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How nutraceutical products can help NHS to sustain dementia's costs

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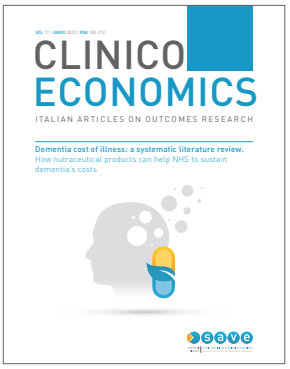

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Dementia cost of illness: a systematic literature review. How nutraceutical products can help NHS to sustain dementia's costs

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INTRODUCTION

The progressive aging of the population is today a challenge for modern society and health systems. Epidemiological change is causing new social and health problems that have never been addressed before. The number of people over 60 years of age has now reached 900 million worldwide, or 12% of the population, with an estimated 2.4 billion in 2050, or 21% of the total population.[1] Many of these individuals are already suffering from chronic degenerative diseases, dementia being one of the most serious and disabling. Dementia is a syndrome characterized by acquired impairment in one or more functions, such as memory, attention, orientation, language, thinking, behavior and ability to perform everyday activities.[2] The seriousness of this clinical condition can vary, but it is often highly disabling on a personal level, and onerous on the social-welfare level.[3] The most frequent form of cognitive decline is Alzheimer's disease (AD), a neurodegenerative condition making up 50% to 60% of all dementias.[4] In early stages of the disease, patients are mostly cared for in the community, receiving informal care and support for ADLs (activities of daily living) from mostly female caregivers, although the number of male caregivers is increasing and it can be estimated to be 40% of health workers.[5-7] Increasing severity, worsening of cognitive and physical functions, and presence of behavioral and psychiatric symptoms (BPSD) contribute to a growing burden on family caregivers,[8] and augmenting demand for formal community support services.[9] Once the subjective caregiver burden becomes overwhelming, institutionalization is necessary for many patients. Worldwide, around 50 million are estimated to have dementia, and there are nearly 10 million new cases every year.[2] If disease prevalence and incidence trends do not change in the next years, this number is projected to reach 82 million by 2030 and 152 million by 2050.[2] These are significant and worrying numbers, however it should be noted that recent data indicate values of slowing dementia incidence at least in developed countries, partly due to the preventive measures adopted (greater cardiovascular assistance, greater awareness of the role of a correct lifestyle), highlighting the importance of these measures and the need to implement them over time, to reduce the economic impact of disease that today is large and destined to grow without adequate interventions.[10,11] The world economic burden of cognitive decline is high and increasing especially in developing countries, so much that it is estimated that Alzheimer and other dementias will become between the first three leading cause of burden of disease in high-income countries by 2030, and raises different challenges to public healthcare and assistance systems for the elderly.[12] Currently, the global costs of dementia are estimated to be around 1 trillion US dollars and this figure will rise to three trillion US dollars by 2030.[13] Dementia-related costs are associated with medical care, direct costs of formal care, and indirect costs of informal care. Although people with dementia need continu-

ous, integrated, and holistic assistance, their care currently is not highly specialized, often fragmented, poorly coordinated, and unable to effectively meet the needs of patients and their families.[14] Compared with other long-term care users, dementia patients require extensive personal care, including supervision, and time for providing assistance with daily activities, resulting in higher costs of care and economic impact on patients, families and healthcare systems.[15] This situation has led patients, their families, and caregivers to look for alternative treatments, with the purpose to improve the quality of life of patients by relieving the burden of the disease.[16] While secondary forms can be therapeutically solved once the cause is found, primary dementias can't be cured, because the underlying pathophysiologic mechanisms are not completely understood. Up to now, research has produced drug therapies that, if administered early, can delay the clinical evolution of the disease by a few years, and offer patients and their families a considerably long period of better quality of life, even if sometimes associated with problems of safety in long time. Alternative or complementary therapeutic approaches, such as nutraceutical products, are now finding foothold near conventional therapies.[17]

The word "nutraceutics" (from "nutrition" and "pharmaceutics") highlights the pharmacological effect of some nutritional elements, which are identified as useful for the prevention or treatment of conditions or diseases. "Neuro-nutraceuticals" can be divided in nutraceuticals with useful properties for maintaining the normal functions of the central nervous system (CNS), and nutraceuticals with useful properties for treating diseases that can compromise cognitive functions (or with nootropic effects on healthy individuals).[17] In clinical terms, the above definition can be translated into two actions: (1) prevention of (systemic or not systemic) diseases impairing CNS vascularization, affecting CNS metabolism, or producing inflammation (e.g., atherosclerosis, diabetes, multimorbidity, endogenous/exogenous toxicosis, lack of essential elements); (2) promotion of an adequate brain activity (daily involvement in stimulating activities, improvement in cerebral flow, neurotransmission, and neuronal metabolism).[18] Many published studies indicate that the informal care costs account for much of AD total costs associated with AD. Slowing down the process of cognitive decline and dementia can result in cost savings due to a delayed or reduced need for caregivers, healthcare professionals and social support.[5,15]

The need for new therapeutic and assistance approaches has proved to be necessary in association with the drugs used today: since they only have a symptomatic action, their effectiveness tends to decrease with the progression of the disease. Also non-pharmacological treatments are important for the prevention of AD or as adjuvants in other treatments, tending to delay cognitive decline.[16] Research funded by the European Union and entrusted to independent scientists, published by The Lancet Neurology, demonstrated the effectiveness of a patented mix of active nutrients (including omega-3 fatty acids, phospholipids, anti-oxidants and B vitamins) in preserving brain tissue, memory and the ability to carry out the activities of daily living in 311 subjects showing the first signs of mild cognitive decline (LipiDiDiet RCT).[19] LipiDiDiet was a 24-month randomised, controlled, double-blind, parallel-group, multicenter trial (11 sites in Finland, Germany, the Netherlands, and Sweden), with optional 12-month double-blind extensions. The trial enrolled individuals with prodromal Alzheimer's disease. Patients were randomly assigned (1:1) to active nutraceutical product (n=153) or control product (n=158). Although the intervention had no significant effect on the NTB primary endpoint over 2 years in prodromal Alzheimer's disease, cognitive decline in this population was much lower than expected, rendering the primary endpoint inadequately powered. In addition, secondary endpoints of disease progression measuring cognition and function benefits and hippocampal atrophy were observed, highlighting that further studies on nutritional approaches are needed.[19]

Therefore, nutraceutics, at least according and using the conditions described in the published study,[19]may represent a step forward, helping to slow down brain ageing and the neuronal degeneration. And even if it

does not provide healing prospects, it certainly helps give patients a few more years with a higher quality of life: prolonging self-awareness, insight ability and independent IADL and ADL, is also an important goal.[14] No direct studies measuring the economic impact of the use of nutraceuticals in the treatment of patients with cognitive decline have been carried out yet. Instead, cost of illness (COI) studies are available for cognitive decline and dementia. This type of study aims to identify and measure all the costs of a disease, describing the economic burden of a specific pathologic condition, and consequently savings that could be obtain if the course of disease were to be arrested or slowed down.[20] Therefore, COI studies are necessary to proceed with subsequent research steps in the field of new approaches and therapeutic or preventive strategies. Indeed, cost-of-illness studies are an important source of information for health policy makers, especially for chronic diseases that weigh heavily on health expenditures. They provide comprehensive data for decision making and planning of healthcare services by making the distributions of several cost components transparent.[21]

AIMS OF THE STUDY

Since there is international consensus that dementia is the one of the most burdensome disease for modern societies, we aimed to quantify estimates of this burden in published data through cost-of-illness studies available in scientific literature. More specifically, given the progressive and irreversible worsening nature of dementia and the available evidence showing rising cost with increase in severity, as well as the possibility of managing patient in different living conditions (at home in the community, or in a nursing home),[5,15,22] we paid attention to these aspects analyzing scientific literature, in order to trace cost subgroups based on the severity stage and how the dementia patient care is provided, highlighting the impact of these variables on total cost and secondly, to estimate the possible impact on costs of strategies slowing down the course of the disease. COI studies allow to examine complexity of dementias burden, and we focused on Alzheimer's disease (AD) in particular, considering at the same time health and social care, cash allowances, informal care, and out-of-pocket expenditure by families. To identify, evaluate and summarize data on cost of dementia and cognitive decline, we developed a systematic review worldwide. Systematic reviews are useful tools for researchers, practitioners and healthcare decision-makers, encouraged to make use of the latest research and information about best practice, and to ensure that decisions are demonstrably rooted in this knowledge.[23] Therefore, it was our goal to develop an analysis that offered a wide-ranging overview of the cost studies conducted on dementia, a starting point for further analyses.

MATERIALS AND METHODS

The review was conducted following the general principles published in the Centre for Reviews and Dissemination (CRD)'s guidance for conducting systematic reviews and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement, inclusion and evaluation of studies in this review was based on PICOS (Population, Intervention, Comparators, Outcome and Study design) issues.[23,24] Health care decisions for individual patients and for public policy should be informed by the best available research evidence.[23] CDR's guidance and PRISMA statement are recommended as sources of good practice by agencies such as the National Institute for Health Research Health Technology Assessment (NIHR HTA) program, and the National Institute for Health and Clinical Excellence (NICE) and are used widely internationally. PICOS corresponds to a useful tool for making explicit the questions of the revision. PICOS issues define review question that can be framed in terms of the population, intervention(s), comparator(s), outcomes and study design. The use of this tool allows to determine specific inclusion criteria to be adopted in the process of selecting studies.[23,24]

ELIGIBILITY OF THE EXAMINED PUBLICATIONS

This systematic review included published cost of ill-

ness and economic evaluation, based on clinical studies or economic models of adults with dementia in general, and focusing specifically on AD patients, severity status (mild, moderate, severe) and living condition (home/institution). We considered studies including following PRISMA-defined PICOS criteria: (1) Population: Male/Female adults community-dwelling and/or institutionalized diagnosed with dementia regardless of severity stage; (2) Intervention: no specific type of treatment was considered among inclusion criteria; (3) Comparators: main comparison sought with baseline dementia patient conditions, the presence of a comparator cohort was considered permissible but not required for inclusion; if present, was allowed as comparison: patient not suffering from dementia or in pre-diagnosis status. Main comparison sought was with baseline dementia patient conditions; (4) Outcomes: primary economic outcome was total cost related to disease, divided into different cost components (direct medical-cost, direct non-medical-cost, indirect cost, formal/informal cost), variously reported according to the perspective of the study; in the studies carrying out a stratification by cost subgroups the main clinical outcomes considered for their effects on costs were: severity stage of disease (mild, moderate, severe), living condition (community-dwelling/institutionalized) and comorbid conditions; (5) Study designs: cost of illness and economic evaluation studies based on clinical studies (cross-sectional/prospective/retrospective observational method studies including patients follow-up/medical records/registries/questionnaires or randomized controlled trial) or economic model, mainly based on clinical studies or prevalence-based approach, that can allow the extraction of an average total cost per patient during a specific period of time (e.g. one month, six months, one year etc.), easily resettable at a total cost per patient per year (so, cost of illness studies incidence-based reporting lifetime costs were excluded); both societal and healthcare payer (Medicare, NHS, National Health-care System) perspective were adopted for the inclusion.

