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SYSTEMATIC REVIEW

The Costs of Dementia in Europe: An Updated Review and Meta-analysis

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Abstract

Background and Objective The prevalence of dementia is increasing, while new opportunities for diagnosing, treating and possibly preventing Alzheimer's disease and other dementia disorders are placing focus on the need for accurate estimates of costs in dementia. Considerable methodological heterogeneity creates challenges for synthesising the existing literature. This study aimed to estimate the costs for persons with dementia in Europe, disaggregated into cost components and informative patient subgroups.

Methods We conducted an updated literature review searching PubMed, Embase and Web of Science for studies published from 2008 to July 2021 reporting empirically based cost estimates for persons with dementia in European countries. We excluded highly selective or otherwise biased reports, and used a random-effects meta-analysis to produce estimates of mean costs of care across five European regions.

Results Based on 113 studies from 17 European countries, the estimated mean costs for all patients by region were highest in the British Isles (73,712 EUR), followed by the Nordics (43,767 EUR), Southern (35,866 EUR), Western (38,249 EUR), and Eastern Europe and Baltics (7938 EUR). Costs increased with disease severity, and the distribution of costs over informal and formal care followed a North-South gradient with Southern Europe being most reliant on informal care.

Conclusions To our knowledge, this study represents the most extensive meta-analysis of the cost for persons with dementia in Europe to date. Though there is considerable heterogeneity across studies, much of this is explained by identifiable factors. Further standardisation of methodology for capturing resource utilisation data may further improve comparability of future studies. The cost estimates presented here may be of value for cost-of-illness studies and economic evaluations of novel diagnostic technologies and therapies for Alzheimer's disease.

Key Points

This study is the most comprehensive review and meta-analysis to date of the costs in persons with dementia in Europe. Costs are presented disaggregated by type of resource use, disease severity, care setting and region, based on 113 studies capturing patient-level cost data for over 300,000 persons with dementia.

Mean annual costs vary substantially between regions, from almost 8000 EUR in Eastern Europe and the Baltics, to over 70,000 EUR in the British Isles, and were considerably higher in institutionalised patients and those with more severe disease.

These data can be utilised in future economic modelling, for example of the cost effectiveness of disease-modifying interventions.

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1 Introduction

1.1 Rationale

Dementia is a syndrome characterised by a decline in cognition and loss of functional abilities, commonly caused by neurodegenerative disorders including Alzheimer's disease (AD). As a result of the combination of population growth and increasing life expectancy, the global prevalence of dementia is expected to rise from 55 million cases in 2019 to 139 million cases in 2050 [1]. In Europe, the number of cases is expected to rise by almost 80% over the same period, from 14.1 to 25 million cases. The high level of care needed for persons with dementia (PWD) causes significant stress to loved ones, caregivers and healthcare systems. Thus, the rapidly growing prevalence of dementia spells an enormous burden to health and social care systems.

There are important differences between countries in how dementia care is organised, funded and delivered. A key difference lies in the balance between formal (i.e. paid care from healthcare professionals or organisations) and informal care (i.e. unpaid care through a patient's social network). Evidence points to a cultural and institutional gradient from North to South Europe, with informal care being more prominent in Southern European countries [2]. This has consequences for costs and limits the transferability of economic studies between countries and regions.

In order to adequately allocate resources to and within dementia care, and to assess the potential value and cost effectiveness of new technologies to diagnose, treat and prevent dementia disorders, it is imperative to understand the economic impact of dementia across Europe. Specifically, the costs of care in different stages of dementia severity are a critical input for health economic evaluations. Currently, often a single source of cost data is used in economic models, rather than a comprehensive assessment of all potentially available sources of cost data [3].

A number of systematic reviews have previously examined the cost in PWD. Quentin et al. [5] identified 28 studies (14 European) published before 2008, noting an increase in both formal and informal costs by disease severity. Furthermore, since the publication of our own review of the costs of dementia in 2009 [4], the number of dementia cost-of-illness publications has increased substantially. Schaller and colleagues [6] reviewed 27 studies published in 2003–12, including 15 from Europe, and identified institutionalisation and informal care as important cost drivers, but also a high variability in methodology across studies. Marešová et al. [7] reviewed studies published in 2007–2017, and included eight studies (of which six European) in a meta-analysis of total costs by disease severity. Cantarero-Prieto and colleagues found 26 studies published in 2010–2018, and estimated the total costs of care in Europe based on results from ten studies [8].

Previous reviews have consistently found that methodological differences across studies make it difficult to combine or even compare results across studies, and none has attempted to produce meta-analytic estimates of care costs based on the full range of published studies. Few multinational studies use consistent measurements and data collection procedures across countries [2, 9–15]. Furthermore, although efforts have been made to standardise the assessments of care costs [16, 17], there is no universal standard for categorising resource use, making across study comparisons challenging. Therefore, a comprehensive meta-analysis accounting for methodological heterogeneity is needed to synthesise the current literature.

1.2 Objectives

The purpose of this study was to compile the results from cost-of-dementia studies in Europe to obtain meta-analytic estimates of the annual medical, non-medical and informal care cost per PWD. Additionally, we aimed to stratify costs into informative categories, such as region, disease severity and care setting.

2 Methods

2.1 Eligibility Criteria

In addition to the 16 studies identified in our previous review, we conducted a literature search for studies reporting cost estimates for PWD in European countries published in 2008 or later. Studies presenting data for PWD with any underlying cause: AD vascular dementia, dementia with Lewy bodies or dementia with unknown aetiology were included. To be included in the analysis, studies were required to report data on estimates for at least one cost item of interest (direct medical costs, non-medical costs and/or informal care costs). Studies were required to be based on empirical data in a defined study population and with a reported sample size. We included studies where (1) the source of the data was described, (2) the study population was identified and (3) the cost estimates were clearly presented so that the type of cost, currency and year of costing could be identified.

We excluded economic models and other analyses that were based on cost data reported elsewhere as well as hypothetical cost calculation studies. Studies presenting aggregated data across multiple European regions were excluded. We did not exclude studies based on language, nor did we exclude studies that reported cost data for other populations (e.g. healthy elderly individuals), provided costs for PWD were reported separately.

2.2 Quality Assessment

We qualitatively assessed studies for the presence of methodological issues that would compromise the validity of cost estimates. We excluded studies that selected only patients utilising a specific resource (e.g. hospitalisations) without considering the population at risk, or that considered only costs related to a specific symptom or complication (e.g. behavioural disturbances). Additionally, we excluded studies that focused only on the last years of life (i.e. decedent studies), and studies that only included costs for diagnosis or only out-of-pocket payments. Such partial or selective studies could not be easily incorporated in the meta-analysis to contribute towards the estimate of costs of care.

