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2018

Document Version:
Other version

[Link to publication](#)

Citation for published version (APA):

Saha, S., Gerdtham, U.-G., Toresson, H., Minthon, L., & Jarl, J. (2018). *Economic Evaluation of Nonpharmacological Interventions for Dementia Patients and their Caregivers - A Systematic Literature Review*. (Working Papers; No. 2018:10).

Total number of authors:
5

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Working Paper 2018:10

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April 2018



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Economic Evaluation of Nonpharmacological Interventions for Dementia Patients and their Caregivers - A Systematic Literature Review

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Abstract

Background: The rising prevalence of dementia represents an important public health issue. There is currently no available cure for dementia disorders, only symptom-relieving therapies which can be either pharmacological or non-pharmacological. The number of non-pharmacological interventions for patients with dementia disorders and their caregivers have been increasing in recent years without much knowledge on their cost-effectiveness. The objective is to review the existing evidence on cost-effectiveness of non-pharmacological interventions targeting patients with dementia disorders, their caregivers, and the patient-caregiver dyad.

Method: A systematic search of published economic evaluation studies in English was conducted using specified key words in relevant databases and websites. Data extracted included methods and empirical evidence (costs, effects, ICER) and we assessed if the conclusions made in terms of cost-effectiveness were supported by the reported evidence. The included studies were also assessed for reporting quality using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist.

Results: We included seventeen studies in this review categorised into three groups: physical exercise, occupational therapy, and psychological/psychosocial treatment. In almost all the studies (except one), economic evaluation was performed for a randomised controlled trial alongside the non-pharmacological intervention or retrospectively. There was a considerable heterogeneity in methodological approaches, target populations, study time frames, and perspectives as well as types of intervention. This prevents an informative comparison between most of the studies. However, we found that physical exercise was the most-effective non-pharmacological interventions for patients with dementia. For occupational therapy and psychological/psychosocial interventions we found mixed results although the majority was not cost-effective.

Conclusion: More economic evaluation studies are required in non-pharmacological interventions. However, the interventions need to have a strong study design with the intention to perform economic evaluation in parallel.

Keywords: Dementia; Non-pharmacological interventions; Caregivers

JEL Classification: H43; I10; I18

Acknowledgement

The study was funded by Eli Lilly and Company, Copenhagen, Denmark. The Health Economics Unit at Lund University also receives core funding from Government Grant for Clinical Research, and Region Skåne (Gerdtham).

Background

Dementia is a syndrome with progressive deterioration in several cognitive domains that interfere with activities of daily living. Alzheimer's Disease (AD) is the most common dementia disorder and accounts for 60 – 70% of dementia cases [1-3]. Current estimates demonstrate that there are over 46.8 million people in the world suffering from dementia in 2015 with the number expected to rise to over 131.5 million by the year 2050 [4].

Dementia affects many levels of society. Firstly, the individual suffers from impairments in cognition and functioning as well as impaired quality of life and shortened life expectancy [5]. Secondly, the relatives suffer from gradually losing a family member and in return receive a high care burden for the affected person. Indeed, the need for informal care increases when dementia progresses with deteriorating cognition and functioning [6].

Thirdly, dementia has a strong economic impact on the society. Care for persons with dementia is very costly and resource-demanding for both the formal and informal sector [7]. The worldwide societal costs for dementia were estimated to be 604 billion US dollars in 2010, of which 252 billion dollars in costs for informal care (for caregivers) [7]. These costs are expected to increase in the future because of population aging.

There is currently no available cure for dementia disorders, only symptom-relieving therapies. These can be either pharmacological (use of drugs) [8] or non-pharmacological [9].

The number of non-pharmacological interventions for patients with dementia disorders and their caregivers have been increasing in recent years [9] and many have been shown to be effective in reducing behavioral and psychological symptoms of dementia [10]. A recent systematic review identified 179 Randomized Controlled Trials (RCT) using non-pharmacological components for patients with dementia and their caregivers [11]. Existing effective interventions include cognitive simulation, physical exercise, behavioural-, and

occupational therapy, targeting caregivers and persons with dementia disorders separately [12-14] or jointly [15-17].

Such large number of available and generally effective intervention highlights the importance to compare interventions with respect to the outcomes in relation to the cost. Lacking this information constitutes a barrier to policy making. Economic Evaluation (EE) is an analytical technique which identifies, measures, values and compares the cost and outcomes of two or more alternative programs or interventions. Economic evaluations can ensure that the limited available resources are allocated as efficiently as possible, i.e. that resources are used in a way that maximizes the benefits [18].

A systematic literature review is a way to summarize available knowledge in a field, identify common characteristics of existing studies, and highlight areas where more research is required. Some systematic literature reviews of EE of non-pharmaceutical interventions partly covering dementia disorders have already been conducted. One review considered only occupational therapy for any disease (dementia and non-dementia related) [19] while another focused only on interventions on caregivers of dementia patients for both pharmaceutical and non-pharmaceutical interventions [20]. A third review included all non-pharmacological interventions but only up until year 2011 [21]. An updated systematic review of non-pharmacological interventions with a broad approach including both patients and caregivers and all dementia disorders is therefore lacking, especially given the increased interest and concern for dementia disorders during the last decade.

The objective is to review the existing evidence of cost-effectiveness of non-pharmacological interventions targeting patients with dementia disorders, caregivers, and the patient-caregiver dyad.

Methodology

To answer the research question we performed a systematic literature review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [22]. Moreover, the guidelines for incorporating economic evidence from the Campbell and Cochrane Economics Methods Group [23] has been followed including search criteria, data extraction, synthesis and critical analysis.

Search strategy

A systematic search was performed, to identify relevant published articles, in both health economics and biomedical databases from 01.01.2000 till 31.12.2015. The databases were Medline (Pubmed), Embase and ECONbase, EconLit, Cumulative Index to Nursing and Allied Health (CINAHL), The National Bureau of Economic Research, Latin American and Caribbean Literature on Health Sciences Database (LILACS) and Popline. In addition, we searched specific economic evaluation databases; the Centre for Reviews and Dissemination database maintained by NHS (<http://www.crd.york.ac.uk/CRDWeb/>), and the Cost-effectiveness analysis registry (<http://healtheconomics.tuftsmedicalcenter.org/cear4/Home.aspx>). We also searched additional articles from the reference lists of included studies. The details of the search strategy, key words, and initial hits are provided in Annex 1 for the reproducibility and transparency of the work.

Inclusion and exclusion criteria

The literature search covers EEs of all types of non-pharmacological interventions targeting patients with dementia disorders, their caregivers, and the patient-caregiver dyad. We define non-pharmacological interventions as individual treatment not including drugs. This means

that EEs of interventions focusing on (1) early diagnosis or screening of dementia and (2) overall management of the dementia patients in home/community care/ residential care are excluded, as well as EEs of (3) pharmaceuticals. These three types of interventions will be presented in subsequent reports.

Studies were included if they satisfy the criteria: (1) non-pharmacological intervention targeting dementia including mild cognitive impairment; (2) the interventions targeted the patients, their caregivers and/or the patient-caregiver dyad; (3) were EE such as Cost minimization analysis (CMA), Cost-Effectiveness Analysis (CEA), Cost-Utility analysis (CUA) and Cost-Benefit Analysis; and (4) reported in English in peer-reviewed journals.

