Considering the societal perspective in economic evaluations: a systematic review in the case of depression

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Abstract

Background: Depressive disorders are associated with a high burden of disease. However, due to the burden posed by the disease on not only the sufferers, but also on their relatives, there is an ongoing debate about which costs to include and, hence, which perspective should be applied. Therefore, the aim of this paper was to examine whether the change between healthcare payer and societal perspective leads to different conclusions of cost-utility analyses in the case of depression.

Methods: A systematic literature search was conducted to identify economic evaluations of interventions in depression, launched on Medline and the Cost-Effectiveness Registry of the Tufts University using a ten-year time horizon (2008–2018). In a two-stepped screening process, cost-utility studies were selected by means of specified inclusion and exclusion criteria. Subsequently, relevant findings was extracted and, if not fully stated, calculated by the authors of this work.

Results: Overall, 53 articles with 92 complete economic evaluations, reporting costs from healthcare payer/provider and societal perspective, were identified. More precisely, 22 estimations (24%) changed their results regarding the cost-effectiveness quadrant when the societal perspective was included. Furthermore, 5% of the ICURs resulted in cost-effectiveness regarding the chosen threshold (2% of them became dominant) when societal costs were included. However, another four estimations (4%) showed the opposite result: these interventions were no longer cost-effective after the inclusion of societal costs.

Conclusions: Summarising the disparities in results and applied methods, the results show that societal costs might alter the conclusions in cost-utility analyses. Hence, the relevance of the perspectives chosen should be taken into account when carrying out an economic evaluation. This systematic review demonstrates that the results of economic evaluations can be affected by different methods available for estimating non-healthcare costs.

Keywords: Cost-utility analysis, CUA, Quality-adjusted life years, QALY, Societal perspective, Incremental cost-utility ratio, ICUR, Direct costs, Indirect costs, Depression
Background

In 2015 depressive disorders affected 322 million people worldwide, making up more than 4.4% of the world’s population, and affecting women (5.1%) more than men (3.6%) [1]. Thus, even though different mental disorders can be highlighted, depression is considered as one of the most prominent mental disorders, as it is ranked fourth in the top ten causes with the largest amount of years lived with disability in Europe [2]. The disease not only causes high levels of distress and negative effects in those who suffer from it, even leading to early retirement or premature mortality, but also in their relatives, making it a growing public health issue worldwide [3, 4].

The prevalence of depression varies slightly by age with almost 10% of young adults and more than 11% of adolescents [5]. This results in several challenges concerning the individual productivity and work ability leading to a downward spiral of unemployment and financial burdens [6, 7]. To ease the symptoms of depression, many effective interventions and therapeutic approaches, such as cognitive therapy or medication, are available. However, especially antidepressants can cause various side effects [8]. Furthermore, due to the underestimation of the disease prevalence and possible concerns about the associated costs, the adverse effects of medication and stigmatization, many people suffering from depression remain without any treatment [9]. Besides this, depressive disorders are strongly associated with stigmatization. More precisely, evidence suggests that public stigma, defined as opinions about personal beliefs of what most people think, is (i) positively related to self-stigma and negatively associated with help-seeking for mental health problems [10], (ii) contributes to treatment discontinuity, and (iii) leads to poorer quality of life, self-esteem and worsened health status [11]. Consequently, the analysis of stigma effects and its economic consequences has led to an increasing interest in the existing literature [10], showing that stigma and discrimination related to mental health problems might lead to adverse economic effects, as it negatively affects employment, income and healthcare costs [12]. Moreover, anti-stigma campaigns for people with mental health problems have been proved to be a cost-effective alternative [13].

Taking into account all mentioned before, there is a growing public health interest in the economic effects of depression by a higher use of healthcare services (which range from 508 € to 24,069 €) as well as vast labour productivity losses (ranging from 1963 € to 27,364 € per person per year) [14]. Across 28 European countries, the weight of societal costs can amount for more than 64% of the total economic burden of depression, with 76 billion euros in terms of losses related to premature mortality and morbidity [15]. The relevance of such costs has been confirmed in country-specific populations, where productivity losses represented half of the economic burden of depression [16].

Within this framework, economic evaluations are useful tools that can help decision-makers to prioritize healthcare interventions or policies in order to achieve not only improvements in health, but also ensuring the financial sustainability of public health systems. Particularly, the economic evaluations carried out in the field of depression have been performed in order to prevent depression [17], improve treatment adherence [16] or compare alternative treatments or interventions [18]. In spite of the existing amount of literature, comparability of economic evaluations poses several challenges [19, 20]. One of the main reasons is the selection of the most appropriate perspective [21]. Taking into account the importance of non-healthcare costs, it seems to be necessary to focus on encouraging their inclusion in any economic evaluation as well as emphasizing its role, as it has been done in other areas [22]. However, to the best of our knowledge, there is no evidence in the field of depression that has assessed the relevance of including or excluding costs beyond the healthcare ones. Therefore, the main aim of this paper is to analyse the role played by non-healthcare costs (labour productivity loss and/or informal care costs) in the economic evaluations carried out in any intervention for people with depression. More precisely, we would determine whether the inclusion/exclusion of societal costs could alter the results and conclusions of the economic evaluations in any intervention for such target population.

Method

Data source and search strategy

A systematic literature review was performed with the aim of identifying economic evaluations of any intervention in depression, taking into account the PRISMA methodology. It has not been prospectively registered anywhere. To identify economic evaluations of any intervention in depression, the search strategy was conducted in Medline using the following key words: “cost-benefit analysis” OR “quality adjusted life year” OR “cost-benefit” OR “economic evaluation” OR “cost-effectiveness” OR “cost-utility” OR “economic analysis” AND “depression” OR “depress*”, whereby MeSH terms and natural key words in titles and abstracts were combined. In order to ensure the sensitivity of the strategy, we searched for “depression” in the Cost-Effectiveness Analysis (CEA) Registry from the Tufts University. This publicly available comprehensive database uses a formalized review process to identify original economic evaluations containing cost-utility analysis (CUA) and to provide detailed information on these studies [23]. Both search strategies were limited to a period of 10 years from 30
November 2008 to 30 November 2018. The studies’ eligibility criteria included i) being an original study published in a peer-reviewed scientific journal ii) being an economic evaluation, more precisely a cost-utility analysis or a CEA and CUA, of any intervention related to depression regardless of whether the intervention was performed in patients with depression or to prevent depression; iii) in case of being an economic evaluation in more than one disease (i.e. anxiety), costs for depression were reported separately or it was explicitly stated that a majority of the participants were depressed; iv) including societal costs (informal care costs and/or productivity losses) in the analysis; v) using quality-adjusted life years (QALYs) in CUA vi) providing results separately for each perspective applied (healthcare and societal perspective); vii) and being written in English.

Data extraction
After removing duplicates, an assessment considering the inclusion and exclusion criteria and data extraction was conducted by LP, BR, JD and LH. While three researchers were responsible for the first revision of titles and abstracts (LP, BR, IA), the full-text screening and data extraction was carried out by JD and LH, and double checked by LP and BR. Whenever there was a disagreement in screening process, the paper was reviewed by a third researcher (WG).

We extracted the following variables from each included study: authors, year of publication, perspective (society or healthcare payer/provider), country, type of intervention (prevention, screening/diagnostic, pharmaceutical therapy, non-pharmaceutical intervention, combined intervention, collaborative care), type of analysis (CUA or CEA/CUA), time horizon, discount rates used for costs and/or outcomes, study design, costs included, currency and type of sensitivity analysis (SA) (deterministic, probabilistic). Moreover, information about the analysis including the incremental costs, incremental QALYs, incremental cost utility ratio (ICUR), authors’ conclusions, whether the inclusion of societal costs changed the results or the conclusion about the adoption of the assessed intervention as well as the threshold were excerpted. In case of incomplete or misleading information, original authors were not contacted. To improve the comparability of the results, the incremental costs and ICURs were standardized by inflating the original currency to euros in 2018 prices using the Harmonised index of consumer prices [24]. Supplementary information can be obtained from the authors on request.

