

Mortality from dementia in a community-dwelling Brazilian population

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SUMMARY

Background The influence of dementia on mortality has not yet been reported for a Latin American country.

Objectives To evaluate the influence of dementia on mortality of a community-dwelling elderly population in Brazil, and to verify the extent to which the diagnosis of dementia is reported on death certificates.

Methods A cohort of 1,656 individuals, aged 65 and over, was screened for dementia at their domiciles, in 1997. The same population was re-evaluated in 2000, and information on deaths was obtained from relatives and from the municipal obituary service. Kaplan-Meier curves were used for the survival analysis, and the mortality risk ratio (MMR) was calculated using Cox proportional hazards models.

Results We obtained data from 1,393 subjects, corresponding to 84.1% of the target population. The number of deaths was 58 (51.3%) among the patients with dementia and 163 (12.7%) among those without dementia in 1997 ($p < 0.0001$). Dementia and Alzheimer's disease (AD) decreased survival, with hazards ratios of 5.16 [95% Confidence Interval (CI): 3.74–7.12] for dementia and 4.76 (95% CI: 3.16–7.18) for AD. The Cox proportional hazards model identified dementia (MMR = 3.92, 95% CI: 2.80–5.48) as the most significant predictor of death, followed by age, history of stroke, complaints of visual impairment and heart failure and by severe arterial hypertension in the baseline evaluation. Dementia and/or AD were mentioned in only 12.5% of the death certificates of individuals with dementia.

Conclusions Dementia causes a significant decrease in survival, and the diagnosis of dementia is rarely reported on death certificates in Brazil. Copyright © 2005 John Wiley & Sons, Ltd.

KEY WORDS—dementia; Alzheimer's disease; mortality; survival; vascular dementia; developing country; Latin America; Brazil

INTRODUCTION

The role of dementia, particularly Alzheimer's disease (AD), as a major killer has been recognized since 1976 when Katzman stated that 'AD may rank as the fourth or fifth most common cause of death in the United States' (Katzman, 1976). Thereafter, several studies have confirmed that the survival of patients

with dementia is considerably reduced in developed countries (Barclay *et al.*, 1985; Braco *et al.*, 1994; Hoyert and Rosenberg, 1997; Agüero-Torres *et al.*, 1999; Baldereschi *et al.*, 1999; Ostbye *et al.*, 1999; Brookmeyer *et al.*, 2002; Tschanz *et al.*, 2004).

In the developing world, which accounts for perhaps two-thirds or more of all patients with dementia (Prince, 2000), there is a paucity of studies on the subject. In Shanghai, China, the mortality for AD was as high as the mortality for cancer (Katzman *et al.*, 1994). In Nigeria, the impact of dementia on mortality was similar to that observed in an elderly African-American community in the United States (Perkins *et al.*, 2002).

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As far as we know, the influence of dementia on mortality has never been reported for Latin American countries, which have seen a rapid increase in life expectancy over recent decades (Mangone and Arizaga, 1999). There are several cultural and socio-economic factors that may have opposite effects on mortality for dementia in different countries. For example, the lack of health care for dementia and for co-morbidities probably contributes toward reducing survival, while the availability of family caregivers and less institutionalization probably has the contrary effect. This multi-factorial relationship makes the use of data from other regions questionable for public health planning and for provision of information to caregivers, patients and their families.

The exact ranking of dementia as the cause of death in the developed world has been difficult to establish because death certificates usually misreport dementia or AD (Olichney *et al.*, 1995; Ganguli and Rodriguez, 1999). To our knowledge, no study has yet evaluated the extent to which the diagnoses of dementia or Alzheimer's disease (AD) are reported on death certificates of individuals with dementia in a developing country.

The aims of this study were to evaluate the influence of dementia on mortality in a community-dwelling elderly population in Brazil, and to verify the extent to which the diagnoses of dementia, or types of dementia, are reported on death certificates.