Studies were excluded if they were: (1) cost studies such as cost-of-illness analysis; (2) reviews, notes, commentaries, editorials related to dementia in scientific journals; and (3) study protocol or study design of interventions.

Selection and data extraction

After each search in the above-mentioned databases the initial hits were exported into EndNote and duplicates were removed. All articles were screened based on the inclusion and exclusion criteria, first based on titles and abstracts and second based on the full text. The selection of the articles was done by one co-author while a second co-author reviewed all studies where assessment according to inclusion or exclusion criteria was challenging.

We extracted data from the selected articles along two main dimensions; the result of the study (empirical evidence) and how the results have been derived (methodology). In terms of result, we extracted the Incremental Cost Effectiveness Ratio (ICER) from the selected articles, as well as its components (costs and outcomes). Furthermore, we scrutinized whether the intervention was reported as cost-effective by the authors and whether the reported information support the conclusions, based on different scenarios presented in Table 1. We

categorized the included studies based on whether the health outcomes were measured as utility index or other outcomes e.g. improvement on Mini Mental State Examination (MMSE) score.

Studies were appraised for quality of reporting using the CHEERS statement [24]. This checklist was produced with the aim of harmonizing the presentation of information and raising the quality standard of EEs. The CHEERS guideline has 24 items in six categories (title and abstract, introduction, methods, results, discussion and other). The items were scored using ‘Yes’ (reported in full), ‘No’ (not reported), and ‘Not Applicable’. In order to assign a score of reporting, we assigned a score of 1 if the requirement of reporting was completely fulfilled for that item and 0 otherwise. Therefore, the maximum score for an article that reported all information was 24.

Results

The literature search identified seventeen studies. A flow chart of the study selection procedure is presented in Figure 1, and the detailed characteristics of the included studies are presented in Table 2. The interventions can be categorised into three groups: physical exercise, occupational therapies, and psychological/psychosocial treatment, where the latter is further divided based on the target groups: patients, patient-caregivers dyads and caregivers/family members. Of the seventeen identified studies, three targeted patients only, six studies targeted caregivers, and eight studies targeted the patient-caregiver dyad.

Physical exercise

Physical exercise programs have been suggested to preserve cognitive performance of the elderly and even slow the progression of Alzheimer disease depending on the structure of the

exercise programs, intensity and duration [25, 26]. We found three EEs of physical exercise interventions that targeted dementia patient.

Davis et al. performed a CEA of a physical exercise interventions for patients with mild cognitive impairment from a healthcare perspective [27]. Two types of physical exercises, resistance training and aerobic training, were compared with balance and tone classes. The effectiveness was measured by Stroop test which is a test of selective attention and conflict resolution. The 6-month intervention was effective in increasing the Stroop score for both intervention groups (resistance training group and aerobic training group) compared to the control group. The total cost for both intervention groups was also lower than the control group. Thus, the interventions were less costly and more effective (i.e. dominating) than balance and tone classes.

D'Amico et al. performed both CEA and CUA of a RCT of physical exercise for dementia patients for 12 weeks [28] from both healthcare and societal perspectives. The intervention was individually tailored together with a caregiver and consisted of 20-30 minutes daily walking, gradually increasing the intensity, compared to treatment as usual. The effectiveness was measured as behavioral and psychological symptoms related to dementia and Quality-Adjusted Life-Years (QALY) using the DEMQOL-proxy instrument. The researchers found the intervention less costly and more effective while considering the disease-specific indexes from the healthcare perspective. From societal perspective, the intervention was reported as cost-effective when using disease-specific outcomes but not when using QALY. The researchers faced difficulties in estimating the amount of time an unpaid caregiver spend with someone with dementia, which might have an impact on the cost estimation.

Pitkala et al. [29] did not perform a formal EE, but provided enough information for us to assess the cost-effectiveness of an RCT of two different exercise programs compared with usual care for patients with Alzheimer's disease in Finland from a healthcare and social

service perspective. The programs were group-based exercise and tailor-made home-based exercise and performed over a 12-month period. The effectiveness was measured by physical functioning and prevention of fall. After one-year, physical functioning had deteriorated for all groups but to a lower degree among the home-based and group-based exercise programs compared to usual care. Moreover, both exercise programs had a lower number of fall cases and lower total cost per person than the usual care group.

Occupational therapy

Occupational therapy interventions are systematic approaches designed to improve or maintain functioning and independence of dementia patients. Occupational therapy interventions focus on adapting the environment, modifying the task, teaching the skill, and educating the patients as well as caregivers to increase participation in and performance of daily activities. There is a growing body of empirical research suggesting that occupational therapy based intervention is effective in promoting physical health, cognitive functioning, activity and wellbeing of dementia patients [30].

Graff et al. performed a CEA of a 3-month occupational therapy intervention targeting patients with mild to moderate dementia and their caregivers [31]. The intervention's focus was on improving patients' homes and environments to help patients perform daily activities and also improving caregivers' competence in supervision, problem solving and coping strategies. A treatment was considered successful if led to improvements in three aspects: the patient's daily functioning, patient's daily activities and the caregiver's competence. The occupational therapy was able to successfully treat 37% of the patient-caregiver dyad whereas usual care was successful in 1% of the cases. The cost was on average €1,748 lower in the intervention group (insignificant). The caregiver's cost was measured by the friction cost method and valued at eight euros per hour.

Gitlin et al. [32] performed a CEA of a program that aimed to train families in performing three customized activities based on the patients' preserved capabilities, previous roles, habits and interests. This was done in eight sessions over four months. Patients on the waiting list for occupational therapy were the control group. The effectiveness for the caregiver was measured as the number of hours saved on actively caring for the patient and on standby. Researchers estimated the ICER \$2.37 per hour i.e. active informal caregiving can be reduced by one hour at a cost of 2.37, daily. On duty time can be reduced at a cost of \$1.10 per hour daily.

Psychological therapy or Psychosocial interventions for the patients

Psychological therapies as treatment of dementia can be many types such as cognitive stimulation therapy, music therapy, reminiscence therapy, mental exercise etc. Cognitive Stimulation Therapy (CST) offers activities involving cognitive processing; usually in a social context and often group-based, with an emphasis on enjoyment of activities. CST benefits cognition in people with mild to moderate dementia [33, 34]

Knapp et al. performed both CEA and CUA of a CST intervention for patients with dementia in the UK [35]. The CST was performed for seven weeks, twice weekly for 45 minutes in an RCT. The effectiveness was measured by the Mini Mental State Examination (MMSE) and QALY by the disease-specific instrument Quality of Life-Alzheimer Disease (QoL-AD). The ICER for CST was £75.32/ additional point of the MMSE scale £22.82/ additional point on the QoL-AD scale. The researchers acknowledged that the study might have been too small to test the cost-effectiveness hypothesis and that the follow-up period of seven weeks was relatively short.

D'Amico et al. performed both CEA and CUA of an intervention where the intervention group received CST for seven consecutive weeks in a 6-month RCT [36]. The CST was combined with usual care whereas the control group received usual care only. The outcomes

were measured as improvement in cognition by the Alzheimer's disease cognition assessment scale (ADAS-cog) and QALY measured by both EQ-5D and QoL-AD. After 6 months, no statistically significant differences between the groups were found in terms of cost or effects. The intervention group had non-significant higher QALY gain (0.017 by proxy EQ-5D) resulting in an ICER of £26,835 per QALY gained.

