapter 4.2). Light-to-moderate alcohol intake has been reported to be associated with a lower risk of atherosclerosis. Since atherosclerosis has been linked to a higher risk of dementia, we hypothesised that moderate alcohol consumption might be associated with a reduced risk of dementia. We therefore evaluated the relation between alcohol intake and risk of dementia and whether this association was dependent on specific alcoholic beverages (chapter 4.3).

Current knowledge on the prognosis of dementia and Alzheimer's disease is limited. To evaluate the effect of interventions on the risk of institutionalisation and mortality among patients with Alzheimer in different stages of the disease, it is important to have detailed information on the natural progression of Alzheimer's disease.We developed a prognostic risk function to predict rate of cognitive decline, institutionalisation, and death in Alzheimer's disease based on characteristics of Alzheimer patients derived from the Rotterdam Study (chapter 5).

In chapter 6, the main results of the studies described in this thesis are reviewed and discussed in the light of other studies and current insights in the association between vascular factors and Alzheimer's disease, and suggestions for future research are given.

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2

FREQUENCY OF DEMENTIA

2.1

Incidence of dementia

Abstract

Objective: *To estimate gender specific incidence rates of dementia and its subtypes in the general population*
Design: *Population-based prospective cohort study*
Setting: *Ommoord, a suburb of Rotterdam, the Netherlands*
Subjects: *7,046 non-demented participants of the Rotterdam study aged 55 years and older.*
Main outcome measurement: *Incident dementia and subtypes of dementia.*
Results: *In 40,441 person-years of follow-up (mean 5.7 years) we identified 395 new cases of dementia, yielding an overall incidence of 9.8 per 1,000 person-years, in those 55 years and over. Incidence ranged from 0.4 per 1,000 person-years at age 55-59 years to 74.1 per 1,000 person-years at age 95 years and older. Alzheimer's disease was the most frequent subtype of dementia (293 cases; 7.2 per 1,000 person-years). Vascular dementia was diagnosed in 57 participants (1.5 per 1,000 person-years). Overall, dementia incidence was similar for men and women (rate ratio women versus men: 1.00, 95% CI: 0.80-1.24). However, after 90 years of age dementia incidence declined in men but not in women (rate ratio 2.61, 95% CI: 1.04-6.56), in particular for Alzheimer's disease (rate ratio 5.79, 95% CI: 1.40-23.90). The overall incidence of vascular dementia was lower in women than in men (rate ratio 0.57, 95% CI: 0.34-0.97).*
Conclusions: *This large population-based study suggests no gender differences in the incidence of dementia up to high age. After 90 years of age the incidence of Alzheimer's disease is higher for women than for men. The incidence of vascular dementia is higher for men than for women in all age groups.*

Introduction

Dementia is one of the major health problems in our ageing societies. Therefore, reliable estimates of the frequency of dementia are important. Incidence studies have reported inconsistent results on the occurrence of dementia by gender. Some studies suggested a higher incidence rate in women than in men, especially after age 85,[1-6] whereas other studies showed no gender difference.[7-11] As to Alzheimer's disease, dementia's major subtype, most studies reported higher incidence rates for women than for men.[2, 3, 8, 12] The discrepancies between the various studies may result from small sample size, particularly in the highest age range, use of different diagnostic criteria and differences in completeness of follow-up.

We previously reported incidence data from the Rotterdam Study, a large population-based study conducted in the Netherlands, after a relatively short follow-up of on average two years. We now have more than 40,000 person years of follow-up and were able to investigate possible gender differences in incidence of dementia and its subtypes.

Methods

Study design

The Rotterdam Study is a population-based prospective cohort study among 7,983 persons aged 55 years and older.[13] Baseline examinations took place between 1990 and 1993. Participants were interviewed at their homes and thereafter, during two sessions, examined at the research centre. Follow-up examinations took place in 1993-1994 (first follow-up) and in 1997-1999 (second follow-up).

Study population

The study was conducted in Ommoord, a suburb of the city of Rotterdam, the Netherlands. At baseline, all inhabitants aged 55 years and older, including those living in institutions, were invited to participate. Of 10,275 eligible persons, 7,983 agreed to take part in the study, and 7,528 (94.3%) were screened and examined for dementia.[14] Of these, 474 persons were diagnosed with dementia.

During follow-up, another 8 persons were considered demented at baseline in retrospect. This resulted in a cohort of 7,046 participants at risk for dementia.

Diagnosis of dementia

For dementia screening and diagnosis during baseline and follow-up we adhered to a three-step protocol.[15] Briefly, all participants were screened with a short test of cognition (Mini Mental State Examination[16] and the Geriatric Mental State schedule, organic level[17]). Screen positives (persons scoring below 26 on the MMSE or more than 0 on the GMS) underwent further cognitive testing with the Cambridge examination for mental disorders of the elderly (CAMDEX),[18] which included an informant interview. Persons suspected of dementia were examined by a neurologist, underwent neuropsychological testing, and if possible a brain scan was made by magnetic resonance imaging. Of the participants suspected of dementia and whose dementia work-up was not complete, medical files were reviewed for additional diagnostic information.

In addition to active dementia screening, we were alerted by the participants' general practitioners of interval cases of dementia or cognitive disturbances at a regular basis.[15] Study physicians evaluated all reports of incident memory problems or dementia. For non-respondents to the follow-up examination, informants and medical files were consulted in order to make a diagnosis of dementia. In addition, the Regional Institute for Outpatient Mental Health Care (RIAGG), which covers the entire study population, was consulted at a regular basis and all reports were checked. This psychiatric service can be consulted both directly and by referral for social and psychiatric problems. A geriatric section is responsible for nursing home or other dementia care facility indications. Surveillance of the population through the general practitioner and RIAGG reports continued up to December 31, 1999. Of both the in-person-screened individuals and those monitored through general practitioners and RIAGG, the study diagnosis of dementia was made according to established criteria (NINCDS-ADRDA, NINDS-AIREN, DSM-III-R) by a panel that reviewed all existing information.[15, 19-21]

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 at the second follow-up examination, at the date of invitation for second follow-up examination (for non-responders), at the age of onset of dementia or at death. The age of dementia onset was assumed to be the midpoint between the last known date when a person was not demented and the first date of dementia diagnosis (either by in-person-screening or based on information from medical files). Incidence rates were estimated by age, gender, by dementia subtype and by response category (first and second follow-up). We calculated Poisson standard errors and 95 percent confidence intervals. The difference in incidence between men and women was expressed as a rate ratio, which was calculated with proportional hazards regression analysis. To adjust most efficiently for age, we used age as the time scale in the proportional hazards models.[22] Entry time was defined as age at study entry. Additionally, we performed a stratified analysis in age categories.

Results

In Table 1 characteristics of the study population are summarised. Of the total cohort (n = 7,046) at risk of developing dementia, 1,403 persons (19.9%) died during follow-up. For the second follow-up examination 48 persons who had moved to a nursing home far from the research centre were not invited and for those information was obtained through general practitioners. Follow up was virtually complete (99.6%) until December 31, 1999 (complete information during the first follow-up period, 26 persons lost to follow-up during second follow-up period).

Table 1. Characteristics of participants in the study on dementia incidence, the Rotterdam Study.

	First follow-up (1993-1994)			Second follow-up (1997-1999)		
	No.	%	% women	No.	%	% women
Screened in person	5,571	79.1	58.8	4,133	62.9	58.4
Refusal of screening-test†	999	14.2	68.9	1,484	22.6	68.3
Died before follow-up examination	476	6.8	54.6	927	14.1	56.0
Lost to follow-up	-	-	-	26	0.4	57.7
Total cohort	7,046	100	59.9	6,570*	100	60.3

*Population alive after first follow-up (7,046 - 476)

† Including 48 persons who were not invited because they moved to a nursing home far from the research centre

After 40,441 person-years of follow-up (mean follow-up period 5.7 years), 395 new cases of dementia were identified, 215 in those examined in person and 180 by general practitioner and mental health services monitoring. Alzheimer's disease was diagnosed in 293 (74 %); 216 of those had probable Alzheimer's disease and 77 had possible Alzheimer's disease, of whom there were 30 with co-existing cerebrovascular disease. Vascular dementia was diagnosed in 57 (14 %) and other dementias in 37 (9 %). A subtype of dementia could not be determined in 8 persons (2 %). The proportion of subtypes differed between men and women: 64 % of male cases were diagnosed with Alzheimer's disease and 21 % with vascular dementia; for female cases these proportions were 79 and 12, respectively.

Table 2 and Figure 1a show the age- and gender-specific incidence rates of dementia. The incidence rate of dementia steeply increased with age from 0.4 per 1,000 person-years at age 55-59 years to 74.1 per 1,000 person-years at age 95 and older. The age-specific incidence rates were similar for men and women up to 90 years of age. However, after this age the incidence rates for women continued to rise, whereas for men the incidence rates dropped.

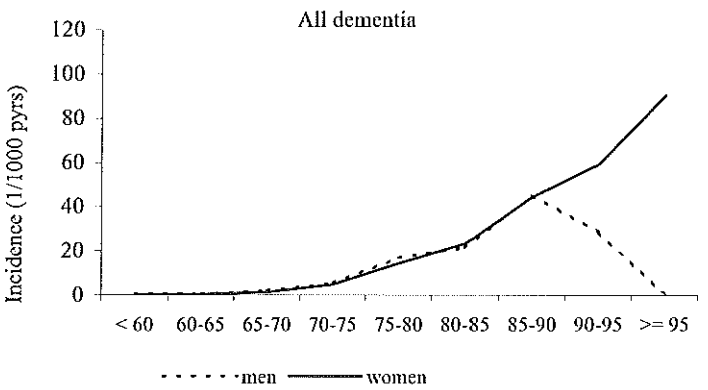

Figure 1a. Age- and gender-specific incidence of all dementia in the Rotterdam Study, 1990-1999.

Comparison of the incidence between the in-person screened and those whose information on dementia status came from informants and medical files revealed

Table 2. Age- and gender specific number of person-years at risk, dementia cases, and incidence rates (per 1,000 person-years, with 95% confidence interval (CI), in a Dutch general population, the Rotterdam Study, 1990-1999.

	Women				Men				Total population			
Age category (years)	Person years at risk	No. of dementia cases	Incidence rate	95% CI	Person years at risk	No. of dementia cases	Incidence rate	95% CI	Person years at risk	No. of dementia cases	Incidence rate	95% CI
55-59	1,578	0	0.0	0.0-5.1	1,122	1	0.9	0.1-6.3	2,701	1	0.4	0.1-2.6
60-64	4,493	2	0.5	0.1-1.8	3,324	2	0.6	0.2-2.4	7,818	4	0.5	0.2-1.4
65-69	4,855	7	1.4	0.7-3.0	3,875	8	2.1	1.0-4.1	8,731	15	1.7	1.0-2.9
70-74	4,568	22	4.8	3.2-7.3	3,348	18	5.4	3.4-8.5	7,916	40	5.1	3.7-6.9
75-79	3,832	55	14.4	11.0-18.7	2,361	40	16.9	12.4-23.1	6,192	95	15.3	12.6-18.8
80-84	2,695	63	23.4	18.3-30.0	1,303	28	21.4	14.8-31.1	3,998	91	22.8	18.5-28.0
85-89	1,600	71	44.4	35.2-56.0	510	23	45.1	30.0-67.9	2,110	94	44.5	36.4-54.5
90-94	626	37	59.1	42.8-81.5	175	5	28.7	11.9-68.8	801	42	52.4	38.8-71.0
≥ 95	144	13	90.2	52.4-155.4	31	0	0.0	0.0-255.9	175	13	74.1	43.1-127.7
Total	24,392	270	11.1	8.9-10.8	16,049	125	7.8	6.5-9.3	40,441	395	9.8	8.9-10.8

that there were no major differences in incidence up to age 85 years. Above age 85 more demented persons were identified by personal examination than by evaluation of medical files (rate ratio 1.9, 95% CI: 1.2-3.0). The difference in incidence between men and women at very high age could not be explained by differences in case finding.

In Table 3 and Figure 1b, and 1c the age- and gender-specific incidence rates of Alzheimer's disease and vascular dementia are presented. The incidence of both Alzheimer's disease and vascular dementia increased with age, except for the oldest age groups in men where the incidence of Alzheimer's disease declined.

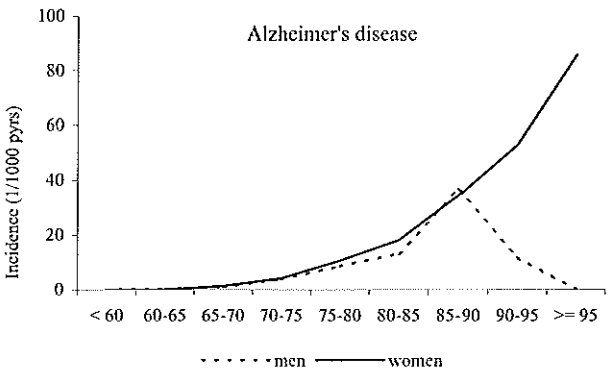

Figure 1b. Age- and gender- specific incidence of Alzheimer's disease in the Rotterdam Study, 1990-1999

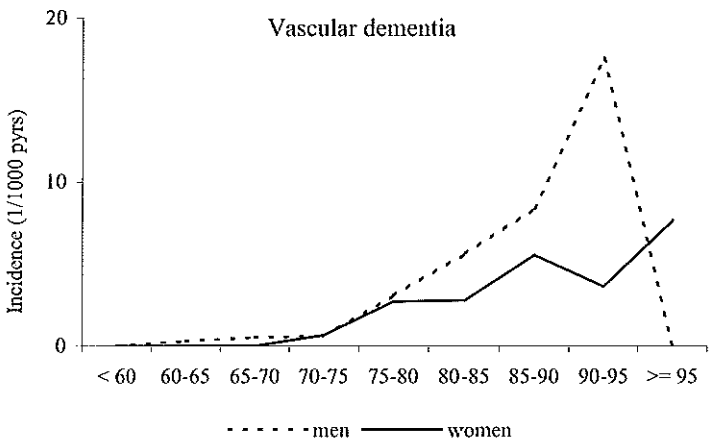

Figure 1c. Age- and gender- specific incidence of vascular dementia in the Rotterdam Study, 1990-1999.

Table 3. Age- and gender specific incidence rates of Alzheimer's disease and vascular dementia.

	Women				Men				Total population			
	Alzheimer's disease		Vascular Dementia		Alzheimer's disease		Vascular Dementia		Alzheimer's disease		Vascular Dementia	
Age category (years)	Incidence rate	95% CI	Incidence rate	95% CI	Incidence rate	95% CI	Incidence rate	95% CI	Incidence rate	95% CI	Incidence rate	95 % CI
55-59	0	0.0-5.1	0	0.0-5.1	0	0.0-7.1	0	0.0-7.1	0	0.0-7.1	0	0.0-7.1
60-64	0	0.0-1.8	0	0.0-1.8	0.3	0.0-2.1	0.3	0.0-2.1	0.1	0.0-0.9	0.1	0.0-0.9
65-69	1.4	0.7-3.0	0	0.0-0.0	1.0	0.4-2.8	0.5	0.1-2.1	1.3	0.7-2.3	0.2	0.1-0.9
70-74	4.2	2.7-6.6	0.7	0.2-2.1	3.9	2.3-6.8	0.6	0.2-2.4	4.1	2.9-5.8	0.6	0.3-1.6
75-79	10.6	7.8-14.5	2.7	1.5-5.1	8.6	5.8-12.7	3.1	1.5-6.5	9.7	7.6-12.4	2.9	1.8-4.6
80-84	18.1	13.7-24.1	2.8	1.3-5.9	13.2	8.2-21.3	5.6	2.7-11.9	16.5	13.0-21.1	3.7	2.2-6.3
85-89	34.4	26.3-44.9	5.5	2.8-11.1	36.3	22.9-57.7	8.4	3.1-22.3	34.8	27.7-43.9	6.2	3.6-11.0
90-94	53.0	37.7-74.5	3.6	0.9-14.6	11.8	3.0-47.3	17.5	5.7-54.3	44.2	31.7-61.6	7.0	2.9-16.7
≥ 95	85.7	48.6-150.8	7.6	1.1-54.1	0	0.0-255.9	0	0.0-255.9	70.0	39.8-123.3	6.2	0.9-43.7
Total	8.8	7.7-10.1	1.3	0.9-1.9	4.8	3.9-6.0	1.7	1.1-2.4	7.2	6.4-8.1	1.5	1.1-1.9

Table 4 shows the age-adjusted rate ratio's of dementia, Alzheimer's disease and vascular dementia for women compared to men. Overall, there was no difference in dementia incidence between men and women (rate ratio 1.00, 95% CI: 0.80-1.24). Also, the overall incidence of Alzheimer's disease did not significantly differ (rate ratio: 1.20, 95% CI: 0.93-1.56). However, after 90 years of age, women were at higher risk to develop dementia and Alzheimer's disease (rate ratio dementia: 2.61, 95% CI: 1.04-6.56: rate ratio Alzheimer's disease: 5.79, 95% CI: 1.40-23.90). The incidence of vascular dementia was significantly lower for women compared to men at all ages (overall rate ratio: 0.57, 95% CI: 0.34-0.97).

Table 4. Age-adjusted rate ratio of dementia, Alzheimer's disease and vascular dementia for women compared to men.

Age category (years)	All dementia types	Alzheimer's disease	Vascular Dementia
55-74	0.83 (0.50–1.38)	1.12 (0.62–2.05)	0.46 (0.11–1.91)
75-79	0.89 (0.59–1.33)	1.03 (0.62–1.69)	0.92 (0.35–2.41)
80-84	1.06 (0.68–1.66)	1.33 (0.76–2.31)	0.51 (0.18–1.47)
85-89	1.02 (0.64–1.63)	0.98 (0.57–1.67)	0.69 (0.21–2.29)
≥ 90	2.61 (1.04–6.56)	5.79 (1.40–23.90)	0.27 (0.05–1.38)
Total	1.00 (0.80–1.24)	1.20 (0.93–1.56)	0.57 (0.34–0.97)

Discussion

We assessed the incidence of dementia in a large population based ongoing cohort study and examined subtypes of dementia and differences between men and women. Up to age 90 we found no gender difference in dementia incidence, whereas above that age men seemed to be at lower risk than women. The overall incidence of Alzheimer's disease was similar in men and women. Over the age of 90 years the incidence of Alzheimer's disease was higher for women than for men. The risk of vascular dementia was higher for men than for women across all age groups.

A strength of our study is that we followed a large cohort of elderly over a period of nearly ten years. We examined all participants extensively for dementia and other outcome measurements. Through the extensive monitoring

system we obtained a virtually complete follow-up of the cohort. Age-specific incidence rates were up to high age quite similar for both the in-person-screened persons and for those whose medical files were studied. The virtually complete follow-up and a large number of person years of follow-up enabled us to obtain precise and reliable incidence rates of dementia up to high age.

In recent years a number of population-based studies on the incidence of dementia have been reported.[2, 5, 6, 8, 10] They show discrepant findings on distribution of gender and subtype. Most studies comprised no more than 2,000 participants that were followed for 2-4 years and as a result the estimates were often imprecise. Moreover, in several studies the follow-up was not complete due to refusal. Recently, incidence data on a large Canadian cohort have been published.[23, 24] The Canadian Study of Health and Aging is in size comparable to the Rotterdam Study. To estimate incidence rates of dementia in deceased persons the Canadian study used information from informants and death certificates, but in addition used a 13-item predictive algorithm based on baseline data and informant information that had been developed based on 71 subjects. A diagnosis of Alzheimer's disease and vascular dementia was limited to survivors. Not surprisingly, the resulting age-specific incidence rates of dementia were higher than in Rotterdam and other European incidence studies.[2, 8] Although the incidence rates for women at old age were higher than for men, the difference was less pronounced in the Canadian Study than in the Rotterdam Study.

Two pooled analyses have been done to include more person years of follow-up in the highest age categories. The EURODEM study[1] included 28,768 person years of follow-up and a more extensive collaborative study in Europe included 42,996 person years of follow-up.[25] Both studies found that the incidence of dementia and Alzheimer's disease continued to increase with age up to age 85-90, after which rates increased in women but not in men.

Up to high age total dementia incidence was comparable between men and women. However, after 90 years of age the incidence of Alzheimer's disease was higher for women, whereas the incidence of vascular dementia was higher for men. Since it has been suggested that cerebrovascular pathology is less often symptomatic in women,[26] we may hypothesise that in women vascular dementia is misdiagnosed as Alzheimer's disease. Another possibility is that this difference in subtype distribution is due to a gender difference in stroke

incidence and prognosis.[27] The divergence of dementia incidence between men and women at high age may be partly due to survival differences between men and women. Possibly, selective survival of men at lower risk for dementia may have occurred.

In conclusion, this large population-based study suggests that the incidence of dementia is similar for men and women up to high age. However, at very old age the risk of Alzheimer's disease may be higher for women than for men and the risk of vascular dementia may be higher for men.

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3

BLOOD PRESSURE AND DEMENTIA

3.1

Blood pressure and risk of dementia. Results from the Rotterdam Study and the Gothenburg H-70 Study

Abstract

The association between blood pressure and dementia is debated. Results from population-based studies on blood pressure and dementia are inconclusive, and most are performed in subjects younger than 80 years of age. We examined the relation between blood pressure and dementia and the possible effect modification of this relation by age in a pooled dataset based on two prospective population-based studies. Subjects came from the Rotterdam study (n = 6,668), a longitudinal population-based study among subjects aged 55 years and over, and from the Gothenburg H-70 Study (n = 317), a study on subjects age 85 years at baseline. Screening and diagnostic procedures for assessment of dementia were similar at baseline and follow-up and comparable between studies. We estimated relative risks of dementia using Cox' proportional hazards regression analysis, adjusted for age, gender and study location.

Average follow-up was 2.1 years. During this period 196 subjects developed dementia. The risk of dementia decreased with increasing blood pressure level (per 10 mm Hg systolic blood pressure: RR: 0.93, 95% CI: 0.88-0.99; per 10 mm Hg diastolic blood pressure: RR 0.89, 95% CI: 0.79-1.00). This association was confined to subjects who used antihypertensive medication. Persons who were demented at baseline had a stronger blood pressure decline during follow-up than those who were non-demented.

This study suggests an inverse association between blood pressure and dementia risk in elderly persons on antihypertensive medication. Possibly, they may need higher blood pressure levels to maintain adequate cerebral perfusion. Alternatively, lower blood pressure may be secondary to brain lesions in preclinical stages of dementia.

Introduction

There is increasing evidence that vascular risk factors are associated with different forms of dementia.[1, 2] Hypertension is one of the most important risk factors for stroke and coronary heart disease, and has been reported to be a risk factor for both Alzheimer's disease and vascular dementia.[1] This relation seemed supported by a recent trial where antihypertensive treatment in elderly people with isolated systolic hypertension was associated with a lower incidence of dementia.[3] However, results from cross-sectional observational studies are inconclusive. Both high[4, 5] and low[2, 6-8] blood pressure have been associated with cognitive impairment, dementia and subtypes of dementia. Others found no association.[9, 10] Longitudinal studies suggested that increased systolic blood pressure predicts reduced cognitive function or dementia 15-25 years later.[11-13] However, when the blood pressure was measured at the time of cognitive testing at high age, lower blood pressure was associated with lower cognitive performance or dementia.[7, 8, 12] It is not clear whether low blood pressure is a cause or a consequence of dementing disorders.[7, 8] Furthermore, relatively few data are available on the relationship between blood pressure and incident dementia, especially in the very old. Most population-based studies do not have enough subjects in the highest age categories to show any significant results. To overcome these power problems, we combined the data of two comparable population based studies in order to investigate the relation between blood pressure and risk of dementia in different age categories.