METHODS

The study was conducted in Catanduva, located in São Paulo state, southeastern Brazil, a town with 100 913 inhabitants according to the 1996 Brazilian census. In 1997, we randomly selected a quarter of the addresses from each sub-district list of addresses where individuals aged 65 or over resided, so as to screen 25% of the domiciles. The methods and results of the prevalence study have recently been published (Herrera *et al.*, 2002). Briefly, 1656 elderly individuals were screened during the months of January and February 1997 by 20 graduate students from the Catanduva School of Medicine, using a general health questionnaire where the main health problems and medications that were being taken were ascertained, the Mini-Mental State Examination (MMSE; Folstein *et al.*, 1975; Bertolucci *et al.*, 1994) and the Pfeffer Functional Activities Questionnaire (Pfeffer *et al.*, 1982). Also, arterial blood pressures were taken. All subjects who screened positive were selected for diagnostic evaluation, which was undertaken from the end of April to the beginning of June 1997, involving

interview by a neurologist (EH), who obtained a clinical history and performed a general physical and neurological examination, with emphasis on cognitive testing. For the latter, a second MMSE was performed in addition to tests of attention (digit span forward and backwards), memory (immediate and delayed recall of ten simple drawings of common objects; Nitrini *et al.*, 2004), verbal fluency (animals), abstraction (proverb interpretation), calculation, construction (copy of three geometric figures and drawing of a house), clock drawing, tactile gnosis, limb and buccofacial praxis, motor planning, and right-left orientation. The evaluation also included the Clinical Dementia Rating Scale (CDR, Morris, 1993) for the assessment of severity of dementia. Subjects with difficulty in performing the cognitive tests due to auditory, visual or other physical problems that could have interfered with their performance, as well as those with insufficient knowledge of the Portuguese language were all excluded from the study. All these data were analyzed by three neurologists (RN, PC, EH), resulting in 118 individuals fulfilling the diagnostic criteria for dementia according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (American Psychiatric Association, 1994), representing a prevalence of 7.1%. Patients with dementia were then submitted to a diagnostic work-up that included the following exams: routine blood tests; tests for liver, kidney and thyroid functions; cholesterol and triglycerides; serum B₁₂ level; serology for syphilis; chest X-ray; electroencephalogram, and computed tomography of the head. The clinical diagnoses were made following consensus by the same three neurologists based on the data from clinical history, neurological examination and laboratory and CT findings, according to previously published criteria, namely: National Institute of Neurological and Communicative Disorders and Stroke- Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann *et al.*, 1984) for AD; National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria (Román *et al.*, 1993) for vascular dementia (VaD) and for AD with cerebrovascular disease (AD + CVD); McKeith *et al.*'s criteria (McKeith *et al.*, 1996) for Lewy-body dementia (LBD); Lund and Manchester criteria (1994) for frontotemporal dementia.

For the present study, 17 graduate students of the Catanduva School of Medicine endeavored to re-screen all 1656 individuals, at the subjects' homes between April and May 2000 (for more details on

the incidence arm of the study see Nitrini *et al.*, 2004). The information on deaths between the end of the diagnostic evaluation in June 1997 and the beginning of the incidence study in April 2000 was obtained from the relatives or through inspection of the town's Obituary Service records. Informed consent was obtained from all participants, or from a family member when appropriate.

Mortality rates according to the presence of dementia in 1997, age, gender, educational and socioeconomic levels and to the type and the severity of dementia were analyzed.

Survival of the non-demented and demented individuals was investigated, where survival according to dementia type was also analyzed. The influence on survival of the variables age (greater than or equal to *vs* less than the median), gender, educational level (greater than or equal to *vs* less than the median of years of schooling; and illiterate *vs* literate), socioeconomic level (ranked from A, highest, to E, lowest, according to the Brazilian Association of the Institute of Market Research; see Herrera *et al.*, 2002, for details), and of co-morbid conditions and arterial blood pressure at baseline were investigated.

For the analysis of the death certificates of the individuals with dementia, all the listed causes of death, either as the underlying cause of death or contributory cause, were included to verify how often the terms 'dementia', 'Alzheimer's disease' or 'senility' had been mentioned. The reported causes of death of the patients with dementia were recorded.

