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COSTS OF DEMENTIA IN LOW- AND MIDDLE-INCOME COUNTRIES: A SYSTEMATIC REVIEW

Angeladine **Kenne Malaha**^a, Clémence **Thébaut**^{a,b}, Dayna **Achille**^a, Pierre-Marie
Preux^{a,c}, Maëlen **Guerchet**^{a*}

(a) Inserm U1094, IRD UMR270, Univ. Limoges, CHU Limoges, EpiMaCT -
Epidemiology of chronic diseases in tropical zone, Institute of Epidemiology and
Tropical Neurology, Omega Health, Limoges, France

(b) Leda-Legos, PSL Research University, Paris Dauphine University, Paris, France

(c) CHU, Centre d'Epidémiologie de Biostatistique et de Méthodologie de la
Recherche, Limoges, France

Running title: Dementia costs in low/middle-income countries

*Corresponding author:

Maëlen **Guerchet**, PhD

Inserm U1094, IRD UMR270 – EpiMaCT

Faculty of Medicine

2 rue du Dr Marcland, 87025 Limoges Cedex

Tél. : 05 55 43 58 20 - Fax : 05 55 43 58 21

Email : maelenn.guerchet@ird.fr

ABSTRACT

Background

The proportion of people living with dementia in low- and middle-income countries (LMICs) is expected to reach 71% by 2050. Appraising the economic burden of the disease may contribute to strategic policy planning.

Objective

To review studies conducted on the costs of dementia in LMICs, describe their methodology and summarize available costs estimates.

Methods

Systematic review, including a search of health, economics and social science bibliographic databases. No date or language restrictions were applied. All studies with a direct measure of the costs of dementia care were included.

Results

Of the 6,843 publications reviewed, 17 studies from 11 LMICs were included. Costs of dementia tended to increase with the severity of the disease. Medical costs were greater in the mild stage, while social and informal care costs were highest in the moderate and severe stages. Annual cost estimates per patient ranged from PPP\$131.0 to PPP\$31,188.8 for medical costs; from PPP\$16.1 to PPP\$10,581.7 for social care services and from PPP\$140.0 to PPP\$25,798 for informal care. Overall, dementia care can cost from PPP\$479.0 to PPP\$66,143.6 per year for a single patient.

Conclusion

Few studies have been conducted on the costs of dementia in LMICs, and none so far in Africa. There seems to be a need to provide accurate data on the burden of disease in these countries to guide public health policies in the coming decades.

46 **Keywords:** Dementia; Alzheimer's disease; Cost of illness; Disease Burden;
47 Systematic review; Low-Income; Middle-Income.

INTRODUCTION

An estimated 57.4 million people worldwide were living with dementia in 2019. This number is expected to increase to 152.8 million by 2050, mainly due to population growth and ageing [1]. According to the World Health Organization (WHO), much of this increase will be in low- and middle-income countries (LMICs) where 60% of people with dementia (PWD) already live. This figure could rise to 71% in 2050 [1,2].

In the latest Global status report on the public health response to dementia, the annual global cost of dementia has been estimated at US\$ 1.3 trillion in 2019, up from US\$818 billion in 2015. This figure is expected to reach US\$1.7 trillion by 2050 [3,4]. In LMICs, these costs amount to about US\$341.0 billion, divided into US\$59.4 billion for direct medical costs, US\$61.0 billion for direct social sector costs and US\$220.6 billion for informal care. For high-income countries (HICs), these costs are US\$972.3 billion, US\$153.9 billion, US\$387.7 billion and US\$430.8 billion respectively [3]. Therefore, informal care costs account for half (49.6%) of the total cost of dementia worldwide, with 64.7% in LMICs and 44.3% in HICs, while evidence show that about 84% of PWD worldwide live with their families [3,5].

Cost-of-illness (COI) studies aim to assess the economic burden of health problems on the whole population [6–8]. They are useful for determining the current status of a disease care system and its costs, as well as for assessing changes over time or between diseases, to assist in public health decision-making [8,9]. However, evaluating the costs of dementia remains a complex exercise. It requires distinguishing between costs categories, identifying costs attributable to the disease, managing different data sources, and conducting accurate analyses [10,11]. A few studies have estimated the global costs of dementia [4,5,10–12]. The 2010 and 2015 reports on the economic impact of Alzheimer's disease [4,12] used the annual cost of dementia per

person in each country, where available, computed with the projected number of PWD living in the country. Analyses also included imputations and a set of assumptions for countries with missing or insufficient data. For LMICs with very little primary data, authors reported using data from neighboring or comparable countries, gross domestic product, and health care expenditure per capita [4,12], which led to less reliable or accurate estimates for these regions.

As mentioned in the Alzheimer's Disease International report on dementia in sub-Saharan Africa, the lack of original cost data remains the weakest link in assessing the burden of dementia in the region [13]. Therefore, this review was conducted to identify costs of dementia studies conducted to date in LMICs with the aim of describing their methods, summarizing the available data and identifying the challenges of such studies in resource-limited settings.

MATERIALS AND METHODS

We conducted a systematic review on the costs of dementia in LMICs and the methodologies used for their evaluation. All original research articles from studies conducted in LMICs (according to World Bank classification on January 1st 2020) and presenting a cost evaluation of any aspect of dementia care were considered. Disease cost categories are generally related to direct medical (i.e related to the medical care system), social care (i.e formal services provided outside of the medical care system) and informal care (related to the time spent by non-paid relatives on care) [12].