Martikainen et al. evaluated the cost-utility of adding a cognitive-behavioural family intervention to usual care, to allow patients with mild Alzheimer's disease to continue to live at home, rather than in institutional care in Finland [37]. Unlike other studies included in this review, this study used a decision analytic (Markov) model to evaluate the intervention. The model was run for 5 years with a societal perspective. The intervention was less costly and more effective compared to the usual care or current practice in Finland. However, it was not reported whether the cost and effect differences were significant or not.

Psychosocial interventions for the patients-caregiver dyad

We found three studies where psychosocial interventions were provided to the patient-caregiver dyad. Sogaard et al performed a CUA of a psychosocial intervention for Alzheimer's patients and their caregivers in Denmark [38]. The participants were randomized to an intensive, multicomponent, semi-tailored program with counselling, education and support (psychosocial care), while the control group received structured and systematic follow-up care. The total duration of the intervention was three years including the follow-up. Researchers found that the psychosocial intervention did not increase QALY in the intervention group compared to the control group, neither for the patients nor the caregivers. The costs were also higher in the intervention group.

Woods et al. performed both a CEA and CUA of a pragmatic RCT where "reminiscence" was used as an intervention targeting dementia patients and their caregiver over a 10-month

period [39]. The outcomes were measured as patient's QALY by QoL-AD and caregiver's psychological distress. The intervention group was characterized by high cost and reduced QALY. The caregivers also reported higher anxiety comparing to the usual treatment group. Joling et al. performed an EE of a family meeting intervention, a psychosocial intervention for the dementia patients and their caregivers over 12 months [40]. The intervention consisted of counselling sessions focusing on psychoeducation, problem solving techniques and mobilization of family networks of both patient and primary caregivers. The control group received standard care without the family meetings. The effectiveness was measured as QALY of the patient-caregiver dyad and the incidence of depression and/or anxiety of the caregivers. The intervention group had higher cost, an insignificant QALY gain and insignificant reduction of the incidence of depression and/or anxiety in caregivers.

Psychosocial interventions for the caregivers and family members

Dahlrup et al. [41] performed a CUA of a psychosocial intervention targeting the caregivers of dementia patients in Sweden. The intervention included education regarding the disease and patient management with a follow-up time of up to five years. The control group received no such kind of intervention. The effectiveness was measured as QALY for the caregivers when the patients were living at home and in a nursing home, respectively. The perspective of the analysis was not clear although a societal perspective is inferred. No ICER was calculated as there was no difference in total cost between the groups. However, a positive effect on QALY was shown when the patient was living at home.

Gaugler et al. [42] performed a CEA of a community-based program, "adult day services" for dementia patients, and analysed the costs of the program and how it affected the caregivers. The adult day services provided out-of-home services which included therapeutic activities, health monitoring, socialization, medical care and transportation. The analysis was performed

comparing to a control group where caregivers' dementia patients did not have day services. The study is not an EE per se, but ICER can be calculated based on the presented information. The outcomes included reduction of depression and workload of the caregivers over three months and one year measured by Role Overload Scale and Centre for Epidemiological Studies Depression Scale. The calculated ICERs were \$2.20 per unit of depression reduction and \$4.51 per unit of workload reduction in the one-year time frame. Two studies estimated the cost-effectiveness of the START intervention in the UK, a psychological intervention specially designed for family members of dementia patients. One study evaluated the short-term benefit of the intervention (8-month) [43] while the other evaluated the long-term benefit (2-year) [44]. The intervention group received eight sessions of coping intervention and usual treatment whereas the control group received usual treatment. The effectiveness was measured by Hospital Anxiety and Depression Scale total score (HADS-T) and QALY (EQ-5D). There was a significant effect of the intervention in terms of HADS-T as it was reduced both in the short- and long-term, while no significant effect was noted in terms of QALYs. The costs were lower in the intervention group, but not statistically significantly.

Nichols et al. [45] performed a CEA of a multicomponent psychosocial intervention for caregivers of AD patients to reduce stress and burden as well as to improve ability to manage the behavioral problems of the patient. The 6-month intervention consisted of nine individual sessions delivered at the caregiver's home and three telephone sessions. The outcome was measured as hours per day not caring for the patient. The ICER was US\$5 per hour per day not spent in caregiving.

Wilson et al. [46] performed a CUA of a psychosocial intervention designed for caregivers. The intervention was to provide social support by a trained volunteer befriender. The befriender visited weekly over a period of at least 6 months. The effectiveness was measured

by QALY (EQ-5D) after 15 months. The intervention was effective in increasing QALY of the participants compared to the control group and the ICER was £105,954 per QALY.

Discussion

The identified studies differ in many aspects such as type of interventions, length of the study period, target groups, sample size, efficacy, perspective, included costs and outcomes, and instruments to measure the outcomes. This makes general comparison across all studies difficult to achieve as there are also differences in the setting of the different studies, e.g. different healthcare systems, community or nursing home care, clinical practices, population values, availability and accessibility of drugs and technologies. However, we will discuss the main differences between studies in relation to the results.

Cost-effectiveness is at its heart a subjective concept as it refers to if an intervention is worth its costs, *i.e.* the decision-maker willingness-to-pay for the outcome under study. This will differ between settings but also between individuals, and it is therefore essential that the authors of EEs are clear about the valuation of the outcomes when determining an intervention's cost-effectiveness. Preferably a societal valuation should be used when reporting cost-effectiveness although this value is generally unknown. An exception is the value of a QALY where NICE in the UK uses a cost-effectiveness threshold range of £20,000 to £30,000 per QALY gained [47, 48]. There are no official guidelines for the USA and Australia, 50,000 US\$/QALY is frequently employed as a threshold in the USA [49] and 50,000 AUS\$/Disability Adjusted Life Year (DALY) in Australia [50]. For all other outcome measure, each study needs to establish the societal valuation of the used outcome in order to, potentially, claim cost-effectiveness. A few exceptions exist however; if the intervention is both better (worse) and less (more) costly than the comparator (scenarios 2 and 4 in the Table 1), it is (not) preferred irrespective of the valuation of the outcome measure. For simplicity, we will term all clearly preferred alternatives as cost-effective in the continued discussion.

Cost-effectiveness of non-pharmacological interventions using QALY as the outcome measure

In table 3, we presented the cost-effectiveness of the included articles using QALY as reported by the authors as well as our own assessment based on the reported information. In most cases our assessments are in line with the reported conclusions, normally as no significant difference in either costs or effects were noted [36, 38-40, 43, 44, 46]. However, in some cases, our assessment differs, normally not finding interventions cost-effective although they were reported as such [28, 37]. Several studies have reported cost-effectiveness based on an ICER calculated on insignificant cost and effect differences between the intervention and control groups. However, if the study cannot show that the intervention is effective in either improving the outcomes or reducing the costs, the intervention cannot be said to be better than the alternative and cannot be considered cost-effective. That is, a favourable ICER based on insignificant differences such as the case of D'Amico et al. [28] is not reliable and should not be used in the decision-making process, although such studies are often useful in directing future research. It is foremost important to present the confidence interval on the differences between costs and effects of the intervention and its comparators. In one study the confidence interval or information on statistical significance was not presented and the cost-effectiveness of the intervention is therefore considered "unknown" although the researchers deemed the intervention cost-effective [37].

