REVIEW ARTICLE

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The main cost drivers in dementia: a systematic review

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Objectives: Because of the increasing prevalence of dementia worldwide, combined with limited healthcare expenditures, a better understanding of the main cost drivers of dementia in different care settings is needed.

Methods: A systematic review of cost-of-illness (COI) studies in dementia was conducted from 2003 to 2012, searching the following databases: PubMed (Medline), Cochrane Library, ScienceDirect (Embase) and National Health Service Economic Evaluations Database. Costs (per patient) by care setting were analyzed for total, direct, indirect and informal costs and related to the following: (1) cost perspective and (2) disease severity.

Results: In total, 27 studies from 14 different healthcare systems were evaluated. In the included studies, total annual costs for dementia of up to $70,911 per patient (mixed setting) were estimated (average estimate of total costs = $30,554). The shares of cost categories in the total costs for dementia indicate significant differences for different care settings. Overall main cost drivers of dementia are informal costs due to home based long term care and nursing home expenditures rather than direct medical costs (inpatient and outpatient services, medication).

Conclusions: The results of this review highlight the significant economic burden of dementia for patients, families and healthcare systems and thus are important for future health policy planning. The significant variation of cost estimates for different care settings underlines the need to understand and address the financial burden of dementia from both perspectives. For health policy planning in dementia, future COI studies should follow a quality standard protocol with clearly defined cost components and separate estimates by care setting and disease severity. Copyright © 2014 John Wiley & Sons, Ltd.

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Introduction

Globally, healthcare expenditures for dementia were estimated to be US$604bn in 2010 (Wimo *et al.*, 2013). Compared with other long-term care users, dementia patients are in need of extensive personal care, including supervision, and time for providing assistance with daily activities, resulting in higher costs of care (Gustavsson *et al.*, 2011a). This results in a high economic impact of dementia on patients, families and healthcare systems. There is no cure for dementia today. Thus, the agreement on a new international approach on dementia research at the recent G8 summit highlights the importance of dementia as it is placing significant pressure on care systems around the world. Because of the expected increase in the number of dementia patients, costs are expected to increase by 85% by 2030, making dementia possibly the most expensive disease in our society (ADI, 2010).

Within this context, cost-of-illness (COI) studies are an important source of information for health policy makers. They provide comprehensive data for decision making and planning of healthcare services by making the distributions of several cost components transparent (Wimo, 2010). From 1997 to 2003, several reviews of COI studies of dementia have been conducted (Ernst and Hay, 1997; Wimo *et al.*, 1997;

Bloom *et al.*, 2003; Leung *et al.*, 2003; Quentin *et al.*, 2010). However, the contribution of different cost components differs by care setting, which has not been analyzed in detail yet. Therefore, the purpose of this article is to conduct an international systematic literature review of COI studies on dementia focusing on community versus institutional costs. Additionally, recommendations for future COI studies in dementia are presented. With current and increasing pressures to limit expenditure for healthcare provision and the fact that there is no cure for Alzheimer's disease (AD) today, a better understanding of the main cost drivers for different care settings in dementia can help health policy makers design efficient care management programs.

Methods

A systematic literature search was performed in the following databases: PubMed (Medline), Cochrane Library, ScienceDirect (Embase) and the National Health Service Economics Evaluations Database. Articles published within the last 10 years (2003–2012) were considered, owing to the fact that the last treatment breakthrough for AD was in 2002, when the first novel class of AD medications acting on the glutamatergic system by blocking *N*-methyl-D-aspartate-type glutamate receptors emerged (Reisberg *et al.*, 2003; Wilcock, 2003). To identify COI studies of dementia, appropriate disease-related MeSH terms in the combination of the following search terms were chosen: "dement* AND cost*," "Alzheimer* AND cost*," "dement* and economics" and "Alzheimer* AND economics." Additional articles, identified in references or citations of the retrieved articles or by author were added ("citation snowballing"). The search methodology was in line with the guidelines of "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (Moher *et al.*, 2011), except for the use of the PICOS review system.

Search results were independently reviewed and screened by two researchers at three levels: titles, abstracts and full text papers. Selection criteria were adopted from relevant checklists of international health economic guidelines (Drummond and Jefferson, 1996; Evers *et al.*, 2005) and were in accordance with the COI evaluation checklist of the COI guide to critical evaluation (Larg and Moss, 2011). In addition, abstracts were excluded from further consideration (a) if they were reviews of existing economic studies related to dementia; (b) if they were studies not reported in English or German; (c) if their primary objective was not the estimation of costs in dementia; and (d) if the study was primarily a modeling study.

Finally, the remaining papers were included in a comprehensive analysis of cost estimates, considering underlying study characteristics. In order to identify main cost drivers, studies were evaluated on whether the following cost categories were included: total, direct, indirect and informal costs. To enable comparability, all costs were transformed into annual costs per patient. In addition, all cost data were first inflated to 2013 values in local currency. If studies reported estimates not in local currency, costs were calculated back to local currency on the basis of reported currency exchange rates. Afterwards, inflated costs were converted to US dollars (year 2013) using gross domestic product purchasing power parity conversion rates for each country (OECD, 2014). This methodology has been described elsewhere (Andlin-Sobocki *et al.*, 2005).

Currently, there are no common consensus statements or guidelines for conducting COI studies in dementia. We identified five methodological articles addressing critical aspects for future COI research in dementia (Jonsson and Wimo, 2009; Gustavsson *et al.*, 2010; Mauskopf *et al.*, 2010; Mauskopf and Mucha, 2011; Costa *et al.*, 2012), highlighting three major important factors that are influencing costs in dementia: (1) care setting; (2) cost perspective (cost categories and components); and (3) disease severity. Therefore, these critical factors are carefully reviewed as part of our analysis of the main cost drivers in dementia. Further, study characteristics such as definition of disease, study population size, mean age, country, date of study and funding source have been considered.

Results

The systematic literature search identified 2254 articles. One more study was identified additionally by citation snowballing. After removing duplicates ($n = 1152$), titles of 1102 articles were screened. By screening titles, 994 articles were removed because they did not deal with COI studies of dementia. The abstract screening ($n = 108$) identified 59 articles for full-text analysis. A further 32 articles did not meet the selection criteria. The final analysis included 27 articles. The identified studies were analyzed by study characteristics (Table 1) as well as cost components and estimates (Tables 2–6).

Characteristics of included studies

Study sample. Studies were included if a clear definition of the study population was given (diagnosis of

Table 1 Study design characteristics

No	Reference (author, year)	Country	Perspective	Definition of dementia	Type of dementia	Costs by disease severity	Method to define disease severity	Data source and collection method	Epidemiological approach	Year of data	Study population size	Mean age (*SD*)	Funding source
Studies analyzing costs for community setting													
1	Allegri *et al*. (2007)	Argentina	S	NINCDS–ADRDA	AD	+	MMSE: >20, 20–11, <11	Patients and primary caregiver of clinic (interviews with economic data of last 3 months) retrospective, cross-sectional	Prevalence	2007	100	74.7 (*SD* = 7.7)	Patient advocacy group
2	Beeri *et al*. (2002)	Israel	S	NINCDS–ADRDA	AD	—	—	Patients and primary caregiver interviews prospective, longitudinal (6 months; baseline and monthly telephone interviews)	Prevalence	2002	121	76.4 (*SD* = 7.5)	Public funds
3	Chan *et al*. (2009)	Taiwan	NS	ICD-9-CM code of 331.0	AD	—	—	National Health Insurance Research Database of Taiwan's NHI program (random sample) retrospective	Prevalence	2000–2002	69.780	≥60 years	NA
4	Gustavsson *et al*. (2011b)	Different countries	NS (S)	NINCDS–ADRDA	AD	+	ADAS cog	Randomized, double-blind, twin trial (only data collected before treatment), prospective, multicenter, longitudinal (baseline, 6, 12, 18 months)	Prevalence	NA	1378	75.0 (*SD* = 8.1)	Pharm
5	Herrmann *et al*. (2006)	Canada	S	DSM-IV	AD	+	BPSD: yes/no	Canadian Outcomes Study in Dementia, caregiver records prospective, longitudinal (recorded monthly for 1 year)	Prevalence	NA	500	76.3 (*SD* = 6.2)	Pharm
6	Kraft *et al*. (2010)	Switzerland	S	ICD-10 codes F00-F03 G300, G301, G308, G309	Diagnosis of dementia	+	NS	Swiss national statistics and surveys + international reviews + expert interviews, retrospective	Prevalence	2007	NS	NS	Patient advocacy group
7	Lopez-Bastida *et al*. (2006)	Spain	S	Physician diagnosis	AD	+	CDR: 0/1/2/3	Alzheimer's Disease Association (Canary Islands)—sample, mailed questionnaire retrospective, cross-sectional	Prevalence	2001	237	75.5 (*SD* = 8.5)	Public funds
8	Mesterton *et al*. (2010)	Sweden	S	Physician-certified diagnosis of AD	AD	+	MMSE: 20–26, 10–19, 0-9	Interviews, medical records (patients and caregivers) retrospective (past 12 months), cross-sectional	Prevalence	2007–2008	233	79.5 (*SD* = 8.2)	Pharm
9	Newcomer *et al*. (2005)	USA	P	Physician-certified diagnosis of an irreversible dementia	AD; VaD	+	Mortality risk score: low/high	Medicare Alzheimer's Disease Demonstration Evaluation; eight-site randomized trial; interview + claims records, prospective, longitudinal (baseline, 12 months)	Prevalence	1989–1994	3.858	NS for patients	Pharm

