Journal of Alzheimer's Disease 96 (2023) 947–966
DOI 10.3233/JAD-230487
IOS Press

Systematic Review

A Literature Review on the Burden of Alzheimer's Disease on Care Partners

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Handling Associate Editor: Elżbieta Kuźma

Accepted 12 September 2023
Pre-press 11 November 2023

Abstract.
Background: Many individuals with Alzheimer's disease (AD) are dependent on nonprofessional care partners. Providing informal care can result in emotional, physical, and financial burdens; however, there is a need for a better understanding of the impact of AD on care partners to support the clinical and economic assessment of potential new treatments.
Objective: We conducted a literature review to evaluate the burden experienced by care partners of individuals with AD.
Methods: Electronic screening and supplementary searches identified studies published from 2011 to 2022 describing the association between AD and the quality of life (QoL) and physical health of care partners, and the economic or financial burden of AD.
Results: Following electronic screening, 62, 25, and 39 studies were included on care partner burden, cost, and healthcare resource use in AD, respectively. Supplementary searches identified an additional 32 studies, resulting in 149 unique studies. These studies showed that care partners of individuals with AD report moderate to severe burden. Higher burden and lower QoL were observed in those caring for individuals with more severe AD. Care partners of individuals with AD experience higher burden, lower QoL, and higher levels of stress, depression, and anxiety than those without caring responsibilities. Informal care costs increased with AD severity and accounted for the greatest proportion of overall societal cost.
Conclusions: Care partners of individuals with AD experience emotional and economic burden, which increases with AD severity. These impacts should be quantified comprehensively in future studies and captured in economic evaluations of AD interventions.

Keywords: Alzheimer's disease, caregivers, financial stress, quality of life

INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia [1]. The preclinical phase of the disease is characterized by normal cognition and

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abnormal brain biomarkers; this is followed by the mild cognitive impairment (MCI) stage and then by clinically apparent dementia (which is sometimes classified as mild, moderate, or severe based on ability to perform activities of daily living [ADLs]) [1, 2]. According to the most recent World Health Organization figures, it is estimated that 55 million people were living with dementia in 2019, a number that is expected to rise to 139 million in 2050 [3]. Taking MCI due to AD into account, one study estimated that over 100 million people worldwide are on the AD continuum [4]. In the United States (US) alone, AD dementia is estimated to affect 6.5 million people, which is projected to increase to 13.8 million by 2060 [5].

The majority of people with MCI due to AD or AD dementia live in the community rather than institutions such as assisted living centers or nursing homes, and most are dependent on nonprofessional care partners, who are typically (but not exclusively) spouses, partners, or close family members [1]. As the disease progresses, the reliance on the care partner increases, which can result in considerable physical, emotional, and financial burdens on care partners [6, 7]. Historically, research on the impact of AD has focused on outcomes relating to those living with the condition, providing important endpoints for clinical research that will ultimately improve future outcomes for patients.

The impacts on care partners are not always captured in conventional economic evaluations, meaning the economic burden experienced by care partners is not always considered when assessing the value of a treatment or intervention [8, 9]. Several systematic reviews have been published on the impact of dementia in general on care partners [10–14], but it is important to gain an understanding of the impact of AD specifically. The care partner experience may be influenced by various differences between AD and other dementias, notably disparities in the likelihood of individuals experiencing particular symptoms; whereas cognitive and behavioral symptoms are more common in some subtypes of dementia, motor symptoms present more commonly in other subtypes [15–18].

We conducted a literature review with systematic and non-systematic elements encompassing a broad range of outcomes. The aim was to better understand how caring for an individual with AD impacts care partners' quality of life (QoL) and physical and mental health, in addition to any economic impacts.

MATERIALS AND METHODS

Systematic literature reviews

Three systematic literature reviews (SLRs) were designed to identify evidence published between January 2011 and November 2021 on: 1) the association between AD and care partners' QoL and physical health; 2) costs of AD (both indirect and direct); and 3) healthcare resource use in AD. Direct costs are those directly attributable to patient care (for example, hospital appointments); indirect costs are those that are not directly related (for example, informal care costs). Broad search terms were used for costs and resource use, which were expected to capture all costs relevant to care partners, including costs of care. PubMed, Embase, the Cochrane Library, PsycINFO, bioRxiv, medRxiv, clinical trials, and Google Scholar were searched using the Silvi.ai platform, an artificial intelligence-based end-to-end screening and data extraction tool [19]. Search terms that were entered into Silvi.ai are detailed in Supplementary Table 1, and were based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols (PRISMA) principles [20]. An attempt to submit the study protocol to PROSPERO was made, but due to the COVID-19 pandemic PROSPERO did not accept scoping, mapping, or literature reviews at the time of search initiation.

Citation screening, full text review, and data extraction

Titles and abstracts were screened by two independent reviewers to determine whether they met the inclusion criteria (Table 1), in accordance with 2009 PRISMA guidelines [20]. Duplicates were automatically removed by Silvi.ai through Digital Object Identifier recognition. Primary publications were included, and review articles were excluded; however, the reference lists of review articles were screened for relevant literature to support the reviews. Only English language publications were included, but there was no restriction by geography. All publications that met the entry criteria for review were obtained as full articles and reassessed against the same criteria by a single reviewer.

