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ORIGINAL PAPER

Relationship between global severity of patients with Alzheimer's disease and costs of care in Spain; results from the co-dependence study in Spain

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Abstract

Objective The objectives of this analysis were to examine how patients' global severity with Alzheimer's disease (AD) relates to costs of care and explore the incremental effects of global severity measured by the clinical dementia rating (CDR) scale on these costs for patients in Spain.

Methods The Codep-EA study is an 18-multicenter, cross-sectional, observational study among patients (343) with AD according to the CDR score and their caregivers in Spain. The data obtained included (in addition to clinical measures) also socio-demographic data concerning the patient and its caregiver. Cost analyses were based on resource use for medical care, social care, caregiver productivity losses, and informal caregiver time reported in the resource utilization in dementia (RUD). Lite instrument and a complementary questionnaire. Multivariate regression analysis was used to model the effects of global severity and other socio-demographic and clinical variables on cost of care.

Results The mean (standard deviation) costs per patient over 6 months for direct medical, social care, indirect and informal care costs, were estimated at €1,028.1 (1,655.0), €843.8 (2,684.8), €464.2 (1,639.0) and €33,232.2 (30,898.9), respectively. Dementia severity, as having a CDR score 0.5, 2, or 3 with CDR score 1 being the reference group were all independently and significantly associated with informal care costs. Whereas having a CDR score of 2 was also significantly related with social care costs, a CDR score of 3 was associated with most cost components including direct medical, social care, and total costs, all compared to the reference group.

Conclusions The costs of care for patients with AD in Spain are substantial, with informal care accounting for the greatest part. Dementia severity, measured by CDR score, showed that with increasing severity of the disease, direct medical, social care, informal care and total costs augmented.

Keywords Alzheimer · Clinical dementia rating scale · Direct medical costs · Social care costs · Indirect costs · Informal care costs

JEL-Classification: H51 · I12 · I18

Introduction

Alzheimer's disease (AD) is a chronic neurodegenerative disorder presenting as a progressive loss of intellectual and cognitive abilities [1]. AD is the most frequent neurodegenerative cause of dementia, representing 60–70 % of cases [2], and has shown to result in a major cause of disability in the elderly, leading to loss of independence, high strain on caregivers, and increasing costs to society [2, 3].

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AD causes a substantial burden on individuals and their families and caregivers, as individuals with AD require a high amount of healthcare, as well as social and economic services [1, 4]. The progression of dementia inevitably leads to increasing need for care and supervision [5]. As a result, institutionalization may become necessary, or, alternatively, the amount of professional home care or informal care required by patients who remain in the community is likely to be substantial [6]. Thus, with regard to the economic impact of dementia on society, formal nursing care and informal care represent significant cost categories besides costs of medical care [5]. With progression of the disease, the need for care and supervision rises [5] with the financial impact of dementia predicted to increase substantially in the next 50 years owing to an increased prevalence of dementia in this time period [7]. The total number of people with dementia is projected to nearly double every 20 years to 65.7 million in 2030 and 115.4 million in 2050 [8].

In addition, the cost of care increases with disease progression. At the time of diagnosis, although there is some cognitive impairment and short-term memory loss, the care required is much less than that at later stages of AD when most patients require total support with basic self-care and may also exhibit difficult-to-manage behaviors [9].

Current evidence of the existing relationship between AD severity measures and costs has been published in recent literature review by Mauskopf et al. [10], which included 29 studies published between 1993 and 2008. The objective was presenting mean costs (direct, indirect, or total) by AD disease severity, defined using measure of cognition, functional status, and behavior. It was shown that that mean total costs of AD increase with disease severity regardless of severity-measurement method. The relative difference in mean total costs between patients with severe disease compared to those with moderate disease, or moderate disease compared to mild disease, was fairly consistent across studies, suggesting that any of the disease-severity measures may be used to broadly categorize patients by cost. However, when regression analysis included multiple disease-severity measures, independent associations with costs were noted for the different measures. Cognitive and functional status measures were consistently associated with direct costs, whereas functional status and behavioral measures were consistently associated with indirect costs and caregiver hours. Based on other literature review by Jönsson and Wimo [3] on published data on costs of care for patients with diagnosed dementia or possible/probable AD, it was observed that few studies assessed aspects though of disease severity other than cognitive function, which has mostly been assessed with the mini-mental state examination (MMSE). Several studies [11–15] have been identified that demonstrated a strong relationship between total costs of care and the level of dementia severity measured by the CDR scale.