Materials and methods

Study population

Data were pooled from two population-based studies: the Rotterdam Study and the H-70 Study from Gothenburg. The Medical Ethics Committee approved both studies and informed consent was obtained of all participants. The Rotterdam Study is a population-based prospective cohort study among persons aged 55 years and older, including those living in institutions.[14] Baseline examinations took place between 1990 and 1993. During this period, 7,528 (94.3 % of total cohort) underwent extensive screening for dementia.[15] Dementia diagnosis was made in 482 persons, of whom 339 had blood pressure measurements at baseline. Of those without dementia, 378 (5.4 %) subjects were excluded

because of missing data on blood pressure measurements. The remaining 6,668 were followed for an average of 2.1 years, until the second round of examinations in 1993 and 1994. At these examinations, 5,468 (82.0 %) participants were screened for dementia. Information was obtained from close informants and general practitioners on those subjects who died before follow-up (5.4%) or were not re-examined in person (12.6%).[16]

The H-70 study is a longitudinal population study of 70-year-olds in Gothenburg, which started in 1971. In 1986-87, all 85-year olds born between July 1st, 1901 and June 30th, 1902, registered for census purposes in Gothenburg, Sweden, were invited to take part in a health survey. Both people living in the community and those in institutions were included. A neuropsychiatric examination was performed on a systematic subsample (n = 494), which has been described in detail elsewhere.[17] Diagnosis of dementia was made in 147 subjects, of whom 140 had blood pressure recordings at baseline. The remaining 347 subjects were followed till the second examination three years later when the subjects were 88 years old (mean follow-up 2.2 years). Of those, 188 (54.2%) subjects were re-examined by a psychiatrist, 73 (21.0%) had died and 86 (24.8%) refused examinations. Information on 132 of those who deceased or refused was obtained from medical records or other sources. Sufficient information was thus obtained on 320 subjects.[18] Three individuals had no blood pressure recordings at age 85, leaving 317 non-demented subjects at risk for dementia to be included in this study.

In both studies subjects who had repeated blood pressure examinations were younger than subjects who had their blood pressure only measured at baseline. However, baseline blood pressure levels and gender distribution were similar.

Diagnosis of dementia

In the Rotterdam Study dementia screening and diagnosis during baseline and follow-up followed a three-step protocol, as described in detail elsewhere.[15] Dementia diagnosis was made according to internationally accepted criteria[19-21] by a panel that reviewed all existing information.

The neuropsychiatric examinations in the H-70 study were performed by trained psychiatrists, in the subject's home or at institutions.[17] Identical procedures for the diagnosis of dementia were used at ages 85 and 88.[18] These

were based on the neuropsychiatric examination and the close informant interview, using internationally accepted criteria.[19, 21, 22]

Blood pressure and other baseline measurements

In the Rotterdam Study blood pressure was measured in sitting position at the right upper arm with a random-zero sphygmomanometer. The average of two measurements, separated by a count of the pulse rate, was used in the analysis. During an interview at home a trained research assistant registered current drug consumption. Of institutionalised participants, medication was reported by the medical staff. In the H-70 study blood pressure was measured in sitting position at the right upper arm after 5 minutes rest using a mercury manometer. Systolic and diastolic blood pressure were registered to the nearest 5 mm Hg. During a house call, a registered nurse registered prescribed and actually taken medication.[23] The following variables were measured and tested as possible confounders or intermediates: baseline Mini-Mental State Examination (MMSE), diabetes,[24] education dichotomised in less than 7 years of education or more, and smoking at baseline categorised as never, past and current smoking. In both studies a history of stroke was assessed at baseline and verified with medical records by a neurologist and a history of myocardial infarction was assessed by direct questioning and on ECG.

Data analysis

Differences in baseline characteristics between the two study populations above age 85 years were tested with analysis of covariance, adjusting for age and gender. The relative risk of dementia by increase in systolic or diastolic blood pressure was calculated with Cox' proportional hazards regression and presented with a 95% confidence interval (95% CI), controlling for age, gender and study population. This was done using blood pressure both as a continuous (per 10 mm Hg) and as a categorical variable in the proportional hazards regression model. 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 (use of antihypertensive medication, diabetes, smoking, education, history of myocardial infarction and history of stroke, baseline MMSE) added to the models. We examined the role

of antihypertensive medication use on blood pressure and dementia by performing a stratified analysis.

Heterogeneity between the Rotterdam Study and the Gothenburg H-70 study with regard to the relation between blood pressure and dementia was tested using an interaction term for blood pressure and place of residence. Because this interaction term was non-significant ($p = 0.54$), we were able to pool the data on subjects aged 85 and over from the two studies, adding an indicator for place of residence. All analyses were also performed for major subtypes of dementia.

Finally, we examined blood pressure change during follow-up. We therefore compared this change between dementia patients (both prevalent and incident) and non-demented participants at both occasions with linear regression analyses adjusting for age and gender.

Table 1. Baseline characteristics of the study population, means (SD) or percentages (%).

	55-74 years (N = 4987)	75-84 years (N = 1336)	≥ 85 years (N = 662)	Total population (N = 6985)
Baseline age (yrs)	64.9 (5.5)	79.2 (2.8)	87.1 (2.8)	69.7 (9.3)
Gender (%women)	56.9	64.6	74.0	60.0
Antihypertensive drugs (%)	27.5	44.4	49.9	32.9
Baseline SBP (mm Hg)	136.8 (21.4)	146.3 (22.8)	155.1 (24.9)	140.3 (22.8)
Baseline DBP (mm Hg)	74.2 (11.2)	72.3 (12.2)	75.3 (13.1)	74.0 (11.6)

SBP = systolic blood pressure, DBP = diastolic blood pressure

Results

Baseline characteristics are given in Table 1. During a follow-up period of 2.1 years 134 subjects of the Rotterdam Study (RS) and 62 subjects of the Gothenburg H-70 study (GS) developed dementia. Baseline and follow-up blood pressure above age 85 were higher in Gothenburg compared to Rotterdam ($p < 0.001$)(data not shown). Use of antihypertensive medication was similar (RS: 52.6%, GS: 41.1%, $p = 0.25$). At old age, the incidence of Alzheimer's disease was similar in both studies (RS: 35.4/1,000 pyrs, GS: 40.2/1,000 pyrs). However, the incidence of vascular dementia was higher in Gothenburg

(36.1/1,000 pyrs) than in Rotterdam (9.8/1,000 pyrs). Follow-up blood pressure measurements were available for 5,583 (83.7%) subjects without dementia at baseline and for 153 (32.0%) subjects with dementia at baseline.

Adjusted relative risks of dementia per 10 mm Hg increase in baseline blood pressure are given in Table 2. Overall, lower systolic and diastolic blood pressure at baseline were associated with a higher risk of dementia at follow-up. The relative risk tended to decrease with increasing age. Stratified analyses on antihypertensive drug use revealed that this association was only found among antihypertensive drug users. The risk of dementia was not associated with blood pressure levels in subjects who did not use antihypertensive medications at baseline (Figure 1).

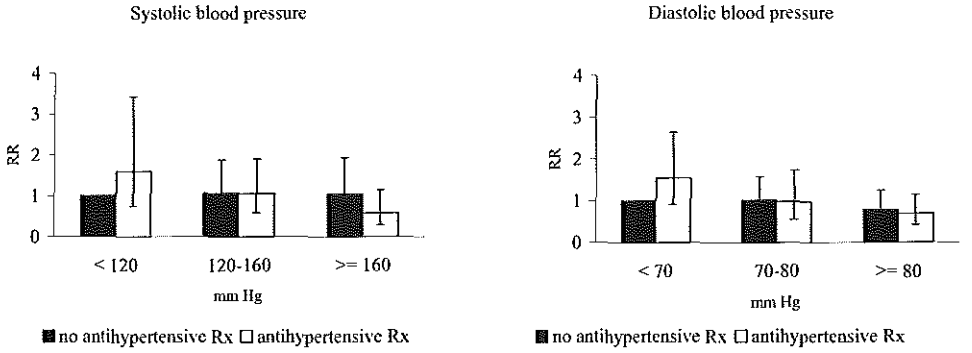

Figure 1. Antihypertensive medication use (Rx) and relative risk of dementia.
Left: three categories of blood pressure level, stratified on medication use: < 120, 120-160, ≥160 mm Hg, lowest category without medication as reference.
Right: three categories of blood pressure level, stratified on medication use: < 70, 70-80, ≥ 80 mm Hg, lowest category without medication as reference.

The association between lower systolic and diastolic blood pressure at baseline and the risk of dementia at follow-up was observed across all age strata, in men as well as in women and both in Alzheimer's disease and vascular dementia (Table 3). When we adjusted for possible confounders (education, smoking, antihypertensive medication, diabetes, history of stroke and history of myocardial infarction, baseline MMSE) the estimates did not change (data not shown).

Table 2. Adjusted relative risk for dementia associated with baseline blood pressure*.

	55-74 years	75-84 years	≥ 85 years	Total
N (number of demented)	N = 4987 (25)	N = 1336 (68)	N = 662 (103)	N = 6985 (196)
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
SBP (per 10 mm Hg)				
Total population	0.96 (0.80-1.16)	0.95 (0.85-1.06)	0.89 (0.82-0.97)	0.93 (0.88-0.99)
No antihypertensive Rx	1.06 (0.83-1.35)	1.00 (0.86-1.17)	0.96 (0.85-1.07)	1.00 (0.92-1.09)
Antihypertensive Rx	0.84 (0.62-1.13)	0.92 (0.78-1.07)	0.83 (0.72-0.94)	0.86 (0.78-0.95)
DBP (per 10 mm Hg)				
Total population	0.93 (0.65-1.32)	0.95 (0.77-1.16)	0.82 (0.70-0.97)	0.89 (0.79-1.00)
No antihypertensive Rx	0.93 (0.59-1.48)	1.09 (0.84-1.42)	0.82 (0.66-1.03)	0.95 (0.82-1.12)
Antihypertensive Rx	0.91 (0.51-1.62)	0.83 (0.61-1.13)	0.80 (0.62-1.03)	0.82 (0.68-0.98)

*Adjusted for age, gender and study population

SBP = systolic blood pressure, DBP = diastolic blood pressure, Rx = medication

Table 3. Adjusted relative risk for subtypes of dementia associated with baseline blood pressure*.

(number of demented)	Total AD (124)	AD without CVD (106)	AD with CVD (18)	Vascular dementia (46)
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
SBP (per 10 mm Hg)				
Total population	0.96 (0.89-1.03)	0.92 (0.85-1.00)	1.18 (0.98-1.42)	0.93 (0.82-1.06)
No antihypertensive Rx	1.02 (0.92-1.14)	0.97 (0.87-1.08)	1.36 (1.05-1.76)	1.04 (0.89-1.21)
Antihypertensive Rx	0.91 (0.81-1.02)	0.89 (0.79-1.01)	1.02 (0.76-1.36)	0.77 (0.61-0.97)
DBP (per 10 mm Hg)				
Total population	0.94 (0.82-1.09)	0.91 (0.77-1.06)	1.17 (0.81-1.69)	1.01 (0.79-1.28)
No antihypertensive Rx	0.97 (0.79-1.18)	0.90 (0.72-1.13)	1.37 (0.87-2.16)	1.09 (0.82-1.45)
Antihypertensive Rx	0.93 (0.74-1.16)	0.93 (0.73-1.18)	0.91 (0.51-1.63)	0.89 (0.59-1.34)

*Adjusted for age, gender and study population
AD = Alzheimer's disease, CVD = cerebrovascular disease
SBP = systolic blood pressure, DBP = diastolic blood pressure, Rx = medication

Dementia appeared associated with a decrease in blood pressure during follow-up (Figure 2). In all age categories we observed a larger decrease in blood pressure in prevalent dementia patients compared to subjects without dementia. Subjects with incident dementia also decreased more in blood pressure level than persons without dementia. This difference however was not statistically significant.

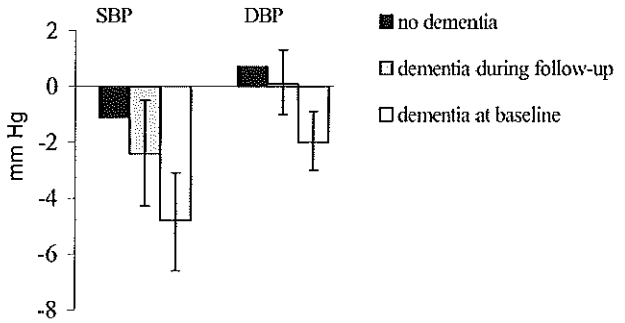

Figure 2. one-year change in blood pressure. Subjects without dementia compared to subjects with prevalent or incident dementia.

Discussion

We found that both baseline systolic and diastolic blood were inversely associated with the risk of dementia, but only in subjects who used antihypertensive medication.

Major advantages of the Rotterdam Study and the Gothenburg H-70 study to investigate risk factors and predictors for dementia are the longitudinal and population-based design, the fact that blood pressure was assessed before onset of dementia, and the complete (Rotterdam Study) or nearly complete (Gothenburg H-70 study) follow-up of the population at risk of dementia. By pooling the data of the two studies we were also able to reach firm results in the very old age group. There were however some differences between the studies. The Rotterdam Study used a three phase comprehensive diagnostic work-up including a screening phase for dementia detection. Although this procedure has a high sensitivity and specificity[14, 15, 25] we may have missed some cases of dementia. In the H-70 study all subjects were examined by a psychiatrist and all subjects had a close informant interview. The incidence of dementia in the H-70

study was higher compared to the Rotterdam Study. This difference was mainly caused by a higher incidence of vascular dementia. The incidence of Alzheimer's disease was identical. Blood pressure was higher in Gothenburg than in Rotterdam both in demented and in non-demented individuals. Differences of this magnitude however are very common between different studies, even if they take place in the same country. These differences can possibly be explained by a difference in the way of blood pressure assessments between both studies[26] or by a difference in time of measurement between the studies (H-70: 1986/1987; RS: 1990/1993) causing a period effect in blood pressure levels.[27] Therefore, we assume that the differences between the two studies are not related to the outcome.

Few longitudinal population based studies have examined blood pressure and dementia in the very old. Recently, in line with our findings, the Kungsholmen Project reported that non-demented individuals with a systolic blood pressure below 140 mm Hg were at increased risk of dementia during a three year follow-up.[28] However, in that study also a baseline systolic blood pressure above 180 mm Hg was related to an increased risk of dementia, a finding that we could not confirm. Several studies have reported that high blood pressure in midlife is related to low cognitive performance in old age.[12, 13, 29] In one of these, the Honolulu-Asia Aging Study, a low blood pressure was associated with lower cognitive performance in a cross-sectional analysis at the time of cognitive testing. This is in line with a previous report from the Gothenburg Study that blood pressure levels of those who developed dementia between age 79 and 85 were increased at age 70 years but declined thereafter at a faster rate than in those who did not develop dementia. Indeed, in that study, blood pressure tended to be lower in the years directly preceding dementia.[11] This also concurs with several cross-sectional studies that showed that above age 75 years low blood pressure is related to low cognitive performance[2] or dementia.[6, 7] Consequently, the follow-up period in our present study may have been too short to find the long-term effect of elevated blood pressure.

Our main finding that low blood pressure increases the risk of dementia after two years may either reflect that low blood pressure causes or contributes to dementia or that incipient dementia leads to a drop in blood pressure. As for the first explanation, we observed an inverse association between blood pressure and dementia mainly in subjects who used antihypertensive medication.

Antihypertensive medication probably reflects hypertension of longer duration, even if the blood pressure is normalised at the time of measurement. One could consider that subjects who use antihypertensive medication are the subjects with the more severe atherosclerosis and are more susceptible to pressure drops causing inadequate blood flow through the brain. Systemic hypotension with associated reduced cerebral blood flow may give rise to a spectrum of ischaemic neuronal lesions in vulnerable areas of the brain,[30] especially in watershed areas[30, 31] and may also lead to ischaemic loss of myelin in the white matter.[32] Persons who survive until old age, despite atherosclerotic lesions, may require increasing levels of blood pressure to maintain adequate cerebral blood flow. In that situation, low blood pressure can result in chronic hypoperfusion, which then could lead to cognitive impairment and dementia.

A second explanation for our findings could be that low blood pressure is a consequence of incipient dementia. In support of this, we found that blood pressure was lower in subjects with manifest dementia at baseline and declined more rapidly in this group than in the non-demented during follow-up. These findings are supported by reports that blood pressure declines in the years preceding dementia onset[11] and further declines during the course of Alzheimer's disease.[33] Several areas that are involved in central blood pressure regulation are affected in Alzheimer's disease. Burke et al reported a strong correlation between the number of C1 neurones in the medulla oblongata and blood pressure in Alzheimer patients.[33] Skoog et al reported that cerebral atrophy was correlated to lower blood pressure in 85-year-olds.[7] Cross-sectional studies in younger age groups generally report a lower cognitive performance in hypertensives compared to normotensives.[34, 35] It is possible that the subtle cognitive impairment reported in middle-aged and younger elderly hypertensives are early manifestations of subclinical neurodegenerative processes that ultimately may lead to both dementia and low blood pressure.

It is also possible that both mechanisms are involved, but act in different subgroups. This would fit observations that low blood pressure increases the short-term mortality but predicts better long-term survival. Apparently, elderly persons with low blood pressure are a mixture of two subgroups: people with low blood pressure due to multiple chronic diseases, including atherosclerosis, and people with low blood pressure who are in good health.[36]

In summary, our results show that baseline blood pressure predicts dementia in elderly who use antihypertensive medication. Whether low blood pressure is causally related to dementia or the result of the dementia process still remains unclear. Prospective studies with a longer duration of follow-up are required to further unravel the relation between blood pressure and dementia.

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3.2

Blood pressure and risk of dementia: the Rotterdam Study

Abstract

Background *Hypertension increases the risk of stroke and vascular dementia, but has also been suggested to increase the risk of Alzheimer's disease. Studies with long duration lend support for this suggestion. However, studies with short duration have found that low blood pressure increased the risk of Alzheimer's disease. We examined the association between level of blood pressure and change in blood pressure and the risk of dementia.*

Methods *The study is based on 6,141 participants of the Rotterdam Study, a population-based study on subjects aged 55 years and over in Rotterdam, the Netherlands, who had their blood pressure assessed at baseline (1990-1993) and were still alive and non-demented at the first follow-up examination (1993-1994). The cohort was followed for incident dementia until December 31, 1999.*

Findings *During 24,692 person-years of follow-up 211 persons developed dementia. Higher baseline blood pressure levels were associated with an increased risk of dementia (relative risk (RR) per 10 mm Hg increase in SBP: 1.05, 95% CI 0.99-1.12; DBP: RR 1.07, 95% CI: 0.95-1.21), especially for persons aged 55-75 years (SBP: RR 1.18, 95% CI: 1.06-1.31; DBP: RR 1.24, 95% CI: 1.01-1.51). Persons with a more than 5 mm Hg decline in blood pressure between baseline and first follow-up were at increased risk of dementia compared to persons with stable blood pressure levels (SBP: RR 1.95, 95%CI: 1.31-2.89; DBP: RR 1.81, 95%CI: 1.22-2.68). Relations were strongest for vascular dementia, but also present for Alzheimer's disease.*

Interpretation *These findings are compatible with the view that high blood pressure increases the risk of Alzheimer's disease. A decline in blood pressure may either be a cause or a consequence of the dementia process.*

Introduction

Hypertension is an established risk factor for stroke and vascular dementia.[1] Recently hypertension has also been suggested as a possible risk factor for Alzheimer's disease.[2, 3] A link between hypertension and Alzheimer's disease seems supported by a recent trial in which antihypertensive treatment in elderly people with isolated systolic hypertension was associated with a lower incidence of Alzheimer's disease.[4] Follow-up studies with long duration generally showed high blood pressure to be associated with an increased risk of Alzheimer's disease.[2, 3] By contrast, studies with short duration suggested that hypertension is associated with a lower risk of Alzheimer's disease.[5-7]

We examined the relation between the level of blood pressure and the change in blood pressure and the risk of dementia, using data from the Rotterdam Study, a large follow-up study conducted in the Netherlands.

Methods

Study population

The Rotterdam Study is a population based prospective cohort study among 7,983 persons aged 55 years and older, including those living in institutions.[8] The study was approved by the Medical Ethics Committee of the Erasmus University. Participants gave written informed consent and permission to retrieve information from treating physicians. At baseline (1990-1993), 7,528 subjects (94.3% of the total cohort) underwent extensive screening for dementia[9] and 482 persons were identified with prevalent dementia. The cohort was re-examined in 1993-1994 and in 1997-1999. In addition, the total cohort is continuously monitored for incident dementia cases via computerised linkage between the study database and medical records from general practitioners and the Regional Institute for Outpatient Mental Health Care (RIAGG).[9]

Of the 7,046 subjects at risk for dementia 6,668 had blood pressure measurements available at baseline. We excluded 20 persons of whom we were unable to obtain sufficient information on dementia status at the end of their second follow-up period. Since we hypothesised that the short-term relation between blood pressure and risk of dementia may be different from the relation over a longer period, and we therefore also wanted to investigate change in

blood pressure in relation to risk of dementia, we excluded the first follow-up period (14,090 person-years (on average 2.1 years)) from the analyses. In this period 137 subjects developed dementia and an additional 370 died. Our analytical sample therefore effectively consisted of the 6,141 persons who were alive and non-demented at the first follow-up examination.

Diagnosis of dementia

Dementia screening and diagnosis during baseline and follow-up examinations were similar.[9] Briefly, all subjects were screened with a short test of cognition (Mini Mental State Examination[10] and the Geriatric Mental State schedule, organic level[11]). Screen positives underwent further cognitive testing, and an informant interview was obtained. Persons suspected of dementia were examined by a neurologist and underwent neuropsychological testing. To differentiate vascular dementia from Alzheimer's disease a brain scan was made by magnetic resonance imaging (MRI) or computed tomography (CT). Dementia diagnosis was made according to internationally accepted criteria (NINCDS-ADRDA, NINDS-AIREN, DSM-III-R) by a panel that reviewed all existing information.[9, 12-14]

Blood pressure and other baseline measurements

Baseline and follow-up blood pressure levels were measured in sitting position at the right upper arm with a random-zero sphygmomanometer. The average of two measurements, separated by a count of the pulse rate, was used in the analysis. Pulse pressure was defined as the difference between systolic and diastolic blood pressure. At baseline and first follow-up participants were asked to report and show all medication used during the week preceding the interview. Subsequently, all drugs were classified according to their corresponding Anatomical-Therapeutical-Chemical-code (ATC-code).