Search strategy

Bibliographic databases on health, health economics and social sciences were searched: Pubmed/Medline, Embase, Global health, PsycINFO, PsycARTICLES (via OVID), Web of science and Econlit. The main grey literature resources in the health

field were also searched (GreyLit, ProQuest, Georgetown University resource and Google scholar). No language or date restrictions were applied. Search strategies consisted of combinations of different keywords related to the disease (dementia, Alzheimer's, cognitive disorder / impairment), costs (cost, valuation, expenses, and burden) and settings (low-income, middle-income, resource limited, developing country and, the list of the 137 LMICs countries (according to the World Bank on January 1st, 2020 [14])). Specific equations for each database as searched on March 2nd 2020 are presented in Supplementary material 1. An updated search using the same strategy was conducted on December 28th 2021 to identify potential new studies of interest.

Studies selection

Results obtained from the searches on the different bibliographic databases were imported and processed using the Rayyan QCRI tool [15]. In a first step, duplicates were removed. Then, following a blind selection method, two investigators (AKM and DA) assessed the eligibility of the selected articles based on titles and abstracts. The proportion of agreement between the two investigators was measured; conflicting articles at this stage were all retained for the next stage. Full texts of selected references were retrieved, and the corresponding authors were contacted to request the manuscript when those were not available. Full-texts were then evaluated by the same two investigators (AKM and DA) for the final inclusion decision. Conflicting articles were discussed and the inclusion decision was made with a third investigator (MG or CT).

Protocols, reviews and meta-analyses were not included, but were examined to identify any relevant study for consideration. In addition, references of selected articles were checked. For publications in languages other than English and French (those in

Spanish, Portuguese and Chinese), collaborators were asked to provide a translation and/or description of the studies in order to make a decision on eligibility and to extract the data of interest.

During the selection process, articles were excluded according to the Population, Intervention, Comparator and Outcome (PICO) framework. Laboratory experiments (i.e fundamental research on Alzheimer's Disease / dementia, including in-vitro studies and studies in non-human populations), studies not addressing dementia care, and studies conducted outside LMICs were considered as wrong population. Wrong publication types included narrative review, meta-analysis, overview article, letter to the editor and commentaries. Studies without a direct measure of dementia cost were accounted as wrong outcomes. Studies for which the full-text was not retrieved despite multiple searches and contact with the authors were also excluded.

Quality assessment

Although various guidelines have been published for assessing the quality of economic evaluation in health care [16,17], they mainly focus on cost-effectiveness analyses. In the absence of a standard instrument to evaluate cost-of-illness studies, we assessed the quality of articles using a checklist, derived from the guide proposed by Larg and Moss [7] and the checklist developed by Kline-Budde et al. [18] for their review on bipolar disorders. Full description of the quality assessment criteria used is provided in Supplementary material 2.

Data processing and analysis

Full-texts were reviewed and data extracted using a standardized extraction grid developed in Epi Info 7 and Microsoft Excel®. Data were collected on study design, population characteristics and costing methods. Particular attention was paid to the

costing perspective (i.e the point of view from which costs are considered). Studies may measure costs to a health care system, a third-party payers, commercial sectors, government or participants and their families [19]. In this review, the perspective was collected as specified in the original article. Instruments used to collect and value health resource utilization were also explored, to check the use of standard validated tools such as the Resource Utilization in Dementia (RUD) instrument [20] or questionnaires specifically designed by researchers for the purpose of their study. Costing approaches used to value informal care time were also assessed. Various methods for the valuation of informal care are available in the literature. On the one hand, there are revealed preference methods that are based on real-life decision data: 1) the opportunity cost method, which aims to estimate the cost of the opportunity to earn income or partake in leisure activities that an individual forgoes when engaging in informal care; 2) the replacement cost, or proxy good method, which assigns costs based on the market value that the care services would cost if they were provided by a professional provider. On the other hand, stated preference studies obtain value by asking respondents directly what economic value they attach to informal care through contingent valuation or conjoint analysis [21,22].

When information was not presented in the original article as required for extraction, available data were converted to the accurate value and unit. For example, all sex ratios and gender figures were converted to male percentage. When data was not available or presented in a non-transformable format, it was considered missing. When summarizing data, weighting was done using the representativeness of each category in the total sample. For example, to calculate the total medical costs of a given study presented by disease severity, the proportion of participants in each stage was taken into account. Monetary data were converted into local currency unit (LCU) using the

exchange rate provided by the authors. Where these were not available, we used exchange rates provided by the World Bank for the country in the year of the study cost [23]. Costs were then updated to their 2020 value using country-specific deflators provided by the World Bank [24], and converted to 2020 dollar purchasing power parities (PPP) using official conversion factors [25].

All costs were collected under the original items as provided by studies. They were then grouped into a dozen of health resource services and finally into the three main cost-of-illness categories (i.e. direct medical care, social care and informal care). Some studies presented costs results directly in the three main categories which does not allow for a desegregated presentation; these are presented only in total costs descriptions.

The protocol of this systematic review was registered in PROSPERO (registration number CRD42020169898) before data extraction began.

RESULTS

From the initial search, 11,168 publications were identified and extracted from the databases. Details are presented in Supplementary material 3. Figure 1 shows the articles selection flow chart according to updated PRISMA guidelines [26]. After eliminating duplicates, 6,843 publications were assessed for eligibility. Of the 91 eligible articles, 74 full-text were retrieved and evaluated for final inclusion. Of these, 56 were excluded for the following reasons: not a cost-of-illness study ($n = 10$); not an original research ($n = 13$); modelling studies ($n = 8$) and study conducted in high-income countries ($n = 25$). The latest updated search identified two recent studies that were included in the analyses.

Finally, 20 articles representing 17 individual studies were selected for this review. Butman et al. [27] presented preliminary results of a study subsequently published by

Allegri et al. [28] ; similarly, the pilot study conducted by Ferretti et al. [29] in Brazil was completed and final results published by the same authors [30]. In both cases, only the final publications [28,30] were considered for the analyses. Jia et al. [31] and Yan et al. [32] presented different costs for the same cluster-randomized observational study in China, so their characteristics and results were merged.