In this study, we use data from the Co Dependence in Alzheimer's disease (Codep-AD) study to estimate the costs of direct medical care, social care, productivity losses/indirect costs, and informal care for a sample of patients with AD in Spain over a period of 6 months. The aims of the present study were as follows: (1) to examine how patients' global severity of dementia as indicated by CDR score relates to costs of caring for a patient with this disease, and (2) to estimate the incremental effect of global severity on costs for patients with AD and to identify important cost drivers. This is accomplished by cross-sectional analysis comparing costs in different stages of AD. A proper understanding of dementia severity and the societal costs caused by this disease and how they affect families, health and social care services, and governments is fundamental to raising awareness, so that the government and health and social care systems are better prepared for health care planning and achieving proper prioritization of resources and interventions.

Methods

Study sample

The Codep-AD study conducted in 2011–2012 was an 18-multicenter, cross-sectional, observational study among patients with AD according to the clinical dementia rating (CDR) score and their caregivers in Spain. The data of 343 patients and their caregivers was prospectively collected through the completion of a clinical report form (CRF) during a one visit/assessment at an outpatient center or hospital, including all instruments that were administered.

Participants for the study for each of the 18 centers were identified at each individual center or hospital. Inclusion criteria required patients to have received a diagnosis of possible or probable AD according to the diagnostic and statistical manual of Mental Disorders (Fourth Edition; DSM-R IV) [16]. Probable or possible AD was diagnosed according to the NINCDS-ADRDA criteria [17]. The severity of dementia for each patient was established by the clinical dementia rating (CDR) scale global score [18]. Other criteria included the presence of a reliable and trustworthy caregiver to accompany the patient during the study visit and the person responsible for helping the patient in their basic and instrumental needs of daily life and to provide supervision at home for a minimum of at least 10 h per week. The caregiver did not need not to be a member of the family or live with the patient. All patients and responsible caregivers had to sign an informed consent form.

Patients were excluded from the study if they had comorbid illness, which was a significant independent cause of disability (e.g., dense hemiplegia or Parkinson's disease), had a clinical status that predicted an outcome short-term mortality, if the clinical study investigator opined that the patient and caregiver were not able to comply with the study protocol or if patients were participating in a clinical trial. Local ethics approval was obtained for the study.

A range of data was collected for each participant via a case report form including medical assessments and structured questionnaires. All medical assessments were completed by a physician and a psychologist at the patient's outpatient center or hospital. All remaining data on socio-demographic and other clinical details, health and social care utilization and caregiving hours, were collected via structured caregiver questionnaires. Summary statistics for socio-demographic characteristics and clinical-related variables of the 343 study participants according to CDR score are presented in Table 1.

Dependent cost variables

Five cost variables were identified, estimated, and examined in the statistical analysis. These included medical care costs (1), social care costs (2), indirect costs (3), informal care (4), and total costs including all cost variables (5) (Tables 2, 3). Medical care costs are generally reimbursed in Spain with social care costs receiving full or partial reimbursement depending on the region, which has not been further investigated for the purpose of this study. Data on resources for the estimation of the five costs variables were obtained from the resource utilization in dementia (RUD) [19]. Lite instrument and a complementary questionnaire that included aspects related to the utilization of resources not collected in the RUD lite questionnaire were both completed by the psychologist of the caregiver. This supplemental questionnaire included among others aspects such as modifications at home to improve the patientś safety, transport costs of the patient and pocket money for patient care.

Medical care costs were estimated for a set of resources including hospitalizations, emergency visits, diagnostic and monitoring tests, outpatient specialist visits, health and social care professional consultations and health materials. Data on utilization over a 6-month period were collected and the total costs for medical care were estimated by applying a unit cost for each resource activity. Unit costs were derived from different local Spanish sources and expressed in EUR 2013. Prices were updated according to the consumer index by the Spanish National Institute for Statistics [20] (see Table 2).

Social care costs were calculated from estimates of the number of nights living in institutionalized setting, attendance of a day care center, number of complimentary services (day care at home, help at home, nurse home visits, meal delivery, transport services to day care center) and performed home modifications. Data on utilization were collected and the total costs for social care were estimated by applying a unit cost expressed in EUR 2013 (Table 3) for each resource activity in number of nights/days, received payments for home modifications and number of services over the last 6 months.

Indirect costs associated with lost productivity of the caregiver were calculated from estimates of reduced working hours per month and the loss of full and half working days per month. Unit costs for the loss of productivity were based on the national average wage per hour for a woman and man (%women/men 86.2 %) of €11.98 obtained from Spanish National Institute for Statistics expressed in EUR 2013. The total costs were estimated by applying the hourly average weight to the lost working hours over a 6-month period, whereas a half lost working day counted for 4 h and a full working day for 8 h.