The following baseline variables were used as possible confounders: diabetes, defined according to WHO criteria for epidemiological studies of diabetes as the use of antidiabetes medication or a random or post-load serum glucose level greater than 11 mmol/l;[15] education, dichotomised in primary education or less and more than primary education; smoking, categorised as never, past and current smoking; total cholesterol (mmol/l); body mass index (weight (kg)/height (m^2)); and blood pressure lowering medication. A history of

stroke was assessed at baseline and verified with medical records by a neurologist and a history of myocardial infarction was assessed by direct questioning and verified by ECG and general practitioner or cardiologist. Apolipoprotein E (APOE) 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]

Statistical analysis

The relative risks of dementia by levels of baseline systolic and diastolic blood pressure and by levels of pulse pressure were calculated with Cox' proportional hazards regression and presented with a 95% confidence interval (95% CI), controlling for age, age^2, and gender. This was done both by entering blood pressure as a categorical (quintiles) and as a continuous variable in the proportional hazards regression model. We examined if gender or age modified the relation in subanalyses where we stratified by gender and age (55-74, 75 years and older). In addition, age and gender were evaluated for potential interaction with blood pressure by adding separate terms to the regression models (age (continuously) x blood pressure (continuously); gender x blood pressure (continuously)). To check if associations could be attributed to confounding, analyses were repeated with possible confounders added to the models. We repeated the analyses excluding persons on blood pressure lowering medication at baseline.

For the analysis on change in blood pressure level between baseline and first follow-up, we excluded 842 persons (13.7 %) who had no second blood pressure measurement. The risk of dementia was calculated using change in blood pressure per year as a categorical variable (increase > 5 mm Hg; increase ≤ 5 to a decrease < 5 mm Hg; decrease ≥ 5 mm Hg) in the proportional hazards regression model. All analyses were adjusted for age, age^2 and gender. Because baseline blood pressure level may be correlated to change in blood pressure we repeated the analyses adjusting for baseline blood pressure level. However, since adjusting for baseline level may cause bias due to regression towards the mean[17] and because the results did not differ from the unadjusted relative risks, we present the analyses unadjusted for baseline blood pressure levels. All analyses were repeated adjusting for possible confounders. In addition, we repeated the

analyses excluding persons on blood pressure lowering medication either at baseline or at first follow-up examination.

To account for misclassification of subtypes of dementia, we performed additional analyses restricted to those cases where the dementia diagnosis was supported by neuroimaging (either MRI or CT).

Table 1. Baseline characteristics of participants of the Rotterdam Study.

	Total Population (n = 6,141)	55-74 years (n = 4,817)	≥ 75 years (n = 1,324)
Age (years)	68.2 (8.3)	64.8 (5.4)	80.4 (4.3)
Gender (% women)	59.6	57.3	68.0
Blood pressure lowering drugs (%)	30.3	26.7	43.4
Systolic blood pressure (mm Hg)	139.1 (22.1)	136.7 (21.4)	147.8 (22.6)
Diastolic blood pressure (mm Hg)	73.9 (11.3)	74.3 (11.1)	72.7 (12.0)
Pulse pressure (mm Hg)	65.1 (17.7)	62.4 (16.6)	75.1 (18.3)
Diabetes (%)	9.4	8.0	14.5
Smoking : Current (%)	22.8	25.2	14.0
Former (%)	42.5	44.4	35.6
Never (%)	34.6	30.4	50.4
Primary education or less (%)	35.9	30.9	54.4
Total cholesterol (mmol/l)	6.7 (1.2)	6.7 (1.2)	6.5 (1.3)
Body mass index (kg/m^2)	26.4 (4.0)	26.3 (4.0)	26.6 (4.0)

Figures are proportions (%) or means (SD)

Results

Baseline characteristics are given in Table 1. During a total of 24,692 person-years of follow-up 211 participants developed dementia. Alzheimer's disease was diagnosed in 158 patients (74.9%) (148 without and 10 with cerebrovascular disease), vascular dementia was diagnosed in 32 patients (15.2%) and 21 subjects (10.0%) were diagnosed with other dementia. We obtained neuroimaging in 93 dementia cases (44.0%; 39.9% of Alzheimer cases and 68.8% of vascular dementia cases).

Non-responders to the first follow-up examination were on average older, were more frequently female and had higher baseline systolic and diastolic blood pressure levels compared to responders. Mean change in systolic blood pressure was 1.1 mm Hg increase per year (SD 10.8), mean change in diastolic blood pressure was 1.4 mm Hg increase per year (SD 6.5).

Adjusted relative risks of dementia and subtypes of dementia per 10 mm Hg increase in baseline blood pressure level are given in Table 2. Increasing baseline systolic and diastolic blood pressure levels and increasing pulse pressure levels were associated with an increased risk of dementia, particularly in younger subjects (interaction between age and systolic blood pressure: p = 0.013). The association was present for both Alzheimer's disease and vascular dementia.

Table 2. Adjusted relative risk for subtypes of dementia associated with baseline blood pressure level*.

	Total population	55-74 years	≥ 75 years
Systolic BP (per 10 mm Hg)			
All dementia	1.05 (0.99-1.12)	1.18 (1.06-1.31)	0.98 (0.91-1.07)
Alzheimer's disease	1.03 (0.96-1.11)	1.15 (1.01-1.30)	0.97 (0.88-1.07)
Vascular dementia	1.22 (1.04-1.43)	1.37 (1.04-1.81)	1.10 (0.89-1.35)
Diastolic BP (per 10 mm Hg)			
All dementia	1.07 (0.95-1.21)	1.24 (1.01-1.51)	1.00 (0.86-1.17)
Alzheimer's disease	1.01 (0.88-1.17)	1.12 (0.89-1.42)	0.97 (0.82-1.16)
Vascular dementia	1.42 (1.05-1.91)	2.51 (1.50-4.22)	1.03-(0.68-1.56)
Pulse pressure (per 10 mm Hg)			
All dementia	1.05 (0.97-1.14)	1.18 (1.04-1.34)	0.97 (0.88-1.08)
Alzheimer's disease	1.04 (0.95-1.14)	1.18 (1.02-1.37)	0.97 (0.86-1.09)
Vascular dementia	1.18 (0.97-1.43)	1.09 (0.77-1.53)	1.14-(0.88-1.46)

*Adjusted for age, age^2, gender, diabetes, cholesterol, body-mass-index, education, blood pressure lowering medication, history of stroke, history of myocardial infarction, APOE genotype

Gender specific analyses revealed no differences regarding the risk of Alzheimer's disease. The risk of vascular dementia was higher for men (RR per 10 mm Hg increase in SBP: 1.38, 95% CI: 1.10-1.74; DBP: RR 1.75, 95% CI: 1.12-2.73) than for women (RR per 10 mm Hg increase in SBP 1.08, 95% CI: 0.86-1.37; DBP: RR 1.21, 95% CI: 0.80-1.84). After exclusion of persons who used blood pressure lowering medication at baseline the relative risks did not change appreciably. Also, the analyses confined to cases with neuroimaging (n = 93) yielded similar relative risks for subtypes of dementia.

Table 3 shows the relative risk of dementia associated with change in blood pressure level from baseline to first follow-up in categories of change in blood pressure level. A decline of more than 5 mm Hg in systolic or diastolic blood

pressure level was associated with an increased risk of dementia at follow-up. This relation was present for both Alzheimer's disease (SBP: RR 1.58, 95% CI: 1.00-2.49; DBP: 1.81, 95% CI: 1.22-2.68) and vascular dementia (SBP: RR 7.88, 95% CI: 2.07-30.00; DBP: 2.65, 95% CI: 0.99-7.13).

Table 3. Adjusted relative risk for subtypes of dementia associated with a change in blood pressure from baseline to first follow-up (n = number of cases)*.

	All dementia (n = 159)	Alzheimer's disease (n = 123)	Vascular dementia (n = 20)
Systolic Blood Pressure			
Increase > 5 mm Hg	1.25 (0.85-1.84)	1.17 (0.77-1.79)	2.43 (0.57-10.27)
Increase ≤ 5 and decrease < 5 mm Hg	1.0	1.0	1.0
Decrease ≥ 5 mm Hg	1.95 (1.31-2.89)	1.58 (1.00-2.49)	7.88 (2.07-30.00)
Diastolic Blood Pressure			
Increase > 5 mm Hg	0.88 (0.59-1.31)	1.00 (0.65-1.53)	0.42 (0.09-1.94)
Increase ≤ 5 and decrease < 5 mm Hg	1.0	1.0	1.0
Decrease ≥ 5 mm Hg	1.81 (1.22-2.68)	1.60 (0.99-2.57)	2.65 (0.99-7.13)

*Adjusted for age, age^2, gender, diabetes, cholesterol, body-mass-index, education, blood pressure lowering medication, history of stroke, history of myocardial infarction, APOE genotype

The association was not significantly different for men and women and similar for younger and older persons. Change in pulse pressure was not associated with risk of dementia. The analysis in which we excluded persons who used blood pressure lowering medication at baseline or follow-up yielded practically similar results for decline in systolic blood pressure (RR 2.24, 95% CI: 1.26-3.99), but a lower risk of dementia associated with a decline in diastolic blood pressure (RR 1.39, 95% CI: 0.73-2.62).

Discussion

We found that elevated blood pressure levels were associated with a long-term increased risk of dementia. A decline in blood pressure over a relatively short period was associated with an increased risk of dementia. These findings were more marked for vascular dementia, but also present for Alzheimer's disease.

A strength of our study is that we followed a large cohort of elderly subjects with repeated detailed examinations including dementia screening over a period of nearly 10 years and that follow-up was virtually complete. This allowed us to

investigate change in blood pressure level in relation to risk of dementia. However, there are some methodological issues that need to be discussed. First, subjects had to survive long enough to obtain a second blood pressure measurement. Subjects who died between baseline examination and first follow-up may have had a more severe decline in blood pressure compared to those who survived.[18] This could however only have led to an overestimation of the relative risk if the mortality rate was higher in non-demented than in demented, and we consider that unlikely. Second, one might consider that we have overestimated the relative risk of Alzheimer's disease due to misclassification of cases with vascular dementia into Alzheimer's disease. Although exclusion of dementia patients without neuroimaging did not change our results, we can not entirely exclude this possibility.

Our findings lend further support to the notion that high blood pressure may increase the long-term risk of low cognitive performance[19-22] and dementia.[2, 3] The studies on dementia reported up to now comprised only men[3] or had a relatively small sample size,[2] but were consistent with our results. Several possible explanations for the long-term increased risk of dementia in participants with high baseline blood pressure levels may be offered. First, hypertension is a major risk factor for stroke and single strategic or multiple infarcts may lead to vascular dementia.[23] Second, hypertension is the outstanding risk factor for cerebral white matter lesions.[24, 25] These lesions are associated with cognitive dysfunction in non-demented subjects,[26] and abundantly present in demented subjects.[27, 28] Third, hypertension can lead to endothelial damage and impaired blood brain barrier function.[29] Alterations in the blood brain barrier function may impair the transport of crucial nutrients and metabolites to the brain or allow circulating toxic agents to gain access to the brain tissue. It remains still to be elucidated whether and how this may eventually contribute to the development of Alzheimer's disease.[28, 29]

A decline in blood pressure was associated with a short-term increased risk of dementia, irrespective of baseline blood pressure level. Possible explanations for this include that a decline in blood pressure may either be a consequence of dementia or be a cause of dementia. As for the first explanation, some authors suggested that a decline in blood pressure might be a consequence of brain lesions associated with dementia, since several areas that are involved in central blood pressure regulation are affected in Alzheimer's disease.[30-32] A second, but

equally possible, explanation is that lowering of the blood pressure beyond a critical threshold increases the risk of dementia through chronic hypoperfusion, especially in elderly persons with longstanding hypertension.[33, 34] Based on current existing data it is impossible to judge whether the first explanation, the second explanation, or a combination of both accounts for the association between a decline in blood pressure and development of dementia.

Our study suggests that it may be important to closely monitor blood pressure levels in the elderly and supports the hypothesis that early control of high blood pressure may reduce the risk of dementia in the elderly.

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3.3

Blood pressure medication and risk of dementia: the Rotterdam Study

Abstract

There is increasing evidence that hypertension may contribute to the development of dementia. We investigated the relation of antihypertensive drug use and the risk of dementia in the cohort of the population based Rotterdam Study. The study cohort included 7,046 elderly, free of dementia at baseline. Dementia was diagnosed in a stepwise procedure. Participants were first screened. Screen positives were further tested. Those suspected of dementia underwent a diagnostic work-up. Dementia and its subtypes were diagnosed according to prevailing criteria. A Cox' proportional hazards model was used to estimate relative risks. After a mean follow-up of 2.2 years, subjects taking antihypertensive medication at baseline (n=2,015) had a reduced incidence of dementia (adjusted relative risk, 0.76; 95% confidence interval 0.52-1.12). This risk reduction was most pronounced for vascular dementia, (adjusted relative risk, 0.30; 95% confidence interval 0.11-0.99). For Alzheimer's disease the relative risk was 0.87, not significant. Dementia may be prevented by antihypertensive treatment. In order to confirm any relation in Alzheimer's disease larger observational studies with longer follow-up are needed.

Introduction

There is increasing evidence that hypertension may contribute to the development of cognitive impairment and dementia,[1-4] although there is certainly no general agreement on the mechanism.[5] This logically leads to the hypothesis that lowering of the blood pressure with antihypertensive treatment might protect against the development of cognitive dysfunction and dementia.

In the Framingham Heart Study, there was no longitudinal association after over 15 years of follow-up between cognitive function and blood pressure

among subjects using antihypertensive drugs. However, in untreated subjects both higher systolic and diastolic blood pressure, were associated with worse cognitive performance later in life.[6] In a recently published 20-year follow-up study, it was also shown that the association between hypertension at baseline and the development of cognitive dysfunction was strongest in untreated men.[4]

Until now, however, evidence of a beneficial effect of antihypertensive treatment on the development of dementia in epidemiological studies is scarce. In the prospective population-based Kungsholmen study in subjects aged 75 years and older, use of antihypertensive medication was studied in relation to the onset of Alzheimer's disease (AD). Among the non-demented subjects, persons with antihypertensive medication in general and diuretic monotherapy at baseline had a significantly reduced risk of developing both total dementia and AD.[7, 8] Other evidence comes from the Systolic Hypertension in Europe trial (Syst-Eur), in which treatment of isolated systolic hypertension with nitrendipine was associated with a borderline significant protective effect for total dementia. However, follow-up time was short (median 2 years) and numbers of demented subjects were very small in this study.[9]

It is now clear that treatment of hypertension leads to a risk reduction of both cardiovascular morbidity and mortality. A possible consequence is that ethical problems will arise in the design and conduct of future clinical trials to assess the effect of blood pressure lowering on the risk of dementia. Therefore we investigated the association between use of antihypertensives and the incidence of dementia in the Rotterdam Study, a large observational prospective population based study.

Methods

Study population

The Rotterdam Study is a prospective population-based cohort study of neurological, cardiovascular, locomotor and ophthalmological diseases in the elderly. After approval of the Medical Ethics Committee, all inhabitants of Ommoord, a suburb of Rotterdam in The Netherlands, aged 55 years or more and living in the district for at least one year were invited in 1990-1993 to participate in the study. Of the 10,275 eligible subjects, 7,983 (78%) participated and signed informed consent. During the home interview, trained interviewers

administered a questionnaire covering, among other topics, socio-economic background, medical history and medication use. During subsequent visits to the research center, subjects underwent additional interviewing and clinical examinations, including screening and diagnosis of dementia. Complete data on dementia were available in 7,528 subjects. A diagnosis of dementia was made in 482 persons. The remaining 7,046 non-demented subjects were followed for an average of 2.2 years until the second round of examinations in 1993 and 1994. At these examinations, 5,571 (79%) participants were actively screened for dementia. Of 999 (14%) subjects who were not re-examined and 476 (7%) who died during follow-up, information on cognitive function was obtained from close informants and general practitioners.

Drug exposure and other baseline measurements

During the home interview participants were asked to report and show all medication used during the week preceding the interview. Subsequently, all drugs were classified according to their corresponding Anatomical-Therapeutical-Chemical-code (ATC-code).[10] For the current study, a classification was made according to the nature of the drug-class: diuretics, beta-blockers, ACE-inhibitors, calcium channel blockers and other antihypertensives. We assumed that drugs with antihypertensive properties were used chronically, as hypertension rarely subsides spontaneously. At the research center height and weight were measured. Blood pressure was measured in the sitting position at the right upper arm with a random-zero sphygmomanometer and calculated as the mean of two consecutive measurements. Diabetes mellitus was defined as the use of anti-diabetic medication or at least one blood-glucose assessment higher than 11 mmol/l, according to WHO-criteria for epidemiological studies.[11] A history of stroke was assessed during the baseline interview and verified with medical records by a neurologist. The ratio of the systolic blood pressure at the ankle to the systolic blood pressure at the arm was calculated for each leg. Peripheral arterial disease was considered present when this ankle-arm index was lower than 0.9 on at least one side.[12]

In addition, prescription-filling data, provided by the 7 pharmacies in the Ommoord region, were available for approximately 99% of the cohort as of January 1991. These data comprise quantitative information on each individual prescription.

Case ascertainment of dementia

Both at baseline and at the follow-up examination, subjects were screened for dementia in a stepwise procedure. Subjects were screened on cognitive function using the Mini-Mental State Examination (MMSE)[13] and the Geriatric Mental State schedule (GMS).[14] Those scoring 25 or below on the MMSE or scoring 1 or more on the GMS were selected for further diagnostic evaluation. This included more detailed neuropsychological testing and an informant interview based on the Cambridge Examination for Mental Disorders of the Elderly,[15] as well as neurological examination. Some participants underwent magnetic resonance imaging of the brain. A clinical diagnosis of dementia was made according to the DSM-III-R criteria for dementia by a panel that reviewed all existing information. A sub-diagnosis of AD was made according to the NINCDS-ADRDA criteria.[16] A sub-diagnosis of vascular dementia was made in accordance with the NINDS-AIREN criteria.[17] After a mean follow-up of 2.2 years, a total of 162 demented subjects, including 116(73%) subjects with AD, of which 15 also had cerebrovascular disease, and 22(14%) subjects with vascular dementia, were diagnosed.

Confounding variables

The following variables were considered possible confounders and were therefore entered into the statistical models: age, gender, diastolic and systolic blood pressure (mm Hg), history of stroke and diabetes mellitus. Additional adjustments were made for body mass index (BMI: kg/m^2), smoking (never, former, current), education (<7 years, ≥7 years), living situation (independent, home for the elderly), baseline MMSE and peripheral arterial disease.

Statistical analyses

Analysis of covariance adjusted for gender and age, was used to compare characteristics of subjects with and without antihypertensives at baseline. We used Cox' proportional hazards regression analysis to calculate relative risks with 95% confidence intervals (95% CI) for total dementia, Alzheimer's disease with and without cerebrovascular disease and vascular dementia by reported use of antihypertensive drugs. For categorical data with missing values we incorporated missing indicator variables in the model.

Subsequently, as we did a complete subjects analysis with respect to the continuous variables we excluded 622 subjects of whom 376 had a missing blood pressure measurements, 243 a missing Mini Mental State Examination (MMSE) and 404 a missing body mass index (BMI). The mean age in this excluded group was higher than in the remainder of the population (77.6 vs. 68.6 years), they were more often females (71.9% vs. 58.7%) and were far more often inhabitants of homes for the elderly (36.7% vs. 4.7%).

To reduce the possibility of differential reporting of drug use because of pre-clinical dementia at baseline, in a sub-analysis, we excluded subjects who were diagnosed with dementia within one year after baseline examination.

The risk of dementia in subjects with hypertension and associated co-morbidity may be different from subjects without hypertension. In a second sub-analysis, we therefore excluded all untreated subjects without hypertension according to the WHO criteria[18] and calculated relative risks of treatment for dementia (sub)types. According to the WHO hypertension is defined as a diastolic blood pressure of at least 95 mm Hg and/or a systolic blood pressure of at least 160 mm Hg.

Next, we studied the effect of gender. We examined whether gender modified the relation by calculating relative risks for men and women separately. To examine confounding by indication we stratified according to monotherapy with first- (diuretics/beta-blockers) and second-line antihypertensive treatment (remaining drugs and combinations of drugs).

In order to examine whether misclassification of exposure was important in our study, we examined a sub-population of our cohort that had a first time examination after June 30 1991 (n=5,101) and were not living in a home for the elderly. We used this cut-off, as pharmacy data were only available as of January 1991. We then calculated the percentage of subjects that reported both antihypertensive drug use at baseline and filled an antihypertensive prescription in the 6 months before baseline examination. As the duration of a prescription is normally limited to 3 months it is likely that most drugs were captured using a six month period.

Finally, we examined whether a competing risk was a likely explanation for our findings, meaning that the encountered protective effect of antihypertensives may have been a consequence of increased mortality instead of a real effect.

Results

Of the 6,416 subjects included in the present study, 118 subjects developed dementia, of which 82 had AD and 18 had vascular dementia. In Table 1, baseline characteristics are given for subjects with and without exposure to an antihypertensive drug. Mean age, diastolic- and systolic blood pressure and BMI were significantly higher in users of antihypertensive drugs. Furthermore, relatively many women were users and users more frequently had diabetes, peripheral arterial disease and a history of stroke. Finally, users were less often current smokers than non-users. The mean MMSE, grade of education and the proportion of subjects living independently were comparable between groups.

Of the 6,416 subjects 31.3% used antihypertensive medication of which 21.1% used monotherapy, 8.5% used two drugs and 1.7% used three or more drugs. In total 14.6 % reported use of beta-blockers, 15.3 % reported use of diuretics, 5.9 % reported use of calcium antagonists, 5.7 % reported use of ACE-inhibitors and 1.9 % reported use of other antihypertensives.

Table 1. General characteristics of participants at baseline†.

Baseline measurements	Non-users N=4401	Users of antihypertensive drugs N=2015	Ancova*
Age (years)	67.4	71.4	P<0.001
Female gender (%)	57.0	62.5	P=0.003
MMSE	27.6 (17-30)	27.6 (16-30)	Ns
Body mass index	25.8	27.4	P<0.001
Diastolic blood pressure (mm Hg)	73.1	75.1	P<0.001
Systolic blood pressure (mm Hg)	137.7	142.5	P<0.001
Smoking (%)			
Current	24.6	18.8	P<0.001
Education of more than 7 years (%)	36.1	35.6	NS
Diabetes mellitus (%)	8.1	14.2	P<0.001
Housing (%)			
Home for the elderly	4.5	5.2	NS
Markers of vascular disease (%)			
Peripheral arterial disease	15.5	21.1	P<0.001
History of stroke	1.6	3.9	P<0.001

*Age and gender adjusted analysis of covariance.
†Values represent means or percentages

Table 2 shows a non-significant risk reduction for dementia in general in users of antihypertensive drugs. The risk reduction was significant and most prominent for vascular dementia. Furthermore, it was present independent of adjustments made for potential confounders. Overall there were 70 dementia cases in the untreated group and 48 in the treated group.

Table 2. Use of any type of antihypertensive drug at baseline and the risk of dementia expressed as relative risk (95% confidence interval).

Dementia type	Number of demented subjects	Relative risk* N=6416	Relative risk† N=6416
Total dementia††	118	0.76 (0.52-1.12)	0.67 (0.45-1.00)
Total Alzheimer's disease	82	0.87 (0.56-1.37)	0.77 (0.49-1.24)
AD without vascular pathology	68	0.94 (0.57-1.53)	0.83 (0.49-1.39)
AD with vascular pathology	14	0.64 (0.21-1.91)	0.63 (0.20-1.93)
Vascular Dementia	18	0.33 (0.11-0.99)	0.30 (0.09-0.92)

*Cox' proportional hazards regression analysis adjusted for age, gender, diastolic and systolic blood pressure, diabetes mellitus and stroke.

†Additional adjustment for body mass index, baseline MMSE, smoking, education, living situation and peripheral atherosclerotic disease.

