Acta Psychiatrica Scandinavica

Acta Psychiatr Scand 2011: 124: 372–383

DOI: 10.1111/j.1600-0447.2011.01754.x

ACTA PSYCHIATRICA SCANDINAVICA

Incidence and lifetime risk of dementia and Alzheimer's disease in a Southern European population

Lobo A, Lopez-Anton R, Santabárbara J, de-la-Cámara C, Ventura T, Quintanilla MA, Roy JF, Campayo AJ, Lobo E, Palomo T, Rodriguez-Jimenez R, Saz P, Marcos G. Incidence and lifetime risk of dementia and Alzheimer's disease in a Southern European population.

Objective: To calculate both the incidence rates and the lifetime risk (LTR) of dementia and Alzheimer's disease (AD).
Methods: A two-phase case-finding procedure was implemented in a cohort of 4057 cognitively intact individuals 55+ years of age living in Zaragoza, Spain, and followed-up at 2.5 and 4.5 years. Age- and sex-specific incidence rates were calculated. A mortality-adjusted, multivariate model was used to document LTRs.
Results: The incidence rate of dementia continued to rise after the age of 90 years, but was slightly lower than in North and West European studies. Only a tendency for an increased LTR with age was observed. Thus, LTR was 19.7% for a 65-year-old woman and 20.4% at the age of 85 years, the corresponding figures for AD being 16.7% and 17.6%. The LTR of AD was higher in women and was about twice as high among illiterate individuals when compared with individuals with higher educational levels.
Conclusions: The incidence rate of dementia in this Southern European city was slightly lower than in previous studies in North-West Europe. LTR of dementia and AD seems to be slightly increased with age. The association of illiteracy with higher LTR of AD is intriguing.

A. Lobo[1,2,3,4], R. Lopez-Anton[3], J. Santabárbara[3,5], C. de-la-Cámara[1,2,3,4], T. Ventura[2,3,4,6], M. A. Quintanilla[1], J. F. Roy[3,7], A. J. Campayo[1,2,3,4], E. Lobo[1,3,4,5], T. Palomo[3,8], R. Rodriguez-Jimenez[3,8], P. Saz[2,3], G. Marcos[3,4,5,9]

[1]Psychiatry Service, Hospital Clínico Universitario, [2]Department of Medicine and Psychiatry, Universidad de Zaragoza, Zaragoza, [3]Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Ministry of Science and Innovation, Madrid, [4]Instituto Aragonés de Ciencias de la Salud (I+CS), [5]Department of Preventive Medicine and Public Health, Universidad de Zaragoza, [6]Hospital Universitario Miguel Servet, [7]Department of Psychology and Sociology, Universidad de Zaragoza, Zaragoza, [8]Department of Psychiatry, Hospital Universitario 12 de Octubre, Madrid and [9]Medical Records Service, Hospital Clínico Universitario, Zaragoza, Spain

Key words: aged; epidemiology; incidence; dementia; Alzheimer disease; risk

Dr. Antonio Lobo, Servicio de Psiquiatría, Hospital Clínico Universitario, Planta 3, Avd. San Juan Bosco, 15, 50009 Zaragoza, Spain.
E-mail: alobo@unizar.es

Accepted for publication June 30, 2011

Significant outcomes

- This study suggests that the incidence rate of dementia in a South European city is slightly lower than in most studies reported in North American and North European countries.
- The lifetime risk (LTR) of both dementia and Alzheimer's disease (AD), calculated with multivariate statistical methods, shows only a slight trend to increase with age and might be a preferred method for communicating disease risk for individuals and for the mass media.
- The LTR of AD was about twice as high among illiterate individuals when compared to individuals with higher educational levels.

Limitations

- We do not have data on ApoE and hospital diagnosis in all cases.
- Neuroimaging was available in only a small percentage of cases of dementia.
- We only report LTR population estimates, but for any given individual, the estimated LTR would vary with the possible risk factors not controlled in this study

Introduction

The primary common finding of a considerable number of recent studies into the incidence of dementia and Alzheimer's disease (AD) is that the exponential rate increases with age (1, 2). However, consistent and reliable incidence estimates are still deemed necessary (3), and controversies exist, in particular regarding the continued rate increase in the oldest of the elderly (4). Furthermore, current knowledge is derived mainly from North American and North European countries, but the lower rates of the incidence of dementia reported in South European cities (2) need confirmation, because geographical differences stimulate environmental hypotheses.

Incidence rates of dementia are essential for public health planners to estimate the projected disease burden in a population. While incidence rates reflect the actual experience of a cohort, risk estimates are required to predict how much disease a population may expect. Lifetime risk (LTR), calculated at several ages, has been defined as the probability that a person of that age would at some time in his or her life suffer from the condition. However, the competing risk of death should be considered to estimate LTR in conditions particularly frequent in old age, such as dementia (5). LTR is an under-researched subject in the field of dementia (6), although empirical research suggests it might be a preferred method for communicating disease risk, both for individuals and for the mass media (7). The Rotterdam Study (5) and the Framingham Study (8) are important and provide data on the LTR of dementia, but both of these studies used univariate methods to calculate LTR based on cumulative incidence. New studies of LTR using multivariate techniques to control for sex and education might be a major contribution to the field of dementia epidemiology because, in some studies, both female sex (9) and low educational level (10, 11) have been reported to increase the risk of dementia. Research studies into a low level of education as a risk factor for dementia are particularly opportune in countries such as Spain, where the educational level attained by a substantial proportion of the elderly, born in the first third of the 20th century, was quite limited (12).

Aims of the study

To estimate the incidence rates and to document mortality-adjusted lifetime risk (LTR), of dementia and its major subtype, Alzheimer's disease (AD), in a community-based sample of cognitively intact individuals in a Southern European population. We also set out to verify whether the rate of dementia in this population is lower than previously reported in the literature, and we hypothesized that the LTR of both dementia and AD would be higher among the less educated participants.

Material and methods

Study design and sample

The ZARADEMP project (ZARAgoza DEMentia DEPression project) was designed as a longitudinal, community-based study to examine the incidence of dementia and the risk factors in incident cases of dementia. It was carried out in Zaragoza, a typical, large city in Spain, with an important proportion of inhabitants coming from surrounding rural areas (12). A stratified random sample of individuals 55 years of age and older, with proportional allocation by age and sex, drawn from the eligible individuals (n = 157 787) in the Spanish official census lists of 1991, was invited to participate in the baseline examination. A cohort of 3578 individuals without dementia was considered necessary to fulfill the main objectives in the study. The initial sample size was corrected for predictable mortality, migration, and refusals, taking into consideration the results of the previous Zaragoza Study on the prevalence of dementia in the same population (13), as well as the first year of the field work. In the baseline study, 4803 individuals were interviewed. For the follow-up, because we were interested in cognitively intact individuals, we excluded subjects considered to be cases or subcases of dementia at baseline (see definitions below; n = 746), for a starting sample of 4057 participants. The ZARADEMP Study participants underwent a baseline assessment (Wave I, starting in 1994) and two follow-up visits, starting in 1997 (Wave II) and in 1999 (Wave III) (Fig. 1). Further details of the objectives and methods of the project have been described elsewhere (12). The Ethics Committee of the University of Zaragoza and the Fondo de Investigación Sanitaria (FIS) approved this study, according to Spanish Law, and all individuals provided written informed consent.