2.3 Search Strategy

The literature search was conducted in the databases PubMed, Embase and Web of Science. We began with broad search criteria including the concepts 'Cost', 'Economic', 'Dementia' and 'Alzheimer', and iteratively optimised the strategy to give a manageable number of hits to review. We found that restricting some search terms to title fields greatly improved specificity while not compromising the sensitivity of the search, as the search identified studies quoted in previous reviews. We did not limit the search to European countries, as we found that many studies did not explicitly state the geographic setting in searchable fields. The final search term string was as follows: (cost[Title] OR costs[Title] OR economic[Title] OR economics[Title]) AND (Alzheimer OR dementia). The same search string was used in all databases, and the literature search was completed in July 2021.

2.4 Selection and Data Extraction Process

Screening of search hits and extraction of key study characteristics (study design, study population, year of data collection, country, resource use measurements, year of costing and currency) was conducted by two independent reviewers (LJ, OF), after which results were tabulated and discrepancies reconciled through consensus. Data on individual cost items were then extracted by a single reviewer (LJ). For each cost estimate, the following data were extracted: study, country, population, setting (community or institution), sex, disease stage, resource use item, mean or median cost, standard deviation, confidence interval or interquartile range and sample size. Costs were then aggregated by study and cross-checked against the original publications to identify and correct any errors in data extraction. Methods and results are reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [18].

2.5 Data Harmonisation and Cost Estimation

Cost data were classified into three major categories: direct medical costs, direct non-medical costs and informal care costs. Direct medical care costs include inpatient care, outpatient care (encompassing specialist as well as primary care, visits to nurses and other healthcare professionals) and pharmaceuticals. Direct nonmedical care includes residential care (nursing home, group living or other institution) and community care (all other non-medical care services such as home help, day care and delivered meals). Informal care costs were separated into costs related to caregiver productivity loss, and costs related to lost caregiver leisure time. The reason for this distinction is that different opportunity costs are often assigned to lost work time and lost leisure time, respectively, for caregivers. All cost data were extracted verbatim as reported in publications, and later recoded to match the categories outlined above. Thus, costs that were reclassified according to our categories are in some cases reported differently than in the original publications. All costs were converted to Euros (EUR) 2021 by first converting from local currency to EUR using historic exchange rates from the year of costing for each study.[1] Historic cost data in EUR were then inflated to 2021 EUR through the European Union harmonised index of consumer prices.[2]

The majority of studies that reported costs by disease severity used the Mini-Mental State Examination (MMSE) to stratify patients ($n = 35$) [19]. The scores were stratified into mild dementia (MMSE ≥ 20), moderate dementia (MMSE 10–20) and severe dementia (MMSE < 10). If the cut-off values used in the individual studies did not match these intervals precisely, the closest interval was chosen for each subgroup. Eleven studies reported costs stratified by the Clinical Dementia Rating Scale ($n = 9$) [20] or the Global Deterioration Scale [21] ($n = 2$), for which we used the corresponding levels for mild, moderate and severe dementia, respectively.

Seven studies reported costs stratified by the Dependence Scale [22] ($n = 3$) or other measures of activities of daily living dependency ($n = 4$), while two studies reported costs by the degree of behavioural disturbances (the Cohen Mansfield Agitation Inventory [23] or the Neuropsychiatric Inventory [24]). For these studies, the reported subgroups were mapped into mild, moderate and severe dementia based on the mean reported MMSE scores or distributions across Clinical Dementia Rating (CDR) levels for each subgroup. Just over half of the studies did not report costs for specific levels of disease severity ($n = 58$).

[1] Downloaded from Eurostat https://ec.europa.eu/eurostat/web/exchange-and-interest-rates/data/database, table ert_bil_eur_a, accessed 14 August 2021.

[2] Downloaded from https://ec.europa.eu/eurostat/web/hicp, accessed 14 August 2021.

For studies that reported standard errors (SEs), standard deviations (SDs) were calculated from $SD = SE \times \sqrt{n}$. For studies reporting only 95% confidence intervals (CIs), SDs were obtained by $SD = \frac{\sqrt{n} \times (U\ 95\%\ CI - L\ 95\%\ CI)}{2 \times 1.96}$ [25]. We assumed statistical independence between cost categories, thus the variance of the sum of the cost components was estimated by the sum of the variance of the components.

Countries were grouped into regions according to a modification of the United Nations classification of world regions [26]. Northern Europe was split into the British Isles (UK, Ireland) and the Nordic countries (Sweden, Norway, Denmark, Finland). The Nordic countries were reported separately as many studies originated from these countries that were also relatively similar in care system structure. The Baltic countries were grouped with Eastern Europe, as levels of Gross Domestic Product (GPD) and care spending are closer than with Northern Europe (Table 1).

Study designs were classified as the following categories: *retrospective database analyses* when based on secondary analysis of existing data, *prospective observational studies* when involving longitudinal data collection in a non-interventional setting, *clinical trials* when including randomisation, *surveys* when based on data collected through postal or online surveys and otherwise as *cross-sectional observation studies* when collecting data at a single timepoint.

2.6 Imputations

As some studies presented only aggregations of cost components (e.g. total direct medical cost), a complete break-down by cost component was computed by applying the distribution over cost components from other studies within the same region for the same care setting and disease severity. Where no other studies were available in the same group, consecutive broader groupings were utilised until all studies had been matched with breakdown over cost components. Missing standard deviations were imputed based on the mean coefficient of variation for the same cost component across all studies. We assumed that the total sample size distributed equally across subgroups for two studies [27, 28], which did not report the sample size by subgroup.

