Mortality with Dementia: Results from a French Prospective Community-based Cohort

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Despite the magnitude of the problem, little is known about the duration of dementia. Survival and risk factors of mortality with dementia and the impact of dementia on the risk of death were investigated using the Personnes Agées Quid (PAQUID) prospective population-based cohort study between 1988 and 1998. Statistical models dealing with interval censoring were performed. Among 3,675 participants aged 65 years or older and initially nondemented, 2,923 have been followed up for 8 years. Of these, 281 persons with incident dementia were actively diagnosed. The mean age of onset of dementia was 82.3 years. In the total population, the relative risk of dying after developing dementia was estimated to be 1.82 (95% confidence interval (CI): 1.77, 2.68) when adjusted for sociodemographic variables and comorbidity. Deaths from cerebrovascular diseases and respiratory diseases were particularly increased among persons with dementia, compared with those without. The median survival time of the persons with dementia was estimated to be 4.5 years. Women with dementia had a longer survival than did men with dementia, particularly for Alzheimer-type dementia (relative risk = 0.47, 95% CI: 0.27, 0.83). Educational level was not significantly associated with survival in persons with dementia. These results provide further evidence of the malignancy of dementia, which will be a challenge for the 21st century. Am J Epidemiol 2001;154:642–8.

Alzheimer disease; dementia; mortality; prognosis

As with all major public health problems, the duration of the disease is a key factor in dementia for family, practitioner, and society. Despite the magnitude of the problem, knowledge of how serious dementia is and its consequences on the population remains imprecise. Dementia is a major source of disability in the population (1). Precise knowledge on survival with dementia is useful for the family and the practitioner who have to decide how to manage the patient. For society, the survival time of persons with dementia affects the burden due to it. Therefore, health policy decision makers need precise data on survival with dementia for health care planning.

More than 100 studies have been carried out on survival with dementia, and most have found an increased risk of dying among persons with dementia compared with those without. However, data are often not obtained from community-based studies but from selected groups, that is, institutions or clinical settings, and cannot be applied to the general population. Indeed, in a review of the literature, van Dijk et al. (2) found that survival is conditioned by the reference population, with a lower survival for studies conducted in an institution than in community-based studies. In addition, even among community-based studies, 2-year survival was found to vary from 37 percent to 86 percent, probably depending on study designs (2). The majority of the studies conducted on community-based samples (3–11) have been based on prevalent cases, in which the onset of the disease is not known. Onset of dementia is insidious and progressive and thus cannot be determined exactly. Onset is often considered either as the time of the first symptoms of the disease or as the time of the first consultation. However, the earlier one sees the patient after the onset, the more precise the estimation of the onset will be; thus, onset will be estimated more precisely in incident than in prevalent cases.

Few community-based studies have used incident cases of dementia (12–14), and dementia cases were actively screened in only one of them (14). Active detection of dementia makes it possible to take into account cases undiagnosed by their practitioner, a scenario frequent in France (15). In such a recent study in Sweden based on the Kungsholmen project (14), the risk of death among Alzheimer’s disease cases was estimated to be 2.0 compared with that of nondemented persons. However, in the latter study, the onset of the disease was considered to be the time of diagnosis, and statistical analyses did not take into account the problem of interval censoring in cohort studies, where participants are not followed up continually but receive repeated cross-sectional screenings at time intervals.
This could bias the results, particularly because of a lack of accuracy in the determination of disease onset.

The aim of this paper was to evaluate survival and risk factors of mortality with dementia and to quantify the impact of dementia on total mortality, using statistical models dealing with interval censoring, on a French prospective population-based cohort with active search for incident cases of dementia at each follow-up screening.