The underlying concepts of healthcare and societal costs followed Drummond et al. [25]. Therefore, healthcare costs encompass e.g. intervention costs, outpatient (incl. general practitioners and specialists) and inpatient services, medication and societal service costs. On the contrary, societal costs are defined as lost resources in consequence of absenteeism, presenteeism, premature death and costs of informal care [25]. We focus on the distinction between the healthcare payer/provider perspective and societal perspective. While the healthcare payer perspective includes the aforementioned healthcare costs, the societal perspective further considers societal costs.

Results
By the initial search, 1273 articles were identified, of which 1263 were found in Medline and additional ten by the Tufts CEA registry. After reviewing all abstracts, 952 studies were excluded as duplicates or did not meet inclusion criteria. Three hundred twenty-one publications remained for the full text screening, of which 268 were excluded because they did not use QALYs (23 articles), four were identified as duplicated or reduced versions of an included publication, in 129 no societal costs were included and 25 did not include a complete economic evaluation or did not focus on depression (64 articles). Furthermore, we identified seven that followed a review design and 16 publications that did not report the perspectives of interest separately. Thus, a total of 53 articles met the full inclusion criteria and were therefore included in this review [26–78] (Fig. 1).

Study characteristics
The majority of the 53 economic evaluations were carried out in the Netherlands (28%) [29, 30, 38, 41–43, 49, 51, 54, 57, 67, 71–73, 76] and the United Kingdom (26%) [28, 33, 35, 36, 44, 46, 47, 50, 52, 60–62, 75, 78]. Five studies derive from Spain [27, 39, 63, 64, 66] and four respectively from the United States [45, 48, 68, 69] and Germany [31, 32, 37, 40]. Three studies analysed data from Sweden [55, 56, 59] and another two from India [58, 77]. The remaining six studies used data from Japan [65], Greece [53], Canada [74], Belgium [26], Korea [34] and Finland [70].

Concerning the perspective, 22 of the studies (42%) applied the societal perspective [30, 38, 40–43, 45, 48, 49, 53–57, 59, 63, 66, 67, 69, 71–73, 76]. Eighteen studies conducted an evaluation considering both positions [26–29, 31, 32, 34, 37, 39, 50, 51, 58, 62, 64, 65, 74, 75, 77] and 12 focused on the healthcare perspective and calculated societal costs separately [33, 35, 36, 44, 46, 47, 52, 60, 61, 65, 70, 78]. One study did not explain which perspective was used [68]. Nevertheless, it was possible to extract costs and consequences separately for healthcare and society from the data included in the results table.

Considering the intervention type, 26% of the studies compared two or more different pharmaceuticals [26, 28, 34, 36, 38, 53, 55–57, 59, 62, 66, 69, 70], whereby the main part of the articles evaluated non-pharmaceutical interventions such as cognitive behavioural therapy or
other psycho-educational therapies. Collaborative care interventions were evaluated in eight studies [27, 40, 42–44, 49, 60, 72] and seven articles focused on a combination of pharmaceutical and psychological interventions [46, 50, 54, 58, 65, 67, 75]. Preventive approaches [29, 32, 39] and screening or diagnostic tools [31, 45, 48] were used in three studies respectively. In almost all cases, standard care or treatment as usual was the comparator, regardless of the individual intervention type.

The majority (70%) of the 53 economic evaluation studies included CEA as well as CUA. Regarding the study design, most of the publications reported data from randomized controlled trials (RCT) [27–33, 35, 38–44, 46, 47, 49–52, 54, 58, 60–64, 66, 67, 69, 71–73, 76–78] and 16 studies used a modelling approach for the calculations [26, 34, 36, 37, 45, 48, 53, 55–57, 59, 65, 68, 70, 74, 75].

In 16 studies, both aspects of societal costs were included [29–33, 35, 44, 49–51, 58, 68, 71–73, 76]. The other studies used either productivity losses [26, 27, 34, 36–43, 45–48, 52–57, 59, 61, 63–67, 69, 70, 74, 75, 77, 78] or costs of informal care only [28, 60, 62]. The approach to estimate societal costs was not always explicitly depicted. When stated, the approach to value productivity losses was almost balanced between the human capital approach [31–33, 37, 39, 40, 46, 50, 61, 63,
and the friction costs method [26, 30, 38, 41–43, 49, 51, 52, 54, 57, 71, 72, 76], whereas one study used both [29]. In terms of the friction costs method, the replacement time varied between 123 and 161 days. Regarding informal care given by relatives or friends, most of the studies applied the proxy good method [28–33, 44, 49, 51, 60, 62, 71–73, 76] and only two used the opportunity cost method for their estimations [35, 50]. A comprehensive overview of the main characteristics relative to the methods and other context of cost estimation used is given in Table 1.

The calculations were verified by SA in almost every study, except one publication [54]. Most of them used a probabilistic SA [27, 30, 31, 33, 38, 40–43, 47, 50, 52, 58, 59, 63, 71, 75–78] or a combination of both types (deterministic and probabilistic) of SA [26, 32, 34–36, 39, 44, 48, 49, 51, 53, 55, 56, 60, 61, 65, 69, 70, 72]. Thirteen articles evaluated a time horizon of less than 1 year [28, 31, 47, 55–58, 62, 64, 66, 67, 69, 76]. Twenty-five monitored the study population for 1 year [26, 27, 29, 30, 32–35, 38, 41, 42, 44, 46, 49, 50, 54, 59, 60, 63, 65, 68, 70, 73, 77, 78] and 15 evaluated a larger time horizon within a range from 13 months to lifetime [36, 37, 39, 40, 43, 45, 48, 51–53, 61, 71, 72, 74, 75]. In the latter cases, 11 of these analyses used a discount rate between 3 and 5% for discounting the costs [33, 36, 37, 39, 45, 48, 52, 53, 61, 71, 75]. However, only four of them discounted both costs and QALYs [36, 52, 61, 75].

Results of economic evaluations
In 20 of the publications more than one result was calculated leading to a total of 92 individual results [26, 28, 38, 41, 44, 45, 49, 53, 56, 57, 59, 62, 63, 65, 67, 68, 70, 71, 74, 76]. All stated or obtained results were compiled and compared regarding the two perspectives by focusing on the changes in quadrants and conclusions (see Table 2).

In seven studies, the economic evaluation of the intervention resulted in negative incremental QALYs [30, 38, 41, 43, 52, 65, 71]. Another three studies calculated incremental costs higher than the corresponding national willingness-to-pay threshold per QALY from both perspectives, thus resulting in the intervention not being cost-effective at all [29, 49, 54]. In one of these studies, only the unadjusted intention-to-treat analysis was not cost-effective, while adjusted analysis was cost-effective from the healthcare perspective [49]. Regarding the differences in incremental costs, 19 estimations from 14 studies showed cost savings when societal costs were included [26, 28, 38–40, 42, 44, 53, 57, 59, 60, 62, 65, 73]. However, only two of these results ended up in a decision change concerning the ICUR [65, 73]. From the 16 studies that explicitly conducted an evaluation from both perspectives, the majority of the studies did not identify a substantial change in the cost-effectiveness of the focused intervention(s) [26–29, 31, 32, 34, 37, 39, 58, 62, 74, 75, 77]. Nevertheless, 20 single results out of these studies led to lower incremental costs by inclusion of societal costs [26–28, 31, 32, 34, 39, 58, 62, 74, 75, 77]. Irrespective of the perspective of the evaluation, 15 single estimations accounted for increasing incremental costs when societal costs were included [28, 29, 33, 35–37, 45, 46, 50, 51, 54, 62–64, 67].