Statistical analysis

Univariate analysis of frequency of mortality data was performed using Pearson's chi-square, and comparison between means of demographic data of independent groups by *t* test. For survival analysis, the Kaplan-Meier model was applied and Cox hazards ratios were calculated, whereas for multivariate analysis, Cox proportional hazard models were used and the mortality risk ratio (MRR) calculated. Preliminary analysis revealed that the missing data were not significantly different from those obtained, and showed that their absence occurred at random. As the missing data amounted to less than 20% of the total, missing continuous data were completed by the central value (mean for the parametric values and median for the non-parametric values), while missing categorical values were substituted by the normal value. Factors identified as predictors in the univariate analysis ($p < 0.15$) were then candidates for inclusion in multivariate analysis. When there

were not pre-established cut-off scores, the median was used. The software packages Epi-Info 6.0 (Centers for Disease Control and Prevention, Atlanta, Georgia, USA) and the Statistical Package for the Social Sciences for Windows, version 10.0, were used for data collection and statistical analysis.

RESULTS

Data were obtained from 1393 subjects (84.1.0% of the target population).

Information was obtained from 113 out of the 118 individuals diagnosed with dementia in 1997, of which 58 (51.3%) had died, while 163 without dementia (12.7%) had also died ($p < 0.0001$; chi-square = 115.86). Table 1 shows that the patients with dementia were older and less educated than the non-demented individuals, a finding that had already been reported in the prevalence study (Herrera *et al.*, 2002). When the entire population was considered, mortality rates were higher in the older group (age \geq median; $p < 0.001$) and in the illiterates ($p = 0.045$), but did not differ according to gender or socioeconomic level.

With regard to the type of dementia, 31 (48.4%) out of the 64 patients with AD had died while 7 (63.6%) out of the 11 patients with VaD, 9 (60.0%) out of the 15 patients with AD associated with cerebrovascular disease and 11 (47.8%) out of the 23 with other types of dementia had also died. These differences were not significant ($p = 0.69$).

When the severity of the dementia was considered, 17 (37.8%) of the 45 patients classified as CDR 1.0, 23 (56.1%) of the 41 CDR 2.0 and 18 (66.7%) of the 27 CDR 3.0 had died. These differences were significant ($p = 0.045$; chi-square = 6.22).

Table 1. Demographic features of the deceased and non-deceased individuals

	Deceased individuals		Non-deceased individuals	
	Dementia at baseline		Dementia at baseline	
	Yes (<i>n</i> = 58)	No (<i>n</i> = 163)	Yes (<i>n</i> = 55)	No (<i>n</i> = 1117)
Age*				
Range	65–94	65–96	65–94	65–94
Mean (SD)	83.3 (6.7)	76.0 (7.7)	78.6 (7.2)	71.8 (5.7)
Gender				
F	40	83	40	643
M	18	80	15	474
Years of schooling				
Mean (SD)	1.7 (2.6)	2.8 (3.3)	1.2 (2.1)	2.7 (3.5)

*Age at the baseline study in 1997.

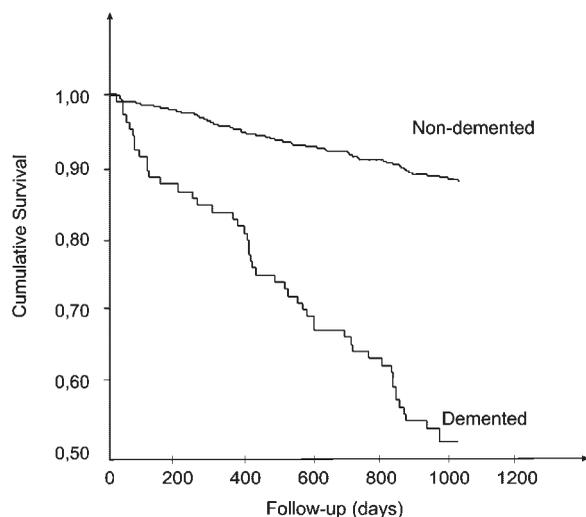


Figure 1. Kaplan-Meier survival curves of demented and non-demented individuals

The dates of death were known for 146 of the 163 non-demented individuals and for 50 of the 58 deceased individuals who had dementia in 1997. Kaplan-Meier curves (Figure 1) showed that dementia significantly reduced survival [hazard ratio = 5.16, 95% confidence interval (CI): 3.74–7.12]. When dementia types were considered, AD (probable and possible, excluding cases with cerebrovascular disease) (Figure 2) reduced survival (hazard ratio = 4.76, 95% CI: 3.16–7.18), as did VaD (hazard ratio = 7.01, 95% CI: 3.10–15.88), AD associated