2.7 Meta-analysis

Meta-analytic estimates of mean costs were generated separately for each cost component within each region, care setting and level of disease severity. In total, 420 separate meta-analyses were conducted: by seven cost components, five regions, three care settings (community, institution, all) and four disease severity categories (mild, moderate, severe, all). Results from these meta-analyses were then combined into final cost estimates and aggregated into total medical,

Table 1 Number of included studies and sample size by region, population and study methodology

Categories	No. of studies	Sample size
All studies	113	3,187,26
British Isles	36	15,311
Ireland	4	577
UK	32	14,244
Multiple countries	1	490
Eastern Europe and Baltics	5	61,390
Czechia	1	119
Estonia	2	495
Hungary	2	60,776
Nordics	23	182,164
Denmark	5	106,375
Finland	6	72,443
Norway	3	350
Sweden	11	2726
Multiple countries[a]	1	270
Southern Europe	26	12,035
Italy	5	1215
Portugal	3	225
Spain	18	9933
Multiple countries[a]	1	662
Western Europe	39	48,036
Austria	1	1341
Belgium	2	741
France	9	2691
Germany	21	41,282
The Netherlands	11	1491
Multiple countries[a]	1	490
Care setting		
All[b]	41	286,287
Community	67	24,718
Institution	20	7931
Disease severity		
All[b]	58	286,806
Mild	44	10,394
Moderate	53	14,570
Severe	39	6986
Diagnosis		
Dementia[c]	71	179,468
AD	41	137,185
DLB	1	194
VaD	2	2089
Study methodology		
Cross-sectional	33	13,234
Prospective	33	13,108
Retrospective	18	287,102
Clinical trial	29	5492

[a]Studies reporting aggregated data for multiple countries within a region

[b]All refers to studies reporting aggregated data only

[c]Aetiological diagnosis not specified

AD Alzheimer's disease, *DLB* dementia with Lewy bodies, *VaD* vascular dementia

non-medical and informal care costs. Statistical precision of meta-analytical estimates was based on actual sample size, excluding imputations. Studies were pooled using a random-effects model with inverse variance weighting. The random-effects model was chosen (over a fixed-effect model) as we expected considerable methodological heterogeneity across studies. For each meta-analysis, we report the studies included, sample size, per-study mean costs and the meta-analytic cost estimate with 95% CI. Between-study heterogeneity was assessed with the chi-squared test and I^2 statistic [25].

To explore the effect of relevant covariates on cost estimates, separate linear meta-regression models were estimated for each cost component with the following covariates: study method, diagnosis (all dementia vs AD, AD vascular dementia, dementia with Lewy bodies), region, disease severity, care setting and time period (before 2005, 2005–2009, 2010–2014, 2015 and later). All analyses were conducted in R Studio 1.4.1717 using the *meta* package [29].

3 Results

3.1 Study Selection

Figure 1 presents the PRISMA flow chart for the literature search. The initial search contained 2209 hits after the removal of duplicates. After review of the title and abstract, 205 studies were accessed and assessed for eligibility. The most common reasons for exclusion were studies based on top-down methodology ($n=32$), duplicate reports of the same study ($n=28$) and insufficiently reported cost data ($n=28$). The final selection for analysis included 113 studies, which includes the 16 studies published before 2008 from our previous review.

3.2 Study Characteristics

Table 1 presents an overview of characteristics of the studies included in the meta-analysis. In total, 113 studies were included, capturing data for 318,936 patients from 17 European countries [2, 9–15, 27, 28, 30–131]. Most studies were relatively small, with a median sample size per study of 233 patients. Excluding retrospective studies, the median sample size was 198 (range 22–1678). Participants had an average age of 79 years (range 47–101 years). Western Europe was covered by 34.5% of publications ($n=39$), followed by the British Isles ($n=36$), Southern Europe ($n=26$), the Nordics ($n=23$), and Eastern Europe and the Baltics ($n=5$). The UK, Germany and Spain were covered by the most publications (32, 21 and 18 studies, respectively), while the largest numbers of patients were captured by retrospective studies in Denmark, Finland, Hungary and Germany (Table 1). Primarily, studies included patients with unspecified dementia ($n=71$) or patients with AD ($n=41$), while a small number of studies captured other dementia disorders: vascular dementia ($n=2$) and dementia with Lewy bodies ($n=1$). Cross-sectional and prospective observational designs were most common, each represented by 33 studies, while 18 retrospective database studies and 29 clinical trials were included.

Studies were most frequently conducted in community-dwelling patients ($n=67$), while 20 studies reported data specifically for institutionalised patients and 41 studies enrolled patients both from the community and institutions and did not report costs separately by care setting. Fifty-five studies reported cost data by disease severity for 32,130 patients. Only two studies presented cost data separately by sex. A detailed summary of each included study is provided in the Electronic Supplementary Material.

In Table 2, we show a summary of the number of studies providing evidence on different cost components by geographic region and care setting. The study counts presented in the table were produced before any imputations were carried out. The distribution of studies is highly uneven, with many studies providing evidence on costs in community care, particularly in Western Europe and the British Isles. Eastern Europe and the Baltics have comparatively fewer institutional care studies and only a handful of studies report costs.

3.3 Meta-analytic Cost Estimates

Detailed results from the individual meta-analyses for each cost component and for each subgroup are presented in the ESM. The median number of studies included in each analysis was 5 (range 1–28). There was moderate heterogeneity across studies, indicated by a mean I^2 statistic of 55%. I^2 was similar across disease severity levels, but lower in the institutional care setting (33%) compared with the community setting (72%). This can be expected as costs in the institutional setting are dominated by the cost of residential care, which is relatively uniformly assessed across studies. Heterogeneity was lowest in Southern Europe (39%) and highest in Eastern Europe (73%).

Table 3 presents estimated mean costs by region, based on data averaged across care settings and disease severity levels. The mean annual cost per PWD ranged from 7938 EUR (Eastern Europe and Baltics) to 73,712 EUR (British Isles); the Nordics, Southern and Western Europe fell between these values with 43,767 EUR, 35,866 EUR and 38,249 EUR, respectively. The higher cost in the British Isles region was mainly driven by a higher cost of caregiver leisure time loss, which in turn was not caused by a single outlying study but rather several studies reporting high costs