From the healthcare perspective, ten out of twelve papers reported that the focused intervention dominated the comparator [47, 61, 70] or had a positive ICUR [33, 35, 36, 44, 46, 60, 78] below the threshold applied. When the societal costs were included, the majority of them showed no relevant changes to the direct costs-results [35, 36, 46, 47, 52, 61, 70, 78]. In two cases, the results changed from the intervention having a positive ICUR below the used threshold to being dominant [44, 60]. One study demonstrated a conclusion change for both single results from not being cost-effective when adopting the healthcare perspective to highly dominant when societal costs were included [65]. However, one study changed from a positive ICUR to a value markedly above the chosen threshold of 30,000 British pounds with respect to the obtained data from the healthcare perspective [33].

In addition, when the societal perspective was selected, two results changed and became cost-effective compared to the analysis only including direct healthcare costs [73, 76]. One of these studies ascertained a complete change from a value high above the willingness-to-pay for one QALY to cost savings when societal costs were included, thus becoming not only cost-effective but also dominant [73]. In that special case the scientists evaluated an augmented cognitive behavioural therapy compared to a computerized cognitive training program in post-stroke depressive patients. Another eight economic estimations out of six studies changed from being below the threshold to dominate the standard care or other comparators [40, 42, 53, 57, 59, 73]. One of the interventions altered from being cost-effective to rise above the threshold when societal costs were included [49]. Further, one study changed in a similar way but results from negative incremental costs and negative incremental QALYs [41]. In most of the single results from the societal perspective, no important changes in terms of being cost-effective were obtained [45, 48, 53, 55, 56, 62, 67, 69, 72].

Figures 2 and 3 give an overview of main variations in the inflated ICURs from healthcare to societal perspective (Please note, that outliers must be excluded for the visualization.). It can be seen that the inclusion of societal costs led to a wider spread of single values in all directions (see Figs. 2 and 3).
| Authors, publication year | Country | Perspective | Intervention Type | Type of Economic evaluation | Time horizon | Discount rate | Studytype/ Type of model | Costs included | Currency (base year) | Type of sensitivity analysis |
|---------------------------|---------|-------------|-------------------|-----------------------------|--------------|--------------|-------------------------|----------------|----------------------|-----------------------------|
| Annemans et al. 2014 [26] | BE      | Healthcare and societal perspective | Pharmaceutical therapy | CUA | 1 year | NA | Decision tree model | Direct costs: intervention costs, primary care  Indirect costs: absenteeism, suicide | EUR (2011) | Deterministic and probabilistic |
| Aragones et al. 2014 [27] | ES      | Healthcare and societal perspective | Collaborative care | CEA, CUA | 1 year | NA | RCT | Direct costs: health care, intervention  Indirect costs: absenteeism | EUR (2011) | Probabilistic |
| Banerjee et al. 2013 [28] | UK      | Healthcare and societal perspective | Pharmaceutical therapy | CUA | 13 weeks, 39 weeks | NA | RCT | Direct costs: medication, health and social care  Indirect costs: informal care | GBP (2009) | Deterministic |
| Biesheuvel-Leliefeld et al. 2018 [29] | NL | Healthcare and societal perspective | Prevention | CEA, CUA | 1 year | NA | RCT (multi-center) | Direct costs: primary & secondary care, mental health care, home care, medication, intervention  Indirect costs: absenteeism, presenteeism, informal care | EUR (2013) | Deterministic |
| Bosmans et al. 2008 [30] | NL | Societal perspective | Non-pharmaceutical intervention | CEA, CUA | 1 year | NA | RCT | Direct costs: primary & secondary care, non-health care, medication  Indirect costs: absenteeism, informal care | EUR (2002) | Probabilistic |
| Brett-schneider et al. 2017 [31] | DE | Healthcare and societal perspective | Screening/diagnostic | CUA | 6 months | NA | RCT | Direct costs: inpatient & outpatient care, psychotherapist, medication, nursing care  Indirect costs: absenteeism, informal care | EUR (2012) | Probabilistic |
| Buntrock et al. 2017 [32] | DE | Healthcare and societal perspective | Prevention | CEA, CUA | 1 year | NA | RCT (pragmatic) | Direct costs: health care use, out-of-pocket  Indirect costs: absenteeism, presenteeism, informal care | EUR (2013) | Deterministic and probabilistic |
| Chalder et al. 2012 [33] | UK | Healthcare perspective | Non-pharmaceutical intervention | CEA, CUA | 1 year | 3.5% (costs) | RCT (pragmatic) | Direct costs: primary & secondary care, intervention, medication, patient & carers  Indirect costs: absenteeism | GBP (2009) | Probabilistic |
| Choi et al. 2016 [34] | KR | Healthcare and (limited) societal perspective | Pharmaceutical therapy | CUA | 1 year | NA | Markov model | Direct costs: psychiatrist, AE, outpatient care, emergency, laboratory tests, medication  Indirect costs: absenteeism, suicide | KRW (2014) | Deterministic and probabilistic |
| Dixon et al. 2016 [35] | UK | Healthcare perspective | Non-pharmaceutical intervention | CUA | 1 year | NA | RCT (multicentre) | Direct costs: primary & secondary care, medication, inpatient, ambulance, intervention, personal social services, out-of-pocket  Indirect costs: absenteeism | GBP (2012/13) | Deterministic and probabilistic |
| Ehrman et al. 2012 [36] | UK | Healthcare perspective | Pharmaceutical therapy | CEA, CUA | 5 years | 3.5% (costs and QALYs) | DES model | Direct costs: inpatient and outpatient, medication  Indirect costs: absenteeism | GBP (2011) | Deterministic and probabilistic |
| Evans-Lacko et al. 2016 [37] | DE | Healthcare and societal (employer) perspective | Non-pharmaceutical intervention | CUA | 27 months | 3.5% (costs) | Decision tree model | Direct costs: screening, GP visits, primary care, inpatient, psychotherapist  Indirect costs: absenteeism, presenteeism | EUR (2013) | Deterministic |
| Eveleigh et al. 2014 [38] | NL | Societal perspective | Pharmaceutical therapy | CUA | 1 year | NA | RCT (cluster) | Direct costs: health services & resources, intervention  Indirect costs: absenteeism | EUR (2012) | Probabilistic |
| Authors, publication year | Country | Perspective | Intervention Type | Type of Economic evaluation | Time horizon | Discount rate | Study type/ Type of model | Costs included | Currency (base year) | Type of sensitivity analysis |
|---------------------------|---------|-------------|-------------------|----------------------------|-------------|--------------|--------------------------|----------------|----------------------|-------------------------|
| Fernandez et al. 2018 [39] | ES      | Healthcare and societal perspective | Prevention | CUA | 1.5 years | 3.5% (costs) | RCT (cluster) | Direct costs: medication, intervention, indirect costs: absenteeism, presenteeism | EUR (2012) | Deterministic and probabilistic |
| Gensichen et al. 2013 [40] | DE      | Societal perspective | Collaborative care | CEA, CUA | 2 years | NA | RCT (pragmatic) | Direct costs: psychiatric inpatient care, outpatient psychologic care, psychiatrists & GP visits, medication, indirect costs: absenteeism | EUR (2009) | Probabilistic |
| Gerhards et al. 2010 [41] | NL      | Societal perspective | Deterministic and probabilistic | CEA, CUA | 1 year | NA | RCT | Direct costs: healthcare use, costs for patient & family, indirect costs: absenteeism | EUR (2007) | Probabilistic |
| Goorden et al. 2015 [42]  | NL      | Societal perspective | Collaborative care | CUA | 1 year | NA | RCT (cluster) | Direct costs: health care use, indirect costs: absenteeism, presenteeism | EUR (2013) | Probabilistic |
| Goorden et al. 2014 [43]  | NL      | Societal perspective | Collaborative care | CUA | 13 months | NA | RCT | Direct costs: health care use, productivity costs: absenteeism, presenteeism | EUR (2009) | Probabilistic |
| Green et al. 2014 [44]    | UK      | Healthcare perspective | Collaborative care | CEA, CUA | 1 year | NA | RCT | Direct costs: intervention, health & social care service, supervision, specialists, indirect costs: absenteeism, informal care | GBP (2011) | Deterministic and probabilistic |
| Groessl et al. 2018 [45]  | US      | Societal perspective | Screening/diagnostic | CEA, CUA | 3 years | 3% (costs) Markov model | Direct costs: medical services, intervention, indirect costs: absenteeism | USD (2016) | Deterministic |
| Hollinghurst et al. 2014 [46] | UK | Healthcare perspective | Combined intervention | CUA | 1 year | NA | RCT | Direct costs: health & social care services, intervention, out-of-pocket, indirect costs: absenteeism | GBP (2010) | Deterministic |
| Hollinghurst et al. 2010 [47] | UK | Healthcare perspective | Deterministic and probabilistic | CEA, CUA | 8 months | NA | RCT | Direct costs: primary and community contacts, mental health-related secondary care, social services, out-of-pocket, indirect costs: absenteeism | GBP (2007) | Probabilistic |
| Hornberger et al. 2015 [48] | US | Societal perspective | Pharmaceutical therapy | CEA, CUA | patient’s lifetime | 3% (costs) Decision tree model | Direct costs: medication, inpatient & outpatient, psychotherapy, intervention, indirect costs: absenteeism | USD (2013) | Deterministic and probabilistic |
| Joling et al. 2013 [49]    | NL      | Societal perspective | Collaborative care | CEA, CUA | 1 year | NA | RCT | Direct costs: ambulatory care, home care & other support, day hospital, inpatient, indirect costs: absenteeism, informal care | EUR (2009) | Deterministic and probabilistic |
| Kessler et al. 2018 [50]   | UK      | Healthcare and societal perspective | Combined intervention | CEA, CUA | 1 year | NA | RCT | Direct costs: inpatient & outpatient care, private counselling, prescription charges, over-the-counter medication, complementary therapies, private home care, indirect costs: absenteeism | GBP (2016) | Probabilistic |
| Kolovos et al. 2016 [51]   | NL      | Healthcare and societal perspective | Non-pharmaceutical intervention | CEA, CUA | 13 months | NA | RCT | Direct costs: health care & non-health care, indirect costs: absenteeism, presenteeism, informal care | EUR (2013) | Deterministic and probabilistic |
| Kuyken et al. 2015 [52]    | UK      | Healthcare perspective | Non-pharmaceutical intervention | CEA, CUA | 2 years | 3.5% (costs and QALYs) RCT | Direct costs: primary & secondary care, medication, social care & voluntary sector services, intervention, out-of-pocket, indirect costs: absenteeism, presenteeism | GBP (2011/12) | Probabilistic |
### Table 1 Summary of the main characteristics of the selected studies (Continued)