††This includes 18 subjects with an other type of dementia: Parkinson's dementia (n=4), other type (n=13) and undetermined (n=3)

Risk reduction was similar when we excluded those subjects with a diagnosis of dementia in the first year of follow-up or a follow-up of less than a year (number of demented subjects=27) (data not shown). For AD the reduction in risk was, although not significant, most prominent in those with vascular pathology. Exclusion of untreated subjects without hypertension revealed comparable risk estimates (Table 3).

Table 3. Relative risk of dementia according to drug use after exclusion of all normotensive subjects (diastolic blood pressure <95 mmHg and systolic blood pressure <160 mmHg) without treatment.

Dementia type	Number of demented subjects	Relative Risk (95% CI)*
Total dementia	61	0.67 (0.35 to 1.32)
Total AD	45	0.99 (0.47 to 2.12)
Vascular Dementia	10	0.11 (0.02 to 0.74)

*Cox proportional hazards regression analysis adjusted for age, gender, diastolic and systolic blood pressure, stroke, diabetes mellitus

Stratified analysis revealed larger risk reductions for men (RR 0.52; 95% CI 0.22-1.20) than for women (RR 0.93; 95% CI 0.59-1.46) and for first line therapy than second line therapy (data not shown) for total dementia. However,

in both instances confidence intervals overlapped largely. Stratification for individual drugs could not confirm earlier suggestions that calcium-channel blockers (RR 0.70; 95% CI 0.32-1.52) and or diuretics (RR 0.83; 95% CI 0.33-1.30) in particular are protective in the onset of dementia.

In those living independently at baseline the accordance of reported use with actually filled prescriptions in the pharmacy was high and not significantly different for both healthy subjects (n=4,703: 94.6%) and demented subjects at follow-up (n=40: 92.9%).

Of the 622 subjects excluded from the analysis approximately 40% reported use of bloodpressure lowering drugs and the overall incidence of dementia was 29.9/1,000 person years.

With respect to the issue of competing risks age, gender, blood pressure and follow-up time adjusted mortality was lower in the treated as compared to untreated subjects with hypertension (9.0% vs. 7.5%), although this difference was not significant (p=0.09).

Discussion

In this population based prospective cohort study, we found a risk reduction of dementia in users of antihypertensive drugs. This risk reduction was most prominent and significant for vascular dementia and more pronounced in males. Risk reduction for AD was, although not significant, most prominent in those with concomitant vascular disease.

Several issues of validity need to be discussed when interpreting these results, in particular potential information bias and confounding by indication. First, we should consider whether misclassification of exposure may have affected our results. A major concern in earlier, cross-sectional or retrospective, drug studies on dementia was the potential for bias due to underreporting of drug use among cases by proxy informants. Although our study only comprised subjects who were not demented at baseline, one might fear subtle impairment of memory in the pre-clinical phase of dementia and therefore less reliable answers and potentially different health related behavior. A spurious protective effect might then be the consequence of underreporting of antihypertensive drug use in cases. To assess this problem we performed separate analyses for a sample

restricted to those not demented in the first year of follow-up and found similar risk estimates.

Furthermore, in a study on the concordance of reported cardiovascular drug use at baseline and the actually filled prescriptions in the pharmacy an overall high correspondence was found for participants of the Rotterdam Study.[19] For the present study we examined a subset of the analytical sample and found no major differences between demented and non-demented at follow-up with respect to reported use and filled prescriptions in the local pharmacy. Although we have no information on compliance, it seems unlikely that differential misclassification of antihypertensive drug use may explain the results. A second possibility of misclassification of exposure may have occurred because patients were not asked how long they had been treated. As demented subjects were older, the probability of detection of hypertension over time may have been higher and therefore also the probability of treatment may have been higher. If present, however, such a bias would have led us to an underestimate of the actual effect.

Misclassification of hypertension may also have happened as a consequence of the disease, as it has been suggested that blood pressure drops in the pre-clinical phase of AD.[20] When such a pressure drop happened before baseline this might theoretically have led to discontinuation of antihypertensive treatment and therefore to an underestimation of long-standing treatment of hypertension at baseline in subjects who became demented, resulting in a potential overestimation of the protective effect. However, it is not common practice to stop antihypertensive treatment, and we consider it unlikely that this kind of misclassification has affected our results.

In a study on the effects of antihypertensives on dementia confounding by indication is an important issue as there is evidence that long-standing hypertension could lead to dementia.[1-4] It is conceivable that physicians tend to prescribe less antihypertensives to subjects with pre-clinical symptoms of dementia because of fear of diminishing brain perfusion or because of expected inappropriate use. Although we tried to minimize this problem by adjusting for a number of putative confounders and the exclusion of subjects demented within 1 year from baseline, we can not exclude the possibility that there may be some residual confounding. However, residual confounding would probably have led us to underestimating the effect of antihypertensives in dementia. This could

explain the lack of a statistically significant effect in AD but not the observed risk reduction in VD. An alternative explanation for finding no significant effect in AD may be the lack of power at the relative risk that we observed, in particular for the stratified analyses. We calculated that the minimal overall risk reduction that we could find was approximately 40% given a power of 80% and an alpha of 5%.

Subjects with missing values in continuous variables were excluded. Although these subjects were more often users of antihypertensives use and had a higher incidence of dementia, we think that this was mainly a consequence of higher age. Even when the missing-status was associated with a higher chance of getting dementia it is unlikely that this was differential between users and non-users of antihypertensive drugs.

A final problem may be the phenomenon of competing risk. This is an event that removes a subject from being at risk for dementia. The most important competing event in our study seems death. However, as the adjusted death rate in treated subjects was not significantly higher than in untreated subjects with high blood pressure this makes it less likely as an explanation for our findings. Given the existing evidence how should our study be valued? In contrast to the Syst-Eur trial[21] and the Kungsholmen study[7] we did not find a significantly reduced risk of dementia. However, although not significant, in the overall analyses we found a risk reduction of approximately 30%, which equals the reduction found in the Kungsholmen Study. The most plausible explanation for the lack of significance in our study is the higher mean age in the Kungsholmen Study leading to a higher exposure prevalence and higher incidence of dementia. Although it is known that treatment of hypertension reduces associated morbidity, to our knowledge no prior study has shown a risk reduction of vascular dementia. Moreover, our results do not indicate that there are harmful effects with respect to the occurrence of the dementia subtypes they once more stress the importance of adequate antihypertensive treatment.

It has been suggested that there are gender differences with respect to treatment responsiveness of prevalent dementia to other drugs[22] as well as in contribution of other risk factors. In our study in incident demented there was also evidence for a difference, although confidence intervals overlapped. With respect to these gender differences it is unclear whether they are real and if so whether they are attributable to preferential prescribing of certain drugs, the

degree of treatment or the contribution of hypertension to the development of dementia within the sexes.

In conclusion, we found that antihypertensive medication was associated with a lower risk of dementia. Our results were only significant and more outspoken for vascular dementia, but there was a tendency for antihypertensive medication to be associated with lower risks of AD as well. As future placebo controlled trials are not likely to be executed because of ethical complications, studies with longer follow-up, a larger sample of demented subjects and longitudinal exposure data are needed to further explore this association.

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4

ATHEROSCLEROSIS AND DEMENTIA

4.1

Cerebral hemodynamics, cognitive decline and dementia in the Rotterdam Study

Abstract

Background *Transcranial Doppler (TCD) is a noninvasive tool to measure cerebral blood flow (CBF) velocity and cerebrovascular CO_2 reactivity in cerebral arteries. Clinical TCD studies have demonstrated a decrease in blood flow velocity in the proximal tract of the middle cerebral artery in patients with Alzheimer's disease. A reduced cerebrovascular CO_2 reactivity, indicating cerebral small vessel pathology, has been found in vascular dementia patients. It is unclear wether cerebral blood flow velocity and cerebrovascular CO_2 reactivity are decreased in persons with cognitive impairment.*

Design/methods *We examined the association between cerebral hemodynamics, as measured by means of TCD, and dementia and cognitive performance in 2,107 participants of the Rotterdam Study, a large population-based study in the Netherlands.*

Results *A total of 18 individuals were diagnosed with dementia. All cerebral hemodynamic parameters were lower in demented compared with non-demented persons (mean difference end diastolic CBF: 5.7 cm/sec, 95%CI: 2.0–9.7; peak systolic CBF: 14.0 cm/sec, 95%CI 5.2–22.8; mean CBF: 8.6 cm/sec, 95%CI: 3.4–13.8; cerebrovascular CO_2 reactivity: 0.2 %/kPa, 95%CI: -1.1–1.4). Among non-demented subjects those who had declined in the period before TCD assessment had the lowest CBF velocity and cerebrovascular CO_2 reactivity. Persons with low cognitive performance had a lower cerebrovascular CO_2 reactivity as well.*

Conclusion *Our data suggest that cerebral blood flow velocity and cerebrovascular CO_2 reactivity are decreased in persons with dementia and are lower in persons with impaired cognitive performance.*

Introduction

Transcranial Doppler ultrasonography (TCD) is a noninvasive tool to measure cerebral blood flow velocity in cerebral arteries.[1] Neuroradiologic techniques including SPECT and PET have shown reductions of global and regional cerebral blood flow in patients with Alzheimer's disease.[2, 3] Furthermore, a decrease in blood flow velocity in the proximal tract of the middle cerebral artery in Alzheimer patients has been demonstrated in clinical TCD studies.[4-8] This association has not been examined in the general population. An abnormal cerebral blood flow and impaired vascular response to metabolic demand, indicating cerebral small vessel pathology,[9] have been observed in vascular dementia.[10, 11] It is unclear whether cerebral blood flow and cerebrovascular CO_2 reactivity are already decreased in persons with cognitive impairment who are not demented.

In this study, we examined the association between cerebral hemodynamics (including cerebral blood flow velocity and cerebrovascular CO_2 reactivity), measured by means of TCD, and cognitive decline and dementia, within the Rotterdam Study, a large population based study in the Netherlands.

Methods

Study population

The study is based on the Rotterdam Study, a population based prospective cohort study that is ongoing since 1990.[12] TCD assessment was added to the core protocol for the second re-examination (1997-1999), in which 4,730 persons participated. Of these, 4,214 visited the study research centre. In 1,113 participants we were unable to perform TCD due to logistic reasons (no research assistant available). Adequate transcranial Doppler data were obtained in 2,107 of the 3,101 participants (67.9 %) in whom we tried to assess cerebral blood flow velocity and cerebrovascular CO_2 reactivity. The other 994 participants had window failure on both sides (n = 769), difficulty to participate due to restlessness or discomfort (n = 38) or data were lacking due to other reasons (n = 187).

Transcranial Doppler Assessment

Transcranial Doppler ultrasonography monitoring was performed (Multi-Dop X-4, DWL, Sipplingen, Germany) and the cerebral blood flow velocity (cm/sec) was measured in the middle cerebral artery on both sides if possible. End diastolic, peak systolic and mean cerebral blood flow velocities were recorded automatically. Cerebrovascular CO_2 reactivity measurements were done as follows. The cerebral blood flow velocity in the middle cerebral artery was measured continuously and the participants first breathed room air through an anaesthetic mask, tightly fit over mouth and nose, until a steady expiratory end-tidal CO_2 was obtained. Participants were then asked to inhale a mixture of 5% carbon dioxide in 95% oxygen for two minutes. Cerebrovascular CO_2 was defined as the percentage increase in cerebral blood flow velocity occurring during inspiration of 5% CO_2, divided by the absolute increase in end-tidal CO_2 in the same period (%/kPa). End-tidal CO_2 pressure (kPa) was recorded continuously with a CO_2 analyser (Multinex, Datascope, Hoevelaken, The Netherlands). End-expiratory CO_2 was assumed to reflect arterial CO_2.[13] TCD-8 DWL special software (VMR-CO_2) was used. All transcranial Doppler data were stored on hard disk for off-line analysis.

Diagnosis of dementia

Dementia screening and diagnosis followed a three-step protocol, as described in detail elsewhere.[14] Briefly, all subjects were screened with a short test of cognition (Mini Mental State Examination (MMSE)[15] and the Geriatric Mental State schedule, organic level[16]). Screen positives underwent further cognitive testing, and an informant interview was obtained. Persons suspected of dementia were examined by a neurologist and underwent more elaborate neuropsychological testing. If possible an axial T1, T2 and coronal T1 cerebral MRI scan was made in order to assess hippocampal and cortical atrophy and to exclude other causes of dementia. Dementia diagnosis was made according to internationally accepted criteria (NINCDS-ADRDA, NINDS-AIREN, DSM-III-R) by a panel that reviewed all existing information.[14, 17-19]

Measurements of cognitive function

As part of the cognitive assessment the following neuropsychological tests were administered: the Dutch version of the 30-point Mini Mental State

Examination;[15] an abbreviated Stroop test consisting of three subtasks[20] (in Part 1, the subject reads color names printed in black ink, in Part 2, the subject has to name the color of squares, in Part 3, the subject has to name the color in which the color names are printed and disregard their verbal content[21]); the Letter Digit Substitution Task, which is a modified version of the Symbol Digit Modalities Test;[22] and a verbal fluency test in which as many animals as possible had to be named within 60 seconds. The MMSE is a global cognitive test developed to use in dementia screening[15] and appeals mainly to cortical functions. The Stroop test and verbal fluency test are timed tasks that measure executive control functions (mental flexibility, vulnerability to interference, concept shifting), sustained attention and mental speed. The Letter Digit Substitution Task is used to assess complex scanning and visual tracking.[22]

The MMSE had been administered during previous examination rounds (1990-1993; 1993-1994) of the Rotterdam Study and the Rotterdam Scan study (1995-1996)[23] as well. Therefore, we were able to examine cognitive decline in the period preceding the TCD assessment (on average 6.5 years). We assumed a linear decline over time and calculated the rate of decline in MMSE for all participants with at least two measurements (n = 3,062) and who were still non-demented at time of the last MMSE measurement.

Data analysis

We used the mean of right and left hemodynamic parameters for the analyses if both middle cerebral arteries could be insonated adequately. In case of one-sided window-failure, the contralateral cerebral hemodynamic parameter was used in the analyses. Differences in characteristics between persons with successful TCD measurements (n = 2,107) and without successful TCD measurements (n = 994) were compared using analysis of covariance adjusted for age and gender.

To assess the relation between hemodynamic parameters and cognitive function and dementia, we first compared these parameters between demented and non-demented persons. Next, we investigated within non-demented persons the cross-sectional relation between cerebral blood flow velocity and cerebrovascular CO_2 reactivity and cognitive test scores. Finally, we compared within non-demented persons the hemodynamic parameters between those who had declined on the MMSE in the preceding period and those who had not.

The relation between cerebral hemodynamic parameters and dementia was assessed by analysis of covariance and by logistic regression analysis where we used hemodynamic parameters as the determinant and dementia as outcome. The relation between cerebral hemodynamic parameters and neuropsychological test performance was assessed by means of multivariate regression. Neuropsychological test results were available on more than 99% of the subjects in this study. If data were missing because the person was cognitively unable to complete the test, rather than excluding him or her from the analyses, we assigned that person the worst score that was obtained among those who did complete the tests. Otherwise subjects were excluded from that particular analysis. The relation between hemodynamic parameters and cognitive decline was assessed by analyses of covariance and by logistic regression analysis. Individual rates of decline in MMSE scores were calculated based on at least two and maximal five MMSE scores with the use of a random effects model (SAS 6.12, PROC MIXED). We used all baseline and follow-up MMSE-measurements as outcome variable, time of measurement as independent variable with time at baseline examination as t=0, and the intercept and time of MMSE measurement as random effects. The estimated fixed effect and the individual random effect were added to obtain the estimated slopes and intercepts of the individual MMSE scores. We defined cognitive decline as a decline of more than two standard deviations from the mean decline of the total non-demented population (0.20 points per year). All analyses were adjusted for age and gender. Additional adjustments were made for education, dichotomised in primary education or less and more than primary education.

Table 1. Characteristics of participants in the study population with and without transcranial Doppler (TCD) examinations.

	TCD* (n = 2,107)	No TCD* (n = 994)	Adjusted difference† (95% CI)
Age (yrs)	71.2 (6.5)	73.6 (6.7)	2.4 (1.9;2.9)
Gender (%women)	46.7	78.2	31.6 (28.0;35.2)
Systolic blood pressure (mmHg)	142.9 (20.8)	145.7 (21.7)	1.8 (0.2;3.5)
Diastolic blood pressure (mmHg)	75.4 (11.2)	75.1 (11.1)	0.8 (-0.0;1.7)
Primary education or less (%)	25.1	34.3	1.9 (-1.6;5.5)
Dementia (%)	0.9	1.7	0.4 (-0.5;1.2)

* Values represent means (SD)

† Adjusted difference adjusted for age and gender

Results

Table 1 shows the characteristics of participants with and without adequate TCD measurements. Subjects without TCD measurements were on average older, more frequently female and had a higher systolic blood pressure compared to those with TCD measurements.

Of the 18 demented with TCD assessment (9 men and 9 women) 16 were diagnosed with Alzheimer's disease and 2 with vascular dementia. Dementia patients had either minimal (n = 12, Clinical Dementia Rating Scale = 1) or mild dementia (n = 6, Clinical Dementia Rating Scale = 2).[24] In 11 of the 18 dementia patients (61 %) we obtained MRI (9 Alzheimer's disease, 2 vascular dementia). Of the Alzheimer patients, 7 had moderate to severe atrophy and 2 patients had normal scans. Besides the atrophy, 3 patients had also mild white matter lesions.

Table 2. Comparison of cerebral hemodynamic parameters in persons with and without dementia.

	No dementia* (n = 2,089)	Dementia* (n = 18)	Adjusted difference† (95% CI)	Odds ratio‡ (95% CI)
End diastolic CBF velocity (cm/s)	32.5 (9.0)	22.0 (5.7)	5.7 (2.0;9.7)	0.31 (0.15-0.61)
Peak systolic CBF velocity (cm/s)	86.5 (19.0)	70.0 (16.1)	14.0 (5.2;22.8)	0.62 (0.46-0.83)
Mean CBF velocity (cm/s)	50.5 (11.6)	38.0 (8.6)	8.6 (3.4;13.8)	0.40 (0.24-0.68)
Cerebrovascular CO_2 reactivity (%/kPa)	3.9 (2.6)	2.9 (2.4)	0.2 (-1.1;1.4)	0.97 (0.76-1.22)

*Values represent means (SD)
†Adjusted difference (95% CI), adjusted for age and gender
‡Odds ratio (95% CI), adjusted for age and gender, per 10 cm/s increase in cerebral blood flow velocity
CBF = cerebral blood flow

Cerebral blood flow velocity was significantly lower in demented than in non-demented persons (Table 2). Cerebrovascular CO_2 reactivity was lower in demented than in non-demented participants, but the difference was not statistically significant. When we repeated these analyses confined to patients with Alzheimer's disease, the results were virtually the same as for all dementia patients.

Non-demented participants with higher cerebral blood flow and cerebrovascular CO_2 reactivity tended to perform better on cognitive tests (Table 3). Additional adjustment for education did not essentially change the results.

Table 3. Adjusted difference in test score by increasing cerebral blood flow velocity (per 10 cm/sec) and by increasing cerebrovascular CO_2 reactivity (per %/kPa)*.

	Stroop (sec)					
	Part 2	Part 3	Part (3-2)	MMSE	Wordfluency (animals/min)	Letter Digit Substitution Task (letters/min)
Mean neuropsychological test result (SD)	24.5 (5.4)	62.5 (40.2)	38.1 (38.5)	27.9 (1.7)	21.4 (5.4)	27.6 (6.8)
Cerebral blood flow velocity (per 10 cm/s)						
End diastolic	-0.34 (-0.61;-0.07)	0.51 (-2.50;1.51)	-0.17 (-2.12;1.77)	0.03 (-0.05;0.12)	0.14 (-0.13;0.41)	0.06 (-0.27;0.39)
Peak systolic	-0.12 (-0.24;0.00)	0.08 (-0.82;0.98)	0.20 (-0.67;1.07)	0.01 (-0.03;0.04)	0.02 (-0.10;0.13)	0.05 (-0.09;0.20)
Mean	-0.24 (-0.44;-0.04)	-0.12 (-1.63;1.40)	0.12 (-1.34;1.58)	0.02 (-0.05;0.08)	0.07 (-0.13;0.27)	0.07 (-0.17;0.32)
Cerebrovascular CO_2 reactivity (per %/kPa)	-0.04 (-0.13;0.05)	0.14 (-0.53;0.81)	0.18 (-0.45;0.83)	0.05 (0.02;0.07)	0.12 (0.03;0.20)	0.19 (0.08;0.29)

*Regression coefficient and 95% CI, adjusted for age and gender

Table 4 shows the comparison of blood flow velocities and cerebrovascular CO_2 reactivity between participants with and without cognitive decline in the period preceding TCD assessment. Persons with cognitive decline had lower cerebral blood flow velocities compared to those without cognitive decline. Mean cerebrovascular CO_2 reactivity was also lower in persons with than without cognitive decline (cerebrovascular CO_2 reactivity: 0.8 %/kPa; 95% CI: 0.2-1.4). Additional adjustment for education level did not change the results.

Table 4. Comparison of cerebral hemodynamic parameters in persons with and without cognitive decline*.

	No cognitive decline¶ (n = 2,008)	Cognitive decline¶ (n = 81)	Adjusted difference† (95% CI)	Odds ratio‡ (95% CI)
End diastolic CBF velocity (cm/s)	32.6 (9.0)	29.2 (8.6)	0.73 (0.55-0.97)	0.73 (0.55-0.97)
Peak systolic CBF velocity (cm/s)	86.7 (18.9)	80.6 (18.6)	0.85 (0.75-0.97)	0.85 (0.75-0.97)
Mean CBF velocity (cm/s)	50.6 (11.5)	46.3 (11.2)	0.77 (0.62-0.95)	0.77 (0.62-0.95)
Cerebrovascular CO_2 reactivity (%/kPa)	3.9 (2.7)	2.9 (1.8)	0.86 (0.76-0.96)	0.86 (0.76-0.96)

*Cognitive decline defined as a decline of more than two standard deviations from the mean decline of the non-demented population

¶ Values represent means (SD)

†Adjusted difference (95% CI), adjusted for age and gender

‡Odds ratio (95% CI), adjusted for age and gender, per 10 cm/s increase in cerebral blood flow velocity

CBF = cerebral blood flow

Discussion

We found in a large population-based study that cerebral blood flow velocity was not only significantly lower in persons with dementia, but also in non-demented persons with cognitive decline as compared to cognitively intact subjects. Likewise, the cerebrovascular CO_2 reactivity was significantly lower in persons with cognitive decline and in those with impaired cognitive performance and tended to be lower in dementia patients.

Before further discussing our findings we want to consider whether selection bias may have influenced our findings. First, since participants had to attend the research centre for TCD assessment, persons with severe dementia and persons with severe comorbidity are underrepresented in our study sample. The relatively healthy sample in our study may have attenuated the strength of the associations. Second, TCD was not assessed in 26 percent of all persons visiting the research centre. However, since this was a random sample of all eligible persons that visited the research centre it is unlikely that this has biased our

results. Third, we failed to obtain adequate TCD data in 32 percent of participants in whom we tried to assess hemodynamic parameters, mainly due to window failure. This rate is in accordance with previous findings from clinical studies.[25, 26] This could have biased our results if window failure were related to cognitive performance or dementia, which we consider unlikely.