SEARCH STRATEGY, SCREENING, AND DATA EXTRACTION

An electronic literature search about all available articles meeting the inclusion criteria was carried out using Medline (PubMed), the Cochrane Library and Google Scholar up to July 2019. In addition, cross-referencing from the articles found was used to complete the search.

The keywords used to search titles and abstracts were *dementia*, *Alzheimer Disease*, *cost of illness*, *economic impact*, *cost analysis*, combined using the AND, OR Boolean operators. To assess global economic impact of dementia according to inclusion criteria, we included cost of illness studies and economic evaluation of clinical studies developed on patients with dementia, and more specifically we focused on Alzheimer's disease, as it is the most frequent form of dementia. So, we included studies carried out on patients diagnosed with dementia in general, including AD patients, and studies conducted on AD population, while studies developed exclusively for other type of dementia were excluded. Case reports, purely descriptive studies and previous COI reviews (systematic or not) on this topic were excluded. In addition, studies were excluded if their primary objective was not estimation of dementia cost, if they were focused on caregiver and informal care, or if they were mainly economic model based on incidence-approach reporting lifetime costs. Abstract publications were not included due to lack of sufficiently detailed data, only full texts were included among those potentially relevant. The search has been filtered considering only articles published in English and appeared starting from year 2000. The reference lists of sources were reviewed for studies not previously identified. Methodological quality of included studies was evaluated using quality assessment tool for economic evaluation developed based on model described by Drummond,[25] and adapted to COI by Molinier et al,[26] yet adopted in a COI methodological review.[22] Heterogeneity was not analyzed and no quantitative pooling of data from these studies was undertaken. From all articles that met the review criteria, basic infor-

mation was extracted by an independent researcher and reported in summary tables created with Excel®. From each publication the following data were extracted: authors, year of publication, country, study design, type of disease, patients' sample size, baseline characteristics (mean age, gender, severity stage, patient living condition), dementia definition, cost evaluation methods (tools adopted to collect resource consumption and type of unit cost valuation) and perspective adopted. For each study method used for dementia diagnosis and for evaluation of severity were sought. If included in studies outcomes, also complications impact on cost was analyzed. Then, to identify main cost driver direct (medical/non-medical), indirect and informal costs were considered as cost outcome measures and extracted from studies. Specifically, when studies offered subgroups analyses, we focused on changes in disease costs related to severity and living condition. When studies presented cost estimates for more than three stages of disease (mild, moderate and severe), we selected estimates corresponding to these three stages of dementia. For each study we extracted items cost of interest per patient related to the study period and the average total cost, if available, otherwise it was calculated. To provide consistency in comparing results, we adopted annual cost per patient as summary measure and when it was not directly available it was calculated starting from study period reported in each study. Moreover, total annual cost per patient were inflated to 2019 values in local currency and converted in euro (€ 2019). Some studies did not report explicitly make the currency year. In these cases, we adopted the year of the reported source for the unit costs included in the analysis. Studies characteristics description, the main cost results extracted from studies and total annual cost for all population e subgroups were reported in summary tables. During data search and extraction phase we did not contact study authors to obtain additional information. Because of methodological and clinical heterogeneity between studies, a narrative synthesis was applied. Numbers of studies screened, assessed for eligibility, and included in the review, has been ideally reported with a flow diagram in the Results (Figure 1). Assessment of risk of bias in included studies was conducted at outcome and study level, the internal and external validity were texted. For each study we considered clarity and completeness in reporting information on study design and methods (description of: design, setting, locations, relevant dates, including periods of recruitment follow-up, and data collection). The sample size, patient's inclusion criteria and level of precision in presenting results were the main aspects considered in the assessment of risk of bias potentially able to influence the cumulative estimate of the result. Summary of descriptive statistics were presented as mean±standard deviation (SD) and n (%).

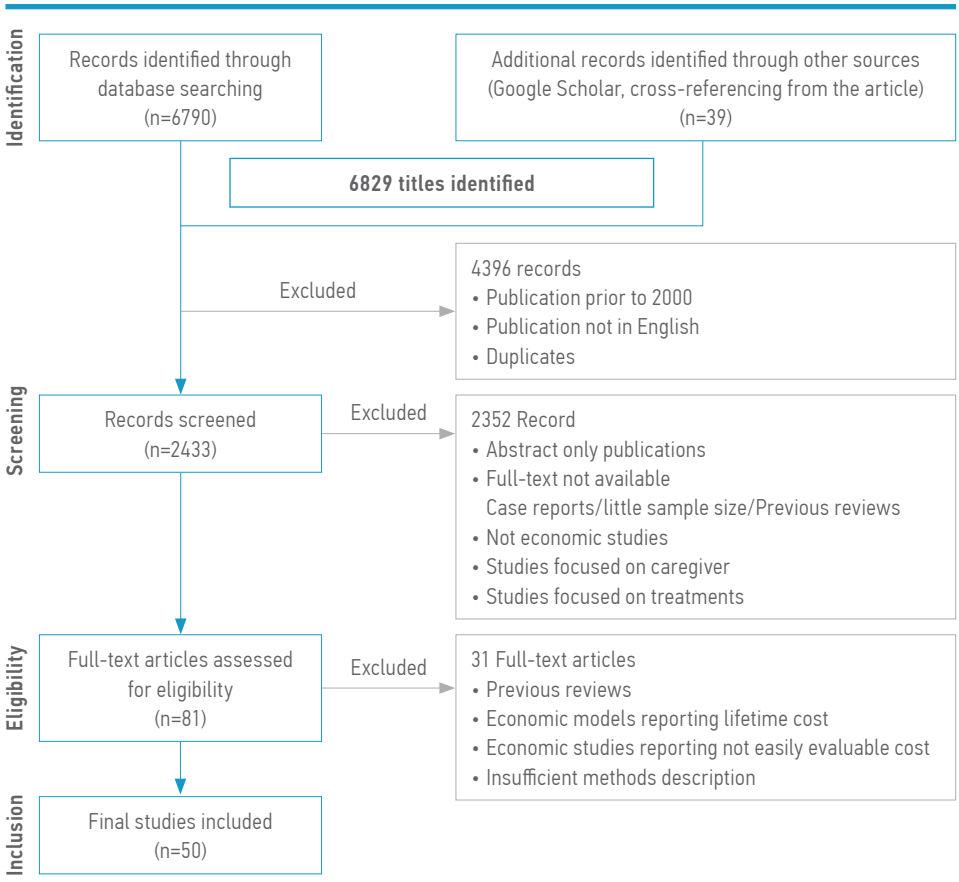
RESULTS

A total of fifty economic studies were included in our systematic review; the study selection process is detailed in Figure 1. As shown in flow diagram of the selection process below (Figure 1), 6829 records were identified in the first search of the database and after the inclusion of additional records identified through other sources (Google Scholar, cross-referencing from the articles). Then we excluded 4396 texts because published not in English, before 2000 or because they were duplicates. Consequently, 2433 abstract were screened, 2352 of these were considered not eligible, due to not in accordance with inclusion criteria, mainly: abstract only publications, full-text not available, simple case report/descriptive analysis/previous reviews, not economic studies or not focusing on dementia, mainly focused on caregiver, treatment or diagnosis. At the end of this process, 81 full-text articles were assessed for eligibility and after full-text viewing and elimination of further 31 studies which did not comply with the pre-established selection criteria, 50 articles were finally included in the review.

INCLUDED STUDIES CHARACTERISTICS

43 studies were conducted from societal perspective, while remaining 7 studies adopted healthcare payer's perspective. We decided to include both points of view, but the respective studies were analyzed separately.

FIGURE 1
Flow diagram of included studies selection process: data identification, screening, eligibility and inclusion



The primary characteristics of included studies are summarized in Table 1 (societal perspective) and 2 (healthcare payer's perspective). Cost of illness studies and economic evaluation on dementia/AD included were mainly developed on the basis of observational trial data, only three studies had randomized population [27,45,50] and four were prevalence-based economic models.[28,29,43,54] Included studies reported cost results for 27 countries: Argentina (1), Belgium (1), Brazil (1), Czech Republic (1), Chile (1), China (2), Denmark (2), Finland (1), France (3), Georgia (1), Germany (6) , Hungary (1), Israel (1), Italy (2), Norway (2), Japan (1), Korea (1), Peru (1), Portugal (1), Singapore (1), Spain (6), Sweden (5), Switzerland (1), Taiwan (2) Turkey (1), UK (5), USA (6). Three studies were multicentric, developed in more than one country. The study population size ranged from large samples in prevalence-based studies and in studies with large dementia patients' cohorts (e.g. 102,560; 69,780 cases,)[54,73] to a minimum of 42 cases.[64]

The mean age varied among studies, the most presented a mean age in the range 74-85. Care setting was variable among included studies, 25 studies considered cost analysis for a mixed setting (community-dwelling patient/institutionalized patient), 7 of them reported estimates separately by care setting. 23 studies developed cost analysis on community-dwelling patient, while only 2 studies were on institutionalized patients.