(*Continues*)

Table 1 (Continued)

No	Reference (author, year)	Country	Perspective	Definition of dementia	Type of dementia	Costs by disease severity	Method to define disease severity	Data source and collection method	Epidemiological approach	Year of data	Study population size	Mean age (*SD*)	Funding source
10	Rapp *et al*. (2012)	France	S	Diagnosis of French memory clinic	AD	+	MMSE (score between 12 and 26) >20 to ≤0	Plan de Soin et d'Aide spécifique á la maladie d'Alzheimer sample, randomized trial, face-to-face interview, prospective, longitudinal (baseline, Year 1, Year 2)	Prevalence	2003–2005	1.131	79.8 (*SD* = 5.7)	Pharm
11	Rigaud *et al*. (2003)	France	S	NINCDS–ADRDA, DSM-IV	AD	+	MMSE: >21, 16–20, 11–15, <10	Questionnaire, single-center (outpatients), retrospective, cross-sectional	Prevalence	—	50	80.6 (*SD* = 5.4)	Pharm
12	Schwarzkopf *et al*. (2011)	Germany	S	Dementia diagnosis by physician	Dementia	+	MMSE: 18–24, 10–17, <10	Insurance claims data and caregiver interviews; cluster-randomized trial, prospective, longitudinal (24 months, yearly telephone interviews); cost data from 2005 to 2008	Prevalence	2005–2008	383	80.4 (*SD* = 6.8)	Public funds
13	Wang *et al*. (2008)	China	NS (S)	DSM-IV-TR	AD	+	MMSE: 21–26, 11–20, 0–10	Single-center (Department of Neurology, Ruijin), interview, retrospective, cross-sectional	Prevalence	2005–2006	67	74.0 (*SD* = 8.6; range: 53–90)	Basic research program
14	Zencir *et al*. (2005)	Turkey	NS (S)	DSM-IV	AD	+	MMSE: 15–30, 10–14, <10	Face-to-face interview (patients and caregivers); data for informal costs by daily time sheets (caregiver) of 15 days, prospective	Prevalence	2003	42	70.5 (*SD* = 8.9)	Patient advocacy group
15	Zhu *et al*. (2008)	USA	NS (S)	NINCDS–ADRDA, DSM-III-R	AD, DLB	—	—	Predictors II cohort, multicenter cohort study, prospective, cross-sectional	Prevalence	1998–2004	170	75.0 (*SD* = 7.6)	Public funds
16	Zhu *et al*. (2006a)	USA	NS	NINCDS–ADRDA, DSM-III-R	AD	—	—	Predictors II cohort, multicenter cohort study prospective, longitudinal (7 years), annual assessment of resource utilization; 82.4% in this study had two or more assessments; reported living in an institutional setting (nursing homes, assisted living facilities, retirement homes) at some point during the study	Prevalence	1998–2004	170	74.9 (*SD* = 7.7)	Public funds
Studies analyzing costs for institutionalized setting													
1	Allegri *et al*. (2007)	Argentina	S	NINCDS–ADRDA	AD	+	MMSE: >20, 20–11, <11	Patients and primary caregiver of clinic (interviews with economic data of last 3 months) retrospective, cross-sectional	Prevalence	2007	100	74.9 (*SD* = 7.6)	Patient advocacy group
2	Beeri *et al*. (2002)	Israel	S	NINCDS–ADRDA	AD	—	—	Patients and primary caregiver interviews prospective, longitudinal (6 months; baseline and monthly telephone interviews)	Prevalence	2002	121	81.5 (*SD* = 5.9)	Public funds

3	Kraft *et al*. (2010)	Switzerland	S	ICD-10 codes F00-F03 G300, G301, G308, G309	Diagnosis of dementia	+	NS	Swiss national statistics and surveys + international reviews + expert interviews, retrospective	Prevalence	2007	NS	NS for patients	Patient advocacy group
4	Mesterton *et al*. (2010)	Sweden	S	Physician-certified diagnosis of AD	AD	+	MMSE: 20–26, 10–19, 0–9	Interviews, medical records (patients and caregivers), retrospective (past 12 months), cross-sectional	Prevalence	2007–2008	233	79.5 (*SD* = 8.2)	Pharm
Studies analyzing costs for mixed settings (proportions for settings indicated in %)													
1	Coduras *et al*. (2010)	Spain	NS (S)	DSM-IV 290.00 or 290.10; NINCDS–ADRDA	AD	—	—	Paper-and-pencil case reports, prospective, multicenter cohort study, longitudinal (baseline, 6, 12 months); setting: 7.1% of patients institutionalized	Prevalence	2003–2006	560	76.7 (*SD* = 6.4)	NA
2	Jakobsen *et al*. (2011)	Denmark	S	NS	AD	—	—	Postal, self-administered questionnaire, cross-sectional, retrospective Setting: 61% at home; 35% care facility	Prevalence	2010	469	75.0 (*SD* = age > 50	Pharm
3	Jonsson *et al*. (2006)	Sweden, Denmark, Finland, Norway	S	Diagnosis of AD according to diagnostic criteria utilized in clinical practice	AD	+	MMSE: 26–30, 21–25, 15–20, 10–14, 0–9	Questionnaires prospective, multicenter study, longitudinal (baseline, 6, 12 months) Setting: institutionalized patients by disease stage: 5%/27%/40%	Prevalence	NA	272	75.9 *SD* not available	Pharm
4	Kang *et al*. (2007)	Korea	NS (S)	ICD-10: F00-F03, G30	NS	+	ADL: low, moderate, high	Claims data of the Korean National Health Insurance and survey data (patients and caregivers), retrospective, cross-sectional (survey) Setting: 49% institutionalized; 51% community	Prevalence	2005	609	73.7 (*SD* = 8.9)	Pharm
5	Leicht *et al*. (2011)	Germany	S	DSM-IV	NS	+	CDR: 0 = normal, 0.5 = very mild, 1 = mild, 2 = moderate, 3 = severe	Multicenter, German Study on Ageing, Cognition and Dementia in Primary Care Patients; third follow-up wave retrospective, cross-sectional Setting: 35.8% institutionalized	Prevalence	2007–2009	176	85.3 (*SD* = 3.7) aged > 75	Public funds
6	Livingston *et al*. (2004)	UK	NS	DSM-IV	AD	+	ADL: Non-dependent, ND-IFD dependent	Validated assessment instruments, patients and caregiver, prospective, longitudinal (baseline and at 6 months) Setting: institutionalized by disease stage: 5%/30%/60% (percentages per care setting only in a form of a figure; presented numbers are approximations)	Prevalence	NA	224	Aged > 55	NA

(*Continues*)

Table 1 (Continued)