To our knowledge, this is the first population-based study examining cerebral hemodynamic parameters in relation to dementia and cognitive decline. Some small, clinical studies suggested no differences in basal flow velocities between healthy controls and Alzheimer patients and lower flow velocities and diminished vasomotor responses in multi-infarct dementia patients.[6, 11] It should be noted that these studies used highly selected Alzheimer patients to exclude confounding by vascular pathology. In our study, we were unable to evaluate differences between Alzheimer's disease and vascular dementia since we had only two vascular dementia patients in our sample.

The explanation for our finding that cerebral blood flow velocity is lower in dementia patients and persons with cognitive dysfunction compared to non-demented persons is still unclear. The reduced flow velocities may represent consequences of reduced metabolic needs due to neuronal tissue loss.[26, 27] Neuroradiologic techniques including SPECT and PET have shown reductions of global and regional cerebral blood flow in subjects with Alzheimer's disease.[2, 3, 8, 26] Flow abnormalities in persons with very mild dementia have also been found.[7] An alternative explanation is that a decline in cerebral blood flow velocity is a risk factor for dementia. A decrease in blood flow velocity results in decreased delivery of oxygen.[28] Hypoxia may affect cognitive function[29] and may cause ischaemic neuronal lesions in vulnerable areas of the brain,[30] especially in watershed areas.[30, 31] Our observation that cerebral blood flow velocity was already lower in persons with cognitive decline, without dementia, does fit with both explanations. Follow-up studies with repeated assessments are needed to distinguish between these mechanisms.

Transcranial Doppler ultrasonography is one of the safest and most inexpensive as well as the most reliable techniques to evaluate cerebral arterial reserve capacity.[32] A low vasomotor response may indicate small vessel pathology.[9] In our study, cerebrovascular CO_2 reactivity was lower in persons with cognitive decline or low cognitive performance, lending further support to the hypothesis of a role for vascular risk factors and vascular disease in the

aetiology of cognitive decline and dementia. The fact that we did not find a significantly lower cerebrovascular CO_2 reactivity in persons with dementia may reflect lack of power. However, it is also possible that this was a group of relatively healthy and 'pure' Alzheimer patients who were free of vascular comorbity.

In conclusion, our study demonstrates that cerebral blood flow velocity is significantly lower in persons with dementia and cognitive decline than in persons with intact cognition. Also, cerebrovascular CO_2 reactivity was lower in persons with reduced cognitive function. Whether the lower blood flow velocity and vasomotor response are a cause or a consequence of dementia remains to be elucidated. Future research should include more non-invasive diagnostic tools to investigate cerebral hemodynamics, such as transcranial Doppler.

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4.2

Atherosclerosis and the risk of dementia and Alzheimer's disease in a 6-years follow-up study: the Rotterdam Study

Abstract

Background *Evidence is accumulating that vascular disorders are implicated in dementia and its most frequent subtype, Alzheimer's disease. In an earlier report from the Rotterdam Study we showed that the prevalence of dementia, Alzheimer's disease and vascular dementia increased with the degree of atherosclerosis. Here we report a 6-years prospective follow-up study of atherosclerosis and the incidence of dementia and its subtypes.*

Methods *We examined the relation between atherosclerosis and risk of dementia in the Rotterdam Study, a prospective population-based study of 7,983 subjects aged 55 years and over. 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 generalised atherosclerosis. From these indicators a score of atherosclerosis ranging from 0 (no atherosclerosis) to 3 (severe atherosclerosis), was constructed.*

Findings *After a mean follow-up of 5.7 years, 395 new cases of dementia were identified. Of 6,142 persons (309 cases) of the total cohort at risk of developing dementia, information was available on at least one indicator of atherosclerosis. Wall thickness of the common carotid arteries and presence of plaques in the carotid arteries were significantly associated with all dementia and Alzheimer's disease. The relative risks of all dementia, Alzheimer's disease and vascular dementia increased by the score of atherosclerosis (severe atherosclerosis compared to no atherosclerosis: all dementia: RR 1.58; 95% CI: 1.02-2.44; Alzheimer's disease: RR 1.76, 1.07-2.89; vascular dementia: RR 1.62, 0.55-4.77).*

Interpretation *Our findings suggest that atherosclerosis is associated not only with a small group of vascular dementia, but also with the major subtype of dementia, Alzheimer's disease.*

Introduction

Evidence is accumulating that vascular disorders are implicated in dementia and its most frequent subtype, Alzheimer's disease.[1, 2] Atherosclerosis has also been linked to dementia, and we previously reported that various indicators of atherosclerosis are associated with prevalent dementia.[3]

Here we report a 6-years prospective follow-up study of atherosclerosis and the incidence of dementia and its subtypes in 395 new cases of dementia identified in 7,046 participants at risk for dementia.

Methods

Study design

The Rotterdam Study is a population based prospective cohort study among 7,983 persons aged 55 years and older living in a suburb of Rotterdam, the Netherlands. The objective of the study is to investigate determinants of chronic and disabling diseases.[4] The study has been approved by the Medical Ethics Committee of the Erasmus University. Participants gave written informed consent and permission to retrieve information from treating physicians. Baseline examinations took place between 1990 and 1993. Participants were interviewed at their homes and thereafter, during two sessions, examined at the research centre. At baseline, 7,528 persons (94.3% of total cohort) underwent extensive screening for dementia[5] and 482 persons were identified with prevalent dementia. This resulted in a cohort of 7,046 participants at risk for dementia. The cohort was re-examined in 1993-1994 and in 1997-1999.

Diagnosis of dementia

Dementia screening and diagnosis during baseline and follow-up examinations were similar.[5] Briefly, all subjects were screened with a short test of cognition (Mini Mental State Examination[6] and the Geriatric Mental State schedule, organic level[7]). Screen positives underwent further cognitive testing, and an informant interview was obtained. Persons suspected of dementia were examined by a neurologist and underwent neuropsychological testing. To differentiate vascular dementia from Alzheimer's disease a brain scan was made by magnetic resonance imaging (MRI) or computed tomography (CT). In

addition to dementia screening in person, the total cohort is continuously being monitored for detection of interval cases of dementia by means of computerised linkage of the study database with general practitioners medical records and the database of the Regional Institute for Outpatient Mental Health Care (RIAGG).[5] Of both the in-person-screened individuals and those monitored through general practitioners and mental health services, a diagnosis of dementia was made according to established criteria (NINCDS-ADRDA, NINDS-AIREN, DSM-III-R) by a panel that reviewed all existing information.[5, 8-10]

Measurements of atherosclerosis and other baseline 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 risk factors for 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.[11] 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.[12] 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-to-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 generalised atherosclerosis.[13, 14] 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.

Baseline blood pressure was measured in sitting position at the right upper arm with a random-zero sphygmomanometer. The average of two measurements, separated by a count of the pulse rate, was used. Apolipoprotein-

E (APOE) 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.[15] Serum total and high-density lipoprotein (HDL) cholesterol concentrations were determined by an automated enzymatic procedure.[16] Body mass index was determined as body weight (in kg) divided by height squared (in m^2). Smoking was categorised as never, former and current smoking.

Statistical analysis

The associations between atherosclerosis, and dementia, Alzheimer's disease and vascular dementia were analysed as follows. First, the relative risks of dementia associated with indicators of atherosclerosis were calculated with Cox' proportional hazards regression and presented with a 95% confidence interval (95% CI), controlling for age, age^2, and gender.

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 three locations of carotid arteries (left or right bifurcation, left or right internal- or common carotid arteries), average wall-thickness of common carotid arteries in the highest quintile of the distribution, and evidence of peripheral arterial disease, defined as ankle-to-brachial index less than 0.90. The cut-off points for indicators of atherosclerosis were selected approximately according the upper quintile of the distribution. This atherosclerosis score was analysed in four categories corresponding to score values of 0-3. With a Cox' proportional hazards model, the relative risk for each category of atherosclerosis for dementia and its subtypes was calculated, adjusting for age, age^2, and gender.

Third, we investigated possible biological interaction between the atherosclerosis score and the apolipoprotein-E polymorphism.[17] To investigate the combined effect of APOE and atherosclerosis, the study population was dichotomised according to atherosclerosis score, and classified into four groups: (1) APOE3E3 carriers with an atherosclerosis score of 0 or 1 (reference group); (2) Carriers of APOE*4 with an atherosclerosis score of 0 or 1; (3) APOE3E3 carriers with an atherosclerosis score of 2 or 3; (4) APOE*4 carriers with an atherosclerosis score of 2 or.

No major differences in the association between atherosclerosis and dementia were observed between men and women, and therefore the estimates are

presented for men and women combined. These associations were virtually not altered after adjustment for blood pressure, total cholesterol and body mass index, and therefore presented with adjustments for age, age^2 and gender.

Results

In Table 1 characteristics of the study population are summarised. After a mean follow-up of 5.7 years, 395 new cases of dementia were identified. Alzheimer's disease was diagnosed in 293 (74%) persons and vascular dementia was diagnosed in 57 (14%) persons. Of 6,142 persons (309 cases) of the total cohort at risk of developing dementia, information was available on at least one indicator of atherosclerosis. The percentage of missing values was 13% for peripheral arterial disease, 36% for wall thickness of common carotid arteries, 23% for plaques in carotid arteries and because this was a composite score 46% for the atherosclerosis score. Persons without measurements were on average older, but did not significantly differ in gender distribution or dementia incidence.

Table 1. Baseline characteristics of the study population.

	Men	Women	Total Population
Age (years)	68.3 (55-96)*	70.3 (55-106)	69.5 (55-106)
Systolic blood pressure (mm Hg)	138.7 (21.7)	139.8 (22.6)	139.3 (22.3)
Diastolic blood pressure (mm Hg)	74.5 (11.5)	73.2 (11.4)	73.6 (11.5)
Total cholesterol (mmol/L)	6.3 (1.1)	6.8 (1.2)	6.6 (1.2)
Body Mass Index (kg/m^2)	25.7 (3.7)	26.8 (4.1)	26.3 (4.0)
Smoking (%)			
Never smoked	8.2	54.2	35.6
Smoked in the past	61.9	27.8	41.6
Current smoker	29.9	18.1	22.8

*Values represent means and ranges for age, and means and standard deviations for other variables.

Wall thickness of the common carotid arteries and presence of plaques in the carotid arteries were significantly associated with all dementia and Alzheimer's disease (Table 2). The relative risks of all dementia, Alzheimer's disease and vascular dementia increased by the score of atherosclerosis (Table 3).

Table 2. Relative risk of Alzheimer's disease, vascular dementia and total dementia with indicators of atherosclerosis*

	Alzheimer's disease	Vascular dementia	All dementia
Peripheral arterial disease	1.14 (0.85-1.53)	1.31 (0.70-2.45)	1.13 (0.87-1.45)
Wall thickness common carotid arteries†	1.16 (1.01-1.32)	1.20 (0.93-1.57)	1.11 (1.00-1.26)
Wall thickness common carotid arteries, highest quintile versus lower quintiles	1.26 (0.92-1.73)	1.43 (0.76-2.71)	1.17 (0.89-1.53)
Plaque in bifurcation: no plaques	1.0	1.0	1.0
plaque either in left or right	1.08 (0.74-1.56)	1.28 (0.58-2.85)	1.14 (0.83-1.57)
plaque present in both	1.12 (0.78-1.60)	1.33 (0.62-2.84)	1.21 (0.89-1.64)
Plaque in internal carotid arteries			
no plaques	1.0	1.0	1.0
plaque either in left or right	1.27 (0.88-1.82)	0.42 (0.14-1.23)	1.14 (0.84-1.57)
plaque present in both	1.41 (0.97-2.05)	1.75 (0.88-3.49)	1.37 (1.00-1.89)
Plaque in common carotid arteries			
no plaques	1.0	1.0	1.0
plaque either in left or right	0.89 (0.58-1.38)	0.74 (0.29-1.89)	0.80 (0.54-1.17)
plaque present in both	1.59 (1.00-2.52)	1.45 (0.56-3.74)	1.41 (0.94-2.11)
Plaques in carotid arteries dichotomised in less than three locations versus more than three locations	1.36 (1.02-1.82)	1.51 (0.83-2.74)	1.32 (1.03-1.68)

*Adjusted for age, age^2 and gender

†Relative risk of one SD (0.22 mm) increase of wall thicknes

Table 3. Relative risk of Alzheimer's disease, vascular dementia and total dementia with indicators of atherosclerosis*.

(n = number of cases)	Alzheimer's disease (n = 151)	Vascular dementia (n = 35)	All dementia (n = 208)
Atherosclerosis score	1.0	1.0	1.0
	0.74 (0.48-1.13)	0.59 (0.22-1.60)	0.77 (0.54-1.10)
	1.24 (0.79-1.96)	1.92 (0.81-4.52)	1.24 (0.84-1.82)
	1.76 (1.07-2.89)	1.62 (0.55-4.77)	1.58 (1.02-2.44)
P-value for trend	p = 0.04	p = 0.07	p = 0.03

*Adjusted for age, age^2 and gender

Persons with evidence for atherosclerosis (score 2 or 3) and the APOE*4 genotype had an increased risk of all dementia (RR 3.1, 95% CI: 2.4-5.9), of Alzheimer's disease (RR 4.1, 95% CI: 2.4-6.8), and of vascular dementia (RR 4.7, 95% CI: 1.5-14.5)(Table 4).

Table 4. Relative risk of Alzheimer's disease, vascular dementia and total dementia by atherosclerosis and apolipoprotein genotype*.

Genotype†	Alzheimer's disease Atherosclerosis		Vascular dementia Atherosclerosis		All dementia Atherosclerosis	
	–	+	–	+	–	+
ApoE 33	1.0	1.93	1.0	2.17	1.0	1.80
	(reference)	(1.17-3.18)	(reference)	(0.80-5.90)	(reference)	(1.17-2.77)
ApoE 4+	2.65	4.05	2.89	4.71	2.72	3.71
	(1.73-4.07)	(2.40-6.81)	(1.13-7.37)	(1.53-14.51)	(1.89-3.91)	(2.35-5.86)

*Adjusted for age, age^2 and gender

†ApoE 33: apolipoprotein-E ε3/ε3 genotype; ApoE 4+: apolipoprotein-E ε2/ε4, ε3/ε4, or ε4/ε4

Discussion

The main finding of this study is that indicators of atherosclerosis are associated with the risk of dementia and both of its main subtypes, Alzheimer's disease and vascular dementia. Some limitations of our study have to be discussed.

It is likely that some error has occurred in the measurement of atherosclerosis indicators. Such error would have led to misclassification and to underestimation of any true association between atherosclerosis and dementia, provided that the measurement error occurred to the same extent among the dementia patients and the non-demented participants. We used ultrasonographic indicators of

atherosclerosis, but increased thickness of the intima media wall of the common carotid artery may not necessarily reflect atherosclerosis. Another concern is how dementia and its subtypes are diagnosed. Our study used diagnostic procedures with relative high sensitivity and specificity through a three-phase diagnostic work-up.[5,18,19] Without confirmation at necropsy, however, subtyping of dementia remains unreliable. In a main analysis, we classified primary Alzheimer's disease, complicated by cerebrovascular disease, as Alzheimer's disease. However, an additional analysis in which cerebrovascular patients were excluded from the Alzheimer group yielded essentially the same results as the main analysis. Although we can not fully exclude misclassification, we believe that this analysis supports the view that atherosclerosis is associated with Alzheimer's disease.

Atherosclerosis may be related to dementia in several ways. Firstly, atherosclerosis may cause hemodynamic changes leading to neuronal damage in vulnerable areas of the brain. Also, atherosclerosis may impair the blood-brain barrier function as a result of cerebral vessel wall damage.[20] Finally, vascular damage associated with atherosclerosis superimposed on already existing Alzheimer pathology may lead to an earlier detection of otherwise subclinical Alzheimer's disease.

Our findings suggest that atherosclerosis is associated not only with a small group of vascular dementia, but also with the major subtype of dementia, Alzheimer's disease. The magnitude of the association is generally smaller than we have reported before in our prevalence study.[3] The attenuation of the magnitude of the association may be due to measurement error, as discussed before, or to the generally observed decrease of associations with age.

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4.3

Alcohol consumption and risk of dementia: the Rotterdam Study

Abstract

Background *Light-to-moderate alcohol consumption reduces the risk of coronary heart disease and stroke. Because vascular disease may be associated with cognitive impairment and dementia, alcohol consumption may also affect the risk of dementia.*

Methods *We examined the relation between alcohol consumption and risk of dementia in the Rotterdam Study, a prospective population-based study of 7,983 subjects aged 55 years and over. The study population consisted of all subjects who were non-demented at baseline (1990-1993) and had complete data on alcohol consumption (n=5,395). We used proportional hazards regression analysis, adjusted for age, gender, systolic blood pressure, total cholesterol, education, smoking and body mass index. The reference category included individuals who did not consume alcohol.*

Results *The average follow-up was 6.0 years. During this period 197 subjects developed dementia (146 Alzheimer's disease, 29 vascular dementia, 22 other dementia). Mean alcohol consumption was 0.87 glasses per day. Light-to-moderate drinking (1 to 3 glasses/day) was significantly associated with a lower risk of dementia (relative risk 0.58, 95% confidence interval: 0.38-0.90) and vascular dementia (relative risk 0.29, 95% confidence interval: 0.09-0.93) and diminished the effect of APOE*4 on the risk of dementia. The relation between alcohol and dementia did not vary by type of alcoholic beverage.*

Conclusions *These findings are compatible with the view that light-to-moderate alcohol consumption may lower the risk of dementia in an elderly population.*

Introduction

Light-to-moderate alcohol consumption is associated with lower risks of coronary heart disease, ischemic stroke and total mortality in elderly men and women.[1-3] Since evidence is increasing that vascular disease is associated with cognitive impairment and dementia,[4-6] light-to-moderate alcohol intake might also reduce the risk of dementia and Alzheimer's disease. A population-based prospective study in Bordeaux, France reported an inverse association between wine consumption and the risk of dementia.[7] We quantified the relation between alcohol consumption and the risk of dementia and subtypes of dementia; specifically whether the effect varied by type of alcoholic beverages.

Methods

Study population

This study was carried out as part of the Rotterdam Study, a population based prospective cohort study for which residents aged 55 years and over of a suburb of Rotterdam, the Netherlands, including those living in institutions, were asked to participate.[8]

During the baseline examination (1990-1993), participants were interviewed at home by a trained research assistant. Information was obtained on current and past health, medication, lifestyle, and risk indicators for chronic diseases. The participants subsequently visited the study center twice for clinical examinations. A food-frequency questionnaire was administered to participants who attended the second visit at the study center (n = 7,006). The questionnaire was not administered during the pilot phase of the Rotterdam Study (n = 273) nor to nursing home residents (n = 492). Furthermore, 477 subjects did not receive a dietary questionnaire due to logistic reasons. Persons with dementia might provide unreliable answers regarding their food patterns and therefore the questionnaire was not administered or excluded afterwards (n = 97). For the same reason we excluded subjects who were screenpositive (MMSE score below 26, or a GMS score greater than 0) and scored below 80 points on the CAMCOG,[9] which is the neuropsychological test administered in the case-finding procedure for dementia (n = 60). Due to logical inconsistencies in the dietary interviews, 212 additional respondents were excluded afterwards,

resulting in 5,395 completed reliable questionnaires. Follow-up examinations took place in 1993-1994 and in 1997-1999.

Alcohol intake

Before the baseline center visits, participants received a checklist on which they indicated all foods and drinks they consumed at least once during the preceding year. The completed checklist formed the basis of an interview at the study center by a trained dietician. An extensive, validated semiquantitative food frequency questionnaire was used.[10, 11] The questionnaire comprised 170 food items and all relevant beverages, including tea, coffee, and alcohol.[11] The reference period was the year preceding the interview. First, subjects were asked if they ever drank alcohol. If the answer was affirmative, we asked about the frequency of drinking. Persons who reported to drink alcohol at least twice a month, were further inquired about average amounts of specific beverages (wine, beer, liquor and fortified wine types (e.g. sherry, port)). There were 28 participants who reported to use alcohol less than twice a month. They did not differ from non-drinkers with respect to age, gender, smoking status and educational level and were classified as non-drinkers of alcohol. In addition, participants were asked if they had changed their pattern of alcohol consumption during the preceding five years (less than they used to drink, more than they used to drink) and if they had consumed more than six alcoholic beverages on one day during the last year (binge drinking). Average daily dietary nutrient intake was calculated by multiplying the frequency and amount consumed for each food item by its nutrient content listed in an automated version of the Dutch Food Composition Table.[12]

Diagnosis of dementia

Dementia screening and diagnosis during baseline and follow-up examinations followed a three-step protocol, as described in detail elsewhere.[13] Briefly, all subjects were screened with a short test of cognition (Mini Mental State Examination[14] and the Geriatric Mental State schedule, organic level[15]). 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 neurologist, underwent neuropsychological testing, and if possible a brain scan was made by magnetic resonance imaging. In addition, the

total cohort was continuously monitored for incident dementia cases via computerized linkage between the study database and computerized medical records from general practitioners and the Regional Institute for Outpatient Mental Health Care (RIAGG).[13] Dementia diagnosis was made in accordance with internationally accepted criteria (NINCDS-ADRDA, NINDS-AIREN, DSM-III-R) by a panel that reviewed all existing information.[13, 16-18]

Other baseline measurements

The following baseline variables were used as possible confounders: age, gender, diabetes, defined according to WHO criteria for epidemiological studies of diabetes as the use of medication for diabetes or a random or post-load serum glucose level greater than 11 mmol/l[19]; systolic blood pressure, measured in sitting position at the right upper arm with a random-zero sphygmomanometer; education, dichotomized in primary education or less and more than primary education; smoking, categorized as never, past and current smoking; and body mass index (weight (kg)/height (m^2)). Apolipoprotein E (APOE) 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.[20] Homozygotes for the APOE*4 allele and heterozygotes were combined and designated as the APOE*4 category. During the home interview participants were asked to report and show all medication used during the week preceding the interview. Subsequently, all drugs were classified according to their corresponding Anatomical-Therapeutical-Chemical-code (ATC-code).[21]

Statistical Analysis

We estimated the risk of dementia associated with alcohol consumption in categories (no alcohol intake; less than one glass per week; one or more glasses per week and less than one per day; 1 to 3 glasses per day; 4 or more glasses per day) with Cox' proportional hazards regression analysis, controlling for age and gender. The relative risk was presented with a 95% confidence interval (95% CI). No alcohol intake was used as reference category. To examine whether gender or age modified the relation we calculated relative risks for men and women separately and in strata of age (55-74, 75 years and older). Age and gender were evaluated for potential statistical interaction with alcohol by adding

separate terms to the regression models (age (continuously) x alcohol intake category; gender x alcohol intake category). Since stratified analysis on APOE*4 suggested a stronger effect of alcohol within the stratum of APOE*4 allele carriers, we investigated possible biologic interaction. To investigate the combined effect of APOE and alcohol, the study population was dichotomized according to alcohol intake and, to yield maximum statistical power, classified into four groups: (1) intake of alcohol and APOE*4 allele absent (reference group); (2) intake of alcohol and APOE*4 allele present; (3) no alcohol intake and APOE*4 allele absent; (4) no alcohol intake and APOE*4 allele present. Possible interaction was studied according to the principles as described by Rothman.[22, 23] Briefly, interaction of factors A and B was considered to be a departure from additivity, and present if: $(RR_{A+B+} - RR_{A+B-}) - (RR_{A-B+} - 1) > 0$.