Supplementary targeted searches

To include relevant literature published after the initial search, supplementary targeted searches were

Table 1
Eligibility criteria for the care partner burden and cost and healthcare resource use systematic literature reviews

	Care partner burden review	Cost and healthcare resource use review
Patient population	Care partners of people with Alzheimer's disease	People with Alzheimer's disease and care partners
Intervention/ comparator	Any	
Outcomes	• Care partners' quality of life • Care partners' burden • Care partners' health, including comorbidities • Care partner-reported outcomes used to measure impact/burden on care partners	• Economic burden • Cost analysis (indirect and direct costs) • Expenses • Out-of-pocket costs • Resource utilization
Study design	Any	
Reference types	Primary manuscripts Exclusion: Congress publications, systematic reviews, meta-analyses, animal/*in vitro* studies, case reports and case series, and review articles	
Date restrictions	2011–2021	
Language restrictions	English language	
Country	No restriction	

conducted to identify relevant studies published between January 2021 and October 2022. Searches were performed using PubMed and Google using the search terms included in Supplementary Table 2. The screening and full-text review of references identified in searches were conducted by a single reviewer, using pre-determined eligibility criteria (Supplementary Table 3).

Data extraction and prioritization

Detailed data, including study setting and methods, patient characteristics, and study results, were entered into a data extraction table and quality checked. The following research questions were explored:

1) How does caring for an individual with AD affect care partners' QoL?
2) How does caring for an individual with AD affect care partners' physical health?
3) How does caring for an individual with AD affect care partners' cost burden and healthcare resource use?
4) To what extent do care partners of people with AD experience work impairment?
5) What aspects of caregiving contribute to informal care costs?
6) What is the relationship between the patient's AD severity and the impacts on the care partner, in terms of their health, QoL, costs, and resource use?
7) To what extent does informal caregiving contribute to the total societal costs associated with AD?

Commonly reported care partner burden instruments

The Zarit Burden Interview (ZBI) is a commonly used instrument for assessing care partner burden [21]. The 22-item ZBI is the most common version of this instrument [22], but many shorter versions (including the 12-item and 4-item ZBIs) also exist [22]. The total score of the 22-item ZBI ranges from 0 to 88 and is assigned the following levels of severity [23]: 0–20 – little to mild burden; 21–40 – mild to moderate burden; 41–60 – moderate to severe burden; ≥ 61 – severe burden. The 12-item ZBI ranges from 0 to 48, with a score of 0–10 indicating no to mild burden, 10–20 indicating mild to moderate burden, and > 20 indicating high burden [23]. The 4-item ZBI ranges from 0 to 16, with a score ≥ 8 indicating high burden [23].

The Caregiver Burden Inventory (CBI) comprises 24 closed questions spanning five dimensions (time-dependence, developmental, physical, social, and emotional burden) [24]. Each is scored between 0 (not at all relevant) and 4 (very relevant), with a total score in the 0–96 range [25]. A total score ≥ 24 indicates need for respite, and a total score ≥ 36 indicates a high risk of burnout [26].

RESULTS

Search results

PRISMA flow diagrams for the three reviews are shown in Supplementary Figures 1, 2, and 3. For the burden of AD on care partners SLR (Supplementary Figure 1), 911 papers were included for screening by abstract and title, resulting in 97 references being included for full text review. In total, 62 references met the inclusion criteria at full text review and were included for data extraction [27–88]. For the cost burden SLR (Supplementary Figure 2), 1,043 papers were included for screening by abstract and title, resulting in 125 references being included for full text review. In total, 25 references met the inclusion criteria at full text review and were included for data extraction [89–113]. For the healthcare resource use SLR (Supplementary Figure 3), 722 papers were included for screening by abstract and title, resulting in 56 references being included for full text review. In total, 39 references met the inclusion criteria at full text review and were included for data extraction [90, 97–99, 105, 106, 109, 111, 114–144]. An additional 32 relevant studies published between 2021 and 2022 were identified in the supplementary targeted searches [104, 145–175].

In total, 149 unique studies were identified across the three SLRs and the supplementary targeted searches [27–175]. Studies including individuals with AD or AD and dementia (referred to hereafter as mixed population studies) were included in the evidence base for the SLR; studies including individuals with general/non-AD dementia and all-cause MCI or MCI that was not identified clearly as 'MCI due to AD' were excluded at the reporting stage. Seven mixed population studies were included to avoid excluding potentially relevant data pertaining to AD. Additionally, given that broad search terms were used for the cost and healthcare resource use SLRs, studies that did not include data on care partners were excluded at the reporting stage.

Data sources and study characteristics

Of the studies included in the data extraction, 59 studies reported data from Europe [28, 36, 39, 41, 43, 47, 48, 50, 68–70, 74, 78–82, 88–90, 96, 100, 102, 105, 107, 108, 110, 111, 115–123, 126, 128, 130–138, 147, 150, 151, 154, 155, 162, 166, 168, 169, 172, 175]. Thirty-seven reported data from Asia [27, 34, 35, 49, 51, 52, 54, 56–59, 63, 65, 67, 73, 83–87, 98, 99, 104, 109, 112, 113, 125, 142, 143, 146, 156, 157, 159, 164, 165, 170]. Thirty-two studies reported data from the US [29, 32, 33, 42, 45, 46, 53, 60, 62, 71, 72, 91–94, 97, 101, 103, 106, 114, 124, 127, 139, 141, 145, 148, 149, 152, 161, 163, 167, 174], and four studies reported data from Canada [30, 44, 140, 158]. Fewer studies reported data from Australia (two [37, 61]) and South America (eight [38, 40, 55, 64, 76, 77, 160, 173]). Fourteen studies reported data from multiple countries [31, 50, 66, 70, 75, 89, 95, 110, 111, 128, 134, 144, 153, 171]. A breakdown of the geographic origins of studies identified in the SLR and supplementary searches is provided in Supplementary Table 4.