Data collection

Several standard tools, previously validated in Spain, were incorporated in the ZARADEMP interview (12), including the Examen Cognoscitivo Mini-Mental (ECMM) (14), the Spanish version of the Mini-Mental State Examination (MMSE) (15) for the screening of cognitive function. Both validity coefficients and population norms in this

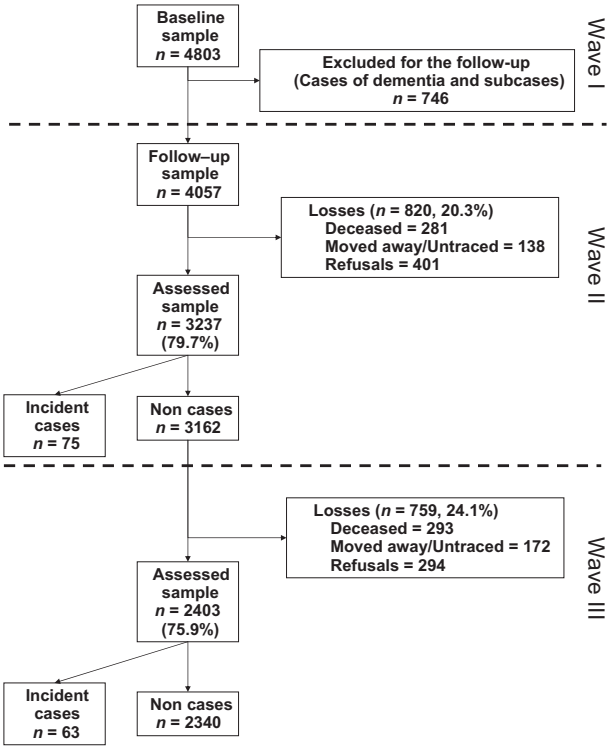

Fig. 1. Flow diagram of the ZARADEMP Project.

official version of the MMSE are very similar to those reported in the USA (16). The mental state of the study participants was assessed using the validated Spanish version of the Geriatric Mental State B (GMS-B) (13, 17, 18), a semi-structured standardized clinical interview that may be used by lay interviewers. The GMS-B includes neuropsychological items and provides a 'threshold global score' that discriminates between 'non-cases', 'subcases', and 'cases' of dementia. Psychiatric history was taken using the History and Aetiology Schedule (HAS) (19), a standardized method accompanying the GMS. This collects psychiatric history data from a caregiver or directly from the respondent when he or she is judged to be reliable. Instrumental and basic activities of daily living were assessed using the Lawton and Brody scale (20) and Katz's Index (21), respectively. A series of studies completed in Spain have documented, in clinical samples, efficiency coefficients similar to those reported by the original authors (22, 23). Information on medical conditions considered to be risk factors of dementia, specifically AD and vascular dementia (VaD), was collected using the EURODEM Questionnaire (24). This instrument may be used by trained lay interviewers. Each item in the interview has been operationally defined, according to previously agreed EURODEM criteria. Detailed information on medical conditions in this study has been reported elsewhere (25). Systematic checks on the reliability of the assessments were implemented to prevent the 'reliability-drift'.

Dementia case finding

A two-phase epidemiological case-finding process for dementia was implemented in the baseline study (Wave I) and a similar method in the follow-up waves (Waves II and III). In phase I in each wave, well-trained and regularly supervised lay interviewers (senior medical students) conducted the ZARADEMP interview at the subjects' homes or place of residence. Interviewers in the follow-up waves were unaware of the results of the baseline interview. Medical reports and laboratory data, which are frequently available at most people's homes in Spain, were consulted to complete the data. Outside caregivers were interviewed when the participant was considered to be unreliable (in cases of dementia and approximately 10% of subcases of dementia). Participants were nominated as 'probable cases' on the basis of GMS threshold 'global' score (1/2) and/or Mini-Mental (23/24) standard cut-off points.

In phase II, the 'probable cases' of dementia were reassessed at the subjects' homes or place of residence by research psychiatrists. The same assessment instruments and methods were used as well as Hachinski's scale (26) to help in differentiating between AD and VaD, and a neurological examination was performed to help in the diagnostic process. The validity of this diagnostic process has been previously documented (13). Identified cases of dementia were presented to a panel of four research psychiatrists. Variables in the ZARADEMP interview were operationalized to conform to the DSM-IV (27) criteria used to diagnose the cases. For the diagnosis of 'incident case' of dementia and type of dementia, agreement by at least three of the psychiatrists was required.

To document the accuracy of the panel diagnosis of dementia, a proportion of cases was invited for a hospital diagnostic work-up, which included neuroimage studies and a complete neuropsychological diagnostic battery, and NINCDS-ADRDA criteria (28) were applied to diagnose AD.

Data analysis

We obtained the age-specific incidence per 5-year band (presented as rates per 1000 person-years). Age bands are based on the age at entry to the baseline study. The follow-up period ended at the second follow-up examination (Wave III) for the non-demented, at the date of invitation for

refusals, at the date of moving away or death (based on actual data from the Civil Registry), or at the time of onset of dementia for the cases. The time of onset of dementia was estimated to be the time from the baseline to the midpoint between diagnosis and the previous examination. Incidence figures were also estimated by sex and by dementia subtype. The incidence rate ratio (IRR) was used to compare incidence rates.

The highest achieved level of education was assessed during the initial home interview in the baseline study. We categorized education into three levels: illiterate (unable to read and write, and <2 years of formal education), primary (complete or incomplete), and secondary school or higher.

Multivariate models of analysis were used to calculate the risk of developing dementia over time, and the competing risk of death was taken into account. We used the cumulative incidence function (CIF) approach to display the risk of patients experiencing the event of interest (overall dementia or AD), taking into account the competing event (death) as time progressed (29). To analyze the effect of baseline predictors (sex and educational level) on the CIF, we used the Fine and Gray (30) regression model for the subdistribution hazard. This model modifies the Cox proportional hazard model to allow for the presence of competing risks. To examine the assumption of proportional subdistribution hazards, we visually inspected Schoenfeld-type residuals, which were later confirmed by testing the time-varying effect of each covariate using Scheike and Zhang's test (31). Confidence intervals were computed using Kalbsfleisch and Prentice's method (32) completed by bootstrap resampling. For all analyses, 'R' program, version 2.9.2, R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org with *cmprsk* and *timereg* libraries, was applied.

Results

In Fig. 1, several characteristics of the study population are summarized. Of the total cohort ($n = 4057$) at risk of developing dementia, 3237 (79.7%) were screened in person for dementia in the first follow-up, and 2403 (75.9%) in the second follow-up. Among the reasons for loss to follow-up, attrition through death was $n = 574$ and dropouts were $n = 1005$ (Table 1). No differences by age and sex were observed in dropouts when compared with participants, but the proportion of illiterate individuals was significantly higher among the former ($n = 95$, 9.5% vs. $n = 168$, 6.7%; $z = 2.63$, $P = 0.008$).

