Prospective One-Year Cost-of-Illness Study in a Cohort of Patients with Dementia of Alzheimer's Disease Type in Spain: The ECO Study

Alicia Coduras[a], Isabel Rabasa[a], Ana Frank[b], Felix Bermejo-Pareja[c], Secundino López-Pousa[d], Jesús-María López-Arrieta[a], Juan Del Llano[a,*], Teresa León[e] and Javier Rejas[f]

[a]*Gaspar Casal Foundation, Madrid, Spain*
[b]*Department of Neurology, University Hospital "La Paz", Madrid, Spain*
[c]*Department of Neurology, University Hospital "12 de Octubre", Madrid, Spain*
[d]*Department of Neurosciences, Unitat de Valoració de la Memòria i les Demències, Hospital Santa Caterina, Girona, Spain*
[e]*Pfizer Global Pharmaceuticals, New York, New York, USA*
[f]*Health Outcomes Research Department, Medical Unit, Pfizer España, Alcobendas (Madrid), Spain*

Abstract. In this study, we analyzed the economic impact of one-year healthcare and non-healthcare resources utilization by patients with dementia of Alzheimer's disease (AD) under usual medical practice in Spain. A one-year, prospective, naturalistic, multicenter cohort study was designed to recruit patients with mild, moderate to severe, and severe AD according to Clinical Dementia Rating scale: the ECO study. Healthcare resources (medical visits, drugs and concomitant treatments, complementary and diagnostic tests, institutionalization and use of home-nursing facilities) and non-healthcare resources (inventory materials, consumables, professional and non-professional caregivers' time for care and supervision) were recorded and valued at 2006 prices. A total of 560 patients with possible/probable AD by DSM-IV-NINCDS-ADRDA criteria were included in the study: 68% women, 77 ± 6 years old, 29% treatment naïve. Monthly average cost per patient was €1,425.73, and increased 10.08% at the end of the study (baseline monthly cost; €1,316.22). Non-healthcare costs (€1059.00, 74.30% of total cost) decreased €4.30/month (0.40%) at the end of the year, while healthcare costs, which presented a total average of €366.66, grew by €136.94 in the period (54.06%), mainly due to cost of drugs, nursing home utilization, and institutionalization. The 87.26% of the overall cost (€1,244.22) was not financed by National Health Service (NHS), and the majority of this cost corresponded to caregiver-associated cost. The caregiver's total burden represented 70.86% of the overall cost-of-illness. In conclusion, monthly overall mean cost of dementia of AD type was high in Spain (€1,412.73). Almost 88% of the cost-of-illness is funded by the patient's own family, adding a financial burden to the suffering of these families.

Keywords: Costs, dementia of Alzheimer type, healthcare resources utilization, non-healthcare resources, prospective, Spain

INTRODUCTION

Alzheimer's disease (AD) is the most frequent cause of dementia in individuals over 64 years of age in industrialized countries [1]. In general, this disease con-

*Corresponding author: Dr. Juan Del Llano Señarís, Fundación Gaspar Casal, General Díaz Porlier, 78–8° A, 28006 Madrid, Spain. Tel.: +34 91 4016219; Fax: +34 91 4015299; E-mail: juan.delllano@fgcasal.org.

stitutes a leading socioeconomic problem since individuals with dementia require a high amount of healthcare and social and economic services both for the patients as well as their family and caregivers [2–4]. This disease has some of the highest healthcare and non-healthcare costs, with the costs being especially high for the patient's family, particularly in the terminal stages of the disease [2,5,6].

In the United States, it is estimated that there are currently around 4 million individuals suffering from this disease [7]. Spanish epidemiological data estimate an alarming rate that currently fluctuates between 4.6% and 14.5% for the population over 65 years of age, reaching an approximate number of 400,000 to 500,000 patients, though underdiagnosis of this type of dementia is considerable and, therefore, the real rate would be even higher if all cases were recorded [8–11]. In Western countries with a higher rate of aging population, it is well known that this type of dementia constitutes a leading socioeconomic problem [2–4,12–14]. The affected population in Europe is now over 5 million people and AD constitutes the third-leading disease in terms of economic and social costs in developed countries.

AD is directly related to age and, currently, its consequences are more visible due to an increase in life-expectancy and advances in diagnosis. For example, the Spanish population over 65 years of age in 2005 was over 7.3 million (16.6% of the total population), while population forecasts estimate that it will reach 16.4 million by 2050 which, according to these estimations, would be 30.8% of the population [14,15]. This may give an idea of the magnitude of the problem in aging populations in Western countries.

Therapeutic management of this disease consists of symptomatic treatment of cognitive deterioration or affective behavioral problems. Currently, there are different drugs for the treatment of mild to moderately severe AD that may affect the course of the disease over the short to medium term in both the progression of neurological symptoms as well as the social and family impact of the disease [16,17]. Nevertheless, the majority of studies that have addressed the cost of AD have been done from a specific perspective (prevalence) or from a retrospective point of view by reviewing the impact of the disease on the use of healthcare and non-healthcare resources and their associated costs. The certainty with which the social and health-related care of this disease accrues a high total cost, the economic analysis of which being very complex when all of the goods and services used in the diagnosis, treatment, and care of the patient are taken into account (both those financed by the public healthcare system as well as those covered by the patient and their family) from a purely transverse perspective, of which several studies exist in the scientific literature [2–6,12,13,18–21], makes the approach to AD through prospective follow-up of a wide and representative cohort of patients and their caregivers, thoroughly compiling and analyzing the use of all healthcare and non-healthcare resources, more reliable by making a precise estimation of the actual cost of the disease. This is the reason the ECO study has been carried out.

Therefore, the objective of this study has been to determine the prospective cost of AD in Spain as well as to provide results of the statistical comparison of a group of five working hypotheses proposed in the ECO study and their conclusions. These hypotheses serve to contrast to what extent the total monthly cost of healthcare and non-healthcare resources required for AD in Spain are derived from: 1) the specific diagnostic-therapeutic management that the patient receives; 2) patient follow-up in medical institutions (outpatient consultations, institutionalization, attendance at day centers, etc.); 3) clinical deterioration of the disease; 4) patient and primary caregiver sociodemographic characteristics; and 5) the time dedicated to patient care and supervision.

METHODS AND SUBJECTS

Study design

The ECO study was a multicenter, prospective, 12-month, observational, open-label study whose main objective was to assess the burden and costs of AD in Spain and to evaluate the progress of the disease during one year, including patients at different stages of the disease. Patients or their legal representative had given their informed consent and the study protocol was approved by the ethics committee of University Hospital La Paz (Madrid). The study was conducted according to the European and Spanish regulations and guidelines for pharmacoepidemiological studies, and complied with the principles of the Declaration of Helsinki regarding medical research in humans [22]. The study was conducted between 2003 and 2006, and patients were seen in three visits: baseline, 6 and 12 months after inclusion in the study, with an additional visit 4–8 weeks after initiating the study for possible adjustment of patient's therapy.

Patients and sampling

Eligible patients were men and women (two years post-menopausal or surgically sterile) over 50 years old, with a diagnosis of possible or probable AD, consistent with DSM-IV 290.00 or 290.10 and NINCDS-ADRDA criteria, with the ability to participate in study procedures [23]. Patients with mild, mild to moderate, and moderate to severe dementia by Clinical Dementia Rating (CDR) scale [24] were admitted to the study at a 1:2:1 proportion that was considered to represent the distribution of patients in real life based on their severity of dementia in that scale [8–11]. Patients without a reliable and consistent caregiver, or with a concomitant disease that could compromise their participation, or in a clinical situation that predicted an anticipated withdrawal, and those patients or caregivers who did not want, or were not able, to participate in study procedures were excluded.

A stratified multistage probabilistic sample without replacement was drawn. The sampling frame was all health regions from the 17 autonomous communities of Spain. The first stage consisted of the selection of the neurology clinics within each health region. The number of neurology clinics to be selected in each region was proportional to the population of the region. The probability of selection of each neurology clinic was related to the population of the area covered by the clinic. In the second stage, one neurologist per clinic chosen at random within those with previous experience in clinical and epidemiological research in neurology was invited to participate. Those refusing to participate were replaced by others also selected at random in the same clinic. The third stage consisted of the selection of patients. Patients were selected by a systematic sampling strategy from the daily list of all patients with an appointment with each of the participating neurologists meeting inclusion and exclusion criteria previously mentioned, and maintaining the abovementioned proportion of subjects according to their severity of dementia in the CDR scale.

