

# Prevalence of Alzheimer's disease and vascular dementia: association with education. The Rotterdam study

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See editorial by Orrell

## Abstract

**Objective**—To estimate the prevalence of dementia and its subtypes in the general population and examine the relation of the disease to education.

**Design**—Population based cross sectional study.

**Setting**—Ommoord, a suburb of Rotterdam.

**Subjects**—7528 participants of the Rotterdam study aged 55-106 years.

**Results**—474 cases of dementia were detected, giving an overall prevalence of 6.3%. Prevalence ranged from 0.4% (5/1181 subjects) at age 55-59 years to 43.2% (19/44) at 95 years and over. Alzheimer's disease was the main subdiagnosis (339 cases; 72%); it was also the main cause of the pronounced increase in dementia with age. The relative proportion of vascular dementia (76 cases; 16%), Parkinson's disease dementia (30; 6%), and other dementias (24; 5%) decreased with age. A substantially higher prevalence of dementia was found in subjects with a low level of education. The association with education was not due to confounding by cardiovascular disease.

**Conclusions**—The prevalence of dementia increases exponentially with age. About one third of the population aged 85 and over has dementia. Three quarters of all dementia is due to Alzheimer's disease. In this study an inverse dose-response relation was found between education and dementia—in particular, Alzheimer's disease.

## Introduction

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

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

## Population and methods

The Rotterdam study is a prospective population based study of several important groups of diseases of old age<sup>4-6</sup>—namely, neurological, cardiovascular, locomotor, and ophthalmological. Between 1990 and 1993 all participants were subjected to detailed interview and examination in order to collect baseline data and ascertain their health status. In a substudy the prevalence of dementia was assessed by a three phase approach. Firstly, all participants were screened with a brief cognitive test. Screen positive subjects then underwent additional testing, and those whose results suggested a possibility of dementia were either subjected to detailed examination or had their medical records used to confirm the diagnosis and establish the type of dementia.

## STUDY POPULATION

All residents of the Rotterdam suburb of Ommoord aged 55 and over (including those living in institutions) were invited to participate in the Rotterdam study. Of the 10 275 eligible subjects, 7983 (78%) accepted. Of the eligible subjects, 7528 (73%) were screened for cognition in the dementia study, the remaining subjects being lost through death or refusal.

## MEASUREMENTS

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

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

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

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

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DIAGNOSIS OF DEMENTIA

Dementia was diagnosed according to the American Psychiatric Association's criteria (DSM-III-R).<sup>11</sup> The subdiagnosis of Alzheimer's disease was based on criteria produced by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.<sup>12</sup> Both possible and probable cases of Alzheimer's disease were grouped in this category. For the subdiagnosis of vascular dementia the DSM-III-R definition of multi-infarct dementia was used.

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

On the basis of the clinical dementia rating scale<sup>14</sup> and the minimal state examination score a division was made between severe impairment (clinical dementia rating scale over 2 or minimal state examination score under 16, referred to below as severe

TABLE II—Prevalence of dementia in each age category

Age (years)	No (%) of women	No (%) of men	Total
55-59	4/688 (0.6)	1/493 (0.2)	5/1181 (0.4)
60-64	3/807 (0.4)	3/625 (0.5)	6/1432 (0.4)
65-69	7/735 (1.0)	5/624 (0.8)	12/1359 (0.9)
70-74	15/712 (2.1)	10/492 (2.0)	25/1204 (2.1)
75-79	37/597 (6.2)	22/365 (6.0)	59/962 (6.1)
80-84	92/477 (19.3)	28/204 (13.7)	120/681 (17.6)
85-89	118/361 (32.7)	29/102 (28.4)	147/463 (31.7)
≥90	86/212 (40.6)	14/34 (41.2)	100/246 (40.7)
Total	362/4589 (7.9)	112/2939 (3.8)	474/7528 (6.3)

dementia) and mild to moderate impairment. In the overall prevalence figures all dementia cases, from mild to severe, were included.

DATA ANALYSIS

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

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

Results

Table I shows the numbers of participants in the dementia study together with their age distribution and the proportion resident in institutions. Of the 7528 study participants, 474 (6.3%) were demented—3.8% (112/2939) of men, 7.9% (362/4589) of women. Age and sex specific prevalences of dementia are shown in table II and figure 1. With the exception of the age category 80-89 years there were no major differences in prevalence between men and women. At ages 80-89 years women had a higher prevalence of dementia than men. About one third of all demented people had severe dementia; this applied to both men and women.