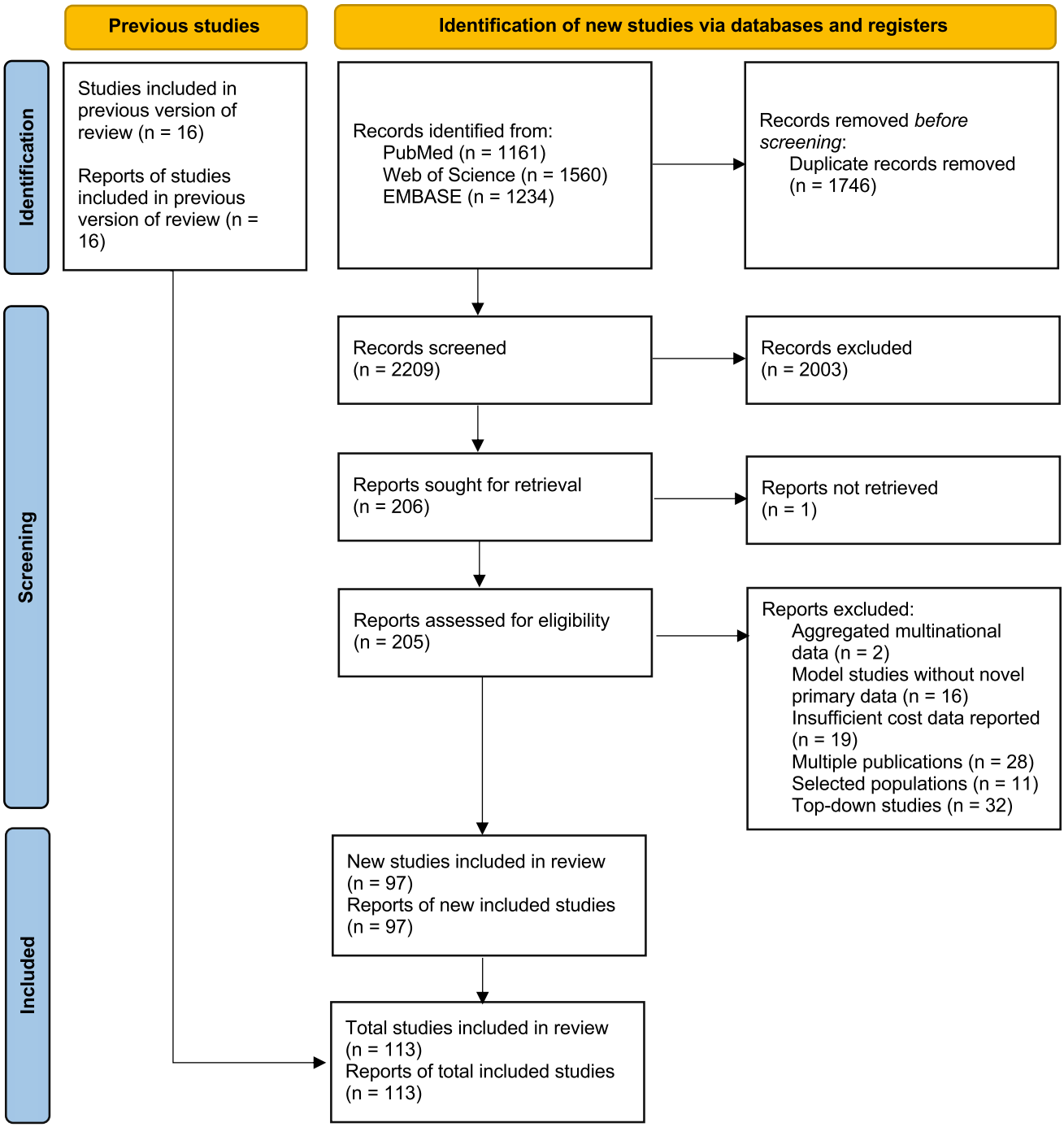

Fig. 1 PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flow chart

for informal care using different methodologies [39, 77, 91, 111].

The distribution of costs over cost components (direct medical costs, direct non-medical costs and informal care costs) varied substantially between regions (Fig. 2). There is a North–South gradient with higher use of formal care services in the Nordics and greater reliance on informal care in Southern Europe, with other regions falling between these extremes while British Isles had a similar cost distribution to Southern Europe.

Table 4 presents costs by disease severity and care setting in each region. The studies included in meta-analytical estimates vary between cells in the table, thus the estimated cost across all severity levels is not necessarily equal to the average of the cost estimates for each severity level. In line with the literature, institutionalised patients generally have

Table 2 Number of studies providing data on different cost components, by region and care setting

Care setting	British Isles			Eastern Europe and Baltics			Nordics			Southern Europe			Western Europe		
	All	Community	Institution	All	Community	Institution	All	Community	Institution	All	Community	Institution	All	Community	Institution
Direct medical costs	5	6	4	1	2	1	5	2	2	4	6	3	6	21	6
Inpatient care	9	15	5	3	2	1	9	4	2	4	8	3	7	20	6
Outpatient care	6	13	4	1	1	0	6	3	1	3	5	2	6	18	5
Pharmaceuticals	7	6	3	2	1	0	6	1	1	4	6	4	6	17	5
Direct non-medical costs	4	9	3	1	1	1	7	4	2	4	10	4	2	18	2
Institutional care	4	8	4	1	1	1	6	5	2	3	6	3	4	15	3
Community care	6	16	4	1	2	1	7	4	2	4	9	3	3	18	4
Total direct costs	5	12	4	2	1	1	5	5	2	5	5	3	5	18	2
Informal care costs	3	11	1	1	2	1	6	4	1	6	11	1	2	21	2
Caregiver work loss	2	2	1	0	1	0	2	3	1	4	3	2	0	6	1
Caregiver time	1	1	0	0	1	0	2	1	0	1	0	0	1	4	0
Total costs	3	4	0	0	0	0	3	6	3	2	1	0	0	6	1

No imputations or aggregations were carried out before counts were produced

higher overall costs than community-dwelling patients, driven by higher direct non-medical costs [2]. Estimated total annual costs of care increased with higher disease severity in all regions, though CIs around estimates are wide. When examined separately within each care setting, the relationship between disease severity and cost is clear in the community setting but less consistent for institutionalised patients. In some regions, costs for institutionalised patients with mild dementia are lower than in community-dwelling patients with mild dementia, but this is based on a small sample size as most institutionalised patients have moderate-to-severe dementia. A major part of the increase in costs in more severe disease is driven by a higher rate of institutionalisation.

Figure 3 presents costs by disease severity and region, disaggregated by cost component. The relationship between costs and disease severity is evident in direct non-medical costs and costs of informal care, while direct medical costs do not clearly increase with disease severity.

Only two studies assessed costs separately for male and female individuals: Ruiz-Adame Reina et al. [103] found that there was an increased proportion of direct, indirect and out-of-pocket spending for male compared with female individuals for direct medical (56.5% on male individuals), indirect (53.1% on male individuals) and out-of-pocket spending (56.7% on male individuals), while Schwarzkopf et al. [107] only looked at direct medical costs and found a light increase in spending on female individuals (48.9% on male individuals).

3.4 Meta-regression

Results from the meta-regression are shown in Table 5. I^2 statistics close to 100% indicate that, as can be expected, heterogeneity between cost estimates was extremely high when pooling data across regions, care settings and severity levels. The amount of heterogeneity explained by the regression model (indicated by the R^2 statistics) was substantial, with a range from 22% for drug costs to 67% for residential care.

