

The Cost of Dementia in Europe

A Review of the Evidence, and Methodological Considerations

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Abstract

Alzheimer's disease (AD) is a leading cause of disability in the elderly, leading to a high burden on caregivers and costs to society. This article describes the current level of data availability regarding the costs of AD in Europe, summarizes and compares findings from previous studies in different countries, and discusses the applicability of available data for modelling purposes.

A literature review was conducted for papers in any language reporting data on costs of care for patients with diagnosed dementia or possible/probable AD. Only papers reporting patient-level data on costs were included. A total of 16 studies were identified: from the Nordic region (4), the UK (3), Spain (3), France (2), Italy (2), Belgium (1) and Germany (1). There is large variation in total cost estimates, depending on, for example, differences in study methodology, setting, type and severity of patients included, range of costs assessed and the choice of principle for valuing informal care. The median value for total annual care costs in all studies was €28 000

(range €6614–€64426) [year 2005 values]. Few studies assessed aspects of disease severity other than cognitive function.

The costs of AD in Europe are substantial and increase with disease severity. Methodological differences between studies make comparison across countries and healthcare systems difficult, and there is a need to standardize methods for assessing and valuing informal care. Patient-level information on resource use is required to analyse determinants of care costs and predict the impact of therapeutic interventions. More data are needed to support future economic evaluations of therapies for AD.

Dementia is a major cause of disability in the elderly, leading to loss of independence, high strain on caregivers, and increasing costs to society. The total economic burden of dementia in Europe has recently been estimated to be €55–€66 billion annually (year 2003 values).^[1,2] The most frequent cause of dementia is Alzheimer's disease (AD), representing 60–70% of cases.^[3] The past decade has seen the introduction of specific treatment options for AD, namely cholinesterase inhibitors and memantine, and several novel, potentially disease-modifying therapeutic approaches are currently under investigation.^[4] This places the focus on the need to make informed decisions on the allocation of resources to and within dementia care.

Data for economic evaluation are increasingly being collected within pivotal clinical trials, which allows for direct comparison of costs as well as effects of alternative treatments. However, such analysis is limited by the large differences between patient management in the clinical trial setting compared with clinical practice – mainly the restrictive inclusion and exclusion criteria in clinical trials, which lead to a non-representative sample of patients – and other methodological problems.^[5] There is therefore a continued need and role for modelling, with the goal of producing better estimates of cost effectiveness in a particular healthcare system.

1. Data Needs for Modelling

The purpose of modelling in the context of economic evaluation is often to extrapolate from short-term trial data on clinical endpoints (e.g.

cognition) to metrics of interest for payers and other decision makers, e.g. total healthcare costs and health utilities.^[6] The accuracy of this extrapolation is dependent both on the quality of the data used as well as the correctness of assumptions imposed during the analysis. To predict how a change in clinical endpoints will impact resource utilization, an understanding of the underlying determinants of resource use and costs is needed. This requires patient-level data on resource use as well as disease severity. Although information on unit costs of specific services (e.g. institutional care), or overall estimates of costs of dementia care in a particular healthcare system, can also be useful, such information does not replace the need for patient-level data.

The progression of AD brings about changes in multiple domains: cognition; physical function; activities of daily living (ADL) abilities; and behaviour and social roles for patients and caregivers. Similarly, treatments aimed at slowing the progression of dementia can potentially lead to benefits in all these areas. Estimating the cost effectiveness of treatments for AD involves modelling costs and effects over longer time horizons, and thus leads to a need for data on how costs relate to different aspects of disease severity.^[7] Previous models have been based largely on cognitive function, since this is the primary endpoint in most drug trials and has also showed strong correlations with care costs.^[8] However, basing models solely on cognitive function may lead both to overestimation of cost effectiveness if the link between cognition and costs is confounded by, for example, the ADL function, and to underestimation of cost effectiveness due to the omission of important

treatment effects in noncognitive areas. Availability of data on costs in relation to multiple domains of disease severity is therefore central to the economic evaluation of AD therapies.