Overall, after an average follow-up period of 54 months, 138 new cases of clinically definite dementia were identified and included in the analysis. AD was diagnosed by the panel of psychiatrists in 87 cases (63.0%), VaD in 28 cases (20.3%), and other dementias in 23 cases (16.7%). Twenty-four of these incident 'cases' of dementia accepted the hospital diagnostic work-up. The diagnosis of dementia was confirmed in 23 cases (95.8%), and the diagnosis of the type of dementia was confirmed in 21 cases (87.5%). Compared to non-cases, cases of dementia and of AD were older and more likely to be female and illiterate (Table 1).

Table 2 shows age and sex-specific incidence rates of dementia and AD. With a total of 16 025 follow-up person-years, the overall incidence of dementia was 8.6 per 1000 person-years and the overall incidence of AD was 5.4 per 1000 person-years. The incidence increased markedly with age and continued to rise after the age of 90 years in both women and men. Among women, the incidence rate of both overall dementia (dementia) and AD was significantly higher in the age group of 90+ years when compared with the groups of

Table 1. Characteristics of participants in the study

	Baseline sample	Follow-up sample	Dropouts	Non-cases*	Cases of dementia†	Statistic‡	Cases of AD†	Statistic§
	$n = 4803$	$n = 4057$	$n = 1005$	$n = 2340$	$n = 138$	(P value)	$n = 87$	(P value)
Women, n (%)	2771 (57.7)	2229 (54.9)	599 (59.6)	1303 (55.7)	86 (62.3)	$z = 1.44$ (0.1)	61 (70.1)	$z = 2.55$ (0.01)
Baseline age, mean (SD)	73.4 (9.8)	72.1 (9.1)	70.3 (8.6)	70.0 (7.8)	82.0 (8.0)	$t_{2476} = 17.53$ (<0.01)	83.72 (7.13)	$t_{2425} = 16.13$ (<0.01)
Educational level, n (%)								
Illiterate	520 (10.8)	315 (7.8)	95 (9.5)	141 (6.1)	27 (19.6)	$z = 5.97$ (<0.01)	19 (21.8)	$z = 5.61$ (<0.01)
Primary	3507 (73.0)	3019 (74.4)	765 (76.1)	1728 (74.3)	99 (71.7)	$z = 0.44$ (0.7)	59 (67.8)	$z = 1.13$ (0.3)
Secondary school or higher	717 (14.9)	690 (17.0)	134 (13.3)	458 (19.7)	12 (8.7)	$z = 3.05$ (<0.01)	9 (10.3)	$z = 2.00$ (0.0)

AD, Alzheimer's disease.
*Non-cases at the end of follow-up.
†Cases identified during follow-up.
‡Non-cases vs. cases of dementia.
§Non-cases vs. cases of AD.

Table 2. Age- and sex-specific number of person-years at risk, number of dementia cases, and incidence rates [per 1000 person-years, with 95% confidence interval (CI)]

	Total dementia				Alzheimer's disease		
	Person-years at risk	No. of dementia cases	Incidence rate	95%CI	No. of Alzheimer's disease cases	Incidence rate	95%CI
Total							
55–59	673	0	0.0	0–5.5	0	0.0	0–5.48
60–64	3609	1	0.3	0–1.5	0	0.0	0–1.02
65–69	3516	8	2.3	1–4.5	2	0.6	0.07–2.06
70–74	3174	9	2.8	1.3–5.4	4	1.3	0.34–3.23
75–79	2109	16	7.6	4.3–12.3	9	4.3	1.95–8.10
80–84	1352	17	12.6	7.3–20.1	10	7.4	3.55–13.60
85–89	1251	46	36.8	26.9–49.1	30	24.0	16.2–34.2
90+	342	41	119.7	85.9–162.6	32	93.5	63.9–131.9
All ages	16 025	138	8.6	7.2–10.2	87	5.4	4.35–6.70
Men							
55–59	312	0	0.0	0–11.8	0	0.0	0–11.82
60–64	1724	0	0.0	0–2.1	0	0.0	0–2.14
65–69	1566	6	3.8	1.4–8.3	0	0.0	0–2.36
70–74	1312	2	1.5	0.2–5.5	2	1.5	0.18–5.51
75–79	847	4	4.7	1.3–12.1	0	0.0	0–4.36
80–84	578	7	12.1	4.9–25	5	8.6	2.81–20.18
85–89	589	20	33.9	20.7–52.4	11	18.7	9.3–33.4
90+	122	13	106.6	56.8–182.3	8	65.6	28.3–129.3
All ages	7050	52	7.4	5.5–9.7	26	3.7	2.41–5.40
Women							
55–59	361	0	0.0	0–10.2	0	0.0	0–10.22
60–64	1885	1	0.5	0–3.0	0	0.0	0–1.96
65–69	1949	2	1.0	0.1–3.7	2	1.0	0.12–3.71
70–74	1862	7	3.8	1.5–7.7	2	1.1	0.13–3.88
75–79	1262	12	9.5	4.9–16.6	9	7.1	3.26–13.54
80–84	774	10	12.9	6.2–23.8	5	6.5	2.10–15.08
85–89	661	26	39.3	25.7–57.6	19	28.7	17.3–44.9
90+	220	28	127.0	84.4–183.5	24	108.9	69.7–162.0
All ages	8975	86	9.6	7.7–11.8	61	6.8	5.20–8.73
IRR†			1.3*	0.91–1.87		1.84**	1.15–3.04

†Incidence rate ratio (IRR) for all ages, women vs. men.
*P = 0.1; **P = 0.009.

85–89 years (IRR = 3.2, 95%CI 1.8–5.7 in dementia; IRR = 3.8, 95%CI 2.0–7.3 in AD). A similar pattern was observed in men, and differences were statistically significant in both dementia (3.1, 95%CI 1.4–6.6) and AD (3.5, 95%CI 1.2–9.6).

Figure 2 shows the age-specific incidence of dementia for the current study, compared with that of other relatively large studies which used similar procedures. Incidence rates tend to be slightly lower in our study and, in particular, were significantly lower in age groups 70–85 years when compared to all North-West European studies reviewed.

Overall incidence rates for both dementia and AD were higher in women in comparison to men, the differences being statistically significant in AD (IRR = 1.84; 95%CI 1.15, 3.04; $P < 0.01$) (Table 2). In relation to education, the incidence rate of dementia among the illiterate (23.5 per 1000 person-years, 95%CI 15.46–34.13) was significantly higher than in either individuals with primary education (8.3 per 1000 person-years, 95%CI 6.76–10.12) or in those with secondary or higher educational level (4.2 per 1000 person-years, 95%CI 2.17–7.35). (Illiterate vs. primary, IRR = 2.82, 95%CI 1.77–4.35, $P < 0.01$; illiterate vs. secondary school or higher, IRR = 5.58, 95%CI 2.73–12.08, $P < 0.01$). Similarly, the incidence rate of AD among the illiterate (16.5 per 1000 person-years, 95%CI 9.94–25.78) was significantly higher than in both individuals with primary education (4.9 per 1000 person-years, 95%CI 3.77–6.39) and with secondary or higher educational level (4.2 per 1000 person-years, 95%CI 1.44–5.99). (Illiterate vs. primary, IRR = 3.33, 95%CI 1.88–5.67, $P < 0.001$; illiterate vs. medium/high, IRR = 3.92, 95%CI 1.81–8.86, $P < 0.01$).