There were some important differences in cost estimates depending on study methodology. Compared with cross-sectional studies (reference category), retrospective designs gave somewhat higher costs for inpatient care. This could be due to a longer follow-up time and more accurate recall in retrospective studies, increasing the likelihood of accurately capturing rare hospitalisation events. The cost for caregiver time varied substantially across methodologies; the high cost in retrospective study designs is driven by a single study reporting informal care data from an administrative database [33]. Randomised trials also reported higher costs for informal care compared with cross-sectional or prospective observational designs, potentially because of a greater use of comprehensive assessment scales for informal care.

Table 3 Annual mean costs per person with dementia, by region and cost component (95% confidence interval), Euros

	British Isles	Eastern Europe and Baltics	Nordics	Southern Europe	Western Europe
Direct medical costs	5630 (4336–6924)	1218 (249–2186)	5439 (4002–6877)	3292 (2106–4478)	6189 (5234–7145)
	$n=10$	$n=3$	$n=13$	$n=7$	$n=12$
Inpatient care	3509 (2345–4674)	309 (152–466)	3212 (1993–4431)	537 (113–962)	2448 (1788–3108)
	$n=9$	$n=3$	$n=12$	$n=6$	$n=12$
Outpatient care	962 (601–1323)	329 (18–641)	985 (416–1554)	734 (359–1110)	2386 (1778–2994)
	$n=9$	$n=3$	$n=10$	$n=6$	$n=12$
Pharmaceuticals	1159 (725–1593)	579 (0–1483)	1242 (735–1749)	2020 (978–3062)	1356 (1027–1684)
	$n=9$	$n=3$	$n=11$	$n=7$	$n=12$
Direct non-medical costs	15530 (7758–23,303)	3169 (0–7508)	26,595 (19,483–33,708)	6926 (3131–10,722)	16,008 (12,060–19,955)
	$n=8$	$n=3$	$n=11$	$n=7$	$n=10$
Institutional care	9511 (2282–16,739)	2242 (0–6495)	21631 (14,800–28,462)	2617 (0–5279)	9154 (6066–12,243)
	$n=7$	$n=3$	$n=11$	$n=7$	$n=9$
Community care	6020 (3163–8877)	926 (64–1789)	4964 (2984–6945)	4310 (1605–7015)	6853 (4394–9313)
	$n=7$	$n=3$	$n=11$	$n=7$	$n=8$
Total direct costs	21,160 (13,281–29,040)	4386 (0–8833)	32035 (24,778–39,291)	10218 (6242–14,195)	22,197 (18,135–26,259)
	$n=10$	$n=3$	$n=14$	$n=8$	$n=12$
Informal care costs	52,552 (0–114,583)	3551 (2432–4671)	11,733 (95–23,370)	25,647 (6046–45,249)	16,052 (6763–25,340)
	$n=5$	$n=2$	$n=8$	$n=8$	$n=6$
Caregiver work loss	1740 (122–3358)	581 (0–1619)	861 (453–1270)	915 (106–1725)	1061 (429–1694)
	$n=5$	$n=2$	$n=8$	$n=8$	$n=5$
Caregiver time	50812 (0–112,822)	2970 (2548–3392)	10,871 (0–22,501)	24732 (5147–44,317)	14,991 (5724–24,257)
	$n=5$	$n=2$	$n=8$	$n=6$	$n=6$
Total costs	73712 (11,182–136,242)	7938 (3352–12,523)	43,767 (30,053–57,481)	35,866 (15,865–55,867)	38,249 (28,111–48,386)
	$n=10$	$n=3$	$n=15$	$n=10$	$n=12$

Mean costs were averaged across care settings and disease severity levels

n number of studies contributing to each estimate

Few studies reported cost data for other diagnoses than AD, and there were no systematic differences depending on diagnosis (AD, AD vascular dementia, dementia with Lewy bodies or dementia without specific aetiological diagnosis). Cost differences by disease severity were statistically significant only for residential care and informal care costs, but with a trend toward higher cost in more severe disease for other cost components except inpatient care. Institutionalised patients had higher costs for accommodation and outpatient medical care, but lower costs for all other services including informal care. There was no clear time trend of costs, though the latest time period had numerically lower costs across all components, except for drug costs, compared with the earliest period.

4 Discussion

4.1 Findings in Context

In this study, we estimate the costs of dementia in Europe by synthesising evidence from a large body of literature mainly published over the past two decades. Though there is extensive diversity across the 113 studies included in the analysis, our study demonstrates the feasibility of producing meta-analytic estimates of costs of care regions and informative subgroups.

4.1.1 Annual Costs of Care

The mean total annual cost estimates presented here are largely consistent with previous estimates; a recent assessment of the global costs of dementia conducted by the World Health Organization reported a mean annual cost per PWD