A summary of published cost-of-illness studies in AD was previously published in 2005.^[9] This paper aims to update and expand on these findings, to describe the current level of data availability on the costs of AD in Europe, and to summarize and compare findings from previous studies in different countries. The possibilities and limitations of using the available data for the purpose of economic evaluation are also discussed.

2. Literature Review

A literature review was conducted for papers reporting data on costs of care for patients with diagnosed dementia or possible/probable AD. Only papers reporting original patient-level data were included. Top-down cost-of-illness studies, where data are only presented on the aggregate level, were excluded since normally this type of data does not allow stratification on disease severity and therefore is less useful for modelling purposes. Also, when patient-level data are available it is easily possible to incorporate the uncertainty around the cost estimates in a stochastic economic evaluation, while this is considerably more difficult when costs are derived from multiple sources or based on top-down cost-of-illness estimates.

MEDLINE, EMBASE and Current Contents were searched for the following terms (in any field): (Dementia OR Alzheimer*) AND (Cost OR Economic) AND (Europe* OR Austria OR Belgium OR Cyprus OR Czech Republic OR Denmark OR Estonia OR Finland OR France OR Germany OR Greece OR Hungary OR Ireland OR Italy OR Latvia OR Lithuania OR Luxembourg OR Malta OR Netherlands OR Norway OR Poland OR Portugal OR Slovakia OR Slovenia OR Spain OR Sweden OR Switzerland OR United Kingdom), where '*' is the wildcard character. There was no limitation on the year of publication or language, although

an English language abstract or title was required to match the search terms. The search was updated in April 2008.

The automatic database search identified 590 references. Titles were then reviewed manually to exclude irrelevant papers. After this review, the abstracts of 54 remaining papers were retrieved and reviewed manually [a complete list is available in the Supplement Digital Content 1, <http://links.adisonline.com/PCZ/A44>]. After reviewing the abstracts, a total of 13 references matching the criteria remained and were included in the review: one Belgian study,^[10] two studies each from France,^[11,12] Italy^[13,14] and the Nordic region^[8,15] and three studies each from Spain^[16-18] and the UK.^[19-21]

One additional study known to the authors, published as a book chapter, was included in the review.^[22] In addition, published economic evaluations of treatments for AD were reviewed to identify data sources used in the evaluation that have not been published separately. Economic evaluation papers were identified through previous review papers on acetylcholinesterase inhibitors^[7] and memantine,^[23] and through a search in the Health Economic Evaluation Database (HEED).^[24]

Many economic evaluations have drawn upon multiple secondary data sources for estimating costs of care, often using calculated costs rather than estimates based on resource use data collected from patients and caregivers. Others are based on data sets that were already identified in the literature search.^[25] Two Swedish^[26,27] and one Finnish^[28] economic evaluations estimated costs of elderly with dementia identified through two different population-based studies: the Kuopio 75+ study^[29] and the Kungsholmen project.^[30] Thus, two additional studies were included in the review,^[27,28] bringing the total to 16.

To date there have been four clinical drug trials in AD that have collected resource use data.^[31-34] However, none has presented costs by disease severity, but only as a comparison between treatment arms. Also, the care provided within a clinical trial context differs from standard care, which limits the usefulness of clinical

trial data on costs for modelling purposes. These studies were therefore not included.

2.1 Presentation of Cost Estimates

All costs have been converted to € (year 2005 values) using GDP purchasing power parity conversion rates and general price indices for each country.^[35] This methodology has been described in detail elsewhere.^[1] When possible, costs are presented stratified by disease severity assessed by the Mini Mental State Examination (MMSE).^[36] The cut-offs for mild, moderate and severe disease vary somewhat between studies, but in general scores above 20 points are considered mild, 10–19 points moderate and <10 points severe disease. The Clinical Dementia Rating (CDR) has also been employed; CDR 1 signifies mild dementia, CDR 2 moderate dementia and CDR 3 severe dementia. All costs are annual cost per patient unless otherwise stated.