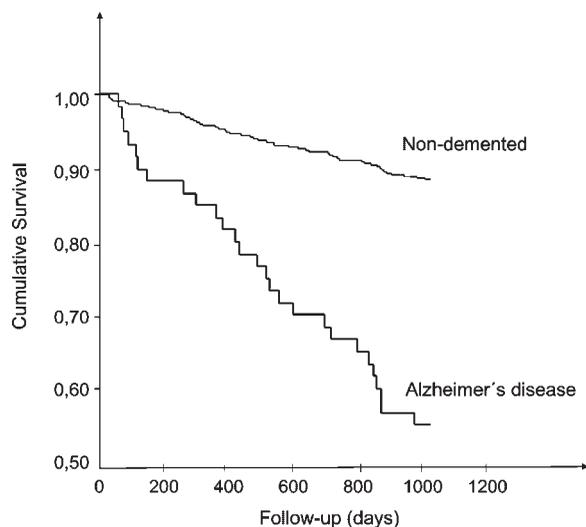


Figure 2. Kaplan-Meier survival curves of patients with Alzheimer's disease and non-demented individuals

Table 2. Mortality Risk Ratio (MRR) and 95% Confidence Interval (CI)

	MRR	95% CI	P
Dementia	3.92	2.80–5.48	<0.001
Age*	2.32	1.64–3.28	<0.001
History of stroke	2.26	1.39–3.67	0.001
Visual impairment	1.80	1.16–2.79	0.009
Heart failure	1.81	1.21–2.69	0.004
Severe arterial hypertension	1.46	1.02–2.09	0.040

*Age at the baseline study in 1997 (greater than or equal to vs less than the median).

with cerebrovascular disease (hazard ratio = 7.37, 95% CI: 3.61–15.03) and other dementias (hazard ratio = 4.29, 95% CI: 2.19–8.41). These differences among dementia types were not statistically significant.

The most frequently reported co-morbid conditions were high blood pressure (35.6%), diabetes (10.6%), heart failure (10.1%), dizziness (7.6%), visual impairment (6.5%), arthralgia (6.4%), history of head trauma with loss of consciousness (6.1%) and history of stroke (3.9%). Factors identified as predictors in the univariate analysis ($p < 0.15$) were dementia, age, illiteracy, severe arterial hypertension (higher than 179/109 for either systolic or diastolic pressure) and the following reported co-morbid conditions: stroke, visual impairment, heart failure, gait disturbances, headache, high cholesterol level, chronic pulmonary disease, Parkinson's disease and arthralgia. In the multivariate analysis, dementia, age, history of stroke, heart failure, visual impairment and severe arterial hypertension were included (Table 2). Sex and socioeconomic level were not included in the multivariate analysis ($p > 0.15$ in the univariate analysis).

In 40 death certificates of individuals with dementia, AD was mentioned four times and 'senile dementia' only once. Taken together, dementia and AD were mentioned in 5 out of 40 death certificates (12.5%). The less precise diagnosis of 'senility' was mentioned twice. The most frequently reported cause of death was pneumonia (40.0%), followed by respiratory failure (27.5%), heart failure (20.0%), septicemia (20.0%), stroke (20.0%), carcinomas (17.5%), cardiorespiratory arrest (15%), renal failure (12.5%), arrhythmia (10%), pulmonary embolism (7.5%), acute myocardial infarction (5.0%) and coronary artery disease (5.0%).

DISCUSSION

The influence of dementia on mortality was very high in this community, compared with a cross-cultural

study that found similar influence of dementia on mortality in developed and developing countries (Perkins *et al.*, 2002).