MATERIALS AND METHODS

Study population

Information for this study was gathered from the Personnes Agées Quid (PAQUID) cohort. The PAQUID research program is a prospective cohort study of a representative sample of community residents aged 65 years or over, living in southwestern France (Departments of Gironde and Dordogne). The cohort began in 1988. Three criteria had to be met for inclusion: to be at least 65 years of age by December 31, 1987; to be living at home at the time of the initial data collection phase; and to give written informed consent to participate in the study. The sample was randomly chosen from the electoral rolls, on which each French citizen, except those under guardianship, can register. A three-step procedure with stratification by size of the urban unit, age, and sex was used. Among the 5,554 persons selected, 3,777 (68 percent) agreed to participate in the study. These 3,777 participants (2,792 in Gironde and 985 in Dordogne) were representative of the age-sex distribution of the elderly of this area (15). Nonresponders did not differ from responders for age, gender, and educational level. The general methodology of the PAQUID study has been described previously (16). An ethical review committee has approved the PAQUID study.

Data collection

Data were collected by means of a questionnaire administered at home by trained psychologists. The initial interview included items about sociodemographic characteristics, objective and subjective physical health, functional assessment, depressive symptomatology, and a battery of neuropsychological tests, including an evaluation of global mental status, the Mini-Mental State Examination (17). Physical health was evaluated by self-reported diseases or symptoms. Treated diabetes, a history of heart disease, stroke, or hypertension, and dyspnea were considered. A variable of comorbidity was created when participants reported history of at least one of these diseases or symptoms. Functional status was evaluated using the activities of daily living scale excluding the item of maintaining continence (18). Participants who needed help for at least one of the five activities were classified as “disabled.”

After the initial interview, participants were followed up with the same baseline procedure at 1, 3, 5, and 8 years in Gironde and at 3, 5, and 8 years in Dordogne.

Data on vital status were collected throughout the follow-up. Dates and causes of death were collected from death certificates, by way of the national registry of mortality statistics. Causes of death were classified according to the International Classification of Diseases, Ninth Revision (19): cancer (codes 140–208 and 230–239); cardiovascular diseases, excluding cerebrovascular diseases (codes 390–427 and 440–455); cerebrovascular disease (codes 430–438); and respiratory disease (codes 460–511).

Diagnosis of dementia

At baseline, intellectual functioning was examined through a series of psychometric tests that have been shown to be among the most sensitive for assessing cognitive decline in elderly persons. Then, the psychologists systematically filled in a standardized questionnaire designed to obtain the A (memory impairment), B (impairment of at least one other cognitive function), and C (interference with social or professional life) criteria for dementia according to the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R) (20). In a second stage, participants who met these DSM-III-R criteria were seen by a senior neurologist, who confirmed and completed the DSM-III-R criteria for dementia and filled in the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria for Alzheimer’s disease (21) and the Hachinski score for vascular dementia (22) to document the dementia diagnosis and its etiology: probable or possible Alzheimer’s disease, vascular dementia or Alzheimer’s disease with cerebrovascular disease, and other types of dementia. An informant was consulted by the neurologist when available. All ancillary information was considered, including medical charts and brain imaging, if available. Finally, a consensus meeting allowed us to definitely classify each case. Comparable procedures of screening of dementia are usually used in other cohort studies (23). Diagnosis of incident dementia cases followed the same procedure at each follow-up assessment as for the baseline screening, but in order to increase the screening sensitivity, another criterion was added to qualify for the neurologic examination. Participants were selected for this stage if they met the A, B, and C DSM-III-R criteria for dementia or if they had lost three points or more on the Mini-Mental State Examination score.

Statistical analysis

Mortality with dementia was analyzed according to age, sex, and educational level. Educational level was divided in two categories: at least primary school level as validated by a diploma (the Certificat d’Etudes Primaires (CEP)) versus no diploma (24). Analyses were performed for dementia due to all causes and Alzheimer’s disease.

First, the impact of mortality with dementia on the general population was considered, comparing mortality among persons with incident dementia and those without and partitioning competing causes of death. Then, we analyzed the mortality with dementia among persons with incident dementia.
1. To quantify the impact of dementia on total mortality, we performed a Cox model with delayed entry, in which the time-scale is the age of the participants (25), taking the occurrence of dementia as a time-dependent variable and considering the age of onset of dementia to be at the middle of the interval between the last follow-up without dementia and the first follow-up with dementia. Relative risks of death from dementia and Alzheimer’s disease were provided with 95 percent confidence intervals. Relative risks for competing causes of death were provided.