3. Cost of Dementia

Table I summarizes the methodology of the 16 identified studies. The year of costing was stated in most papers; wherever not, the year of publication was used to adjust cost estimates to 2005 values. Twelve studies included patients with a diagnosis of probable or possible AD, while four studies included subjects with dementia of any aetiology. Seven studies included subjects living in institutions as well as in the community, while the rest only considered those living in the community.

Four studies identified subjects with dementia or AD through a screening programme in a general population of elderly, while the other studies included patients already identified and diagnosed in the healthcare system. Seven studies had a prospective design, with data collection at baseline and at follow-up visits at 6 and/or 12 months, while seven studies were cross sectional. In all these studies except one, resource data were collected retrospectively for a period before the interview, at each data collection point. The recall period for which resource use data were measured ranged from 1 week to 1 year (most commonly 3 months).

Two studies were based only on retrospective analysis of data collected for other purposes,

while two studies were based on mail questionnaires. Medical care, formal non-medical care and informal care were assessed by nine of the studies, while six did not estimate at least one of these cost items. The source of funding is presented in table I when stated.

In table II, estimated costs are stratified on disease severity, assessed by the MMSE in most studies. There is large variation in total cost estimates, depending on differences in study methodology, setting, type and severity of patients included, range of costs assessed and the choice of principle for valuing informal care. The median value for total annual care costs in all studies was about €28 000 per patient (median costs are calculated instead of mean costs due to the large variance in estimates between studies).

All studies report a strong relationship between disease severity and costs of care, with costs in severe dementia many times higher than costs in mild disease. Three papers also compared the data with control samples of elderly without dementia and found that costs were substantially lower in the control samples. These strong results are found across all studies, independent of country or healthcare system, and also of the type of study design or range of cost items assessed.

Table III presents costs by resource type (medical care, formal non-medical care and informal care), when possible. Percentages of totals are presented for the eight studies with complete data on all three resource items. Large variations are also observed here, with the share of costs attributed to informal care ranging from 8% to 78%. This most likely reflects differences in the hourly cost assigned to informal care, but also international differences in care structure with a higher reliance on informal caregivers in Southern Europe. Table IV presents the hourly cost of informal care and the average number of hours per day, when available. A brief analysis of the studies by country or region is presented below.

3.1 Belgium

In the National Dementia Economic Study,^[10] 2784 elderly patients in primary care were

Table I. Overview of methodology in cost of illness studies

Study, country	Year of costing	Year of data collection	Subjects ^a	Method (follow-up)	Comparator group	Stratification	Funding	Recall period for resource use	Cost items		
									medical	non-medical	informal
Scuvee-Moreau et al., ^[10] Belgium	2002?	1999–2001?	AD ^{b,c}	Prospective observational study (6 and 12 mo)	Two cohorts: cognitive impairment but no dementia, and no cognitive impairment	MMSE	NA	1 wk	Y	Y	Y
Sou�tre et al., ^[11] France	1991	NA	AD	Cross-sectional (no follow-up)	None	MMSE	I	3 mo	Y	Y	Y
Rigaud et al., ^[12] France	1996	NA	AD ^d	Cross-sectional (no follow-up)	General population	MMSE, ADL, IADL, NPI, GDS	I	6 mo	Y	Y	Y
Schulenberg et al., ^[22] Germany	1995	NA	AD ^b	Cross-sectional (no follow-up)	None	MMSE	NA	3 mo	Y	Y	Y
Cavallo and Fattore, ^[13] Italy	1995	1995	AD	Mail questionnaire (no follow-up)	None	None reported	NA	1 wk	N	Y	Y
Trabucchi, ^[14] Italy	1996?	NA	AD	Prospective observational study (6 and 12 mo)	None	MMSE, CDR, ADL	NA	NA	N	Y	Y
Kronborg Andersen et al., ^[15] Denmark	1997	1992–6	DM ^{b,c}	Prospective population-based observational study (12 mo)	490 matched controls	CDR	G	NA	Y	Y	N
J�nsson et al., ^[8] Nordic region	2003	2001–3	AD ^b	Prospective observational study (6 and 12 mo)	None	MMSE, NPI	I	3 mo	Y	Y	Y
J�nsson et al., ^[27] Sweden	1998	1987–96	DM ^{b,c}	Prospective population-based observational study (no follow-up)	None	MMSE	G	1 wk	Y	Y	N