| Authors, publication year | Country | Perspective | Intervention Type | Type of Economic evaluation | Time horizon | Discount rate | Studytype/Type of model | Costs included | Currency (base year) | Type of sensitivity analysis |
|---------------------------|---------|-------------|-------------------|-----------------------------|--------------|---------------|------------------------|----------------|---------------------|-----------------------------|
| Maniadakis et al. 2013    | GR      | Societal perspective | Pharmaceutical therapy | CEA, CUA | 2 years | 3.9\% (costs) | Markov model | Direct costs: inpatient care, outpatient visits, medication, laboratory tests, AE | EUR (2012) | Deterministic and probabilistic |
| Meuldijk et al. 2015      | NL      | Societal perspective | Combined intervention | CEA, CUA | 1 year | NA | RCT | Direct costs: primary care, non-healthcare use | EUR (2013) | NA |
| Nordstrom et al. 2012     | SE      | Societal perspective | Pharmaceutical therapy | CEA, CUA | 6 months | NA | Decision tree model | Direct costs: hospitalization, ambulatory care, medication | EUR (2009) | Deterministic and probabilistic |
| Nordstrom et al. 2010     | SE      | Societal perspective | Pharmaceutical therapy | CEA, CUA | 6 months | NA | Decision tree model | Indirect costs: absenteeism | EUR (2009) | Deterministic and probabilistic |
| Nuijten et al. 2012       | NL      | Societal perspective | Pharmaceutical therapy | CUA | 26 weeks | NA | Decision tree model | Direct costs: inpatient care consultations, medication | EUR (2010) | Deterministic and probabilistic |
| Patel et al. 2017         | IN      | Healthcare and societal perspective | Combined intervention | CEA, CUA | 3 months | NA | RCT | Direct costs: outpatient, inpatient, medication, intervention, laboratory tests | USD (2015) | Probabilistic |
| Ramsberg et al. 2012      | SE      | Societal perspective | Pharmaceutical therapy | CEA, CUA | 1 year | NA | Decision tree model | Direct costs: medication, primary care, specialist care | EUR (2009) | Probabilistic |
| Richards et al. 2016      | UK      | Healthcare perspective | Collaborative care | CEA, CUA | 1 year | NA | RCT (cluster) | Direct costs: primary, secondary & community care, social care, out-of-pocket | GBP (2011) | Deterministic and probabilistic |
| Richards et al. 2017      | UK      | Healthcare perspective | Non-pharmaceutical intervention | CEA, CUA | 1.5 years | 3.9\% (costs and QALYs) | RCT | Direct costs: hospital services, primary care, social service, complementary services, medications | GBP (2013/14) | Deterministic and probabilistic |
| Romeo et al. 2013         | UK      | Healthcare and societal perspective | Pharmaceutical therapy | CEA, CUA | 39 weeks | NA | RCT | Direct costs: inpatient, day hospital, outpatient, social care, occupational therapy, emergency | GBP (2009/10) | Deterministic |
| Romero-Sanchez et al. 2017| ES      | Societal perspective | Non-pharmaceutical intervention | CEA, CUA | 1 year | NA | RCT | Direct costs: medications, medical tests, use of health-related services | EUR (2014) | Probabilistic |
| Rubio-Valera et al. 2013  | ES      | Healthcare and societal perspective | Non-pharmaceutical intervention | CEA, CUA | 6 months | NA | RCT | Direct costs: public & privately funded primary & secondary care, tests, hospitalisation, medications | EUR (2009) | Deterministic |
| Sado et al. 2009          | JP      | Healthcare perspective | Combined intervention | CEA, CUA | 1 year | NA | Decision tree model | Direct costs: medications, consultant & psychotherapy fees, inpatient | JPY (2005) | Deterministic and probabilistic |
| Serrano-Blanco et al. 2009| ES      | Societal perspective | Pharmaceutical therapy | CUA | 6 months | NA | RCT | Direct costs: medications, GP visits, specialized medical visits | EUR (2001) | Deterministic |
| Authors, publication year | Country | Perspective | Intervention Type | Type of Economic evaluation | Time horizon | Discount rate | Studytype/Type of model | Costs included | Currency (base year) | Type of sensitivity analysis |
|---------------------------|---------|-------------|------------------|-----------------------------|--------------|---------------|-----------------------|----------------|-----------------------|----------------------------|
| Simons et al. 2017 [67]   | NL      | Societal perspective | Combined intervention | CEA, CUA | 32 weeks | NA | RCT | Direct costs: health care use, medications, intervention Indirect costs: absenteeism, presenteeism | EUR (2012) | Deterministic |
| Simpson et al. 2009 [68]  | US      | NA | Non-pharmaceutical intervention | CEA, CUA | 1 year | NA | Decision tree and Markov model | Direct costs: inpatient, GP visits, emergency, medications Indirect costs: absenteeism, informal care | USD (2006) | Deterministic |
| Snedecor et al. 2010 [69] | US      | Societal perspective | Pharmaceutical therapy | RCT + modelling | NA | 2 months/6 months | Decision tree and Markov model | Direct costs: medication, medical & health services Indirect costs: absenteeism, presenteeism | USD (2007) | Deterministic and probabilistic |
| Soini et al. 2017 [70]    | FI      | Healthcare perspective | Pharmaceutical therapy | CUA | 1 year | NA | Decision tree and Markov model | Direct costs: psychiatrist & GP visits, psychotherapist, hospitalisations, medications Indirect costs: absenteeism | EUR (2014) | Deterministic and probabilistic |
| Stant et al. 2009 [71]    | NL      | Societal perspective | Non-pharmaceutical intervention | CEA, CUA | 3 years | 3 and 5% (costs) | RCT | Direct costs: inpatient & community care, healthcare, medications, intervention, non-medical Indirect costs: absenteeism, informal care | EUR (2003) | Probabilistic |
| van der Aa et al. 2017 [72] | NL     | Societal perspective | Collaborative care | CEA, CUA | 2 years | NA | RCT (multicenter) | Direct costs: primary & secondary care, medications, intervention Indirect costs: absenteeism, presenteeism, informal care | EUR (2013) | Deterministic and probabilistic |
| van Eeden et al. 2015 [73] | NL     | Societal perspective | Non-pharmaceutical intervention | CEA, CUA | 1 year | NA | RCT (multicenter) | Direct costs: care provider utilization, complementary care, home care, medications, intervention, patient & family Indirect costs: absenteeism, informal care | EUR (2012) | Deterministic |
| Vasiliadis et al. 2017 [74] | CA     | Healthcare and societal perspective | Non-pharmaceutical intervention | CEA, CUA | 40 years | NA | DES model | Direct costs: medical and non-medical Indirect costs: absenteeism | CAD (NA) | Deterministic |
| Vataire et al. 2014 [75]  | UK      | Healthcare and societal perspective | Combined intervention | CUA | 5 years | 3.5% (costs and QALYs) | DES model | Direct costs: inpatient, AE, GP & psychiatrist visits, medication, Indirect costs: absenteeism, suicide | GBP (2011) | Probabilistic |
| Wamerdám et al. 2010 [76] | NL      | Societal perspective | Non-pharmaceutical intervention | CEA, CUA | 12 weeks | NA | RCT | Direct costs: medical & non-medical, intervention, out of pocket, family & patients Indirect costs: absenteeism | EUR (2007) | Probabilistic |