Prevalences of Alzheimer's disease, vascular dementia, Parkinson's disease dementia, and other dementias are shown in figure 2. Overall, 72% of the dementias were of Alzheimer type, 16% were vascular dementia, 6% were Parkinson's disease dementia, and 5% were other dementias. Table III shows the sex specific prevalences and numbers of cases of the types of dementia in 10 year age groups. There were no substantial differences between men and women in the proportions of dementia types.

The relative risks of dementia (adjusted for age and sex) decreased with increasing educational status (fig 3). Among people with the two lowest levels of education significantly more dementia was diagnosed than among those with the highest level of education (relative risks 3.2 (95% confidence interval 2.2 to 4.6) and 2.0 (1.3 to 3.2) respectively). Similarly for Alzheimer's disease the two lowest educational levels were associated with increased relative risks (4.0 (2.5 to 6.2) and 2.3 (1.3 to 4.1) respectively). For vascular dementia, only the least educated were at significantly increased risk (2.1 (1.0 to 4.5)). Other dementias,

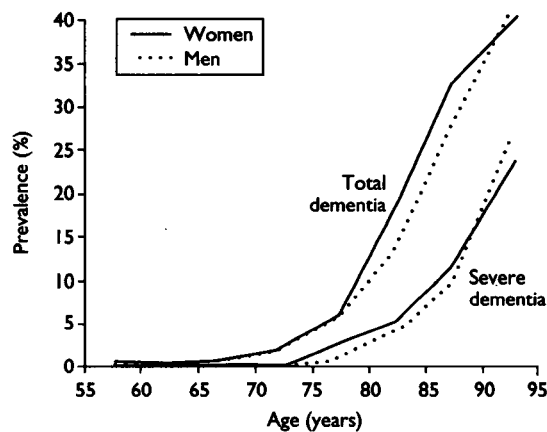


FIG 1—Prevalences of total dementia and severe dementia plotted at mean age of each five year age category

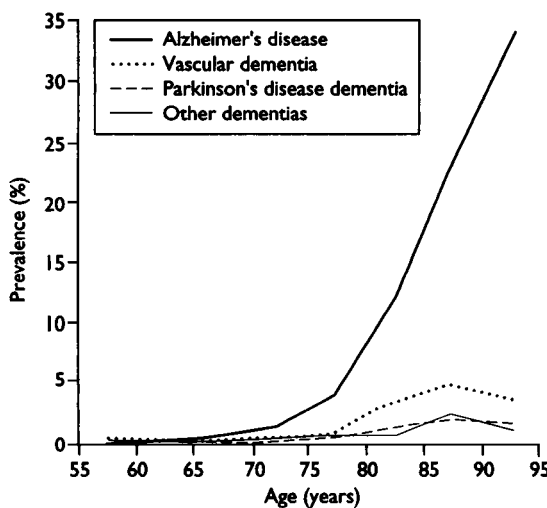


FIG 2—Prevalences of Alzheimer's disease, vascular dementia, Parkinson's disease dementia, and other dementias plotted at mean age of each five year age category

TABLE I—Characteristics of study population

	Women	Men	Total
No eligible	6325	3950	10 275
No (%) of participants in Rotterdam study	4878 (77)	3105 (79)	7 983 (78)
No (%) included in dementia prevalence study	4589 (73)	2939 (74)	7 528 (73)
Age range (years) (median)	55-106 (70)	55-97 (68)	55-106 (69)
No (%) living in institutions	710 (15)	186 (6)	896 (12)

TABLE III—Prevalences of Alzheimer's disease, vascular dementia, Parkinson's disease dementia, and other dementias\*

Age (years)	No (%) of women	No (%) of men	Total
<i>Alzheimer's disease</i>			
55-64	2 (0.1)	2 (0.2)	4 (0.2)
65-74	15 (1.0)	9 (0.8)	24 (0.9)
75-84	90 (8.4)	31 (5.4)	121 (7.4)
≥ 85	156 (27.2)	34 (25.0)	190 (26.8)
Total	263 (5.8)	76 (2.6)	339 (4.5)
<i>Vascular dementia</i>			
55-64	3 (0.2)	2 (0.2)	5 (0.2)
65-74	3 (0.2)	3 (0.3)	6 (0.2)
75-84	22 (2.0)	12 (2.1)	34 (2.1)
≥ 85	28 (4.9)	3 (2.2)	31 (4.4)
Total	56 (1.2)	20 (0.7)	76 (1.0)
<i>Parkinson's disease dementia</i>			
55-64	1 (0.1)	0	1 (0.04)
65-74	2 (0.1)	1 (0.1)	3 (0.1)
75-84	11 (1.0)	2 (0.4)	13 (0.8)
≥ 85	10 (1.7)	3 (2.2)	13 (0.8)
Total	24 (0.5)	6 (0.2)	30 (0.4)
<i>Other dementias</i>			
55-64	1 (0.1)	0	1 (0.04)
65-74	2 (0.1)	2 (0.2)	4 (0.2)
75-84	6 (0.6)	5 (0.9)	11 (0.7)
≥ 85	5 (0.9)	3 (2.2)	8 (1.1)
Total	14 (0.3)	10 (0.4)	24 (0.3)