Continued next page

Table I. Contd

Study, country	Year of costing	Year of data collection	Subjects ^a	Method (follow-up)	Comparator group	Stratification	Funding	Recall period for resource use	Cost items		
									medical	non-medical	informal
Francois et al., ^[28] Finland	2001	1998	DM ^{b,c}	Population-based cross-sectional survey (no follow-up)	None	MMSE	I	NA	Y	Y	Y
Boada et al., ^[17] Spain	1996	NA	AD	Cross-sectional study (no follow-up)	None	MMSE	NA	12 mo	Y	Y	Y
Atance Martinez et al., ^[16] Spain	2000	1991–2000	AD ^b	Retrospective hospital cost database (up to 10 y)	None	None reported	NA	NA	Y	N	N
Sou�tre et al., ^[19] UK	1999?	1994	AD	Cross-sectional study (no follow-up)	56 matched controls	MMSE	I	3 mo	Y	Y	Y
Wolstenholme et al., ^[20] UK	1998	1988–99	AD or VaD	Retrospective analysis of longitudinal study data (mean 40 mo)	None	MMSE, Barthel scores	I, G	NA	Y	Y	N
Livingston et al., ^[21] UK	2003	NA	AD	Prospective observational study (6 mo)	None	Dependency, MMSE	I	3 mo	Y	Y	Y
Lopez-Bastida et al., ^[18] Spain	2001	2001	AD	Mail questionnaire (no follow-up)	None	CDR	G	12 mo	Y	Y	Y

a Unless otherwise stated, patients resided in the community and were already identified and diagnosed in the healthcare system.

b Included institutionalized patients.

c Patients were identified through a screening programme.

d Patients were required not to receive cholinesterase inhibitor treatment.

AD = possible or probable Alzheimer's disease; **ADL** = activities of daily living; **CDR** = Clinical Dementia Rating; **DM** = dementia of any aetiology; **G** = research grant; **GDS** = Global Deterioration Scale; **I** = industry funding; **IADL** = instrumental activities of daily living; **MMSE** = Mini Mental State Examination; **N** = no; **NA** = not available; **NPI** = Neuropsychiatric Inventory Questionnaire; **VaD** = vascular dementia; **Y** = yes.

Table II. Mean annual costs of care per patient by disease severity (€, year 2005 values adjusted using purchasing power parities)

Study	Country	Patients (n)	Annual costs			
			mild dementia	moderate dementia	severe dementia	all subjects
Scuvee-Moreau et al. ^[10]	Belgium	386	6 974	11 538	23 484	14 673
Sou�tre et al. ^[11]	France	51	4 783	NA	7 792	6 435
Rigaud et al. ^[12]	France	50	6 339	15 961	53 574	22 959
Schulenberg et al. ^[22]	Germany	158	3 673	10 120	19 446	12 040
Cavallo and Fattore ^[13]	Italy	423	NA	NA	NA	52 406
Trabucchi ^[14]	Italy	103	NA	NA	NA	28 691
Kronborg Andersen et al. ^[15]	Denmark	245	10 113	15 058	22 521	10 752
J�nsson et al. ^[8]	Nordic region	272	4 953	15 013	30 581	14 038
J�nsson et al. ^[27]	Sweden	70	4 942	20 561	40 180	27 236
Francois et al. ^[28]	Finland	137?	7 670	9 265	16 398	33 333
Atance Martinez et al. ^[16]	Spain	337	NA	NA	NA	30 525
Boada et al. ^[17]	Spain	337	18 311	23 522	31 759	27 595
Sou�tre et al. ^[19]	UK	128	41 982	65 041	86 254	64 426
Wolstenholme et al. ^[20]	UK	100	13 488	22 169	36 132	32 468
Livingston et al. ^[21]	UK	224	NA	NA	NA	35 287
Lopez-Bastida et al. ^[18]	Spain	237	18 372	31 795	52 137	37 287

NA = not available.

screened for dementia: 218 individuals living in the community and 168 institutionalized patients were diagnosed with dementia (113 with cognitive impairment but no dementia, and 106 with no cognitive impairment). Subjects were assessed at baseline and again at 6 and 12 months. Resource use data were collected in detail by telephone interview for the duration of 1 week at two points during the follow-up period. Total average cost was €14 673 per annum.