To check if associations could be contributed to confounding, analyses were repeated with possible confounders added to the models (education, smoking, body-mass-index, diabetes, and systolic blood pressure). All analyses were repeated with dementia subtypes (Alzheimer's disease, vascular dementia) as the outcome.

The risk of dementia and dementia subtypes associated with specific types of alcoholic beverages was analyzed as follows. For each individual we expressed the amount of intake of wine, beer, liquor and fortified wine types as a percentage of that individual's total alcohol intake. Next, we added these alcohol-type specific variables to the model that already contained amount of alcohol intake in categories as described above. The change in likelihood between the model with total amount of alcohol and the model with total amount as well as types of alcohol reflects whether the risk of dementia was dependent on specific alcoholic beverages rather than on alcohol itself. The risk of dementia associated with intake of specific types of alcoholic beverages (beer, liquor and fortified wine types) was expressed relative to the risk associated with wine drinking.

To check if the observed relation between alcohol intake and risk of dementia was due to a selection in the reference group (no alcohol intake) we repeated the analyses excluding those who reported use of medication in which alcohol intake was contraindicated (anxiolytics, antidepressants, and hypnotics). In addition, we excluded participants with a history of alcoholism (n = 4) and those with alcohol consumption less than twice a month (n = 28).

Table 1. Baseline characteristics of participants of the Rotterdam Study*.

	Alcohol consumption (no. of drinks)				
	No alcohol	< 1/wk	≥ 1/wk - < 1/day	1 - 3/day	≥ 4/day
Number of subjects	1113	1156	1518	1443	165
Age (years)	69.2 (8.1)	68.4 (7.8)	67.2 (7.7)	66.9 (7.4)	65.2 (6.4)
Gender (% women)	75.1	76.5	58.6	38.3	13.3
Blood pressure (mm Hg)					
Systolic	140.0 (22.8)	139.6 (21.9)	137.4 (22.2)	137.4 (21.2)	142.4 (20.8)
Diastolic	73.0 (11.2)	73.8 (11.0)	73.4 (11.2)	73.9 (11.2)	77.4 (10.7)
Smoking (%)					
Never smoked	47.1	48.1	33.8	14.8	6.1
Smoked in the past	33.2	34.9	44.9	55.0	41.2
Current smoker	19.7	17.0	21.3	30.2	52.7
Body mass index	26.6 (4.2)	26.6 (3.9)	26.6 (3.5)	26.0 (3.2)	26.1 (3.6)
Diabetes	14.5	7.9	6.4	9.6	14.9
Primary education or less	45.9	37.8	30.9	27.7	28.5
APOE*4 allele present(%)	29.5	25.8	27.1	28.7	22.2

*Mean (SD) or percentage

Finally, we repeated the analyses excluding participants who reported a change in their pattern of alcohol consumption in the past five years, as past reported intake may not accurately reflect current intake in these participants.

Results

During 32,341 person-years of follow-up (mean follow-up of 6.0 years), 197 participants developed dementia. Alzheimer's disease was diagnosed in 146 (74.1 %) patients (134 without and 12 with cerebrovascular disease), vascular dementia was diagnosed in 29 (14.7 %) patients and 22 (11.2 %) were diagnosed with other types of dementia.

Table 1 shows the baseline characteristics of the study population according to categories of alcohol consumption. Mean alcohol consumption was 0.87 glasses per day (SD 1.27) and higher for men (1.37, SD 1.57) than for women (0.51, SD 0.84). As alcohol intake increased, the percentage of never smokers decreased sharply.

Table 2. Distribution of alcohol intake in the Rotterdam Study, expressed as proportion (%) of the population taking a specific type of alcohol and average intake (SD) in those taking that specific type of alcohol.

	Beer		Wine		Liquor		Fortified wine types	
	%	drinks/day	%	drinks/day	%	drinks/day	%	drinks/day
Total	21.0	0.73 (1.05)	37.0	0.38 (0.57)	35.0	1.39 (1.49)	32.3	0.51 (0.68)
Men	44.3	0.79 (1.10)	29.6	0.46 (0.67)	60.5	1.56 (1.57)	17.9	0.59 (0.69)
Women	4.8	0.32 (0.44)	42.1	0.33 (0.51)	17.2	0.97 (1.17)	42.4	0.48 (0.68)

Table 2 shows the distribution of consumption of alcoholic beverages in the study population. The mean intake of beer and liquor was higher for men than for women and the mean intake of fortified wine types (e.g. sherry, port) was higher for women. Men and women drank equal amounts of wine.

The overall effect of alcohol consumption on the risk of dementia is shown in Table 3. Compared to no alcohol consumption, light-to-moderate drinking (1 to 3/day) was associated with a significantly lower risk of dementia (relative risk 0.58, 95 % CI: 0.38-0.90). The lower risk was most prominent among men, although the statistical interaction between gender and alcohol consumption was not significant ($p = 0.49$). None of the women drinking four or more drinks per day had dementia at follow-up, thus we were unable to estimate relative risks. The effect of alcohol was mainly present for vascular dementia (Table 3).

Table 3. Relative risk of subtypes of dementia according to alcohol consumption

(n = number of cases)		RR dementia (95% CI)				
		No alcohol	< 1/wk	≥ 1/wk - < 1/day	1 - 3/day	≥ 4/day
All dementia	Total	1.0	0.82 (0.56-1.22)	0.75 (0.51-1.11)	0.58 (0.38-0.90)	1.00 (0.39-2.59)
(n = 197)	Men	(reference)	0.60 (0.27-1.34)	0.53 (0.28-1.00)	0.40 (0.21-0.74)	0.88 (0.32-2.44)
	Women		0.91 (0.58-1.44)	0.91 (0.55-1.49)	0.85 (0.47-1.57)	-
Alzheimer's	Total	1.0	0.91 (0.58-1.44)	0.91 (0.58-1.44)	0.72 (0.43-1.20)	1.17 (0.35-3.55)
disease	Men	(reference)	0.40 (0.11-1.50)	0.81 (0.35-1.86)	0.52 (0.22-1.20)	1.16 (0.30-4.47)
(n = 146)	Women		1.05 (0.64-1.72)	0.92 (0.53-1.62)	0.96 (0.49-1.85)	-
Vascular	Total	1.0	0.80 (0.30-2.13)	0.37 (0.12-1.12)	0.29 (0.09-0.93)	1.58 (0.31-8.04)
Dementia	Men	(reference)	1.22 (0.30-5.01)	0.31 (0.07-1.41)	0.26 (0.06-1.09)	1.65 (0.29-9.48)
(n = 29)	Women		0.50 (0.12-2.01)	0.44 (0.09-2.25)	0.46 (0.05-3.92)	-

*Adjustment for age, gender, body-mass-index, systolic blood pressure, diabetes, smoking, and education

As shown in Table 4a, light-to-moderate alcohol consumption was associated with a lower risk of dementia both in absence and presence of the APOE*4 allele.

Table 4a. Relative risk of dementia associated with alcohol intake stratified by absence or presence of the APOE*4 allele*.

	APOE*4 absent cases (total)	APOE*4 absent (n = 3743)†	APOE*4 present cases (total)	APOE*4 present (n = 1426)
No alcohol	29 (757)	1.0 (reference)	33 (317)	1.0 (reference)
< 1/wk	25 (816)	1.03 (0.60-1.78)	19 (283)	0.71 (0.40-1.25)
≥ 1/wk - < 1/day	29 (1,060)	1.07 (0.62-1.85)	17 (394)	0.46 (0.25-0.84)
1 - 3/day	16 (987)	0.53 (0.27-1.03)	20 (397)	0.51 (0.28-0.93)
≥ 4/day	1 (123)	0.50 (0.07-3.78)	4 (35)	1.33 (0.45-3.99)

*Values are relative risks (95% CI), adjusted for age, gender, body-mass-index, systolic blood pressure, diabetes, smoking, and education

†Of 226 persons (4 dementia cases) APOE status was not determined

However, the association with alcohol intake was already present for lower amounts of alcohol intake in carriers of the APOE*4 allele. The interaction effect was (4.00 - 1.18) - (2.43 - 1) = 1.39 (95% CI –0.87 to 3.67)(Table 4b). This means that in our sample and when compared to non-APOE*4 carriers who did use alcohol, persons who both carried an APOE*4 allele and did not drink had a 140% higher risk of becoming demented than one would estimate from the separate effects of carrying an APOE*4 allele and alcohol abstinence.

Table 4b. Relative risk of dementia associated with both alcohol intake and APOE*4.*

Alcohol intake	APOE*4 absent	APOE*4 present
No alcohol intake	1.18 (0.75-1.84)	4.00 (2.62-6.11)
Alcohol intake	1.00 (reference)	2.43 (1.72-3.43)

*Values are relative risks (95% CI), adjusted for age, gender, body-mass-index, systolic blood pressure, diabetes, smoking, and education

The lower risk of dementia associated with light-to-moderate alcohol drinking was more marked in participants younger than 75 years of age than in participants aged 75 years and older (55-74 years: relative risk 0.43, 95% CI: 0.23-0.81; ≥ 75 years: relative risk 0.77, 95% CI: 0.42-1.40; p interaction: 0.09). However, when we calculated the absolute risk differences between non-drinking and light-to-moderate drinking in the two age strata, the risk differences were similar (absolute risk difference 55-74 years: 1.6%; ≥ 75 years: 2.2 %).

We found no evidence that the risk of dementia or subtypes of dementia associated with one type of alcoholic beverage was different from another type of alcoholic beverage. A model in which we included specific types of alcoholic beverages (wine, beer, liquor and fortified wine types) besides alcohol in categories was not significantly better than the model without specific types of alcoholic beverages ($p = 0.40$). This is also reflected in Table 5 that shows the relative risk of dementia associated with either drinking of beer, liquor or fortified wine types to wine drinking.

Table 5. Relative risk of dementia according to specific types of alcoholic beverages (relative risk of drinking beer, liquor or wine-types compared to wine drinking)*.

	Wine	Beer	Liquor	Fortified wine types
Total	1.0 (reference)	0.64 (0.25-1.61)	1.36 (0.76-2.42)	1.33 (0.77-2.27)
Men	1.0 (reference)	0.59 (0.17-2.62)	1.63 (0.61-4.36)	1.32 (0.39-4.45)
Women	1.0 (reference)	1.07 (0.24-4.75)	1.26 (0.59-2.72)	1.26 (0.69-2.29)

*Adjusted for age, gender, total alcohol intake in categories, body-mass-index, systolic blood pressure, diabetes, smoking, and education

Only 346 (6.4%) participants reported a change in drinking pattern during the last five years. A higher percentage of people with changed drinking patterns reported drinking less (5.4%), as compared to respondents who reported drinking more (1%). The results essentially did not change with iterative exclusion of participants with changed drinking patterns (6.4%), history of alcoholism (0.1%), persons who drank less than twice a month (0.5%), or exclusion of binge drinkers (6.2%).

Medication use that contraindicated drinking alcohol (anxiolytics, hypnotics and antidepressants) was reported by 691 (12.8%) participants. Again, exclusion of these subjects did not alter the results appreciably.

Discussion

We observed that persons with light-to-moderate alcohol intake had a lower risk of dementia and vascular dementia than persons who never drank alcohol. This lower risk was most robust in men and in participants younger than 75 years of age. The effect of light-to-moderate alcohol intake was stronger in carriers of the APOE*4 allele. Our data did not suggest a differential effect of specific types of alcoholic beverages, besides the effect of alcohol itself.

Some limitations of this study have to be considered. Alcohol consumption was based on a semiquantitative food frequency questionnaire. Although assessment of alcohol intake embedded in a food frequency questionnaire shows high reproducibility,[24-26] under- or overreporting is possible. Several studies report that errors are, in general, linearly related to intake.[27] If underreporting is indeed linearly related to the level of intake, serious bias in estimates of health risk can occur, but it will still be possible to rank subjects according to their alcohol intake. Because of this underreporting, the amounts of alcohol consumption associated with certain health risks may in fact be higher than those indicated.

An important feature of the Rotterdam Study is that alcohol intake was assessed in cognitively healthy persons, before the onset of dementia. Therefore, it is unlikely that cognitive impairment has influenced alcohol intake at baseline. An advantage is that we were able to examine the risk of dementia associated with specific types of alcoholic beverages (wine, beer, liquor and fortified wine types).

Earlier, the PAQUID study in Bordeaux, France[7] reported that wine seemed associated with a lower risk of dementia. However, wine was the only source of alcohol reported by more than 95 percent of the regular drinkers in the PAQUID study. Therefore, this study was unable to distinguish between sources of alcohol intake.

Several mechanisms may be responsible for the inverse relation between alcohol consumption and dementia. A first possibility is that alcohol might act through reduction of cardiovascular risk factors[1-3] either through an inhibitory effect of ethanol on platelet aggregation[28] or through alteration of the serum lipid profile.[29] Our finding that the lower risk was mainly observed for vascular dementia is in agreement with this hypothesis. A second possibility is that alcohol may have a direct effect on cognition through release of acetylcholine in the hippocampus. There is substantial evidence that acetylcholine facilitates learning and memory.[30] It has been suggested that the effect of alcohol on acetylcholine release in the hippocampus is biphasic: in rats, a low concentration of alcohol (0.8 g/kg) stimulated acetylcholine release, while higher alcohol concentrations (2.4 g/kg) were inhibitory.[31] This might explain our finding that light-to-moderate alcohol intake was associated with a lower risk of dementia, while higher intake was associated with an increased risk.

We found that not drinking alcohol combined with presence of the APOE*4 allele seemed to be associated with a higher risk of dementia than could be expected from the separate relative risks associated with not drinking alcohol or presence of the APOE*4 allele. Evidence for a mediating effect of APOE in the relation between alcohol and cognitive function has been suggested in one study,[32] but was not confirmed in another.[33] Oxidation of APOE permits binding of APOE to ß-amyloid, which is assumed to increase plaque formation among carriers of the APOE*4 allele.[34] The antioxidative effect of alcohol may suppress this binding.[35] Alternatively, since APOE*4 is associated with lower levels of HDL cholesterol and higher levels of LDL cholesterol, light-to-moderate alcohol consumption may protect against dementia by improving the lipid profile of APOE*4 carriers.[36]

The detailed food frequency questionnaire enabled us to examine various amounts and different sources of alcohol intake, rather than just examining the risk associated with absence or presence of alcohol intake.[37] Our observation that there is no difference in risk associated with different types of alcoholic beverages is consistent with recent findings of the Canadian Study of Health and Aging[38] and with findings from several studies on coronary heart disease.[1,39,40]

In conclusion, we found that light-to-moderate alcohol intake was associated with a lower risk of dementia and vascular dementia irrespective of the source of alcohol intake. Light-to moderate alcohol consumption diminished the effect of APOE*4 on the risk of dementia. These findings are compatible with the view that light-to-moderate alcohol consumption may lower the risk of dementia in an elderly population.

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5

PROGNOSIS OF DEMENTIA

5.1

Prognosis of Alzheimer's disease. The Rotterdam Study

Abstract

The aim of this study was to construct a prognostic model to predict the progression of Alzheimer's disease. Prevalent and incident cases with Alzheimer's disease came from the Rotterdam Study, a population-based prospective cohort study of persons aged 55 years and older, including those living in institutions. Rate of cognitive decline, as measured by the Mini-Mental State Examination (MMSE score), was predicted by a random effects model. Risk of institutionalization and death were estimated with polynomial logistic regression analysis.

At baseline, 306 subjects were diagnosed with prevalent Alzheimer's disease and had complete data on living conditions and cognitive function. After a mean follow-up of 2.1 years, 95 subjects with incident Alzheimer's disease had been diagnosed. Prevalent patients showed a slower decline in cognitive function than incident patients ($p = 0.004$). For prevalent and incident Alzheimer's disease patients high age and low cognitive performance were the strongest predictors for institutionalization and death.

These prognostic risk functions can provide information on the decline of Alzheimer patients and might be used to better evaluate the effect of treatments for Alzheimer's disease.

Introduction

Alzheimer's disease (AD), the most frequent subtype of dementia,[1] is an important cause of disability in the elderly. Several studies have shown an exponential increase in the incidence rate of AD with age[2, 3] and because of the aging of our western population we may expect a dramatic rise in the number of patients with AD in the years to come. Since there is as yet no cure for AD, the

majority of AD patients will need long term care, which imposes a major burden on the health care system. In the Netherlands, about one tenth of the yearly health care budget is spent on nursing homes, and in 40% of the nursing home patients, dementia is the main diagnosis.[4]

Death and admissions to chronic care facilities represent two major outcome events in the natural course of AD with a direct bearing on the costs.[5, 6] Current knowledge on the prognosis of dementia and AD is limited. Most studies have focused on relatively young-old adults (65+ years) and reported on hospital or nursing home populations.[7-11] Although numerous population based prognostic studies on prevalent Alzheimer patients have been done,[12-16] studies on incident Alzheimer patients from population-based cohorts are limited.[17, 18]

The aim of this study is to develop a risk function to predict the prognosis of Alzheimer patients in different disease stages, based on cognitive decline, institutionalization and death. Because analyses based on prevalent cases include a mixture of new and long existing cases, this may lead to an overrepresentation of long existing cases and thus to biased estimates of survival. Therefore, we studied disease progression separately for incident and prevalent Alzheimer patients.

Materials and Methods

Study design and population

Patients with Alzheimer's disease came from the Rotterdam Study, a population-based prospective cohort study among persons aged 55 years and older, including those living in institutions.[19] Baseline examinations, including a home interview and an extensive physical examination, took place between 1990 and 1993. Of the 7,983 subjects who participated (response 78%), 7,528 (94%) underwent extensive screening for dementia. At baseline, 482 subjects were diagnosed with dementia, of whom 353 had Alzheimer's disease.[3, 20] This resulted in a cohort of 7,046 subjects at risk for dementia. In 1993 and 1994 follow-up examinations took place. In addition, the cohort was continuously monitored by means of computerized linkage of the study database with medical records from general practitioners and the Regional Institute of Outpatient Mental Health Care (RIAGG).

After a mean duration of follow-up of 2.1 years, 162 incident cases of dementia had been identified, and 116 of them were diagnosed with Alzheimer's disease.[3] Information on living conditions, Mini Mental State Examination (MMSE) at time of study diagnosis and vital status at follow-up was available for 306 patients (86.7 percent) with prevalent AD and for 95 patients (81.9 percent) with incident AD. Both prevalent and incident patients were followed until the end of the study period (censoring date was April 1, 1998).

Dementia diagnosis

Similar screening and diagnostic procedures for dementia were used at baseline and follow-up[20]. First, a brief test of cognition (MMSE and Geriatric Mental Schedule organic A (GMS)) was administered. Screen-positives (MMSE < 26 or GMS >0) underwent further neuropsychological testing by one of the study physicians with the CAMDEX diagnostic interview, which included an informant interview. Subjects who were suspected of dementia were examined by a neurologist, tested by a neuropsychologist and, if possible, underwent a brain MRI. Dementia diagnosis was made according to DSM-III-R criteria by a panel that reviewed all existing information. A subdiagnosis of AD was made according to the NINCDS-ADRDA criteria.[21]

At baseline, 18% of the subjects screened in person was screen positive. Of those, 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 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 RIAGG.

At follow-up examination, 79% of the total cohort at risk to develop dementia was screened in person for dementia. Of those, 10% were screen positive on the cognitive screening test. 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 test.

Cognitive function

To assess cognitive decline we used the Dutch version of the 30-point MMSE, which was used to screen for dementia.[22] The MMSE includes questions on orientation to time and place, registration, attention and calculation, recall, language and visual construction. Although this screening test was originally created for a clinical setting, it is extensively used in epidemiological studies, and has proven to be a reliable and valid indicator of cognitive impairment[2, 23] and cognitive decline.[12, 24, 25]

Of the 306 prevalent Alzheimer patients who had a MMSE measurement at baseline, 35% died between baseline and re-examination. At follow-up (on average 2 years later), 82 or the 199 patients who were still alive had a second reliable MMSE assessment. On 88 of the 95 incident Alzheimer patients blood was available for APOE testing and those were invited for additional standardized follow-up examinations by a neurologist, at intervals of approximately 15 months. Of the 73 patients who were still alive 15 months after the first examination, 61 agreed to participate and of the 42 who were alive at time of the third examination, 40 patients participated.

Activities of daily living

At the baseline home interview we administered the Katz-index[26] (activities of daily living) and the Lawton scale[27] (instrumental activities of daily living). Because in our questionnaire the question about continence was lacking we made a five-point scale on the ADL score. The IADL score was categorized in three groups: 0-6, 6-12, >12. Missing data on one or two items of the ADL or IADL scale were imputed according to dementia severity class (CDR-score).[28] When subjects had more than two missing items, the total score was considered missing.

Institutionalization

Living conditions (living independently, in a home for the elderly or in a nursing home) were obtained from the municipality for each participant at the baseline and follow-up examination, at the time of death, and at the censoring date (April 1, 1998). Home for the elderly is defined as medium care (breakfast and diner are supplied, assistance with dressing). Nursing home is defined as full care. The

midpoint between two dates was used as the date of transition from one condition to the other.

Mortality

Vital status of the participants was obtained from the municipality and general practitioners on a biweekly basis. The end of the follow-up period was set at April 1, 1998.

Other Measurements

As possible predictor variables we considered the following: age, gender, level of education (completed primary education, lower vocational or general education, and intermediate or higher vocational or general education, college or university) (UNESCO), and caregiver availability (living alone or living with a partner or relative). Apolipoprotein E (APOE) 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.[29]

Statistical analysis

To compare baseline characteristics of prevalent and incident Alzheimer cases we used a t-test (age), nonparametric tests (Kruskall-Wallis) for continuous variables (MMSE), and chi-square tests for categorical variables.

We first developed a function to estimate an individual's rate of cognitive decline based on certain initial characteristics with a random effects model (SAS 6.12, PROC MIXED). We assumed a linear rate of decline. We used all baseline and follow-up MMSE-measurements as outcome variables and age, gender, education, follow-up time and an interaction term of time with all of the other variables as covariates. The intercept and time variables were specified as random effects. Addition of baseline ADL, IADL or caregiver availability did not statistically improve the model at the $\alpha = 0.05$ level. APOE genotype did improve the prediction function and was therefore included in the model. Separate models were made for prevalent and incident patients. We also made a combined prediction function for prevalent and incident cases to test whether they declined at a statistically significant different rate.

Second, we developed a set of functions to estimate an individual's absolute risk of institutionalization and death based on certain characteristics. Several transitions were considered possible: from living independently to a home for the elderly, from a home for the elderly to a nursing home, or from living independently to a nursing home. Furthermore subjects were always at risk of dying. The follow-up time of each subject was divided in intervals of six months. We made separate records for every subject at each interval, containing the living situation at start and end of the interval, and a number of covariables. Out of these records we composed three datasets, based on the living situation at the beginning of the interval (subjects living independently, subjects living in a home for the elderly and subjects living in a nursing home). Polynomial logistic regression analysis (SAS 6.12, PROC CATMOD), with age, gender and predicted MMSE score at start of the interval included as covariates, provided conditional odds ratios of possible transitions for each of the three living conditions. Out of these conditional odds ratios, absolute risks of institutionalization or death could be calculated given a certain age, gender, and MMSE score. To compare the risk of institutionalization and death between incident and prevalent patients we made a combined function adding interaction terms of all the covariates with an indicator for prevalent or incident patient.