| Weobong et al. 2017 [77]  | IN      | Healthcare and societal perspective | Non-pharmaceutical intervention | CUA | 1 year | NA | RCT | Direct costs: healthcare use Indirect costs: absenteeism, informal care | USD (2015) | Probabilistic |
| Wiles et al. 2014 [78]    | UK      | Healthcare perspective | Non-pharmaceutical intervention | CEA, CUA | 1 year | NA | RCT | Direct costs: healthcare use, intervention, social services Indirect costs: absenteeism | GBP (2011) | Probabilistic |
| Author & publication year | N° of estimation | Healthcare perspective | Societal perspective | Change in results\(^a\) conclusions\(^b\) | threshold value |
|--------------------------|-----------------|------------------------|---------------------|------------------------------------------|----------------|
| Annemans et al. 2014 \[26\] | 1 | 16 | 0.003 | 6352 | 6946 | -258 | 0.003 | -86,000 | -94,049 | YES | NO | 30,000 |
| | 2 | -5 | 0.004 | -1250 | -1,367 | -387 | 0.004 | -96,750 | -105,805 | NO | NO | |
| | 3 | -37 | 0.008 | -4625 | -5058 | -829 | 0.008 | -103,625 | -113,323 | NO | NO | |
| | 4 | -50 | 0.009 | -5556 | -6076 | -902 | 0.009 | -100,222 | -109,602 | NO | NO | |
| | 5 | -104 | 0.016 | -6600 | -7108 | -1618 | 0.016 | -101,125 | -110,589 | NO | NO | |
| | 6 | -128 | 0.015 | -8533 | -9332 | -1591 | 0.015 | -106,067 | -115,994 | NO | NO | |
| | 7 | -118 | 0.006 | -19667 | -21507 | -843 | 0.006 | -140,500 | -153,650 | NO | NO | |
| Aragones et al. 2014 \[27\] | 8 | 183 | 0.045 | 4056 | 4435 | 157 | 0.045 | 3499 | 3826 | NO | NO | 30,000 |
| Banerjee et al. 2013 \[28\] | 9 | 693 | 0.03 | 23100 | 29070 | 705 | 0.03 | 23500 | 29583 | NO | NO | 30,000 |
| | 10 | 404 | 0.005 | 8080 | 10,172 | -1106 | 0.005 | -22,120 | -27,962 | YES | NO | |
| | 11 | -289 | 0.002 | -14450 | -18191 | -1811 | 0.002 | -90550 | -113990 | NO | NO | |
| Biesheuvel-Leufeld et al. 2018 \[29\] | 12 | 1107 | 0.03 | 33025 | 35216 | 2114 | 0.03 | 63051 | 67234 | NO | NO | 30,000 |
| Bosmans et al. 2008 \[30\] | 13 | 181 | -0.00045 | -353333 | -427866 | -751 | -0.00045 | 1,668,889 | 2,020,926 | YES | NO | NA |
| Brett Schneider et al. 2017 \[31\] | 14 | - | 0.0067 | -153881 | -166182 | -1309 | 0.0067 | -195,373 | -210,991 | NO | NO | 50,000 |
| Buntrock et al. 2017 \[32\] | 15 | 135 | 0.01 | 13500 | 14,396 | 134 | 0.01 | 13,400 | 14,289 | NO | NO | 20,000 |
| Chalder et al. 2012 \[33\] | 16 | 296 | 0.014 | 20,834 | 24,091 | 1813 | 0.014 | 129,500 | 149,744 | YES | NO | 30,000 |
| Choi et al. 2016 \[34\] | 17 | -50 | 0.00131 | -3826718 | -2785 | -623 | 0.00131 | -47,574,733 | -34,379 | NO | NO | NA |
| Dixon et al. 2016 \[35\] | 18 | 177 | 0.031 | 5710 | 7463 | 324 | 0.031 | 10,452 | 13,662 | NO | NO | 30,000 |
| Ekman et al. 2012 \[36\] | 19 | 323 | 0.038 | 8591 | 11,076 | 485 | 0.043 | 11,173 | 14,405 | NO | NO | 30,000 |
| Evans-Lacko et al. 2016 \[37\] | 20 | 1280 | 0.005 | 25600 | 27,298 | 2107 | 0.005 | 42,140 | 44,936 | NO | NO | 50,000 |
| Evellegh et al. 2014 \[38\] | 21 | -57 | -0.02 | 2850 | 3039 | -1681 | -0.02 | 70,180 | 75,790 | NO | NO | 80,000 |
| | 22 | -97 | -0.03 | 3233 | 3448 | 1088 | -0.03 | -36,267 | -39,166 | YES | NO | |
| Fernandez et al. 2018 \[39\] | 23 | 24 | 0.002 | 1194 | 1289 | -16 | 0.002 | -819 | -884 | YES | NO | 30,000 |
| Gensichen et al. 2013 \[40\] | 24 | 989 | 0.002 | 38429 | 44,579 | -1322 | 0.002 | -66,092 | -76,668 | YES | NO | NA |
| Gerhards et al. 2010 \[41\] | 25 | -484 | -0.01 | 48400 | 55,508 | -1787 | -0.01 | 178,700 | 204,943 | NO | YES\(^5\) | 80,000 |
| | 26 | -83 | -0.01 | 8300 | 9519 | -451 | -0.01 | 45,100 | 51,723 | NO | NO | |
| Goorden et al. 2015 \[42\] | 27 | 1173 | 0.002 | 53,717 | 57,281 | -1131 | 0.002 | -56,550 | -60,301 | YES | NO | 80,000 |
| Goorden et al. 2014 \[43\] | 28 | -709 | -0.05 | 14589 | 16,346 | -2226 | -0.05 | 44,520 | 49,882 | NO | NO | NA |
| Green et al. 2014 \[44\] | 29 | 271 | 0.019 | 14,248 | 18,139 | -313 | 0.019 | -16,465 | -20,961 | YES | NO | 30,000 |
| Author & publication year | N° of estimation | Healthcare perspective | Societal perspective | Change in threshold value |
|--------------------------|-----------------|------------------------|---------------------|--------------------------|
|                          | ΔCost | ΔQALY | ICUR (currency/QALY) | ICUR (2018 €/QALY) | ΔCost | ΔQALY | ICUR (currency/QALY) | ICUR (2018 €/QALY) | results<sup>a</sup> | conclusions<sup>b</sup> |
| Groessl et al. 2018 [45] | 31    | 316   | 0.051               | 6198               | 7875   | −1246 | 0.051               | −24,434            | −31,042            | YES NO |
|                          | 2918  | −0.10 | −29,180             | −27,459            | −2598  | 0.10  | −25,980             | −24,448            | NO NO NO 50,000 |
| Hollinghurst et al. 2014 [46] | 32    | 2 −0.17 | −35,066             | −33,694            | −5810  | 0.17  | −34,176             | −32,161            | NO NO NO |
| Hollinghurst et al. 2010 [47] | 33    | 125   | 0.034               | −17,173            | −29,240 | −330  | 0.034               | −9,706             | −16,526            | NO NO |
| Hornberger et al. 2015 [48] | 34    | 0.316 | −11,744             | −9,484             | 3764   | 0.316 | −11,911             | −9,619             | NO NO NO 50,000 |
| Joling et al. 2013 [49]   | 35    | 75    | 0.04                | 1875               | 2101   | 4149  | 0.04                | 157,534            | 168,375            | NO YES 30,000 |
|                          | 36    | 187   | 0.006               | 31,167             | 34,920 | 2631  | 0.006               | 438,299            | 491,086            | NO NO |
| Kessler et al. 2018 [50]  | 37    | 69    | 0.00935             | 7380               | 10,280 | 463   | 0.00935             | 49,572             | 69,052             | NO YES 20,000 |
| Kolovos et al. 2016 [51]  | 38    | −38   | 0.01                | −3800              | −4052  | 1579  | 0.01                | 157,900            | 168,375            | YES YES 30,000 |
| Kuyken et al. 2015 [52]   | 39    | 124   | −0.04               | −3103              | −4018  | 449   | −0.04               | −11,229            | −14,618            | NO NO NA |
| Maniadakis et al. 2013 [53] | 40   | 350   | 0.026               | 13,682             | 14,776 | 14    | 0.026               | 547                | 613                | NO NO NO 50,000 |
|                          | 41    | 269   | 0.034               | 7959               | 8595   | −215  | 0.034               | −6324              | −7086              | YES NO |
|                          | 42    | 154   | 0.015               | 10,591             | 11,438 | −28   | 0.015               | −1867              | −2092              | YES NO |
|                          | 43    | 273   | 0.03                | 9183               | 9917   | −129  | 0.03                | −4300              | −4818              | YES NO |
| Meuldijk et al. 2015 [54] | 44    | 1880  | 0.005               | 376,000            | 400,943 | 4795 | 0.005               | 959,000            | 1,022,619          | NO NO 33,600 |