No	Reference (author, year)	Country	Perspective	Definition of dementia	Type of dementia	Costs by disease severity	Method to define disease severity	Data source and collection method	Epidemiological approach	Year of data	Study population size	Mean age (*SD*)	Funding source
7	Murman *et al*. (2007)	USA	S, P	NINCDS–ADRDA	AD, DLB	—	—	Cohort study, structured interview, prospective, longitudinal (baseline, 1-year follow-up). Setting: 35% institutionalized; 65% community	Prevalence	NA	150	76.7 (*SD* = 8.5)	NA
8	Schwarzkopf *et al*. (2012)	Germany	S	ICD-10: F00-F03 and G30	Dementia	—	—	Health insurance claims data; case–control study, retrospective Setting: 67.9% living in the community	Prevalence	2005–2007	9.147	81.6 (*SD* = 7.4)	Public funds
9	Suh *et al*. (2006)	Korea	S	Diagnosis of dementia	dementia	—	—	Korea National Survey of Long-term Care Need (LTC survey); Markov model, prospective, setting: 4% institutionalized; 96% community	Prevalence	2002	Simulation	Ages > 50	NA
10	Wimo and Winblad (2003)	Sweden	S	NS	AD, VaD	+	NS mild, moderate, severe	Nordanstig Cohort prospective, longitudinal, interviews Setting: NS		NA	NA	NA	NA
11	Zhu *et al*. (2006b)	USA	NS	NINCDS–ADRDA, DSM-III-R	AD	—	—	Predictors II cohort, multicenter cohort study prospective, longitudinal (7 years), annual assessment of resource utilization; medium follow-up: 2.5 years Setting: 85.9% at home	Prevalence	1998–2004	170	76.4 (*SD* = 8.1)	Public funds

AD, Alzheimer's disease; VaD, vascular dementia; S, societal perspective; P, third-party/payer perspective; DLB, dementia with Lewy bodies; NINCDS–ADRDA, Alzheimer's Association Criteria; DSM, Diagnostic and Statistical Manual of Mental Disorders; MMSE, Mini mental state examination; ADL, activities of daily living; BPSD, Behavioral and Psychological Symptoms of Dementia; CDR, Clinical Dementia Rating; ICD, International Classification of Diseases; NA, not available; NS, not specified; SD, standard deviation.

dementia). Dementia is a chronic and progressive disease that affects several brain functions (APA, 1994). Deficits in cognitive function are often accompanied by deterioration in emotional control, social behavior or motivation. The most common staging of dementia is mild/early stage (first year or two), moderate/middle stage (second to fourth or fifth years) and severe/late stage (fifth year or later); however, symptoms and length of stages vary (ADI, 2009). The most common cause of dementia is AD, accounting for 60–70% of cases (ADI, 2010). This is reflected in our included studies, where most study participants were diagnosed with AD. Ten studies focused not exclusively on AD and included other dementias such as vascular dementia (VaD) or dementia with Lewy bodies (DLB). Dementia was defined according to: the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (McKhann *et al.*, 1984) ($n = 4$), Diagnostic and Statistical Manual of Mental Disorders, fourth edition, criteria (APA, 2000) ($n = 5$), both criteria ($n = 5$), International Classification of Diseases ($n = 4$) and confirmed diagnosis by a medical doctor ($n = 7$). Two studies reported a confirmed diagnosis without detailed information.

The study population size ranged from a maximum of 69,780 cases (Chan *et al.*, 2009) to a minimum of 42 cases (Zencir *et al.*, 2005). The mean age varied from a minimum of 70.5 years (Zencir *et al.*, 2005) to a maximum of 85.3 years (Leicht *et al.*, 2011). Average mean age of included studies is 77.1 years ($SD = \pm 7.3$). This is because dementia prevalence increases significantly with age; people aged >65 years are the most affected (Prince *et al.*, 2013). Several epidemiological studies indicate the exponential growth of prevalence rate with age (from around 0.8% in the 60- to 64-year band to 27.1% in the 85+-year age group; ADI, 2008). In total, 11 studies considered the impact of age on costs in dementia, whereby five studies identified no significant changes in results and another five studies reported a significant influence of age on costs in dementia. One study (Coduras *et al.*, 2010) reported detailed cost estimates for different age groups (cf. Table 2); however, it came to the conclusion that total costs do not depend on age.

Reviewed studies showed COI results for 14 countries: Argentina ($n = 1$), Canada ($n = 1$), China ($n = 2$), Denmark ($n = 1$), France ($n = 2$), Germany ($n = 3$), Israel ($n = 1$), Korea ($n = 2$), Spain ($n = 2$), Sweden ($n = 4$), Switzerland ($n = 1$), Turkey ($n = 1$), the UK ($n = 1$), and the USA ($n = 3$). Two studies were conducted in more than one country. In total, 15 studies were conducted in Europe (54%), six in North America (21%), five in Asia (18%) and one in South America, whereas one study conducted a twin trial in more than one continent.

Care setting. Four studies conducted cost analysis for a mixed setting but also reported estimates separately by care setting (Beeri *et al.*, 2002; Allegri *et al.*, 2007; Kraft *et al.*, 2010; Mesterton *et al.*, 2010). In contrast, 10 studies estimated costs for mixed settings without separate analysis by care setting. Further 13 studies analyzed costs for community-dwelling patients. In total, eight of the latter studies indicate an augmenting number (>60%) of community-dwelling patients. The most comprehensive COI studies were those derived by Allegri *et al.* (2007) and Mesterton *et al.* (2010), who stratified costs by disease severity as well as seperating them by community-dwelling and institutionalized patients for direct medical, direct non-medical and informal costs.

Cost by disease severity. Seventeen studies analyzed costs by disease severity, but several measures of disease severity were considered: cognitive function ($n = 12$; Mini mental state examination (MMSE), ADAS-cog (Alzheimer's Disease Assessment Scale Cognition) and Clinical Dementia Rating (CDR)), activities of daily living (ADL; $n = 2$), behavioral symptoms ($n = 1$; Behavioral and Psychological Symptoms of Dementia (BPSD)), mortality risk score ($n = 1$). The most common method was the MMSE in eight studies. However, different cut-off points were applied in the studies. The CDR was applied in two studies, whereas the ADAS-cog was used in one study. Scores of ADL scales were used in two studies. One study applied a mortality risk score (Newcomer *et al.*, 2005). The BPSD instrument was used in one study, and two studies did not specify their method.

Cost estimates

The majority of the studies stated a societal perspective ($n = 15$), reporting at least direct costs and either indirect or informal costs, except for two studies reporting only one cost category (Jakobsen *et al.*, 2011; Schwarzkopf *et al.*, 2012). One study adopted a third-party payer perspective, reporting direct costs exclusively Newcomer *et al.*, 2005. In addition, 10 studies did not explicitly state the study perspective; however, this could be derived in six of the 10 studies as societal—as direct costs and either indirect or informal costs were calculated.

Table 2 Cost components by setting

	Reference (author, year)												
	Allegri et al. (2007)	*Beeri et al.* (2002)	*Kraft et al.* (2010)	*Mesterton et al.* (2010)	*Chan et al.* (2009)	*Gustavsson et al.* (2011*b*)	*Herrmann et al.* (2006)	*Leicht et al.* (2011)	*Lopez-Bastida et al.* (2006)	*Newcomer et al.* (2005)	*Rapp et al.* (2012)	*Rigaud et al.* (2003)	*Schwarzkopf et al.* (2011)
Care setting													
Community based	+	+	+	+	+	+	+	+	+	+	+	+	+
Institutionalized	+	+	+	+	–	–	–	–	–	–	–	–	–
Mixed	–	–	–	–	–	–	–	–	–	–	–	–	–
Age group													
Costs by age group	–	–[a]	–	–[b]	–[a]	–	–[b]	–[c]	–	–	–	–	–
Disease severity													
Costs by Disease severity	+	–	+	+	–	+	+	+	+	+	+	+	+
Stratification method	MMSE	–	NS	MMSE	–	ADAS-cog	BPSD	CDR	CDR	Mortality risk score	MMSE	MMSE	MMSE
Cost components													
Direct costs	+	+	+	+	+	+	+	+	+	+	+	+	+
Direct medical	+	+	+	+	+	+	+	+	+	NS	+	+	+
Outpatient care	+	+	+	+	+	–	+	+	+	NS	+	NS	+
Inpatient care	+	+	+	+	+	+	+	+	+	NS	+	NS	+
Medication	+	+	+	+	NS	–	+	+	+	–	+	NS	+
Direct non-medical	+	+	+	+	–	NS	+	+	+	+	+	+	+
Home care	+	+	+	+	–	NS	+	+	+	+	+	+	+
Nursing home	+	+	+	+	–	NS	–	+	–	–	–	–	–
Transport	–	–	–	–	–	NS	–	–	–	–	–	–	–
Indirect costs	–	–	–	–	–	–	–	–	+	–	–	–	–
Informal costs	+	+	+	+	–	+	+	+	+	–	+	+	+
Replacement	+	+	+	–	–	–	NS	+	–	–	+	+	+
Opportunity	–	–	–	+	–	+	NS	–	+	–	–	–	–
Total costs	+	+	+	+	–	+	+	+	+	–	+	+	+