Functional outcome measures

The evolution of the disease was assessed at baseline, month 6, and month 12 using the following functional measurement scales: 1) CDR [24]: a five-point scale to evaluate the staging severity of dementia (CDR-0 = no cognitive impairment, CDR-0.5 = very mild dementia, CDR-1 = mild, CDR-2 = moderate, CDR-3 = severe). It is composed of six domains (Memory, Ori-

entation, Judgment and Problem Solving, Community Affairs, Home and Hobbies, and Personal Care), which are scored individually, assessing the patient's cognitive ability to function in each area. The overall CDR rating is obtained by applying an algorithm; 2) Mini-Mental State Examination (MMSE) [25]: a thirty-point scale with five domains (Orientation, Registration, Attention and Calculation, Memory, and Language) to assess cognitive functioning (0 = lowest functioning to 30 = highest functioning). The version used was that of Blesa et al., 2001 [26], corrected by age and educational level; 3) Blessed Dementia Rating Scale (BDRS) [27]: rating scale to assess functional activity. The range is between 0 and 17, with higher scores indicating greater functional dependence. It has three domains (daily activities, habits, and personality and behavior) and several items within each one; 4) Zarit burden scale [28]: scale to assess the burden of the caregiver. It is composed of 22 items with the usual feelings experienced by those taking care of another person. Frequency of experiencing each individual feeling is rated from 0 to 4 (0=never, 1=rarely, 2=sometimes, 3=quite frequently, 4=nearly always). Total score ranges from 0 to 88, with higher scores indicating greater burden; 5) Health Utilities Index-Mark 3 (HUI-3) [29,30]: scale to measure health status with 8 attributes (vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain), with 5 or 6 levels of functional ability/disability within each one. Possible scores range from −0.29 to 1. It is compatible with multi-attribute preference functions, which provide a method for computing a summary health-related quality-of-life (HRQL) score for each health state. The questionnaire was completed by the patient and by the caregiver.

Data collection and cost estimation

Data were collected through a paper and pencil case report form designed *ad hoc* for this study. Assessment of the use of health and non-health resources was performed by extracting information from medical records in the case of health care resources and by interviewing the patient's caregiver in the case of non-healthcare resources both related to AD. The following data were collected: demographics, administrative data, medical history of EA, previous and current treatments, clinical status of patient as measured by previously mentioned scales (CDR, MMSE, BDRS, and HUI-3), and information regarding utilization of healthcare and non-healthcare resources. To collect health and non-health resources consumption, we used a modified version of

the RUD (Resource Utilization in Dementia) questionnaire [31]. This modified version was adapted into Spanish and validated in a pilot study previous to the ECO study [32].

The average monthly cost per patient due to AD, both overall and per component, has been calculated using the total monthly healthcare and non-healthcare costs. Included among the healthcare costs are specific medication, concomitant medication, medical consultation (primary care physician, geriatrics, neurology, and other specialists), hospital admissions due to AD in the 6 months prior to the visit being considered, medical testing performed in the last 6 months, attendance at day centers and admission to residences, and institutionalization of the patient. Among the non-healthcare costs, time was calculated, in hours per week, for care and supervision at home carried out by caregivers, both professional and informal caregiving. Considered among hours of care were those hours dedicated to carrying out basic activities of daily living (eating, washing, getting dressed, etc) and instrumental hours (going to the doctor, preparing food, shopping, etc.), while supervision included time for accompanying the patient without performing any specific tasks (going for a walk, watching television, etc.). Time frame for time devoted to patients was the last week, and then extrapolated to one month.

Also calculated were inventory items, consumables, and structural reforms made at home due to AD, as well as patient transportation for healthcare needs. Recorded among inventory items were acquisitions of wheelchairs, walkers, bathroom accessories, bathing chairs, shower handrails, safety bars, nightlights, emergency alarms, adjustable beds, ulcer-prevention mattresses, and structural changes. In the case of consumables, those due to the use of disposable swabs, dressing material, and diapers were calculated.

The time horizon of the study was one year, and 2006 prices were used for cost calculations. Overall and average monthly costs were calculated by multiplying unitary cost by resources consumption during the 6-month previous to the visit, then extrapolated to one month. Costs were categorized by indirect, direct healthcare, and direct non-healthcare costs. Also costs were separated according to the source of funding; the public health system or the patient's own family. Indirect costs were computed through the method of human capital (substitution costs), by multiplying the number of days of work absence in the case of informal caregivers by the mean salary earning declared by informal caregiver in the study. However, hours of care by

informal caregivers and explicitly devoted to patients' care were computed as direct non-healthcare costs and priced as the median of caregiver income collected in the study. Supervision time costs by informal caregivers were also priced with the same values as it was considered an opportunity cost [33,34].

Prices of healthcare resources were obtained from the Pharmacist Colleges General Council catalogue for drugs, healthcare costs databases from Soikos Institute and Oblikue Consulting [35–37]. The costs of inventory items, consumables, and changes made to the home were obtained from the patient/caregiver or by using publicly-available rates in the event that this information was not available from the patient. The costs of home modifications were estimates made by the patient's family. Time of care and supervision by formal caregivers were priced as an average cost of a sample of companies and/or associations which offer this type of service such as Home Instead Senior Care, A.E.A.D., and others. Other patient out-of-pocket expenses (transportation due to medical visit, patient's drugs or health resources, structural repairs at home as a consequence of the disease, etc.) were priced and their costs as patient/caregiver declared. Table 1 summarized main unitary costs used in the study.

Sensitivity analysis

A sensitivity analysis was carried out with the assigned cost of informal caregiver as this variable was considered to have the higher level of uncertainty and could be different that the one used from the own study. Then, the assigned cost in base case scenario was changed according with a recent review of informal cost in different regions of Spain [38]. Then, the maximum and the minimum values showed in that review were used as new scenarios. The highest price was 20.41 €/hour and the lowest prize was 7.32 €/hour, with an average price of 13.86 €/hour.

Statistical analysis

Descriptive statistics were applied to all variables, including measures of central tendency and of statistical variability for quantitative variables, as well as absolute and relative frequencies for qualitative variables. The Kolmogorov-Smirnov test was applied to test normality assumption of variables. First, the average monthly cost due to AD has been linked to patient-specific sociodemographic variables (age, gender, marital status, living arrangements, years of education, level of

Table 1
Unitary cost (€) and their sources of the healthcare and non-healthcare resources used in the study

Resource	Cost (€)			Source
Medical visits	Public		Private	Oblikue consulting database 2006
Primary care	10.58		40.0	
Geriatrician	108.18		150.0	
Neurologist	83.94		135.0	
Other specialist	48.44		142.5	
Hospitalization (Neurology ward per day)		251.0		Soikos cost database 2006
	Public	Semi-public	Private	
Geriatric care home (€/month)	772.0	754.5	1034.5	Average cost
Nursing home (€/month)	98.0	85.50	361.0	ECO study
Transportation (day)			7.0	ECO study
Complementary tests				
Blood test			25.7	Soikos cost database, 2006
Vitamin B12			16.8	
Folic acid			16.5	
Thyroid hormones: T3, T4 and TSH			25.5	
CT			113.7	
Liver function tests			13.0	
Neuropsychological examinations			46.7	
Kidney function			19.5	
Syphilis serology			12.0	
Urinalysis			3.6	
ECG (electrocardiogram)			19.3	
Chest x-ray			19.8	
EEG (electroencephalogram)			56.4	
MRI			343.7	
Brain SPECT			368.9	
HIV antibodies			33.2	
APOE4			22.6	
Lumbar tap			70.3	
Brain arteriogram			801.7	
PET (brain scanner)			900.0	
Caregiver time of care and supervision				
1 hour of care by professional caregiver			11.37	Home Instead Senior Care, AEAD, and others
1 hour of care by non-professional caregiver)			3.13	Median of caregiver monthly income from ECO Study
1 hour of supervision by professional caregiver			9.48	Home Instead Senior Care, AEAD, and others
1 hour of supervision by non-professional caregiver			3.13	Median of caregiver monthly income from ECO Study

education, and income); to the severity of AD (CDR, MMSE, BDRS) and their state of health (HUI-3); as well as caregiver-specific sociodemographic variables (age, gender, marital status, years of education, type of caregiver, monthly hours of care and supervision, income); state of health (HUI-3), and level of burden (ZARIT). The univariate General Linear Model has been used to make statistical inferences [39–41] using SPSS V 15 software and to link the monthly progression of costs over the course of the study to the clinical and sociodemographic variables collected in the study. The average total monthly cost has also been linked with variables which represent the daily amount of AD-specific drugs taken by the patient. The unit of measurement used has been the daily dose, given that

it is better understood from a clinical point of view and because in order to compare this variable to the dependent variable (over a one month period), one can simply multiply the dose by a constant (30 days) without changing the modeling results.