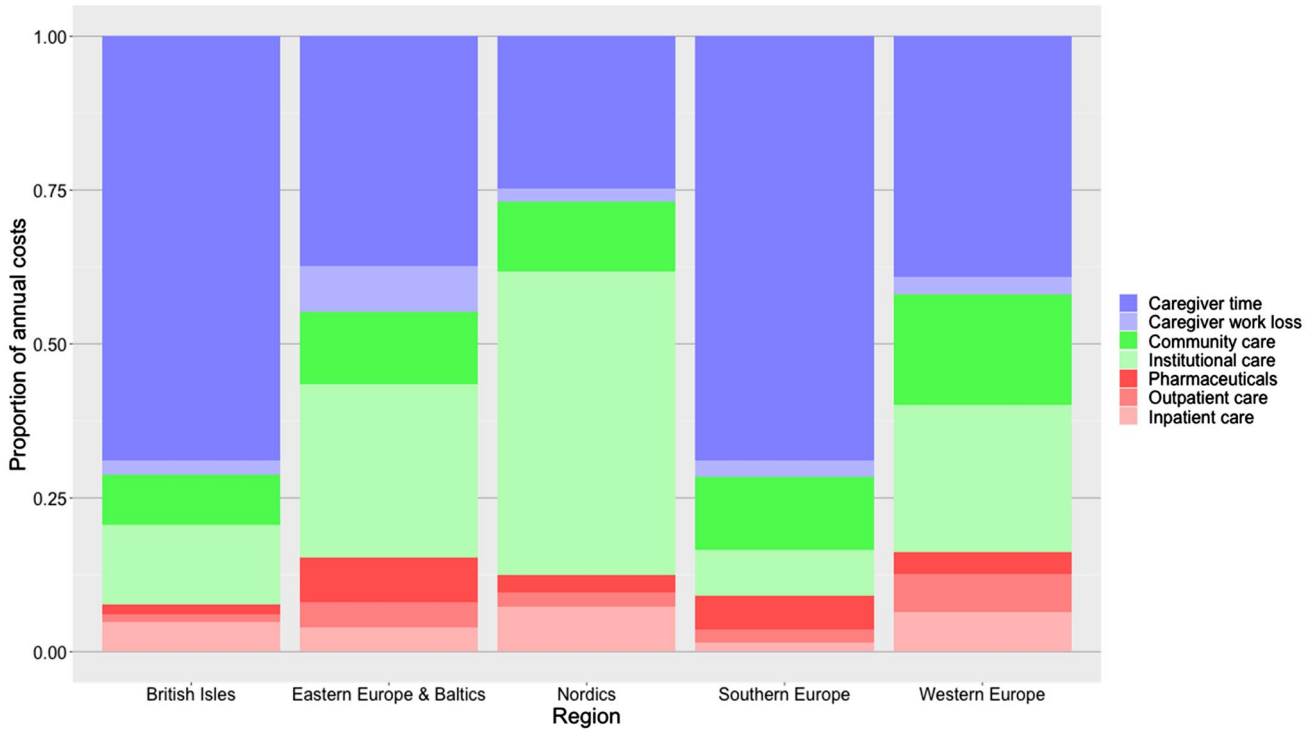

Fig. 2 Distributions of dementia cost over components, by region

in Europe of US$31,114 [1]. Marešová et al. [7] estimated the costs in mild, moderate and severe dementia to 16,659, 22,677 and 33,726 EUR per year, respectively, based on a meta-analysis of eight mainly European studies. Cantarero-Prieto and colleagues reported a mean annual cost care in Europe of 32,507 EUR based on ten studies [8], while Schaller et al. estimated mean annual costs to $31,896 based on an international sample of 11 studies [6].

Few studies thus far have collected cost data across multiple European countries using uniform data collection methodology, allowing direct comparison of resource utilisation and costs across countries. Published after the conclusion of our analysis, Meijer et al. [132] analyzed survey data from 11 European countries to assess out-of-pocket health and social care and unpaid formal care. They found that informal care made up 50–90% of the total cost of dementia and estimated the total cost per individual to be between 2689 EUR in Estonia to 15,468 EUR in Germany per year. Their lower estimates compared with the present study could potentially be attributed to under-sampling patients with severe dementia and overestimating the proportion of out-of-pocket spending to total spending [133].

4.1.2 Distribution Over Cost Components

Dementia care costs across Europe were dominated by informal care and direct non-medical costs (i.e. residential care and home care). There was a distinct contrast between regions in terms of the balance of informal care and direct non-medical care. The Nordics and Western Europe had higher direct non-medical costs compared with informal care, while Southern Europe had the lowest direct non-medical costs. The variability in cost across a North-to-South gradient has been noted in the literature and is likely owing to differences in cultural expectations of ageing and familial duty, as well as the availability and coverage of formal care services [134]. Differences in valuations of informal care may also play an important role, and should be the topic of further study as there is currently no established consensus regarding the appropriateness of alternative methods for valuing informal caregiving time.

In the World Health Organization report, annual direct medical costs were estimated to US$3624, direct non-medical costs US$13,128 and informal care costs US$14,393 [1]. These results are of similar magnitude and distribution over cost categories as the estimates reported here, if averaged across European countries.

In comparison to multi-national studies with a standardised data collection, our results of the cost breakdown between informal care and formal care closely match the estimates published in the ICTUS study [2]. Our finding of high informal care costs in the UK and Ireland have also been observed in other studies. In the GERAS study [14], the UK had substantial higher caregiver time as well as more

Table 4 Mean annual care costs by care setting, disease severity and region (95% confidence interval), Euros

Setting	Severity	British Isles	Eastern Europe and Baltics	Nordics	Southern Europe	Western Europe
Community	Mild	30,098 (13,517–46,679)	3360 (0–8068)	24,928 (19,699–30,157)	21,452 (19,066–23,837)	28,642 (20,697–36,587)
		$n=6$	$n=2$	$n=5$	$n=6$	$n=11$
Community	Moderate	37,008 (23,190–50,827)	5205 (0–10675)	28,444 (19,519–37,369)	26,610 (22,075–31,145)	46,220 (30,341–62,098)
		$n=9$	$n=3$	$n=6$	$n=9$	$n=14$
Community	Severe	51,567 (22,142–80,993)	6081 (0–12286)	32,732 (24,316–41,148)	31,495 (26,190–36,799)	37,626 (27,258–47,993)
		$n=5$	$n=2$	$n=5$	$n=6$	$n=7$
Community	All	36,776 (20,025–53,526)	5398 (0–11058)	27,740 (20,250–35,230)	25,020 (15,659–34,380)	38,208 (31,103–45,313)
		$n=17$	$n=2$	$n=8$	$n=14$	$n=25$
Institution	Mild	59,764 (0–158,891)	18,928 (0–40433)	75,098 (30,863–119,333)	43,006 (0–99,771)	43,096 (5673–80,520)
		$n=2$	$n=1$	$n=2$	$n=2$	$n=3$
Institution	Moderate	48,183 (43,610–52,756)	19,446 (5726–33,166)	61,687 (36,991–86,384)	51,065 (36,401–65,728)	54,327 (22,916–85,737)
		$n=4$	$n=2$	$n=5$	$n=4$	$n=4$
Institution	Severe	47,655 (40,007–55,302)	19,123 (9271–28,974)	61,805 (35,596–88,015)	60,272 (35,031–85,513)	51,432 (19,159–83,705)
		$n=3$	$n=1$	$n=4$	$n=4$	$n=3$
Institution	All	36,029 (2447–69,611)	19,309 (11,805–26,812)	77,225 (61,180–93,270)	36,706 (18,368–55,044)	49,846 (30,217–69,475)
		$n=3$	$n=1$	$n=3$	$n=5$	$n=6$
All	Mild	19,909 (14,977–24,841)	7616 (1929–13,304)	20,876 (16,690–25,061)	20,420 (10,479–30,361)	31,984 (18,254–45,714)
		$n=5$	$n=2$	$n=7$	$n=8$	$n=6$
All	Moderate	34,223 (25,263–43,183)	9670 (4904–14,435)	37,540 (30,391–44,690)	40,953 (9996–71,909)	47,934 (29,324–66,544)
		$n=9$	$n=3$	$n=10$	$n=10$	$n=7$
All	Severe	61,958 (10,603–113,312)	11,236 (3797–18,675)	58,198 (45,291–71,105)	61,906 (14,167–109,645)	56,104 (30,761–81,447)
		$n=6$	$n=2$	$n=9$	$n=8$	$n=6$
All	All	73,712 (11,182–136,242)	7938 (3352–12,523)	43,767 (30,053–57,481)	35,866 (15,865–55,867)	38,249 (28,111–48,386)
		$n=10$	$n=3$	$n=15$	$n=10$	$n=12$

N number of studies contributing to each estimate

caregivers missing work days compared with Germany and France.

