

## Incidence and Risk of Dementia

### The Rotterdam Study

Alewijn Ott,<sup>1</sup> Monique M. B. Breteler,<sup>1</sup> Frans van Harskamp,<sup>2</sup> Theo Stijnen,<sup>1</sup> and Albert Hofman<sup>1</sup>

To assess age-, sex-, and subtype-specific incidence rates of dementia and to calculate the risk of dementia, the authors performed a large, community-based, prospective cohort study on dementia as part of the Rotterdam Study. Participants were recruited among residents of a suburb of Rotterdam, aged 55 years and older. Baseline examinations took place between 1990 and 1993. The average follow-up was 2.1 years. Screening for dementia followed a three-stage protocol. Medical records of subjects who had died or could not be examined in person were evaluated. Of 7,046 subjects who were nondemented at baseline, 162 developed dementia during 15,135 person-years of follow-up, resulting in an overall incidence rate of 10.7 per 1,000 person-years. From the youngest to the oldest 5-year age category, the incidence rate increased from 0.6 to 97.2 per 1,000 person-years. Only in men did the increase level off after age 85. Overall, the incidence rate per 1,000 person-years was 7.7 for Alzheimer's disease and 1.5 for vascular dementia. Dementia incidence rates and dementia-free Kaplan-Meier survival tables were used to calculate age- and sex-specific cumulative risks of dementia. Although the incidence rates of men and women up to age 85 were similar, the lifetime risk of dementia for 55-year-old women was twice as high as for men (0.33 vs. 0.16), reflecting both the higher life expectancy of women and the higher dementia risk at very old age. *Am J Epidemiol* 1998;147: 574-80.

Alzheimer's disease; dementia; dementia, vascular; disease-free survival; follow-up studies; incidence; survival analysis

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

person's absolute (unconditional) risk of developing dementia in the next few years or during the rest of his or her life. To calculate these absolute risks, one should take into account the competing risk of dying. We performed a large prospective study on the incidence of dementia in the community, which enabled us to calculate period and lifetime risks of developing dementia.

## MATERIALS AND METHODS

### Study design

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

Between 1990 and 1993, participants were interviewed at their homes and thereafter, during two sessions, examined at the research center, in order to

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Abbreviations: CAMDEX, Cambridge examination for mental disorders of the elderly; GMS, Geriatric Mental State Schedule; MMSE, Mini-Mental State Examination; RIAGG, regional institute for outpatient mental health care.

<sup>1</sup> Department of Epidemiology and Biostatistics, Erasmus University Medical School, Rotterdam, Netherlands.

<sup>2</sup> Department of Neurology, Erasmus University Medical School and Academic Hospital, Rotterdam, Netherlands.

Reprint requests to Dr. Alewijn Ott, Department of Epidemiology and Biostatistics, Erasmus University Medical School, P.O. Box 1738, 3000 DR Rotterdam, Netherlands.

ascertain their health status and to collect baseline data. Follow-up examinations took place from mid-1993 to the end of 1994.

### Study population

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

### Dementia case finding

Dementia screening and diagnosis at baseline and follow-up followed the same three-step protocol and diagnostic criteria. First, with a combined Mini-Mental State Examination (MMSE) (4) and Geriatric Mental State Schedule (GMS-A, organic level) (5), the population was screened for dementia. This test was administered by trained research assistants. Second, subjects scoring below 26 on the MMSE or more than 0 on the GMS were considered screen positive and subsequently examined by one of four study physicians with the Cambridge examination for mental disorders of the elderly (CAMDEX) (6), which includes an informant interview. Finally, participants who were judged to be demented or suspected of dementia after the CAMDEX were examined by a neurologist, given relevant blood examinations, tested by a neuropsychologist, and evaluated with a nuclear magnetic resonance imaging scan of the brain. 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 the dementia screening, the total cohort was continuously being monitored for detection of interval cases of dementia or cognitive disturbances through linkage of the general practitioner's automated medical record system to the database of the Rotterdam Study. The general practitioners have been involved in the Rotterdam Study since the beginning and are well triggered to note early symptoms of