In addition, the univariate General Linear Model has also been used to relate the average monthly cost to the variables related to institutionalizing the patient and to attendance at day centers, the severity of AD and the patient's state of health, as well as the level of predictive value provided by the caregiver's general state of health and the caregiver's burden [39–42]. The level of severity of the patient's AD has been represented using CDR, MMSE, and BDRS scores [24–27]. The latter variable has been addressed on an overall basis and also

Table 2
Sociodemographics and clinic characteristics of patients ($n = 560$) in ECO study cohort and caregivers average time of care and supervision at baseline

Characteristic	Value
Gender; female (%)	381 (68.0)
Age (years)	76.74 ± 6.43
B.M.I. (kg/m^2)	25.92 ± 3.58
Marital status (%)	
Single	26 (4.6)
Married/Partner	290 (51.8)
Separated/Divorced	3 (0.5)
Widowed	237 (42.3)
Missing Data	4 (0.7)
Living arrangements (%)	
Alone	46 (8.2)
With partner or children	389 (69.5)
With relatives/neighbors/friends	32 (5.7)
In a nursing home	40 (7.1)
Others/missing data	53 (9.5)
Caregiver relationship (%)	
Spouse or partner	205 (36.6)
Spouse or partner and children	14 (2.5)
Children	210 (37.5)
Other family	35 (6.3)
Neighbors/friends/others	38 (6.8)
Missing data	58 (10.4)
Educational level (%)	
Illiterate in some degree	228 (40.7)
Primary studies	271 (48.4)
Intermediate or graduate studies	56 (10.0)
Others/missing data	5 (0.9)
Years of education: Mean $\pm$ S.D.	5.38 ± 3.88
New Diagnosis (%)	158 (28.9)
Clinical or health state scales (range)	
CDR Scale:0–3, Mean $\pm$ S.D.	1.14 ± 0.91
CDR first category (0–0.5) percent	37.7%
CDR second category (1–2) percent	53.4%
CDR third category (3) percent	8.9%
MMSE Scale (0–30), Mean $\pm$ S.D	18.06 ± 5.35
BDRS-T Scale (0-17) Mean $\pm$ S.D	9.68 ± 4.84
ZARIT Scale (0-88) Mean $\pm$ S.D	29.92 ± 15.46
HUI-3 Scale (0-1), Patient, Mean $\pm$ S.D	0.44 ± 0.31
HUI-3 Scale (0-1), Caregiver, Mean $\pm$ S.D	0.62 ± 0.34
Care and supervision time	
Weekly hours unpaid patient care, Mean $\pm$ S.D	31.05 ± 33.94
Weekly hours paid patient care, Mean $\pm$ S.D	2.41 ± 9.92
Weekly hours patient care total, Mean $\pm$ S.D	33.46 ± 36.09
Weekly hours unpaid patient supervision, Mean $\pm$ S.D	35.50 ± 38.05
Weekly hours paid patient supervision, Mean $\pm$ S.D	2.53 ± 11.49
Weekly hours patient supervision total, Mean $\pm$ S.D	38.03 ± 39.80

Values are mean $\pm$ standard deviation or percentages.

divided into its three components or sub-scales: Everyday activities, Habits and Personality, and Drive. Additionally, qualitative analysis of the CDR and MMSE variables was performed by summarizing the scores in the following intervals or categories: CDR; 0–0.5, 1–2 and 3, MMSE; > 19, 11–19, < 11 [40]. General state of health is represented by the HUI-3 score using the multi-attribute function values from the Spanish version of the scale [30] and the level of caregiver burden using the ZARIT scale score [28].

RESULTS

A total of 560 patients were recruited for the ECO study economic analysis. The primary sociodemographic and clinical characteristics at the time of inclusion of the patients can be seen in Table 2. The

Table 3
Last 6 months before baseline visit and yearly average monthly costs, overall and by item, throughout the study visits

Cost item (€year 2006)	Baseline	1–6 months	6–12 months	Yearly (1–12 months)
Non-healthcare resources				
Inventory materials	13.65 (61.8)	18.17 (73.3)	5.75 (15.6)	11.96 (44.4)
Nappies	1.15 (2.6)	9.16 (22.6)	12.18 (26.8)	10,67 (24.7)
Swabs and dressing materials	1.91 (7.3)	0.22 (0.8)	2.89 (10.0)	1.55 (5.4)
Remunerated care & supervision	153.51 (687.6)	166.86 (645.0)	362.92 (1,326.1)	264.89 (985.5)
Unpaid care & supervision	892.70 (842.3)	844.98 (781.9)	645.76 (646.0)	745.37 (713.9)
Housing structural reform	None	20.09 (144.9)	29.12 (206.3)	24.60 (175.6)
Total	1,062.9 (1,601.6)	1,059.5 (1,044.7)	1,058.6 (1,566.9)	1,059.0 (1,305.8)
Paid by patients or their family	1,061.76 (1,110.6)	1,050.36 (1,037.0)	1,046.44 (1,557.6)	1,048.40 (1297.3)
Financed by the public health system	1.15 (2.6)	9.16 (22.6)	12.18 (26.8)	10.67 (24.7)
Healthcare resources				
Main drugs	53.23 (64.07)	123.88 (48.32)	127.66 (43.91)	125.77 (46.11)
Medical visits by type of physician				
General practitioner	1.76 (7.12)	1.71 (6.82)	2.02 (8.30)	1.86 (7.56)
Geriatricians	5.61 (17.93)	3.10 (14.81)	3.19 (17.94)	3.14 (16.37)
Neurologist	9.54 (21.45)	6.52 (16.41)	5.88 (15.86)	6.20 (16.13)
Other specialist	1.96 (9.04)	1.17 (6.44)	0.92 (6.42)	1.04 (6.43)
Concomitant medication	4.71 (18.95)	5.67 (18.49)	7.98 (31.63)	6.82 (25.05)
Complementary and diagnostic tests	47.29 (45.54)	11.49 (27.66)	9.78 (21.15)	10.63 (24.41)
Hospitalizations (counting the last one)	4.03 (95.46)	16.14 (371.36)	1.79 (33.52)	8.96 (202.44)
Geriatric care homes	75.37 (270.43)	101.32 (328.36)	143.21 (391.30)	122.26 (359.83)
Nursing home[1]	43.68 (145.07)	65.18 (176.14)	76.07 (220.35)	70.62 (198.24)
In-home sanitary care	5.64 (44.25)	6.05 (43.19)	10.59 (118.79)	8.32 (81.00)
Other professional care	0.48 (11.33)	0.84 (16.35)	1.17 (17.27)	1.00 (16.81)
Total	253.31 (326.21)	343.06 (521.37)	390.25 (453.77)	366.66 (587.57)
Paid by the patients or their family	123.38 (299.38)	169.46 (359.14)	222.18 (426.36)	195.82 (392.75)
Financed by the public health system	129.93 (135.37)	173.60 (379.32)	168.07 (145.47)	170.84 (262.40)
Overall costs	1,316.22 (1927.81)	1,402.58 (1189.05)	1,448.87 (1642.57)	1,425.73 (1415.81)
Paid by patients or their family	1,185.14 (1,137.2)	1,219.82 (1,062.5)	1,268.62 (1,608.8)	1,244.22 (1,335.6)
Financed by public health system	131.08 (135.69)	182.76 (381.95)	180.25 (154.65)	181.51 (268.3)

[1]Including transportation to the centre when needed. Values are expressed as mean (standard deviation).