| Nordstrom et al. 2012 [55] | 45    | −16   | 0.00865             | −1831              | −2052  | −169  | 0.00865             | −19,555            | −21,910            | NO NO 33,600 |
| Nordstrom et al. 2010 [56] | 46    | −41   | 0.025               | −1647              | −1846  | −507  | 0.025               | −20,264            | −22,704            | NO NO 33,600 |
|                          | 47    | −17   | 0.025               | −687               | −770   | −483  | 0.025               | −19,308            | −21,633            | NO NO 33,600 |
| Nuijten et al. 2012 [57]  | 48    | 103   | 0.0062              | 16,363             | 18,116 | −263  | 0.0062              | −42,419            | −46,963            | YES NO 80,000 |
|                          | 49    | 126   | 0.0166              | 7553               | 8362   | −1992 | 0.0166              | −120,000           | −132,854           | YES NO |
| Patel et al. 2017 [58]    | 50    | 46    | 0.005               | 9333               | 7991   | 5     | 0.005               | 957                | 819                | NO NO NA |
| Ramsberg et al. 2012 [59] | 51    | 14    | 0.0036              | 3732               | 4181   | −123  | 0.0036              | −34,167            | −38,282            | YES NO NA |
|                          | 52    | −159  | 0.0045              | −35,333            | −39,589 | −327  | 0.0045              | −72,667            | −81,418            | NO NO |
|                          | 53    | −11   | 0.0052              | −2115              | −2370  | −206  | 0.0052              | −39,615            | −44,387            | NO NO |
|                          | 54    | −55   | 0.0072              | −7639              | −8559  | −325  | 0.0072              | −45,139            | −50,575            | NO NO |
|                          | 55    | −79   | 0.0086              | −9186              | −10,292 | −404  | 0.0086              | −46,977            | −52,634            | NO NO |
|                          | 56    | −147  | 0.0117              | −12,264            | −14,077 | −588  | 0.0117              | −50,256            | −56,309            | NO NO |
|                          | 57    | −179  | 0.0131              | −13,664            | −15,310 | −673  | 0.0131              | −51,374            | −57,561            | NO NO |
| Author & publication year | N° of estimation | Healthcare perspective | Societal perspective | Change in results<sup>a</sup> | conclusions<sup>b</sup> | threshold value |
|---------------------------|-----------------|------------------------|---------------------|-----------------------------|----------------|----------------|
| Richards et al. 2016 [60] | 59 | 271 0019 14,248 18,102 | −313 0019 −16,465 −20918 | YES | NO | 20,000 |
| Richards et al. 2017 [61] | 60 | −343 005 −6865 −8661 | −2070 005 −41,392 −52220 | NO | NO | 30,000 |
| Romeo et al. 2013 [62] | 61 | 693 003 23,100 28,702 | 705 003 23,500 28,842 | NO | NO | 30,000 |
| Romeo-Sanchiz et al. 2017 [63] | 62 | 404 005 8080 10,040 | −1106 005 −22,120 −27,149 | YES | NO | |
| Romeo-Sanchiz et al. 2017 [63] | 63 | −289 002 −14,450 −17,954 | −1811 002 −90,550 −111,135 | NO | NO | |
| Romero-Sanchiz et al. 2017 [63] | 64 | −632 00567 −11,153 −11,743 | −644 00567 −11,390 −11,993 | NO | NO | 25,000 |
| Romeo-Sanchiz et al. 2017 [63] | 65 | −466 00751 −6204 −6533 | −479 00751 −6381 −6719 | NO | NO | |
| Romeo-Sanchiz et al. 2017 [63] | 66 | −322 00793 −4060 −4274 | −409 00793 −5160 −5434 | NO | NO | |
| Romeo-Sanchiz et al. 2017 [63] | 67 | −295 00824 −3576 −3765 | 41 00824 497 523 | YES | NO | |
| Rubio-Valera et al. 2013 [64] | 68 | 962 001 3592 4025 | 1866 001 9872 11,061 | NO | NO | 30,000 |
| Sado et al. 2009 [65] | 69 | 27,411 008 342,638 2887 | −693,858 008 −8,673,225 −73,089 | YES | YES | 30,000 |
| Serrano-Blanco et al. 2009 [66] | 70 | 27,411 003 913,700 7700 | −693,858 003 −23,128,600 −194,904 | YES | YES | |
| Simons et al. 2017 [67] | 71 | 71 −0.06 −1180 −1444 | 639 −0.06 −10,643 −13,020 | NO | NO | NA |
| Simpson et al. 2009 [68] | 72 | 423 007 6043 6526 | 1141 007 16,300 17,603 | NO | NO | 80,000 |
| Simpson et al. 2009 [68] | 73 | 1052 013 8092 8739 | 1741 013 13,392 14,463 | NO | NO | |
| Snedecor et al. 2010 [69] | 74 | NA NA 34,999 34,286 | NA NA 6667 6531 | NO | NO | 50,000 |
| Soini et al. 2017 [70] | 75 | NA NA −1123 −1100 | NA NA −7621 −7466 | NO | NO | |
| Stant et al. 2009 [71] | 76 | 174 00058 30,000 26,060 | 81 00058 13,881 12,058 | NO | NO | 50,000 |
| Stant et al. 2009 [71] | 77 | −223 00134 −16,642 −17,523 | −1074 00134 −80,149 −84,392 | NO | NO | NA |
| Stant et al. 2009 [71] | 78 | −128 00166 −7711 −8119 | −957 00166 −57,651 −60,702 | NO | NO | |
| Stant et al. 2009 [71] | 79 | −110 0025 −4400 −4633 | 520 0025 −28,800 −30,325 | NO | NO | |
| Stant et al. 2009 [71] | 80 | −238 00276 −8623 −9080 | −1390 00276 −50,362 −53,028 | NO | NO | |
| van der Aa et al. 2017 [72] | 81 | 653 −0.21 −3110 −3277 | 1616 −0.21 −7695 −9222 | NO | NO | NA |
| van der Aa et al. 2017 [72] | 82 | 1231 −0.16 −7694 −9220 | 1644 −0.16 −10,275 −12,314 | NO | NO | |
| van der Aa et al. 2017 [72] | 83 | 713 −0.04 −17,825 −21,362 | 1054 −0.04 −26,350 −31,579 | NO | NO | |
| van Eeden et al. 2015 [73] | 84 | 1281 001 107,455 116,045 | −1913 001 −160,390 −173,211 | YES | YES | 40,000 |
| Vasiliadis et al. 2017 [74] | 85 | −0.17 −9435 −7887 | −2590 017 −15,235 −12,412 | NO | NO | NA |
| Author & publication year | N° of estimation | Healthcare perspective | Societal perspective | Change in results<sup>a</sup> conclusions<sup>b</sup> | threshold value |
|--------------------------|------------------|------------------------|---------------------|-----------------------------|-----------------|
| Vataire et al. 2014 [75] | 87               | ΔCost 1604 ΔQALY 017 ICUR (currency/QALY) −9435 ICUR (2018 €/QALY) −7687 | ΔCost 1904 ΔQALY 017 ICUR (currency/QALY) −11,200 ICUR (2018 €/QALY) −9125 | NO NO | 30,000 |
| Warmerdam et al. 2010 [76] | 88               | ΔCost 243 ΔQALY 0078 ICUR (currency/QALY) −3115 ICUR (2018 €/QALY) −5066 | ΔCost 1400 ΔQALY 0078 ICUR (currency/QALY) −17,949 ICUR (2018 €/QALY) −29,128 | NO NO | 30,000 |
| Weobong et al. 2017 [77] | 89               | ΔCost 455 ΔQALY 001 ICUR (currency/QALY) 45,500 ICUR (2018 €/QALY) 52,182 | ΔCost 256 ΔQALY 001 ICUR (currency/QALY) 22,609 ICUR (2018 €/QALY) 25,929 | NO YES | 30,000 |
| Wiles et al. 2014 [78] | 90               | ΔCost 405 ΔQALY 001 ICUR (currency/QALY) 40,500 ICUR (2018 €/QALY) 46,448 | ΔCost 147 ΔQALY 001 ICUR (currency/QALY) 11,523 ICUR (2018 €/QALY) 13,215 | NO YES | 30,000 |
| Duevel et al. Health Economics Review (2020) 10:32 | 91               | ΔCost 18 ΔQALY 0011 ICUR (currency/QALY) −1721 ICUR (2018 €/QALY) −1474 | ΔCost 155 ΔQALY 0011 ICUR (currency/QALY) −14,438 ICUR (2018 €/QALY) −12,362 | NO NO | 16,060 |
|              | 92               | ΔCost 850 ΔQALY 0057 ICUR (currency/QALY) 14911 ICUR (2018 €/QALY) 19,138 | ΔCost 814 ΔQALY 0053 ICUR (currency/QALY) 15,358 ICUR (2018 €/QALY) 17,237 | NO NO | 30,000 |