Disease severity and cognitive status are important for patient status and costs evaluation. Various disease severity measures were adopted in included studies. Two validated tools are Mini mental state examination (MMSE) and Clinical Dementia Rating (CDR), that were the most adopted in included studies, in 29 and 8 respectively. Further tools used were Activities of Daily Living (ADL) score (1), Dementia Functional Assessment Staging (D FAST) scale (1), Dependency score (DS) (1), SPMSQ, Short Portable Mental Status Questionnaire (1), and BIMS, Brief Interview for Mental Sta-

tus (BIMS) (1). In the case of 10 studies the method to assess severity was not clearly specified. In most of the studies dementia was defined according to National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA) and/or Diagnostic and Statistical Manual of Mental Disorders IV edition (DSM) (n=20); ICD, International Classification of Disease (ICD) (n=8), though less used tools (SS-IQCODE, Spanish Short-version, AGECAT algorithm, DemTect, National Institute of Aging–Alzheimer's Association criteria, SPMSQ, Short Portable Mental Status Questionnaire and Brief Interview for Mental Status, BIMS) were also used (n=7). In the case of the remaining studies (n=15) diagnosis definition was not specified or was provided by the general practitioner.

COST ESTIMATES

Most of the studies adopted societal perspective (n.43), reporting at least direct costs and either indirect and/or informal costs. 18 studies reported informal costs, the remaining analyzed direct and indirect cost categories. 7 of the included studies were based on the healthcare perspective reporting only direct costs and less details about the stratification into subgroups. Table 3 and 4 show the main results of included studies from societal and healthcare perspective respectively. The type and number of included cost categories varies widely between studies and it can be partially explained through differences in the adopted perspectives and healthcare systems. Direct costs were obtained from medical care system resources consumption divided into direct medical (outpatient and inpatient visits and medication) and non-medical costs that are provided outside the medical care system (e.g., nursing home, home help and transportation).[77] Indirect costs refer to production losses in the working population (e.g., impaired productivity while working, sick leave and early retirement). Indirect costs are less relevant in dementia, where most of the affected are older people who are often retired.[15,77] Informal costs refer to the amount of unpaid informal caregiver's time provided for care. For informal cost calculation, two different main methods are used.[78] The replacement cost approach aims to assign a monetary value for informal care time based on the cost of care by professional caregivers (formal care). The opportunity cost approach is the value of the best alternative forgone for the informal caregiver, for example, lost leisure time or lost production.[15,79] The majority of studies included adopted applied opportunity cost approach. Despite the variability in term of direct, indirect and informal cost ranges among studies, it is possible to identify common trends. Studies conducted according to societal perspective, that have taken the three main cost items into consideration, highlight the significant impact of informal cost on the total cost. As far as the internal division in direct medical and non-medical cost, the panorama is diversified with a greater number of European studies indicating the higher impact of non-medical cost, while USA and Asian studies indicate otherwise. Some characteristics of the analyzed studies influence cost estimates: type of healthcare system, study objectives (estimation of total costs vs. net costs), patient characteristics (care setting: community-dwelling vs. institutionalized patients), included cost categories (inclusion or not of informal care), disease severity status. Therefore, the comparison of the results can be achieved considering these specific elements.

Specifically, we aimed to highlight the difference in total cost among studies focusing on disease severity stratification (mild, moderate, severe) and living condition (community-dwelling/institutionalized). To allow comparison among studies and ensure homogeneity in reporting results, we calculated the average annual cost for each study, as the main cost outcome, then we extrapolated mean annual cost related to subgroups: disease severity and living condition. All cost obtained were inflated to 2019 values in local currency and converted in euro (€ 2019). Table 5 and 6 report these results, allowing to compare mean results among studies and observe severity status and living condition impact on costs.

Mean annual total cost of illness among the 43 socie-

TABLE 1

Primary characteristics of societal perspective included studies (continues on the next page: 1 of 3)

Author	Ref.	Year	Country	Perspective	Study design	Disease	Population size
Yan et al.	27	2019	China	S	CROT	AD	3,046
Wittemberg et al.	28	2019	UK	S	PBEM	D	D people in England ≥65 y D people in England ≥35 y
Sado et al.	29	2018	Japan	S	PBEM	D	D people in Japan ≥40 y
Ferretti et al.	30	2018	Brasil	S	CSOS	D	156 61 mild 74 moderate 21 severe
Michalowsky et al.	31	2018	Germany	S (HCP)	CSOS	D	425 254
Bruno et al.	32	2018	Italy	S	POS	D	198 29 (15%) mild AD-D 80 (40%) moderate AD-D, 89 (45%) moderately severe/severe AD-D
Olazaràn et al.	33	2017	Spain	S	POS	AD	380 116 mild; 118 moderate; 146 moderately severe/severe
Reed et al.	34	2017	Multicentric France Germany UK	S	POS	AD	Tot 1,495 France 419 Germany 550 UK 526
Hojman et al.	35	2017	Chile	S	CSOS	D	330
Holmerova´et al.	36	2017	Czech Republic	S	POS	AD/D	119 (106 AD; 13 D) 36 mild, 66 moderate, 17 severe
Farre et al.	37	2016	Spain	S	CSOS	D	174
Kandiah et al.	38	2016	Singapore	S	CSPS	D	255 88 young onset dementia (YOD) (AD 54, FTD 22, VaD 10, PDD 2) 167 late onset dementia (LOD) (AD 133, FTD 24, VaD 4, PDD 6)
Ku et al.	39	2016	Taiwan	S	POS	D	231 102 mild 88 moderate 41 severe
Lenox-Smith et al.	40	2016	UK	S	POS	AD	526 (200 mild, 180 moderate, 146 moderately severe/severe)
Frahm-Falkenberg et al.	41	2016	Denmark	S	ROS	D	78,715 patiens 312,813 controls
Åkerborg et al.	42	2016	Sweden	S	ROS	D	296 170 D 126 No-D
Wimo et al.	43	2016	Sweden	S	PBEM	D	based on Sweden demographic statistics and dementia prevalence 14,000
Custodio et al.	44	2015	Perù	S	ROS	D	136 Not D 30; AD 44; Frontotemporal dementia 18; Vascular Dementia 44

Abbreviations: S, Societal, CROT, Cluster randomized observational trial, PBEM, prevalence-based economic model, CSOS, cross-sectional observational study, POS, prospective observational study, ROS, retrospective observational study; RCT, randomized controlled trial; CS-ROS, cross-sectional retrospective observational study; CRT cluster-randomized trial; AD, Alzheimer' Disease; D, Dementia; ADRD, Alzheimer' Disease and related dementias; F, female; MMSE, mini-mental state examination; ADL score, Activities of Daily Living score; D FAST scale, Dementia Functional Assessment Staging scale; DS, dependency scale; CDR scale, Clinical

Mean age Gender	MMSE	Living conditions	Cognitive status/severity status mainly measure	Definion of dementia
72.27±9.40; 54.2% F	13.76±9.14	mix setting	MMSE	NINCDS–ADRDA
- (Office for National Statistics UK)	-	mix setting	MMSE	AGECAT algorithm
- (Japan National Database)	-	mix setting	-	NS
72.90 (10.20); 58.33 F	-	CD	D FAST scale	NS
80.2 (5.3); 56.5% F 80.7 (5.4); 55.5% F	22.8 (4.9) 21.8 (5.0)	CD	MMSE	DemTect
77.5 (7.23); 60.1%F 76.2 (7.12); 48.3%F 77.0 (7.65); 61.3%F 78.3 (6.85); 62.9%F	23.0 (22.3; 23.6) 17.8 (17.4; 18.1) 10.4 (9.7; 11.1)	CD	MMSE	National Institute of Aging-Alzheimer's Association criteria
75.7 (8.2); 63.4 %F	-	CD	MMSE	National Institute of Aging-Alzheimer's Association criteria
79.4 (6.81); 62.3% F 75.2 (7.55); 49.6% F 78.5 (7.79); 54.2% F	17.2 (5.73) 17.7 (6.72) 17.3 (6.40)	CD	MMSE	NINCDS-ADRDA
76.78 (10.11); 62.5 %F	-	CD	-	SS-IQCODE survey
64.0 (20.0); 58% (48.7) F	-	mix setting	MMSE	NS
82.5 (SD 7.3) 66.1% F	16.1 (5.4)	CD	MMSE	NS
symptom onset 57.0 (5.1) ; 51,7%F symptom onset 75.0 (5.9) ; 61,7%F	16.7 (7.0) 18.1 (6.5)	CD	MMSE	DSM-IV
80 (SD 6.9) 60% F	-	CD	CDR or Chinese MMSE	DSM-IV
78.5 (7.8) 54.2% F	17.3 [6.4]	CD	MMSE	NINCDS-ADRDA
≥80=60%; 70-79=26%; 60-69=7% 50-59=3%; 40-49=1%	-	mix setting	-	ICD-10 diagnoses: F00/G30 AD; F01 vascular dementia; F03 dementia not otherwise specified
79-83=112 (37.8%);67.9%F 84-87=95 (32.1%) 88+ years=89 (30.1%)	20.51 (7.16) 17.02 (7.73) 25.21 (1.16)	mix setting	MMSE DS score	NS
Age stratification based on demographic statistics	-	mix setting	-	NS
67.13 (2.29); 19%F 71.87 (5.17); 29%F 67.72 (3.10); 10%F 69.09 (4.45); 24%F	Not D 28.53 (1.20); AD 22.43 (3.34); FTD 25.78 (1.40); VD 20.98 (2.48)	CD	CDR scale MMSE	DSM-IV-TR NINCDS-ADRDA

Dementia Rating Scale; SPMS, Short Portable Mental Status questionnaire; CD, community-dwelling patients; I, institutionalized patients; mix setting (community-dwelling and institutionalized patients); NINCDS–ADRDA, National Institute of Neurological and Communicative Disorders and Stroke- Alzheimer's Disease and Related Disorders Association criteria; DSM, Diagnostic and Statistical Manual of Mental Disorders III/IV edition; ICD, International Classification of Disease (X Revision); SS-IQCODE, Spanish Short-version of the Informant Questionnaire of Cognitive Decline in the Elderly; SPMSQ, Short Portable Mental Status Questionnaire.