Results

Baseline characteristics of the prevalent and incident Alzheimer cases are given in Table 1. Prevalent and incident cases were similar with respect to age and gender. At time of first examination after diagnosis more prevalent cases lived in a home for the elderly. None of the dementia cases lived in a nursing home at baseline. As expected, prevalent patients were in a more severe stage of the disease and performed worse on the MMSE. They were also less educated. The mean duration of disease in prevalent Alzheimer patients was 3.1 years (SD 2.6). After a mean follow-up of 2.2 yrs (SD 1.25) 74.2 percent (n = 227) of the prevalent cases had died. At time of death or at the end of the study period 15.7 percent (n = 48) lived at home, 60.8 percent (n = 186) lived in a home for the elderly and 23.5 percent (n = 72) lived in a nursing home. After a mean follow-up of 2.8 yrs (SD 1.28), 53.7 percent (51) of the incident cases had died. At time of death or at the end of the study period 25.3 percent (n = 24) of the incident

cases still lived at home, 44.2 percent (n = 42) in a home for the elderly and 30.5 percent (n = 29) in a nursing home.

Table 1. Characteristics of study population at time of first examination after disease onset: Rotterdam Study (1990-1998).

	Prevalent Alzheimer's disease N = 306	Incident Alzheimer's disease N = 95
Mean age (years)(SD)	84.9 (6.5)	84.3 (7.2)
Gender (% women)	77.1% (236)	80.0% (76)
Living in home for elderly at baseline (%)	69.0% (211)	45.3% (43)
Severity of disease (CDR) % (n)		
Minimal	17.3% (53)	24.2% (23)
Mild	39.9% (122)	60.0% (57)
Moderate	31.4% (96)	14.7% (14)
Severe	11.4 %(35)	1.1% (1)
Education (%) (n)		
Low	77.1(168)	69.1 (56)
Intermediate	14.7 (32)	11.1 (9)
High	8.3 (18)	19.8 (16)
Median (range) baseline MMSE	17.2 (0-28)	19.7 (11-27)
APOE*4 (%) (n)	87 (28)	30 (32)
APOE*2 (%) (n)	32 (10)	8 (8)
APOE*3 (%) (n)	134 (44)*	50 (53)

*53 (17%) of prevalent and 7 (7%) of incident patients had no information on APOE status
APOE*4: apolipoprotein-E ε2/ε4, ε3/ε4, or ε4/ε4 genotype
APOE*2: apolipoprotein-E ε2/ε2, ε2/ε3 genotype
APOE*3: apolipoprotein-E ε3/ε3 genotype

The variables that were finally included in the prediction function for MMSE were gender, age, education, ApoE genotype, follow-up time in years and interaction terms of time with all those variables (for coefficients see table 2). As an example, we used these coefficients to calculate the change in the predicted MMSE-score over time for a prevalent case and an incident case, separately for a highly educated male and female person aged 80 years (Figure 1). Prevalent cases started at approximately the same MMSE level as incident cases but showed less decline in the MMSE score than incident cases (p = 0.004).

Table 2. Estimated coefficients to predict the MMSE-score at a given point in time for Alzheimer patients: Rotterdam Study (1990-1998).

	Prevalent AD (n = 306)	Incident AD (n = 95)
	coefficient	coefficient
Intercept	32.92	23.71
Male	-0.79	1.10
Female	*reference*	*reference*
Age (years)	-0.15	-0.05
Primary education	-1.05	-0.20
Intermediate education	-0.42	0.20
High education	*reference*	*reference*
APOE*4	-1.27	0.57
APOE*2	0.55	-0.47
APOE*3	*reference*	*reference*
Time (yrs)	-4.65	0.45
T*male	-0.11	-0.11
T*female	*reference*	*reference*
T*age	0.03	-0.04
T*primary education	0.55	0.36
T*intermediate education	0.92	1.33
T*high education	*reference*	*reference*
T*APOE*4	0.59	-0.28
T*APOE*2	0.02	-1.61
T*APOE*3	*reference*	*reference*

APOE*4: apolipoprotein-E ε2/ε4, ε3/ε4, or ε4/ε4 genotype

APOE*2: apolipoprotein-E ε2/ε2, ε2/ε3 genotype

APOE*3: apolipoprotein-E ε3/ε3 genotype

T = time in years, T*covariate = interaction of time with covariate

In table 3 and 4 the coefficients from the polynomial logistic regression analyses to estimate the transition probabilities for living situation are given. Appendix 1 demonstrates how to use the coefficients. For AD cases living at home, age was the strongest predictor for moving to a home for the elderly. Women with prevalent AD were at higher risk of entering a home for the elderly after one year compared to men with prevalent AD. Low MMSE was a major predictor for institutionalization and death for prevalent as well as for incident AD patients.

Table 3. Coefficients from a polynomial logistic regression model to estimate transition probabilities for a prevalent Alzheimer patient: Rotterdam Study (1990-1998).

		Living situation at t = 1					
		Home for elderly		Nursing home		Death	
Living situation at t = 0		estimate	p-value	estimate	p-value	estimate	p-value
At home	Intercept	-19.48	< 0.001	-2.98	0.19	-3.87	0.14
	Time	-0.07	0.75	0.30	0.04	-0.07	0.70
	Age	0.19	< 0.001	-0.01	0.86	0.05	0.08
	Female	2.25	0.05	-0.05	0.89	-0.76	0.09
	MMSE	-0.14	0.10	-0.001	0.99	-0.18	< 0.001
Home for elderly	Intercept			-0.80	0.80	-5.42	0.002
	Time			0.29	0.02	0.08	0.26
	Age			-0.03	0.46	0.06	0.003
	Female			0.54	0.38	-0.61	0.007
	MMSE			-0.09	0.007	-0.08	< 0.001
Nursing home	Intercept					-6.31	0.05
	Time					-0.20	0.35
	Age					0.07	0.05
	Female					-0.19	0.75
	MMSE					-0.06	0.14

Table 4. Coefficients from a polynomial logistic regression model to estimate transition probabilities for an incident Alzheimer patient: Rotterdam Study (1990-1998).

		Living situation at t = 1					
		Home for elderly		Nursing home		Death	
Living situation at t = 0		estimate	p-value	estimate	p-value	estimate	p-value
At home	Intercept	-19.64	0.006	2.57	0.44	-6.42	0.26
	Time	-0.35	0.38	-0.57	0.02	0.15	0.62
	Age	0.18	0.01	-0.01	0.71	0.05	0.46
	Female	-0.49	0.59	0.10	0.85	0.02	0.98
	MMSE	0.06	0.63	-0.21	< 0.001	-0.09	0.23
Home for elderly	Intercept			13.93	0.09	-8.90	0.04
	Time			-1.25	0.08	-0.64	0.009
	Age			-0.21	0.03	0.11	0.02
	Female			6.66	< 0.001	-1.00	0.13
	MMSE			-0.30	0.06	-0.10	0.17
Nursing home	Intercept					-4.96	0.39
	Time					-0.45	0.19
	Age					0.04	0.56
	Female					0.02	0.98
	MMSE					0.11	0.04

t = 0: time of study diagnosis; t = 1: living situation after one year after study diagnosis

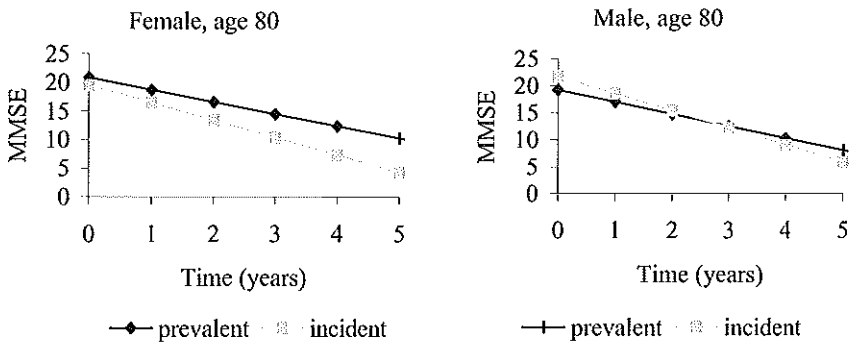

Figure 1. Change in MMSE-score over time based on patient characteristics.

Figure 2 shows the transition probabilities for a female patient, with an MMSE-score of 15, living at home at baseline. Probabilities are shown for age 70, 80 and 90. The probability to enter a home for the elderly increased with age. This pattern is observed in both prevalent and incident Alzheimer cases, although less clearly among incident cases.

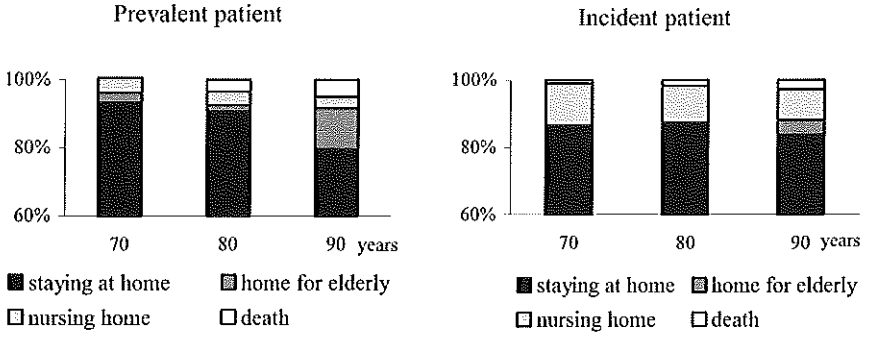

Figure 2. Transition probabilities after one year for a female patient, MMSE = 15, living at home at baseline, for different ages.

As an example figure 3 shows the transition probabilities for a female, aged 80 with an MMSE-score of 15 living at home (a), living in a home for elderly (b) and living in a nursing home (c). From the combined prediction function we could estimate that prevalent cases had a slightly higher probability to die than incident cases, except when they already were living in a nursing home.

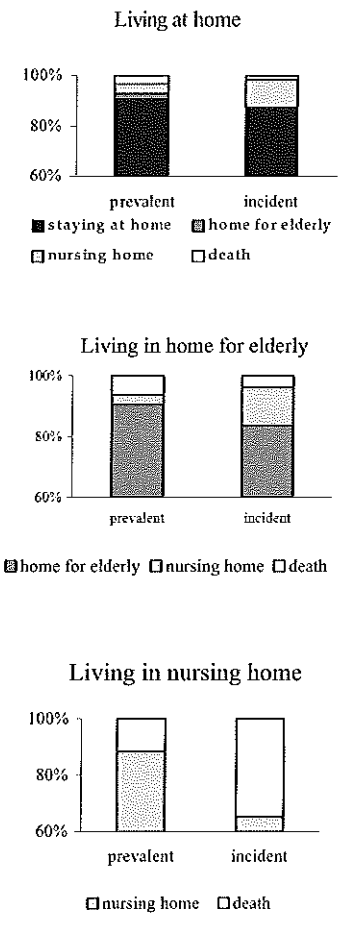

Figure 3. Transition probabilities after one year for a female patient age 80, MMSE = 15, living at home, in a home for the elderly or in a nursing home.

Incident cases living in a nursing home had a 35 percent chance of mortality after one year, compared to 12 percent among prevalent cases. These differences, however, were non-significant ($p = 0.84$). Incident cases also seemed to move more quickly from a home for the elderly to a nursing home compared to prevalent cases ($p = 0.09$). For male subjects these results were more or less the same, except that the probability to remain in a home for the elderly was higher among incident male compared to incident female cases.

Discussion

In this large population-based study we developed prognostic risk functions to predict cognitive decline and a function to predict risk of institutionalization and death based on certain individual baseline characteristics. Since the prevalent and incident cases were analyzed separately, the effect of different stages of disease could be examined. We observed a steeper decline in cognitive function for incident compared to prevalent AD cases. Moreover, incident dementia cases that lived in a home for the elderly at baseline were more likely to move to a nursinghome

during follow-up than prevalent cases.

Major advantages of the Rotterdam Study to investigate progression of disease include the longitudinal and population-based design and the complete follow-up with respect to institutionalization and mortality.

A limitation of this study is that the prediction model for cognitive function is based on a maximum of three measurements of the MMSE. However, with the random effects model we could include all cases, not just those who survived long enough to have two or three measurements. Another limitation is that we lacked the power to examine the effect of comorbidity (stroke, myocardial infarction) on institutionalization and death.

We assumed a linear decline in cognitive function. A trilinear model of decline has also been proposed, in which rapid change occurs in the midrange of disease severity with relative plateaus early and late in the disease.[30] This trilinear model would explain why we find a more rapid decline for the incident Alzheimer patients compared to the prevalent patients. Cases in the more severe stages of disease could have reached the plateau phase late in the disease. Katzman et al.[31] found that only the most severely demented showed a slower rate of subsequent decline and attributed the finding to a floor effect. Furthermore, the non-linear trend appears to be small and linear models seem to prove the best fit to longitudinal cognitive data in Alzheimer's disease.[32] Therefore, we used the linear model.

Several studies have reported severity of dementia (MMSE score, ADL, CDR) at study entry to be a major predictor of time to admission to a nursing home.[7-10] In Alzheimer's disease, several factors have been related to shorter survival. These include functional disability,[7, 33, 34] male gender[11, 34, 35] and increasing age.[11, 34, 35] Aguero-Torres et al.[12] found in a longitudinal population-based study that shorter survival was related to male gender, advanced age, low education level and functional disability at baseline. In our study we found that male gender, advanced age and a low MMSE score at the beginning of an interval were associated with shorter survival. The better prognosis in women can probably be partly explained by the fact that healthy women have a higher life expectancy at any age.[11] The survival advantage of women with AD relative to men may also occur as a result of fewer comorbid clinical conditions associated with the diagnosis of dementia.[37] ADL and IADL did not enter the model for predicting MMSE. It is possible that this was partly due to the global

scales that we used, however, it is also possible that ADL and IADL are less important in predicting cognitive decline in demented subjects than in predicting dementia.[7, 38] We were not able to evaluate the role of ADL, IADL and caregiver availability in predicting institutionalization and death because we lacked detailed information on these items at the beginning of each 6-month interval.

In this study we developed a function to predict an individuals decline in MMSE score over time and to predict the risk of institutionalization and death. We showed a major difference in predicted prognosis between prevalent and incident Alzheimer cases. There probably was an overrepresentation of slowly progressive dementia and an underrepresentation of rapidly progressive dementia among the prevalent dementia cases, since the rate of cognitive decline was lower among prevalent than among incident cases. This might be the result of a higher mortality among very rapidly progressive dementia cases. Patients derived from a cross-sectional study tend to be less rapidly progressive with respect to cognitive decline, institutionalization, and mortality compared to patients derived from a longitudinal study.[12, 39]

Prognostic models from epidemiological studies can provide information on the decline of a group of Alzheimer patients or can be used to get a prediction about an individual's prognosis. The coefficients derived from these models can be used to construct a simulation model of the disease process. Such simulation models allow the estimation of the possible impact of a treatment, for example with relation to health costs. Finally, prediction of the risk of institutionalization and death of Alzheimer's disease may be useful for health care planning on a larger scale.[40]

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Appendix 1:

Example: What are the probabilities for an 80 year old woman with Alzheimer's disease who is living at home and has a MMSE score of 15, that one year later

a. she will live in a home for the elderly
b. she will live in a nursing home
c. she will have died
d. she will still live at home

a. Logodds to move from home to home for the elderly:
   intercept+T*1+age*80+female*1+MMSE*15 = -3.85
   Odds to move from home to home for the elderly:
   EXP(-3.85) = 0.021
   Probability to move from home to home for the elderly:
   1/(1+ 0.021)
   Absolute probability to move from home to home for the elderly: 19.4 %
   (Formula 1)

b. Logodds to move from home to a nursing home: -3.13
Odds to move from home to a nursing home:
EXP(-3.13) = 0.044
Probability to move from home to a nursing home: 1/(1+0.044)
Absolute probability to move from home to a nursing home:
4.0 % (Formula 2)

c. Logodds to die when living at home: -3.27
Odds to die when living at home: EXP(-3.27) = 0.038
Probability to die when living at home: 1/(1+0.038)
Absolute probability to die when living at home:
3.4 % (Formula 3)

d. Absolute probability to stay at home:
1- ($P_{elderly}$+P_{nurse}+P_{death}) = 90.7 %

Formula 1: $P_{elderly}$*(1-P_{nurs})*(1-P_{death})/(1-($P_{elderly}$*P_{nurse})-($P_{elderly}$*P_{death})-(P_{nurse}*P_{death})+ (2*$P_{elderly}$*P_{nurs}*P_{death}))
Formula 2: P_{nurse}*(1-$P_{elderly}$)*(1-P_{death})/(1-($P_{elderly}$*P_{nurse})-($P_{elderly}$*P_{death})-(P_{nurse}*P_{death})+ (2*P_{home}*$P_{elderly}$*P_{nurs}))
Formula 3: P_{death}*(1-P_{nurse})*(1-$P_{elderly}$)/(1-($P_{elderly}$*P_{nurse})-($P_{elderly}$*P_{death})-(P_{nurse}*P_{death})+ (2*P_{home}*$P_{elderly}$*P_{nurs}))

6

GENERAL DISCUSSION

6

General discussion

The aim of the research described in this thesis was to further elucidate the role of vascular pathology in dementia and Alzheimer's disease and to identify possible underlying mechanisms.

All chapters in this thesis are based on studies performed within the Rotterdam Study, a large population-based prospective cohort study that is ongoing since 1990 and includes 7,983 participants of 55 years and older. The cohort at risk for dementia consisted of 7,046 persons who have been followed from baseline up to December 31, 1999. The cohort was re-examined twice (1993-1994; 1997-1999). In addition, the cohort is continuously monitored through linkage of the Rotterdam Study database with medical records from general practitioners and the Regional Institute for Outpatient Mental Health Care (RIAGG). During 40,441 person-years of follow-up, we identified 395 new cases of dementia.

In the following we will review our main findings and discuss them in the light of other studies and current insights in the relation between vascular factors and Alzheimer's disease. Subsequently we will discuss the clinical relevance of our findings. We will end with some recommendations for future research.

Main Findings

Until December 31, 1999 we identified 395 patients with incident dementia within the Rotterdam Study cohort, for an overall incidence rate of dementia of 9.8 per 1,000 person-years in those of 55 years of age or over. Alzheimer's disease was most frequently diagnosed (74%), followed by vascular dementia (14%). The overall incidence rate of dementia was very similar for men and women, as were age-specific incidence rates up to the age of 90 years. Women were more likely to develop Alzheimer's disease, whereas men were more often diagnosed with vascular dementia. This difference can possibly be explained by a higher stroke incidence in men or a misclassification of vascular dementia into

Alzheimer's disease in women, since cerebrovascular pathology may less often be symptomatic in women.[1] After 90 years of age the incidence rate of dementia declined in men but not in women, probably due to more selective survival in men.

We took two different approaches to address the issue of possible vascular involvement in the aetiology of dementia and Alzheimer's disease. First, we investigated the relation between vascular risk factors and markers of vascular disease and the occurrence of dementia, in particular Alzheimer's disease. Second, we investigated whether cerebrovascular impairment was associated with Alzheimer's disease.

Vascular risk factors and markers for vascular disease

We investigated blood pressure, change in blood pressure, alcohol consumption, and markers of atherosclerosis in relation to the risk of dementia, Alzheimer's disease and vascular dementia.

At short-term follow-up (on average 2 years), blood pressure was not associated with risk of dementia in persons younger than 85 years of age, whereas in older persons increasing levels of blood pressure were associated with lower risks of dementia. Also, use of blood pressure lowering medication was associated with a lower risk of dementia and vascular dementia. By contrast, at longer follow-up (on average 6 years), higher baseline blood pressure levels were associated with an increased risk of dementia, in particular for persons younger than 75 years. A decline in blood pressure was associated with an increased risk of Alzheimer's disease and vascular dementia in the years thereafter. Our findings fit with results from several other longitudinal studies[2, 3] and suggest that high blood pressure increases the long term risk of dementia. It remains a question how a decline in blood pressure is related to risk of dementia. Some authors suggested that lowering of the blood pressure beyond a critical threshold increases the risk of dementia through chronic hypoperfusion, especially in elderly persons with longstanding hypertension.[4, 5] An alternative, but equally possible, explanation is that a decline in blood pressure is a consequence of brain lesions associated with dementia, since several areas that are involved in central blood pressure regulation are affected in Alzheimer's disease.[6, 7] In support of this, we found that blood pressure was lower in subjects

with manifest dementia at baseline and declined more rapidly in this group than in the non-demented during follow-up. The explanations are not mutually exclusive.

We found that light-to-moderate alcohol intake (1-3 glasses per day) was associated with a lower risk of dementia and vascular dementia, irrespective of the source of alcohol intake. It has been suggested that the association of alcohol with dementia is through release of acetylcholine in the hippocampus.[8] However, the fact that associations were strongest for vascular dementia makes it more likely that the effect is through reduction of cardiovascular risk factors,[9-11] either through an inhibitory effect of ethanol on platelet aggregation[12] or through alteration of the serum lipid profile.[13] The beneficial effect of alcohol intake was stronger in carriers than in non-carriers of an apolipoprotein ε4 allele. Since the ε4 allele is associated with lower levels of HDL cholesterol and higher levels of LDL cholesterol, light-to-moderate alcohol consumption may protect against dementia by improving the lipid profile of apolipoprotein ε4 allele carriers.[14] Alternatively, alcohol may suppress oxidation of apolipoprotein-E[15] that permits binding to ß-amyloid, which is assumed to increase plaque formation among carriers of the apolipoprotein ε4 allele.[16]

Plaques in the carotid arteries and thickening of the carotid artery vessel wall significantly increased the risk of dementia and Alzheimer's disease. The risk of dementia increased with the amount of atherosclerosis. The same trend was observed for Alzheimer's disease and vascular dementia. Atherosclerosis can be related to dementia in several ways. Atherosclerosis may cause hemodynamic changes leading to neuronal damage in vulnerable areas of the brain. Also, atherosclerosis may impair the blood-brain barrier function as a result of cerebral vessel wall damage.[17] Finally, vascular damage associated with atherosclerosis superimposed on already existing Alzheimer pathology may lead to an earlier detection of otherwise subclinical Alzheimer's disease.

Functional cerebrovascular impairment

Transcranial Doppler is a non-invasive tool to measure cerebral blood flow velocity and cerebrovascular CO_2 reactivity in cerebral arteries. We obtained TCD assessment on 2,107 participants in the second re-examination of the Rotterdam Study. Cerebral blood flow velocity was significantly lower in persons with dementia, but also in persons with cognitive decline, without

dementia. Reduced blood flow velocities may represent consequences of reduced metabolic needs due to neuronal tissue loss.[18, 19] Alternatively, a decline in cerebral blood flow velocity may be a risk factor for dementia, due to a decreased delivery of oxygen and resulting hypoxia.[20] The observation that cerebral blood flow velocity was already lower in persons with cognitive decline, without dementia, does fit both explanations. Cerebrovascular CO_2 reactivity was lower in persons with cognitive decline and in those with low cognitive performance and seemed lower in persons with dementia. Atherosclerosis may disturb the integrity and function of the arterial wall and thereby affect cerebrovascular CO_2 reactivity. A low cerebrovascular CO_2 reactivity may also indicate small vessel pathology.[21] Our findings support the hypothesis of a role for vascular risk factors and vascular disease in the aetiology of cognitive decline and dementia. Whether the lower blood flow velocity and vasomotor response are a cause or a consequence of dementia can not be judged from this cross-sectional study.