\*Table excludes five undetermined cases.

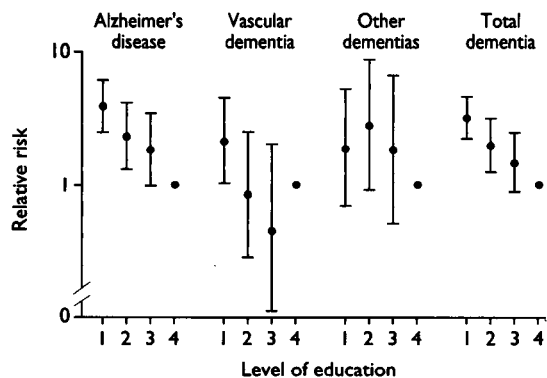


FIG 3—Association of level of education with subtypes of dementia (adjusted for age and sex) expressed as relative risks (points) and 95% confidence intervals (bars) (log scale). Level 4 is reference level

including Parkinson's disease dementia, were not significantly associated with education. The trend of a higher prevalence of dementia with less education was highly significant ( $P < 0.0001$ ). Similar trends were observed for Alzheimer's disease and vascular dementia ( $P < 0.0001$  and  $P = 0.01$ , respectively).

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

### Discussion

We have presented detailed age specific prevalences of dementia and dementia subtypes that indicate

Alzheimer's disease as the main contribution to the exponential increase of dementia with age. Our data also show a consistent trend of a higher risk of dementia with lower educational level. This effect of educational status could not be explained by a confounding effect of cardiovascular disease.

All recent population based studies on the prevalence of dementia with standardised diagnostic criteria show an exponential increase with age and a predominance of Alzheimer's disease as the cause of the dementia. However, age specific prevalences vary considerably between studies. This may be due to study design, population sampling methods, or real geographical variations.

Our study is the largest European study of its kind, allowing more precise estimates of prevalence. Compared with a pooled reanalysis of 12 European studies,<sup>3</sup> our study showed slightly lower prevalences below the age of 75 and slightly higher prevalences above age 80. Differences in screening and the type of population were the most likely causes. A high sensitivity and specificity of the diagnostic procedure was ensured by the three phase comprehensive diagnostic work up.<sup>15</sup>

A major concern in prevalence studies is non-participation. The Rotterdam study, of which the dementia study was only a part, had a fairly high participation rate (almost 80%). However, the non-response may have been selective. If non-response distorted the study results it probably produced an underestimate of the prevalence of dementia. We consider it unlikely that non-response influenced the proportions of dementia.

Without confirmation at necropsy, subtyping dementia remains uncertain. Also the current diagnostic criteria that we used are of limited accuracy, which complicates all large population based dementia studies and which we could not improve even by basing the subdiagnoses on a great number of reliable data. Alzheimer's disease was the main contributor to the steep increase in dementia prevalence with age. We observed only a little increase with age in vascular dementia and even less in Parkinson's disease dementia and other dementias. We classified primary Alzheimer's disease complicated by cerebrovascular disease as Alzheimer's disease. This may be why we found a somewhat higher prevalence of Alzheimer's disease than reported in other European studies.<sup>16</sup>

In common with other studies, we found a higher prevalence of dementia in groups with less education.<sup>17-21</sup> It has been suggested that the education effect could be due to diagnostic bias. There is, indeed, a possibility that early dementia might be missed in a highly educated person, though we do not think that this occurred often in our series because the combined minimal state examination and geriatric mental state schedule is a very sensitive screening test.<sup>15</sup> That the education effect also applied to vascular dementia led us to consider whether the association of education with dementia might be due to confounding by cardiovascular disease. This is possible, as cardiovascular disease is associated with both education and dementia. Particularly vascular dementia—but also Alzheimer's disease—is correlated with cardiovascular disease,<sup>13 22 23</sup> and cardiovascular disease is more prevalent in people with less education.<sup>24 25</sup> However, control for possible confounding by cardiovascular disease did not substantially decrease the magnitude of the association of education with dementia, nor with the subtypes of dementia.