diseases of interest to the study. All reports of incident events including onset of memory problems or dementia were regularly evaluated by the study physicians. For nonrespondents to the follow-up examination who were reported to have memory problems or dementia, information was obtained from informants and medical files in order to make a diagnosis of dementia. In addition, the regional institute for outpatient mental health care (RIAGG), covering the entire study population, provided information. This psychiatric service can be consulted both directly and by referral regarding social and psychiatric problems, and it is responsible for nursing home or other dementia care-facility indications. Their diagnoses are based on (informant) interviews, neurologic and neuropsychologic examination, and relevant blood biochemistry and serology. From this service, once a year information was obtained on newly diagnosed dementia or amnesic syndrome in study participants. Surveillance of the population through the general practitioners and RIAGG reports continued up to the end of 1994. Subjects who were reported as having memory problems or suspected of dementia before this date were followed until the cause of the memory problems or dementia diagnosis was clear.

Of both the in-person-screened subjects and those monitored by general practitioners and RIAGG, the study diagnosis of dementia was made by a panel that reviewed all existing information. A diagnosis of Alzheimer's disease was based on criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (7). According to those criteria, a subdivision into possible and probable Alzheimer's disease was made. Vascular dementia was diagnosed in accordance with criteria reported by the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (8). As proposed in the latter criteria, we also categorized a subgroup of Alzheimer's disease with cerebrovascular disease. For other dementias, we used criteria from the *Diagnostic and Statistical Manual of Mental Disorders: DSM III-R* (9). The highest achieved level of education was assessed during the initial home interview. To adjust for education, we categorized educational level into six grades.

### Data analysis

The age at baseline/follow-up was defined precisely by converting age in days to years with two decimals. 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 screening, at the age at onset of dementia, or at death. For both screened and reported cases, the age at onset of dementia was taken to be the midpoint between baseline age and the age at diagnosis. For subjects without a second screening, follow-up through the reports from treating physicians continued until the end of 1994. Incidence figures were estimated by sex, by dementia subtype, and by response status. Poisson standard errors and 95 percent confidence intervals were calculated from the number of incident cases per follow-up period. The difference in incidence between groups of subjects was expressed as a rate ratio, which was calculated with proportional hazards regression, adjusting for age and if applicable other variables.

To calculate the risk of developing dementia over time, the competing risk of death was taken into account. Using incident dementia and mortality data from the study cohort, we first made dementia-free survival functions with the Kaplan-Meier method (10). The age at baseline was used as the entry time variable; the age at follow-up, dementia onset, or death was used as the exit time; and both incident dementia and death were viewed as failures. Next, the cumulative absolute risk of dementia over a period was calculated as the integrated product of the 5-year age band-specific dementia incidence multiplied by the dementia-free survival (10, formula 7.10, p. 169). These risks of developing dementia were calculated separately for nondemented men and women at ages of 55, 65, 75, and 85 years.

## RESULTS

In table 1 several characteristics of the study population are summarized. Of the total cohort ( $n = 7,046$ ) at risk of developing dementia, 79 percent were screened in person for dementia. Of those who were not examined at follow-up and for whom information

on dementia was obtained solely through general practitioners and the RIAGG, 476 had died and 999 refused the screening tests. The proportion of subjects who were not examined in person increased with age, from 9 percent in the youngest to 45 percent in the oldest age category, and was in all age groups somewhat higher in women than in men. Mortality was higher among men.