However, it is known that in EE studies, costs and effects are very disperse and it may be difficult to find significant differences between two comparators. This is especially problematic in terms of costs as the sample size calculations normally are based on the outcome measure [31, 35, 40, 43, 44]. Many studies handle the uncertainties around costs and effects by presenting Cost-Effectiveness Acceptability Curve (CEAC) which is a good

practice that should be included in all EE studies. CEAC was developed as an alternative to producing confidence intervals around the ICER. However, there is no agreement in the research communities on when to claim an intervention cost-effective based on the findings from the CEAC. For example, Livingston et al. [44] reported an intervention cost-effective based on CEAC when the probability of being cost-effective was 67% at £20,000 WTP whereas Wilson et al. [46] did not report cost-effectiveness when the intervention had 42% probability to be cost-effective at £30,000. It should be noted that decision makers are advised not to implement an intervention based on the findings from the CEAC [51-53] and that the correct interpretation of the CEAC is with regard to the uncertainty around the estimated cost-effectiveness ratio.

Cost-effectiveness of non-pharmacological intervention using other outcome measures

There is a monetary valuation or threshold for QALY which researchers as well as policy makers can rely upon when comparing different interventions in terms of cost-effectiveness despite the disagreement about the actual value. However, there is no agreed upon valuation for other effectiveness measurement such as HADS, HADS-T, MMSE score, ZBI etc., which are common in the identified studies in this review (Table 4). In addition, no study makes a convincing case for what the valuation should be of the used outcome measure. This means that only in those cases where the intervention either is better but not different in terms of cost, cheaper but not different in terms of effect, or both better and cheaper than the alternative (or the other way around) is the cost-effectiveness argument clear. In the identified studies, we mainly find that physical exercise interventions dominate standard care and the interventions performed under the conditions described can therefore with relative certainty be considered cost-effective compared to standard care [27, 29]. But for many of the included studies where the interventions are better but also more costly, cost-effectiveness is

claimed without establishing the value of the outcome measure. In Knapp et al [35], for example, improvement in MMSE score was considered cost-effective at an ICER of £75.32/ additional point on the MMSE. However, it is not established in the study that the societal valuation of one additional point in MMSE is above £75.32. The ICER for MMSE might be cost-effective from a societal point of view, compared to the ICER of already established treatment (i.e. drug donepezil) of dementia. But without establishing this in the study, it is not possible to make any conclusions regarding the cost-effectiveness of non-dominant interventions. Thus, we argue that labelling these interventions as “cost-effective” is inappropriate and we interpreted the cost-effectiveness of these interventions as “unknown”. Future research is needed to reach an agreement among researchers and policymakers regarding the valuation of commonly used outcome measures, such as MMSE and prevented falls.

Perspective of analysis

The perspective of analysis varies a lot in the selected studies for example, only societal perspective [31, 38, 40, 45, 46], only healthcare perspective [27, 39], both healthcare and societal perspective [29, 36, 43, 44]. Sometimes the perspective was not either explicitly mentioned [37, 41, 42] or mentioned without proper explanations [28, 35]. For example, Knapp et al used Personal Social Service (PSS) perspective without description of what costs need to be included in the PSS perspective. On the other hand, what D’Amico [28] refers as health and social care perspective can be understood as a healthcare perspective.

Cost-Effectiveness Analysis (CEA) and Cost-Utility Analysis (CUA)

We labelled a study as CEA if the outcome was not a utility-based index (e.g. QALY) and CUA study if it was (Table 2). We found that QALYs have been measured by a generic

instrument such as EQ-5D or disease specific such as DEMQOL (Table 3). Using a generic measure such as EQ-5D to obtain QALY as an outcome for any intervention is generally recommended [54] for an economic evaluation study. There is a debate on using EQ-5D to measure the effectiveness of any intervention for dementia population. One group is arguing that EQ-5D may not be an appropriate tool to detect changes in mental well-being of the patients with dementia [55, 56] while others are in favour of using EQ-5D[57, 58]. A disease-specific measure such as DEMQOL has been used in some of the included studies [28, 36]. Using both a generic instrument (i.e. EQ-5D) and a disease specific instrument (i.e. DEMQOL) may be beneficial for both policy makers and clinicians. However, we did not find any effect on cost-effectiveness irrespective of using EQ-5D or DEMQOL.

Two studies from the UK that did not find significant effect of the interventions compared to the comparators used proxy-QALY where the questionnaire was completed by someone else on behalf of the patient [28, 36]. Proxy rated QALY have been found to provided lower ICER than self-rated QALY [36]. It has been suggested that self-rated and proxy QALY often have low levels of agreement and not to be assumed to substitute for each other [59].

Researchers argue that the CEA which uses a natural unit as measurement is more relevant to clinicians [60] while CUA is more relevant to decision-makers [54] as this enable comparison between different interventions. Instead of having either QALY or disease specific measures, estimation based on both might be helpful for both clinicians and decision-makers which was observed in many studies [28, 35, 36, 39, 43, 44, 46]. We also recommend this practice despite the fact that results vary depending on the choice of health outcomes in some studies [43, 44] (Table 3 and Table 4).

Caregivers

In the World Alzheimer Report, the cost of informal care contributed 42% of total cost worldwide [7] for Alzheimer care. Informal care plays an important role in cost-effectiveness analysis. It is difficult to estimate the cost of informal care for a number of reasons. First, it is debatable what types of activities should be considered as caregiving. For example, the World Alzheimer Report considers both time related to helping patients with Activities of Daily Living (ADL) and support with Instrumental Activities of Daily Living (IADL) as caregiving whereas Joling KJ et al. [40] also included monitoring activities. Second, it is difficult over a long period of time to monitor each activity of caregivers which may lead to recall and interpolation bias. Third, there is much controversy regarding the valuation of time for informal care [61].

In line with the World Alzheimer Report, we also found that caregiver's cost had a substantial effect on the results of the included studies. How this cost component has been dealt with determines, in many cases, whether the intervention is cost-effective or not. For example, the D'Amico et al. study claimed that inclusion of caregivers' cost make the intervention not to be cost-effective from a societal perspective while it is cost-effective from a health care perspective (not including informal care) [28]. However, it is not clear whether they have included the caregivers' health outcomes in the analysis. One assumption made in several studies is that informal care cost should not be included as caregivers are not in their productive age [31, 36, 37]. However, following standard economic theory, loss of leisure time and non-market productivity is a societal cost and should be included in the societal perspective.

Dementia is expected to affect people close to the patient directly and indirectly through the burden of informal care. Most studies included in this review have included some form of caregivers' outcome in the analyses. In two studies, we found that caregivers from the control group had gained more QALY than the caregivers from the intervention group [37, 38]. The

researchers argued that, being in the intervention group provided an extra burden to the caregivers and thus affected their overall quality of life. Inclusion of caregiver's cost generally have a strong impact on the cost-effectiveness outcome as suggested in a recent review of informal care cost in EE studies [62] and should be included in all EE targeting dementia disorders.