68% were women with an average age of almost 77 years, more than half (51.8%) were married or lived with a partner, while 42.3% were widows/widowers. The 69.5% lived with family, either with their partner or children. The primary types of relationship between the patients and their caregivers at the initial visit were filial (37.5%) and marital (36.6%). An 89.1% of the sample did not have higher than a primary school level of education, with almost half of this group showing some level of illiteracy. Almost 29% of the sample was diagnosed with AD on the initial visit with the majority, 53.4%, being at an average severity-level of moderate, that is, a CDR score between 1 and 2 points (see Table 2).

The results highlight the fact that, on average, more time is dedicated to supervision than to care. This is in keeping with the patient's average condition at a given visit as well as a much higher level of dedication, both in care and in supervision, on the part of unpaid caregivers (Table 2).

Table 3 shows the average long-term monthly cost of study costs, total and separated in their primary com-

ponents. The higher cost corresponds to the portion of care and supervision performed by unpaid personnel and approaches a total 12-month period average of almost 745.37/month, having shown a progressive reduction over the length of the study of 5.35% and 27.66% at 6 and 12 months respectively when compared to the baseline value. This reduction is offset by the incorporation of the paid professional caregiver in the care of the patient, substituting the care performed by informal caregivers. Additionally, a higher tendency to institutionalize the patient and greater use of day centers may be part of the reason for the change in the makeup of the cost components with hardly any change in the patient's total cost over the course of the study. It also shows that the burden of the average monthly cost of inventory items, consumables, and structural reforms performed in the home due to AD is very low when compared to the portion dedicated to patient care and supervision.

On the other hand, the incongruity between the proportion of the final cost paid for by the public healthcare system and that paid by the patient or their family is very

Table 4
Overall last 6 months average monthly costs throughout the study visits by patient's sociodemographic characteristics

Sociodemographic parameter		Baseline	6 months	12 months
	50–59	1555.2 (680.7)	1411.0 (501.9)	1452.9 (780.6)
	60–69	1233.9 (908.3)	1156.1 (918.8)	1074.9 (1143.7)
	70–79	1494.9 (179.6)	1358.3 (1096.3)	1388.3 (1336.0)
Age group	80–89	1728.1 (1265.5)	1716.4 (1450.1)	1809.8 (2199.0)
	90–99	1913.2 (873.8)	1920.4 (1095.3)	2014.9 (1171.2)
	R^2 (p value)	0.017 (0.224)	0.027 (0.105)	0.022 (0.016)
	Male	1501.5 (1016.2)	1303.7 (935.9)	1216.6 (1016.7)
Gender	Female	1576.6 (1245.2)	1533.5 (1313.1)	1629.8 (1868.7)
	R^2 (p value)	0.001 (0.043)	0.008 (0.010)	0.014 (0.000)
	Single	1361.2 (1072.7)	1202.8 (1155.5)	1662.7 (2039.3)
	Married/Partner	1567.7 (1154.1)	1443.5 (1065.5)	1394.2 (1321.4)
Marital Status	Separated/Divorced	606.0 (575.3)	816.2 (452.0)	489.4 (401.8)
	Widowed	1577.0 (1221.0)	1521.8 (1380.1)	1632.5 (1962.4)
	R^2 (p value)	0.005 (0.891)	0.005 (0.453)	0.007 (0.075)
	Alone	1093,7 (997,4)	1047,9 (954,8)	1264,1 (1574,1)
	Partner or children	1586,5 (1070,9)	1508,7 (1192,8)	1509,4 (1616,6)
Living Arrangements	Family/Neighbors/Friends	1867,7 (1685,3)	1440,6 (1462,3)	1715,7 (2090,2)
	Residence	1815,3 (1879,7)	1701,6 (1664,1)	1931,7 (2368,0)
	R^2 (p value)	0.022 (0.012)	0.014 (0.164)	0.007 (0.205)
	Illiterate	1401.2 (849.3)	1439.6 (887.3)	1238.1 (961.6)
	Functional Illiterate	1703.3 (1389.1)	1617.7 (1267.6)	1676.9 (2023.1)
	Primary School	1501.3 (1101.1)	1401.1 (1272.0)	1461.5 (1562.2)
	Technical, other non-regulated	1394.7 (697.4)	1280.8 (699.2)	1437.6 (1009.4)
Level of Education	Teaching, Mid-level Career	1217.1 (510.2)	999.4 (614.9)	926.4 (543.9)
	Graduate School	1798.1 (1679.6)	1539.7 (1421.2)	1470.3 (1747.7)
	Unknown	1292.6 (845.5)	1016.9 (344.8)	948.3 (605.3)
	R^2 (p value)	0.012 (0.226)	0.012 (0.182)	0.009 (0.260)
	< €360/month	1594.6 (884.8)	1601.4 (1449.7)	1578.7 (1541.9)
	€361–601/month	1713.8 (1384.8)	1541.5 (1260.2)	1647.0 (2113.8)
	€602–901/month	1557.7 (1005.4)	1441.1 (1009.7)	1337.6 (1125.3)
Patient's income	€902–1202/month	1386.8 (669.6)	1304.0 (808.9)	1182.7 (806.0)
	€1203–1803/month	1295.5 (1151.5)	945.9 (854.4)	1264.6 (1327.9)
	> €1803/month	2443.0 (1998.6)	2108.3 (1590.3)	1980.9 (1925.2)
	R^2 (p value)	0.021 (0.000)	0.017 (0.245)	0.010 (0.133)

Values are means (Standard deviation).

noticeable. In large part, the public healthcare system only finances 1.00% of non-healthcare resources while it covers 49.5% of healthcare resources. Consequently, it is not unusual for the 88% total average monthly cost of the disease to be absorbed by the patient or their family. Note that non-healthcare costs constitute the largest component in the cost of managing AD.

Regarding the patient's sociodemographic variables (Table 4), it is noted that the patient's age group does not play an important role in the average monthly cost due to AD at the baseline visit or at 6 months, while at 12 months it increases to 2.2% which, though low, is statistically significant. Additionally, it is noted that women show a higher average monthly consumption than men at all study visits, particularly at 6 and 12 months of follow-up. Although significant differences in total cost are seen at the initial visit according to the patient's living arrangements and income range, these variables, including the patient's level of education and

marital status, nevertheless had a statistically significant predictive value for the total cost of AD despite the seeing lower numerical values in separated/divorced patients and in patients who live alone (Table 4).

The results of the total average monthly costs for AD as they relate to the caregiver's sociodemographic variables are shown in Table 5. From these, one can see that both the caregiver's total level of education, as well as the type of caregiver, their marital status and income have a low (under 10% in all cases) but statistically significant predictive value for the average total monthly cost of AD over the course of almost all study visits (Table 5). As such, when the caregiver is a spouse or partner, divorced/separated, or has a university level of education, the monthly cost is higher. The type of caregiver is the most important variable of the sociodemographic variables that describe the primary caregiver together with the variable that describes the caregiver's own income. The average total cost is greater in the

Table 5
Overall last 6 months average monthly costs throughout the study visits by main caregiver's sociodemographic characteristics