Characteristics of included studies

Characteristics of the 17 included studies are summarized in Table 1. Out of 137 low- and middle-income countries, only 11 were represented in this review, including six studies in China [31–37]; 2 in Brazil [30,38]; and one in each of the following countries: Argentina [28], Colombia [39], India [40], Iran [41], Peru [42], Philippines [43], Romania [44], Thailand [45] and Turkey [46]. Our dataset covered all epidemiological regions of the Global Burden of Disease, with the exception of Africa. Regional coverage was as follow: 1 from Eastern Mediterranean [41]; 2 from South-East Asia [40,45]; 2 from Europe [44,46]; 5 from the Americas [28,30,38,39,42] and 7 from Western Pacific [31–37,43]. Studies were conducted between 2003 and 2020. All studies performed a retrospective collection of data in the previous 1-12 months, except studies from Turkey [46] and Philippines [43], which added a 15-day and 5-year prospective data collection period on time spent in informal care, respectively.

The majority of studies focused on Alzheimer's Disease only (12/20), 5 studies included all types of dementia and the remaining four did not specify dementia subtypes in their study population. In almost all studies, case identification was based on a previous dementia diagnosis. A few updated or verified the diagnosis before inclusion in the studies. Disease definition followed standard criteria including ICD-10, DSM-IV-TR and/or NINCDS – ADRDA, plus various clinical or imaging investigations. Some studies excluded patients with mild cognitive impairment [29,30], early onset

dementia [41] or limited functional independence [42]. Only four studies reported the mean disease duration: 2.7 years, 51.0 months, 60.1 months and 5.1 years in China [34], Romania [44], Brazil [30] and Thailand [45] respectively.

The majority of studies examined all three categories of costs (direct medical, social and informal care costs). Three studies [36,38,39] investigated only medical costs, while Wang et al. [35] only looked at informal care costs. Zencir et al. [46] and Mould-Quevedo et al. [33] did not collect data on social and informal care costs respectively. Items included in each cost category varied widely. For direct medical costs, most studies included outpatient, inpatient and medication costs. Some reported only medication [30,38,39] or hospitalization [36] costs. Regarding medication costs for instance, Soares et al. [38] in Brazil reported the costs of dementia-specific drugs dispensed by a government dispensing center. Meanwhile in Colombia, Prada et al. [39] considered direct insurance reimbursement for all-condition drugs of dementia patients. In one study from China, Wang et al. [34] included the costs of official dementia drugs, but also those of traditional medicine. Social care costs included travel expenses and formal care services where appropriate, but also food expenses [31,41]. With regard to informal care costs, most studies reported estimates of time spent on care, without much detail on the activities considered. Two studies considered the patient loss-of-productivity [30,44] and one included the costs of health services for the treatment of the caregiver [30]. Although the majority of studies valued caregiver time by the replacement cost methods (which assigns a monetary value to caregiver's time based on what it would cost to replace informal care activities with formal care), the proxy used varied considerably, ranging from national minimum or average wage, to the salary of a nurse in a public institution, or to the caregivers' salary. Table 2 provides more details on the design characteristics of the included studies.

Results from the quality assessment of the studies are presented in Table 3. Almost all studies provided basic information on the study design and population characteristics, such as objectives, sample size and demographics. Eight out of the 17 studies clearly indicated the cost estimate perspective. Only Allegri et al. [28] and Custodio et al. [42] included a group of healthy participants in their sample, although they did not use this information to calculate disease-specific net costs. Only the cluster-randomized study in China presented the results of a sensitivity analysis [31,32]. Most studies (9/17) failed to present separate information on the number of services used before getting in their valuation. Very few studies performed sensitivity analyses to account for uncertainties in key indicators. Onetiu et al. [44] for instance estimated the cost of time spent on informal care by a replacement cost approach using the national minimum wage, the average national wage and the caregiver's salary. Finally, all studies presented and discussed methodological limitations.

Costs estimates

Annual costs of dementia per patient according to disease severity are summarized in Table 4. Annual domestic government health expenditures in 2020 for each country are also shown in this table. Overall, in all costs categories, dementia costs tend to increase with disease severity. Prada et al. [39] calculated the ratio of direct insurer expense to mild stage at 1.62 for moderate and 4.87 for severe stages; i.e. compared to a mild patient, a moderate stage patient will use 62% more resources and a severe stage patient 387% more resources. Medical costs are generally highest in the mild stage, while social costs (including institution fees) and informal care costs become more important in the moderate and severe stages. Regardless of the disease stage, we found a wide range of estimates of annual per patient costs in the studies. Medical costs ranged from PPP\$131.0 in India [40] to PPP\$31,188.8 in China [45]; social costs

from PPP\$16.1 in Philippines [43] to PPP\$10,581.7 in China [31,32]; and informal care costs from PPP\$140.0 in India [40] to PPP\$25,798 in China [45]. Overall, dementia care can cost from PPP\$479.0 in India [40] to PPP\$66,143.6 in China [31,32] per year for a single patient.

DISCUSSION

Findings

Studies included in this systematic review comprised 17 cost-of-illness studies on dementia in 11 LMICs across all GDB regions except Africa. These studies were conducted from 2003 to 2020 and focused mostly on Alzheimer's disease. All estimates of dementia costs increase with disease severity and informal care costs tend to exceed medical costs.