4.1.3 Costs by Setting and Disease Severity

There was a higher cost associated with patients living in nursing homes compared with those who were community dwelling. However, this result was contingent on the methodology used to value informal care, highlighting the importance of standardised practice for evaluating informal care costs.

Although the CIs around our estimates were wide, costs increased with disease severity, in particular informal care and direct non-medical costs. This finding has been widely reported by many individual studies as well as two large reviews with a broad geographic scope [5, 6]. Schaller et al. reported mean annual costs of US$22,113 in mild dementia, US$42,930 in moderate dementia and US$51,659 in severe dementia [6]. This corresponds to an increase of 94% in moderate versus mild disease, and 134% in severe versus mild disease. This is consistent in magnitude with our estimates, though we see a steeper gradient in some regions such as Southern Europe (101% and 203%, respectively) and a less steep gradient in Eastern Europe (27%, 48%) and Western Europe (50%, 75%). Further, we found that mean costs were more similar across regions when broken down

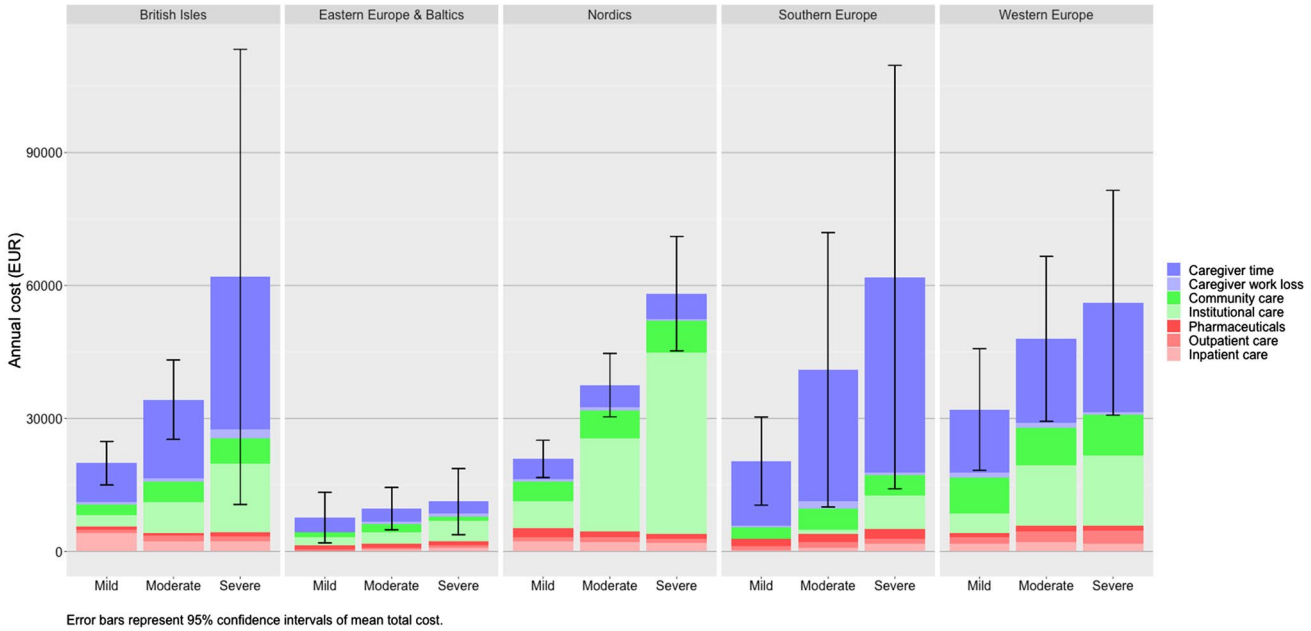

Fig. 3 Mean annual costs per person with dementia, by disease severity, and region

by disease severity compared with pooled estimates, namely, if also disaggregated by care setting.

4.2 Strengths and Limitations

In contrast to most previous reviews of costs of dementia, we pool all available studies providing estimates of individual cost elements for specified patient populations in terms of region, care setting and disease severity. By disaggregating cost data and patient populations, we can explain much of the disparities across studies, and residual heterogeneity is managed through the application of a random-effects meta-analysis. This arguably provides a systematic and transparent approach for summarising all available cost data and producing estimates of mean costs of care for specific regions and patient populations, which can later be utilised for example in cost-of-illness and cost-effectiveness modelling studies. Accurate estimates of costs of care by disease stage are critically important, for example economic evaluations of novel disease-modifying therapies in AD [135].

In contrast to our previous reviews, we elected not to adjust costs for differences in purchasing power across countries, but used standard exchange rates to convert costs into EUR. There were several reasons: all our analyses grouped countries by regions of similar purchasing power, which reduces the necessity for further adjustment. Additionally, the main objective of the study was to provide relevant estimates of costs of dementia care within each European region, rather than providing comparable estimates across regions.

The chosen approach also comes with limitations and is based on assumptions that are difficult to fully underpin with data. Computation of SDs and CIs relies on assumptions of independence of cost components. This is unlikely to fully hold, but at the same time it is not obvious which sign these correlations might take. Consequently, the presented measures of dispersion should be interpreted with caution. Additionally, the imputation of disaggregated cost components based on cost distributions from other studies relies on the assumption of comparability across similar studies.

There are also sources of heterogeneity that are not considered in our analysis. We did not attempt to disaggregate costs into resource use and unit costs or to disentangle differences in resource utilisation versus valuation of resources. This is of special relevance for informal care, where different valuation principles (e.g. replacement cost vs opportunity cost methods) can lead to disparate cost estimates. Harmonising the measurement and valuation of informal care would potentially decrease heterogeneity across studies and produce more comparable, though not necessarily more 'correct', cost estimates. Further, with a random-effects model, meta-analytic estimates are more likely to be influenced by small studies reporting outlying cost estimates, compared with fixed-effects models.