Informal care costs were calculated from estimates of caregiving hours provided by the primary and secondary caregiver for each patient with a caregiver or with data on caregiving hours available. This includes the total number of hours dedicated to basic activities daily living (ADL) and instrumental activities of daily living (IADL) activities over the previous month, as well as supervision of the patient. The hours of care per task were summed to obtain an estimate of the daily caregiving hours per patient. As it is difficult to value informal care, a replacement cost approach [21] was used to value and quantify the cost of informal caregiver time, whereby all care hours are costed at the level of remuneration required to hire an equivalent professional. For the replacement cost, the hourly rate for healthcare assistance at home of €15.71 per hour (EUR 2013) was used. No distinction was made between employed and employed caregivers. The daily informal care cost per patient was calculated by multiplying total care hours by the hourly wage rate and extrapolated to obtain an estimate of informal care cost over a 6-month period. The total costs including all cost variables were equal to the sum of all costs over a 6-month period. In case extreme values for some direct medical costs were observed and in case misinterpretation of the type and number of resources was suspected, these resources were excluded to prevent overestimation of costs.

Independent variables

The independent variables adopted in this analysis included a range of socio-demographic characteristics and clinical

Table 1 Socio-demographic variables and clinical characteristics

Variable	CDR scale				
	0.5 (*n* = 18)	1 (*n* = 116)	2 (*n* = 102)	3 (*n* = 103)	*p* value
Patient-related variables					
Sex, *n* (%)					
Male	9 (50.0 %)	38 (32.8 %)	33 (32.4 %)	32 (31.4 %)	0.5
Female	9 (50.0 %)	78 (67.2 %)	69 (67.6 %)	70 (68.6 %)	
Age					
Mean (SD)	76.2 (7.8)	77.0 (7.4)	79.7 (7.0)	80.5 (7.4)	<0.001[b,c]
Place of residence, *n* (%)					
Own/family home	18 (100.0 %)	116 (100.0 %)	98 (97.0 %)	100 (98.0 %)	0.3
Institutionalized	0 (0.0 %)	0 (0.0 %)	3 (3.0 %)	2 (2.0 %)	
Civil status, *n* (%)					
Married/partner	10 (55.6 %)	72 (62.1 %)	58 (56.9 %)	58 (56.9 %)	0.8
Others	8 (44.4 %)	44 (37.9 %)	44 (43.1 %)	44 (43.1 %)	
Years of diagnosis					
Mean (SD)	1.2 (1.3)	1.7 (2.1)	2.1 (1.7)	3.4 (2.7)	<0.001[a,b,c,d]
Caregiver-related variables					
Relation, *n* (%)					
Spouse	8 (44.4 %)	54 (50.0 %)	37 (41.1 %)	40 (44.0 %)	0.6
Others	10 (55.6 %)	54 (50.0 %)	53 (58.9 %)	51 (56.0 %)	
Age					
Mean (SD)	56.9 (16.4)	61.7 (14.2)	59.4 (14.3)	60.4 (13.2)	0.5
Sex, *n* (%)					
Male	9 (50.0 %)	44 (37.9 %)	32 (31.7 %)	31 (30.1 %)	0.3
Female	9 (50.0 %)	72 (62.1 %)	69 (68.3 %)	72 (69.9 %)	
Living with patient, *n* (%)					
Yes	12 (66.7 %)	79 (68.1 %)	71 (70.3 %)	75 (72.8 %)	0.9
No	6 (33.3 %)	37 (31.9 %)	30 (29.7 %)	28 (27.2 %)	
Clinical characteristics					
CIRS					
Mean (SD)	5.9 (3.1)	5.3 (3.3)	5.4 (4.0)	6.0 (4.6)	0.9

Statistic differences (Mann–Whitney with Bonferroni correction: level =0.05/6 $\cong$0.008)

Pearson Chi-square test for qualitative variables; Kruskal–Wallis test for quantitative variables

n number of patients, *SD* standard deviation, *CIRS* cumulative illness rating scale

[a] CDR score 0.5 and CDR score 3

[b] CDR score 1 and CDR score 2

[c] CDR score 1 and CDR score 3

[d] CDR score 2 and CDR score 3

measures. Socio-demographic data included the patients' age, gender, years since diagnosis, and place of residence (institutionalized vs. carer).

The CDR [22–24] was administered to determine the clinical severity of dementia. The questionnaire was conducted by a psychologist to the caregiver and the patient, only in case that there was no prior evaluation available (6 months as maximum for patient inclusion). The scale sets a score of five levels according six areas (memory, orientation, judgment and problem solving, social, leisure and personal care) using an algorithm. The score ranges from 0 (healthy) to three (severe dementia) determines the severity of dementia. The CDR offers an operational classification offers that permits the grouping subjects for later study purposes.