Tables 3 and 4 give the 10- to 30-year period risk as well as the LTR of dementia and AD, respectively. In women, a slight trend of increased LTR with age was observed, but differences between age groups were not statistically significant. Table 3 shows, for example, that a 65-year-old non-demented woman has a 19.7% lifetime probability of suffering dementia and a probability of 20.4% at

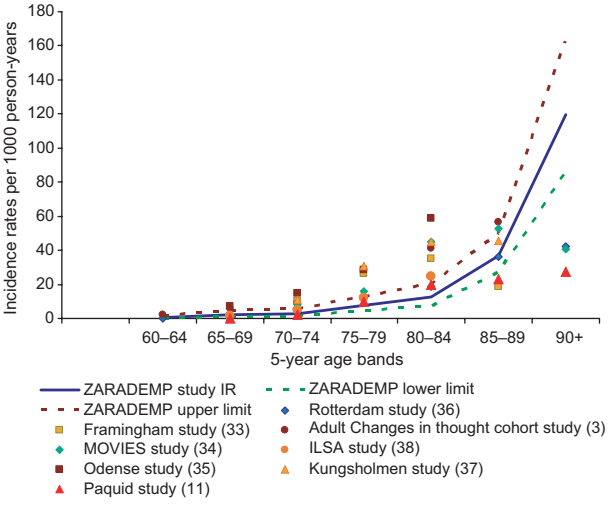

Fig. 2. Age-specific incidence rates and CIs (per 1000 person-years) of dementia in the ZARADEMP Project. Lower CI limits from other studies in USA (3, 33, 34), Denmark (35), Netherlands (36), Sweden (37), France (11), and Italy (38) are presented for comparison.

the age of 85. The corresponding figures for AD were 16.7% and 17.6%. However, an association is observed between low education and LTR of both dementia and AD, the risk of dementia being more than twice as high and the risk of AD about twice as high among illiterate women when compared with women with the highest educational level. For example, the risk of dementia among illiterate women was 2.26 times higher for 65-year-old women, and 2.31 times for 85-year-old women. The corresponding figures for AD were 1.89 and 2.25, respectively.

In men, LTR increases slightly with age but, again, differences between age groups were not statistically significant. Table 3 shows, for example, that a 65-year-old non-demented man has a lifetime probability of 14.1% of suffering dementia and of 16.8% at the age of 85. The corresponding figures of AD were 8.4% and 10.9%, respectively. The slight increment of LTR of both dementia and AD with age is shown in Fig. 3. For comparison with previous studies, the figure presents the LTR from age 65 years. An association was also observed in men between low education and LTR of both dementia and AD, the risk of dementia being more than twice as high and the risk of AD about twice as high among illiterate men when

Table 3. Age-, Sex-, and educational level-specific mortality-adjusted 10-, 20- and 30-year, and lifetime-risk estimates* for dementia at index ages 55, 65, 75, and 85 years

	10 Years	20 Years	30 Years	Lifetime risk
*Men**				
55 Years	0.0 (0.0–0.3)	0.6 (0.3–1.0)	2.5 (1.8–3.2)	13.7 (12.3–15.3)
Illiterate	0.1 (0.0–4.3)	1.1 (0.2–4.0)	4.4 (1.9–8.7)	23.6 (17.0–30.7)
Primary	0.1 (0.0–0.4)	0.6 (0.3–1.1)	2.5 (1.8–3.4)	13.8 (12.0–15.6)
Secondary school or higher	0.0 (0.0–1.6)	0.4 (0.1–1.5)	1.8 (0.8–3.4)	10.1 (7.4–13.2)
65 Years	0.6 (0.3–1.0)	2.5 (1.8–3.3)	12.6 (11.0–14.2)	14.1 (12.5–15.9)
Illiterate	1.0 (0.1–5.1)	4.6 (1.6–10.1)	21.8 (14.2–30.5)	24.4 (16.4–33.3)
Primary	0.6 (0.2–1.2)	2.5 (1.7–3.5)	12.5 (10.7–14.5)	14.1 (12.2–16.2)
Secondary school or higher	0.4 (0.1–1.7)	1.8 (0.8–3.7)	9.3 (6.6–12.6)	10.5 (7.6–14.0)
75 Years	2.0 (1.2–3.2)	12.6 (10.4–14.9)	–	14.2 (12.0–16.7)
Illiterate	3.3 (0.6–10.1)	19.8 (11.0–30.5)	–	22.3 (12.9–33.3)
Primary	2.1 (1.2–3.5)	13.0 (14.4–15.8)	–	14.7 (12.0–17.7)
Secondary school or higher	1.3 (0.3–4.1)	8.5 (4.9–13.2)	–	9.6 (5.8–14.6)
85 Years	14.4 (10.9–18.4)	–	–	16.8 (13.0–21.0)
Illiterate	22.3 (9.6–38.2)	–	–	25.7 (11.9–42.0)
Primary	14.8 (10.7–19.6)	–	–	17.2 (12.8–22.2)
Secondary school or higher	9.4 (3.7–18.4)	–	–	10.9 (4.6–20.4)
*Women**				
55 Years	0.0 (0.0–0.2)	0.9 (0.6–1.3)	3.6 (3.0–4.4)	19.8 (18.4–21.3)
Illiterate	0.1 (0.0–1.3)	1.5 (0.6–3.1)	6.1 (4.0–8.8)	31.1 (26.5–35.8)
Primary	0.1 (0.0–0.3)	0.8 (0.5–1.3)	3.4 (2.7–3.4)	18.6 (16.9–20.3)
Secondary school or higher	0.0 (0.0–2.2)	0.6 (0.1–2.1)	2.5 (1.1–4.7)	13.7 (10.1–17.9)
65 Years	0.8 (0.5–1.3)	3.6 (2.8–4.5)	17.6 (16.0–19.3)	19.7 (18.0–21.5)
Illiterate	1.4 (0.4–3.9)	6.1 (3.3–10.0)	28.1 (22.0–34.4)	31.2 (24.9–37.7)
Primary	0.8 (0.4–1.3)	3.3 (2.5–4.3)	16.4 (14.6–18.3)	18.4 (16.5–20.4)
Secondary school or higher	0.6 (0.1–2.4)	2.4 (1.0–5.0)	12.3 (8.5–16.8)	13.8 (9.8–18.5)
75 Years	3.0 (2.1–4.1)	18.0 (15.8–20.3)	–	20.3 (18.0–22.8)
Illiterate	4.5 (1.9–8.8)	26.1 (19.2–33.6)	–	29.3 (22.0–36.9)
Primary	2.9 (1.9–4.2)	17.4 (14.9–20.0)	–	19.6 (17.0–22.3)
Secondary school or higher	1.8 (0.3–6.0)	11.4 (6.2–18.4)	–	13.0 (7.4–20.2)
85 Years	17.7 (14.2–21.5)	–	–	20.4 (16.7–24.4)
Illiterate	25.5 (15.6–36.6)	–	–	29.3 (18.8–40.7)
Primary	17.1 (13.1–21.5)	–	–	19.8 (15.6–24.4)
Secondary school or higher	10.9 (3.6–22.7)	–	–	12.7 (4.6–25.0)

*Risks shown as percentages (95%CI).