3.2 France

The two French studies identified were both cross-sectional surveys with small sample sizes (51 and 50 patients, respectively).^[11,12] Both studies included the full spectrum of formal and informal care for AD patients living in the community, and presented costs stratified by MMSE score.

In the 1995 paper by Sou tre et al.,^[11] cost of unpaid informal care (3.8–4.5 hours/day) was estimated at \$US527–\$US692 per 3 months, corresponding to about €1.7 per hour in 2005 values. This estimate was based on average GDP per capita. In the more recent study by Rigaud et al.,^[12] informal care was valued at

€8.45 per hour (average rate for housekeeping work). This explains much of the difference in overall costs between the studies, with the study by Rigaud et al.^[12] presenting higher cost estimates, in particular in patients with more severe cognitive impairment.

The study by Rigaud et al.^[12] also included an estimate of care costs in a reference population of non-demented elderly aged ≥70 years; these costs were small by comparison (about €4000 per year compared with €6339–€53 574 for subjects with dementia with mild to severe cognitive impairment).

3.3 Germany

A single study from Germany was found, in which costs in 158 AD patients were estimated from a payer's perspective from 3-month retrospective registry data. Costs of medical care were estimated from the number of contacts multiplied by unit costs, while non-medical care (formal and informal) was instead calculated from charges per level of dependency. Informal care was thus considered only to the extent that they are reimbursed by a third-party payer. To increase

Table III. Mean annual costs of care per patient by cost category, and share of total costs (€, year 2005 values adjusted using purchasing power parities)

Country	Cost (% of total)			
	medical care	formal non-medical care	informal care	total costs
Belgium ^[10]	8 218 (56)	5 222 (36)	1 233 (8)	14 673
France ^[11]	2 198 (34)	1 946 (30)	2 292 (36)	6 435
France ^[12]	4 910 (21)	4 151 (18)	13 898 (61)	22 959
Germany ^[22]	1 850 (15)	5 494 (46)	4 696 (39)	12 040
Italy ^[13]	NA	NA	NA	52 406
Italy ^[14]	NA	NA	NA	28 691
Denmark ^[15]	3 330	7 422	NA	10 752
Nordic region ^[8]	3 113 (22)	7 167 (51)	3 757 (27)	14 038
Sweden ^[27]	74	27 161	NA	27 236
Finland ^[28]	NA	NA	NA	33 333
Spain ^[16]	NA	NA	NA	30 525
Spain ^[17]	2 851 (10)	3 377 (12)	21 366 (77)	27 595
UK ^[19]	15 913 (25)	4 317 (7)	44 196 (69)	64 426
UK ^[20]	1 818	30 650	NA	32 468
UK ^[21]	NA	NA	NA	35 287
Spain ^[18]	4 676 (13)	2 403 (6)	30 208 (81)	37 287

NA = not available.

comparability with other studies, we divided the non-medical costs into formal or informal depending on whether the majority of care was provided by formal or informal caregivers. The estimated mean total cost of care was €12 040 per year.

3.4 Italy

Two cost-of-illness studies were identified for Italy.^[13,14] Both studies only assessed formal and informal non-medical care, no data on costs of medical care were presented. This is indicative of the structure of dementia care in Italy, which falls largely outside the medical care system. Further, both data sets included information on disease severity; however, total costs were not presented stratified on disease severity in either publication. Both studies were directed towards AD patients living in the community.