Main hypotheses

There are at least four mechanisms that may underlie the association between vascular factors and dementia (see figure).

1. AD pathology → Alzheimer's disease
   Vascular factors → Vascular disease, vascular dementia
2. Vascular factors → Alzheimer's disease
3. Alzheimer's disease → Vascular factors
4. Vascular factors ↓
   AD pathology → Alzheimer's disease

1. Co-incidence of Alzheimer's disease and vascular dementia (co-morbidity): It is possible that Alzheimer's disease pathology and cerebrovascular disease are unrelated but co-exist within one person. Vascular damage superimposed

on existing Alzheimer pathology may act to unmask otherwise subclinical Alzheimer's disease.[22] More than one third of Alzheimer cases exhibit variable cerebrovascular pathology, even though Alzheimer's disease is diagnosed at autopsy.[23]And patients with vascular dementia often have Alzheimer pathology at autopsy even though there was no clinical picture of Alzheimer's disease. The pathology that causes clinical symptoms first, may determine whether the dementia syndrome is classified as Alzheimer's disease or as vascular dementia, whereas the majority of cases are actually mixed-type dementias.

2. Vascular factors cause Alzheimer's disease. Most vascular risk factors impair or reduce cerebral perfusion in some way. Impaired perfusion will affect the microcirculation and delivery of energy substrates required for optimal brain cell function.[4] Disturbances in the glucose-oxygen delivery to neurons can lead to abnormal protein synthesis and eventually to production of senile plaques and neurofibrillary tangles.
3. Alzheimer's disease causes vascular factors. The relation may be inverse, and there is actually some evidence that this is sometimes the case. Deposited ß-amyloid has a toxic effect on vascular endothelium.[24] Metabolic and neuronal changes that occur in the course of Alzheimer's disease may lead to a disturbed central blood pressure regulation and to autonomic dysfunction with orthostatic hypotension and decreased heart rate variability.[7, 25]
4. Biological interaction between vascular factors and Alzheimer pathology. Vascular pathology and Alzheimer pathology may enhance each other in bringing out a dementia syndrome. Vascular disorders, such as chronic hypertension, are associated with increased vascular permeability with protein extravasation.[17] The impaired blood brain barrier function increases the possibility that substances from serum penetrate the blood brain barrier and reach the brain, where they may interfere with neuronal function and may lead to amyloid accumulation. The distribution of amyloid was found to be related to blood vessels, suggesting that its origin may be vascular rather than neuronal.[26] Vascular factors may also accelerate the pathogenesis of Alzheimer's disease through ischaemia and resulting formation of free radicals.[27]

Which of the four outlined schedules is the correct one? Vascular factors and Alzheimer pathology may co-exist and probably they do. However, mechanism 1 can not explain the consistently and significantly increased risks of Alzheimer's disease that are associated with vascular risk factors, unless we severely misclassify large numbers of patients. Several prospective studies are now available that show that vascular risk factors increase the long-term risk of dementia, which suggests that although mechanism 3 may play a role, this most likely is a limited one. To further unravel possible mechanisms 1, 2 and 4 we need more specific disease markers, and repeated assessment of risk factors and outcome.

Methodological considerations

While epidemiological and other evidence is accumulating that vascular risk factors and indicators of vascular disease might be important in the cause and progression of dementia and Alzheimer's disease, some issues that need particular attention become apparent.

First, the distinction between Alzheimer's disease with vascular pathology and vascular dementia is often very difficult and maybe even impossible. There is little agreement on what should be criteria for vascular dementia, and the criteria that are being used show bad reproducibility.[28] Although the NINCDS-ADRDA criteria for Alzheimer's disease are widely accepted and show good reproducibility,[28] they still do not guarantee that the clinical syndrome of Alzheimer's disease refers to one clearly delineated disease entity. It may actually be a mixture of Alzheimer pathology and cerebrovascular pathology. Until we have better ways to distinguish between subtypes of dementia, it may be more informative to consider overall dementia and to distinguish according to aetiology, without the assumption that these subgroups indeed reflect clearly separable diagnostic entities.

A second issue is the time of diagnosis in relation to neuronal damage. Alzheimer's disease may develop over a long period of time. At time of exposure assessment, Alzheimer pathology may have already started. Rather than studying determinants of clinically overt dementia, we may want to investigate determinants of early markers of incipient dementia. Possible candidates are cerebral changes that we can detect with neuroimaging, in particular atrophy and

white matter lesions. To the extent that these are indeed early markers of incipient dementia, they may serve as a proxy measure. An approach that focuses on the detection of persons at risk for dementia in an early, and preferably presymptomatic, stage would also make sense from a more clinical perspective where we want to prevent the development and progression of dementia. This also calls for identification of markers of early disease (e.g. brain atrophy, white matter changes, and serum levels of beta amyloid) and for investigation of determinants of those markers.

A final issue is how to discern the time order of events. Neuronal damage that eventually leads to Alzheimer's disease may develop over a long period. Since vascular pathology may also develop over decades it can become difficult or even impossible to distinguish what is cause and what is consequence. Also, since most vascular risk factors are not stable over time, change in vascular risk factor level may be more important than actual level. To investigate these relations, we need long prospective follow-up studies. By now, several studies, including our own, have the necessary data to address questions of sequence of events. The analysis of such complex datasets used to be extremely difficult, but has become much more feasible due to new methods for analysis of repeated measurements and imputation of missing values that have become available over the last years. [29, 30]

Clinical relevance

Research on vascular factors in the aetiology of dementia and Alzheimer's disease is fostered by the idea that this might offer clues for preventive intervention. Although observational epidemiological studies are not specifically designed to give guidelines for clinical practice, we would like to consider if and how our findings can bear on current clinical practice.

The studies described in chapter 3 indicate that the relation between blood pressure and dementia is complicated and time-dependent. High blood pressure was associated with an increased risk of dementia. A decline in blood pressure was a risk factor for dementia independent of baseline blood pressure level. Use of blood pressure lowering medication was associated with a lower risk of dementia two years later, whereas persons who used blood pressure lowering medication but also had a low blood pressure were at increased risk of dementia.

From this study and also from others we might conclude that hypertension contributes to the development of Alzheimer's disease [2, 3, 31] and thus that treatment of hypertension would reduce the incidence of dementia. However, since it is possible that a decline in blood pressure also causes or contributes to dementia, it is too early to recommend blood pressure lowering as a means to prevent dementia.

Light-to-moderate alcohol intake was associated with a lower risk of dementia. Because of underreporting of alcohol intake in epidemiological studies it is difficult to set sensible limits for levels beneficial to the development of dementia. Moreover, we have to be cautious recommending taking alcoholic beverages in order to prevent dementia, because it has been shown that in a large population, any increase in alcohol consumption is associated with a proportionate increase in heavy drinking.[32]

Our findings suggest that atherosclerosis is not only associated with a small subgroup of vascular dementia, but also with Alzheimer's disease. Screening for and treatment of risk factors for atherosclerosis may not only lead to a lower risk of cardiovascular disease but may also contribute to a lower risk of dementia.

Future research

We have tried to further quantify the role of vascular factors in the aetiology of dementia and Alzheimer's disease.

We studied blood pressure level in relation to dementia. However, blood pressure measured in late life may not reflect blood pressure levels earlier in life. A more direct measure of life time cumulative hypertensive damage, in particular to the cerebrovascular small vessels, is needed to further elucidate the role of hypertension in the aetiology of dementia and in particular Alzheimer's disease. The distinct type of changes that occur in retinal arterioles during different phases of hypertensive disease may provide such a measure.[33]Another approach to establish a causal relationship between hypertension and dementia is to perform a double blind randomised trial on the effects of treatment of hypertension. Recently, the Syst-Eur trial showed that treatment of isolated systolic hypertension possibly reduced the risk of Alzheimer's disease.[31] However, the primary hypothesis in this trial was that a reduction in blood pressure would protect against vascular dementia. As placebo controlled trials in

persons fulfilling established criteria for treatment are not possible on ethical grounds and considerable lowering of the blood pressure might be harmful, the only option would be to perform a placebo controlled trial in persons with mild hypertension.

Our studies indicated the potential role of cerebral hypoperfusion in the pathogenesis of dementia. Since the research on cerebral blood flow velocity and cerebral vasomotor reactivity was done cross-sectionally and comprised a limited number of dementia cases, the objective of future research should be to assess the role of cerebral blood flow in a prospective study with long follow-up. Techniques that are used to measure cerebral blood flow include Transcranial Doppler, structural and functional magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT), and positron emission tomography (PET). However, Transcranial Doppler is probably the only technique that is suitable for examining persons in large population based studies.

Alzheimer pathology starts probably long before it causes clinical symptoms. Future research should aim at identification of very early stages of the disease. Possible markers of preclinical stages of disease include levels of beta amyloid or tau in plasma, structural brain changes as white matter lesions and hippocampal and medial temporal lobe atrophy, and functional brain markers.[34-36] To the extent that these will be found to indeed reflect incipient Alzheimer's disease, they may serve as more specific outcome measures in etiologic studies.

Findings from studies on the combined effect of apolipoprotein-E and vascular factors suggest that genetic factors may interact with vascular factors in the development of dementia. Future research should further investigate the interaction of genetic factors with vascular factors (e.g. angiotensin I converting enzyme, IL-1A polymorphism).[37-39]

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7

SUMMARY

7.1

Summary

This thesis describes our research to further explore the role of vascular pathology in dementia and Alzheimer's disease and to identify possible underlying mechanisms. All studies were performed within the Rotterdam Study, a population-based prospective cohort study on frequency and determinants of disease among elderly persons. At baseline (1990-1993) 7,983 inhabitants of Ommoord, a suburb of Rotterdam, the Netherlands, who were 55 years of age or older, participated. Follow-up examinations were done in 1993-1994 and 1997-1999. In addition, study participants are continuously being followed for the development of cognitive problems or dementia through an extensive monitoring system through medical records from general practitioners and the Regional Institute for Outpatient Mental Health Care (RIAGG). At baseline, 482 persons of the 7,528 that were cognitively evaluated were diagnosed with dementia.

Study participants without dementia at baseline (7,046) were followed for on average 5.7 years **(chapter 2.1)**. During that period 395 persons developed dementia. Alzheimer's disease was the most frequent subtype of dementia (293 cases, 74%). Vascular dementia was diagnosed in 57 participants (14%). The rate at which new dementia develops (incidence) is expressed in cases per 1,000 persons-years of follow-up. The overall incidence rate was 9.8 per 1,000 person-years for all types of dementia, 7.2 per 1,000 person-years for Alzheimer's disease, and 1.5 per 1,000 person-years for vascular dementia. The incidence rate ranged from 0.4 per 1,000 person-years at age 55-59 years to 74.1 per 1,000 person-years at age 95 years and older. Up to age 90 years there was no difference in dementia incidence between men and women. However, after that age dementia incidence declined in men but not in women. Across all age groups women were more likely to develop Alzheimer's disease, whereas men were more often diagnosed with vascular dementia.

In **chapter 3**, we studied the relation between blood pressure and the risk of dementia, and dementia subtypes. We first studied the short-term (on average 2

years) relation between blood pressure level, blood pressure lowering medication, and dementia **(chapter 3.1)**. In persons younger than 85 years of age blood pressure was not associated with risk of dementia, whereas in older persons increasing levels of blood pressure were associated with lower risks of dementia. This decreased risk among hypertensive elderly was entirely due to a strong inverse association in persons using blood pressure lowering medication. Use of blood pressure lowering medication was associated with a lower risk of vascular dementia **(chapter 3.3)**. We then studied the relation between blood pressure level and risk of dementia over a longer period after the baseline assessment (on average 6 years). Higher baseline blood pressure levels were associated with an increased risk of dementia, in particular for persons younger than 75 years of age. This association was observed for vascular dementia as well as for Alzheimer's disease. Finally, we examined the relation between change in blood pressure and subsequent risk of dementia. We found that a decline in blood pressure was associated with an increased risk of Alzheimer's disease and vascular dementia in the years thereafter, irrespective of baseline blood pressure level **(chapter 3.2)**.

In **chapter 4** we investigated the relation between indicators of vascular disease and occurrence of dementia and cognitive impairment. In **chapter 4.1** we investigated cerebrovascular function as assessed by means of Transcranial Doppler in relation to cognitive dysfunction and dementia. We measured cerebral blood flow velocity, a measure of perfusion of the brain, and cerebrovascular CO_2 reactivity, which reflects the ability of small cerebral arteries to dilate under the influence of certain stimuli in order to increase cerebral blood flow in case of increased demands. Atherosclerosis may disturb the integrity and function of the arterial wall and thereby its capacity to dilate on these stimuli. Our data suggested that cerebral blood flow velocity and cerebrovascular CO_2 reactivity were decreased in persons with dementia and were already lower in persons with low cognitive performance. In **chapter 4.2** we reported our findings on indicators of atherosclerosis and risk of dementia. Plaques in the carotid arteries and thickening of the carotid artery vessel wall were significantly associated with an increased risk of dementia and Alzheimer's disease. The risk of dementia increased with the amount of atherosclerosis. In **chapter 4.3** we evaluated the role of alcohol consumption on the risk of dementia and dementia subtypes. Persons who drank one to three glasses of

alcohol per day had a 40 percent lower risk of dementia as compared to persons who never drank alcohol. The risk of vascular dementia was even 70 percent lower. The effects were similar for drinking wine, beer, liquor or fortified wine-types. The association between alcohol and dementia was modified by the Apolipoprotein-E genotype in that the risk reduction with moderate alcohol intake was stronger in persons with an Apolipoprotein ε4 allele.

In **chapter 5** we described the natural progression of disease among Alzheimer's disease patients. We constructed a function based on age, gender, education and Apolipoprotein-E genotype to predict the rate of cognitive decline in Alzheimer patients. In addition, we developed functions to estimate a demented individual's risk of institutionalisation and death based on age, gender and cognitive performance. We considered prevalent and incident dementia patients separately. Prevalent patients showed a slower decline in cognitive function than incident patients. For prevalent and incident Alzheimer's disease patients high age and low cognitive performance were the strongest predictors for institutionalisation and death.

In **chapter 6** we discussed the results of the studies presented in this thesis. The possible underlying mechanisms were addressed in the light of our findings and some directions for future research were given. Various vascular factors, of which some are modifiable, were significantly associated with the risk of dementia. Most vascular factors were also related to Alzheimer's disease. Whether the association reflects co-incidence of Alzheimer's disease and vascular disease, a causal relation between vascular factors and Alzheimer's disease, or a biologic interaction between vascular factors and Alzheimer pathology remains unclear.

Future research should aim at further elucidating possible mechanisms in the relation between vascular factors and dementia. Emphasis should be on studying determinants of early, preferably preclinical, disease.

7.2

Samenvatting

Dit proefschrift beschrijft onderzoek naar de rol van vasculaire factoren in het ontstaan van dementie en de ziekte van Alzheimer. Het onderzoek werd verricht als onderdeel van het Erasmus Rotterdam Gezondheid en Ouderen (ERGO) onderzoek, een prospectief bevolkingsonderzoek naar frequentie en oorzaken van chronische ziekten bij ouderen. Het ERGO onderzoek begon in 1990-1993 met 7983 inwoners van Ommoord, een wijk van Rotterdam, die op dat moment 55 jaar en ouder waren. In 1993-1994 en in 1997-1999 werd iedereen opnieuw onderzocht. Vanaf het begin van de studie zijn deelnemers gevolgd en is bijgehouden of mensen cognitieve problemen of dementie kregen. Dit vond onder andere plaats door koppeling van geautomatiseerde huisartsenbestanden aan het ERGO databestand en door regelmatige controle van medische dossiers bij het RIAGG. Aan het begin van het onderzoek werd bij 482 van de 7528 personen die onderzocht werden op hun mentale functies dementie vastgesteld.

Deelnemers zonder dementie syndroom aan het begin van de studie (7046), werden gemiddeld 5,7 jaar gevolgd (**hoofdstuk 2.1**). Tijdens deze periode ontwikkelden 395 personen een dementie syndroom; bij 293 personen was daarbij sprake van de ziekte van Alzheimer (74%) en bij 57 personen werd een vasculaire dementie vastgesteld (14%). De incidentie, ofwel het aantal nieuwe ziektegevallen dat zich in de loop van een tijdsperiode voordoet, voor mensen van 55 jaar en ouder was 9,8 per 1000 persoonsjaren voor dementie; 7,2 per 1,000 persoonsjaren voor de ziekte van Alzheimer en 1,5 per 1,000 persoonsjaren voor vasculaire dementie. De incidentie nam toe van 0,4 per 1000 persoonsjaren voor mensen van 55-60 jaar tot 74.1 per 1000 persoonsjaren voor mensen van 95 jaar en ouder. De incidentie van dementie was tot 90 jarige leeftijd gelijk voor mannen en vrouwen; boven die leeftijd leek de incidentie voor mannen af te nemen, terwijl deze voor vrouwen bleef toenemen. Over alle leeftijdsgroepen heen werd bij vrouwen vaker dan bij mannen de ziekte van Alzheimer vastgesteld en bij mannen vaker dan bij vrouwen vasculaire dementie geconstateerd.

Hoofdstuk 3 beschrijft ons onderzoek naar de relatie tussen de bloeddruk en de kans op dementie en subtypen van dementie. Eerst bestudeerden we de korte termijn (gemiddeld 2 jaar) invloed van de hoogte van de bloeddruk en bloeddrukverlagende medicijnen op het ontstaan van dementie **(hoofdstuk 3.1)**. Voor personen jonger dan 85 jaar was de hoogte van de bloeddruk niet gerelateerd aan de kans op dementie. Bij oudere personen daarentegen was een hogere bloeddruk gerelateerd aan een lagere kans op dementie, echter alleen bij mensen die bloeddruk verlagende medicijnen gebruikten. Het gebruik van bloeddruk verlagende medicijnen bleek geassocieerd met een lagere kans op het krijgen van dementie, en met name op het krijgen van vasculaire dementie **(hoofdstuk 3.3)**. Vervolgens onderzochten we welke invloed de hoogte van de bloeddruk had op het ontstaan van dementie na een langere periode (gemiddeld 6 jaar). Een hoger bloeddruk niveau bleek gerelateerd aan een hogere kans op dementie, met name bij mensen jonger dan 75 jaar. Dezelfde relaties werden gevonden voor de ziekte van Alzheimer en voor vasculaire dementie **(hoofdstuk 3.2)**.

In **hoofdstuk 4** onderzochten we of afwijkingen aan de vaatwand gerelateerd waren aan het optreden van dementie en cognitieve problemen. In **hoofdstuk 4.1** bestudeerden we met behulp van een Transcraniële Doppler functionele afwijkingen aan de hersenvaten in relatie tot dementie en cognitieve problemen. Daarbij registreerden we de doorbloedingsnelheid van de hersenen en de reactie van de hersenvaten op toediening van kooldioxide. Dit laatste geeft het vermogen van de kleine hersenvaten weer om uit te zetten onder invloed van bepaalde prikkels en zodoende de doorbloeding van de hersenen te vergroten. Onder andere aderverkalking kan de functie van de vaatwand, en daarmee het vermogen om uit te zetten als reactie op prikkels, aantasten. Uit dit onderzoek bleek dat zowel de doorbloedingsnelheid als het vermogen om uit te zetten verminderd waren bij demente personen en bij personen met cognitieve problemen. In **hoofdstuk 4.2** rapporteerden we onze bevindingen over slagaderverkalking en de kans op dementie. Verkalking- en verdikking van de halsslagaderwand waren gerelateerd aan het ontstaan van dementie en de ziekte van Alzheimer. De kans op dementie nam toe met toenemende verkalking van de halsslagader. In **hoofdstuk 4.3** bestudeerden we de invloed van het drinken van alcohol op het krijgen van dementie, de ziekte van Alzheimer en vasculaire dementie. Personen die 1 tot 3 glazen alcohol per dag dronken hadden 40%

minder kans op het krijgen van dementie dan personen die geen alcohol dronken. De kans op vasculaire dementie was zelfs 70 procent lager. Het maakte niet uit of de alcohol afkomstig was uit bier, wijn, sterke drank of sherry. De associatie van alcohol met dementie werd beïnvloed door het Apolipoproteïne-E genotype. Dragers van het Apolipoproteïne ε4 allel hadden meer baat bij het drinken van alcohol dan niet-dragers van het ε4 allel.

In **hoofdstuk 5** beschreven we de prognose van de ziekte van Alzheimer. Om achteruitgang in cognitieve functies te kunnen voorspellen maakten we een predictieve functie gebaseerd op gegevens over leeftijd, geslacht, opleiding en Apolipoproteïne-E genotype. Daarnaast ontwikkelden we functies waarmee voor een demente persoon de kans geschat kan worden om te worden geïnstitutionaliseerd of te overlijden, uit gegevens over leeftijd, geslacht en cognitief functioneren. We maakten aparte functies voor mensen die de ziekte al langer hadden (prevalente cases) en personen waarbij de ziekte net ontstaan was (incidente patiënten). Personen met al langer bestaande dementie vertoonden een langzamere achteruitgang in cognitief functioneren dan personen die de ziekte pas hadden gekregen. Hoge leeftijd en lage cognitieve functie waren in beide groepen de sterkste voorspellers voor institutionalisering en dood gaan.

In **hoofdstuk 6** zijn de bevindingen van het onderzoek, beschreven in dit proefschrift, besproken. Mechanismen die onze bevindingen mogelijk kunnen verklaren werden genoemd en we deden aanbevelingen voor toekomstig onderzoek. Diverse risicofactoren voor hart- en vaatziekten, waarvan sommigen beïnvloedbaar, bleken geassocieerd met de kans op dementie. De meeste van deze risicofactoren waren ook geassocieerd met de kans op de ziekte van Alzheimer. Of deze associatie veroorzaakt wordt doordat de ziekte van Alzheimer en vasculaire factoren onafhankelijk van elkaar vaak voorkomen, door een direct oorzakelijk verband tussen de ziekte van Alzheimer en vasculaire factoren of door biologische interactie van vasculaire factoren met Alzheimer pathologie blijft onduidelijk. Toekomstig onderzoek zal gericht moeten worden op het ophelderen van mechanismen die ten grondslag kunnen liggen aan deze relatie. Daarbij dient de nadruk te liggen op het bestuderen van determinanten van zo vroeg mogelijke stadia van preklinische dementie.

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About the author

Annemieke Ruitenberg was born on March 15th, 1971 in Leiden, the Netherlands. She graduated in 1989 at the "Corderius College" in Amersfoort, and studied for one year Human nutrition at the Agricultural University in Wageningen. In 1990 she started her medical study at the Erasmus University in Rotterdam, the Netherlands. During this period she participated in a research project at the Department of Paediatric infectious diseases (Prof. dr R. de Groot, Sophia Children's Hospital, Rotterdam, the Netherlands) on sepsis in children. She graduated from medical school in 1996. In 1997 she started the work described in this thesis at the Department of Epidemiology & Biostatistics (head: Prof. dr A. Hofman) of the Erasmus Medical Centre in Rotterdam. Part of this work was done at the Institute of Clinical Neuroscience, Department of Psychiatry, University of Göteborg, Sweden (head Dr. I. Skoog). In 1999 she obtained a Master of Science in Clinical Epidemiology at the Netherlands Institute for Health Sciences in Rotterdam. January 1, 2001, she will start her residency in Neurology at the Department of Neurology, Erasmus Medical Centre Rotterdam (Head: Prof. dr F.G.A. van der Meché).