The reclassification of costs into our defined cost categories was unproblematic in most cases; however, for some resource types, in particular nursing services, there was inconsistency across publications whether to classify these as direct medical cost or a direct non-medical (community care) cost. Though we attempted as far as possible to apply a

Table 5 Meta-regression of mean annual costs, by cost component, Euros

	Direct medical costs			Direct non-medical costs		Informal care cost	
	Inpatient	Outpatient	Drugs	Residential care	Home care	Productivity loss	Caregiver time
Intercept	2310**	1139**	732**	9501**	5550**	461**	24,957**
Study methodology							
Cross-sectional (reference)							
Prospective	220	−255	−110	1659	881	−35	−6703**
Retrospective	1225**	−197	90	−5946**	−550	1982**	38,811**
Clinical trial	551	−549**	91	1618	−233	357**	9904**
Diagnosis							
Dementia (reference)							
Alzheimer's disease	−284	−131	−5	−311	−2031**	163*	2731
Vascular dementia	264	−89	109	1194	−2945	749	1257
Lewy body dementia	516	NA	NA	NA	NA	NA	NA
Region							
British Isles (reference)							
Eastern Europe and Baltics	−1563**	−1002**	−310	−7450**	−4299**	−141	−14,387**
Nordics	91	−1	411**	5649**	330	8	−10,539**
Southern Europe	−652**	−159	702**	−2880	−648	157	−2712
Western Europe	−36	773**	508**	41	1503*	137	−5576*
Disease severity							
All (reference)							
Mild	−175	−100	42	−3480**	−350	−140	−4925*
Moderate	−56	178	52	360	400	40	−389
Severe	−301	87	60	4374**	1259*	−80	1725
Care setting							
All (reference)							
Community	−37	−13	−202*	−10,272**	1219*	84	−84
Institution	−635**	600**	−484**	26,312**	−5542**	−532**	−12,304**
Time period							
< 2005 (reference)							
2005–2009	−125	430*	379**	4255**	135	65	−1637
2010–2014	−307	288	100	515	153	134	1235
2015–	−327	−3	269	−1079	−3362**	−25	−6420
Number of cost estimates	389	355	356	343	344	297	263
I^2 (%)	98.37	99.22	99.62	100	100	100	100
R^2 (%)	26.79	33.04	21.88	66.73	37.85	57.56	39.4

Each column in the table corresponds to a separate regression model. Coefficient estimates in Euros indicating the effect of the variable on cost components. For example, annual inpatient costs for patients with a diagnosis of Alzheimer's disease are 284 Euros lower than the reference category (all-cause dementia)

NA=not applicable, *$p < 0.05$; **$p < 0.01$

consistent approach across studies, there may be some residual inconsistency between estimates in the breakdown of costs between direct medical and direct non-medical costs.

Additionally, the estimates in our study are less precise compared with what would been achieved with more stringent inclusion and exclusion criteria. The inclusion of studies with large variations in methodology has likely inflated heterogeneity, which is illustrated by the impact of study methodology seen in the results of the meta-regression. However, we were also able to observe the complementary strengths of different methodologies, for example the greater sensitivity of large retrospective database studies to measure costs of rare but costly events such as hospitalisations, and the greater level of detail on informal care recorded in prospective clinical trials. Furthermore, applying strict criteria for quality and homogeneity across studies can lead to exclusion of the majority of reports and make the resulting analysis less conclusive [7]. In the literature search, some search

terms were limited to the title field. This may have resulted in potentially relevant studies not being identified, and thus the search may not have been completely exhaustive.

We did not attempt to attribute causality to dementia costs, i.e. what we estimate is costs in PWD, rather than costs specifically due to dementia. A number of the studies included in this review also provided estimates of attributable costs, usually by calculating the difference between costs in PWD to costs in a control group of elderly individuals without dementia. The distinction between costs *in* dementia and costs *due to* dementia is relevant for cost-of-illness studies, but perhaps less critical for applications where the focus lies on the gradient of costs across disease stages, as is usually the case in economic evaluations that might leverage these cost estimates.

4.3 Future Research

As informal care constitutes a major component of dementia care costs, it is imperative that future studies measure and valuate informal care in an accurate and transparent manner. The results of the informal care analysis varied based on the method used, which highlights the need for standardisation of capturing informal care costs in future studies. The Resource Utilization in Dementia instrument was the most commonly used scale in the included studies, and has been designed to standardise the measurement of informal care through self-reporting from caregivers [16]. Similarly, to better understand regional differences, there is a need for multi-national studies that use a standardised data collection protocol across each of the sampled countries. The ICTUS [2] and GERAS [14] studies are good examples; however, in particular, high-quality studies of the impact of dementia in Central and Eastern European countries are lacking. Initiatives to enhance consistency and availability of research data across European registries and cohorts currently focus on clinical and biological data but should also be extended to include a harmonised collection of socioeconomic and resource utilisation data.

Over 60% of PWD are estimated to have three or more comorbidities [136], but the extent to which comorbidities might moderate the cost of care is unclear. So far, investigations have been limited by sample size, selected recruitment and limited data collection on co-morbidities. There is also a paucity of studies reporting costs in patients with dementia of other aetiologies than AD.

Finally, with the increasing opportunities for early diagnosis of AD, such as clinically relevant blood-based biomarkers [137], accurate characterisation is needed of the burden of early AD stages (i.e. subjective cognitive decline through mild cognitive impairment and mild dementia). This includes the impact on work capacity in subjects participating in the work force.

5 Conclusions

To our knowledge, this study represents the most extensive meta-analysis of the cost of dementia in Europe to date. Though there is considerable heterogeneity across studies, much of this is explained by identifiable factors. By disaggregating costs and patient subgroups, we attempt to fully utilise the existing literature to produce estimates of mean costs of care by region, care setting and disease severity. These estimates may prove useful in the evaluations of future health technologies, such as precision diagnostics and disease-modifying therapies for AD.

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Declarations

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Author's contributions Study conception and design: LJ, AW. Literature review and data abstraction: LJ, OF, AT. Data management and analysis: LJ, AT. Draft manuscript preparation: AT, LJ. All authors reviewed the results, contributed to and approved the final version of the manuscript.

Conflict of interest Linus Jönsson was previously employed by H. Lundbeck, but this work was unrelated to the employment. He is a minority shareholder in H. Lundbeck and has received license fees for the data collection instrument (Resource Utilization in Dementia). Anders Wimo declares that none of the potential list of conflicts of interest listed has had any impact on the conduct of this study. Oskar Frisell and Ashley Tate have no conflicts of interest that are directly relevant to the content of this study.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material The dataset is available from the corresponding author on reasonable request.

Code availability The R code for data processing and analysis is available from the author on reasonable request.

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