+, available; –, not available; NS, not specified; ADAS-cog, Alzheimer's Disease Assessment Scale Cognition; ADL, activities of daily living; BPSD, Behavioral and Psychological Symptoms of Dementia; CDR, Clinical Dementia Rating; MMSE, Mini-mental state examination.
[a]Controlling for costs for age groups with no significant change in results.
[b]Age was found to be a predictor of higher costs of care; however, no specific cost analysis by age.
[c]Significant change for age in formal care costs (not in other cost categories).

Direct costs. Direct costs are derived from resources of the medical care system and can be divided into direct medical (outpatient and inpatient visits and medication) as well as direct non-medical costs that are derived outside the medical care system (e.g., nursing home, home help and transportation; ADI, 2010).

In total, 22 of the 25 studies considering direct costs reported annual cost estimates per patient (Table 3). Nineteen of the 22 studies considered outpatient care, inpatient care, medication and non-medical cost components, whereas nursing home expenditures were included in nine studies. Thirteen studies reported direct costs for the community-based setting, whereby only nine of those included all four cost components (inpatient care, outpatient care, medication and non-medical costs). The latter studies indicate a mean estimate of \$8257 ($SD = \pm 4427$). The highest costs were reported for France (\$13,790; Rigaud *et al.*, 2003) and Germany (\$13,168; Schwarzkopf *et al.*, 2011). Costs for medication were reported to be the main cost driver in five studies, whereas two studies reported non-medical costs (assistance and paid help) and one study inpatient costs as the main cost driver. Six of the nine studies estimated costs by disease severity on the basis of the following: the MMSE in four studies and BPSD and CDR in one study each (another study did not specify the underlying method). The mean estimate is \$5971 ($SD = \pm 4171$; $n = 7$) for patients with mild dementia, \$8757 ($SD = \pm 4197$; $n = 7$) for the moderate stage and \$13,402 ($SD = \pm 9554$; $n = 4$)

Table 2 (Continued)

Wang et al. (2008)	*Zencir et al.* (2005)	*Zhu et al.* (2008)	*Zhu et al.* (2006a)	*Jakobsen et al.* (2011)	*Jonsson et al.* (2006)	*Kang et al.* (2007)	*Coduras et al.* (2010)	*Livingston et al.* (2004)	*Murman et al.* (2007)	*Schwarzkopf et al.* (2012)	*Suh et al.* (2006)	*Wimo; Winblad* (2003)	*Zhu et al.* (2006b)
+	+	+	+	–	–	–	–	–	–	–	–	–	–
–	–	–	–	–	–	–	–	–	–	–	–	–	–
–	–	–	–	+	+	+	+	+	+	+	+	+	+
–[a]	–[b]	–	–	–[a]	–[a]	–	+	–	–	–[b]	–	–	–
+	+	–	–	–	+	+	–	+	–	–	–	+	–
MMSE	MMSE	–	–	–	MMSE	ADL	–	ADL	–	–	–	NS	–
+	+	+	–	–	+	+	+	+	+	+	+	+	+
+	+	+	–	–	+	+	+	NS	+	+	+	NS	+
+	+	+	–	–	+	+	+	NS	+	+	NS	NS	+
+	–	+	–	–	+	+	+	NS	+	+	NS	NS	+
+	+	+	–	–	+	+	+	–	+	+	NS	NS	+
+	–	+	–	–	+	+	+	+	+	+	+	+	+
+	–	+	–	–	+	+	+	+	+	+	+	+	+
–	–	–	–	–	+	+	+	–	+	–	–	NS	–
+	–	–	–	–	+	–	+	–	–	–	–	–	–
–	–	–	–	–	–	+	–	–	–	–	+	–	–
+	+	+	+	+	+	–	+	+	+	–	+	+	–
+	NS	+	+	+	–	–	–	NS	+	–	+	NS	–
–	NS	–	–	+	+	–	+	NS	–	–	–	NS	–
+	+	+	–	–	+	+	+	+	+	–	+	+	–

for the severe stage. All except one study reported increasing direct costs per disease severity in the community-based setting.

However, the mean estimate for direct costs in the institutionalized setting is \$23,752 ($SD = \pm$23,621; $n = 3$; min = \$5761; max = \$50,501), in average three-fold higher than in the community-based setting, which is due to the main cost driver of nursing home expenditures in all three studies (Beeri *et al.*, 2002; Allegri *et al.*, 2007; Kraft *et al.*, 2010).

The mean estimate for direct costs in a mixed setting ($n = 9$) is \$19,305. For Europe, the study from Gustavsson *et al.* (2011c) reported direct costs of \$23,105 (€16,584 purchasing power parity 2010) per person for a mixed setting ($n = 13$), which is close to our results that indicated a mean estimate of \$23,540 for European studies ($n = 5$). The majority of studies ($n = 6$) reported nursing home expenditures to be the first or second main cost driver.

Indirect costs. Indirect costs refer to production losses in the working population (e.g., impaired productivity while working, sick leave and early retirement). Indirect costs are less relevant in dementia, where most of the affected are older people who are often retired (ADI, 2010). Therefore, only three studies estimated indirect costs (Table 4), indicating a range from \$1253 in the study from Lopez-Bastida *et al.* (2006), which was conducted in a sample of community-dwelling patients, to \$12,579 in the study