2. Mortality among persons with incident dementia, from the onset of the clinical stage until death, was analyzed using a multistate approach (semi-Markov model). We performed a statistical model dealing with interval censoring, which is a common problem in cohort studies. Indeed, in the PAQUID study, participants are not followed up continuously but with cross-sectional screenings at discrete times. Thus, the onset of the disease is not known exactly, and the only information available is that this onset occurred between two follow-up times. We therefore used a semi-Markov model that includes two transitions. The first transition represents the age-specific incidence rates of dementia. The second transition represents the mortality rates of persons with dementia. The model uses information from the incidence data of all people in the cohort. The fact that the time of onset of dementia is not known is taken into account by a penalized likelihood approach (26).

RESULTS

Description

At baseline, 3,777 participants were included in the cohort. Among them, 102 already had dementia and were excluded. Among the 3,675 initially without dementia, at least one complete follow-up examination was performed on 2,923 (79.5 percent). The 752 (20.5 percent) remaining participants did not participate in the follow-up because they had died (n = 413, 11.2 percent) or they refused the follow-up screenings (n = 335, 9.1 percent). Very few participants were lost to follow-up (n = 4, 0.1 percent). A description of participants at each follow-up according to sociodemographic characteristics is given in Table 1.

The 2,923 reevaluated participants included 1,705 (58.3 percent) women, and there were 1,375 (47 percent) participants aged 75 years or older. The mean delay between two follow-up evaluations was 2.2 years. During the follow-up, 281 participants developed an incident dementia, including 189 with Alzheimer-type dementia, 70 with vascular or mixed dementia, and 22 other types of dementia. Persons with incident dementia included 183 (65.1 percent) women. The mean age of onset of dementia was 80 (standard deviation, 6.1) years among men and 83.5 (standard deviation, 6.1) years among women.

At the end of the study, 39.1 percent of the persons with dementia had died versus 22.2 percent among those without. Persons with dementia died of cardiovascular pathology (20.0 percent), stroke (12.7 percent), cancer (12.7 percent), respiratory pathology (10.0 percent), and symptoms, signs, and ill-defined conditions (including senile dementia) (10.9 percent). These proportions were, respectively, 32.3 percent, 9.2 percent, 24.6 percent, 6.4 percent, and 7.2 percent for persons without dementia.

Impact of dementia on mortality

The impact of dementia on total mortality was analyzed using a Cox proportional hazards model with delayed entry, adjusted for sex, educational level, index of comorbidity, and baseline dependency for the activities of daily living scale, by comparing participants with dementia and those

| TABLE 1. Distribution of participants interviewed at each follow-up, according to diagnosis of dementia and sociodemographic characteristics, PAQUID* cohort, France, 1988–1998 |
|---|---|---|---|---|---|---|---|
| | 1 year (Gironde) | 3 years | 5 years | 8 years |
| | Incident demented | Non-demented | Incident demented | Prevalent demented† | Non-demented | Incident demented | Prevalent demented† | Non-demented |
| Age (years) | | | | | | | | |
| 65–74 | 9 | 957 | 15 | 5 | 1,222 | 20 | 10 | 1,184 |
| 75–84 | 6 | 667 | 58 | 3 | 798 | 43 | 36 | 644 |
| ≥85 | 6 | 168 | 19 | 1 | 156 | 15 | 7 | 102 |
| Total | 21 | 1,792 | 92 | 9 | 2,176 | 78 | 53 | 1,930 |
| Sex | | | | | | | | |
| Men | 9 | 748 | 31 | 4 | 934 | 24 | 15 | 796 |
| Women | 12 | 1,044 | 61 | 5 | 1,242 | 54 | 38 | 1,134 |
| Total | 21 | 1,792 | 92 | 9 | 2,176 | 78 | 53 | 1,930 |
| Education | | | | | | | | |
| With CEP* | 10 | 1,268 | 41 | 4 | 1,540 | 45 | 22 | 1,382 |
| Without CEP | 11 | 524 | 51 | 5 | 636 | 33 | 31 | 548 |
| Total | 21 | 1,792 | 92 | 9 | 2,176 | 78 | 53 | 1,930 |

* PAQUID, Personnes Agées Quid; CEP, Certificat d’Etudes Primaires, which validates the primary school level.
† Demented at a previous time of follow-up.