The cumulative index rating scale (CIRS) [25] was administered to the patient to assess multi-morbidity. The scale consists of 14 dimensions that allow the

Table 2 Unit cost estimates

Resource item	Activity	Unit cost (€)	References
Medical care			
Hospital admission	Per admission	458.89	[30–33][a]
Emergency visit	Per visit	222.40	[30–33][a]
Diagnostic and monitoring tests			
Blood test	Per test	18	[31, 34]
Vitamin B12	Per test	5.65	[35]
Folic acid	Per test	5.65	[35]
Thyroid hormones T3, T4, and TSH	Per test	19.23	[35]
Computerized axial tomography (CAT)	Per test	120.57	[35]
Liver tests	Per test	1.17	[33]
Neuropsychological explorations	Per test	118.58	[35]
Renal function	Per test	0.61	[33]
Syphilitic serologic	Per test	15.39	[35]
Urine analysis	Per test	1.54	[35]
Electrocardiography (ECG)	Per test	11.00	[35]
Chest X-ray	Per test	14.25	[35]
Electroencephalography (EEG)	Per test	45.67	[35]
Nuclear magnetic resonance (NMR)	Per test	192.54	[35]
HIV antibodies	Per test	237.29	[32–35][a]
APOE4	Per test	72.28	[36]
Lumbar puncture	Per test	267.15	[32, 35]
Positron emission tomography (PET)	Per test	556.31	[30–32, 35][a]
Medical visits			
Primary care visit	Per visit	34	[35]
Geriatrics	Per visit	68.81	[37]
Neurology	Per visit	68.81	[37]
Psychiatry	Per visit	68.81	[37]
Physiotherapist	Per visit	16.27	[30]
Occupational therapist	Per visit	21.50	[31]
Social assistant	Per visit	33.52	[34]
Psychologist	Per visit	69.95	[31, 32, 38][a]
Health material			
Wheelchair	Per unit	247.32	[32, 34][a]
Walkers	Per pair	60.76	[32, 34][a]
Articulated bed	Per unit	1.906.52	[32, 34][a]
Anti-bedsore mattresses	Per unit	141.42	[32]
Under path	Per unit	0.79	[32]
Remote alarm	Per unit	55.76	[34]
Diapers	Per unit	0.69	[34]
Social care			
Day care	Per visit	30.48	[39]
Healthcare assistant (assistant living)	Per visit	15.71	[39]
Food delivery	Per meal	3.62	[40]
Home nurse	Per visit	29.27	[35]
Transportation services	Per km	0.86	[30, 31][a]
Living in institutionalized	Per month	2.018.61	[39]
Day care center	Per visit	177	[35]
Indirect/productivity loss employed caregiver			
Hourly wage national level	Per hour	11.98	[41]
Informal care			
Replacement cost: healthcare assistant	Per hour	15.71	[39]

[a] Average of different costs provided by hospitals

quantification of chronic conditions considering severity. The scale is scored as the sum for each dimension and although the score ranges between 0 and 56, very high scores are not plausible as they represent concurrent failure of multiple systems which are not compatible with life.

Statistical analysis

Descriptive statistics for the estimated costs of care are presented using univariate ANOVA tables in terms of the mean and standard deviation (SD) for the study sample stratified by CDR score, represented by four categories of global severity including 0.5, 1, 2, and 3.

Multivariate generalized linear regression analyses were carried out to explore the effects of the independent variables on each of the five dependent cost variables. For comparative purposes, upon request the results from a range of alternative model specifications are available from the authors. In each case, the regression model included the following independent variables: CDR score, CIRS score, years since diagnosis, patients' age, living with the caregiver ($0 = $ no; $1 = $ yes), patients' sex ($0 = $ male; $1 = $ female), and the living in an institutionalized setting ($0 = $ no; $1 = $ yes). The CDR score of 1 in the multivariate generalized linear regression analyses was used as a reference score, for which results of these analyses were all compared to the reference category.

In all analyses, the dependent cost variable was modeled in its untransformed scale. The regression coefficients for continuous independent variables showed estimates for the unit change in cost for a unit change in that variable. That is, for a unit increase in the explanatory variable, cost increases by 100 beta %. For dichotomous variables, the coefficient estimated the unit change in cost relative to the reference group for that variable. Statistical significance was explored for two levels at $p < 0.01$ and $p < 0.05$. The model comparison was based on log likelihood or cube root statistics. Data were analyzed with SPSS version 18.0 for Windows (SPSS; Chicago, IL, USA).

Results

The results of the descriptive statistics for medical and non-medical resource utilization, lost caregiver working hours, and informal caregiving hours per day accordingly are presented in Table 3.