Globally, very few studies have been conducted to assess dementia costs worldwide. About 10 years ago, Quentin et al. [47] reviewed cost-of-illness (COI) studies in Europe and North America, including 28 studies. A review published in 2012 by Knapp et al. [48] on the economic evaluation of dementia care identified only 29 individual studies. Similarly, the international review of COI studies on dementia, by Schaller et al. in 2014 [49] found 27 individual studies for the period 2003 to 2012. Our review focusing on LMICs included 17 studies. As reported by Hendriks et al. [50], beyond the complexity of COI studies, the overriding constraint in LMICs is data availability, including lack of accurate financial records and incomplete patient disease registers, as well as lack of expertise to conduct cost studies.

Costs of dementia are high and highly variable. They range from PPP\$479.0 to PPP\$66,143.6 per year for a single patient. These costs are colossal as families remain the main bearers of the burden. Indeed, according to the WHO, in 2016, half of the world's countries spent less than US\$350 per person annually on health-related

expenses, including most LMICs [51]. In 2018, the mean per capita general government domestic health expenditure was US\$134.7 in LMICs and US\$5,562.3 in HICs [52]. In this study, the per-patient costs of dementia reached fifty times these public expenditures.

Dementia costs increase with disease severity; similar results have been reported in other studies and can be explained by the rise in care needs as dependence and impairment increase [47,53,54]. Evidence from the United States suggests that informal care costs decrease with disease severity as patients need more attention and are therefore institutionalized [55]. This was not observed in this review, where informal care costs remained the highest in most studies. Actually, in LMICs, about 95% of patients with dementia live with their families, compared to 69% in HICs [5]. Thus, in these countries where universal health coverage is not achieved, families bear the burden [56].

Limitations

The majority of included studies reported convenience sampling and/or small sample size as a study limitation in their publications. Unfortunately, these two limitations restrict further use of the results as they are difficult to generalize. Half of the included studies (9/17) focused on Alzheimer's Disease only, as this is the main pathology of dementia. It should be noted that, the disease considered for cost evaluation and its definition criteria strongly influence costs estimates. In fact, Custodio et al. reported that fronto-temporal dementia costs were higher than Alzheimer's Disease or vascular dementia ones [42].

Considering there is no standard methodology for cost-of-illness studies and no reference tool for quality assessment, available checklists [7,18] were adapted to assess the studies included in this review, which appeared to be of satisfactory quality.

However, very few studies included a detailed description of service utilization and a clear definition of items considered in each cost category. The way in which services are defined and valued is of crucial value in understanding and comparing the resulting estimates, particularly in the context of LMICs where health care and health financing systems vary. The lack of methodological standard in COI studies is a common and challenging issue to address, as described in other reviews on dementia [6,47,53]. It has also been described in other diseases, including colorectal cancer [8] and diabetes [57].

Collection and valuation of time spent by caregivers on care is rather difficult. First, many activities and services (activities of daily living and instrumental activities of daily living) are done for the older people regardless of their health status and are not considered by caregivers as an additional workload, even when the person can no longer perform them themselves. This is reinforced by the fact that many people still consider dementia to be a normal part of ageing [58]. Secondly, a joint effect should be considered, that of achieving many activities simultaneously, such as shopping for the PWD and caregiver themselves or supervising the PWD while cooking for the entire household. According to monetary valuation, a good number of methods exist, with the difficulties of disaggregating time spent (paid work time, domestic work and leisure time) and defining the unit cost to be applied to each category [22,59]. In the included studies, both opportunity cost and proxy good approaches were used, but were not sufficiently robust and/or their methods not well described. The quality of disease-specific costs estimates strongly rely on the accuracy of data collected and therefore of the collection tools. Therefore, harmonizing the costs items definition and collection is strongly recommended to ensure accuracy and comparability with other studies. Standard collection tools exist, including the Resource Utilization in Dementia (RUD)

Instrument [20]. This is a dementia-specific tool that has been widely used and validated in global settings [60]. Otherwise, a minimum set of items should be collected, such as outpatient, inpatient and medication for medical costs, transport and accommodation for social costs. Attention should be paid to informal care time too, specifying which ADL, IADL or supervision activities were carried out, and how caregiving time was valued in money.

In addition, it was not always clearly stated in all studies which perspective was considered for the costs or whether these were dementia-specific or total patient costs. Key distinctions that may affect the interpretation and use of costs. The majority of studies presented estimates directly in US\$ or local currency. It was therefore necessary to know the precise cost reference date, exchange rate, country-specific inflators and purchasing power parities to convert all estimates into international dollars. This process allowed relevant comparisons of dementia costs between the studies included in this review. However, it limits comparisons with studies from other settings or global estimates which usually present the results in US dollars. Due to the wide heterogeneity of study designs, methodological and costing-related limitations cited above, disease costs summaries provided in this review should be taken with caution.

In this review, modelling studies were excluded. Modelling is a good way to appraise the reality without investing huge resources in complex field surveys. However, the likelihood of a model relies on the proxies used, for example, utilization of health services, market price of health services or reference wage for workers. These data are often neither standardized in resource-limited settings nor available [50]. As a result, many modelling studies may not provide an accurate picture of reality. Thus, in order to identify accurate methods for calculating dementia costs in LMICs, and to

summarize primary costs estimates, we considered only studies with field collection of health services use and costs. Similarly, studies with a top-down cost approach were excluded as they did not include a direct measurement of dementia costs. Although top-down studies are highly valuable, they mainly capture disease-specific medical costs from the state or third party payer perspective, with very little information on social and informal care costs. They also require a number of indicators like the number of dementia cases or health resource utilization, which may not be available in the countries of interest, leading to the use of additional proxies and imputations. Our search strategy included the most plausible sources of publications for the topic. The high rate of duplicates bears out the exhaustiveness of this review. In addition, no language or date restrictions were applied to the searches or results. Moreover, all studies that included cost estimation of any component of dementia care were included and all the costs estimates were converted from US dollars or local currency to purchasing power parity dollars to allow for cost comparisons between studies.