The majority of studies from the SLR were cross-sectional [27, 29–32, 38, 39, 41, 44, 46–49, 51–53, 55–61, 63–69, 71–73, 75, 77, 78, 82–85, 87–89, 91–93, 99, 101, 106, 109, 112, 113, 118, 120, 133, 143, 145–147, 149, 150, 152, 154–175]. Seven studies were interventional controlled trials [35, 36, 40, 43, 76, 86, 90, 176], and 32 studies were longitudinal observational studies [28, 34, 37, 45, 50, 62, 70, 74, 79–81, 94, 99, 103–105, 107, 110, 111, 115, 117, 119, 121, 123, 124, 126, 127, 129–132, 134, 140, 148, 151, 153]. A breakdown of the designs of studies identified in the SLR and supplementary searches is provided in Supplementary Table 4. Across the studies, most care partners were women, although the proportion of female care partners varied by study and country.

The following sections present the findings of the review grouped by the themes that emerged. Key studies addressing each research question are presented in Supplementary Table 5.

Association between AD and care partner burden

The most common instruments used to measure care partner burden were the 22-item ZBI and the 24-item CBI. These are described in the Methods; details of other instruments mentioned in the Results are provided in Supplementary Table 6.

Most studies reported a moderate to severe impact on care partner burden using the ZBI, CBI, or the Burden Index of Caregivers (BIC) [67, 68, 71, 85, 177, 178]. Additionally, several longitudinal studies were identified showing that care partner burden is high even in mild to moderate AD, and that it increases with disease progression [79, 104, 153]. In a multinational study of 616 care partners of individuals with mild to moderate AD, the mean care partner burden, as measured by ZBI-22 score, was 26.0 (indicating a moderate burden) at baseline and, over the 18-month study period, there was a mean increase of 7.4 points [153]. In 69 care partners of individuals with AD in Italy, there was a significant increase in burden as assessed by the CBI after 1 year (mean [standard deviation (SD)] score: 28.9 [18.2] at baseline and 38.7 [14.5] at year 1; $p < 0.05$) [79], and in a Japanese study ($N = 553$), mean care partner ZBI-22 scores significantly increased over 18 months in each of the three AD severity subgroups (mean [95% confidence interval (CI)] scores at baseline and 18 months: 27.2 [24.7–29.8] and 28.5 [25.7–31.3], $p = 0.045$ for mild AD; 27.2 [25.1–29.3] and 28.7 [26.3–31.1], $p = 0.002$ for moderate AD; and 33.6 [31.4–35.7] and 34.7 [32.0–37.5], $p = 0.022$ for moderately severe/severe AD) [104].

Association between AD and care partners' physical and mental health

Limited recent evidence on the association between AD and care partners' physical health was identified. In a Japanese study, 24 out of 300 (8%) care partners reported new health problems after becoming care partners of individuals with AD (the total duration of caregiving ranged from less than 2 years to more than 10 years) [63]. In a study of 146 principal family care partners of individuals with moderate AD in Italy, care partners who worked but did not need to reduce work hours had the best physical health compared with those care partners who worked but had to reduce work hours or who were not employed independently from care [74].

Considerably more studies evaluating aspects such as stress, depression, anxiety, and sleep quality were identified. In a study of 309 care partners of individuals with AD in China, 5.8% had moderate to severe depression and anxiety (9-item Patient Health Questionnaire [PHQ-9] scores ≥ 10). Sleepiness was present in 87.7% of care partners, and 78.3% thought their sleep quality was poor [58]. In a study of 496 care partners of individuals with AD in Japan, the mean PHQ-9 score in care partners of individuals with AD was 8.4, indicating mild depressive symptoms, and the mean Pittsburgh Sleep Quality Index (PSQI) score in care partners of people with AD was 8.1, indicating poor sleep quality [67]. In a study of 60 care partners of individuals with AD in Greece, 50% described themselves as feeling exhausted, 41.7% reported feeling depressed, and 45% reported that they could not sleep due to stress [147].

Interplay between disease characteristics and care partner burden

Several studies reported care partner burden outcomes stratified by AD severity; these studies found that care partner burden was greater in those caring for individuals with more severe AD (Table 2) [50, 68, 73, 129, 151, 153, 176]. In a cross-sectional study of 300 care partners of individuals with AD in Japan, increasing AD severity was significantly associated with poorer care partner EQ-5D scores: The care partners of individuals with severe AD experienced significantly lower EQ-5D health utility scores (mean [SD], 0.75 [0.28]) than the care partners of individuals with mild AD (mean [SD], 0.84 [0.17]; $p < 0.05$). EQ-5D scores did not significantly differ between care partners of individuals with moderate and mild AD [63]. It should be noted that assessment of patients' care needs was used as a surrogate disease severity measure in this study. Similar results were obtained in a Chinese study of 300 care partners; higher AD severity was significantly associated with higher ZBI-22 scores (the mean [SD] ZBI scores of care partners of patients with mild, moderate, and severe AD were 36.15 [14.08], 44.48 [12.80], and 46.06 [12.11], respectively; $p = 0.0001$) [84].

Several studies reported data on the relationship between specific AD symptoms and care partner burden [67, 166, 179]. Symptoms that were associated with increased care partner burden included sleep disturbance, inappropriate sexual behaviors, depression, psychotic episodes, anxiety, nervousness/restlessness, apathy, agitation, impaired functional abilities, aberrant motor behavior, appetite disorders, and irritability [41, 54, 59, 67, 75, 156, 166, 175, 179]. In a mixed population cross-sectional study of 548 individuals with AD or related disorders (ADRD), the ZBI-22 score of care partners increased by 0.03 points for every additional unit of the Neuropsychiatric Inventory (NPI), with five out of the 12 areas of the NPI significantly increasing the ZBI score: Apathy, agitation, aberrant motor behavior, appetite disorders (multivariate linear regression coefficient B [95% CI]: 1.11 [0.78–1.43], 0.80 [0.44–1.16], 0.65 [0.33–0.98], 0.67 [0.32–1.01], respectively; all $p < 0.001$), and irritability (multivariate linear regression coefficient B [95% CI]: 0.37 [0.04–0.70]; $p = 0.03$) [41]. In a mixed population multicenter registry study of individuals with early to moderately advanced dementia in Austria ($N = 556$; mainly with AD but number of individuals not reported), ZBI-22 sum