TABLE 1

Primary characteristics of societal perspective included studies (continues on the next page: 2 of 3)

Author	Ref.	Year	Country	Perspective	Study design	Disease	Population size
Chiatti et al.	45	2015	Italy	S	RCT	D	438 moderate AD
Darbà et al.	46	2015	Spain	S	CSOS	AD	343 CDR 0.5 (n=18) 1 (n=116) 2 (n=102) 3 (n=103)
Gervès et al.	47	2014	France	S	POS	AD	57
Konig et al.	48	2014	Germany	S	CS-ROS	D	128 community-dwelling dementia 48 living nursing home
Vossius et al.	49	2014	Norway	partly S	POS	D (mild)	109 mild D
Schwarzkopf et al.	50	2011	Germany	S	CRT	D	383 247 mild 135 moderate
Gustavsson et al.	51	2011	Multicentric Spain Sweden UK US	S	POS	AD	1222 Spain 305 Sweden 300 UK 317 US 300
Leicht et al.	52	2011	Germany	S	CS-ROS	D	176 D 173 non-D
Reese et al.	53	2011	German	S	CS-ROS	AD	395 272 outpatient; 123 inpatient
Kraft et al.	54	2010	Switzerland	S	PBEM		prevalence based on Harvet et al and EURODEM retes and SFSO Annual Population Statistics=102,560
Ersek et al.	55	2010	Hungary	S	CSOS	D	88
Coduras et al.	56	2010	Spain	S	POS	AD	560
Mesterton et al.	57	2010	Sweden	S	CSOS	AD	233 (Mild 91; Moderate 91; Severe 51)
Zhu et al.	58	2009	US	S	CSOS	AD + DLB	AD (n=170) or DLB (n=25)
Wang et al.	59	2008	China	S	ROS	AD	66 mild 13 moderate 37 severe 16
Allegri et al.	60	2007	Argentina	S	CS-ROS	AD	80 AD mild (48), moderate (30), severe (22) (20 institutionalized) 25 healthy
Kang et al.	61	2007	Korea	S	CS-ROS	D	609 184, low (ALD score ≤ 9) 185 moderate (ADL 10-15) 240 high (ADL 16)
Jönsson et al.	62	2006	Nordic Sweden Denmark Norway Finland	S	POS	AD	272

Abbreviations: S, Societal, CROT, Cluster randomized observational trial, PBEM, prevalence-based economic model, CSOS, cross-sectional observational study, POS, prospective observational study, ROS, retrospective observational study; RCT, randomized controlled trial; CS-ROS, cross-sectional retrospective observational study; CRT cluster-randomized trial; AD, Alzheimer' Disease; D, Dementia; ADRD, Alzheimer' Disease and related dementias; F, female; MMSE, mini-mental state examination; ADL score, Activities of Daily Living score; D FAST scale, Dementia Functional Assessment Staging scale; DS, dependency scale; CDR scale, Clinical

Mean age Gender	MMSE	Living conditions	Cognitive status/severity status mainly measure	Definion of dementia
81.5 (±5.7); 62.1 %F	16 (±3.0)	CD	-	NIA-AA 2011 criteria
76.2 (7.8); CDR 0.5=50%F 77.0 (7.4); CDR 1=67.2%F 79.7 (7.0); CDR 2=67.6 %F 80.5 (7.4); CDR 3=68.6%F	-	mix setting	CDR scale	NINCDS-ADRDA
79 (6); 51% F	19(±5)	CD	MMSE	NS
85.0 (3.2); 66.4% F 86.2 (3.6); 75%F	20.1 17.1	I	CDR scale	DSM-IV-TR
75.6 (7.8); 57%F	23.8 (2.5)	mix setting (I=1)	MMSE	NS
80.4 (6,8); 68.1% 80.0 (6.7); 69.0% 81.1 (6.8); 66.7%	18.7 (3.8) 21.1 (1.7) 14.3 (2.3)	CD	MMSE	NS
CD mild 78y; 51%F; moderate 78y; 54%F; severe 77y; 64%F; I mild 86y; 71%F moderate 84y;79%F severe 82y; 71%F	CD 24 16 5 I 24 14 3	mix setting	MMSE	NS
85.30 (3.75); 68.8%F 84.74 (3.21); 68.8%F	19.37 (5.36) 28.56 (1.19)	mix setting	CDR scale	DSM-IV
outpatients 76.7(±8.2) 63.2 F%; inpatient 83.7(±7.2) 78.9%F	outpatient 18.8 (8.3); inpatient 10.9 (8.4)	mix setting	MMSE	NINCDS-ADRDA
Age stratification based on demographic statistics	-	mix setting	-	Based on ICD-10 codes F000, F001, F002, F009, F010, F011, F012, F013, F018, F019, F020, F022, F023, F028, F03, G300, G301, G308, G309
77.4 (9.2), 59% F	16.70 (7.24)	mix setting	MMSE	NS
77±6; 68% F	18.06±5.35 (CDR :0–3. 1.14±0.91)	mix setting	CDR scale	DSM-IV/ NINCDS-ADRDA
Mild 76.8 (7.4) Moderate 80.6 (8.4) Severe 82.1 (7.7)	Mild 23.7 (2.6); Moderate 14.8 (2.6); Severe 5.5 (3.3)	mix setting	MMSE	NS
AD 75.0 (7.6) 55.3%F DLB 73.5 (8.0) 24%F	AD 22.1; DLB 20.05	CD	MMSE	NINDS-ADRDA
74.0±8.6; 65.2% F 70.6±10.4; 12.1% F 73.5±7.8; 37.9% F 77.9±8.0; 15.2% F	-	CD	MMSE	DSM-IV-TR
mild 74.3±8; 64%F moderate 74.5±7.7 severe 75.3±7.6; 50%F Institut.74.5±7.7; 80%F	mild 24.6±2.4; moderate 15.2±3.1; severe 3.0±3.5 26.1±2.1	mix setting (CD, I, healthy)	MMSE CDR scale	NINCDS-ADRDA
73.7 (8.9); 65.5% F	-	mix setting	ADL score	ICD-10 code (F00-F03, G30)
75.9; 62.7% F	19.2	CD	MMSE MMSE	NS

Dementia Rating Scale; SPMS, Short Portable Mental Status questionnaire; CD, community-dwelling patients; I, institutionalized patients; mix setting (community-dwelling and institutionalized patients); NINCDS–ADRDA, National Institute of Neurological and Communicative Disorders and Stroke- Alzheimer's Disease and Related Disorders Association criteria; DSM, Diagnostic and Statistical Manual of Mental Disorders III/IV edition; ICD, International Classification of Disease (X Revision); SS-IQCODE, Spanish Short-version of the Informant Questionnaire of Cognitive Decline in the Elderly; SPMSQ, Short Portable Mental Status Questionnaire.

TABLE 1

Primary characteristics of societal perspective included studies (continues from the previous page: 3 of 3)

Author	Ref.	Year	Country	Perspective	Study design	Disease	Population size
Lopez-Bastida et al.	63	2006	Spain	S	CSOS	AD	237 47 mild; 95 moderate; 95 severe
Zencir et al.	64	2005	Turkey	S	POS	AD	42 mild (18) moderate (7) severe (17)
Rigaud et al.	65	2003	France	S	CS-ROS	AD	50
Scuvee-Moreau et al.	66	2002	Belgium	S	POS	D	386 D patients 218 comunity/168 istitutionalized MMSE, mild: 83, moderate to mild: 108; moderate: 62; severe: 133 219 reference patients (106 without CD/ 113 with CD)
Wolstenholme et al.	67	2002	UK	S	ROS	D	100
Beeri et al.	68	2002	Israel	S	POS	AD	171 71 community dwelling 50 istitutionalized 50 healthy
Taylor et al.	69	2001	US	S	CS-ROS	ADRD	Severe (n 1,074) Moderate (n 322) None (n 3,438)

Abbreviations: S, Societal, CROT, Cluster randomized observational trial, PBEM, prevalence-based economic model, CSOS, cross-sectional observational study, POS, prospective observational study, ROS, retrospective observational study; RCT, randomized controlled trial; CS-ROS, cross-sectional retrospective observational study; CRT cluster-randomized trial; AD, Alzheimer' Disease; D, Dementia; ADRD, Alzheimer' Disease and related dementias; F, female; MMSE, mini-mental state examination; ADL score, Activities of Daily Living score; D FAST scale, Dementia Functional Assessment Staging scale; DS, dependency scale; CDR scale, Clinical

TABLE 2

Primary characteristics of healthcare payer's perspective included studies

Author	Ref.	Year	Country	Perspective	Study design	Disease	Population size
Deb et al.	70	2017	USA	HCP	ROS	AD	AD-ADRD (n=662) without ADRD (n=13,398)
Caravau et al.	71	2015	Portugal	HCP (NHS)	ROS	D	72 50% D patient/50% no-D patient
Jones et al.	72	2015	UK	HCP (NHS)	CSOS	AD	249
Chan et al.	73	2009	Taiwan	HCP	ROS	AD	69,780 68,000 outpatient care 1,780 inpatient care
Zhao et al.	74	2008	US	HCP	ROS	AD	AD 25,109
Fillit et al.	75	2002	US	HCP	ROS	AD	1366 AD patients 13,660 controls
Martin et al.	76	2000	Georgia	HCP	ROS	AD/D	8,671 AD/D cohort 26,013 controls

Abbreviations: HCP, healthcare payer (formal care and assistance provided by medicare or National healthcare systems); ROS, retrospective observational study; CSOS, cross-sectional observational study; AD, Alzheimer' Disease; D, Dementia; ADRD, Alzheimer' Disease and related dementias; F, female; MMSE, mini-mental state examination; CD, community-dwelling patients; I, institutionalized patients; mix setting (community-dwelling and institutionalized patients); BIMS, Brief