The MRR for dementia was 3.92 in this study, higher than the MRRs from developed countries, which have ranged from 1.9 to 3.6 (Heeren *et al.*, 1992; Jagger *et al.*, 1995; Agüero-Torres *et al.*, 1999; Baldereschi *et al.*, 1999; Ostbye *et al.*, 1999; Witthaus *et al.*, 1999; Jagger *et al.*, 2000). The MRR for dementia was 4.1 for the Yoruba, in Nigeria, while it was 2.2 for African Americans, the difference was not, however, statistically significant (Perkins *et al.*, 2002).

In this study, age was directly related to MRR, although we did not identify the protective effect of the female gender that has been reported in several studies (Katzman *et al.*, 1994; Agüero-Torres *et al.*, 1999; Gambassi *et al.*, 1999; Lapane *et al.*, 2001; Noale *et al.*, 2003).

Illiteracy was associated with higher mortality in the population as a whole, however, this was not included in the multivariate analysis. Likewise, in Shanghai, low education was not a predictor of mortality in dementia in the multivariate analysis (Katzman *et al.*, 1994), and in Nigeria, low education was also not associated with higher mortality in demented individuals (Perkins *et al.*, 2002). In a recent study, a trend toward inverse association of education with mortality risk in dementia was reported (Tschanz *et al.*, 2004).

In the present study, mortality rates did not differ according to the socioeconomic level, either for individuals with dementia or for the population as a whole.

Mortality was higher in those individuals with more severe dementia, a finding that had already been reported (Jorm, 1990; Volicer *et al.*, 1993; Aevansson *et al.*, 1998; Tschanz *et al.*, 2004). Although mortality was also higher in VaD than in AD in this study, the difference was not statistically significant, maybe because the number of patients with VaD was relatively small. The higher mortality of VaD compared to AD had previously been reported (Barclay *et al.*, 1985; Katzman *et al.*, 1994; Agüero-Torres *et al.*, 1999).

Regarding the co-morbid conditions, only history of stroke, heart failure, visual impairment and severe arterial hypertension were associated with higher mortality in the multivariate analysis. The association of previous stroke and heart failure with reduced survival has been reported by several studies on mortality in dementia (Katzman *et al.*, 1994; Noale *et al.*, 2003; Tschanz *et al.*, 2004), and studies on mortality have

reported that visual impairment reduces survival in the elderly (Wang *et al.*, 2001; McCarty *et al.*, 2001) and in adults (Lee *et al.*, 2002).

The reporting of dementia or AD on death certificates in this study was very low (12.5%), and even if the term 'senility' was included as indicative of dementia, the rate would still remain low (17.5%). The level of dementia report on death certificates in developed countries, either as the underlying cause of death or contributory cause, has ranged from 21.5% to 76% (Macera *et al.*, 1992; Olichney *et al.*, 1995; Ganguli and Rodriguez, 1999). A factor that may have contributed to the underreporting in this study is that most of the individuals with dementia were not living in nursing homes in this Brazilian community (Herrera *et al.*, 2002), as it has been found that dementia is more often reported for the demented who die in nursing homes (Ganguli and Rodriguez, 1999). Nursing home residents were not included in this study because in 1997 there were only 62 persons aged 65 or more living in all the nursing homes of Catanduva, where 28 of these patients were considered to be demented (Herrera *et al.*, 2002).

The most frequently reported cause of death in demented individuals in this study was pneumonia. Pneumonia or bronchopneumonia had previously been reported as the leading cause of death in AD ((Burns *et al.*, 1990; Kukull *et al.*, 1994; Olichney *et al.*, 1995) or in dementia (Jorm, 1990; Kammoun *et al.*, 2000).

There are several limitations of this study: data on co-morbid conditions were based solely upon information obtained from the individual or a family member, the date of death was not known for every deceased person, there was no pathological confirmation of both the diagnosis of dementia and the immediate cause of death, and, perhaps most importantly, deceased individuals who were diagnosed as non-demented in 1997 may have developed dementia before death. In a Canadian study (The Canadian Study of Health and Aging Working Group, 2000), 25% of the deceased individuals had developed dementia during a five-year follow-up period. It is probable that the influence of dementia on mortality in our population would have been even greater if we had been able to retrospectively diagnose dementia in the deceased persons.

In conclusion, this study confirms that dementia causes a significant reduction in survival in a developing country, and reveals that the diagnoses of dementia or AD are rarely reported on death certificates in Brazil.

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