Table 3 Annual direct costs per patient

			Average annual direct costs per person				Medical		Non-medical			USD (2005 PPP)			
Study	**Country**	**Year of costs**	**Local currency in year of costs**		**Local currency in 2013**	**USD (2013 PPP)**	**Outpatient care**	**Inpatient care**	**Medication**	**Non-medical**	**Nursing home**	**Disease Severity**	**Mild**	**Moderate**	**Severe**
Community-based setting: **Studies including outpatient, inpatient, medication and non-medical direct cost components**															
Allegri et al. 2007	Argentina	2001	3,189[a,f]	ARS	10,610[a,f]	3,121[a,f]	+	+	+	+	-	-	-	-	-
Beeri et al. 2002	Israel	1999	30,932[a,g]	NIS	41,346[a,g]	10,377[a,g]	+	+	+	+	-	-	-	-	-
Kraft et al. 2010	Switzerland	2007	8,720[g]	CHF	8,884[g]	6,392[g]	+	+	+	+	-	NS[**]	1,525	7,520	7,441
Rigaud et al. 2003	France	1996	9,008[a,f]	EUR	11,656[a,f]	13,790[a,f]	+	+	+	+	-	MMSE	5,126	9,040	20,914
Schwarzkopf et al. 2011	Germany	2008	9,627	EUR	10,319	13,168	+	+	+	+	-	MMSE	9,838	11,232	-
Rapp et al. 2012	France	2004	7,616[a]	EUR	8,775[a]	10,381[a]	+	+	+	+	-	-	-	-	-
Lopez-Bastida et al. 2006	Spain	2001	5,557[a,e]	EUR	7,571[a,e]	11,083[a,e]	+	+	+	+	-	CDR	5,241	7,551	10,207
Herrmann et al. 2006	Canada	2000	2,844[a]	CAD	3,663[a]	2,961[a]	+	+	+	+	-	BPSD	1,143	2,813	-
Wang et al. 2008	China	2006	8,432[a]	RMB	10,651[a]	3,043[a]	+	+	+	+	-	MMSE	2,330	2,335	2,638
Studies including a subset of the direct cost components only															
Newcomer et al. 2005	USA	2002	14,237[a]	USD	18,567[a]	18,567[a]	+	+	-	+	-	MRS	NA	NA	NA
Zhu et al. 2008	USA	2004	7,993[a]	USD	9,853[a]	9,859[a]	-	-	-	+	-	-	-	-	-
Zencir et al. 2005	Turkey	2003	3,362[a,f]	TL	7,485[a,f]	6,816[a,f]	+	-	+	-	-	MMSE	2,197	3,286	3,310
Chan et al. 2009	Taiwan	2002	155[a]	TWD	188,273[a]	12,066[a]	+	+	+	-	-	-	-	-	-
Institutionalized setting: **Studies including outpatient, inpatient, medication and non-medical direct cost components**															
Allegri et al. 2007	Argentina	2001	5,887[a,f]	ARS	19,568[a,f]	5,761[a,f]	+	+	+	+	+	MMSE	-	-	-
Beeri et al. 2002	Israel	1999	44,696[a,g]	NIS	59,744[a,g]	14,994[a,g]	+	+	+	+	+	-	-	-	-
Kraft et al. 2010	Switzerland	2007	68,891[g]	CHF	70,188[g]	50,501[g]	+	+	+	+	+	NS[**]	-	-	-
Mixed setting: **Studies including outpatient, inpatient, medication and non-medical direct cost components**															
Wimo; Winblad 2003	Sweden	2000	188,676[a]	SEK	227,658[a]	26,111[a]	+	+	+	+	NS	NS	12,133	20,787	28,300
Leicht et al. 2011	Germany	2008	18,787[d]	EUR	20,137[d]	25,697[d]	+	+	+	+	+	CDR	16,466	24,449	31,662
Mesterton et al. 2010	Sweden	2007	287,064[a]	SEK	310,621[a]	35,626[a]	+	+	+	+	+	MMSE	14,097	35,318	46,612
Murman et al. 2007*	USA	2001	17,592	USD	23,163	23,163	+	+	+	+	+	-	-	-	-
Jönsson et al. 2006	Scandinavia[c]	2003	126,050[a]	SEK	142,621[a]	16,358[a]	+	+	+	+	+	MMSE	6,336	15,936	32,026
Zhu et al. 2006b	USA	2004	12,587[a]	USD	15,015[a]	15,015[a]	+	+	+	+	-	-	-	-	-
Kang et al. 2007	Korea	2004	6,990,430	KRW	8,976,780	10,460	+	+	+	+	+	ADL	4,370	6,982	14,361
Coduras et al. 2006	Spain	2006	8,164[a]	EUR	9,502[a]	13,910[a]	+	+	+	+	+	-	-	-	-
Suh et al. 2006	Korea	2002	4,613,515[b]	KRW	6,352,560[b]	7,402[b]	+	+	+	+	-	-	-	-	-

+, available; NS, not specified; MMSE, Mini mental state examination; ADL, activities of daily living; BPSD, Behavioral and Psychological Symptoms of Dementia; CDR, Clinical Dementia Rating; MSR, mortality risk score; ▭, main cost driver in direct costs (reported only for those studies stating cost components separately in monetary terms); ▭, second main cost driver in direct costs (reported only for those studies stating cost components separately in monetary terms).

[a]AD patients.

[b]Average of "in the LTC" and "not in the LTC."

[c]Sweden, Finland, Denmark and Norway.

[d]Institutional care/nursing home included.

[e]Direct non-medical costs for primary and secondary caregiver were allocated to informal costs of care.

[f]Average between mild/moderate/severe.

[g]Average between community and institutionalized costs.

[h]Unpaid care was not included also stated as direct costs in the study.

[i]Only patients cared at home by disease severity.

Table 4 Annual indirect costs per patient

Study	Country	Average annual indirect costs per person				Inclusion of		USD PPP 2013			
		Year of costs	Local currency in year of costs	Local currency in 2013	USD (PPP 2013)	Patients	Caregivers	Disease severity	Mild/low	Moderate	Severe/high
Community-based setting											
Lopez-Bastida *et al.*, 2006	Spain	2001	628	EUR 856	1,253	+	–	CDR	1,075	1,219	1,506
Mixed setting											
Kang *et al.*, 2007	Korea	2004	881,980	KRW 1,132,597	1,320	+	+	ADL	885	1,680	1,663
Suh *et al.*, 2006	Korea	2002	7,840,350[b]	KRW 10,795,737[b]	12,579[b]	–	+	–	–	–	–

+, available; NS, not specified; MMSE, Mini mental state examination; ADL, activities of daily living; BPSD, Behavioral and Psychological Symptoms of Dementia; CDR, Clinical Dementia Rating.
[a]AD patients.
[b]Included informal costs (time) of caregiver.

from Suh *et al.* (2006), which was conducted in a mixed setting. Although the studies from Suh *et al.* and Kang *et al.* were both conducted in Korea, they indicate a large range of indirect costs. This is because indirect costs were calculated on the basis of both missed work of caregivers (lost income) and replacement costs (paid caregiver) in the study from Suh *et al.* (2006).

Further differences in cost estimation can be explained by the inclusion of both patients and informal caregivers (Kang *et al.*, 2007) in contrast to the inclusion of exclusively patients (Lopez-Bastida *et al.*, 2006). Indirect costs were analyzed by disease severity in two studies; however, the studies applied different stratification methods.

Informal costs. Informal costs refer to the amount of unpaid informal caregiver's time provided for care. For informal cost calculation, two different main methods are used. The replacement cost approach refers to assigning a monetary value for informal care time on the basis of the cost of care by professional caregivers (formal care). The opportunity cost approach is the value of the best alternative forgone for the informal caregiver, for example, lost leisure time or lost production (Jonsson and Wimo, 2009).

In total, 19 COI studies stated informal cost estimates (Table 5). The majority of studies applied the replacement cost approach (63%), whereas four studies (21%) used the opportunity cost approach. Two studies applied both approaches, whereas three further studies did not specify the underlying method.

Twelve studies reported informal costs for a community-based setting; the mean estimate is \$23,340 ($SD = \pm 16{,}288$). Schwarzkopf *et al.* (2011, Germany) indicated the highest informal costs (\$52,203). All the studies that analyzed informal costs of patients cared for at home identified increased informal costs by disease severity, no matter which stratification method (MMSE, CDR or BPSD) or theoretical approach was applied. The mean estimate for informal costs is \$15,478 ($SD = \pm 15{,}416$; $n = 8$) for patients with mild dementia, \$31,104 ($SD = \pm 25{,}142$) for the moderate stage and \$38,403 ($SD = \pm 33{,}007$) for the severe stage. In contrast, one of the four studies analyzing informal costs by disease stage for a mixed setting reported the highest costs for the moderate stage (Mesterton *et al.*, 2010).