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without. In the total population, the relative risk of dying after developing dementia was estimated to be 1.80 (95 percent confidence interval (CI): 1.46, 2.21). For Alzheimer’s disease, this risk was 1.72 (95 percent CI: 1.34, 2.21). However, there was a significant interaction between dementia and age (relative risk (RR) = 0.95, 95 percent CI: 0.92, 0.98), with a lower impact of dementia on mortality with increasing age. The relative risk of dying with dementia was estimated to be 1.59 (95 percent CI: 1.26, 2.01) among participants aged 75 years or older and to be 1.37 (95 percent CI: 0.91, 2.04) among participants aged 85 years or older. Risks were similar for men and women.

According to causes of death, relative risks were not significantly increased for cancer (RR = 1.22, 95 percent CI: 0.70, 2.13) or cardiovascular disease (RR = 1.12, 95 percent CI: 0.72, 1.75) among persons with dementia, whereas the relative risk was 2.29 (95 percent CI: 1.26, 4.17) for cerebrovascular disease and 2.78 (95 percent CI: 1.40, 5.51) for respiratory disease. The tendency was the same for Alzheimer’s disease, with an increased risk for respiratory disease (RR = 2.82, 95 percent CI: 1.30, 6.17), but the risk for cerebrovascular disease did not reach significance (RR = 1.66, 95 percent CI: 0.75, 3.69).

### Survival with dementia and risk factors

The median survival time from the onset of the disease was estimated to be 4.5 years among persons with incident dementia. Our model provides results at each age of dementia onset, so we chose to provide results for persons developing dementia at 75 and 85 years. The median times of survival according to risk factors are summarized in table 2. Whatever the age of onset of dementia, the median times of survival were higher among women than among men. Among persons with Alzheimer’s disease, there was a protective effect of female sex for the risk of dying, adjusted for educational level, comorbidity, and activities of daily living scale dependency at the time of diagnosis (RR = 0.47, 95 percent CI: 0.27, 0.83). The tendency was the same for dementia from all causes, although the relative risk did not reach statistical significance (RR = 0.70, 95 percent CI: 0.46, 1.08).

For both dementia and Alzheimer’s disease, the median survival time was shorter for participants with the CEP than for those without when dementia began at 75 years, but no difference in survival was observed according to CEP at 85 years (table 2). Educational level did not significantly influence survival among persons with dementia. The relative risk of dying for participants without the CEP was estimated to be 1.00 (95 percent CI: 0.68, 1.46) for dementia and 0.88 (95 percent CI: 0.54, 1.42) for Alzheimer’s disease. Adjustment for sex, comorbidity, and activities of daily living scale dependency at the time of diagnosis did not modify these relative risks, with 1.11 for dementia and 1.00 for Alzheimer’s disease.

Although the effect of both sex and educational level seemed to differ according to the age of dementia onset, no significant interaction was found either between age and sex (RR = 1.01, 95 percent CI: 0.92, 1.10) or between age and CEP (RR = 1.01, 95 percent CI: 0.94, 1.08).

### DISCUSSION

The follow-up of 281 persons with incident dementia allowed us to accurately define mortality with dementia in the general population. The median survival with dementia was 4.5 years. Survival was longer for women compared with men, particularly for Alzheimer’s disease. However, educational level did not significantly modify survival with dementia. The relative risk of dying was estimated to be 1.8 for persons with dementia compared with those without. Among persons with dementia, the risks of dying from cerebrovascular and respiratory diseases were particularly increased.