Overall, after an average follow-up period of 26 months, 162 new cases of dementia were identified, 109 in the group examined in person and 53 through the general practitioner and RIAGG monitoring. Age- and sex-specific incidence rates are given in table 2. With a total of 15,135 follow-up years, the overall incidence was 10.7 per 1,000 person-years. The incidence increased markedly with age. Though the overall incidence was higher in women than men (13.1 vs. 6.9 per 1,000 person-years), age-specific incidence rates were very similar up to the age of 85 years. From that age onward, the incidence in men seemed to level off, whereas in women it continued to rise. However, in the highest age categories in men, incidence estimates were based on small numbers of cases and person-years of follow-up, and the 95 percent confidence intervals overlapped those for women of the same ages. Figure 1 shows the age-specific incidence among the total cohort compared with that from other incidence studies (11–13). In this figure, the only studies included were those that were relatively large and used similar procedures to diagnose dementia at baseline and follow-up and that calculated 5-year age-specific incidence rates of total dementia.

Comparison of the incidence between the in-person-screened and those whose information on dementia status came from informants and medical files revealed that there was no major difference until the age of 85. Above age 85, more demented persons were identified by personal examination than by evaluation of reported possible patients (76.1 per 1,000 person-

TABLE 1. Characteristics of participants in the study on dementia incidence, the Rotterdam Study, 1990–1994\*

	Total		Women (%)	Baseline age (years)		No more than primary education		Baseline MMSE† score		
	No.	%		Mean	SD‡	%	Adjusted difference‡	Mean	SD	Adjusted difference‡
Total cohort	7,046		58.9	69.5	9.1	24.1		27.8	1.9	
Examined in person	5,571	79.1	58.8	68.1	8.3	20.6		27.8	1.8	
No in-person examination during follow-up§	889	14.2	68.9	72.6	9.7	38.8	9.0 (5.8 to 12.4)¶	27.0	2.2	-0.6 (-0.7 to -0.4)
Died before follow-up examination§	476	6.8	54.6	79.9	9.0	41.5	4.4 (0.2 to 9.0)	26.5	2.7	-0.6 (-0.8 to -0.4)

\* This study was conducted in a population-based sample aged 55 years and over.

† MMSE, Mini-Mental State Examination; SD, standard deviation.

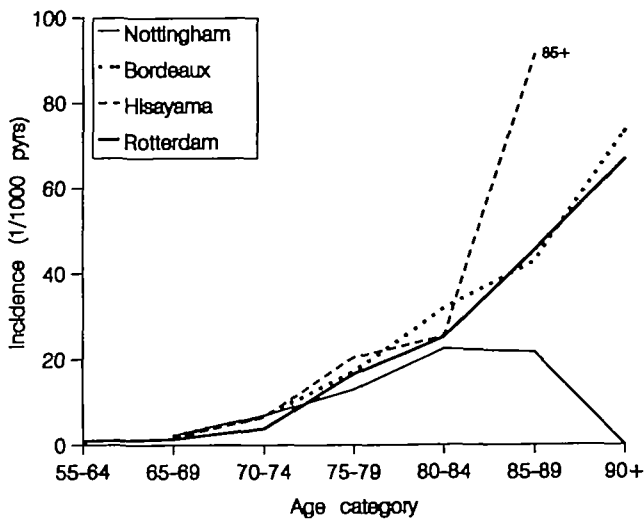
‡ To adjust for age, sex, and education (in the case of the MMSE), both groups were included in a logistic (for education) or linear (MMSE) regression model. The adjusted difference between both groups was calculated from the group coefficient (and standard error).

§ Information through general practitioners, the regional institute for outpatient mental health care, and medical files.

¶ Numbers in parentheses, 95% confidence interval.

**TABLE 2.** Age- and sex-specific number of person-years at risk, number of dementia cases, and incidence rates (per 1,000 person-years, with 95% confidence interval (CI)) in a Dutch general population, the Rotterdam Study, 1990–1994