Three studies reported informal costs for an institutionalized setting. In studies from Allegri *et al.* (2007) and Beeri *et al.* (2002), informal costs referred to the time per patient provided by an informal caregiver, although the patient was institutionalized. Most of

Table 5 Annual informal costs per patient

Study	Country	Average annual informal costs per patient					USD (2013 PPP)			
		Year of costs	Local currency in year of costs	Local currency in 2013	USD (2013 PPP)	Methods	Disease severity	Mild	Moderate	Severe
Community-based setting										
Beeri *et al*., 2002	Israel	1999	44,405[a,b] NIS	59,355[a,b]	14,897[a,b]	Replacement	—	—	—	—
Allegri *et al*., 2007	Argentina	2001	4,940[a] ARS	16,435[a]	4,834[a]	Replacement	—	—	—	—
Schwarzkopf *et al*., 2011	Germany	2008	38,165 EUR	40,908	52,203	Replacement	MMSE	42,133	71,585	—
Lopez-Bastida *et al*., 2006	Spain	2001	22,013[d] EUR	29,990[d]	43,902[d]	Opportunity	CDR	24,635[d]	39,507[d]	67,735[d]
Rapp *et al*., 2012	France	2004	27,516[a] EUR	31,703[a]	37,507[a]	Replacement	MMSE	29,351	45,669	—
Kraft *et al*., 2010	Switzerland	2007	46,581 CHF	47,460	34,148	Replacement	NS	17,251	39,893	79,786
Zhu *et al*., 2008	USA	2004	17,136 USD	21,137	21,137	Replacement	—	—	—	—
Rigaud *et al*., 2003	France	1996	13,817[a] EUR	17,878[a]	21,151[a]	Replacement	MMSE	3,326	12,990	55,383
Wang *et al*., 2008	China	2006	10,568[a] RMB	13,349[a]	3,814[a]	Replacement	MMSE	1,679	3,367	6,582
Herrmann *et al*., 2006	Canada	2000	11,376 CAD	14,654	11,844	NS	BPSD	4,985	—	12,969
Zencir *et al*., 2005	Turkey	2003	2,155[a] TL	4,798[a]	4,369[a]	NS	MMSE	466	4,714	7,964
Zhu *et al*., 2006a	USA	NA[c]	25,381 USD	30,278	30,278	Replacement	—	—	—	—
Institutionalized setting										
Beeri *et al*., 2002	Israel	1999	10,313[a,b] NIS	13,785[a,b]	3,460[a,b]	Replacement	—	—	—	—
Allegri *et al*., 2007	Argentina	2001	416[a] ARS	1,384[a]	407[a]	Replacement	—	—	—	—
Kraft *et al*., 2010	Switzerland	2007	0 CHF	0	0	Replacement	—	—	—	—
Mixed setting										
Mesterton *et al*., 2010	Sweden	2007	29,889[a] SEK	32,341[a]	3,709[a]	Opportunity	MMSE	2,600	4,918	3,534
Coduras *et al*., 2010	Spain	2006	8,944[a] EUR	10,410[a]	15,239[a]	Opportunity	—	—	—	—
Jonsson *et al*., 2006	Scandinavia	2003	46,071[a] SEK	52,128[a]	5,979[a]	Opportunity	MMSE	4,541	7,421	9,985
Jakobsen *et al*., 2011	Denmark	2010	514,628[a,d] DKK	546,068[a,d]	70,599[a,d]	Replacement	—	—	—	—
Murman *et al*., 2007	USA	2001	14,734 USD	19,400	19,400	Replacement	—	—	—	—
Wimo and Winblad, 2003	Sweden	1996	55,265[a] SEK	66,683[a]	7,648[a]	NS	NS	5,119	7,573	9,337
Leicht *et al*., 2011	Germany	2008	11,996 EUR	12,858	16,408	Replacement	CDR	12,155	24,933	26,924

NA, not available; NS, not specified; MMSE, Mini mental state examination; ADL, activities of daily living; BPSD, Behavioral and Psychological Symptoms of Dementia; CDR, Clinical Dementia Rating; MSR, mortality risk score.

[a]AD patients.

[b]Average of institutionalized ($10,700.0) and community-dwelling sample ($2485.0).

[c]Year of costs: 2004.

[d]Inclusion of two caregivers.

the time referred to patients visits. In contrast, Kraft *et al.* (2010) counted informal costs for an institutionalized setting with zero "0".

Total costs. The total (societal) costs of dementia per patient were reported in 21 studies (Table 6). Only two studies included all three cost categories (direct, indirect and informal costs), whereas 19 studies reported total costs for direct and informal costs exclusively. For the community-based setting, 11 studies included informal and direct (outpatient, inpatient, medication and non-medical) costs with a mean estimate of \$31,896 ($SD = \pm 19{,}206$). It is evident that all studies reported informal costs to be the main cost driver, contributing a minimum of 60% to a maximum of 84% to the total costs of dementia. Eight of the 11 studies stratified costs by disease severity, on the basis of MMSE ($n = 5$), CDR ($n = 1$), BPSD ($n = 1$) and not specified ($n = 1$). However, all of the studies indicated increasing costs by disease severity. The mean estimates are \$22,113 ($SD = \pm 17{,}621$; $n = 8$) for mild stage, \$42,930 ($SD = \pm 25{,}873$; $n = 7$) for moderate stage and \$51,659 ($SD = \pm 36{,}763$; $n = 6$) for severe stage of dementia. The highest annual total costs per patient for mild (\$42,133) and moderate (\$71,585) stages of dementia were reported in the study from Schwarzkopf *et al.* (2011), including a comprehensive set of direct and informal cost components. For severe stage of dementia, the highest costs were reported in the study from Kraft *et al.* (2010; \$79,786). Statistically significant results of differences in costs by disease severity according to MMSE and CDR (cognitive function) were reported in five studies: Allegri *et al.* (2007): $p < 0.05$; Mesterton *et al.* (2010): $p < 0.01$; Rapp *et al.* (2012): $p < 0.001$; Schwarzkopf *et al.* (2011) (53): $p < 0.000$; and Wang *et al.* (2008): $p < 0.0001$. Further, Herrmann *et al.* (2006) presented significant results for BPSD ($p < 0.0001$).

For the institutionalized setting, the mean estimate of total costs is \$39,897 ($SD = \pm 25{,}704$; $n = 4$). This implicates higher average costs than in a community-based setting and is also due to the fact that costs for institutionalization contribute to the main cost driver.

The proportion of informal, direct and indirect costs in the total cost estimation is illustrated in Figure 1. The visualization highlights the fact that informal costs are the main cost driver in a community-based setting, whereas direct costs are the main cost driver in an institutionalized setting.

Only three studies (Beeri *et al.*, 2002; Allegri *et al.*, 2007; Kraft *et al.*, 2010) analyzed informal and direct costs separately for community-dwelling patients versus institutionalized patients in the same study population.

Discussion

Identified cost drivers by care setting

Our review is the first providing a detailed description of different cost categories and components as well as cost drivers for different care settings. Overall, an imbalance between the number of studies conducted in a community-based setting ($n = 13$) and studies in an institutionalized setting ($n = 4$) is evident. Findings indicate an average annual estimate of total costs of \$30,554 ($n = 27$) per patient, which emphasizes an increasing economic burden of dementia.

Although total costs by care setting indicate rather small deviations (community-based: \$31,896 ($n = 11$); institutionalized: \$39,897 ($n = 4$)), this review highlights the significant difference in the composition of total costs per patient by care setting: direct costs contribute from 85% up to 100% of the total costs in an institutionalized setting. In contrast, their share is only 16–40% in a community-based setting, where informal care costs (60–84%) are one of the main cost drivers.

Community-based setting. The majority of dementia patients are cared for at home, thereby causing informal costs that put an economic burden on families rather than on healthcare systems. Against this background, it is evident that informal costs are the main cost drivers in the dementia care context (60–84%), followed by medication costs and direct non-medical costs such as assistance, paid help or transport. A major driver for increasing costs within different cost components is a later disease stage. All the studies that analyzed *informal* costs of patients cared for at home identified increased informal costs by disease severity. By comparing the increase of costs from moderate to severe stages between the community-based setting (average increase of \$15,626) and the mixed setting (average increase of \$1,234), it becomes even more evident that there is a much higher increase of informal costs for the community-based setting.

All except one study reported increasing *direct* costs per disease severity in the community-based setting. Main cost drivers for mild/moderate/severe stages were medications and direct non-medical costs.