Cavallo and Fattore^[13] conducted a postal questionnaire survey of 1501 caregivers to AD patients identified through the national patient organization. The response rate was 41% and after excluding institutionalized or deceased patients the sample size was 423 subjects. On aver-

age 8.8 hours of personal care and 16.4 hours of supervision were provided per day per patient. Personal care was valued at the minimum wage for home health aid, and supervision was valued at the minimum monthly wage for live-in employees.

The CoDem study^[14] was a 12-month follow-up of 103 AD patients, with data collection at baseline, 6 months and 12 months. The number of hours of caregiving time ranged from 14.0 to 17.8 in CDR states 1 and 3, respectively. The total cost of care was \$US585.2 per week, or €28 691 per year (2005 values).

3.5 Nordic Region

In a population-based Danish study,^[15] caregivers of 245 demented elderly and 490 controls were interviewed regarding their resource utilization during the past 12 months. Formal medical and non-medical care was assessed, but not informal care. Patients were staged by CDR scores. Except for very mild dementia, costs of care were no different for AD patients than with other elderly with dementia. Costs were higher for subjects with dementia than with matched controls, even

in very mild dementia (CDR 0.5). Total average formal care cost was €10 752 per patient per year. An analysis has also been conducted on changes in costs over time based on this data set.^[37]

In a Nordic study,^[8] 272 patients with AD and their caregivers in Sweden, Norway, Denmark and Finland were included. Data were collected at baseline and again at follow-up visits at 6 and 12 months. The full range of resource use was considered (formal and informal care). The study adopted a fairly low value of informal care: Swedish krona (SEK)28 (€2.6) for lost leisure time and SEK196 (€18.2) for lost work time per hour. Pooling data from all three interviews, the total average cost of care was estimated at €14 038 per year.

In an economic evaluation of donepezil in Sweden, Jönsson et al.^[27] estimated costs of care based on cross-sectional data from a population-based observational study – the Kungsholmen project.^[30] Subjects (n = 70) were diagnosed with dementia at baseline. Only data on drug usage, home help and accommodation were available in the database. Results have also been published for

the whole cohort including subjects without dementia.^[38] Total costs, €27 236 per patient per year, were dominated by costs of accommodation (>90%).

Francois et al.^[28] estimated 6-month costs of care for patients with mild, moderate and severe dementia in the community and institutions, based on resource use data from the Kuopio 75+ study^[29] in Finland. The average yearly cost was €33 333 per patient.

3.6 Spain

In a retrospective review^[16] of a hospital cost database in the Guadalajara region, 337 patients with AD were identified over a period of 10 years (1991–2000). Cost estimates included primary and specialist care, pharmaceuticals, transportation, special accommodation and the cost of invalidity pensions. Total annual cost was €27 595 per patient; no stratification on disease severity was presented.

A cross-sectional survey^[17] of 337 ambulatory AD patients in 23 health centres across Spain in

Table IV. Approaches used to cost informal care

Study	Informal care costing principle	Mean cost per hour ^a	Mean hours per day
Scuvee-Moreau et al. ^[10]			
Souëtre et al. ^[11]	GNP per capita	1.49	4.5
Rigaud et al. ^[12]	Replacement cost, housekeeping work	8.45	5.6
Schulenberg et al. ^[22]	Reimbursement by third-party payer	NA	NA
Cavallo and Fattore ^[13]	Replacement cost	18.92	6.43
Trabucchi ^[14]	Not stated	NA	NA
Kronborg Andersen et al. ^[15]	NI	NI	NI
Jönsson et al. ^[8]	Average wage (working caregivers), value of leisure time (non-working caregivers)	15.99 (working caregivers); 2.28 (non-working caregivers)	4.0
Jönsson et al. ^[27]	NI	NI	NI
Francois et al. ^[28]	Reimbursement by third-party payer	1.32 per day if MMSE >14; 3.29 per day for MMSE 10–14; 6.58 per day if MMSE <10	NA
Atance Martinez et al. ^[16]	NI	NI	NI
Boada et al. ^[17]	NI	NI	NI
Souëtre et al. ^[19]	GNP per capita	6.13	4.98
Wolstenholme et al. ^[20]	NI	NI	NI
Livingston et al. ^[21]	Not stated	2.00	NA
Lopez-Bastida et al. ^[18]	Average wage	Not stated	8.6

a €, year 2005 values adjusted using purchasing power parities.