Table 2
Studies reporting care partner burden for different levels of AD severity

Reference	Country	No. of individuals	MCI, mean (SD)	AD severity Mild, mean (SD)	Moderate, mean (SD)	Severe, mean (SD)
22-item Zarit Burden Interview (scale range 0–88)*						
Haro et al. (2014) [50]	Germany, France, and UK	1,497	–	24.7 (14.2)	29.4 (14.8)	34.1 (14.8)
Sinha et al. (2017) [73]	India	64	–	30.17	51.25	52.50
Belfort et al. (2020) [176]	Brazil	137	–	27.2 (14.4)	32.1 (14.3)	–
Froelich et al. (2021) [153]	Germany, Spain, and UK	616	–	23.85 (14.35)	27.42 (14.34)	–
Nakanishi et al. (2021) [129]	Japan	553	–	27.2 (16.1)	27.2 (15.3)	33.6 (14.8)
Short Zarit Burden Interview (scale range 0–7)*						
Dauphinot et al. (2022) [151]	France	1,998	–	3.1 (1.8)	3.4 (1.8)	3.8 (1.8)
Caregiver burden scale (scale range 0–4)*						
Pudelewicz et al. (2019) [68]	Poland	55	–	1.98 (0.38)	2.76 (0.37)	2.81 (0.38)

*Higher score = higher burden. Values are mean (SD) unless otherwise stated. AD, Alzheimer's disease; CI, confidence interval; MCI, mild cognitive impairment; SD, standard deviation.

scores were significantly higher in the care partners of individuals with depression ($p = 0.0153$), psychotic episodes ($p < 0.0001$), and anxiety and nervousness/restlessness ($p = 0.0481$) than in the care partners of those without these neuropsychiatric symptoms [166].

The severity of symptoms and degree of functional impairment of the individual with AD also correlated with care partner burden. In a multinational analysis of 1,222 care partners of individuals with AD in Spain, Sweden, the United Kingdom (UK), and the US, the severity of behavioral disturbances or changes was the strongest predictor of care partner burden (0.35 SD increase in ZBI-22 score per SD increase in NPI-Questionnaire severity score) [31]. In a mixed population study of 151 care partners in Brazil, the severity of subjective care partner distress correlated with the number, frequency, and severity of symptoms affecting the patients with AD or mixed dementia they cared for. There was a strong and significant correlation between the total score on the NPI caregiver distress scale [180] and the total score on the NPI and the number of neuropsychiatric symptoms ($r = 0.82$ and $r = 0.80$, respectively; both comparisons $p < 0.01$) [77]. In a study of 90 individuals with AD, patient Functional Activities Questionnaire and NPI scores correlated significantly with care partner burden ($p < 0.05$). Of the factors affecting care partner burden, aberrant motor behavior was the only symptom that correlated significantly ($p = 0.043$) [54]. A decrease in the ability of individuals with AD to perform ADLs and instrumental ADLs (IADLs) was associated with increasing care burden, anxiety, depression, and worsened mental health in their care partners [70, 73].

Comparison with care partners of individuals with conditions other than AD, and those without caring responsibilities

Four studies compared the burden of care partners of individuals with AD with that of care partners of individuals with conditions other than AD, and those without caring responsibilities (non-care partners) [45, 57, 65, 73]. A mixed population study of care partners of individuals with ADRD ($n = 56$) and care partners of elderly surgical and medical patients without ADRD ($n = 211$) in the US found that average Delirium Burden instrument for care partners (DEL-B-C) scores were significantly higher in care partners of individuals with ADRD compared with care partners of individuals without ADRD (standardized Beta, $\beta = 0.34$; $p = 0.043$; 95% CI 0.01–0.67) [45]. In a study of care partners of individuals with AD ($n = 32$) and care partners of individuals with elderly people with psychosis ($n = 32$) in India, mean ZBI-22 scores were significantly higher for care partners of individuals with AD (mean [SD], 47.69 [11.49] versus 33.62 [7.57], respectively) [73].

Two studies reported the health-related QoL (HRQoL) of care partners of individuals with AD or dementia compared with care partners of individuals with conditions other than AD. The HRQoL of 206 care partners in China was significantly lower than the Chinese norm across the overall population in the social and environmental domains of the brief version of the World Health Organization Quality of Life Questionnaire (mean [SD], 55.79 [16.56] versus 65.22 [14.24] and 59.24 [12.22] versus 52.33 [13.31], respectively; both comparisons $p < 0.05$) [57]. Care partners of individuals with AD or dementia in a mixed population Japanese study ($n = 805$) experienced significantly lower HRQoL compared with non-care partners ($n = 27{,}137$), as measured by mean 12-Item Short-Form Health Survey version 2 (SF-12v2) scores (mental component summary, 47.9 versus 45.0, respectively; $p < 0.001$; physical component summary, 51.3 versus 50.2, respectively; $p < 0.001$) and EQ-5D scores (0.85 versus 0.79; $p < 0.001$) [65].