CONCLUSION

To the best of our knowledge, this is among the first reviews to focus on the cost of dementia in LMICs. It is valuable regarding appraisal of methodological constraints when evaluating the costs of dementia in resource-limited settings. Findings highlighted once more the scarcity of valuable cost-of-illness studies in these countries, particularly in Africa where original research for primary data collection is essential. The costs of dementia were found to be high, placing an enormous burden on families. These results should serve to raise the alarm on the urgency of dementia and to advocate for dementia-oriented programs and policies.

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401 **DISCLOSURE STATEMENT**

402 All the authors have no conflict of interest to declare.

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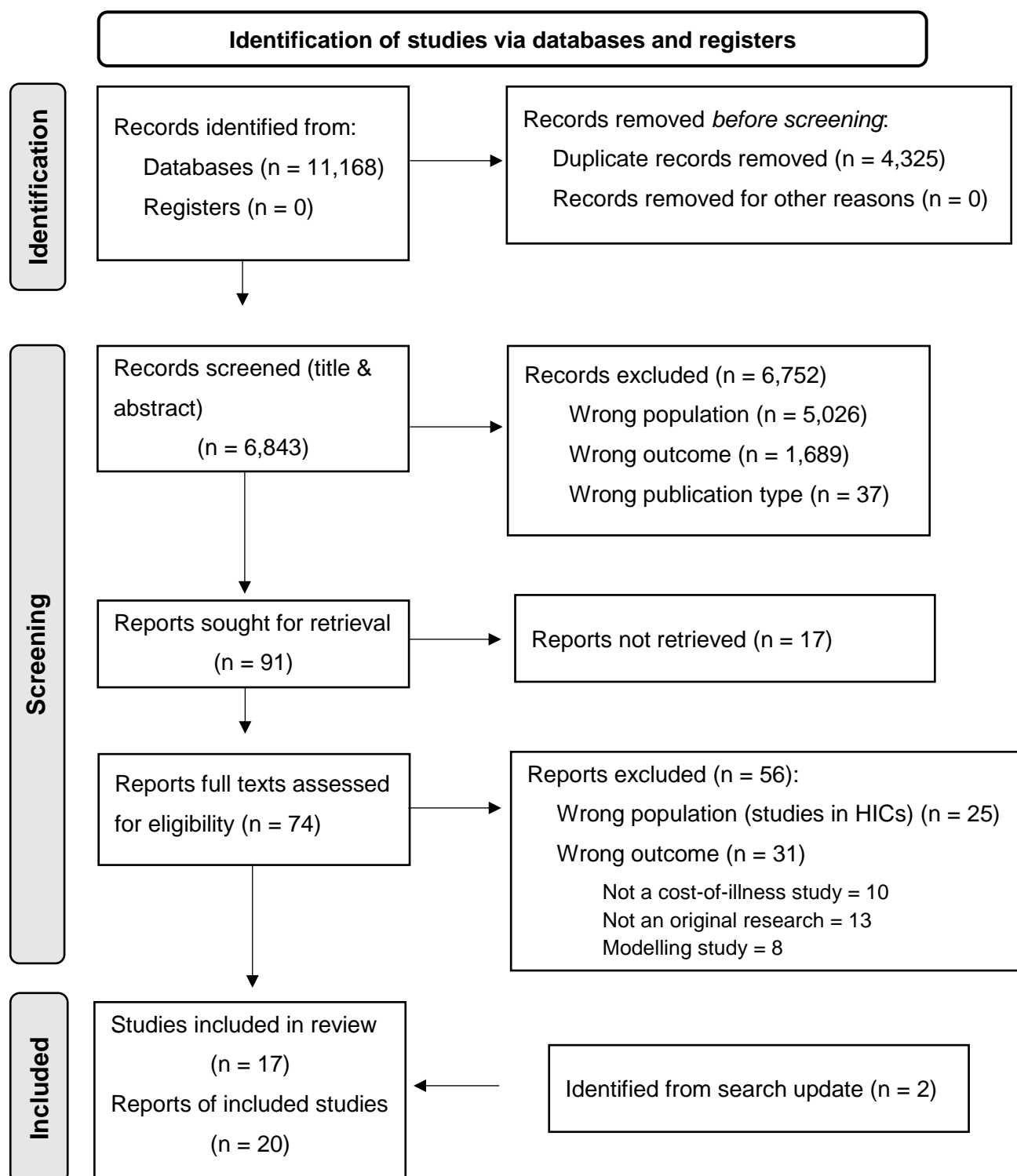
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Figure 1: Articles selection flow diagram