GNP = gross national product; **MMSE** = Mini Mental State Examination; **NA** = details of costing approach not available; **NI** = not included.

1996 recorded resource use and costs during the preceding 12-month period. Patients were examined for cognitive and global function (MMSE, Global Deterioration Scale [GDS]), among other factors. Total cost of medical, non-medical and informal care was €30 525 per year, with informal care costs more than three-quarters of the total costs of care.

Lopez-Bastida et al.^[18] conducted a mail survey of 237 caregivers of patients with AD in outpatient care (response rate 61%). Subjects were stratified according to CDR scores: the average cost was estimated to be €37 287 including medical care, community care and informal care.

3.7 UK

Souëtre et al.^[19] examined costs of formal and informal care in 128 non-institutionalized patients with AD and 56 matched controls. Costs were assessed over the 3-month period preceding the interview, and patients were stratified according to MMSE score. Average costs of care were about €64 426 per patient per year, with a predominance of informal care costs. The cost of informal care was estimated as the sum of lost working days (valued at the average wage rate) and caregiver time (valued at GNP per capita).

Wolstenholme et al.^[20] extracted data retrospectively on 100 patients with AD or vascular dementia from a longitudinal study of behaviour in dementia. Data on medical and non-medical formal care were available, and patients were stratified on MMSE scores as well as on Barthel scores^[39] (a measure of ADL abilities). The maximum follow-up time was about 10 years and the average was 40 months. The average annual cost of formal care was estimated at €32 468.

Costs of care in relation to the degree of physical disability were assessed in a study that followed 224 AD patients for 6 months.^[21] Formal and informal care costs amounted to a total of €35 287 per year. Costs were higher for patients with impairment of personal or instrumental ADL than for patients with no ADL impairment.

4. Discussion

4.1 International Differences in Costs of Care

This review has identified 15 European studies presenting primary data on costs of care for patients with AD and other dementias. All studies were from Northern and Western Europe because there are few data available from central and Eastern Europe. Further, structures of care and the level of costs are likely to be very different in these countries, so any attempt to include them in an estimate of the total cost of dementia in Europe would be associated with high uncertainty.^[2,9]

The median estimate of total costs of care is very high: €28 000 annually. However, it is important to distinguish between costs of patients with AD and costs of AD. To estimate the costs due to AD, different methods could be used, e.g. subtracting costs for matched controls or by subtracting costs in very early AD. Taking a conservative approach – subtracting the median cost in mild disease (about €7000 per year) – the cost of AD could be estimated at about €21 000 annually. However, this is likely still an overestimate, since more cost-of-illness studies tend to be undertaken in high-cost countries. Previous studies estimate the mean cost per case to about €8500–10 700,^[1,2] taking into account lower expenditures in Central and Eastern Europe.

Comparability between the studies included in the review is low because of several factors. Classification of resources into medical, formal non-medical and informal care is not consistent across the studies. For example, residential care is classified as medical resource use by some studies and non-medical by others, depending on the local circumstances. It is therefore difficult to reach strong conclusions about international differences in patterns of care or total care costs. However, the data are consistent with a higher reliance on informal care in southern Europe (Italy, Spain) than in other countries. These international differences highlight the need for novel data on resource use in relation to disease severity specifically for each healthcare system.

4.2 Selection of Study Subjects

Most studies only recruited patients living in the community, excluding institutionalized patients, thereby likely underestimating total costs of care as well as the relationship between disease severity and care costs, since the risk of institutionalization increases with disease severity. On the other hand, informal care costs may be overestimated by the selection of participants, particularly since the studies rely on patients and caregivers volunteering to participate.^[21] These subjects may be particularly motivated and caregivers more involved in the care of the patient than the average subject or caregiver.