Care partners of individuals with AD or dementia also report higher levels of stress, depression, and anxiety compared with non-care partners [38, 60, 65]. In a study in the US, the care partners of spouses with AD ($n = 125$) were significantly more likely to experience depressive symptoms and to meet the clinically significant cutoff for depression compared with the spouses of people without AD ($n = 60$; 40% versus 5%, respectively; $p < 0.001$). Care partners also utilized fewer positive coping and more negative coping strategies compared with non-care partners [60]. A Brazilian study found that family care partners of individuals with AD ($n = 17$) reported a higher number of symptoms of stress, depression, and anxiety than non-care partners ($n = 18$) [38]. In a mixed population Japanese study of the care partners of individuals with AD or dementia ($n = 805$) compared with non-care partners ($n = 27{,}137$), rates of major depressive disorder and anxiety were significantly higher in care partners versus non-care partners (9.9% versus 18.8% and 8.0% versus 15.7%, respectively; $p < 0.001$) [65].

Geographical differences in care partner burden

In studies comparing care partner burden between locations, there were geographical differences in care partner burden. Care partners in a mixed population study in Japan ($n = 805$) had significantly higher SF-12v2 mental and physical component summary subscores than care partners in the US and the EU5 countries (i.e., France, Germany, Italy, Spain, and the UK) ($n = 1{,}887$ and $n = 1{,}426$, respectively), indicating better HRQoL (mean mental component summary subscore, 46.42 versus 43.83 versus 43.47 and mean physical component summary subscore, 50.73 versus 48.00 versus 49.06 for Japan, the US, and the EU5, respectively; both comparisons $p < 0.001$) [66]. Care partners in Japan also had significantly higher mean EQ-5D index scores than care partners in the US (0.80 versus 0.78, respectively; $p < 0.001$). Care partners in the EU5 had better HRQoL than care partners in the US in terms of mean physical component summary subscore (49.06 versus 48.00, respectively; $p < 0.01$) and mean EQ-5D index scores (0.79 versus 0.78, respectively; $p < 0.05$). Differences in the proportion of care partners experiencing major depressive disorder and anxiety were also reported. Rates of major depressive disorder were significantly lower in Japan compared with the US and the EU5 (16.8%, 32.5%, and 29.3%, respectively; $p < 0.001$) and were significantly lower in the EU5 than the US ($p < 0.05$). Similarly, rates of anxiety were significantly lower in Japan than in the US and the EU5 (12.9%, 26.0%, and 22.4%, respectively; $p < 0.001$) and were significantly lower in the EU5 than the US ($p < 0.05$) [66]. In a study assessing care partner burden across seven countries in Asia, there were significant differences in burden between countries [171]. The mean (SD) Caregiver Activity Survey total score was 224.53 (381.42) for China ($n = 101$), 168.00 (93.46) for Hong Kong ($n = 10$), 894.22 (630.88) for the Philippines ($n = 23$), 233.27 (333.15) for Singapore ($n = 52$), 517.23 (955.65) for South Korea ($n = 259$), 358.22 (604.95) for Taiwan ($n = 73$), and 567.50 (578.18) for Thailand ($n = 6$), respectively ($p < 0.0001$). The mean (SD) ZBI-22 total score was 25.31 (14.02) for China ($n = 99$), 25.70 (23.36) for Hong Kong ($n = 10$), 29.39 (19.03) for the Philippines ($n = 23$), 23.13 (15.04) for Singapore ($n = 52$), 23.81 (16.44) for South Korea ($n = 259$), 27.64 (16.48) for Taiwan ($n = 72$), and 8.33 (3.39) for Thailand ($n = 6$), respectively ($p < 0.03$).

Supplementary Figure 4 plots mean ZBI-22 scores for all studies included in this SLR reporting this

Table 3
Work impairment of care partners versus non-care partners

	Care partners	Non-care partners
Activity impairment	25.4%	20.7%
Absenteeism	5.4%	2.9%
Presenteeism-related impairment	22.8%	18.6%
Overall work impairment	25.7%	20.3%

Source: Goren et al. (2016) [49].

outcome split by world region (the Americas, seven studies [62, 64, 160, 173, 176, 177, 181]; Asia, nine studies [57, 58, 73, 84, 85, 104, 164, 170, 179]; and Europe, six studies [28, 48, 50, 131, 153, 154]). The spread of mean ZBI-22 scores was greatest among the Asian studies, which also had some of the highest reported values, indicating higher levels of care partner burden. Values for the Americas and Europe were broadly similar.

Work impairment of care partners

Five studies reported data on impairment of the ability to work of care partners of individuals with AD or dementia [49, 65, 66, 146, 147]. A mixed population study by Goren et al. (2016) comparing matched family care partners of individuals with AD or dementia versus non-care partners demonstrated significantly higher activity impairment, greater absenteeism, presenteeism-related impairment, and overall work impairment (Table 3) [49].

Compared with non-care partners, a higher proportion of family care partners of individuals with AD or dementia in a mixed population study reported work impairment in Japan in terms of rates of absenteeism (4.5% versus 8.1%, respectively; $p < 0.01$), presenteeism (21.9% versus 30.7%, respectively; $p < 0.001$), total work productivity impairment (23.5% versus 33.2%, respectively; $p < 0.001$), and activity impairment (23.5% versus 30.8%, respectively; $p < 0.001$) [65]. Similar proportions of the family care partners of individuals with AD or dementia in a mixed population study in Japan, the EU5, and the US reported work impairment (approximately 30%), with the care partners in Japan experiencing the lowest levels of work impairment (27%), followed by the EU5 at 30.1%, and the US at 33% [66]. These differences may be due to the Japanese study population having the highest proportion of care partners aged 65 years and over and consequently the lowest proportion in employment (53.5%); employment levels in the EU5 and US were similar (57.2% versus 57.3%).

In semi-structured interviews with 11 family care partners (10 children, one spouse) of individuals with AD in Iran, care partners described experiencing role conflict, in which they needed to take time off work, were late to work, or had to be absent from work due to their caregiving commitments [146]. In a study of 60 family care partners of individuals with AD in Greece, some described having to quit work to provide care, or being forced to hire private salaried assistants to provide care during working hours [147].