RCTs and Economic Evaluation

Out of 17 identified studies, 16 performed EE of an RCT. RCTs play a key role in providing estimates of the efficacy of health interventions [63] and are a source of data on resource use, health values, and relative treatment effect [64]. Randomization reduces selection bias, and so RCTs offer high internal validity (“Does this intervention work under the conditions set forth in the study?”), but are less well suited to provide information on external validity (“Will it work in other settings and contexts?”) [65]. Assessing internal validity is important, as without it, one cannot be sure whether the intervention works at all, but resource allocation decisions need to be informed based on studies with high external validity. That is, decision should be made based on information relevant for the actual context. The high reliance on RTC in the field is thus a cause for concern. Studies with DAM could be an alternative where the effectiveness of any specific intervention (e.g. physical exercise/ psychosocial/ psychological therapy) can be obtained from meta-analysis.

Another important aspect of EE of RCTs is that randomization is performed by considering the clinical characteristics and socioeconomic characteristics of the participants (for example, [31, 35, 40, 43, 44]), and not from the point of view of an EE. If the randomization is not even between two groups, which have been found in some studies included in this review [28, 32, 36, 38, 42-44], additional methods are required to control for the differences when performing EEs. With and without adjusting for baseline differences can have a significant

effect on the result as shown in two studies where results were presented both with and without controlling for baseline variables [36, 44]. D'Amico showed that caregiver cost differences were significant between two groups when not adjusting for baseline differences and vice versa [36]. We suggest that researchers should, first, discuss if there are any differences at baseline and then adjust for the differences in the main analysis.

Economic evaluations conducted alongside RCTs follows the (shorter) duration of trial which is considered a drawback [64]. Generally, short duration runs the risk of not providing a good indication of longer-term effects of the intervention and its associated longer-term costs. The endpoints included in the studies are limited to surrogate endpoints such as MMSE score, improvement in physical functioning, HADS score etc. This is of less interest to decision makers compared to “hard endpoints” such as days of institutionalized delayed or life years gained. The duration of the studies included in this review ranges from two months to five years. Only one study used post-trial data when conducting the EE [44], indicating that most studies in the field are limited in terms of follow-up time. It is worth mentioning that the dropout rate is high in RCTs and becomes more problematic with long follow-up [38, 39, 41]. For example, only 2% of the participants remained in the Dahlrup et al. study at the maximum follow-up (60 months) [41] and analyses based on only remaining participants might result in biased estimation. However, this should not discourage long follow-up but instead lead to increased efforts to retain the largest proportion of study participants for the longest possible period and use of register-based follow-up where possible.

Another issue with EE based on RCTs is that within trial evaluation fail to capture the benefits that occur after the trials ends, for example, other health benefits of physical exercise. The positive effect of the intervention is therefore, likely to be underestimated. Good guidelines now exist on conducting EE alongside RCTs [66-68], including some suggestions on methodological improvements [69]. One such improvement is the power and

sample size selection to capture the differences in costs and health effects while considering EE alongside RCTs [70, 71].

Another important aspect is that the effectiveness of non-pharmacological studies largely depends on the skill and motivation of the staff and thus affected by selection bias. This can have an impact of the effectiveness as well as cost-effectiveness of the interventions. It is thus possible that the trials are found to be more cost-effective than if these were routinely implemented in general practice.

Many drawbacks of EE based on RCTs can be overcome by using DAM but only one of the included studies used DAM [37]. Interesting to note is that DAM is much more common in EE of pharmaceutical treatments related to dementia [72, 73]. The rare use of DAM in non-pharmacological interventions is probably due to lack of high-quality, well-funded trials on non-pharmacological interventions in contrast to pharmaceuticals treatment. Building a DAM requires a large investment in terms of time and expertise, something that has not been done in non-pharmacological research in dementia.

Reporting quality assessment

We scored the articles based on the CHEERS statement and observed that the quality of reporting was insufficient for several articles. It can be argued that CHEERS statement is very recent and many of the articles were published before the CHEERS statement. However, other guidelines were available earlier (e.g. [74-77]) and following any of these guidelines would have improved the presentations. We found three studies which were not EE but with enough information to calculate an ICER [29, 41, 42]. These studies performed poor in terms of CHEERS score. Several items were only partially or not reported at all in most articles which impede proper comparison between the studies. Some examples are lack of proper description of costing methods such as unit costs, and sources of costs items (i.e. was the cost

collected at the time of the intervention or collected retrospectively, from registers or from other settings, etc.). We also found that most studies did not have heterogeneity analyses. We hope that the availability of the CHEERS statement will lead to improvements in reporting. However, it should be kept in mind that these guidelines are to ensure the quality of the reporting and not the quality of the study, although a high correlation is expected.

Strength and Limitation

The current literature review poses particular strengths. It includes studies that focused not only on patients but also caregivers and the patient-caregiver dyad. In line with recommendations, we searched key electronic bibliographic databases and other sources with no geographical restrictions. No restrictions were applied on types of EE or country of origin including both RCT based and DAM based EE.

There may have been some potential limitations to our study. We assess the quality of reporting based on CHEERS statement but we have not assessed the methodological rigour of the identified studies. Our conclusions of cost-effectiveness are thus based on the presented information in the studies and do not account for potential weaknesses in methodology. In addition, we have not performed a systematic quantitative assessment to identify key drivers of the cost-effectiveness.

Future research

Future research should focus on more high-quality study (e.g. pragmatic trial) with a longer time frame for measuring both costs and outcomes (health). Since the caregiver burden is substantial, a societal perspective is recommended. In terms of outcome measurements disease specific outcomes combined with generic utility outcomes (e.g. QALY) should be preferred. Although it is a common practice to perform an EE beside an RCT, researchers

should keep in mind that larger samples are required for EE studies. Last but not least, implementation of promising interventions is required to evaluate the cost-effectiveness in a “real-life” setting.

Conclusions

In conclusion, we find that within the different areas, there are different interventions some of which are cost-effective while others are not. Physical exercise targeting dementia patients and caregivers has the potential to be cost-effective. However, more research is required to establish the cost-effectiveness of non-pharmacological interventions overall. It is worth stating that the cost-effectiveness ratio is not the only aspect to consider in decision-making regarding implementation of interventions. Instead, a country and context-specific process for decision making should be considered, reflecting legislation and involving patients group, caregivers and civil society organizations [78, 79].