<sup>a</sup> changes in results regarding the cost-effectiveness quadrant (e.g. from cost-effective to dominant/dominated)

<sup>b</sup> change in conclusions regarding the chosen threshold

<sup>c</sup> not included in the results because the interpretation of the ICUR regarding the chosen threshold is inappropriate in this quadrant (negative incremental costs and QALYs)
Discussion
To the best of our knowledge, this is the first review that examines CUA-studies depending on the change in results by including or excluding societal costs (productivity losses and/or informal care costs) in the field of depression, which might even lead to changes in conclusions. Concretely, our results suggest that when societal costs were considered, some of the economic evaluations carried out in depression changed their conclusions/recommendations, as well as their results. More precisely, of the 92 economic evaluations coming from the 53 articles identified, 22 estimations changed their results regarding the cost-effectiveness quadrant when a societal perspective was included, while 9 estimations changed their conclusions in the decision-making regarding the chosen threshold. In fact, five economic evaluations became cost-effective (three of these single results became dominant) when societal costs were

![Fig. 2 Incremental Cost-Utility Ratios from healthcare perspective](image1)

![Fig. 3 Incremental Cost-Utility Ratios from societal perspective](image2)
included, compared to the analysis which only included healthcare costs. However, in another four estimations the opposite result was found: these interventions were no longer cost-effective after the inclusion of societal costs. Furthermore, twelve economic evaluations changed from being below the threshold to dominate the standard of care or other comparators when the societal perspective was taken into account.

However, it should be noted that the estimations which calculated negative QALYs were limtedly included in the appraisal of the relevance of societal costs in depression. In fact, economic discussions about the appropriateness of the interpretation of incremental cost-utility or cost-effectiveness results are growing increasingly [79–81]. Especially in the case of negative health effects and lower costs, the ratio is positive as well as when observing positive incremental costs and QALYs. Then, results of Incremental Cost-Effectiveness Ratios in quadrant one and three are both positive but with a very different meaning. Considering the included article of Gerhards et al., the reported ICUR might lead to false conclusions without taking into account the underlying differences in costs and QALYs [41]. Alternative approaches like the net-monetary benefit analysis can help decision makers to overcome these pitfalls [82]. Otherwise the results would lead to the conclusion that including societal costs change results in an opposite way [83]. Even though the inclusion of societal costs changed the recommendations derived from the economic evaluations only in a low number of cases, the importance of revealing potential savings in terms of costs that affect not only the healthcare system but also the society as a whole should be considered.