Adapted from: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71

Table 1: General characteristics of included studies

Study	Country	Study period	Settings	Dementia subtype	Sample size	Mean age (years)	Male percentage	Disease severity criteria	Disease severity stages (%)		
									Mild	Moderate	Severe
Aajami et al., [41]	Iran	2017	Urban only	Alzheimer's disease	300	80.0	48.0	MMSE	33.3	33.3	33.3
Allegri et al., [28]	Argentina	NS	Urban only	Alzheimer's disease	125	74.6	19.2	MMSE	48.0	30.0	22
Custodio et al., [42]	Peru	2012 - 2013	Urban only	All types of dementia	106	70.0	39.7	None		NA	
Dominguez et al., [43]	Philippines	2015-2016	Urban & rural	All types of dementia	81	73.8	25.9	None		NA	
Ferretti et al., [30]	Brazil	2011 - 2015	Urban only	Dementia not specified	156	72.9	41.7	FAST Scale	29.1	47.5	13.4
Kongpakwattana et al., [45]	Thailand	2017 - 2018	Urban only	Alzheimer's disease	148	80.1	29.1	MMSE	23.6	39.9	36.5
Malapur et al., [40]	India	NS	Urban & rural	Major Neurocognitive Disorders	50	68.6	60.0	CDR		46	54
Mould-Quevedo et al., [33]	China	2009	Urban only	Dementia not specified	1,387	67.6	52.0	None		NA	
Onetiu et al., [44]	Romania	2013 - 2014	Urban only	Dementia not specified	31	NS	NS	NS	29.0	45.2	25.8
Prada et al., [39]	Colombia	2011 - 2013	Urban & rural	All types of dementia	340	NS	43.0	Drug dispensed	36.1**	44.5**	12.9**
Soares et al., [38]	Brazil	2014	Urban only	Alzheimer's disease	855	78.7	30.6	None		NA	
Wang et al., [34]	China	2005-2006	Urban only	Alzheimer's disease	66	74.0	34.8	MMSE	19.7	56.1	24.2
Wang et al., [35]	China	2008 - 2009	Urban only	Alzheimer's disease	79	NS	21.5	MMSE	25.4	60.6	14.0
XiaoJuan et al., [37]	China	2016 - 2018	Urban & rural	Alzheimer's disease	119	70.8	38.1	MMSE	7.6	67.23	25.2
Jia et al., Yan et al., [31,32]	China	2015 - 2016	Urban & rural	Alzheimer's disease	3,046	75.3	45.8	MMSE	18.7	49.3	32.0
Zencir et al., [46]	Turkey	2003	Urban only	Alzheimer's disease	42	70.5	38.1	MMSE	42.9	16.7	40.4
Zhang et al., [36]	China	2008 - 2013	Urban only	All types of dementia	5,747	77.4	42.8	None		NA	

**Study reported 6.5% of the population with an undefined disease severity stage; CDR: clinical dementia rating scale; FAST: Functional Assessment Staging Tool; MMSE: Mini Mental State Examination; NA: not applicable; NS: not specified.

Table 2: Design characteristics of costs estimations

Study	Data source			Perspective	Type of costs	Costs categories considered	Costs collection tools	Caregiver time valuation
	MR	PI	HI					
Aajami et al., [41]	+	+	-	Societal	UN	Medical – Social – Informal	DQ; self-report checklist	Human capital approach
Allegri et al., [28]	-	+	-	UN	Gross	Medical – Social – Informal	Adapted 10/66 group questionnaire	Replacement costs; MW
Custodio et al., [42]	+	+	-	UN	Gross	Medical – Social – Informal	ZBI; DQ	Replacement costs; MW
Dominguez et al.,[43]	-	+	-	UN	Gross	Medical – Social – Informal	NS	Opportunity costs
Ferretti et al., [30]	-	+	-	Societal	Net	Medical – Social – Informal	ZBI; RUD instrument; DQ	Replacement costs; MW
Kongpakwattana et al., [45]	+	+	-	Societal	Gross	Medical – Social – Informal	RUD Instrument	Opportunity costs
Malapur et al., [40]	-	+	-	UN	Gross	Medical – Social – Informal	DQ	Human capital approach
Mould-Quevedo et al., [33]	-	+	-	UN	UN	Medical - Social	ZBI; DQ	NA
Onetiu et al., [44]	+	+	+	Societal	Gross	Medical – Social – Informal	Modified RUD Instrument	Opportunity costs
Prada et al., [39]	-	-	+	Third party	Net	Medical	None	NA
Soares et al., [38]	+	-	-	UN	Net	Medical	None	NA
Wang et al., [34]	-	+	-	UN	UN	Medical – Social – Informal	DQ	Replacement costs; MW
Wang et al., [35]	-	+	-	UN	Gross	Informal	RUD Instrument	Replacement costs; average employment income
XiaoJuan et al., [37]	-	+	-	Societal	Gross	Medical – Social – Informal	DQ	NS
Jia et al, Yan et al., [31,32]	+	+	-	UN	Gross	Medical – Social – Informal	DQ	NS
Zencir et al., [46]	-	+	-	Societal	Gross	Medical - Informal	DQ; daily time sheets	Replacement costs; wage of a nurse in a public institution
Zhang et al., [36]	-	-	+	Healthcare system	Gross	Medical	None	NA

DQ: designed questionnaire; HI: health insurance; MR: medical records; MW: minimum wage; NA: not applicable; NS: not specified; PI: patient interview; RUD: Resource utilization in dementia questionnaire; UN: unclear; ZBI: Zarit burden interview; +: yes; -: no

Table 3: Quality assessment of included studies

Criteria	Aajami et al, [41]	Allegri et al [28]	Custodio et al, [42]	Dominguez et al., [43]	Ferretti et al, [30]	Kongpakwattana et al, [45]	Malapur et al., [40]	Mould-Quevedo et al, [33]	Onetiu et al, [44]	Prada et al, [39]	Soares et al, [38]	Wang et al, [34]	Wang et al, [35]	XiaoJuan et al [37]	Jia et al, Yan et al, [31,32]	Zencir et al, [46]	Zhang et al, [36]
Aims and methods of the study																	
Study objective	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Inclusion and exclusion	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Non-diseased comparison group or disease-related costs	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Matching or regression analysis	na	-	na	na	na	na	na	na	na	na	na	na	na	na	na	na	na
Sensitivity analysis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-
Costs calculation																	
Data source	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Perspective	+	(+)	-	-	+	+	(+)	(+)	+	+	(+)	(+)	(+)	+	(+)	+	(+)
Cost calculation	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
Cost categories	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Reference (price) year	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
Currency	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Exchange rate	+	+	+	+	+	+	-	+	-	+	-	+	+	-	+	-	+
Inflation and/or discount rates	na	-	-	-	-	-	na	na	-	+	na	-	-	-	-	na	-
Monetary valuation of resource utilisation	-	-	+	+	+	+	+	+	+	-	-	+	+	-	+	+	-
Valuation method	na	na	+	+	+	+	+	-	+	na	na	+	+	na	-	+	na
Presentation of results																	
Sample size	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Demographics	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
Arithmetic mean costs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Standard deviations	+	-	+	+	+	+	-	-	+	-	-	+	+	+	-	+	+
Separate information number of services used	-	+	+	-	+	+	-	-	+	-	-	-	+	-	-	-	+
Discussion																	
Discussion with respect to other results	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uncertainties	-	-	+	-	-	-	-	+	+	-	-	+	+	-	+	+	+
Limitations	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+