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Table 1: Decision rules for economic evaluations (new intervention vs. comparator)

Scenarios	Cost	Outcome	Interpretation
1	↑	↑	Cost-effective if the willingness-to-pay exceeds the ICER
2	↓	↑	Cost-effective (new intervention dominates the comparator)
3	≈	↑	Cost-effective (new intervention dominates the comparator)
4	↑	↓	Not cost-effective (comparator dominates the new intervention)
5	↓	↓	Cost-effective if the willingness-to-accept exceeds the ICER
6	≈	↓	Not cost-effective (comparator dominates the new intervention)
7	↑	≈	Not cost-effective (comparator dominates the new intervention)
8	↓	≈	Cost-effective (new intervention dominates the comparator <i>i.e.</i> cost-saving)
9	≈	≈	Not cost-effective (new intervention and comparator are equal)

Abbreviation: ↑: statistically significantly higher; ↓: statistically significantly lower; ≈: no statistical significant differences

Table 2: Characteristics of the studies with Non-pharmaceuticals intervention

First author, year, country	Analysis	Intervention, Sample size	Comparator, Sample size	Target population	Perspective, time horizon	Costs items	Currency, price year	Outcomes measures	ICER	Sensitivity analysis	CHEERS checklist	Funding source (Govt./ Nongovt./ Industry)
Physical exercise												
Davis, 2013, Canada [27]	CEA (RCT)	Physical exercise; resistance training (n=28) and aerobic training (n=30)	Balance and tone (n=28)	Mild cognitive impairment, females aged 70-80	Healthcare, 6 months	Intervention, healthcare professionals' visits, hospital and laboratory procedures	CAD\$, 2011	Stroop test score	Costs were lower (CAD\$ 316 and CAD\$ 33) and effects higher (7.5 and 7.8) for resistance training and aerobic training, respectively.	Bootstrap	19	Non-government
D'Amico, 2015, UK [28]	CEA, CUA (RCT)	Physical exercise (n=30)	No exercise (n=22)	Dementia patients (non institutionalised) and their caregivers	Health and social care, and societal, 3 months	Intervention, accommodation, hospital services, community services, equipment, daily services, medication and informal care	GBP, 2011	Some index specific to dementia such as NPI, ZBI, GHQ, and QALY	£286,440/QALY from societal perspective	DSA	20	Government
Pitkala, 2013, Finland [29]	CEA (RCT)	Group based physical exercise (n=68) and tailored home-based exercise (n=61)	Usual care (n=65)	Alzheimer; Patient-caregiver dyad	Healthcare and societal, 12 months	Intervention, healthcare services, social services and community services	US\$, 2012	Patient's physical functioning and fall prevention	Group-based exercise has \$235,695 less cost and fall \$719/fall prevented for homebased exercise*	Bootstrap	16	Government
Occupational therapy												
Graff, 2008, The Netherlands [31]	CEA (RCT)	Occupational therapy (n=68)	Usual care (n=67)	Mild to moderate dementia, aged ≥65, Patient-caregiver dyad	Societal, 3 months	Physiotherapists, social workers, general practitioners, hospital specialists, nurse home care, domestic home care, day care, and inpatient care	Euro, NA	Successful treatment based on patients daily functioning, activities and caregivers' competence	Costs were lower (€1,748) and effects were higher (36% successful treatment) for intervention group	Bootstrap	20	Government and non-government
Gitlin, 2010, USA [32]	CEA (RCT)	Tailored activity program including occupational therapy (n=30)	Patients on waiting list for treatment (n=30)	Dementia patient-caregiver dyad	Caregivers perspective, 4 months	Caregiver time, intervention including training, materials and providers time and travel	US\$, NA	Caregivers working hours saved, caregiver standby hours saved	\$2.37 per working hour saved; \$1.10 per standby hour saved	DSA and PSA	20	Government

Psychological therapy or Psychosocial interventions for the patients												
Knapp, 2006, UK [35]	CEA, CUA (RCT)	Cognitive stimulation therapy (n=91)	Usual care (n=70)	Dementia	Healthcare and personal social services, 2 months	Intervention, residential care, hospital services, day services, community services, medication and other accommodation	GBP, 2001	MMSE score and QALY by QoL-AD instrument	£75.32/ additional point of MMSE and £22.82/ additional point in QoL-AD	Bootstrap	20	Government
D'Amico, 2015, UK [36]	CEA, CUA (RCT)	Cognitive stimulation therapy+ usual care (n=104 at baseline and n=93 at follow-up)	Usual care (n=114 at baseline and n=106 at follow-up)	Mild-to-moderate dementia	Healthcare and societal, 6 months	Intervention, residential care, hospital services, day services, equipment and adaptation, community services, medication and caregiver time	GBP, 2011	Alzheimer's disease cognition assessment scale (ADAS-cog), QALY by EQ-5D and QoL-AD	£365,276/QALY from healthcare and £882,801/QALY form societal perspective	DSA	21	Government
Martikainen, 2004, Finland [37]	CUA (DAM)	Cognitive behavioral family intervention	Usual care	Dementia, Patient-caregiver dyad	Not clear, 5 years	Respite care, day care, home nursing visits, home help service, meals on wheels, neurological visits	Euro, 2001	QALY for both the patients and caregiver	Cost was €2,992 lower and QALY gain 0.01 higher	PSA	23	Government
Psychosocial interventions for patient-caregiver dyad												
Sogaard, 2013, Denmark [38]	CUA (RCT)	Psychosocial care (counselling, education and support) (n=163)	Usual care (n=167)	Alzheimer, Patient-caregiver dyad	Societal, 3 years	Intervention, healthcare services, nursing homes, informal care, production loss	Euro, 2008	QALY by EQ-5D	Cost was 3,401 higher and QALY was 0.38 lower	PSA	21	Government
Woods, 2012, UK [39]	CEA, CUA (RCT)	Psychosocial care (Reminiscence therapy) (n=268)	Usual care (n=220)	Dementia, Patient-caregiver dyad	Healthcare, 10 months	Intervention, community care, day care, hospital use for both patient and caregiver	GBP, 2010/2011	QALY by QoL-AD for patients and psychological distress for caregiver	Cost was £1,544 higher and QALY gain was 0.001	Bootstrap	21	Government
Joling, 2013, The Netherlands [40]	CUA, CEA (RCT)	Psychosocial care (Family meetings) (n=48)	Usual care (n=53, complete case)	Dementia, Patient-caregiver dyad	Societal, 12 months	Home care and not home care, treatment, productivity loss and informal care	Euro, 2009	QALY for patient-caregiver dyad, caregivers' depression and anxiety	€157,534/QALY	DSA	21	Non-government
Psychosocial interventions for the caregivers and family members												

Dahlrup, 2013, Sweden [41]	CUA (RCT)	Psychosocial care (education and support group) (n=153)	Usual care (n=155)	Caregivers of dementia patients	Not clear, 5 years	Intervention, home help service, nursing home care	Euro, 2010	QALY	Cost was higher (insignificant) in intervention group QALY unknown	No sensitivity analysis	16	Government
Gaugler, 2003, USA [42]	CEA (RCT)	Adult day service (n=154 for short-term and n=80 for long-term)	No service (n=213 for short-term and n=121 for long-term)	Caregivers of dementia patients	Not clear, 3 months and 1 year	Adult day services, formal services, secondary caregivers time and productivity loss	US\$, 1993	Caregivers workload and depression	\$6.38 and \$4.51 per one unit of work load reduction and \$2.90 and \$2.20 per one unit of depression reduction in short terms and long-term	No sensitivity analysis	15	Government
Knapp, 2013, UK [43]	CEA, CUA (RCT)	Coping strategy for relatives (n=173 at baseline, n=134 at 8 months)	Treatment as usual (n=87 at baseline, n=75 at 8 months)	Family carers of dementia patients	Healthcare and societal, 8 months	Intervention, hospital, community health, community social care for caregiver and hospital, community health, social care and home care	GBP, 2009-10	HADS-T and QALY	£6,000/QALY	DSA	20	Government
Livingston, 2015, UK [44]	CEA, CUA (RCT)	Coping strategy for relatives (n=173 at baseline, n=132 at 24 months)	Treatment as usual (n=87 at baseline, n=64 at 24 months)	Family carers of dementia patients	Healthcare and societal, 24 months	Intervention, hospital, community health, community social care for caregiver and hospital, community health, social care and home care	GBP, 2009-10	HADS-T, HADS depression, HADS anxiety, QoL-AD, QALY	£10,700/QALY	DSA, PSA	21	Government
Nichols, 2008, USA [45]	CEA (RCT)	Psychosocial therapy by individual sessions and phone calls session (n=46)	Check in phone calls (n=46)	Caregivers of Alzheimer's patients	Societal, 6 months	Intervention, travel and caregiver time	US\$, Not clear	Hours on duty	\$5/hour per day not spent in caregiving	No sensitivity analysis	17	Government
Wilson, 2009, UK [46]	CUA (RCT)	Psychosocial support by means of befrienders (n=105)	Usual care (n=113)	Caregivers of dementia patients	Societal, 15 months	Hospital visits, community services and other services for patient and caregiver	GBP, 2005	HADS, QALY	£105,954/QALY	PSA	20	Government