4.3 Measuring and Valuing Informal Care

Although estimates of informal care costs vary between studies, it is clear that these constitute a significant share of total care costs and indicate a burden and strain on informal caregivers. This underscores the need for a societal perspective in cost assessment. If a narrow costing perspective is adopted (e.g. a healthcare payer perspective), this may lead to an underestimation of the benefits from therapies that reduce the burden on caregivers and consequentially an under-utilization of these treatments if the results of the economic evaluation are used to guide treatment decisions.

The measurement and valuation of informal care is an issue of critical importance, and the choice of method has substantial consequences for the results. Few studies report the cost data disaggregated into quantities and unit costs, which may in part be due to limitations on the length of articles. From the studies that report the value assigned to informal care, it is clear that there are large differences in how this is assessed.^[40] There is less variability in estimates of the average caregiver time per day than in the cost per hour, mainly due to different valuation principles. One issue in estimating the amount of time of informal care is the frequent reporting of up to 24 hours per day, leading to very high cost estimates that may overlook aspects of joint production (i.e. caregivers per-

forming multiple tasks simultaneously). Another issue is the distribution of informal caregiving tasks over several caregivers. Many studies have only interviewed the 'primary' caregiver, overlooking the contribution of other people involved in the care of the patient.

Most studies assign a flat rate per day in nursing homes, which does not account for the higher needs and care burden in residents with more severe dementia.^[41] A general conclusion from practically all cost-of-illness studies in dementia is that costs increase with disease severity, most often measured by the degree of cognitive impairment. Two studies^[8,37] have also presented analyses of how changes in costs of care over time relate to changes in cognitive function. This analysis requires repeated observations or longitudinal registry data, and provides further insight into the dynamics of cognitive change and development of care needs.

There is also some evidence that when cognitive function and ADL functionality are considered jointly, the latter has a stronger influence on resource use and costs of care.^[20] This is logical, as the ADL capabilities of the patient can be expected to correlate directly with the level of care needs and thus resource utilization and cost. However, cognitive function and ADL function are strongly interrelated, as cognitive impairment is a main cause of the functional impairment in dementia.

4.4 Applicability for Economic Modelling

Few studies relate costs to indicators of disease severity other than cognition, which has mostly been assessed with the MMSE. To link clinical trial data with epidemiological data in a model requires that the same instruments were used in both data sources, or that it is possible to map one instrument onto the other. In AD drug trials,^[42] MMSE has mostly been employed to stratify patients at baseline, while other instruments have been preferred as the primary outcome measure, such as the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), due to superior sensitivity to change. Previous model studies have therefore either been

based on effects on the MMSE as a secondary endpoint, or by mapping ADAS-Cog results to the MMSE. Both methods introduce additional uncertainty in cost-effectiveness estimates and disregard potential effects on domains other than cognition. Basing future models on existing cost of illness data therefore has important limitations, and careful consideration should be given by modellers to the small number of available studies per country.

4.5 Recommendations for Future Studies

Based on the data summarized in this article we can attempt some modest suggestions for future studies of the cost of illness in dementia. First, we would recommend the use of a validated instrument for the assessment of informal care. The Resource Use in Dementia (RUD) scale, and the abbreviated version RUD Lite, is probably the most well documented and widely used instrument for assessing informal care time in dementia.^[32] Second we recommend assessing disease severity in all of the following domains, using appropriate instrumentation: cognitive function, ADL function and behavioural disturbances. Third due to the high variability of costs across countries and care settings, our recommendation is to stratify the sampling of study subjects so that an adequate sample size is attained within each country and care setting.

5. Conclusions

The annual costs of AD in Europe are substantial and they increase with disease severity. In cost-of-illness studies based on patient-level data, the cost per case of AD varies considerably, with a median of €28 000 per year (range €6614–€64 426). A lack of a standard methodological approach makes comparisons difficult across and within countries and healthcare systems. More studies are needed to improve the volume of data and the breadth and consistency of cost elements included. As a result, these data will become more transparent and reliable, particularly when used in models to conduct economic evaluations of therapies for AD.

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