Table 4. Age-, sex-, and educational level-specific mortality-adjusted 10-, 20- and 30-year, and lifetime-risk estimates* for Alzheimer's disease at index ages 55, 65, 75, and 85 years

	10 Years	20 Years	30 Years	Lifetime risk
*Men**				
55 Years	0.0 (0.0–0.3)	0.2 (0.0–0.4)	1.1 (0.7–1.7)	8.2 (7.1–9.5)
Illiterate	0.0 (0.0–7.5)	0.3 (0.0–3.1)	2.1 (0.6–5.6)	15.1 (9.8–21.4)
Primary	0.0 (0.0–0.4)	0.1 (0.0–0.5)	1.1 (0.6–1.7)	7.8 (6.4–9.2)
Secondary school or higher	0.0 (0.0–2.6)	0.1 (0.0–1.2)	1.0 (0.4–2.4)	7.6 (5.3–10.4)
65 Years	0.1 (0.0–0.5)	1.1 (0.7–1.8)	7.0 (5.8–8.3)	8.4 (7.1–9.9)
Illiterate	0.3 (0.0–4.6)	2.2 (0.4–6.8)	13.0 (7.2–20.6)	15.6 (9.2–23.5)
Primary	0.1 (0.0–0.5)	1.1 (0.6–1.8)	6.6 (5.3–8.1)	7.9 (6.5–9.6)
Secondary school or higher	0.1 (0.0–1.4)	1.1 (0.3–2.6)	6.6 (4.3–9.5)	7.9 (5.4–11.1)
75 Years	1.1 (0.5–2.0)	7.4 (5.8–9.3)	–	9.0 (7.1–11.0)
Illiterate	2.1 (0.2–8.3)	13.7 (6.6–23.4)	–	16.4 (8.5–26.6)
Primary	1.1 (0.4–2.2)	7.2 (5.3–9.5)	–	8.7 (6.6–11.2)
Secondary school or higher	0.9 (0.1–3.4)	6.0 (3.1–10.2)	–	7.2 (4.0–11.8)
85 Years	8.7 (6.0–12.0)	–	–	10.9 (7.8–14.1)
Illiterate	16.6 (6.0–31.7)	–	–	20.5 (8.4–36.2)
Primary	8.3 (5.2–12.2)	–	–	10.3 (6.9–14.6)
Secondary school or higher	7.0 (2.3–15.3)	–	–	8.8 (3.3–17.6)
*Women**				
55 Years	0.0 (0.0–0.2)	0.3 (0.2–0.6)	2.4 (1.9–3.0)	16.7 (15.4–18.1)
Illiterate	0.1 (0.0–1.4)	0.6 (0.1–1.9)	4.3 (2.5–6.7)	28.0 (23.6–32.6)
Primary	0.1 (0.0–0.3)	0.3 (0.1–0.6)	2.1 (1.6–2.8)	15.0 (13.5–16.6)
Secondary school or higher	0.0 (0.0–2.6)	0.3 (0.0–1.6)	2.1 (1.6–2.8)	14.8 (11.0–19.0)
65 Years	0.3 (0.1–0.6)	2.4 (1.8–3.1)	14.0 (12.5–15.6)	16.7 (15.1–18.4)
Illiterate	0.5 (0.1–2.6)	4.2 (2.0–7.7)	23.9 (18.2–30.0)	28.2 (22.1–34.5)
Primary	0.3 (0.1–0.6)	2.1 (1.5–2.9)	12.5 (10.9–14.2)	14.9 (13.2–16.7)
Secondary school or higher	0.3 (0.0–2.0)	2.1 (0.8–4.5)	12.5 (8.7–17.0)	14.9 (10.7–19.7)
75 Years	2.2 (1.4–3.1)	14.3 (12.4–16.5)	–	17.2 (15.0–19.4)
Illiterate	3.8 (1.5–7.9)	23.9 (17.3–31.2)	–	28.3 (21.2–35.9)
Primary	2.0 (1.2–3.1)	13.0 (10.8–15.4)	–	15.6 (13.3–18.1)
Secondary school or higher	1.6 (0.3–5.7)	10.8 (5.8–17.6)	–	13.0 (7.4–20.2)
85 Years	14.2 (11.1–17.7)	–	–	17.6 (14.1–21.4)
Illiterate	24.8 (15.0–35.8)	–	–	30.2 (19.5–41.6)
Primary	12.7 (9.3–16.6)	–	–	15.7 (11.9–20.0)
Secondary school or higher	10.7 (3.5–22.6)	–	–	13.4 (5.0–25.9)

*Risks shown as percentages (95%CI).

compared with those with the highest educational level (Tables 3 and 4). For example, the risk of dementia among illiterate men was 2.32 times higher for 65-year-old men, and 2.36 for 85-year-old men. The corresponding figures for AD were 1.97 and 2.33, respectively. To assess the possibility that cognitive performance at baseline influenced the association of low education and LTR of dementia and AD, we calculated LTR for different baseline scores in the MMSE. However, the association was maintained in both dementia and AD, although LTR differences between illiterate participants and participants with higher educational level were slightly attenuated (data not shown).

LTR of both dementia and AD were higher in women when compared with men, the differences being statistically significant for all entry ages, with the exception of the oldest entry age in cases of dementia (Tables 3 and 4). Furthermore, the differences according to sex were independent of the educational level, although they tended to attenuate in the oldest age of 85 years. Period risk of both dementia and AD increases with age of entry for calculations of risk in both men and women, but also increases with the length of the interval (Tables 3 and 4). For example, the 10-year risk of dementia for a 65-year-old woman was 0.8%, but it was 17.7% for an 85-year-old woman. The corresponding figures for AD were 0.3% and 14.2, respectively.

Discussion

We have confirmed in a Southern European city the heavy burden presented by dementia and its most frequent subtype, AD, because 8.6 and 5.4 per 1000 persons, respectively, may develop the disease each year (39, 40). While the period between waves has been relatively short in our study, some incident dementia cases might have occurred among the deceased people. Therefore, because mortality risk among the demented is higher than among the non-demented (41), the rates reported may be regarded minimum estimates of dementia and AD incidence. As expected, and in