Aspects of caregiving contributing to informal care costs

Ikeda et al. (2021) reported that overall work impairment accounted for the largest proportion of care partners' informal care costs among the family care partners for individuals with AD in Japan, followed by activity impairment, and leaving a job for a care-related reason [98]. Olazarán et al. (2017) reported that care partners' time spent caring for individuals with AD accounted for the largest proportion of care partners' informal care costs in Spain (mean overall time spent on individual with AD in hours per month [95% CI], 235.1 [216.3–253.9]; mean monthly cost attributed to total care partners' informal care costs and care partner time in Euros [95% CI], 1,312 [1,165–1,456] and 1,246 [1,100–1,408], respectively) [105].

Relationship between AD severity and informal care costs

Seven studies across eight countries (France, Germany, Italy, Japan, Spain, Thailand, the UK, and the US) reported that care partners' time spent helping the individual with AD (including with basic ADLs, IADLs, and supervision) increased with AD severity [105, 106, 117, 125, 129, 131, 148]. The monthly cost of caregiving was similar across countries and studies in the evidence identified and increased with the severity of the clinical status of the patient (Supplementary Table 7) [105, 111, 129]. The GERAS study reported that estimated mean monthly care partners' informal costs in Euros differed significantly between groups when caring for individuals with mild, moderate, and moderately severe/severe AD ($p < 0.001$ in each of France, Germany, and the UK): 677, 804, and 1,307 in France; 643, 1,329, and 2,376 in Germany; and 964, 1,135, and 1,730 in the UK, respectively (Table 4) [111]. Seven studies

Table 4
Studies reporting care partner cost burden for different levels of AD severity

Country	Costs	Disease severity			Reference
		Mild	Moderate	Moderately severe/severe	
France	Mean costs per month, Euros*	677	804	1,307	Wimo et al. (2013) [111]; baseline results from the GERAS study
Germany	Mean costs per month, Euros*	643	1,329	2,376	Wimo et al. (2013) [111]; baseline results from the GERAS study
Italy	Mean costs per patient per month, Euros*	1,370	1,223	2,223	Bruno et al. (2018) [117]; 6-month results from the GERAS study
Japan	Mean monthly costs (95% CI), Japanese Yen	88,107 (70,022–109,873)	116,488 (98,598–137,495)	175,845 (150,743–202,611)	Nakanishi et al. (2020) [129]; baseline results from the GERAS-J study
Spain	Mean monthly cost (95% CI), Euros	1,050 (778–1,355)	1,239 (1,018–1,471)	1,580 (1,354–1,828)	Olazarán et al. (2017) [105]; 6-month results from the GERAS II study
UK	Mean costs per month, Euros*	964	1,135	1,730	Wimo et al. (2013) [111]; baseline results from the GERAS study
Thailand	Mean annual costs (95% CI), USD	2,042.89 (1,492.15–2,881.28)	2,699.07 (2,108.62–3,370.22)	4,294.00 (3,672.97–4,995.87)	Kongpakwattana et al. (2019) [125]; real-world cost and HRQoL study
France	Mean 18-month costs (95% CI), Euros	12,556 (10,714–14,417)	18,037 (14,861–21,930)	22,704 (19,589–26,042)	Rapp et al. (2018) [131]; 18-month results from the GERAS study
Japan	Mean 18-month costs (95% CI), Japanese Yen	1,871,647 (1,499,849–2,307,526)	2,181,331 (1,834,939–2,572,250)	3,310,496 (2,817,632–3,827,009)	Nakanishi et al. (2021) [104]; 18-month results from the GERAS-J study

*95% CI not reported. CI, confidence interval; GERAS, Groupe d'Études et de Recherches en Anglais de Spécialité; HRQoL, health-related quality of life; USD, US dollar(s).

across seven countries reported that care partners' cost burden increased with the increasing severity of AD in those they cared for (France, Germany, Italy, Japan, Spain, Thailand, and the UK; see Table 4) [104, 105, 111, 117, 125, 129, 131].

Relationship between AD severity and healthcare resource use of care partners

Three publications reported healthcare resource use by care partners, all of which reported findings from the GERAS studies [105, 111, 129]. In France, Germany, and the UK, the number of outpatient visits by care partners did not significantly differ according to the severity of AD in those that they cared for [111]. In Japan, the number of care partners admitted to hospital and who visited a hospital emergency room did not differ according to AD severity [129]. In Spain, the mean number of care partners requiring outpatient visits increased significantly with increasing AD severity, but there was no difference between AD severity groups in the mean number of care partner emergency room visits [105].

Impact of care giving on total societal costs associated with AD

Data from France, Germany, and the UK suggest that medical costs are not the main driver of the societal cost of AD [111]. Rather, they suggest that informal care (calculated using the higher of either the cost of care partner time or the cost of missing work to provide care) accounts for the greatest proportion of overall societal cost [111]. Five additional studies reported that informal care partners' costs were the largest contributor to total societal costs across six countries (France, Germany, Italy, Japan, Spain, and the UK) [105, 117, 129, 131, 134], and one study in China reported that indirect costs were the largest contributor to total societal costs [99].

However, two studies from Thailand and China reported that direct medical costs were the largest contributor to total societal costs [125, 143], and another study from Iran reported that direct nonmedical costs, such as transportation, food, accommodation, and nursing, were the largest contributor to total societal costs [113]. These studies did not include direct medical and nonmedical costs attributed to AD specifically and may have included costs for comorbidities.