Mean age Gender	MMSE	Living conditions	Cognitive status/severity status mainly measure	Definion of dementia
75.5 (8.5); 70.9%F	-	CD	CDR scale	NS
70.5 (8.9); 61.95 F	13.9 (10.2)	mix setting (CD, I, healthy)	MMSE	NINCDS-ADRDA
F 80.9±6.3; 78% M 80.2±4.4	-	CD	MMSE	NINCDS-ADRDA, DSM-IV
65-74: 18.9%; 75-84: 43.2%; ≥85: 37.9% 71%F 65-74: 26.9%; 75-84: 59.4%; ≥85: 13.7% 52.5%F	-	mix setting	MMSE	DSM-III-R criteria
78 (7.0) 49% F	-	mix setting	MMSE	NS
76.4 (7.5); 56.3%F 81.5 (5.9); 72%F 72.1 (5.9); 88%F	12 (7.9) 4.7 (6.5) 24.6 (3.5)	mix setting (CD, I, healthy)	MMSE	NINCDS–ADRDA
Severe 81.4 Moderate 80.6 None 77.0	-	CD	SPMSQ ADL	SPMSQ

Dementia Rating Scale; SPMS, Short Portable Mental Status questionnaire; CD, community-dwelling patients; I, institutionalized patients; mix setting (community-dwelling and institutionalized patients); NINCDS–ADRDA, National Institute of Neurological and Communicative Disorders and Stroke- Alzheimer's Disease and Related Disorders Association criteria; DSM, Diagnostic and Statistical Manual of Mental Disorders III/IV edition; ICD, International Classification of Disease (X Revision); SS-IQCODE, Spanish Short-version of the Informant Questionnaire of Cognitive Decline in the Elderly; SPMSQ, Short Portable Mental Status Questionnaire.

Mean age/Gender	MMSE	Living conditions	Cognitive status/severity status mainly measure	Definion of dementia
65-75=15.4%; 75> 84.6%; 66.3% F	-	CD	NS	ICD-9-CM codes 290.XX, 291.XX, 294.XX or 331. XX
65–74=2.8%, 75-84=50%, >84=47.2; 83.3% F 65–74=19.4%, 75-84=41.7%, >84=38.9; 47.2% F	-	I	BIMS	BIMS
79.7 (8.5); 54% F	14.6 (6.8)	Mix set	DS, range 0–15; CRD scale, mild, moderate, severe;	NINCDS-ADRDA
14.57% ≥0-80 years	-	Mix set	-	(ICD-9-CM) diagnosis code 331.0
80.1 (6.5); 61.6% F	-	CD	-	ICD-9-CM code 331.0
79.8; 59.6%F 79.5; 59.5%F	-	CD	-	(ICD-9) diagnosis of AD (331.0)
79.96 (9.62); 76.6%F 79.92 (9.61); 76.6%F	-	Mix sett	-	ICD-9-CM diagnosis code indicating AD

Interview for Mental Status; DS, dependency scale; CRD scale, CDR scale, Clinical Dementia Rating Scale; NINCDS–ADRDA, National Institute of Neurological and Communicative Disorders and Stroke- Alzheimer's Disease and Related Disorders Association criteria; ICD, International Classification of Disease.

TABLE 3
Main cost results from societal perspective included studies (continues on the next page: 1 of 4)

Study	Ref.	Cost items Summary	Currency/cost per year/month	
Yan et al. 2019	27	**Total cost**	US $	year
Wittenberg et al. 2019	28	**Total cost**	£	year
Sado et al. 2018	29	**Total cost** healthcare cost social cost Informal cost	JPY	year
Ferretti et al. 2018	30	**Total cost** Direct Costs Indirect cost	US $	month
Michalowsky et al. 2018				
Payer's perspective	31	**Total cost** Medical treatment Formal care	€	year
Societal perspective		**Total cost** Informal care	€	year
Bruno et al. 2018	32	**Total cost** health care cost social care cost informal care cost	€	month
Olazaràn et al. 2017	33	**Total cost** healthcare social care caregiver healthcare caregiver informal care	€	month
Reed et al. 2017	34	**Total cost** France Germany UK	€	18 month
Hojman et al. 2017	35	**Total cost** Direct Medical Cost Direct Social cost Indirect	$	year
Holmerova´ et al. 2017	36	**Total cost** Direct cost Indirect Cost	€	month
Farre et al. 2016	37	**Total cost**	€	month
Kandiah et al. 2016 (AD population)	38	**Total cost** Direct medical Direct non-medical Indirect Productivity loss Informal care	(SGD)	year

Main cost results

Cost per patient in general population or in subgrous (severity stage, comorbid conditions, living condition)

	mild	*moderate*	*severe*		
per patient general popul. US $ 19,144	13,597±14,275	16,789±36,469	26,001±49792		
	Comorbidities 1	2	3	4	≥5
	17,972±53837	18,231±20,557	22,690±29,668	27,918±35,791	38,348±48,296

mild	*moderate*	*severe*
24,400	27,450	46,050

JPY 5,954
784
2,643
3,822

per patient general popul.	*mild*	*moderate*	*severe*
1,405.72	1,023.71	1724.01	1,393.79
61.21	53.14	62.96	78.47
843.63	577.87	1123.68	628.75

per patient general popul.	*mild*	*moderate/severe*
7016 € (7989)	5485 € (6487)	4487 € (5121)
5456 € (6692)	5485 € (6487)	4487 € (5121)
1559 € (3696)	1452 € (3582)	2544 € (4817)
25,877 € (22,056)	25,495 € (20,801)	29,665 € (24,473)
18,327 € (18,764)	18,223 € (17,208)	22,213 € (21,865)

mild	*moderate*	*moderately severe/severe*
1850 (1901)	1552 (1322)	2728 (2184)
210,00	130,00	106,00
270,00	199,00	399,00
1.370,00	1.223,00	2.223,00

per patient general popul.	*mild*	*moderate*	*ms/severe*
€ 2190 (1996; 2386)	1514 (1187; 1868)	2082 (1801; 2390)	2818 (2489; 3160)
289 (237; 357)	272 (181; 408)	236 (199; 284)	346 (246; 491)
589 (503; 680)	192 (115; 276)	608 (458; 774)	892 (731; 1055)
95 (62; 156)	68 (49; 92)	151 (59; 344)	72 (51; 98)
1312 (1165; 1456)	1050 (778; 1355)	1239 (1018; 1471)	1580 (1354; 1828)

per patient general popul.	*mild*	*moderate*	*severe*
33,339	23,883	33,800	41,905
38,197	26,017	42,430	50,947
37,899	30,161	36,038	50,795

per patient general popul.
17,559
3,442
914,000
13,194

per patient general popul.	*mild*	*moderate*	*severe*
€ 1948.8 (1506.2)	1241.2 (1437.3)	2104.5 (1213.6)	2512.1 (1785.3)
230.1 (170.8)	192.2 (140.5)	207.7 (184.1)	272.9 (164.7)
1711.8 (1331.4	951.0 (1332.7)	1872.5 (1141.2)	2155.6 (1827.0)

	mild	*moderate*	*severe*
All population € 1956.2 (SD 1463.9) € 23,121 (per year)	€ 1485.7	€ 1757.9	€ 2315.6
	Comorbidities 1	2	>2
	€ 1752.3	€ 2149.2	€ 2273.5

YOD (54)	*LOD (133)*
20,629 (6,059–37,666)	11,495 (2,607–35,272)
2,020 (1,726–2,253)	2,048 (1,496–2,497)
67 (23–636)	475 (40–7,040)
16,591 (3,827–33,600)	4,378 (0–23,237)
15,000 (3,600–31,190)	2,280 (0–18,524)
0 (0–245)	0 (0–318)

TABLE 3
Main cost results from societal perspective included studies (continues on the next page: 2 of 4)

Study	Ref.	Cost items Summary	Currency/cost per year/month	
Ku et al. 2016	39	**Total cost** Medical costs Social care costs Informal care costs (Opportunity cost)	NT $	year
Lenox-Smith et al. 2016	40	**Total cost** Healthcare cost Social care costs Informal care costs	£	18 month
Frahm-Falkenberg et al. 2016	41	**Total cost before diagnosis D** direct indirect cost **Total cost after diagnosis D** direct indirect cost	€	year
Åkerborg et al. 2016	42	**Total cost (per age)** D patient No-D patient **Total cost (per DS)** D patient No-D patient	€	year
Wimo et al. 2016	43	**Total cost**	SEK	year
Custodio et al. 2015	44	**Total cost** healthcare costs non-healthcare costs	$	3 month
Chiatti et al. 2015	45	**Total cost** health care cost patient cost subtracting the allowance informal care cost	€	year
Darbà et al. 2015	46	**Total cost** Direct medical costs Social care costs Indirect costs Informal care costs	€	6 month
Gerves et al. 2014	47	**Total cost** good proxy method opportunity cost method *formal* *formal non-medical* *informal* good proxy method opportunity cost method	€	month
Konig et al. 2014	48	**Total cost** Medical care Formal Nursing care Other Informal care	€	year
Vossius et al. 2014	49	**Total formal care** Increase in costs (%) Mean costs for institutional care (%)	€	month