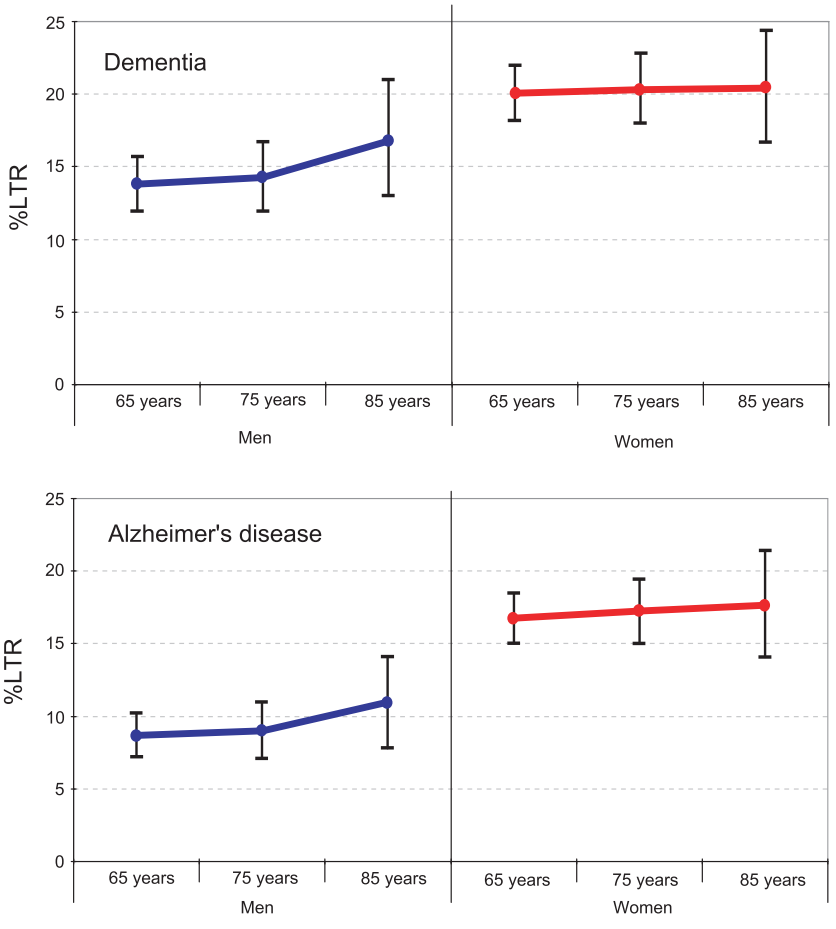

Fig. 3. Lifetime-risk, LTR (CI limits) of dementia and Alzheimer's disease in men and women, in the ZARADEMP Project, at index ages 65, 75, and 85 years.

agreement with previous studies (1), the incidence rate of both dementia and AD increases exponentially with age. Regarding a more controversial issue (4, 37), our data support the notion that the incidence of dementia and AD continues to rise in the oldest old, because, in both men and women, it was more than three times higher in the age group of 90+ years than in the age group of 85–89 years.

Incidence rates of dementia in this population seem to be slightly lower than in most studies reported in the literature, including the studies by Kukull et al. (3) and Ganguli et al. (34) in the USA. Specifically, in agreement with the EURODEM study (2), the incidence rates of dementia in this South European city were significantly lower in age groups 70–85 years than in studies reported in North-West Europe using similar methodology, namely the Rotterdam study (36), the Odense study (35), and the Kungsholmen Project (37), and comparisons above that age were difficult because of small samples and wide interval coefficients. However, the conclusions of both the EURODEM study and the present one about possible regional differences in dementia incidence need confirmation, because important differences of prevalence might be expected if this was repeated across Southern Europe.

The estimation of LTR of dementia and AD at several ages, taking into account competing risks of death, was one of the main objectives in this particular study. In comparison to incidence estimations, quite a different pattern emerges, and in both overall dementia and AD, a slight trend of increased LTR with age was observed, but differences between age groups were not statistically significant. Therefore, the pattern of LTR shown in this study will probably be less alarming than the prevalence curves (42, 43) and incidence curves (2) reported in the literature and available to the public. LTR is an under-researched subject in the field of dementia (6), but the applicability of the estimates seems to be apparent. It has been suggested that LTR calculations can be used as a population risk estimate to aid policy decisions, but mainly as a method for communicating disease risk to individuals and the mass media (6). There is some evidence in the literature related to effective health communication that concepts such as LTR are easier to comprehend than alternative estimates, such as incidence rates (7). The data here

can easily be converted into bar graphs readily accessible to the public, and eventually, nomograms and charts may be produced to show the LTR of dementia and AD. The Framingham Study (8) and the Rotterdam study (5) have previously reported mortality-adjusted LTRs and period risk of dementia, and only the Framingham Study reported AD risks. The Framingham estimates of LTR for dementia were similar to ours. In contrast, the Rotterdam study reported rates almost twice as high. However, interstudy comparisons are difficult because, unlike our study, these reports used univariate models of analysis and we believe the use of multivariate methods would attenuate the risk reported. The relevance of adjusting by sex and education and of the use of an LTR multivariate model, as in this study, is supported by our findings showing an increased incidence rate of dementia and AD in women in relation to men, and in the less educated in relation to the more educated. However, as emphasized by Seshadri et al. (6), future studies should refine LTR estimates with risk-stratified models, especially to enable individual risk prediction. In this respect, vascular risk factors should be considered, because they are known to be associated with an increased risk of dementia and are common in this type of population (44).

As in some previous studies in the literature (2, 9), all indexes of frequency and risk of dementia and AD were higher in women when compared with men. It has been suggested that the divergent rates of dementia in women and men may be partly because of survival differences (45). However, in relation to LTR, differential survival cannot explain the higher risk of dementia among women in this study, because LTR was mortality adjusted. Moreover, in the Zaragoza study, we adjusted for education and sex. A low educational level has also been associated previously with increased mortality (46). Therefore, explanations other than differential survival between men and women must be considered to clarify the increased LTR of dementia and AD among women. The delayed effects on women of estrogen deprivation at menopause are still suggested as an explanation (47), although results of studies about the effects of estrogen therapy on AD have been disappointing (48). However, early menopausal estrogen use might have beneficial effects on the brain, because the window of opportunity hypothesis suggests that the neuroprotective effects of estrogen depends on the age at the time of administration (49).

Our findings in relation to the association between low educational level with frequency and risk of dementia and AD also support the working hypothesis. Firstly, the incidence rate of both dementia and AD were higher among the less educated, and the IRR was statistically significant in both men and women for both dementia and AD. Secondly, the LTR of both dementia and AD was more than twice as high among illiterate participants in comparison to participants with a higher educational level and was independent of age and sex (LTR ratios range from 2.34 to 2.36 among men; and from 2.26 to 2.31 among women for dementia; and range from 1.97 to 2.33 among men; and from 1.89 to 2.25 among women for AD). For dementia, LTR increased as the level of education decreased, while for AD, the highest risk was observed among illiterate participants, but no differences were observed between participants with primary and secondary or higher educational level. Several studies have observed the association of dementia and AD with a low educational level (2, 10), but discrepant results have also been shown, and the authors of the Framingham study have suggested that associations reported may be spurious (50). Differential sensitivity of screening instruments as a possible reason for the increase in dementia risk among poorly educated people must be considered (51, 52), because the re-validated Spanish version of the MMSE is still influenced by the educational background (13, 14). However, we argue that the possibility that, because of the differential sensitivity of the screening, false negative cases of dementia among individuals with higher educational levels escaped the screening in this particular study is considerably minimized. Firstly, the negative predictive value (NPV) of the MMSE in the same population is 97.8%. Secondly, in this particular study, we also used for the screening in the same individuals the cognitive section in the Spanish version of the GMS, whose NPV is 98.3% (13) and is minimally influenced by education (18). Furthermore, following suggestions by previous authors (3), we have also observed that adjusting by cognitive performance at baseline the association of low educational level and LTR of dementia and AD was only mildly attenuated. Therefore, we argue that, in this study, a true association has been found between dementia and low educational level.