Sociodemographic parameter		Baseline	6 months	12 months
	< 50	1486.1 (1240.2)	1406.2 (1454.2)	1371.3 (1327.3)
	50–59	1678.9 (1164.2)	1523.7 (1080.1)	1671.4 (2198.5)
	60–69	1488.0 (1055.3)	1402.0 (1043.9)	1400.6 (1541.0)
Age Group	70–79	1560.6 (1134.5)	1452.2 (1050.8)	1403.2 (1362.0)
	80–89	1653.7 (953.5)	1692.1 (1277.0)	1832.2 (1840.8)
	90–99	3528.8 (..........)	3558.8 (...........)	3864.5 (...........)
	R^2 (p value)	0.010 (0.747)	0.010 (0.749)	0.013 (0.171)
	Male	1605.9 (1174.3)	1557.0 (1142.0)	1648.8 (1940.3)
Gender	Female	1559.6 (1212.0)	1447.5 (1271.3)	1451.4 (1583.7)
	R^2 (p value)	0.000 (0.380)	0.002 (0.882)	0.003 (0.156)
	Married	1526.1 (1076.0)	1451.0 (1181.1)	1475.2 (1582.9)
	Single	1724.8 (1434.2)	1573.3 (1339.8)	1489.7 (1686.8)
	Widowed	1501.3 (851.6)	1449.6 (1275.0)	1887.8 (2611.5)
Marital Status	Separated	1463.5 (1029.5)	1722.9 (1241.4)	1309.5 (953.3)
	Divorced	3284.4 (3106.4)	1849.9 (2177.4)	2113.5 (2777.8)
	Unknown	1872.3 (2245.7)	1633.2 (1872.5)	1956.6 (3085.4)
	R^2 (p value)	0.025 (0.000)	0.003 (0.252)	0.005 (0.047)
	None	1465.9 (941.1)	1501.5 (1070.1)	1382.0 (1128.5)
	Primary School	1507.2 (1055.4)	1424.3 (1267.0)	1374.2 (1469.1)
Level of Education	Secondary	1587.4 (1265.8)	1445.7 (1090.9)	1556.9 (1545.5)
	University	1944.9 (1487.2)	1788.7 (1345.0)	2172.5 (2871.0)
	R^2 (p value)	0.011 (0.009)	0.007 (0.137)	0.018 (0.001)
	Spouse	1093.81 (882.95)	1097.64 (887.24)	884.95 (811.67)
	Children	1079.77 (1015.13)	1079.61 (1001.53)	1096.52 (1691.34)
	Family	725.10 (956.93)	777.50 (1096.85)	885.12 (1510.80)
Type of Caregiver	Spouse+Children	1949.63 (2006.87)	1886.22 (1943.17)	2488.05 (2969.34)
	Close Friends	1093.81 (1687.50)	799.38 (1237.74)	1113.28 (2141.46)
	R^2 (p value)	0.028 (0.007)	0.029 (0.006)	0.032 (0.003)
	Working	1598.0 (1349.8)	1425.2 (1183.0)	1537.1 (1999.5)
	Retired	1649.2 (1106.9)	1594.5 (1180.7)	1559.3 (1562.6)
	Widowed/Disabled	1329.1 (687.9)	1227.2 (679.7)	1160.1 (950.6)
Employment Situation	Unemployed	1676.5 (1143.8)	1736.6 (983.7)	1285.1 (916.5)
	Student	2073.9 (...........)	1633.1 (..........).	1452.9 (..........)
	Self-employed	1492.9 (1090.7)	1415.4 (1329.1)	1488.9 (1539.8)
	R^2 (p value)	0.007 (0.095)	0.009 (0.296)	0.004 (0.421)
	< €360/month	1396.4 (705.6)	1271.2 (760.7)	1217.1 (1006.0)
	€361-601/month	1595.5 (1194.8)	1531.8 (1108.3)	1390.0 (1293.7)
	€602-901/month	1521.3 (1049.4)	1451.1 (1048.5)	1460.1 (1426.8)
	€902-1202/month	1912.0 (1496.3)	1825.4 (1887.4)	1837.1 (2170.8)
Primary Caregiver's Income	€1203-1803/month	1560.7 (1108.9)	1616.1 (1199.6)	1604.5 (1615.0)
	> €1803/month	2040.4 (1672.8)	1611.6 (1332.8)	2224.5 (3544.9)
	Unknown	1396.4 (705.6)	1271.2 (760.7)	1217.1 (1006.0)
	R^2 (p value)	0.029 (0.001)	0.021 (0.002)	0.025 (0.000)

Values are means (Standard deviation).

three visits when the caregiver responsibilities fall on the spouse together with the patient's children. At the baseline visit, this variable explains 2.8% of the total cost, while it explains 2.9% at 6 months and 3.2% at 12 months.

The average total monthly costs due to AD at the different study visits as they related to the clinical variables for AD are shown in Fig. 1. From the results, it may be observed that the MMSE score has a modest (under 5%) but statistically significant predictive value for the average monthly cost at least at the baseline

visit and at 12 months, while the classification on the CDR scale does not show a statistical association with costs. Nevertheless, the indicator for clinical severity that appears to have the greatest predictive and significant value for the total cost is the BDRS score, which is used as a quantitative variable. Total BDRS explains 14.7% ($R^2 = 0.147$) of the total cost at the baseline visit, 13.1% ($R^2 = 0.131$) at 6 months, and 11.1% ($R^2 = 0.111$) at 12 months, with correlation coefficients between 0.33 and 0.38 ($p < 0.001$ in all cases; Fig. 1). By components of the scale, each of them separately
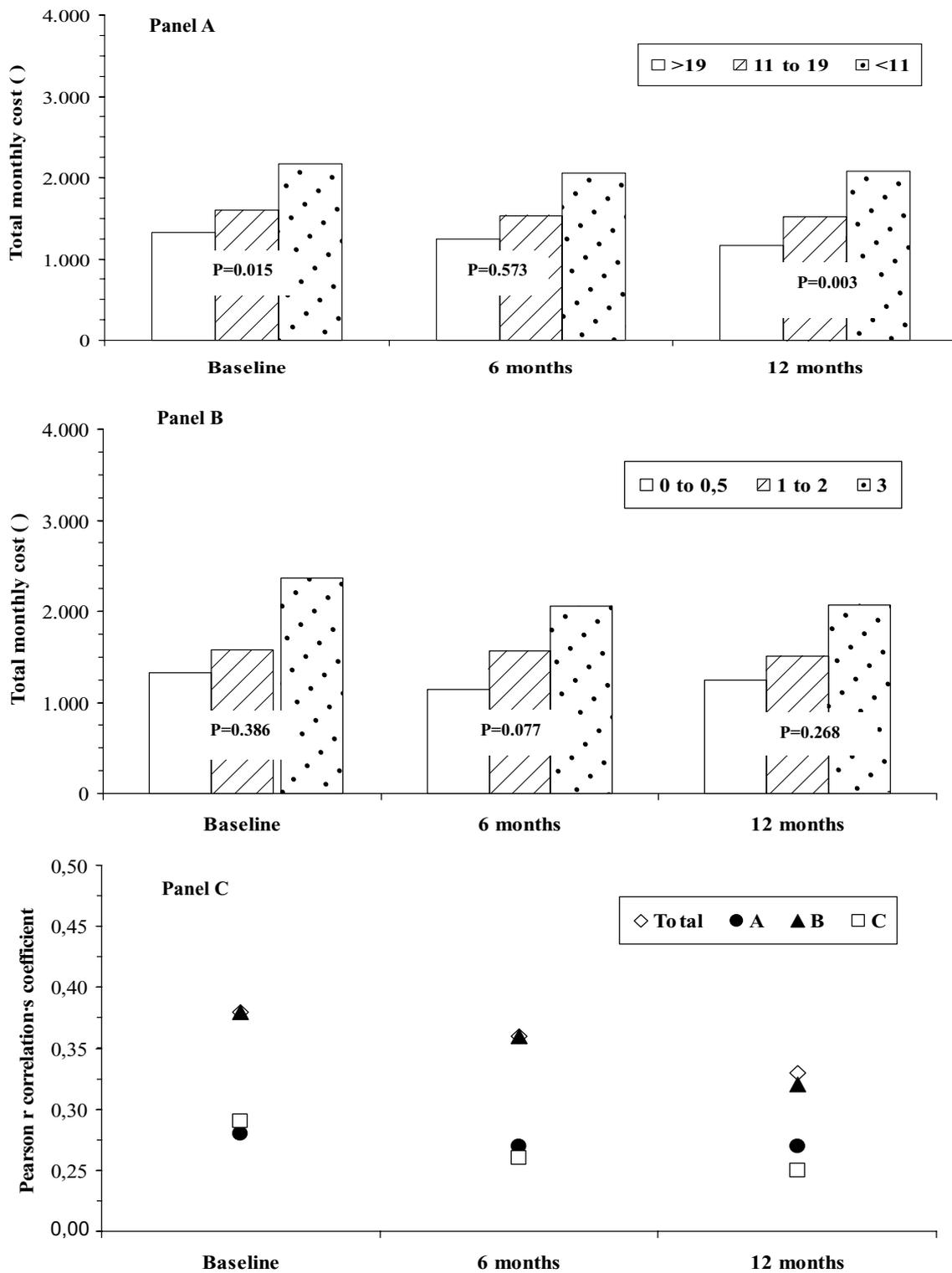
Fig. 1. Last 6 months average total monthly costs throughout the study visits by severity of dementia as assessed by MMSE (panel A) and CDR (panel B) scales, and Pearson correlation with total and sub-scales of the BDRS (panel C). All Pearson r correlation coefficients significant at level of $p < 0.001$. MMSE=MiniMental State Examination, CDR=Clinical Dementia Rating Scale, BDRS=Blessed Dementia Rating Scale.