Nevertheless, even though there are no previous studies that have performed such analysis in the field of depression, and therefore, no direct comparison could be done, the results obtained are in line with those in previous papers in which the authors aimed to analyse the role played by societal costs in economic evaluations in different therapeutic areas [22, 84–86]. Particularly, the consideration of productivity losses could alter the decisions regarding reimbursement of expensive drugs in almost one-third of the cases [85]. In fact, it seems that, depending on the patient’s profile, the type of societal costs included (productivity losses and/or informal care costs) might vary. In the case of depression, due to the profile of such populations where the mean age of onset ranges from 24 to 35 years of age, and where productivity losses might have a higher weight within the economic impact of such a disease [74, 75], it is more common to include only productivity losses in CUA than taking into account informal care or both types of societal costs [87]. Thus, almost 94% of the economic evaluations in mental and behavioural disorders that include the societal perspective solely considered productivity losses as societal costs only, while informal care costs were only taken into account in 29% of those evaluations with a societal point of view. Moreover, it was striking that productivity losses were mostly based on absenteeism and less often on presenteeism or both aspects, even though there is sufficient evidence of the existence of presenteeism in depressive disorders [76, 77]. Actually, it has been estimated that presenteeism costs are five to ten times higher than productivity losses due to absenteeism among people with depression, with differences across age groups, educational level and countries being observed [88]. In addition, the relevance of the different approaches to estimate productivity losses could be doubtful, especially in case of narrower time frames. Almost three-quarters of the articles used a time horizon of 1 year or less whilst differences in absenteeism, depending on the approach to be used, are hard to see during such short periods of time. A 5-year horizon analysis showed, in fact, that absenteeism costs were largely increasing after those 5 years, with additional worse health outcomes among absenteeism reporters than presenteeism ones [89].

Regarding the role of informal caregivers, previous studies proved that the impact of informal care costs differed between studies, depending mainly on the disease considered [22, 84, 86]. These papers evidences the fact that informal care costs were only present in one of the economic evaluations considered, making visible that the role played by non-professional care costs in economic evaluations of depression are not quite frequent. However, there is a study which demonstrated that informal care costs could be quite relevant in the field of depression [46]. More precisely, this study, which changed from being cost-effective to rise above the threshold by including societal costs, had the aim of implementing a preventive intervention for caregivers of dementia patients to minimize their risk of developing a depressive disorder. The CUA of these family meetings includes QALYs as well as direct and indirect costs of caregivers and patients. Since the differences in QALYs were very small and informal care costs represented by far the largest contributor to total costs, it is not surprising that the societal perspective led to different results. Therefore, it should be taken into account that interventions for depression could also affect the family caregivers’ health and, in this case, costs and QALYs of caregivers should be considered in economic evaluations. In this sense, the societal perspective demands to incorporate not only societal costs but also effects on the health of caregivers, as well as other spill-over effects [90–94].

Another relevant aspect that should be highlighted is that costs due to (attempted) suicide were merely included in three out of the 53 studies, although it is
known that the risk for suicide in depressed patients is much higher than in the general population [78]. The risk of suicide is closely related to social stigmatization of persons with depression, which remained fully unconsidered in the identified literature of this review [9, 79–82]. Therefore, due to the importance of such factor in populations with depression and its economic impact on this disease, further economic evaluations should include these cost components so as not to underestimate the real economic consequences of depression. For this purpose, economic evaluations should consider broader time horizons than the ones which are commonly used in this field.

CUAs of interventions for people suffering from depressive disorders include not only the relevant costs but also the estimated QALYs. Existing literature remarks challenges for using the QALY approach in the field of mental health. Although generic instruments seem to be able to reflect the impact of common conditions such as mild to moderate depression, there are general concerns regarding the measurement of Health-related quality of life (HRQoL) in different groups of patients [95]. There is a perceived need for improved instruments that measure health-related quality of life so that QALYs appropriately reflect the pain, suffering, and limitations experienced by people with mental illness [96]. This would help to better capture the effects of the interventions being evaluated. Hence, the reported incremental QALYs may fail to capture the interventions effect and therefore lead to inaccurate ICURs. In addition to the aspects mentioned above, different degrees of severity of depressive disorders can affect the results of economic evaluations. Thus, the societal perspective may be more relevant in case of severe depression, because of potentially higher costs due to presenteeism and absenteeism [97, 98]. As the extent of the disease is not always reported by the authors of the underlying studies and the current review focuses especially on the methodological issues of the involvement of societal costs in economic evaluations, this factor was not included in the analysis.

A few limitations of this review should be mentioned. First, several studies showed inconsistencies between the results described in text and tables. Moreover, some analyses were not fully consistent with the methods. In this case, it was not possible to include every single result stated in the selected studies. Due to the heterogeneity in the SA, we only took into consideration the results reported in the main analysis, leaving out the figures reported in the SA. Secondly, the methods applied in the studies varied widely in terms of time horizon and measurement of costs and QALYs. Some limitations refer to limited time resources. Although the initial search resulted in a large number of 1273 studies, it could have been reasonable to expand the timeframe and to extend the literature search to another database. However, as previous studies show, Tufts CEA registry ensures a more accurate search [99]. In this case, 1263 articles were found from PubMed and 1273 from Tufts, getting 10 additional articles from this registry. Limited time resources even restricted capabilities to contact the authors in case of incomplete or misleading information as well as the implementation of an additional quality assessment (e.g. the Consensus on Health Economic Criteria (CHEC)-list [100]). Therefore, the high heterogeneity and variability of the methods applied in the different economic evaluations might be considered when interpreting the results obtained.

Conclusion

This study contributes to the existing literature by analysing whether the perspective (healthcare payer/provider or societal) of a CUA in the field of depression alters the results and conclusions of the evaluation. Our findings suggest that in some of the studies the inclusion of societal costs of depression leads to substantial changes in both results and conclusions, although wide methodological variations have also been observed. Thus, several analyses led to different conclusions when the intervention was evaluated from a societal compared to a healthcare payer perspective. The results revealed potential savings as well as increases from the evaluated interventions when such costs were included. However, and in purpose to improve comparability, economic evaluations should ideally consider the healthcare as well as the societal perspective leading to more appropriate recommendations. Additionally, future research should consistently follow established guidelines (e.g. CHEERS statement [101]) by reporting all relevant cost components as well as the methods of measurement. In brief, an issue that this paper highlights, is the need for considering the societal perspective when conceptualizing economic evaluations, especially among populations with depression where productivity losses could represent an important weight of its economic impact. Therefore, not considering such effect might lead to an inefficient allocation of resources when designing policies in such target populations.

Abbreviations

AE: Adverse events; CEA: Cost-Effectiveness Analysis; CUA: Cost-Utility Analysis; GP: General practitioner; ICUR: Incremental Cost-Utility Ratio; QALY: Quality-adjusted life year; RCT: Randomized controlled trial; SA: Sensitivity analysis

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Authors’ contributions

All authors developed the literature search. LP, BR and IA performed the literature search and title-abstract screening. JD and LH completed literature search and title-abstract screening. JD and LH undertook the synthesis and made a first draft of this manuscript.
All authors contributed to the drafting and revising of the manuscript. The authors read and approved the final manuscript.

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**Availability of data and materials**
The data analysed during the current study are available from the corresponding authors on request.

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**Competing interests**
The authors declare that they have no competing interests.

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