The timing of this study in a developed country must be emphasized, because we have studied generations of participants born before 1936. The educational level has improved dramatically in recent generations (53), and only exceptionally will illiterate individuals be found in the near future in this country, and similarly in other developed countries, so that the study of the effect of illiteracy will no longer be possible. In contrast, findings in

this study could be tested in developing countries where important cross-national differences in the prevalence of dementia have been reported (54). Several explanations have been offered to account for the association between low educational level and dementia or AD, such as the brain reserve hypothesis, the lack of intellectual stimulus and exercise, or lack of mental hygiene and medical care among less educated people (55). The different pattern found in cases of AD requires confirmation because it might suggest that illiterate individuals have specific risks. The hypothesis might be formulated that AD patients have latent traits manifested early in the development in special circumstances, such as the inability to reach an appropriate language level in difficult academic situations. Illiteracy criteria used in this study included the inability to read and to write. Early linguistic difficulties in AD patients have been previously documented in classical studies such as the Nun Study (56). In relation to this and similar kinds of study, the possibility that AD might be a lifelong illness has been suggested (57).

Several factors add strength to our findings, such as the use of a representative population sample, which includes institutionalized individuals, the high rate of follow-up, the high sensitivity and specificity of the case finding with instruments validated by the group itself, the inclusion of actual mortality data, and the use for the first time of multivariate methods to study LTR. Some limitations also need to be considered, such as the loss to follow-up. The proportion of illiterate individuals was significantly higher among dropouts, when compared with participants. Therefore, had more dropouts participated in the follow-up, the rates of dementia and AD reported here would be higher among the less educated, because this group of individuals has been observed to be at a higher risk. However, this still would reinforce our conclusions about the increased risk of dementia and AD among the illiterate. Another limitation may be the fact that we do not have data on ApoE, and the hospital diagnosis was not completed in all cases of dementia. Furthermore, by design, we only report LTR population estimates, but for any given individual, the estimated LTR would vary with possible risk factors not controlled in this study, such as vascular risk factors and disorders (6), and with the possible success of risk factor management.

In conclusion, this study in a Southern European population confirms that the exponential increase in incidence of dementia continues after the age of 90 years, but the incidence rate tends to be slightly lower than in previous studies in North-West Europe. The study documents the LTR of dementia and AD in a Southern European city for the first time, and only a trend for an increased LTR with age was observed. All indexes of frequency and risk of dementia or AD were higher in women, and the LTR of AD was higher among illiterate individuals. The applicability of LTR findings seems apparent.

Acknowledgements

Supported by Grants from the Fondo de Investigación Sanitaria, Instituto de Salud Carlos III, Spanish Ministry of Health, Madrid, Spain (grants 94/1562, 97/1321E, 98/0103, 01/0255, 03/0815, 06/0617, G03/128). The authors acknowledge the contribution of the lay interviewers, senior medical students, and members of the ZARADEMP Workgroup who participated in the study. We would like to thank professor M.E. Dewey (Institute of Psychiatry, King's College London) for his review of a previous version of this manuscript.

Declaration of interest

We declare that Dr. Lobo had a consultancy with Janssen, and funds have been paid to his institution, and Eli Lilly has funded his assistance to a scientific meeting, both for reasons not related to the current project. Dr. Quintanilla has been funded for acting as associated researcher in the PREFERE study in schizophrenia by Janssen; and by Janssen-Cilag for acting as associated researcher in the LIBERA study in schizophrenia (both projects were not related to the current study). None of the other authors have to disclosure any financial interests that may be affected by material in the manuscript or which might potentially bias it.

References

1. Jorm AF, Jolley D. The incidence of dementia A meta-analysis. Neurology 1998;**51**:728–733.
2. Fratiglioni L, Launer LJ, Andersen K et al. Incidence of dementia and major subtypes in Europe: a collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology 2000;**54**(11 Suppl 5):S10–S15.
3. Kukull WA, Higdon R, Bowen JD et al. Dementia and Alzheimer disease incidence: a prospective cohort study. Arch Neurol 2002;**59**:1737–1746.
4. Ziegler-Graham K, Brookmeyer R, Johnson E, Arrighi HM. Worldwide variation in the doubling time of Alzheimer's disease incidence rates. Alzheimers Dement 2008;**4**:316–323.
5. Ott A, Breteler MM, Van Harskamp F, Stijnen T, Hofman A. Incidence and risk of dementia. The Rotterdam Study. Am J Epidemiol 1998;**147**:574–580.
6. Seshadri S, Wolf PA. Lifetime risk of stroke and dementia: current concepts, and estimates from the Framingham Study. Lancet Neurol 2007;**6**:1106–1114.
7. Fortin JM, Hirota LK, Bond BE, O'connor AM, Col NF. Identifying patient preferences for communicating risk estimates: a descriptive pilot study. BMC Med Inform Decis Mak 2001;**1**:2.
8. Seshadri S, Beiser A, Kelly-Hayes M et al. The lifetime risk of stroke: estimates from the Framingham Study. Stroke 2006;**37**:345–350.