+: yes, clearly presented in the article; (+): not clearly presented; -: no, not described; na: not applicable; *median and interquartile range

Table 4: Annual costs of dementia per patient according to the disease severity stage (PPP\$ 2020)

Study	Mild disease			Moderate disease			Severe disease			Overall			Expenditure [#]
	Medical	social	Informal	Medical	Social	Informal	Medical	Social	Informal	Medical	Social	Informal	
Aajami et al., [41]	498.6	766.9	0	638.6	1869.1	1320.9	2046.9	3665.2	1519.2	1060.3	2098.3	945.7	222.4
Allegri et al., [28]	8146.8	664.6	4792.1	7993.3	3813.7	5281.4	10113.9	14765.4	4082.5	8533.5	4711.5	4782.5	1,221.8
Custodio et al., [42]	-	-	-	-	-	-	-	-	-	8216.7	-	4878.1	551.2
Dominguez et al., [43]	-	-	-	-	-	-	-	-	-	582.7	16.1	8958.9	128.6
Ferretti et al., [30]	1798.6	392.4	12115.5	1828.2	173.6	23588.2	2209.6	0.0	13198.9	1688.1	196.5	16492.5	637.9
Kongpakwattana et al., [45]	24730.5	3998.0	16860.9	33423.0	8690.8	22276.8	32933.6	13008.2	35440.2	31188.8	9156.3	25798.5	480.0
Malapur et al., [40]	-	-	-	63.6	32.4	200.4	188.4	357.8	89.2	131.0	208.0	140.0	74.2
Mould-Quevedo et al., [33]	-	-	-	-	-	-	-	-	-	8844.0	4129.0	-	527.6
Onetiu et al., [44]	3868.8	4748.5	5108.6	2126.2	6387.0	6293.9	5658.3	12132.0	7199.3	3542.8	7394.0	6183.7	1,256.2
Prada et al., [39]	2061.7	-	-	3336.2	-	-	10049.2	-	-	4210.0	-	-	827.4
Soares et al., [38]	-	-	-	-	-	-	-	-	-	448.9	-	-	637.9
Wang et al., [34]	1562.8	829.1	1363.5	1614.6	781.5	2733.8	1814.3	893.8	5344.6	1652.7	818.1	3095.7	427.6
Wang et al., [35]	-	-	13107.8	-	-	19998.7	-	-	45254.1	-	-	21808.8	427.6
XiaoJuan et al., [37]	4062.7	2272.6	-	4618.1	3569.5	-	4226.8	7305.2	-	4477.5	4413.2	-	427.6
Jia et al, Yan et al., [31,32]	-	-	-	-	-	-	-	-	-	26339.0	10581.7	20865.8	427.6
Zencir et al., [46]	5280.9	-	472.7	7738.8	-	4785.4	7794.2	-	8084.3	6706.8	-	4268.0	906.0
Zhang et al., [36]	-	-	-	-	-	-	-	-	-	2944.6	-	-	427.6

[#] Public expenditure on health from domestic sources per capita expressed in international dollars at purchasing power parity (PPP time series based on ICP2011 PPP). Source: World Bank <https://data.worldbank.org/indicator/SH.XPD.GHED.PP.CD>

SUPPLEMENTARY MATERIALS

Supplementary material 1: Search strategy

(performed: 2nd March, 2020; updated: December 28th 2021)

EconLit; Ovidsp (Pubmed/Medline, Embase, global Health, PsycInfo, PsycARTICLES); Scopus (search in abstract field); Web of science; ProQuest (search in abstract field).

(dement* OR Alzhem* OR "cognitive impairment" OR "cognitive dysfunction" OR "cognitive decline" OR "cognitive disorder" OR "memory loss" OR "memory disorder") AND (cost* OR econom* OR "cost of illness" OR "cost analysis" OR "valuation" OR "expenditure" OR "budget" OR financ* OR fund* OR "payment") AND ("Afghanistan" OR "Albania" OR "Algeria" OR "American Samoa" OR "Angola" OR "Armenia" OR "Azerbaijan" OR "Bangladesh" OR "Belarus" OR "Belize" OR "Benin" OR "Bhutan" OR "Bolivia" OR "Bosnia and Herzegovina" OR "Botswana" OR "Brazil" OR "Bulgaria" OR "Burkina Faso" OR "Burundi" OR "Cape Verde" OR "Cambodia" OR "Cameroon" OR "Central African Republic" OR "Chad" OR "China" OR "Colombia" OR "Comoros" OR "Congo Democratic" OR "Congo" OR "Costa Rica" OR "Cuba" OR "Djibouti" OR "Dominica" OR "Dominican Republic" OR "Ecuador" OR "Egypt" OR "El Salvador" OR "Equatorial Guinea" OR "Eritrea" OR "Ethiopia" OR "Fiji" OR "Gabon" OR "Gambia" OR "Georgia" OR "Ghana" OR "Grenada" OR "Guatemala" OR "Guinea" OR "Guinea Bissau" OR "Guyana" OR "Haiti" OR "Honduras" OR "Ivory Coast" OR "India" OR "Indonesia" OR "Iran" OR "Iraq" OR "Jamaica" OR "Jordan" OR "Kazakhstan" OR "Kenya" OR "Kiribati" OR "Korea" OR "Kosovo" OR "Kyrgyz Republic" OR "Lao PDR" OR "Lebanon" OR "Lesotho" OR "Liberia" OR "Libya" OR "Macedonia" OR "Madagascar" OR "Malawi" OR "Malaysia" OR "Maldives" OR "Mali" OR "Marshall