Main cost results

Cost per patient in general population or in subgrous (severity stage, comorbid conditions, living condition)

mild	*moderate*	*severe*		
218,644 (199,843)	308,947 (210,289)	439,972 (250,254)		
85,689 (87,485)	81,782 (88,523)	76,047 (75,240)		
41,331 (93,568)	117,031 (146,962)	173,079 (148,024)		
91,623 (140,151)	110,134 (131,133)	190,846 (202,290)		
mild	*moderate*	*moderately severe/severe*		
25,865 (23,444–£28,538)	30,905 (28,539–£33,371)	43,560 (39,059–48,481)		
2890	3130	3055		17243,333
7172	11351	15521		20603,333
15678	17007	24672		29040
Patient	*Control*	*Net cost dementia patient*		
4630				
3205	2548			
1425	2548	2082		
8595	4051	4544		
7035	4051			
1560				
79-83	84-87	88+		
56,904	57,362	57,362		
13,000	11,000	33,000	3rd	4th
per patient general popul.	1st DS	2nd	33,671 (31,868)	72,571 (21,032)
43,259 (35,030)	9,140 (10,992)	16,979 (23,406)		
17,18				
SEK 398,226				
ND	*AD*	*FTD*	*VD*	
394 [372-607]	1878 [715-4896]	2252 [1397-4705]	1727 [644-4188]	
393	1167 [703-3487]	1544 [849-3296]	908 [471-3126]	
0 [0-198]	666 [0-1508]	667 [0-1409]	667 [0-1409]	
€ 20,128				
€ 4,534				
€ 2,004				
€ 13,590				
per patient general popul	*CDR score 0.5*	*CDR score 1*	*CDR score 2*	*CDR score 3*
32,177.3 (31,836.9)	12,009.5 (15,708.5)	15,738.2 (18,054.9)	34,590.7 (31,695.6)	52,477.4 (34,321.5)
1,028.1 (1,655.0)	770.6 (735.8)	906.3 (1,334.2)	903.2 (1,119.9)	1,348.8 (2,381.8)
843.8 (2,684.8)	1,282.1 (4,061.9)	193.2 (1,211.9)	1,095.2 (3,192.0)	1,210.5 (2,915.3)
464.2 (1,639.0)	719.2 (2,801.3)	219.7 (657.9)	565.2 (1,823.4)	613.0 (1,949.1)
33,232.2 (30,898.9)	10,392.3 (16,055.1)	16,560.4 (17,852.9)	35,898.5 (30,479.8	52,900,3 (32,045.2)
Mild	*Moderate/severe*			
1454.20	3373.29			
1823.9	4288.32			
409.73	622.43			
105.37	343.90			
939.11	2406.96			
1308.8	3321.99			
community dwelling	*living nursing home*			
29,930 (30,492)	33,482 (10,129)			
6001 (8735)	9580 (10,369)			
7947 (16,650)	21,625 (5568)			
179 (1229)	434 (1600)			
15,803 (23,374)	1843 (3474)			
Baseline	*1y*	*2y*	*3y*	*total*
535 (281-799)	1,409 (971-1,874)	2,353 (1,811-2,919)	3,611 (3,022-4,212)	2,420 (1,944-2,923
-	874 (163)	944 (67)	1,258 (53)	-
10.6	43.8	74.2	87.2	74.1

TABLE 3
Main cost results from societal perspective included studies (continues on the next page: 3 of 4)

Study	Ref.	Cost items Summary	Currency/cost per year/month	
Schwarzkopf et al. 2011	50	**Total annual** health care cost informal care cost	€	year
Gustavsson et al. 2011	51	**Total cost** Spain Sweden UK US	€	month
Leitch et al. 2011	52	**Total cost** Medical care Formal Nursing care Informal care	€	year
Reese et al. 2011	53	**Total cost** Direct cost Indirect cost	€	3 month
Kraft et al. 2010	54	**Total cost** Direct Costs Indirect cost	CHF	year
Ersek et al. 2010	55	**Total cost** Direct costs Indirect costs Informal care	€	month
Coduras et al. 2010	56	**Total costs** Paid by patients/their family Financed by public health system	€	month
Mesterton et al. 2010	57	**Total cost** medical costs community care costs informal care costs	US $	year
Zhu et al. 2009	58	**Total cost** Direct medical Cost Direct Non-medical Cost Indirect cost	$	year
Wang et al. 2008	59	**Total costs** Direct medical costs Direct non-medical costs Indirect costs	RMB	year
Allegri et al. 2007	60	**Total costs** direct costs indirect costs	$	year
Kang et al. 2007	61	**Total costs** Direct cost Direct medical Direct non-medical costs Indirect costs	$	year

Main cost results

Cost per patient in general population or in subgrous (severity stage, comorbid conditions, living condition)

per patient general popul	*mild*	*moderate*		
€ 47,571	€ 39,967	€ 62,797		
€ 9,396	€ 9,183	€ 10,496		
€ 38,165	€ 30,803	€ 52,335		
	Community dwelling		*Residential care*	
mild	*moderete*	*severe*	*moderete*	*severe*
1002 (840–1211)	1213 (1091–1350)	1531 (1335–1788)	3942 (3774–4136)	3855 (3728–4067)
1040 (840–1346)	1307 (1094–1583)	1752 (1371–2352)	3716 (3517–4423)	3678 (3498–4186)
834 (697–985)	1193 (1051–1401)	1452 (1264–1803)	2455 (2214–2898)	2236 (2099–2378)
1204 (1020–1609)	1421 (1266–1593)	1837 (1650–2042)	5041 (4656–5826)	5114 (4858–5506)
mild D (121)	*moderate D (32)*	*severe D (23)*	*per patient general popul*	*Control*
24 437 (23 020)	41 125 (28 798)	49 784 (28 028)	30 783 (26 531)	8267 (14 377)
6171 (9013)	7581 (8679)	10 375 (11 185)	6977 (9317)	4828 (7508)
9167 (14 854)	15 193 (15 474)	19 117 (17 740)	11 562 (15 722)	1806 (7269)
8886 (15 133)	18 228 (27 873)	19 684 (31 199)	11 996 (20 943)	1625 (5482)
Home living patients	*Institutionalized patients*	*Per patient general popul*	3,300	
1,864	6,389	MCI	1,200	
1,137	6,122	mild (MMSE 26–30)	1,485	
727	267	severe (MMSE 0–14)	4,800	
Istitutionalized		*community-dwelling*		
moderate to severe	*mild*	*moderate*	*severe*	
68.891	26.186	67.743	122.023	
68.891	2.653	13.323	13.183	
-	23.533	54.420	108.840	
per patient general popul.	*MCI (14)*	*Mild (24)*	*Moderate (22)*	*Severe (14)*
535.71 (735.65)	357.98 (336.30)	355.23 (302.94)	623.60 (997.66)	884.72 (957.71)
282.78 (568.04)	163.70 (260.85)	176.68 (136.28)	420.25 (919.66)	367.72 (518.60)
49.96 (292.24)	5.42 (15.45)	1.22 (3.44)	46.99 (128.16)	182.71 (653.66)
202.97 (286.19)	188.86 (3 00.14)	177.33 (228.80)	156.36 (280.86)	334.29 (355.13)
€ 1,425.73 (1415.81)				
€ 1,244.22 (1,335.6)				
€ 181.51 (268.3)				
Per patient general pop.(233)	*mild (91)*	*moderete (91)*	*severe (51)*	
46,956 (42,337 – 51,929)	23,424 (18,016 – 31,190)	56,783 (47,834 – 64,683)	71,409 (62,483 – 77,913)	
3,155 (2,615 – 3,759)	3,402 (2,656 – 4,503)	2,811 (2,110 – 4,241)	3,328 (2,411 – 5,063)	
39,373 (34,358 – 44,135)	16,919 (11,526 – 24,647)	48,101 (39,339 – 56,276)	63,864 (53,914 – 71,594)	
4,428 (3,284 – 6,700)	3,104 (2,151 – 5,329)	5,871 (3,495 – 11,174)	4,218 (2,318 – 6,843)	
AD	*DLB*			
25,129	35,143			
8,027	12,081			
1,478	947			
17,136	23,036			
Per patient/general pop.	*mild*	*moderate*	*severe*	
19,001±11,037	12,816±4,843	17,507±10,922	27,480±10,365	
5,640±4,944	5,333±4,650	5,510±5,311	6,191±4,524	
2,792±2,199	2,829±3,471	2,667±1,750	3,050±1,965	
10,568±8,209	4,653±2,672	9,329±7,281	18,238±7,891	
healthy	*AD community-dwelling*	*AD institutionalized*	*mild*	*moderate*
1684.1	8129.7	14863.6	5281.6	6633.3
1684.1	3189.2	14 447.6	3420.4	4583.2
	4940.5	416.0	1860.2	2050.1
Per patient/general pop.	*ADL low*	*ADL moderate*	*ADL high*	
$ 7,462	$ 3,698	$ 6,064	$ 11,428	
$ 6,626 (88.8%)	$ 3,182 (86.0%)	$ 5,084 (83.8%)	$ 10,458 (91.5%)	
$ 4,296	$ 2,105	$ 3,259	$ 6,779	
$ 1,817	$ 960,000	$ 1,234	$ 2,924	
$ 836 (11.2%)	$ 516 (14.0%)	$ 980 (16.2%)	$ 970 (8.5%)	

TABLE 3
Main cost results from societal perspective included studies (continues from the previous page: 4 of 4)

Study	Ref.	Cost items Summary	Currency/cost per year/month	
Jönsson et al. 2006	62	**Total cost**	SEK	year
Lopez-Bastida et al. 2006	63	**Total cost** Direct health care costs Direct non–health care Indirect	€	year
Zencir et al. 2005	64	**Total costs** Caregiver cost Medication cost Outpatient physician cost	$	year
Rigaud et al. 2003	64	**Total costs** medical consumption paid assistence (formal) unpaid assistence (informal)	€	month
Scuvee-Moreau et al. 2002	66	**Total cost** health care cost (direct) cost per patient/family (indirect)	€	month
		Total cost health care cost (direct) cost per patient/family (indirect)	€	month
Wolstenholme et al. 2002	67		£	year
Beeri et al. 2002	68	**Total costs** direct costs indirect costs	$	year
Tayor et al. 2001	69	**Total cost**	$	year

tal perspective included studies resulted € 25,967 (SD € 15,722). Focusing on annual costs disease severity related, we observed a mean annual total cost around € 16,268 (SD € 10,011), € 26,201 (SD € 19,109) and € 36,618 (SD € 27,711) for mild, moderate and severe stage respectively, highlighting a cost per severe disease status more than twice as compared with mild status. Regarding care setting, we identified a mean annual cost of about € 27,698 (SD € 21,937) for community-dwelling patient, while mean total cost for institutionalized were € 37,944 (SD € 19,139). Mean annual cost for overall population according to the 7 healthcare payer's perspective studies were € 19,925 (SD € 17,376), while the few cost data on stratification into subgroups did not make possible a synthesis for these. Table 7 and Figure 2 summarize the results mentioned.