DISCUSSION

Overall, the studies identified show that being a care partner to an individual with AD is often associated with emotional and physical strain. Studies reported a moderate to severe impact on care partner burden using the ZBI, CBI, or BIC (even among those caring for individuals with mild AD), and several longitudinal studies reported that care partner burden increases with disease progression [67, 68, 71, 79, 85, 104, 153, 177, 178]. For context, a ZBI score of 24–26, which is in the mild to moderate category, has been suggested as a cut-off score with significant predictive validity for identifying care partners at risk of depression [182]. This increase in care partner burden over time has also been observed in the early stages of dementia: A study of 177 care partners of individuals with MCI in Australia found that care partner burden increased over the study period (3 years). Overall, 21.3% of the care partners were experiencing burden at 1 year, 22.3% at 2 years, and 29.5% at 3 years [37].

Several studies reported that care partner burden is greater in those caring for individuals with more severe AD and that the severity of symptoms and degree of functional impairment of the individual also correlated with care partner burden [50, 54, 68, 70, 73, 77, 104, 151, 153, 176]. Comparative studies identified in this SLR reported that the care partners of individuals with AD experience higher burden and have a lower HRQoL compared with non-care partners and the care partners of those with other illnesses [45, 57, 65, 73]. Care partners of individuals with AD or dementia also report higher levels of stress, depression, and anxiety compared with non-care partners [38, 60, 65]. Care partner burden can affect outcomes for the person with AD, suggesting that the interplay between disease severity and care partner burden is bidirectional: A study of 421 care partners in the US reported that increased care partner burden was associated with a greater likelihood of institutionalization of individuals with AD, even among those with less advanced AD [62].

The degree of care partner burden varied across countries and studies, likely because of differences in healthcare, social care, and welfare systems. In studies comparing care partner burden between countries, the burden was higher in the US and Europe compared with Japan (mixed population study), and there were also significant differences in care partner burden between countries in Asia [66, 171]. The authors of the first study hypothesized that differences in care partner strain between Japan and the US may be influenced by cultural variations; for example, Japanese values of filial piety and interdependence may lead to care partners viewing caregiving as part of life's trajectory, rather than as a disruption to daily life [66]. Another example of cultural practices influencing care partner burden is described in a study of Turkish, Pakistani, and Arabic speaking ethnic minority families in Denmark who provide rotational 24-hour care, in which the person with dementia lives with different family members or has different family members move in with them on a rotational basis [183].

Across the studies reporting mean 22-item ZBI scores, the highest scores (indicating greatest burden) were reported in Asian studies, although this comparison did not control for differences in study methodology or patient disease stage, and should therefore be interpreted with caution. The impact of healthcare, social care, and welfare systems on care partner burden appears to be an understudied topic. A longitudinal study on public policy and the health of in-house care partners in 11 countries in Europe found that informal care partners in Scandinavian and Mediterranean countries were less likely to have experienced declines in health over 2 years than those living in other countries, and that public support policies are significantly related to the health of care partners [184]. However, the authors acknowledged that country-specific studies are needed to fully understand the influence of societal context in each country [184].

Although not within the scope of this review, some studies reported the positive aspects of being a care partner. For example, one study highlighted that self-efficacy (a psychological construct that has been associated with positive thinking, improved control of negative affect, and enhanced motivation) accounts for a significant percentage of the variance in the positive aspects of caregiving, which include feeling useful, feeling appreciated, and finding meaning [72].

Although informal care accounted for the greatest proportion of overall societal cost across different countries, this proportion varied by country and study [105, 111, 117, 129, 131, 134]. It should be noted that the scope of this review did not include costs attributed to quality-adjusted life year (QALY) losses. One study not captured in the review calculated the gross societal value of a disease-modifying AD treatment, and found that patient QALY gains and avoided nursing home costs were the largest cost components (63% and 20%, respectively) [9].

As per the care partner burden findings, care partners' time spent helping the patient increases with the severity of their AD, as does the cost burden [104–106, 111, 117, 125, 129, 131, 148]. There are few literature reviews focusing on the economic burden of AD specifically; however, other reviews have examined the drivers of costs associated with dementia. A study using data from the Health and Retirement Study in the US found that the greatest cost components in dementia are those attributed to nursing home care and caregiving time [185]. A SLR of cost-of-illness studies in dementia conducted from 2003 to 2012 found that the main cost drivers of dementia are informal costs due to home-based long-term care and nursing home expenditures, rather than direct medical costs, such as inpatient and outpatient services and medication, suggesting that the economic burden experienced by care partners has not improved over time [186]. Also in line with this literature review, an SLR conducted from 2008 to July 2021 found that dementia care costs across Europe were dominated by informal care and direct nonmedical costs (i.e., residential care and home care), and that these costs increased with disease severity [187]. Calculations for informal care costs can differ by study, but this was not assessed when extracting these data for this review.

A limitation of this review is that we did not stratify results by sex; this is an interesting topic for further research. However, it is known that the majority of informal care is provided by women [188]. In the studies identified in this review, most care partners were women, but the proportion of female care partners varied by study and country. There is evidence that sex can influence care partner burden, and this is therefore an important consideration for future studies assessing the impact of AD on care partners. A study reporting differences in burden between men and women among care partners of individuals with dementia in the US found that women were more likely to experience emotional and physical burden than men [189]. Furthermore, a cross-sectional study of informal carers in paid employment in Sweden found that female carers provide more hours of informal care across more domains and more often alone than male carers [190].

The review was associated with some limitations. The majority of studies identified were single-arm observational studies and did not contain a reference group, such as including non-care partners or the care partners of patients with conditions other than AD. The findings from these studies should be interpreted with caution, because it is difficult to attribute the effects observed within these studies to the caregiving of patients with AD and to exclude the possibility of other contributing factors. For example, in the study of 146 care partners of individuals with moderate AD in Italy, it was not possible to determine the direction of causation between hours in employment and physical health [74]. Few studies reported the long-term implications of caring for someone with AD on a care partner's QoL and physical health (e.g., the development of comorbidities) and how the clinical characteristics of people with AD contribute to the impact on their care partners. However, this could have been a limitation of the search terms used in this SLR; for example, mortality was not included.