Islands" OR "Mauritania" OR "Mauritius" OR "Mexico" OR "Micronesia" OR "Moldova"
OR "Mongolia" OR "Montenegro" OR "Morocco" OR "Mozambique" OR "Myanmar"
OR "Namibia" OR "Nauru" OR "Nepal" OR "Nicaragua" OR "Niger" OR "Nigeria" OR
"Pakistan" OR "Papua New Guinea" OR "Paraguay" OR "Peru" OR "Philippines" OR
"Romania" OR "Russian Federation" OR "Rwanda" OR "Samoa" OR "Sao Tome and
Principe" OR "Senegal" OR "Serbia" OR "Sierra Leone" OR "Solomon Islands" OR
"Somalia" OR "South Africa" OR "South Sudan" OR "Sri Lanka" OR "St Lucia" OR "St
Vincent and the Grenadines" OR "Sudan" OR "Suriname" OR "Swaziland" OR "Syrian
Arab Republic" OR "Tajikistan" OR "Tanzania" OR "Thailand" OR "Timor-Leste" OR
"Togo" OR "Tonga" OR "Tunisia" OR "Turkey" OR "Turkmenistan" OR "Tuvalu" OR
"Uganda" OR "Ukraine" OR "Uzbekistan" OR "Vanuatu" OR "Venezuela" OR
"Vietnam" OR "West Bank and Gaza" OR "Yemen" OR "Zambia" OR "Zimbabwe" OR
"developing" OR "low income" OR "middle income" OR "intermediate income" OR
"resource limited")

Google scholar (first 200 results only)

(dementia OR Alzheimer OR "cognitive impairment" OR "cognitive disorder" OR
"memory disorder") AND (cost OR economy OR "valuation" OR "expenditure") AND
("low income" OR "middle income" OR "intermediate income" OR "resource limited")

Greylit, Georgetown resources

Keywords: dementia, Alzheimer, cognitive impairment, cost of illness, cost of care, low
and middle income countries

List of all 137 countries considered as LMICs by World Bank on January 1st, 2020

Supplementary material 2: Explanation of quality criteria

Criterion	Description
Aims and methods	
Study objective	The objective(s) and research question(s) of the study was (were) described clearly
Inclusion and exclusion	At least the objective diagnostic criteria (e.g., ICD code and DSM-IV) used to identify eligible patients were reported. The study population was specified
Non-diseased comparison group or disease-related costs	The study included a non-diseased control group in order to calculate excess costs or, if no control group was involved, the costs were due to the disease of interest
Matching or regression analysis	If comparison groups were used: a) they were matched, at least in terms of age and/or gender, to allow a direct comparison between equally dispersed groups with regard to their characteristics or b) regression analysis was carried out in order to control for differences
Sensitivity analyses	Relevant parameters were varied in univariate and/or probabilistic sensitivity analyses in order to address parameter uncertainties (e.g., different unit costs)
Calculation of costs	
Data source	The source of information on healthcare utilization or costs was reported and mentioned specifically
Perspective	The perspective of the cost calculation was reported (e.g., from payer, employer, or societal perspective)
Cost calculation	The method of cost calculation was clearly documented
Cost categories	The study estimated costs from the utilization of different kinds of healthcare services or areas, which meant that more than one category was given, in order to consider, at best, all costs that accrued from the disease under study
Reference year (price)	All costs were valued at the price level of a stated base year
Currency	The currency in which the costs were calculated was reported

Inflation rate and/or discount rate	If data were collected from or estimated for a period longer than one year, costs were adjusted for differential timing and the inflation rate/discount rate was mentioned
Monetary valuing of resource utilization	If data on resource utilization were collected that were valued with unit costs, the latter were reported; if cost data were used, these reflected actual charges
Presentation of results	
Sample size	The sample size was reported
Demographics	The characteristics of the sample were described; at least (mean) age and gender were reported
Arithmetic mean costs	The cost estimates were (partly) presented as arithmetic means
Standard deviations	Standard deviations of cost estimates were (partly) reported as a measure of variability
Separate information of used number of services and costs	Separate information about the number of (health) services and cost were given for all cost categories that were described
Discussion	
Discussion with respect to other studies	The results were discussed in relation to other studies on the same topic
Uncertainties	Was uncertainty around the estimates and its implications adequately discussed
Limitations	The limitations regarding the calculation of costs and the representativeness of the study population, in particular, were discussed in detail

Source: Larg A, Moss JR (2011) Cost-of-illness studies: a guide to critical evaluation. *PharmacoEconomics* **29**, 653–671. & Kleine-Budde K, Touil E, Moock J, Bramesfeld A, Kawohl W, Rössler W (2014) Cost of illness for bipolar disorder: a systematic review of the economic burden. *Bipolar Disord* **16**, 337–353.

Supplementary material 3: search results

Sources	Number of results
Indexed databases	
Econlit	25
Embase (via ovidsp)	2,708
Global health (via ovidsp)	283
PsycARTICLES (via ovidsp)	2,475
PsycInfo (via ovidsp)	809
PubMed/Medline (via ovidsp)	1,340
Scopus (search in abstract field)	1,387
Web of science (via Insermbiblio)	1,471
Grey literature	
Georgetown University resources	0
Google scholar (first 200 results)	200
GreyLit	0
ProQuest (search in abstract field)	470
Overall	11,168