DISCUSSION AND CONCLUSION

The results of our systematic review allow to confirm the great economic burden related to dementia. Many studies have been published on the dementia and related cost over the years, however there still seem to be little awareness about the importance of managing disease in the best way to slow disease progression toward more serious stages, to alleviate patients, caregivers and healthcare systems. With the aim to gather

Main cost results

Cost per patient in general population or in subgrous (severity stage, comorbid conditions, living condition)

Per patient/general pop.	*very mild*	*mild*	*moderate*	*moderately severe*	*severe*
172 121	60 730	93 959	184 081	226 876	374 962

Per patient/general pop.	*mild*	*moderate*	*severe*
28,198	14,956	25,562	41,669
3,668	2,821	3,597	4,161
23,902	11,596	21,354	36,753
628	539	611	755

Mild	*Moderate*	*Severe*
1,766 (1,300–2,231)	3,842 (1,960–5,723)	4,930 (3,714–6,147)
145 (31–259)	1,468 (10–2,925)	2,480 (1,380–3,580)
1,587 (1,130–2,043)	2,315 (1,290–3,341)	2,373 (1,683–3,062)
33 (6–73)	59 (4–171)	18 (3–32)

mild	*moderate*	*moderate-severe*	*severe*
525.2	992.1	1,652.6	4438.4
296.4	375.6	432.3	522.9
52.6	141.8	280.6	900.5
176.2	52.6	939.7	3015.0

AD (community-dwelling 218)

per patient/all CD	*mild*	*moderate/mild*	*moderate*	*severe*
445,56	464,31	410,53	381,24	556,88
263,03	288.19	251,23	211,68	288,1
182,53	176.12	159,3	169,56	268,78

per patient/all I	*mild*	*moderate/mild*	*moderate*	*severe*
2301,72	1555,41	2185,62	2101,32	2465,28
1068,55	329,13	853,94	870,6	1258,06
1233,17	1226,28	1331,68	1230,72	1207,22

mild	*mild to moderate*	*moderate*	*severe*
8312 (SD 5602)	11 643 (SD 7808)	15 681 (SD 9509)	22 267 (SD 14 507)

AD community-dwelling	*AD institutionalized*
17,73	16,995
7,03	14,51
10,7	2,485

Severe ADRD (1074)	*Moderate ADRD (322)*	*No ADRD (3438)*
18,016	10,364	6,490

the available evidence on dementia cost of illness and identify the main drivers of cost, we conducted a systematic review. Our analysis focused on impact on costs of disease severity condition and type of care setting. 50 studies were included in this review, 43 conducted from societal perspective and 7 from healthcare payer's perspective. The main outcome of the study was the definition of the value of the annual mean cost of illness related to dementia, determined by the addition of cost items considered in each study in according with the perspective adopted. The main cost items considered were direct (divided in medical and non-medical cost), indirect and informal costs. All studies reported informal costs to be the main cost driver, followed by direct costs in majority of the studies. Moreover, all the studies indicated increasing costs by disease severity and cost per institutionalized dementia patient resulted higher than community-dwelling patient. Findings from HCP perspective have indicated an average annual total cost per patient of € 25,967 (SD € 15,722) considering the overall population with dementia. Mean annual total cost per patient for mild dementia resulted € 16,268 (SD € 10,011). This annual cost increased to € 26,201 (SD € 19,109) for moderate stage and resulted more than twice for severe dementia, reaching an annual total cost of € 36,618 (SD € 27,711). Regarding care setting,

TABLE 4
Main cost results from healthcare perspective included studies

Study	Ref.	Cost items Summary	Currency/ cost per year/month		Main results Cost per patient in general population or in subgrous (severity stage, comorbid conditions, living condition)				
Deb et al. 2017	70	**Total healthcare cost**	$	year	*ADRD*			*Not-ADRD*	
					14,508 (14,368–14,650)			$ 10,096 (9,999–10,195)	
Caravau et al. 2015	71	**Total direct cost**	€	year	*D patient*			*Not-D patient*	
					15,287			12,289	
Jones et al. 2015	72	**Total direct cost** Direct medical Direct nonmedical costs	£	3 month	*All population*	*DS scale* *0-6*	*7- 8*	*9- 10*	*11- 15*
					4018 1094 2924	2,161 1,050 1,111	1615 946 669	906,101 903 3,101	9,068 1,459 7,609
Chan et al. 2009	73	**Total direct cost**	$	year	*Year 1*	*year 2*		*year 3*	
					1418	3793		5005	
Zhao et al. 2008	74	**Total healthcare cost**	$	year	*AD*			*Control*	
					13,936			10,369	
Fillit et al. 2002	75	**Total direct cost**	$	year	*AD*			*Control*	
		Base case Comorbidities Earlier-stage AD Comorbidities			**9,737** 10,731-20,628 **7,152** 8,506-15,308			5,932 6,927-15,376 4,961 5,651- 14,147	
Martin et al. 2000	76	**Total healthcare cost**	$	year	*AD/D*			*Control*	
					15,346 (8,790)			6,049 (8,216)	

we have identified a mean annual total cost of about € 27,698 (SD € 21,937) for community-dwelling patient and € 37,944 (SD € 19,139) for institutionalized patient. The 7 healthcare payer's perspective studies included reported a mean annual direct cost per patient of € 19,925 (SD € 17,376) in the overall dementia population. The results of the present review were consistent with previously published data.[12,15,80,81] As in previous studies a correlation between severity disease and cost was shown. An element to be considered is the adoption of different methods for disease severity stratification, although most of studies used MMSE or CDR scale. Moreover, even when using the same tools, different cut-off points were adopted in the various studies making comparison more difficult. Therefore, we recommend that in future studies a standardized multidimensional disease severity measure should be adopted, maybe following a consensus process.

Further aspects of interest influencing cost are comorbidities and age, that were considered in a limited number of included studies. Previously, systematic and not systematic review were developed on dementia, the strength of this systematic revision is the inclusion of the most recent evidence in addition to yet reviewed studies, offering an update and search space including studies from 27 countries, and the identification of important cost drivers. Moreover, we considered the importance of -alternative treatments, such as nutraceuticals products, to delay severity disease progression. Regarding limitations of this review, methodological and clinical heterogeneity between studies made a narrative synthesis necessary. Moreover, sample size of the different populations considered didn't allowed pooled metanalysis. The choice to adopt a worldwide overview, including studies with different degrees of health and economic development and different income, can certainly be considered a limit for comparison. However, we thought it important to offer as broad a scenario as possible of the cost of the disease based on the data available to date. The average annual cost of disease was calculated based on of the data provided by each study without weighing the data based on the quality of the study or the population size, this constitutes a

TABLE 5

Mean annual total cost results: overall population and subgroups analysis

					Overall population	Subgroups analysis				
Study	Year	Ref.	Stratification by severity	Stratification by living condition	Annual cost/ patient	Annual cost per mild patient	Annual cost per moderate patient	Annual cost per severe patient	Annual cost per community patient	Annual cost per istitutionalized patient
Yan et al.	2019	27	x		€ 17.629	€ 12.521	€ 15.460	€ 23.944		
Wittenberg et al.	2019	28	x		€ 36.581	€ 27.352	€ 30.771	€ 51.621		
Sado et al.	2018	29			€ 42.503					
Ferretti et al.	2018	30	x		€ 15.580	€ 11.349	€ 19.107	€ 15.449		
Michalowsky et al.	2028	31	x		€ 26.524	€ 26.132	€ 30.407			
Bruno et al.	2028	32	x		€ 25.945	€ 22.577	€ 18.941	€ 33.293		
Olazaràn et al.	2017	33	x		€ 35.863	€ 18.659	€ 25.659	€ 34.729		
Reed et al.	2017	34	x		€ 26.986	€ 19.740	€ 27.753	€ 35.530		
Hojman et al.	2017	35			€ 17.605					
Holmerova´ et al.	2017	36	x		€ 23.970	€ 15.264	€ 25.879	€ 30.898		
Farre et al.	2016	37	x		€ 22.891	€ 17.651	€ 20.885	€ 27.511		
Kandiah et al.	2016	38			€ 9.932					
Ku et al.	2016	39	x		€ 8.693	€ 6.491	€ 9.172	€ 13.062		
Lenox-Smith et al.	2016	40			€ 26.037	€ 20.781	€ 24.831	€ 34.999		
Frahm-Falkenberg et al.	2016	41			€ 9.214					
Åkerborg et al.	2016	42			€ 46.374					
Wimo et al.	2016	43			€ 47.768					
Custodio et al.	2015	44			€ 6.931					
Chiatti et al.	2015	45			€ 20.933					
Darba et al.	2015	46			€ 66.093					
Gerves et al.	2014	47	x		€ 41.008	€ 24.121	€ 56.705	€ 56.705		
Konig et al.	2014	48		x	€ 34.607				€ 33.522	€ 37.500
Vossius et al.	2014	49			€ 32.002					
Schwarzkopf et al.	2011	50	x		€ 53.280	€ 44.763	€ 70.333			
Gustavsson et al.	2011	51	x	x	€ 17.652	€ 14.103	€ 17.882	€ 22.437	€ 55.152	€ 52.185
Leitch et al.	2011	52	x		€ 34.477	€ 27.369	€ 46.060	€ 55.758		
Reese et al.	2011	53		x	€ 14.597				€ 8.321	€ 28.520
Kraft et al.	2010	54	x	x	€ 64.299	€ 27.598	€ 71.396	€ 128.603	€ 58.283	€ 72.606
Ersek et al.	2010	55			€ 7.199	€ 4.771	€ 8.387	€ 11.894		
Coduras et al.	2010	56			€ 20.206					
Mesterton et al.	2010	57	x		€ 49.062	€ 24.475	€ 59.330	€ 74.612		
Zhu et al.	2009	58			€ 27.656					
Wang et al.	2008	59			€ 2.928	€ 1.975	€ 2.698	€ 4.235		
Allegri et al.	2007	60		x	€ 8.237	€ 6.216	€ 7.806	€ 13.231	€ 9.568	€ 17.494
Kang et al.	2007	61			€ 8.212	€ 4.070	€ 6.674	€ 12.577		
Jönsson et al.	2006	62	x		€ 20.179	€ 11.015	€ 21.581	€ 43.960		
Lopez-Bastida et al.	2006	63	x		€ 36.939	€ 19.592	€ 33.486	€ 54.586		
Zencir et al.	2005	64			€ 3.816	€ 1.986	€ 4.322	€ 5.545		
Rigaud et al.	2003	65			€ 33.068	€ 9.129	€ 17.249	€ 77.168		
Scuvee-Moreau et al.	2002	66		x	€ 19.843				€ 7.011	€ 36.187
Wolstenholme et al.	2002	67	x		€ 20.738	€ 11.908	€ 22.466	€ 31.901		
Beeri et al.	2002	68		x	€ 21.573				€ 22.030	€ 21.116
Tayor et al.	2001	69			€ 10.956	€ 7.638	€ 12.198	€ 21.203		