When all individual medical resources were summed and costed, the mean (SD) direct medical costs per patient over 6 months was equivalent to €1,028 (1,655) (Table 4). With respect to social care costs, indirect costs due to productivity loss of the primary or/and secondary caregiver and informal care costs, the mean (SD) cost per patient for these cost variables over 6 months were estimated at €843.8 (2,684.8), €464.2 (1,639.0) and €33,232.2 (30,898.9), respectively. Informal care costs showed to be the highest compared to the other cost variables. When all cost variables were summed the total overalls mean (SD) cost per patient summed up to €32,177.3 (31,836.9) over 6 months.

The average 6-month direct medical costs, social care costs, indirect costs, and informal costs by CDR score are presented in Table 5 and show that costs rise with the global severity of dementia.

Statistic differences according to CDR scores were observed for direct medical costs but only between CDR score 1 and 3 ($p = 0.02$), for social care costs between CDR score 1 and CDR score 2 ($p < 0.001$), and CDR score 1 and CDR score 3 ($p < 0.001$), for informal care costs and total care costs among all CDR scores ($p < 0.001$). No statistical differences were observed in indirect costs according to CDR scores.

The results from the multivariate analyses are presented in Table 6. The results for direct medical costs, social care costs and informal care costs showed that the independent variable that was statistically significant after controlling for other covariates with all the three dependent cost variables was the CDR score 3. An additional one-point increase in CDR score was associated with a significant increase of 45.8 % significance ($p = 0.05$) in direct medical costs, 131.2 % significance ($p = 0.01$) increase in social care costs, and a 1,275.7 % significance ($p = 0.01$) increase in informal care costs over 6 months compared to the reference group. No other independent variable was statistically significant these three cost variables.

Regarding direct medical costs, three independent variables reached statistical significance in the regression

Table 3 Resource use

Resource item	Resource use in mean (SD) or *n* (%)
Medical care	
Days hospitalized (over 6 months)	0.4 (0.6)
Number of emergency services attended (over 6 months)	1.5 (1.5)
Diagnostic tests (over 6 months)	
Blood test	0.7 (0.8)
Vitamin B12	0.4 (0.6)
Folic acid	0.4 (0.6)
Thyroid hormones T3, T4, and TSH	0.4 (0.5)
Computerized axial tomography (CAT)	0.5 (0.5)
Liver tests	0.5 (0.8)
Neuropsychological explorations	0.4 (0.5)
Renal function	0.6 (0.8)
Syphilitic serologic	0.3 (0.5)
Urinalysis	0.5 (0.9)
Electrocardiography (ECG)	0.3 (0.5)
Chest X-ray	0.3 (0.5)
Electroencephalography (EEG)	0.1 (0.3)
Nuclear magnetic resonance (NMR)	0.1 (0.3)
HIV antibodies	0.02 (0.14)
Monitoring tests (over 6 months)	
Blood test	1.1 (1.1)
Vitamin B12	0.4 (0.5)
Folic acid	0.4 (0.5)
Thyroid hormones T3, T4, and TSH	0.4 (0.5)
Computerized axial tomography (CAT)	0.3 (0.5)
Liver tests	0.3 (0.5)
Neuropsychological explorations	0.7 (0.5)
Renal function	0.4 (0.6)
Syphilitic serologic	0.2 (0.4)
Urinalysis	0.6 (0.7)
Electrocardiography (ECG)	0.4 (0.7)
Chest X-ray	0.3 (0.8)
Electroencephalography (EEG)	0.1 (0.3)
Nuclear magnetic resonance (NMR)	0.3 (0.5)
Brain SPECT	0.1 (0.3)
HIV antibodies	0.04 (0.19)
APOE4	0.04 (0.21)
Lumbar puncture	0.02 (0.15)
Positron emission tomography (PET)	0.01 (0.11)
Medical visits (over 6 months)	
Primary care	4.4 (7.5)
Geriatrics	0.08 (0.31)
Neurology	1.0 (0.7)
Psychiatry	0.6 (1.4)
Physiotherapist	1.5 (7.2)