Studying mortality with dementia in the general population raises special difficulties. First, one needs to conduct the study in the community, because dementia diagnosed in a hospital or in a nursing home setting is not representative of cases in the general population. Second, dementia should be actively screened, because it is widely underdiagnosed in the population (15, 27). Third, it is necessary to use incident cases of dementia, for whom the disease onset is better known. Finally, incident cases of dementia have to be followed up for a long time to observe death. Because of these methodological difficulties, few previous studies have investigated mortality with dementia in the community, by using incident cases of dementia (12–14). Even in these few studies, the onset of the disease was difficult to assess. Indeed, unless participants are screened for dementia continuously, the onset of dementia is always imprecise, clearly because of an insidious onset, but also because of interval censoring between the last time when the participant was considered as dementia free and the first time he was diagnosed as having dementia. Thus, the onset has to be estimated, even for incident cases of dementia. With the PAQUID study, we had the opportunity to analyze actively

### TABLE 2. Median times of survival for persons with dementia and Alzheimer’s disease, according to sex and educational level, PAQUID cohort, France, 1988–1998

<table>
<thead>
<tr>
<th></th>
<th>Median time of survival (years)</th>
<th>At 75 years</th>
<th>At 85 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dementia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>4.5</td>
<td>3.5</td>
<td></td>
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<tr>
<td>Women</td>
<td>7.3</td>
<td>4.4</td>
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<tr>
<td>Alzheimer’s disease</td>
<td></td>
<td></td>
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<tr>
<td>Men</td>
<td>4.3</td>
<td>3.7</td>
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</tr>
<tr>
<td>Women</td>
<td>—†</td>
<td>——</td>
<td>——</td>
</tr>
<tr>
<td>Dementia</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Without CEP*</td>
<td>6.9</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>With CEP</td>
<td>5.3</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td></td>
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<tr>
<td>Without CEP</td>
<td>7.4</td>
<td>4.8</td>
<td></td>
</tr>
<tr>
<td>With CEP</td>
<td>5.0</td>
<td>4.3</td>
<td></td>
</tr>
</tbody>
</table>

* PAQUID, Personnes Agées Quid; CEP, Certificat d’Etudes Primaires, which validates the primary school level.
† —, median not reached.
screened incident cases of dementia who were prospectively followed up for several years. In addition, we applied statistical models, taking into account the fact that the disease onset was not known precisely.

Several methodological issues may have influenced our results. Twenty percent of the participants in our cohort were never reevaluated; among them, a large part (55 percent) had died before the follow-up, and the others refused the follow-up examinations. Participants who refused the follow-up examinations could be at higher risk of developing dementia; thus, nonresponse could lead to an underestimation of the incidence of dementia. However, this could bias the prognosis in the group of persons with dementia only if the mortality among persons with dementia who refused the follow-up differed from the mortality among persons with dementia who were evaluated, which is unlikely.

Participants with a very short survival, for whom the onset of dementia occurred between two follow-ups and who died rapidly after this onset, cannot be diagnosed in our cohort and thus are not included in the survival analysis of persons with incident dementia. As in other studies, this could overestimate the survival time with dementia. However, only a specific illness-death model dealing with interval censoring and taking into account these cases of dementia with a very short survival could establish to what extent survival is overestimated. Such a model should be developed.

Another methodological problem is due to difficulties in the diagnosis of dementia in some subgroups of persons, particularly very old people, persons living in an institution, and illiterate, deaf, or depressive persons. This can lead to either a false diagnosis of dementia or a delay of diagnosis among these persons, which could bias survival among persons with incident dementia.

To demonstrate the possible bias when the problem of interval censoring is not taken into account, our results (with the three-state approach) were compared with those using standard models, that is, Kaplan-Meier curves to describe survival among incident participants with dementia and Cox models with delayed entry to analyze the effect of sex and educational level on the risk of mortality among them. For these standard models, the onset of dementia was considered to be the middle of the interval between the last follow-up without dementia and the first follow-up with it. Although differences between the two models were slight, the median survival after developing dementia was about 2 months longer with standard models than with the three-state approach. The larger the interval between the two follow-up evaluations, the greater this overestimation of survival. In addition, using standard models tended to increase the effect of risk factors on the mortality among persons with dementia and also to slightly underestimate confidence intervals. This was particularly visible for the effect of sex and led to erroneous significant factors.

Impact of dementia on mortality

The three-state approach used to describe mortality among persons with dementia, which takes into account the fact that the time of disease onset is not known, could not be applied to evaluate the impact of dementia on mortality among the general population. Indeed, it cannot estimate a date of onset for each participant in our cohort. However, although the estimation of the onset of dementia is of prime importance to describe survival in dementia because it can affect the time of survival by several years (depending on the number of years between the two follow-up evaluations), this estimation is less important in the evaluation of the impact of dementia on mortality, for which the age of the participant is the time scale of the model.