Table 6
Univariate general linear models showing the predictive ability of healthcare and non-healthcare resources to explain total monthly costs at 6 and 12 months of the study

Parameter	β Coefficient	Std. Error	t	Sig.	95% CI	
		6 months				
Intercept	114.676	26.607	4.310	0.000	62.344	167.008
Geriatric care home						
Public	876.229	296.869	2.952	0.003	292.335	1460.123
Private	1035.606	129.016	8.027	0.000	781.852	1289.361
Semi-private	901.279	274.453	3.284	0.001	361.473	1441.085
Medical visits	104.992	28.113	3.735	.000	49.698	160.286
Medical tests	58.068	5.379	10.796	0.000	47.489	68.647
Hospitalization (days)	875.210	275.259	3.180	0.002	333.818	1416.602
Inventory materials	56.057	17.275	3.245	0.001	22.079	90.035
Time of care/supervision	3.265	0.066	49.274	0.000	3.135	3.396
Main caregiver	7.006	0.205	34.144	0.000	6.602	7.409
Professional caregiver	6.075	2.304	2.637	0.009	1.544	10.606
Volunteers	5.301	1.479	3.585	0.000	2.393	8.209
Public organizations						
Nursing home (hours)	2.821	0.297	9.508	0.000	2.237	3.404
Adjusted $R^2 = 0.941$						
		12 months				
Intercept	1303.107	68.444	19.039	0.000	1153.980	1452.235
Time of care/supervision	2.054	0.216	9.503	0.000	1.583	2.525
Main caregiver	10.235	0.214	47.837	0.000	9.769	10.701
Professional caregiver	3.454	0.394	8.770	0.000	2.596	4.312
Public organizations						
Medical visits	116.107	49.529	2.344	0.037	8.192	224.021
Medical tests	98.520	22.135	4.451	0.001	50.292	146.748
Adjusted $R^2 = 0.995$						

maintains significant correlation with costs, although their separate predictive value is lower (Fig. 1). Taken together, the total BDRS is the most important clinical indicator of the patient's level of severity and has the highest predictive value for average total cost at each study visit. Neither the HUI-3 scale, for both patient and caregiver, nor the ZARIT shows any statistically significant predictive value for the patient's total monthly cost for AD.

The univariate General Linear Model with all possible predictive values (Table 6) shows that resulting models, at 6 and 12 months, with an increased predictive ability for the total cost of AD at these visits: $R^2 = 0.941$ and 0.995, respectively. It should be pointed out that at both 6 and 12 months, the time for care and supervision provided to the patient by all types of caregivers, and the number of medical visits and complementary medical tests is statistically associated with the total monthly cost in these visits. Additionally, at the 6 month visit, the number of days' hospitalization, the use or non-use of inventory items and the number of hours at day centers, as well as the type of geriatric residence, is statistically associated with the total average monthly cost of AD.

Sensitivity analysis

The sensitivity analysis carried out to vary the cost per hour of informal care with values extracted from other sources outside the own study is shown in Fig. 2. As could be expected total monthly costs were substantially higher than in base scenario, with increasing proportion of cost paid by the own family. However, the analysis showed the observed moderate increasing trend of total cost a long the time of the study in the three new scenarios.

DISCUSSION

The certainty that social care and health care of AD involves an elevated cost in Western countries [2–6, 18–21] and that an estimation from a purely transverse perspective is limited, justifies that an approach to AD using a prospective follow-up of a wide and representative cohort of patients and their caregivers will be more reliable for estimating the most accurate actual cost of the disease. The ECO study falls within this paradigm which, in addition to calculating the prospective cost of AD, has tried to address a group of five working hypotheses stated at the beginning of this arti-
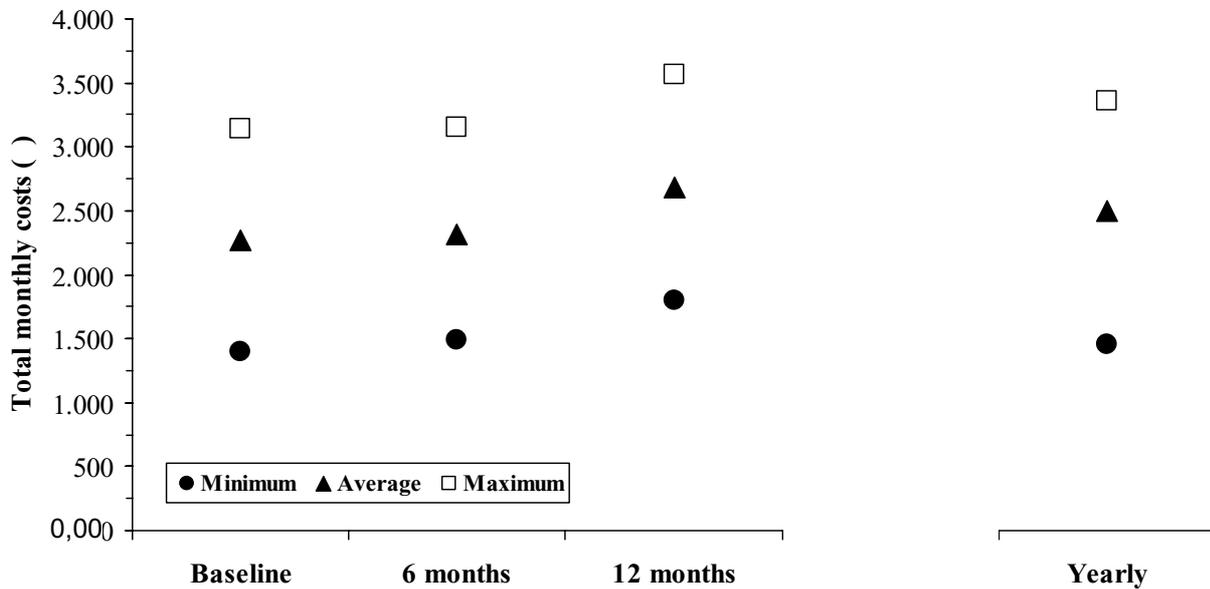
Fig. 2. Sensitivity analysis changing the cost per hour of informal care across minimum, average and maximum values observed in different regions of Spain, by visit and overall (yearly).

cle. These hypotheses serve to contrast to what extent the total monthly cost of healthcare and non-healthcare resources required for AD in Spain are derived from 1) the specific diagnostic-therapeutic management that the patient receives; 2) patient follow-up in medical institutions (outpatient consultations, institutionalization, attendance at day centers, etc.); 3) clinical deterioration of the disease; 4) patient and primary caregiver sociodemographic characteristics; and 5) the time dedicated to patient care and supervision. Monthly overall mean cost of dementia of AD type was high in Spain.

The ECO study has shown that the average total monthly cost per patient of AD during the study period, including healthcare and non-healthcare resources, is approximately €1,425/month (€17,109 per year), with a slight increase of 10.08% from the beginning of the study (€1,316.22) and the end of the study after 12 months of follow-up (€1,448.87), primarily due to a higher increase in healthcare resources including the use of AD-specific drugs. The non-healthcare costs, though greater in total volume, remained essentially unchanged over the course of this one-year study. The first hypothesis, as it relates to diagnostic management, also appears to have been confirmed. The use of these healthcare resources, and therefore the cost, is significantly associated with the average monthly cost at both 6 and 12 months, as calculated from the results shown in Table 7.

The second hypothesis is clearly confirmed in the previous period at the 6 month visit as follows: Total cost depends significantly on the type of residence to which the patient is admitted in the period prior to the 6 month visit, increasing more on average in case of private residence, less when it is subsidized, and least for public ones. This explains the different rates applied by these institutions according to level of social dependence. In the longitudinal study by Zhu and colleagues, a higher cost for institutionalized patients versus those who lived at home was also seen [43]. The number of visits, hospital admissions, and visits to day centers was also significantly associated with the cost of the disease during this period. However, only the medical visits confirm the second *a priori* hypothesis at 12 months.