*Own calculation

Abbreviations: CEA, Cost Effectiveness Analysis; CUA, Cost Utility Analysis; DAM, Decision Analytic Model; DSA, Deterministic Sensitivity Analysis; GHQ, General Health Questionnaire; HADS, Hospital Anxiety and Depression Scale; HADS-T, Hospital Anxiety and Depression Scale total score; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; PSA, Probabilistic Sensitivity Analysis; QALY, Quality Adjusted Life Years; QoL-AD, Quality of Life for Alzheimer disease; RCT, Randomized Controlled Trial; ZBI, Zarit Caregiver Burden Inventory.

Table 3: Reported and evaluated cost-effectiveness of published cost-utility analyses

First author, year, country	Instrument	Reported	Evaluation	Remarks
D'Amico, 2015, UK [28]	DEMQOL-Proxy	Dominant from HSC perspective and not cost-effective in societal perspective	No significant differences in costs and QALY gains were observed from either perspective	Not cost-effective
D'Amico, 2015, UK [36]	EQ-5D, Proxy EQ-5D, DEMQOL, Proxy DEMQOL	Not cost-effective	No significant differences in costs and QALY gains were observed	Not cost-effective
Martikainen, 2004, Finland [37]	Not clear	Cost-effective	95% CIs were not presented for either costs or QALYs. CEAC showed 90% probability to be cost-effective at €20,000 WTP	Unknown
Sogaard, 2013, Denmark [38]	EQ-5D	Not cost-effective	No significant differences in costs and QALY gains were observed	Not cost-effective
Woods, 2012, UK [39]	EQ-5D	Not cost-effective	No significant differences in costs and QALY gains were observed	Not cost-effective
Joling, 2013, The Netherlands [40]	SF-12	Not cost-effective	No significant differences in cost and QALY gains were observed. CEAC showed 35% probability to be cost-effective at €20,000 WTP	Not cost-effective
Dahlrup, 2013, Sweden [41]	EQ-5D	Did not state cost-effectiveness	No significant differences in costs and QALY gains were observed	Not cost-effective
Knapp, 2013, UK [43]	EQ-5D	Cost-effective	No significant differences in costs but significant differences in QALY gains were observed. CEAC showed 99% probability to be cost-effective at £30,000 WTP	Cost-effective
Livingston, 2015, UK [44]	EQ-5D	Cost-effective	No significant differences in costs but significant differences in QALY gains were observed. CEAC showed 67% probability to be cost-effective for QALY at £20,000 WTP	Cost-effective
Wilson, 2009, UK [46]	EQ-5D	Not cost-effective	No significant differences in costs and QALY gains were observed. CEAC showed 42% probability to be cost-effective at £30,000 WTP	Not cost-effective

Abbreviations: CEAC, Cost-effectiveness acceptability curve; DEMQOL, Quality of life dementia; EQ-5D, Euroqol five dimensions; QALY, Quality Adjusted Life Years; WTP, Willingness-to-pay

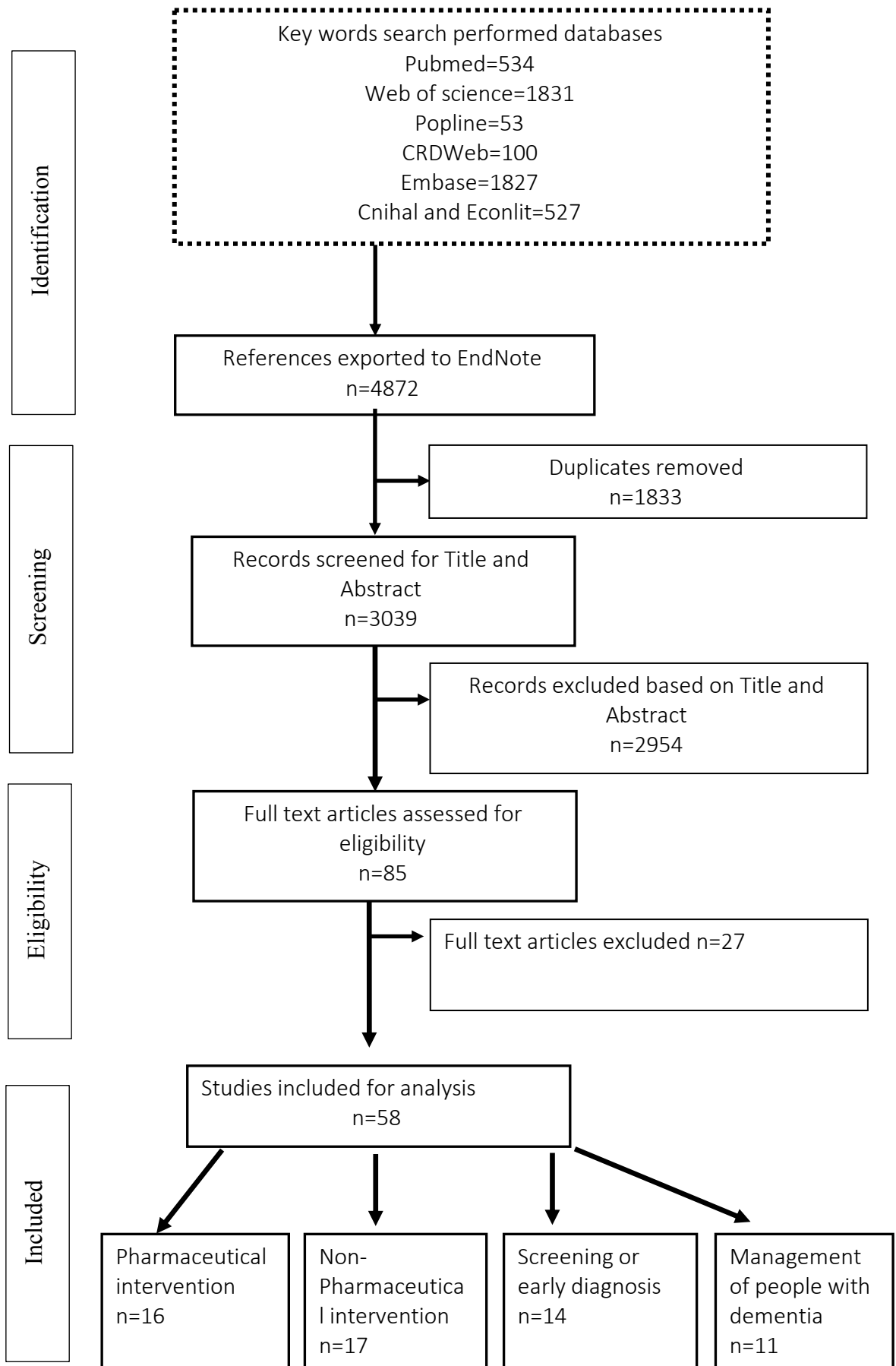
Table 4: Reported and evaluated cost-effectiveness of published cost-effectiveness analyses