Table 3 continued

Resource item	Resource use in mean (SD) or *n* (%)
Occupational therapist	2.6 (15.6)
Social assistant	0.1 (0.4)
Psychologist	1.3 (5.9)
Other	2.4 (7.9)
Health material (over 6 months)	
Wheelchair	23 (8.0 %)
Walkers	16 (5.6 %)
Articulated bed	31 (10.8 %)
Anti-bedsore mattresses	17 (6.1 %)
Underpad	46 (15.9 %)
Dressing materials	13 (4.6 %)
Remote alarm	31 (10.8 %)
Diapers	87 (28.8 %)
Diapers per day	6.0 (19.4)
Social care	
Complementary services (over 6 months)	
Day care	18.6 (42.7)
Assisted living	12.3 (37.7)
Food delivery	1.8 (14.8)
Home nurse	0.5 (2.9)
Transportation services	7.3 (27.0)
Number of nights/living in institutionalized setting (over 6 months)	36.6 (73.2)
Home modifications (over 6 months)	68 (98.6 %)
Attend to day center over 6 months)	88 (26.3 %)
Distance to day center in km (over 6 months)	6.8 (28.6)
Indirect/productivity loss employed caregiver	
Number of hours reduced (hours/week)	7.0 (7.8)
Complete workdays (8 h per day) lost/last month	0.5 (1.1)
Partial workdays (4 h per day) lost/last month	1.9 (5.3)
Informal care	
Primary caregiver for basic ADLs (hours/month)	101.4 (170.0)
Secondary caregiver for basic ADLs (hours/month)	40.7 (94.8)
Primary caregiver for instrumental ADLs (hours/month)	106.8 (153.4)
Secondary caregiver for instrumental ADLs (hours/month)	45.3 (99.7)
Primary caregiver for patient monitoring (hours/month)	128.9 (198.9)
Secondary caregiver for patient monitoring (hours/month)	59.4 (123.9)

SD standard deviation; *n* number of patients; *ADL* activities of daily living

Table 4 Summary of costs (€ 2013) over previous 6 months

Cost variables	Number of observations	Cost (€ 2013)	
		Mean (SD)	Median (IQR)
Direct medical costs	343	1,028.1 (1,655.0)	530.8 (866.5)
Social care costs	343	843.8 (2,684.8)	0.0 (62.8)
Indirect costs	343	464.2 (1,639.0)	0.0 (0.0)
Informal care costs	308	33,232.2 (30,898.9)	24,272.0 (42,134.2)
Total costs	343	32,177.3 (31,836.9)	21,093.3 (43,201.8)

SD standard deviation, *IQR* interquartile range

analysis: CDR score 3, CIRS, and years since diagnosis. A one-point increase in CIRS score was associated with a 7.3 % ($p = 0.01$) increase in direct medical costs over 6 months compared with the reference group. A one-point increase in years since diagnosis, was associated with a 9.6 % ($p = 0.05$) decrease in direct medical costs over 6 months compared with the reference group.

In respect to social care costs, the two independent variables were statistically significant after controlling for other covariates included CDR score 2 and CDR score 3. CDR score 2 was associated with a 108 % increase and CDR score 3 was associated with a 131.2 % increase in social care costs over 6 months compared with the reference group ($p = 0.01$).

Regarding informal care costs, the independent variables, which were statistically significant after controlling for other covariates, were CDR score 0.5, CDR score 1, and CDR score 3, CIRS score and living with the caregiver. A one-point increase in CIRS score was associated with a 36.9 % ($p = 0.05$) increase in informal care costs over 6 months compared with the reference group. Living with the caregiver was associated with a 258.4 % ($p = 0.05$) increase in informal care costs over 6 months compared with the reference group.

No other independent variable reached statistical significance associated with direct medical costs, social care costs, indirect costs, and informal care costs.

In the summed total costs analysis, CDR score 3, CIRS score, and living in an institutionalized setting were all significantly associated with total care costs over 6 months. A one-point increase in CDR score 3 score was associated with a 68.6 % ($p = 0.05$) increase in total care costs, a one-point increase in CIRS score lead to a 82 % ($p = 0.01$) increase in total care costs, whereas living in an institutionalized setting lead to a 33.9 % ($p = 0.01$) increase in total care costs over 6 months compared to the reference group.

Table 5 Resource use and costs (€ 2013) results by CDR scale categories

Variable/analysis	Direct medical costs (€) Mean (SD)	Social care costs (€) Mean (SD)	Indirect costs (€) Mean (SD)	Informal care costs (€) Mean (SD)	Total care costs (€) Mean (SD)
CDR score 0.5	770.6 (735.8)	1,282.1 (4,061.9)	719.2 (2,801.3)	10,392.3 (16,055.1)	12,009.5 (15,708.5)
CDR score 1	906.3 (1,334.2)	193.2 (1,211.9)	219.7 (657.9)	16,560.4 (17,852.9)	15,738.2 (18,054.9)
CDR score 2	903.2 (1,119.9)	1,095.2 (3,192.0)	565.2 (1,823.4)	35,898.5 (30,479.8)	34,590.7 (31,695.6)
CDR score 3	1,348.8 (2,381.8)	1,210.5 (2,915.3)	613.0 (1,949.1)	52,900,3 (32,045.2)	52,477.4 (34,321.5)
p value	$p = 0.02^{d}$	$p < 0.001^{c,d}$	$p = 0.9$	$p < 0.001^{a,b,c,d,e}$	$p < 0.001^{a,b,c,d,e}$

Unit costs are presented in € 2013; *SD* standard deviation, *CDR* clinical dementia rating