9. Chen JH, Lin KP, Chen YC. Risk factors for dementia. J Formos Med Assoc 2009;**108**:754–764.
10. Gurland BJ, Wilder DE, Lantigua R et al. Rates of dementia in three ethnoracial groups. Int J Geriatr Psychiatry 1999;**14**:481–493.
11. Letenneur L, Gilleron V, Commenges D, Helmer C, Orgogozo JM, Dartigues JF. Are sex and educational level independent predictors of dementia and Alzheimer's disease? Incidence data from the PAQUID project. J Neurol Neurosurg Psychiatry 1999;**66**:177–183.
12. Lobo A, Saz P, Marcos G et al. The ZARADEMP Project on the incidence, prevalence and risk factors of dementia (and depression) in the elderly community: II. Methods and first results. Eur J Psychiatry 2005;**19**:40–54.
13. Lobo A, Saz P, Marcos G, Día JL, De-La-Cámara C. The prevalence of dementia and depression in the elderly community in a Southern European population. The Zaragoza study. Arch Gen Psychiatry 1995;**52**:497–506.
14. Lobo A, Saz P, Marcos G et al. [Revalidation and standardization of the cognition mini-exam (first Spanish version of the Mini-Mental Status Examination) in the general geriatric population]. Med Clin (Barc) 1999;**112**:767–774.
15. Folstein MF, Folstein SE, Mchugh PR. Mini-Mental State. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;**12**:189–198.
16. Crum RM, Anthony JC, Bassett SS, Folstein MF. Population-based norms for the Mini-Mental State Examination by age and educational level. JAMA 1993;**269**:2386–2391.
17. Copeland JR, Dewey ME, Wood N, Searle R, Davidson IA, Mcwilliam C. Range of mental illness amongst the elderly in the community: prevalence in Liverpool using the GMS–AGECAT package. Br J Psychiatry 1987;**150**:815–823.
18. Saz P, Día JL, De La Camara C et al. Reliability and validity of the Spanish version of the GMS-AGECAT package for the assessment of dementia and cognitive disturbances. Int J Geriatr Psychiatry 1996;**11**:721–728.
19. Dewey ME, Copeland JRM, Lobo A, Saz P, Día JL. Computerised diagnosis from a standardised history schedule: a preliminary communication about the organic section of the HAS–AGECAT system. Int J Geriatr Psychiatry 1992;**7**:443–446.
20. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969;**9**:179–186.
21. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged. The Index of ADL: a standardized measure of biological and psychosocial function. JAMA 1963;**185**:914–919.
22. Alvarez M, De Alaiz AT, Brun E, Cabañeros JJ, Calzon M, Cosio I. Capacidad funcional de pacientes mayores de 65 años, según el índice de Katz. Fiabilidad del método. Aten Primaria 1992;**10**:812–816.
23. Tárraga LL. Evaluación del deterioro cognitivo y funcional de la demencia. Escalas de mayor interés en la Atención Primaria. In: Boada M, Tárraga LL, eds. El médico ante la demencia y su entorno, Módulo 1. Barcelona: Bayer S.A, 1995:37–50.
24. Launer LJ, Andersen K, Dewey ME et al. Rates and risk factors for dementia and Alzheimer's disease: results from EURODEM pooled analyses. EURODEM Incidence Research Group and Work Groups. European Studies of Dementia. Neurology 1999;**52**:78–84.
25. Lobo-Escolar A, Saz P, Marcos G et al. Somatic and psychiatric comorbidity in the general elderly population: results from the ZARADEMP Project. J Psychosom Res 2008;**65**:347–355.
26. Hachinski VC, Lassen NA, Marshall J. Multi-infarct dementia: a cause of mental deterioration in the elderly. Lancet 1974;**2**:207–210.
27. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th edn. Washington, DC: American Psychiatric Association, 1994.
28. Mckhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;**34**:939–944.
29. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med 2007;**206**:2389–2430.
30. Fine JP, Gray RJ. A proportional hazard model for the subdistribution of competing risks. J Am Stat Assoc 1999;**94**:496–509.
31. Scheike TH, Zhang MJ. Flexible competing risks regression modeling and goodness-of-fit. Lifetime Data Anal 2008;**14**:464–483.
32. Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. New York: John Wiley & Sons Inc., 1980.
33. Bachman DL, Wolf PA, Linn RT et al. Incidence of dementia and probable Alzheimer's disease in a general population: the Framingham Study. Neurology 1993;**43**(3 Pt 1):515–519.
34. Ganguli M, Dodge HH, Chen P, Belle S, Dekosky ST. Ten-year incidence of dementia in a rural elderly US community population: the MoVIES Project. Neurology 2000;**54**:1109–1116.
35. Andersen K, Nielsen H, Lolk A, Andersen J, Becker I, Kragh-Sørensen P. Incidence of very mild to severe dementia and Alzheimer's disease in Denmark: the Odense Study. Neurology 1999;**52**:85–90.
36. Ruitenberg A, Ott A, Van Swieten JC, Hofman A, Breteler MM. Incidence of dementia: does gender make a difference? Neurobiol Aging 2001;**22**:575–580.
37. Fratiglioni L, Viitanen M, Von Strauss E, Tontodonati V, Herlitz A, Winblad B. Very old women at highest risk of dementia and Alzheimer's disease: incidence data from the Kungsholmen Project, Stockholm. Neurology 1997;**48**:132–138.
38. Di Carlo A, Baldereschi M, Amaducci L et al. Incidence of dementia, Alzheimer's disease, and vascular dementia in Italy. The ILSA Study. J Am Geriatr Soc 2002;**50**:41–48.
39. Quentin W, Riedel-Heller SG, Luppa M, Rudolph A, König HH. Cost-of-illness studies of dementia: a systematic review focusing on stage dependency of costs. Acta Psychiatr Scand 2010;**121**:243–259.
40. Caputo M, Monastero R, Mariani E et al. Neuropsychiatric symptoms in 921 elderly subjects with dementia: a comparison between vascular and neurodegenerative types. Acta Psychiatr Scand 2008;**117**:455–464.
41. Dewey ME, Saz P. Dementia, cognitive impairment and mortality in persons aged 65 and over living in the community: a systematic review of the literature. Int J Geriatr Psychiatry 2001;**16**:751–761.
42. Lobo A, Launer LJ, Fratiglioni L et al. Prevalence of dementia and major subtypes in Europe: a collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology 2000;**54**(11 Suppl 5):S4–S9.
43. Sekita A, Ninomiya T, Tanizaki Y et al. Trends in prevalence of Alzheimer's disease and vascular dementia in a Japanese

community: the Hisayama Study. Acta Psychiatr Scand 2010;**122**:319–325.
44. Lobo-Escolar A, Roy JF, Saz P et al. Association of hypertension with depression in community-dwelling elderly persons: results from the ZARADEMP Project. Psychother Psychosom 2008;**77**:323–325.
45. Alzheimer's Association. 2010 Alzheimer's disease facts and figures. Alzheimers Dement 2010;**6**:158–194.
46. Huisman M, Kunst AE, Bopp M et al. Educational inequalities in cause-specific mortality in middle-aged and older men and women in eight western European populations. Lancet 2005;**365**:493–500.
47. Gandy S. Estrogen and neurodegeneration. Neurochem Res 2003;**28**:1003–1008.
48. Shumaker SA, Legault C, Kuller L et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. JAMA 2004; **291**:2947–2958.
49. Rocca WA, Grossardt BR, Shuster LT. Oophorectomy, menopause, estrogen treatment, and cognitive aging: clinical evidence for a window of opportunity. Brain Res 2011;**1379**:188–198.
50. Cobb JL, Wolf PA, Au R, White R, D'agostino RB. The effect of education on the incidence of dementia and Alzheimer's disease in the Framingham Study. Neurology 1995;**45**:1707–1712.
51. Tschanz JT, Welsh-Bohmer KA, Plassman BL, Norton MC, Wyse BW, Breitner JC. An adaptation of the modified mini-mental state examination: analysis of demographic influences and normative data: the cache county study. Neuropsychiatry Neuropsychol Behav Neurol 2002;**15**:28–38.
52. Crane PK, Gibbons LE, Jolley L et al. Differential item functioning related to education and age in the Italian version of the Mini-mental State Examination. Int Psychogeriatr 2006;**18**:505–515.
53. Instituto Nacional de Estadística. INEbase: Demografía y población; Cifras de población y Censos demográficos. http://www.ine.es/inebmenu/mnu_cifraspob.htm. Accessed June 15, 2010.
54. Llibre Rodriguez JJ, Ferri CP, Acosta D et al. Prevalence of dementia in Latin America, India, and China: a population-based cross-sectional survey. Lancet 2008;**372**:464–474.
55. Mcdowell I, Xi G, Lindsay J, Tierney M. Mapping the connections between education and dementia. J Clin Exp Neuropsychol 2007;**29**:127–141.
56. Snowdon DA, Kemper SJ, Mortimer JA, Greiner LH, Wekstein DR, Markesbery WR. Linguistic ability in early life and cognitive function and Alzheimer's disease in late life. Findings from the Nun Study. JAMA 1996;**275**: 528–532.
57. Mortimer JA. Is Alzheimer's disease a lifelong illness? Risk factors for pathological and clinical disease. In: Heston LL, ed. Progress in Alzheimer's disease and similar conditions. Washington DC: American Psychiatric Press, 1997:9–20.