For the third hypothesis, the level of clinical deterioration evaluated with the scales used in the study do not appear to predict or explain the costs of the disease in the presence of the variables that measure utilization of the healthcare resources, that is, the univariate analysis shown in Fig. 1 shows that greater deterioration according to the MMSE score is associated with a significantly higher cost for the disease, at least at the baseline visit and at 12 months, and that the deterioration in activities of daily living and patient behavior according to the BDRS correlates strongly with the total costs of the disease at all visits, particularly in the total score on the scale and sub-scale that measures deterioration of the patient's habits, in such a way that greater deterioration correlates with greater cost, as is seen in the published

scientific literature [43,44]. As a result, the total cost of AD appears to be better explained by the greater use of healthcare and non-healthcare resources that may be associated with the patient's severity as measured by the evaluation scales used in this study, and has been observed previously in other studies published in the literature that have associated the severity of the disease with its cost [2,3,13,45–48].

The fourth proposed hypothesis is confirmed, though not by the data relative to 6 or 12 months. Variables related to the patient's or caregiver's sociodemographic characteristics enter into the predictive model. As a result, the total cost of AD does not depend on gender, age, and level of education, living arrangements, income, or any other variable recorded in the ECO study that describes the characteristics of the patient or the primary caregiver. Nevertheless, it should be pointed out that in the case of evaluation scales, the univariate analysis shows some significant differences according to the patient's and primary caregiver's sociodemographic characteristics. In this regard, the type of caregiver and their level of education or income appear to show significant differences constantly over the course of the study in total cost of the disease, as well as for female patients, a finding that was also observed in the Predictors study by Zhu et al. [49]. While the presence of comorbidities has been associated with an incremental cost for AD [50,51], or the patient's caregiver not living with the patient [49], we have nevertheless not found any study that has observed a significant association between the use of healthcare resources and the caregiver's level of education and income. This should be an issue to study in future studies in this area since we have not found a relationship between a caregiver who lives or doesn't live with the patient.

Finally, the fifth hypothesis clearly confirms, both at the 6 month visit as well as at 12 months, that the number of hours for care and supervision of the patient spent by the primary caregiver, family, friends and neighbors, is the variable with the highest predictive value for total cost, which is congruent with previously published data [18–21,52,53]. This is sensitive to the cost per hour attributed in the analysis and depending on the own patient and family earnings as could be observed in the sensitivity analysis. Additionally, it also confirms that the number of hours of patient care and supervision carried out by paid caregivers represents the variable with the second highest predictive value for the total cost in the period prior to 6 months and the highest in the period prior to 12 months. This confirms that the family of patients with AD show a loosening,

though slight, in the number of informal (the patient's family) care/supervision hours to other more formal (professional caregivers) on a par with the deterioration of the disease. From this result, one can extrapolate that professional caregivers, generally paid by the family, are those that should receive greater intervention when the lack of knowledge, experience or fatigue exhaust the possibilities of offering adequate care to the patient by unpaid caregivers, data also observed in the longitudinal study by Zhu et al. [49]. One would expect this result to be accompanied by confirmation that, as the patient's situation worsens, the participation of professional and paid caregivers is needed more. However, the variables that measure the patient's state of health do not appear to be significant in the multiple models, such that this hypothesis can only be confirmed on an individual level in the results of the univariate analysis used with the clinical progress variables.

On the other hand, we cannot fail to point out that, as another important finding in the study, that the majority of the cost of AD falls to the patient's family; 88% of the total costs in this study, with a slight decrease of around 3% over the course of the study explained by increased use of specific medication financed by the public system. This also occurs with the cost of this disease in other developed economies such as the US [53] or the United Kingdom [54].

The ECO study does not have precedent in Spain in either its design or complexity as it involves so many variables that it practically covers the entire gamut of variables related with calculating the cost of AD. There may be some items or resources that were not included, but their impact would be marginal. That which would really have an effect on the cost has been rightfully considered. Perhaps a limitation to consider is the monetary assignment at the time of care and supervision by informal caregivers which may not be adequate in that it may be less than what is really being paid in daily life. In this case, our estimations will have been conservative. The effort in carrying out this field study has been enormous and complex, but the results obtained make it worthwhile and will allow for advances in the study of the social cost of AD from several points of view. Nevertheless, it should not be forgotten that the ECO study, though designed longitudinally and prospectively, only covered 12 months of follow-up, which may be a short study period for a disease that involves slow, progressive deterioration and requires longer follow-up such as in the study by Zhu et al. [43], in order to more accurately capture the dynamics of resource utilization in this disease. Also, and in accordance with the sensi-

tivity analysis, the cost imputed to informal care seems to be the more sensitive variable in this type of analysis. Then, the total cost observed in the base case scenario could be even higher depending of the cost considered for informal care. In any case, and in conclusion of this study, the prospective cost of AD in Spain is considerably high, with special emphasis on the fact that the majority of its cost is not covered by the public health system but rather by the patient or their family. Given that the prevalence of AD increases dramatically with the gradual aging of the population, we believe that, from a political and social point of view, care of the patient with AD, and their family, constitutes a very important health subject and needs special attention by all healthcare decision-makers. Therefore, the most obvious point is that a much greater level of support in care and supervision studies on the part of the national healthcare system is needed, and that greater investment in information and training of specialized personnel is necessary in the treatment of these patients who, in many instances, may received poor care due to a lack of resources and knowledge on the part of their regular caregivers.

ACKNOWLEDGMENTS

REFERENCES

[1]   Perkins P, Annegers JF, Doody RS, Cooke N, Aday L, Vernon SW. (1997) Incidence and prevalence of dementia in a multiethnic cohort of municipal retirees. *Neurology* **49**, 44-50.

[2]   Boada M, Peña-Casanova J, Bermejo F, Guillén F, Hart WM, Espinosa C, Rovira J (1999) Coste de los recursos sanitarios de los pacientes en régimen ambulatorio diagnosticados de enfermedad de Alzheimer en España. *Med Clin* (*Barc*) **113**, 690-695.

[3]   Leon J, Cheng C, Neumann P (1998) Alzheimer's disease care: cost and potential savings. *Health Affairs* (*Millwood*) **17**, 206-216.

[4]   Huang L, Cartwright W, Hu T (1988) The economic cost of senile dementia in the United States. *Public Health Rep* **103**, 3-7.

[5]   Trabucchi M (1999) An economic perspective on Alzheimer's disease. *J Geriatr Psychiatry Neurol* **12**, 29-38.

[6]   McDaid D (2001) Estimating the costs of informal care for people with Alzheimer's disease: methodological and practical challenges. *Int J Geriatr Psychiatr* **16**, 400-405.

[7]   Brookmeyer R, Gray S, Kawas C (1998) Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. *Am J Pub Health* **88**, 1337-1342.

[8]   García FJ, Sánchez MI, Pérez A, Martín E, Marsal C, Rodríguez Ferrer G, García C, Romero L, Rodríguez MJ, Gutiérrez G (2001) Prevalencia de demencia y de sus subtipos principales en sujetos mayores de 65 años: efecto de la educación y ocupación. Estudio Toledo. *Med Clín* (*Barc*) **116**, 401-407.

[9]   Bermejo F, Gabriel R, Vega S, Morales JM, Rocca WA, Anderson DW (2001) Neurological Disorders in Central Spain (NEDICES) Study Group. The prevalence of dementia and cognitive impairment in three sites in central Spain. A door-to-door study in the elderly. *Neuroepidemiology* **20**, 225-31.

[10] Pi J, Olivé JM, Roca J, Masana LL (1996) Prevalence of dementia in a semi-rural population of Catalunya, Spain. *Neuroepidemiology* **15**, 33-41.

[11] López-Pousa S, Llinàs-Regla J, Vilalta-Franch J, Lozano L (1995) Prevalencia de la demencia en Girona. *Neurología* **10**, 189-193.

[12] Atance-Martínez JC, Yusta-Ízquierdo A, Grupeli-Gardel BE (2004) Estudio del coste en la enfermedad de Alzheimer. *Rev Clin Esp* **204**, 64-69.

[13] López-Sousa S, Garre-Olmo J, Expósito I, Lozano-Gallego M, Hernández-Ferrándiz M, Gelada-Batlle E, Pericot-Nierga I, Vilalta-Franch J (2004) Análisis de los costes de la enfermedad de Alzheimer en función del deterioro cognitivo y funcional. *Med Clín* (*Barc*) **20**, 767-772.