The impact of indirect costs is low in the analyzed studies, owing to the fact that indirect costs are only applied to the working population. As included studies

Table 6 Annual total costs per person

Study	Country	Average annual total costs per person				
		Year of costs	Local currency in year of costs		Local currency in 2013	USD (2013 PPP)
Community-based setting						
Studies including outpatient, inpatient, medication and non-medical direct cost components						
Lopez-Bastida *et al*., 2006	Spain	2001	28,198[a]	EUR	38,416[a]	56,416[a]
Allegri *et al*., 2007	Argentina	2001	8,130[a,b]	ARS	27,048[a,b]	7,955[a,b]
Beeri *et al*., 2002	Israel	1999	73,580[a]	NIS	98,352[a]	24,684[a]
Kraft *et al*., 2010	Switzerland	2007	55,301	CHF	56,342	40,539
Mesterton *et al*., 2010	Sweden	2007	156,823[a]	SEK	169,692[a]	19,462[a]
Rapp *et al*., 2012	France	2004	35,016[a]	EUR	40,345[a]	47,731[a]
Rigaud *et al*., 2003	France	1996	22,825[a,b]	EUR	29,533[a,b]	34,939[a,b]
Schwarzkopf *et al*., 2011	Germany	2008	47,561	EUR	50,979	65,055
Wang *et al*., 2008	China	2006	19,001[a]	RMB	24,000[a]	6,857[a]
Zhu *et al*., 2008	USA	2004	25,129[a]	USD	30,997[a]	30,997[a]
Herrmann *et al*., 2006	Canada	2000	15,576[a]	CAD	20,064	16,217
Studies including several direct cost components						
Gustavsson *et al*., 2011b	Different countries[d]	2006	21,128[a]	USD	23,365[a]	23,365[a]
Zencir *et al*., 2005	Turkey	2003	5,551[a,b]	TL	12,359[a,b]	11,254[a,b]
Institutionalized setting						
Studies including outpatient, inpatient, medication and non-medical direct cost components						
Allegri *et al*., 2007	Argentina	2001	14,834[a,b]	ARS	49,351[a,b]	14,515[a,b]
Beeri *et al*., 2002	Israel	1999	70,529[a]	NIS	94,274[a]	23,660[a]
Kraft *et al*., 2010	Switzerland	2007	68,891	CHF	70,188	50,501
Mesterton *et al*., 2010	Sweden	2007	571,381[a]	SEK	618,270[a]	70,911[a]
Mixed setting						
Studies including outpatient, inpatient, medication and non-medical direct cost components						
Suh *et al*., 2006	Korea	2002	13,074,831	KRW	10,003,333	20,978
Coduras *et al*., 2010	Spain	2006	17,109[a]	EUR	19,913[a]	29,150[a]
Allegri *et al*., 2007	Argentina	2001	7,719[a,b]	ARS	25,680[a,b]	7,553[a,b]
Jonsson *et al*., 2006	Scandinavia	2003	172,000[a]	SEK	194,612[a]	22,321[a]
Leicht *et al*., 2011	Germany	2008	30,783	EUR	32,996	42,107
Mesterton *et al*., 2010	Sweden	2007	316,953[a]	SEK	342,963[a]	39,336[a]
Murman *et al*., 2007	USA	2001	32,326	USD	42,563	42,563
Livingston *et al*., 2004	UK	2003	16,231[a]	GBP	21,179[a]	30,467[a]
Wimo and Winblad, 2003	Sweden	2000	243,272[a]	SEK	293,534[a]	33,667[a]
Studies including several direct cost components						
Kang *et al*., 2007	Korea	2004	7,872,410	KRW	10,109,378	11,780

C, community dwelling; I, institutionalized; NS, not specified; PPP, purchasing power parities; ER, exchange rate; USD, US dollar; EUR, Euro; SEK, Swedish Krona; CHF, Swiss Franc; RMB, renminbi; CAD, Canadian dollar; NS, not specified; parities; ER, exchange rate; USD, US dollar; MMSE, Mini mental state examination; ADL, activities of daily living; NPI, neuropsychiatric inventory; BPSD, Behavioral and Psychological Symptoms of Dementia; CDR, Clinical Dementia Rating.

[a]AD patients.

[b]Average of mild/moderate/severe cost calculations.

[c]Only patients cared for at home by disease severity.

[d]Reported conversion rates for USA.

focused on populations aged 65+ years, indirect costs are underestimated in reviewed studies.

Institutionalized setting. Although only a small number of studies ($n = 4$) reported costs for an institutionalized setting, results of this review indicate that direct non-medical costs (nursing home expenditures) represent the primary share of direct costs in an institutionalized setting (85–100%). These findings are in line with the study from Gustavsson *et al.* (2011c), reporting dementia to be one of the most costly disorders of the brain, owing to very high direct non-medical costs (share of 84%). None of the studies reported indirect costs for an institutionalized setting, which can be explained by the high age of included study participants (mean age = 77.1 years). Informal costs are reported in three studies and referred to patients' visits in two studies, whereas another study valued informal costs as zero. However, the inclusion of informal costs in an institutionalized setting is crucial for a cost analysis in different care settings.

A lack of data about costs by disease stage for an institutionalized setting is evident. Only one study (Mesterton *et al.*, 2010) reported increasing total costs in dementia by disease stage.

Table 6 (Continued)

			USD (2013 PPP)						
Direct costs	Indirect costs	Informal costs	Severity of disease	Definition Mild	MILD	Definition Moderate	MODERATE	Definition Severe	SEVERE
+	+	+	CDR	CDR = 0.5–1	29,828	CDR = 2	50,980	CDR = 3	83,104
+	—	+	—	—	—	—	—	—	—
+	—	+	—	—	—	—	—	—	—
+	—	+	NS[c]	NS	19,196	NS	49,660	NS	89,450
+	—	+	MMSE	MMSE = 20–26	12,369	MMSE = 10–19	28,093	MMSE = 0–9	28,488
+	—	+	MMSE	MMSE = 20–26	38,886	MMSE = 12–20	55,276	—	—
+	—	+	MMSE	MMSE > 21	9,647	MMSE = 11–20	24,290	MMSE = 0–10	81,530
+	—	+	MMSE	MMSE = 18–24	54,668	MMSE = 10–17	85,896	—	—
+	—	+	MMSE	MMSE = 21–26	4,625	MMSE = 11–20	6,318	MMSE = 0–10	9,917
+	—	+	—	—	—	—	—	—	—
+	—	+	BPSD	No BPSD (NPI)	7,684	—	—	BPSD (NPI)	17,466
+	—	+	—	—	—	—	—	—	—
+	—	+	MMSE	MMSE = 15–30	5,671	MMSE = 10–14	12,339	MMSE = 0–9	15,832
+	—	+	—	—	—	—	—	—	—
+	—	+	—	—	—	—	—	—	—
+	—	+	—	—	—	—	—	—	—
+	—	+	MMSE	MMSE = 20–26	67,196	MMSE = 10–19	70,290	MMSE = 0–9	72,876
+	+	+	—	—	—	—	—	—	—
+	—	+	—	—	—	—	—	—	—
+	—	+	MMSE	MMSE > 20	5,168	MMSE 20–11	6,490	MMSE < 11	11,000
+	—	+	MMSE	MMSE 21–25	12,193	MMSE 20–10	26,665	MMSE 0–9	48,660
+	—	+	CDR	CDR = 0.5–1	33,426	CDR = 2	56,252	CDR = 3	68,096
+	—	+	MMSE	MMSE = 20–26	19,623	MMSE = 10–19	47,568	MMSE = 0–9	59,820
+	—	+	—	—	—	—	—	—	—
+	—	+	ADL	ADL	8,116	ADL	23,669	ADL	58,307
+	—	+	NS	NS	19,838	NS	32,531	NS	43,670
+	+	—	ADL	ADL < 10	6,341	ADL 10–15	10,398	ADL > 16	19,596

Health policy implications

Economic expenditures for healthcare systems are more evident in an institutionalized setting, whereas informal costs in a community-based setting put an economic burden on families. Because of the rising number of dementia patients and decreasing numbers of informal caregivers as well as (the lack of) cost-intensive nursing home places and limited financial resources, healthcare systems face several challenges. It is necessary to identify predictors that can be influenced by interventions or services in order to have an effect on the process of institutionalization. Caregiver burden is also one of the predictors of institutionalization in mild and moderate stages of the disease. Therefore, support for informal caregivers should be addressed as a public health priority in health policy planning, especially as caregiver burden was found to be the strongest predictor accessible to interventions (Eska *et al.*, 2013). In addition, informal caregivers are described as "invisible second patients" related to the fact that morbidity among carers of patients with dementia is found to be high (Brodaty and Donkin, 2009). This, in turn, leads to an increase of indirect costs as well as further direct costs for