Statistic differences (Mann–Whitney with Bonferroni correction: level = 0.05/6 ≅ 0.008)

[a] CDR score 0.5 and CDR score 2

[b] CDR score 0.5 and CDR score 3

[c] CDR score 1 and CDR score 2

[d] CDR score 1 and CDR score 3

[e] CDR score 2 and CDR score 3

Comparing these results with those from alternative model specifications available upon request to the authors suggests that estimates for the effects of global severity on costs were consistent as the findings remained consistent across alternative model specifications. The observed correlations give an indication of the variables that will be the most influencing and explanatory in the multivariate analysis. Regarding global severity of dementia measured by the CDR scale, the only cost variable that was not significantly correlated to quantitative clinical variables was the cost variable indirect costs (supporting information).

Discussion

This analysis presented the estimated resource utilization and costs of direct medical care, social care, productivity loss of caregivers, and informal care for a sample of patients with AD living in the community in Spain. The mean (SD) costs per patient over 6 months for direct medical, social care, indirect, and informal care costs, were estimated at €1,028.1 (1,655.0), €843.8 (2,684.8), €464.2 (1,639.0), and €33,232.2 (30,898.9), respectively. Total combined mean (SD) costs per patient summed up to €32,177.3 (€31,836.9) over 6 months. The incremental effect of dementia severity, measured by the CDR with CDR score 1 as a reference group, on the five total cost variables, was also estimated, while controlling for other clinical measures and a range of other socio-demographic characteristics.

In general, we find that the cost results for the Spanish sample reflect those from recent studies [12–15] with informal care being the most important component of costs of care. In our study, we also found that dementia severity, measured as CDR score, was associated with different cost components. Dependent on CDR score, different significant relationships were observed with direct medical care costs, social care costs, informal care costs, and total costs.

Higher scores on the CDR scale, associated with greater global dementia severity, showed to be associated with an increase of costs. Similar results were obtained by various studies [11, 12, 15] showing that increasing CDR scores are associated with changes in costs of care, which confirms that global severity in dementia plays an independent role in explaining variations in costs of care. Our results showed that changes in dementia severity may be associated with significant differences in direct medical care costs, social care costs, informal care costs, and total costs. A one-point increase in the CDR score, that is, a one-unit improvement in CDR score 3 compared to the reference group with CDR score 1, was associated with a 45.8 % ($p = 0.05$) increase in direct medical costs and a 68.6 % ($p = 0.05$) in total cost over 6 months. A one-point increase in CDR score 2 and CDR score 3 was associated with a 108 % ($p = 0.01$) and 131.2 % ($p = 0.01$) increase in social care costs over 6 months compared to the reference group. A one-point increase in CDR score 0.5, CDR score 2, and CDR score 3 was associated with a decrease of 653.7 % ($p = 0.05$), and increases of 756.1 % ($p = 0.01$) and 1,275.7 % ($p = 0.01$) in informal care costs over 6 months compared to the reference group. These findings suggest that early interventions that delay patients' dementia severity may well reduce costs as have clinical benefits, and maintain patients at a less serious stage of illness. The cost and effect though of the intervention will depend upon the disease stage when the intervention is applied, which makes it important to evaluate the costs and benefits of these interventions before introducing and implementing them in clinical practice.

Apart from the impact of global dementia severity on cost, also other significant effects of other independent

Table 6 Multivariate analysis results

Variable/model	Direct medical costs Beta	Social care costs Beta	Indirect costs Beta	Informal care costs Beta	Total care costs Beta
Constant	4.631**	−1.932	−0.991	2.889	4.234**
CDR[a] score 0.5	−0.199	0.389	−0.391	−6.537*	0.430
CDR[a] score 2	0.182	1.080**	0.128	7.561**	0.457
CDR[a] score 3	0.458*	1.312**	0.111	12.757**	0.686*
CIRS	0.073**	0.041	−0.071	0.369*	0.082**
Years since diagnosis	−0.096*	0.111	0.001	0.038	−0.021
Age	0.016	0.024	0.033	0.159	0.015
Lives with carer					
No (base category)	–	–	–	–	–
Yes	−0.031	−0.466	−0.949*	2.584*	0.006
Gender					
Male (base category)	–	–	–	–	–
Female	0.000	0.287	0.532	1.528	0.017
Lives in institutionalized setting[b]					
No (base category)	–	–	–	–	–
Yes	0.463		−2.600	-3.182	3.392**

CDR clinical dementia rating, *CIRS* cumulative illness rating scale

Statistical significance * $p = 0.05$, ** $p = 0.01$

[a] CDR 1 is the reference level

[b] The effect covariate was not analyzed for social care costs as these are part of these costs and highly dependent on the covariate

variables including CIRS, years since diagnosis, living with the carer, and living in an institutionalized setting on some of the different cost components were observed. This may indicate that except for global severity, some of these other independent covariates have an effect on costs and are also drivers of some of the different cost components.