[14] Casado D (2000) Los efectos del envejecimiento demográfico sobre el gasto sanitario: mitos y realidades. *Gac Sanit* **15**, 154-163.

[15] Instituto Nacional de Estadística (2006) Ministerio de Trabajo y Asuntos Sociales. http://www.ine.es/daco/daco42/etcl/etcl0206.pdf, Accessed September 18, 2009.

[16] Bonner L, Peskind E (2002) Pharmacologic treatment of dementia. *Med Clin North Am* **86**, 657-674.

[17] Jann M, Shirley K, Small G (2002) Clinical pharmacokinetics and pharmacodynamics of cholinesterase inhibitors. *Clin Pharmacokinet* **41**, 719-739.

[18] Wimo A, Ljunggren G, Winblad B (1997) Costs of dementia and dementia care: a review. *Int J Geriatr Psychiatry* **12**, 841-856.

[19] Wimo A, Jonsson L, Winblad B (2006) An estimate of the worldwide prevalence and direct costs of dementia in 2003. *Dement Geriatr Cogn Disord* **21**, 175-181.

[20] Kronborg Andersen C, Søgaard J, Hansen E, Kragh-Sørensen A, Hastrup L, Andersen J, Andersen K, Lolk A, Nielsen H,

Kragh-Sørensen P (1999) The cost of dementia in Denmark: the Odense Study. *Dement Geriatr Cogn Disord* **10**, 295-304.

[21] Gutiérrez-Iglesias MA, Aizpurua-Imaz I, Moracho del Río O, Asua-Batarrita J (2000) Análisis de las escalas de medición, eficacia de los tratamientos e impacto sociosanitario de la enfermedad de Alzheimer en el País Vasco. *Med Clin* (*Barc*) **114** (Suppl 3), 93-98.

[22] World Medical Association (2008) Policy: World Medical Association Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. http://www.wma.net/e/policy/b3.htm, Accessed September 18, 2009.

[23] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA work group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology* **34**, 939-944.

[24] Morris JC (1993) The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology* **43**, 2412-2414.

[25] Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12**, 189-198.

[26] Blesa R, Pujol M, Aguilar M, Santacruz P, Bertran-Serra I, Hernandez G, Sol JM, Pena-Casanova J (2001) Clinical validity of the 'mini-mental state' for Spanish speaking communities. *Neuropsychologia* **39**, 1150-1157.

[27] Blessed G, Tomlinson B, Roth M (1968) The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. *Br J Psychiatry* **114**, 797-811.

[28] Zarit SH, Reever KE, Bach-Peterson J (1980) Relatives of the impaired elderly: correlates of feelings of burden. *Gerontologist* **20**, 649-655.

[29] Feeny D, Furlong W, Boyle M, Torrance GW (1995) Multi-attribute health status classification systems. Health Utilities Index. *Pharmacoeconomics* **7**, 490-502.

[30] Ruiz M, Rejas J, Soto J, Pardo A, Rebollo I (2003) Adaptation and validation of the Health Utilities Index Mark 3 into Spanish and correction norms for Spanish population. 120, 89-96.

[31] Wimo A, Wetterholm AL, Mastey V, Winblad B (1998) Evaluation of the healthcare resource utilization and caregiver time in anti-dementia drug trials. In Health Economics of Dementia, Wimo A, Jönsson B, Karlsson G, Winblad B (eds). Chichester, Wiley, pp. 465-477.

[32] Rejas J, Del Llano J López-Arrieta JM, Frank A, Bermejo F, y León T (2005) Validación de un instrumento (Batería ECO) para la evaluación del coste y carga de la enfermedad de Alzheimer (EA). *Neurología* **20**, 441-442.

[33] Brower W, Rutten F, Koopmanschap M (2001) Costing in economics evaluations. In Economic evaluation in health care, Drummond M, McGuire A (eds). Oxford University Press, pp. 69-93.

[34] Smith K, Wright K (1994). Informal care and economic appraisal: a discussion of possible methodological approaches. *Health Economics* **3**, 137-148.

[35] Oblikue Consulting (2007) Oblikue cost database year 2006. http://www.oblikue.com/bddcostes/, Accessed September 18, 2009.

[36] SOIKOS (2006) Database: Centro de Estudios en Economía de la Salud y Política Social. Base de datos de costes sanitarios. Versión 2.2. Barcelona 2006.

[37] Catálogo de Especialidades Farmacéuticas de 2006. Consejo General de Colegios Oficiales de Farmacéuticos de España. Madrid 2006.

[38] Larrañaga I, Martín U, Bacigalupe A, Begiristáin JM, Valderrama MJ, Arregi B (2008) Impacto del cuidado informal en la salud y la calidad de vida de las personas cuidadoras: análisis de las desigualdades de género. *Gac Sanit* **22**, 443-450.

[39] Uriel E, Contreras D, Moltó ML, Peiró A (1990) Econometria: el modelo lineal. Valencia, Editorial AC 412.

[40] Green WH (2003) Econometric Analysis, 5th edition. New Jersey, Prentice Hall 995.

[41] Pindyck RS, Rubinfeld DL (1998) Econometric Models and Economic Forecast, 4th edition. New York, McGraw-Hill. 520.

[42] Fillit HM, Doody RS, Binaso K, Crooks GM, Ferris SH, Farlow MR, Leifer B, Mills C, Minkoff N, Orland B, Reichman WE, Salloway S (2006) Recommendations for best practices in the treatment of Alzheimer's disease in managed care. *Am J Geriatr Pharmacother* **4** (Suppl A), S9-S24.

[43] Zhu CW, Scarmeas N, Torgan R, Albert M, Brandt J, Blacker D, Sano M, Stern Y (2006) Longitudinal study of effects of patient characteristics on direct costs in Alzheimer disease. *Neurology* **67**, 998-1005.

[44] Zhu CW, Scarmeas N, Torgan R, Albert M, Brandt J, Blacker D, Sano M, Stern Y (2006) Clinical characteristics and longitudinal changes of informal cost of Alzheimer's disease in the community. *J Am Geriatr Soc* **54**, 1596-1602.

[45] Hux MJ, O'Brien BJ, Iskedjian M, Goeree R, Gagnon M, Gauthier S (1999) Relation between severity of Alzheimer's disease and costs of caring. *CMAJ* **30**, 1390-1392.

[46] Bianchetti A, Castelletti F, Trabucchi M (2002) Costs of dementia. *Br J Psychiatry* **181**, 533-534.

[47] Wolstenholme J, Fenn P, Gray A, Keene J, Jacoby R, Hope T (2002) Estimating the relationship between disease progression and cost of care in dementia. *Br J Psychiatry* **181**, 533-534.

[48] Rigaud AS, Fagnani F, Bayle C, Latour F, Traykov L, Forette F (2003) Patients with Alzheimer's disease living at home in France: costs and consequences of the disease. *J Geriatr Psychiatry Neurol* **16**, 140-145.

[49] Zhu CW, Torgan R, Scarmeas N, Albert M, Brandt J, Blacker D, Sano M, Stern Y (2008) Home health and informal care utilization and costs over time in Alzheimer's disease. *Home Health Care Serv Q* **27**, 1-20.

[50] Fillit H, Hill JW, Futterman R (2002) Health care utilization and costs of Alzheimer's disease: the role of co-morbid conditions, disease stage, and pharmacotherapy. *Fam Med* **34**, 528-535.

[51] Kuo TC, Zhao Y, Weir S, Kramer MS, Ash AS (2008) Implications of comorbidity on costs for patients with Alzheimer disease. *Med Care* **46**, 839-846.

[52] Bullock R (2004) The needs of the caregiver in the long-term treatment of Alzheimer disease. *Alzheimer Dis Assoc Disord* **18** (Suppl 1), S17-23.

[53] Arno PS, Levine C, Memmott MM (1999) The economic value of informal caregiving. *Health Aff* (*Millwood*) **18**, 182-188.

[54] Lowin A, Knapp M, McCrone P (2001) Alzheimer's disease in the UK: comparative evidence on cost of illness and volume of health services research funding. *Int J Geriatr Psychiatry* **16**, 1143-1148.