Age category (years)	Women				Men			
	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	988	0	0.0	0.0–3.0	707	1	1.4	0.2–10.0
60–64	1,611	2	1.2	0.3–5.0	1,142	1	0.9	0.1–6.2
65–69	1,591	3	1.9	0.6–5.8	1,269	1	0.8	0.1–5.6
70–74	1,683	6	3.6	1.6–7.9	1,110	5	4.5	1.9–10.8
75–79	1,404	25	17.8	12.0–26.3	813	12	14.8	8.4–26.0
80–84	1,031	26	25.2	17.2–37.0	479	12	25.1	14.2–44.1
85–89	695	35	50.4	36.2–70.2	210	6	28.6	12.9–63.7
90–94	263	18	68.3	43.1–108.5	67	2	29.6	7.4–118.5
≥95	63	7	111.5	53.1–233.8	9	0	0.0	0.0–333.0
Total	9,329	122	13.1	11.0–15.6	5,806	40	6.9	5.1–9.4

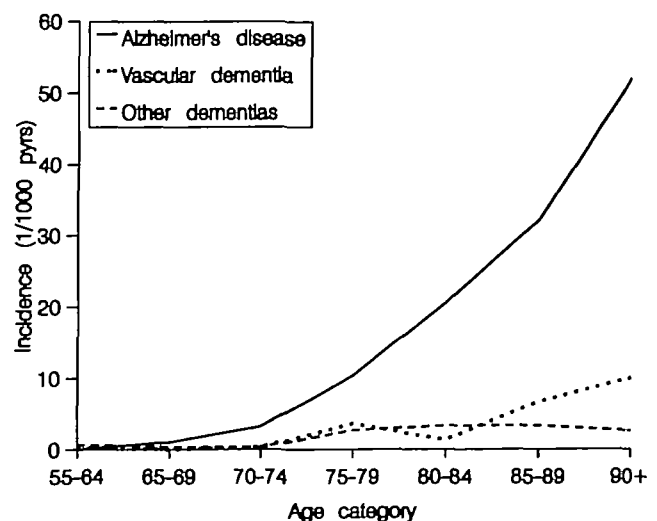


**FIGURE 1.** Age-specific dementia incidence from other studies in Nottingham, England, Bordeaux, France, and Hisayama, Japan, compared with results from the present Rotterdam Study, conducted in a Dutch general population of 55 years and older between 1990 and 1994. pyrs, person-years.

years vs. 31.3 per 1,000, respectively), with an age- and sex-adjusted ratio of 0.5 (95 percent confidence interval 0.3–0.8). The difference in incidence between men and women could not be explained by differences in screening method.

A dementia subtype was determined in 158 cases (98 percent). Alzheimer's disease was diagnosed in 116 (73 percent); 69 of those had probable Alzheimer's disease and 47 had possible Alzheimer's disease, of whom there were 19 with cerebrovascular disease. Vascular dementia was detected in 22 (14 percent) and other dementias in 20 (13 percent). The proportions of dementia subtypes differed between men and women: of male cases, 58 percent were

diagnosed as having Alzheimer's disease and 23 percent as having vascular dementia; of female cases, these proportions were 79 percent and 11 percent, respectively. Overall incidence rates for Alzheimer's disease and vascular dementia in men were 4.0 and 1.6 and, in women, 10.0 and 1.4, per 1,000 person-years, respectively. Though the age-adjusted rates of total dementia did not differ significantly between men and women, women were more often diagnosed with Alzheimer's disease than were men (rate ratio, 1.7; 95 percent confidence interval 1.0–2.6). Men more often developed vascular dementia than did women, though this difference did not reach significance (rate ratio, 1.6; 95 percent confidence interval 0.6–3.8). Figure 2 shows the age-specific incidence of subtypes of de-



**FIGURE 2.** Age-specific incidence of Alzheimer's disease, vascular dementia, and other dementias in a Dutch general population (≥55 years), the Rotterdam Study, 1990–1994. Four cases whose dementia subtype could not be defined are excluded. pyrs, person-years.

mentia for both sexes combined. The Alzheimer's disease incidence increased most strongly with age. The incidence of vascular dementia also increased up to the oldest age categories, whereas the incidence of other dementias remained relatively stable with age.