TABLE 6
Mean annual total direct cost results: overall population

Study	Year	Ref.	Annual direct cost/patient
Deb et al.	2017	70	€ 14.364
Caravau et al.	2015	71	€ 16.388
Jones et al.	2015	72	€ 58.110
Chan et et al.	2009	73	€ 5.248
Zhao et al.	2008	74	€ 15.337
Fillit et al.	2002	75	€ 11.460
Martin et al.	2000	76	€ 18.571

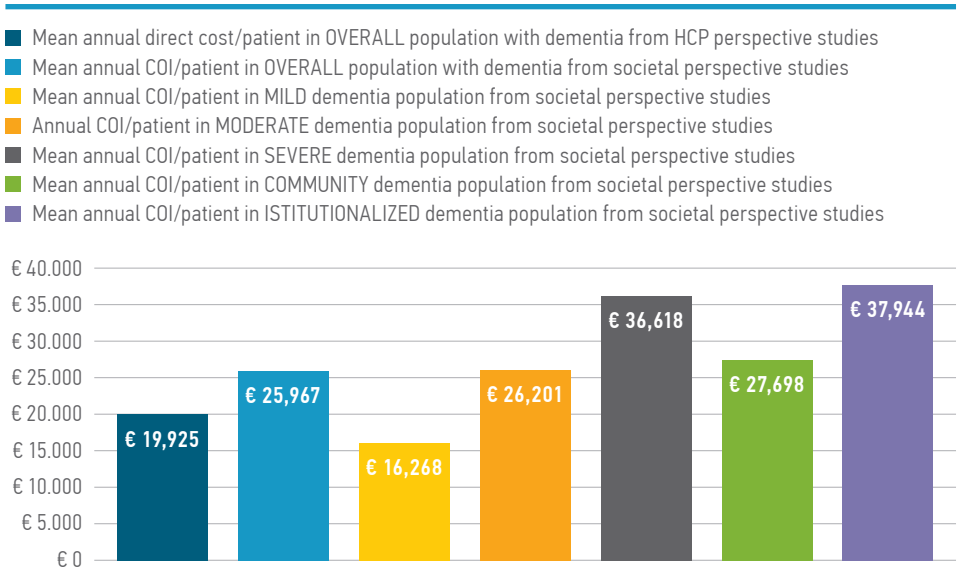
questionable element. Moreover, among limitations it is to be noted that incidence-based studied reporting lifetime costs were excluded, such as studies analyzing primarily cost of disease and informal care focusing on caregivers, in addition all articles not published in English or prior 2000 were excluded, for a comprehensive understanding of cost of illness in dementia, also the results of those studies may provide useful insights. Further limitations stay in study design of included studies that are mainly observational trials presenting potential risk of selection bias in the patients included. The variation of cost estimates for different care settings highlight the need to understand and address the financial burden of dementia from both perspectives. Based on research conducted to carry out this review, we believe it is necessary that future cost-of-illness studies in dementia should follow a quality standard protocol with clearly defined and transparent cost components and separate estimates by care setting and disease severity, given the role of these aspects as cost drivers. Treatment that are effective early in the disease or that can have a preventive effect can postpone the progression of dementia and can offer multiple benefits to families, caregivers and society.[15,82] However, as soon as new effective drugs will be developed and become available on the market, costs for medication are likely to increase even more, especially because there is a trend toward the development of expensive biologicals.[83] The cost scenario shown makes it clear how it is important to get cure for these diseases. Moreover, the availability of more effective treatments could reduce direct non-medical and informal costs of care. In this context, health economic analysis or simulation studies can be supportive and offer tools to evaluate alternative treatments. Although there are few data in the literature that can support the role of nutraceutical product in preventing and slowing down cognitive decline, there is evidence that deserves attention and leaves open fields of analysis. LipiDiDiet research is part of this evidence, it is the first completed long-term randomized controlled trial focusing on prodromal Alzheimer's disease.[19] Given the hypothesis that earlier intervention might be more beneficial, the LipiDiDiet trial was designed to investigate the effects of a multinutrient combination on cognition and related measures in prodromal Alzheimer's disease. [19] The active component adopted in LipiDiDiet research was a multinutrient combination which contains docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), uridine monophosphate, choline, vitamins B12, B6, C, E, folic acid, phospholipids, and selenium. These nutrients were selected based on their estab-

TABLE 7
Mean annual cost per patient in overall population with dementia and subgroups

Study perspective	Mean annual cost/patient in OVERALL population with dementia	Mean annual cost/patient in MILD dementia population	Mean annual cost/patient in MODERATE dementia population	Mean annual cost/patient in SEVERE dementia population	Mean annual cost/patient in COMMUNITY dementia population	Mean annual cost/patient in ISTITUTIONALIZED dementia population
HCP perspective (direct costs)	€ 19,925 (SD €17,376)					
Societal perspective (total COI)	€ 25,967 (SD €15,722)	€ 16,268 (SD €10,011)	€ 26,201 (SD €19,109)	€ 36,618 (SD €27,711)	€ 27,698 (SD €21,937)	€ 37,944 (SD €19,139)

Abbreviations: HCP, healthcare payer's perspective; COI, cost of illness

FIGURE 2
Summary of mean annual costs per patient emerging from the included studies



Abbreviations: HCP, healthcare payer's perspective; COI, cost of illness.

lished biological and neuroprotective properties, and specifically combined to enhance efficacy compared with individual nutrients. Benefit was observed in relevant secondary cognitive-functional and hippocampus atrophy outcome measures, but not in the primary neuropsychological test battery. The hippocampus is affected early in Alzheimer's disease, and the rate of hippocampal atrophy over time is considered a reliable measure of Alzheimer's disease progression.[84] Findings of this study support the hypothesis that intervening early in the disease continuum might achieve benefits more readily than late intervention, and nutraceutical products can play a role in this mission. In fact, the study exposes interesting considerations: the potential impact on disease progression, combined with the feasibility aspects including the observed high long-term compliance, moderate costs of the intervention, the potentially relative ease of implementation in clinical practice, as well as the clear need for treatment, warrant further research on nutraceutical interventions in early Alzheimer's disease.[19] Based on these premises we have developed a simple calculation to evaluate how a slowdown in the transition from one stage of disease to another more severe could have benefit on cost. We calculated that a 10% slowdown in the transition from mild to moderate disease severity could offer saving of about € 993 that rise to € 1,987 if we assume a 20% slowdown. The savings are greater if we consider a slowdown in the transition from moderate to severe disease condition: in this case a 10% slowdown could allow a reduction in total cost of about € 1,042 that increase to € 2,083 for a 20% slowdown. This is our assumption aimed at testing the possible effects of the slowing down of the disease progression on costs. The percentages adopted are mere calculation hypotheses, which can be varied in the model based on any future evidence. Recent analyses, therefore, have shown potential role of nutraceutical products for the prevention of AD or as adjuvants in other treatments, tending to delay cognitive decline.[16,19] In light of this evidence and previous considerations on burden of dementia, nutraceuticals products could have increasingly importance given the absence of effective treatments, their relatively low cost and good tolerance profile. The world of "neuro-nutraceutics" offers good research ideas today and, in the next future, it could open interesting windows on effective and safe treatments, even in patients with diagnosed dementia. Many food-borne substances have shown to be potentially useful in the prevention and treatment of cognitive decline in pre-clinical studies. However, further studies are necessary to confirm their beneficial effect in humans and the potential cost savings generated by their

use. In the near future, "nutraeconomy" is destined to become an essential programming tool in the field of healthcare and of the sustainability of costs related to maintaining wellbeing and to prevention. It goes side by side with a possible, if correctly suggested, reduction in the consumption of drugs associated with the chronic treatment of many diseases.[85] Undoubtedly, if use, "clinical" experience, the quality of nutraceuticals, the level of research and scientific information will go hand in hand, "nutraeconomic" evaluations will be increasingly necessary in the future; these analyses will be useful to analyze the impact in terms of cost-benefit, risk-benefit ratio, quality of life (QoL) and possible savings for NHS, depending on what has been obtained in the prevention or support treatment, where possible.[86] Defining criteria and endpoints for nutraeconomy and for nutraeconomic studies would allow to better assess the economic impact of nutraceutical products on health policies and organizational models relating the healthcare as a whole. This would be an important element to better recognize, define and make the most of the "role of nutraceutical products". Considering the high burden of dementias, confirmed with our review, and of the progressive aging of population, destined to worsen current dementia epidemiologic data, the need to search for new treatment strategies is clear. If more attention is needed for the identification of patients in the early diagnosis, as for the treatments, in addition to conventional drug-therapy, early-stage treatment with a preventive effect, such as nutraceutics, effective non-medical support interventions for dementia patients and informal caregivers have to be considered.

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