The first strength of this study is the stratification of patients into disease severity groups, which enabled estimation of costs of care across the whole disease severity spectrum. The total sample is representative to each specific subgroup of patients and not only the general population with possible or probable AD. The second strength of this study is the use of a structured assessment procedure in which numerous validated instruments are applied. The third strength of this study is that it includes the collection of a broad range of resources for each participant, including direct medical care, social care, productivity loss of caregivers, and informal caregiver hours. The design of the study allowed us to carry out a comprehensive cost analysis including all relevant costs of care from a societal perspective. Although some payers only want to see the costs paid for by the public health care system or in their budget, this would exclude other important values such as the provision of informal care, which was shown to be the most costly resource. A fourth strength is the inclusion of patients residing with caregivers or in the community and patients residing in institutionalized settings.

There are also several limitations in our study that need to be considered when interpreting the results. The number of patients included in our study also came from a relatively small sample size, therefore representativeness for the Spanish population must be judged cautiously. Participants with mild, moderate, and severe AD in our study sample were selected from different hospitals in various Spanish regions, and may represent a non-random sample of AD patients in the community. However, because patients were drawn from multiple locations, generalizability of our findings is enhanced.

Our study had a cross-sectional design, which makes it that reported relationships between variables can only be interpreted as associations, meaning that the causal relationships cannot clearly be determined. An increase in the severity of dementia associated with a worse health state though is associated with higher costs due to additional treatment. On the other side, poorer health may also result from lower costs due to lesser investments in healthcare.

The data on patients' health care costs were reported by patients and caregivers of the patient. In several studies [26, 27] it was shown that caregivers are able to accurately report medical information of the patients they take care of. Although there is no reason to believe that patients or caregivers' reports of patients' health care utilization are inaccurate, differences in the interpretation on the type and number of resources could have influenced the cost outcomes. Here, it must be observed that extreme values for some direct medical costs have been observed and excluded in case misinterpretation of the type and number of resources was suspected. Therefore, future research should explore the burden and distribution of costs and variance that are more representative of large patient populations in the community and in institutionalized care settings and identify the main cost drivers. It is also possible that there are additional costs beyond those collected in the study, which might not have been included. The cost estimates presented in this study are the costs of care of AD patients in different stages of the disease, but not necessarily the costs caused by the disease itself. To estimate the additional costs caused by the disease, we would need to compare our cohort with matched controls without dementia. Another limitation is that there may be some costs that might have been counted double, as some caregivers may have decreased their hours of work in order to provide informal care giving. It is difficult to quantify the extension and therefore the effect on the reported outcomes, though it should be acknowledged as a limitation.

As reported in other studies [8, 9], the existence of uncertainty in valuing informal care has been reported, which makes it complicated and controversial [28, 29]. Normally, informal caregiver time is not reimbursed or available in the market [29], which makes the valuation of caregiver time and results sensitive to the approach adopted. In our analysis, caregiver time was valued including the costs of active care tasks (i.e., basic and instrumental ADLs) as well as supervision for patients having a caregiver. For those patients not having caregivers, caregiver time was set at 0 and excluding those patients not having any caregiving hours reported from the analysis. For both resources, a replacement cost per hour to hire a professional healthcare assistant was used. Including supervision in the costing of informal care could have increased the contribution of informal costs to the total and further increase its relative importance to other resources, as reported by Wimo et al. [21].

Another uncertainty in the assessment of informal care could be the overstatements by some caregivers. Finally, the process of the costing of resource activities was complicated by the lack of one data source for all unit cost data. All unit costs are best estimates of the cost per activity. Therefore it was not possible to identify cost differences across different sites. Further investigation is necessary to examine whether variations in resource utilization and costs reflect regional differences or availability or access of services.

These limitations highlight the need to conduct longitudinal population-based studies to examine whether delaying disease progression confirms our findings and conclusions regarding costs of care differences similar to those found in our study and for revealing existing causal relationships.

Conclusions

The costs of care for patients with AD in Spain are substantial, with informal care accounting for the greatest part. The findings from this study show that dementia severity according CDR score for patients with AD was significantly associated with various components of the cost of care. We find that dementia severity is an important predictor of direct medical costs, social care costs, informal care costs, and total costs. Consequently, interventions that delay progression and maintain patients at earlier stages of the disease by interventions that reduce symptoms may reduce overall costs. The results of our study provide insights into types of evaluated need that decision makers and payers can focus interventions on to control costs and maximize favorable patient outcomes.

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