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

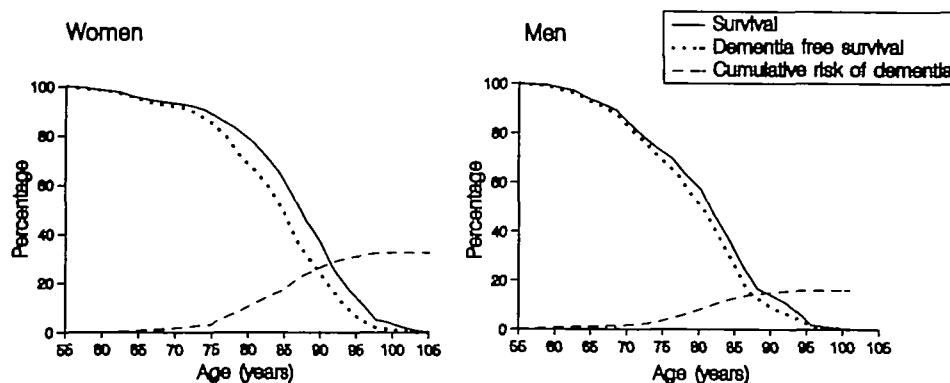
## DISCUSSION

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

The strength of our study is threefold. First, high sensitivity and specificity of the in-person screening were ensured by a three-phase comprehensive diag-

nostic work-up (14), which was similar at baseline and follow-up. Also, diagnoses were made by the same diagnostic panel. Reliability of the diagnoses was further enhanced because most cases and subjects suspected of dementia were followed for months to years to monitor progression of the disease. Second, through the reports from the general practitioners and RIAGG, we could obtain a complete follow-up of all members of the cohort, including those who died, which reduces the potential bias due to selective secondary refusal or death. Age-specific incidence rates were quite similar for the in-person-screened subjects and those whose medical files were studied after being reported with memory problems or possible dementia, though we may have missed mild cases in the latter group, particularly in the highest age bands. In the highest age groups, we may therefore have slightly underestimated dementia incidence. A third advantage of the study is its size, which resulted in stable age-, sex-, and subtype-specific estimates of dementia incidence in the community, despite the relatively short duration of follow-up.

Our incidence rates agree well with those of other studies (figure 1). The discrepancy with the Nottingham and Hisayama study incidence rates above age 85 can be explained by the instability of these rates due to the relatively few person-years of follow-up on which these estimates were based. We found the incidence of dementia for women to continuously increase with age, whereas there appeared to be a leveling off above age 85 for men. This pattern is consistent with reports from other studies (11, 15, 16). A possible explanation is selective survival of men at lower risks for dementia. Moreover, our finding of a higher incidence of Alzheimer's disease in women and a tendency to higher incidence of vascular dementia in men is in agreement with previous studies (12, 13, 16).



**FIGURE 3.** Kaplan-Meier survival curves with and without dementia and the cumulative risk of dementia (competing risk of death taken into account) among 55-year-old women and men, as observed in the Rotterdam Study, 1990–1994.

**TABLE 3. Period and lifetime risk\* of dementia (competing risk of death taken into account) for 55-, 65-, 75-, and 85-year-old nondemented women and men, the Rotterdam Study, 1990-1994**

Age (years)	Period risk (%)								Lifetime risk (%)
	5 years	10 years	15 years	20 years	25 years	30 years	35 years	40 years	
<b>Women</b>									
55	0.0	0.6	1.5	3.1	9.9	17.5	26.3	31.0	32.8
65	0.9	2.6	9.9	17.8	27.2	32.2	34.0	34.4	34.5
75	8.1	16.9	27.3	32.7	34.8	35.3	35.4		35.4
85	18.3	28.2	31.7	32.5	32.7				32.7
<b>Men</b>									
55	0.7	1.1	1.5	3.2	7.7	12.7	15.0	15.9	15.9
65	0.4	2.2	7.1	12.5	14.9	16.0			16.0
75	6.4	13.4	16.6	18.0					18.0
85	8.7	12.3							12.3

\* These risks were estimated using Kaplan-Meier product limit estimates of dementia-free survival and age-specific incidence as observed in a Dutch general population.

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

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