Previous studies have suggested that the care partners of individuals with dementia experience physical conditions secondary to chronic stress, such as increased risk of cardiovascular disease, but these studies were not identified in our review because either they were published before 2011 or they did not include key search terms [191, 192]. The search was limited to studies published since 2011 to focus on the most recent data. Although this created the limitation of excluding older studies, this review has still identified and summarized a large body of evidence covering many aspects of care partner burden. A related limitation is that full updates to the original SLRs were not carried out; nevertheless, supplementary nonsystematic searches were used to identify the most relevant recent publications. Also not identified were studies on the phenomenon of disinvestment, in which care partners put aside their own health needs, potentially resulting in increased disease burden and resource utilization after the end of the caregiving period [193–195].

The review highlighted several evidence gaps that could inform future research. There was little evidence on the work impairment of care partners, and few studies included data on care partners' costs. The lack of data on work impairment may reflect a significant proportion of care partners being of retirement age. Of those that did, informal care costs were largely calculated using time spent caring for the patient and work impairment, and did not include other factors, such as out-of-pocket costs. There was also limited evidence on healthcare resource use by care partners, and no evidence comparing the healthcare resource use of care partners of people with AD against that of non-care partners or the care partners of people with conditions other than AD.

Many previous reviews focus on dementia more broadly, particularly the humanistic burden experienced by care partners and the specific symptoms driving this. As with the present study, those reviews highlight the strong association between behavioral and psychological symptoms, including sleep disturbance and agitation, and care partner burden [10–14]. However, those reviews were typically narrower in scope and often conducted comparisons between dementia subtypes. For example, Torti et al. (2004) described the high degree of burden experienced by care partners of individuals with early-onset dementia, and the different trajectories in care partner burden over time between vascular dementia and AD [13]. van den Kieboom et al. (2020) also described differences in care partner burden over time between dementia with Lewy bodies and AD; care partner distress increased over time in AD, whereas in dementia with Lewy bodies it was higher at baseline but remained stable over time [14]. Ornstein et al. (2012) found that symptoms including depression, aggression, and sleep disturbances were commonly cited as impactful in their review, in which only one third of studies focused exclusively on AD [11]. Those authors also discussed the importance of diagnostic context, given that dementia etiology may influence care partner burden owing to differences in the perceived controllability of behaviors; they hypothesized that care partners who attribute more behaviors to disease (based on their understanding of specific types of dementia) are less likely to experience negative outcomes [11]. Those findings reinforce the value of the present study's focus on AD.

To our knowledge, a limited number of general dementia systematic reviews focus on the economic impact on care partners. However, one study by Angeles et al. (2021) found that disease severity, caregiver factors, and behavioral and psychological symptoms of dementia were associated with high informal care hours and societal cost [196].

In this review, we have considered a wide range of aspects contributing to care partner burden, with no restriction by geography. The majority of regions represented include high-income countries (Europe, Asia, and North America), and some regions are represented by only a small number of countries or not at all (e.g., South America and Africa). To our knowledge, this is also the only literature review focusing specifically on the care partner burden of AD rather than dementia more broadly. A better understanding of the wider impact of AD to include its effect on the QoL and economic burden of the care partners of individuals with AD could help to inform clinical and value assessments of potential interventions for AD. This will allow the full benefit of interventions to be evaluated, not only for individuals with AD, but for society as a whole [6].

Conclusion

Overall, this review highlights the emotional, physical, and economic burden experienced by the care partners of individuals with AD. This burden increases over time and with the severity of AD. As such, it is important that the clinical research and economic evaluations of treatments and interventions for AD should comprehensively capture the impact they have on reducing care partner burden. A better understanding of the impact of geographical differences in care partner burden owing to variations in societal norms, healthcare, social care, and welfare systems will also be important when capturing these outcomes.

ACKNOWLEDGMENTS

The authors are grateful for the contributions of Alice Fodder and Chris Hellmund of Oxford PharmaGenesis for conducting the supplementary searches and providing medical writing support.

FUNDING

This SLR was funded by Novo Nordisk A/S. Medical writing support was provided by Oxford PharmaGenesis, Oxford, UK, with funding from Novo Nordisk A/S.

CONFLICT OF INTEREST

Kristian Steen Frederiksen serves on an advisory board for Novo Nordisk for which he receives no personal remuneration and which is unrelated to this work. Krista L. Lanctôt has acted as an adviser/consultant for BioXcel Therapeutics, Bright Minds Biosciences, Cerevel Therapeutics, Eisai, Exciva, Jazz Pharmaceuticals, IGC Pharma, Kondor Pharma, Lundbeck, Merck, Novo Nordisk A/S, Praxis Precision Medicines, and Sumitomo Pharma. Wendy Weidner is Head of Research and Publications for Alzheimer's Disease International (ADI). ADI is funded by a number of commercial entities including Roche, Otsuka, Biogen, Novo Nordisk, Lilly, Eisai, and Lundbeck. For full list, please see https://www.alzint.org/about-us/funders/. Julie Hviid Hahn-Pedersen is an employee of Novo Nordisk A/S. Soeren Mattke serves on the board of directors of Senscio Systems and the scientific advisory board of AiCure, ALZpath, and Boston Millennia Partners. He has received consulting fees from Biogen, C2N Diagnostics, Eisai, Novartis, and Genentech/Roche.

Krista L. Lanctôt is an Editorial Board Member of this journal, but was not involved in the peer-review process nor had access to any information regarding its peer-review.

DATA AVAILABILITY

The data supporting the findings of this study are available within the article. Further inquiries can be directed to the corresponding author.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-230487.

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