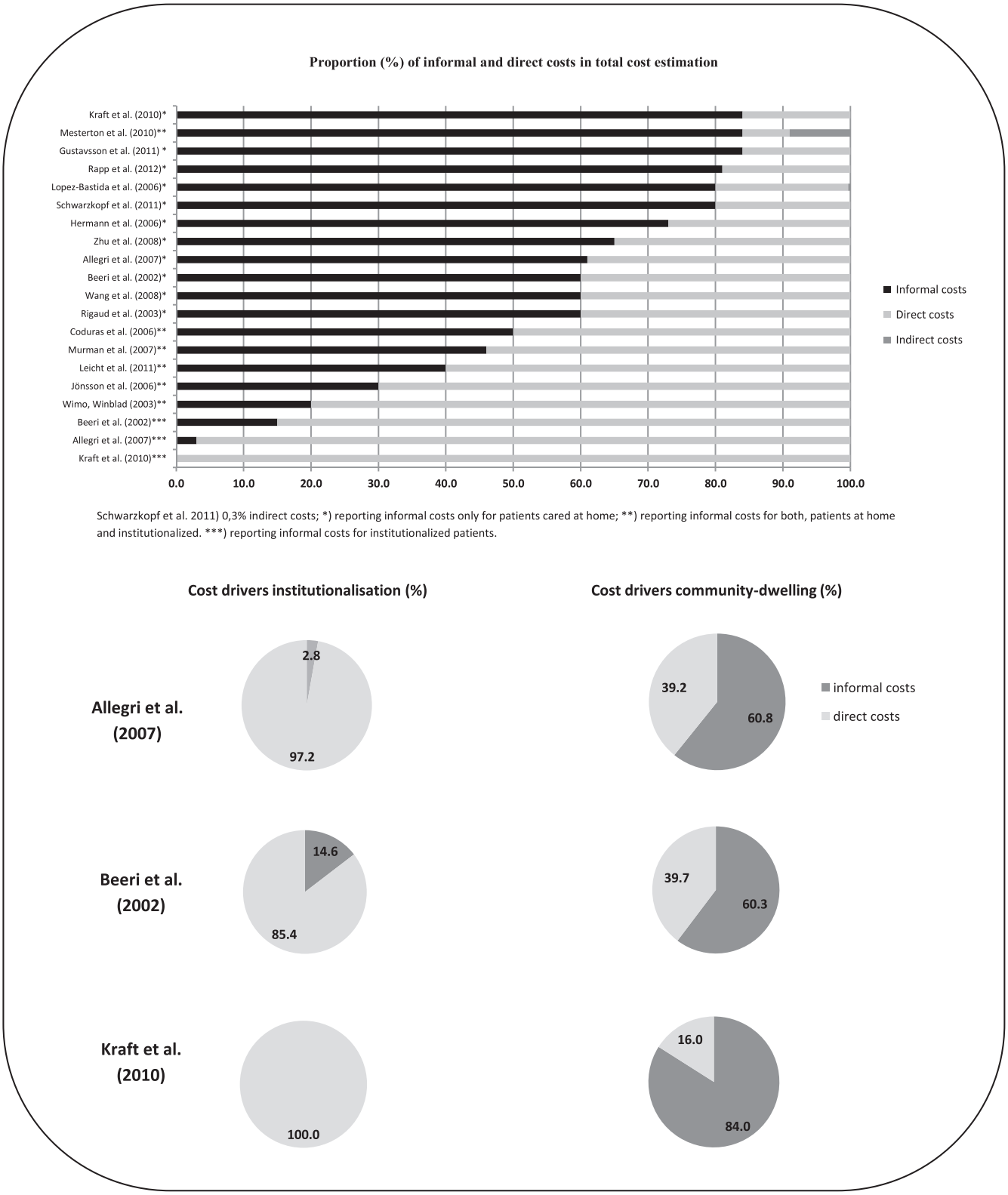

Figure 1 Proportion (%) of informal and direct costs in total cost estimation.

healthcare systems such as medication and outpatient visits, which are not considered with enough detail yet.

Therapies that are effective early in the disease can postpone the progression of dementia and can offer multiple benefits to families, caregivers and society (Fillit and Hill, 2005). However, as soon as new effective drugs are developed and become available on the market, costs for medication are likely to increase even more, especially owing to the fact that a single cure for AD is unlikely to be found (Mangialasche *et al*., 2010). On the other hand, more effective drugs can reduce direct non-medical and informal costs of care. In this context, health economic analysis or simulation studies can enable a better understanding of cost-effectiveness. In addition, effective non-medical support interventions for dementia patients and informal caregivers have to be taken into account.

Methodological challenges and recommendations

Homogeneity. Results highlighted the impact of specific cost components in dementia by care setting; however, challenges with regard to the homogeneity of COI studies in dementia exist. Although most of the reviewed studies apply a societal perspective, the inclusion of different cost categories as well as cost components in direct costs vary. A lack of precise description, cost estimation and transparency in reviewed studies is evident and has been criticized earlier (Bloom *et al*., 2001; Wimo, 2010; Wimo *et al*., 2011; Costa *et al*., 2013). A degree of consensus on the cost categories and cost components to be included in COI studies in dementia is required, especially against the background that dementia affects many different types of costs. Informal costs constitute a major aspect of total costs of dementia. In this context, Gustavsson *et al*. (2011c) addressed the need for robust and established measures to assess resource use in dementia. A recent study from Wimo *et al*. (2013) investigated the application of the "Resource Utilization in Dementia (RUD) instrument" in a global setting. As a result, minor changes to the RUD instrument were made to improve accuracy and precision. The use of RUD is recommended for future COI studies.

The majority of studies included patients diagnosed with AD. Only two studies, which compared AD with other dementias (VaD and DLB), indicated higher costs for VaD and higher indirect costs and lower direct non-medical costs for DLB. Further research on cost drivers in different types of dementia is needed. Overall, the sampling of study participants (age, disease stage and setting) should be considered carefully within future COI studies.

Disease severity. Stratification by disease severity is an important cost determinant. The analysis of this review was consistent with previous results (Mauskopf *et al*., 2010; Mauskopf and Mucha, 2011) and revealed that the majority of studies considered costs by disease severity but applied different methods for stratification. Results of single studies indicated that cognition, functional status and behavior are all correlated with costs of care, but comparisons were difficult because of different underlying measurements and cut-off points. The need for either a multidimensional disease severity measure or a single measurement capturing all three components is highly recommended (Mauskopf *et al*. (2010)).

The influence of age on cost categories is inconsistent across identified studies; therefore, future COI studies should focus on the impact of different age groups on costs in dementia.

Limitations

Our review excluded studies that were primarily modeling studies. Although those studies provide important results for, for example, lifetime costs of dementia (Skoldunger *et al*., 2012; Yang *et al*., 2012), the inclusion would have exceeded the scope of our review. For a comprehensive understanding of COI in dementia, the results of those studies may provide useful insights and could be addressed in an independent review. A second limitation refers to the sample of the study populations. The mean age of studies included is 77.1 years, because of increasing dementia prevalence with age. This implies a non-consideration of persons with early-onset dementias where especially indirect costs are apparent. Studies focusing explicitly on early-onset dementias should be addressed in future COI studies in dementia. In addition, the degree of severity and the proportion of persons residing in special accommodation have to be stated clearly. In this context, Gustavsson *et al*. (2011c) recommend population-based samples; however, large samples are needed.

Conclusion

Results of this review have primarily highlighted that dementia poses a significant and increasing economic burden on families, societies and healthcare systems. The significant variation of cost estimates for different care settings underlines the need to understand and address the financial burden of dementia from both perspectives. Future COI studies would greatly

benefit from a common approach to methodology, especially concerning study design, description and cost component data, thus enabling a more transparent analysis.

Conflict of interest

None declared.

Key points

- Informal care costs are the main cost drivers in the dementia care context, followed by nursing home expenditures and costs for medication.
- Direct costs, including nursing home costs, represent between 85% and 100% of total costs in an institutionalized setting. In contrast, their share of total costs is only 16–40% in a community-based setting.
- Future cost-of-illness studies in dementia should follow a quality standard protocol with clearly defined and transparent cost components and separate estimates by care setting and disease severity.

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