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

### Key messages

- In a case finding study in a general population 9% of subjects aged 65 and over and 34% of subjects aged 85 and over had dementia
- Of all cases of dementia, 72% were cases of Alzheimer's disease
- The pronounced increase in prevalence of dementia with age was due to a substantial increase in Alzheimer's disease
- Alzheimer's disease was more often diagnosed in less educated people
- The association between dementia and education could not be explained by cardiovascular disease comorbidity

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## Severity of heart failure and dosage of angiotensin converting enzyme inhibitors

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inhibitor and had had no change in drug treatment in the previous six weeks.

The dose of angiotensin converting enzyme inhibitor was standardised to the lowest target dose available to improve mortality: captopril 25 mg twice daily,<sup>2</sup> enalapril 10 mg twice daily,<sup>1</sup> lisinopril 10 mg daily,<sup>4</sup> and ramipril 5 mg twice daily.<sup>3</sup> We also chose a clinical scale of equivalence based on drug datasheets: 12.5 mg captopril three times a day was assumed to be equivalent to 5 mg enalapril twice daily and to 5 mg lisinopril once daily.

Forty three patients were not taking any angiotensin converting enzyme inhibitor; 47 were taking captopril, 47 enalapril, 17 lisinopril, one ramipril, one fosinopril, and one perindopril (table). The diagnosis was dilated cardiomyopathy in 66 patients and ischaemic heart disease in 91. Diagnosis was not related to angiotensin converting enzyme inhibitor usage, and 85 patients were taking doses lower than the optimum suggested by the results of survival trials. Captopril was most likely to be given in dosages associated with improved mortality: 13 out of 47 were taking it twice daily and the remaining 34 three times daily. Thirty three of the 47 patients taking enalapril were taking the drug once daily.

There was no difference between the groups of patients in usage of alternative vasodilators. Patients taking an angiotensin converting enzyme inhibitor had more severe heart failure as judged by mean left ventricular ejection fraction (26.0% (SD 12.7%) v 34.6% (18.6%), 95% confidence interval for difference 5.84 to 11.46; P<0.01) and daily dosage of diuretic (85.6 (70.6) v 39.1 (36.2) mg frusemide equivalent, 41.4 to 51.7; P<0.001). Patients taking angiotensin converting enzyme inhibitor had lower mean serum sodium concentrations (138.2 (1.8) v 139.5 (2.7) mmol/l, -1.07 to -1.61; P=0.03) and higher mean concentrations of urea (8.35 (3.56) v 6.10 (1.91) mmol/l, 1.96 to 2.55; P<0.001) and creatine (121.06 (39.49) v 98.82 (17.39) μmol/l, 19.03 to 25.44; P<0.001). There was no correlation between

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Large studies have shown improved survival of patients with heart failure<sup>1,2</sup> and of those recovering from acute myocardial infarction<sup>3,4</sup> after treatment with high doses of angiotensin converting enzyme inhibitors. We studied the usage of angiotensin converting enzyme inhibitors for chronic heart failure in a tertiary referral centre to investigate the relation between the regimen used and patient variables and how this related to the dosages used in the published mortality trials.

### Patients, methods, and results

We examined the drug regimens of 157 patients seen by two consultants in a specialist clinic for chronic heart failure. Chronic heart failure was diagnosed from the finding of impaired left ventricular function on echocardiography, radionuclide ventriculography, or cardiac catheterisation. All patients underwent exercise testing with metabolic gas exchange measurements. All had been reviewed at least once while taking their current angiotensin converting enzyme

Dosage schedules for the three most commonly prescribed angiotensin converting enzyme inhibitors

Regimen	Dose (mg)	No of times daily	Daily dosage	
			Total (mg)	% Of optimum*
Captopril 6-25-50 mg thrice daily	23.0 (13.1)	2-7 (0-45)	61.6 (35.3)	123.1 (70.7)
Enalapril 2.5 mg once daily-40 mg twice daily	10.5 (7.6)	1-3 (0-5)	13.2 (11.9)	66.2 (59.4)
Lisinopril 2.5-20 mg once daily	7.8 (4.4)	1	7.8 (4.4)	77.8 (43.9)

\*To improve mortality.