First author, year, country	Effectiveness measures	Reported	Evaluation	Remarks
Davis, 2013, Canada [27]	Stroop test score	Dominant	The costs were significantly lower and effect was significantly higher in the intervention groups. The CE plane also revealed this.	Cost-effective (Dominant)
D'Amico, 2015, UK [28]	NPI score, ZBI, GHQ, Proxy-DEMQOL	Dominant from HSC perspective and cost-effective from societal perspective	No significant differences in costs and effects were observed. CEAC showed 75% probability of being cost-effective by NPI score at £3,000 WTP from societal perspective	Not cost-effective
Pitkala, 2013, Finland [29]	Total number of fall	Did not state cost-effectiveness	There were significant difference (lower for group-based intervention group) and insignificant difference (higher for home-based) in costs. Significant difference in effect (better for both group-based and home-based).	Cost-effective (Dominant)
Graff, 2008, The Netherlands [31]	Successfully treated	Cost-effective	No significant difference in cost but significant difference in effect was observed. CEAC showed 99% probability to be cost-effective at £20,000 WTP	Cost-effective
Gitlin, 2010, USA [32]	One extra hour per day “doing things”; One extra hour per day “on Duty”	Cost-effective	No significant differences in costs and effects were observed. CE plane shows 79% and 80% probability to be cost-effective at \$3,893 WTP per patient over 4-months (\$32 per day)	Not cost-effective
Knapp, 2006, UK [35]	MMSE score, ADAS-Cog, QoL-AD	Cost-effective	There were significant differences in cost (higher for intervention group) and effects (higher for intervention group). CEAC showed 90% and 60% probability to be cost-effective for MMSE score and QoL-AD, respectively, at £200 WTP	Unknown
D'Amico, 2015, UK [36]	MMSE, ADAS-Cog, QoL-AD, ADCS-ADL, Proxy QoL-AD, Proxy DEMQOL	Cost-effective	No significant differences in costs and effects were observed by any scale. CEAC showed 90% probability to be cost-effective for one-point difference in QoL-AD at £1,400 WTP	Not cost-effective
Woods, 2012, UK [39]	QoL-AD	Not Cost-effective	95% CI of ICERs were broad and included zero value	Not cost-effective

Joling, 2013, The Netherlands [40]	MINI	Not Cost-effective	No significant differences in costs and effects were observed	Not cost-effective
Gaugler, 2003, USA [42]	Caregivers stress and depression	Did not state cost-effectiveness	There were significant differences in cost (higher for intervention group) and effects (higher for intervention group)	Unknown
Knapp, 2013, UK [43]	HADS-T	Cost-effective	There were significant differences in cost (higher for intervention group) and effects (higher for intervention group)	Unknown
Livingston, 2015, UK [44]	HADS-T, patient QoL-AD	Cost-effective	There were no significant differences in cost but significant differences in HADS-T (better for intervention groups) and non-significant differences in QoL-AD	Cost-effective
Nichols, 2008, USA [45]	One hour not caregiving	Cost-effective	Significant differences in effect was observed but no information on cost as such was available	Unknown

Abbreviations: ADCS-ADL, Alzheimer's Disease Cooperative society Study- Activities of Daily Living; ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; CEAC, Cost-effectiveness acceptability curve; DEMQOL, Quality of life dementia; GHQ, General Health Questionnaire; HADS, Hospital Anxiety and Depression Scale; HADS-T, Hospital Anxiety and Depression Scale total score; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; PSA, QoL-AD, Quality of Life for Alzheimer disease; ZBI, Zarit Caregiver Burden Inventory.

Figure 1: A flow chart for selection of articles



Annex 1: Detailed search history in databases with keywords

Pubmed

("economic evaluation"[All Fields] OR "cost-benefit analysis"[MeSH Terms] OR "cost-effectiveness"[All Fields] OR "cost-benefit analysis"[MeSH Terms] OR "cost-benefit analysis"[MeSH Terms] OR "cost benefit"[All Fields] OR "cost utility"[All Fields] OR "cost-utility"[All Fields]) AND (((("dementia"[MeSH Terms] OR "dementia"[All Fields]) OR "dementia"[MeSH Terms]) OR "mild cognitive impairment"[All Fields]) AND ("2000/01/01"[PDAT] : "2015/12/31"[PDAT]) AND English[lang])

= 534

CRDWeb

((dementia)) and ((Economic evaluation:ZDT and Bibliographic:ZPS) OR (Economic evaluation:ZDT and Abstract:ZPS)) IN NHSEED FROM 2000 TO 2016

=100

EMBASE

1. 'dementia'/exp OR dementia
2. 'cost effectiveness' OR 'cost utility' OR 'cost benefit analysis' OR 'economic evaluation'
3. 'mild cognitive impairment':ab
4. #1 OR #3
5. 'cost consequence analysis'
6. #2 OR #5
7. #4 AND #6
8. #7 AND (2000:py OR 2001:py OR 2002:py OR 2003:py OR 2004:py OR 2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py)

=1827

Web of science

1. **TOPIC:** Dementia
2. **TOPIC:** Mild cognitive impairment
3. **TOPIC:** Alzheimer
4. **TOPIC:** Vascular dementia
5. **TOPIC:** Parkinson's disease
6. 1 OR 2 OR 3 OR 4 OR 5
7. **TOPIC:** (cost effectiveness) OR **TOPIC:** (cost-effectiveness analysis) OR **TOPIC:** (cost-effectiveness) OR **TOPIC:** (cost utility analysis) OR **TOPIC:** (cost-utility analysis) OR **TOPIC:** (cost benefit) OR **TOPIC:** (cost-benefit) OR **TOPIC:** (economic evaluation)
8. 6 AND 7 (Refined by: Publication Years (2000 to 2015))
9. 8 (Refined by: Language (English))

= 1831

1. Dementia
2. AB dementia
3. AB dementia OR mild cognitive impairment
4. Cost effectiveness
5. Cost benefit analysis
6. Cost utility analysis
7. Cost-utility analysis in healthcare
8. Economic evaluation
9. Cost consequences analysis in health economics
10. 4 OR 5 OR 6 OR 7 OR 8 OR 9
11. 10 AND 3
12. 11 (limiters- 20000101-20151231)

= 527

Popline

1. ((((Title:dementia) OR (Title:alzheimer)))) AND ((Language:English) AND (Publication Year:[2000 TO 2015]) AND (Peer Reviewed:1) AND (Journal Article:1))
2. ((((Title:cost effectiveness analysis) OR (Title:cost utility analysis) OR (Title:economic evaluation) OR (Title:cost benefit analysis)))) AND ((Language:English) AND (Publication Year:[2000 TO 2015]) AND (Peer Reviewed:1) AND (Journal Article:1))
3. 1 OR 2

= 53