The relative risks of dying in our study were estimated to be 1.8 for dementia and 1.7 for Alzheimer’s disease, and these decreased with age. These results are in agreement with but are slightly lower than those found in previous community-based studies, ranging from 1.4 to 4.1 for Alzheimer’s disease and from 1.9 to 3.0 for dementia (4–7, 12–14, 28), and even higher (RR up to 9.6) among younger participants (11, 28). This can be explained by inclusion of incident rather than prevalent cases of dementia in our study, and by the fact that we took into account morbidity when evaluating the risk of death.

Two causes of death were particularly increased among persons with dementia: cerebrovascular and respiratory diseases. The increase in death by cerebrovascular diseases was essentially due to vascular dementia; however, even among persons with Alzheimer’s disease, there was a trend to an increased risk of cerebrovascular diseases, which is concordant with the implication of vascular mechanisms in the Alzheimer pathology (29). Death due to respiratory diseases, which has already been found to be an important cause of death among Alzheimer’s persons (30, 31), was also increased in both persons with dementia and those with Alzheimer’s disease, compared with those without dementia.

Survival among persons with dementia

As in the general population, the median duration of survival among persons with dementia was most dependent on the sex and age of participants. The median survival times observed in our study were longer than those reported in most previous studies of prevalent cases in the community (3, 5, 10) and even in some studies of incident cases (14). If incident cases are considered, this leads automatically to longer survival. However, clinical studies or Alzheimer Center studies have reported median survival times as long as or longer than ours (32–34), up to 6-year survival. Several explanations may account for this longer survival. First, persons referred to clinical settings for their memory are probably more interested in their health than others and may have less medical comorbidity. Second, the treatment and management of persons with dementia who present to clinical settings could increase their survival. Finally, the mean age of patients in clinical settings is often lower than that in community-based studies.

Effect of sex on survival

The protective effect of female sex observed in our study, particularly in Alzheimer’s disease, is concordant with the results of several studies done with different methodologies.
(7, 8, 14, 33, 35–37). As in the general population, women with dementia are at lower risk of mortality than are men. Although the interaction between age and sex for the risk of dying among persons with dementia was not significant, the effect of sex seemed to decrease with age, with a greater difference between women and men at 75 years than at 85 years. These results are concordant with those observed in the Kungsholmen project, in which sex affected survival among persons with dementia but only under 85 years (14). Factors that explain the longer survival among women in the general population could remain unchanged during the course of the disease. Trials are currently in progress to test the hypothesis that estrogen replacement therapy could affect the progression of Alzheimer’s disease. However, in the PAQUID study, very few women have taken such a therapy, and this cannot explain the longer survival of women with dementia in our sample.

Effect of education on survival

The effect of educational level on survival with dementia was low in our study and was observed only among participants who developed dementia at the youngest age. Previous results concerning the relation between education and mortality among persons with dementia are controversial: some authors have found an increased risk of mortality associated with a high educational level (9, 38), whereas others have not replicated these findings (10) or even found the opposite (37). The hypothesis of brain reserve capacity, according to which development of the cerebral lesions of Alzheimer’s disease at the time of diagnosis is more advanced among more highly educated people than in others, has been proposed to explain the association between high educational level and increased risk of mortality (9, 39). We also observed a tendency, although slight and nonsignificant, to a lower survival in persons with dementia who had the CEP but only among the sons with dementia who had the CEP but only among the youngest. A possible bias of detecting dementia according to educational level cannot be excluded. Indeed, participants with a low educational level have low premorbid cognitive performances and thus could be detected earlier than more highly educated participants. However, this bias is probably reduced by taking into account not only the DSM-III-R criteria but also a loss on the Mini-Mental State Examination score in the screening procedure.

Conclusion

These data provide further evidence of the malignancy of dementia, which is a strong predictor of death, has a short survival time after disease onset, and has a high risk of dying associated with it. In the future, data on survival with dementia will make it possible to evaluate whether the development of medical and social therapies for dementia leads to an increased survival in persons with this pathology.

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