




Assessing the Effect of Including Social Costs in Economic Evaluations of Diabetes-Related Interventions: A Systematic Review

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Background: The economic burden of diabetes from a societal perspective is well documented in the cost-of-illness literature. However, the effect of considering social costs in the results and conclusions of economic evaluations of diabetes-related interventions remains unknown.

Objective: To investigate whether the inclusion of social costs (productivity losses and/or informal care) might change the results and conclusions of economic evaluations of diabetes-related interventions.

Methods: A systematic review was designed and launched on Medline and the Cost-Effectiveness Analysis Registry from the University of Tufts, from the year 2000 until 2018. Included studies had to fulfil the following criteria: i) being an original study published in a scientific journal, ii) being an economic evaluation of an intervention on diabetes, iii) including social costs, iv) being written in English, v) using quality-adjusted life years as outcome, and vi) separating the results according to the perspective applied.

Results: From the 691 records identified, 47 studies (6.8%) were selected. Productivity losses were included in 45 of the selected articles (73% used the human capital approach) whereas informal care costs in only 13 (when stated, the opportunity cost method was used in seven studies and the replacement cost in one). The 47 studies resulted in 110 economic evaluation estimations. The inclusion of social costs changed the conclusions in 8 estimations (17%), 6 of them switching from not cost-effective from the healthcare perspective to cost-effective or dominant from the societal perspective. Considering social costs altered the results from cost-effective to dominant in 9 estimations (19%).

Conclusion: When social costs are considered, the results and conclusions of economic evaluations performed in diabetes-related interventions can alter. Wide methodological variations have been observed, which limit the comparability of studies and advocate for the inclusion of a wider perspective via the consideration of social costs in economic evaluations and methodological guidelines relating to their estimation and valuation.

Keywords: diabetes, social costs, informal care, productivity losses, economic evaluation, health technology assessment

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Plain Language Summary

- Despite the heavy burden of social costs related to diabetes, there is still a lack of evidence about the consequences of excluding them from economic evaluations of interventions targeting people with diabetes.

- Our findings showed that, of the 738 records that consisted of a full diabetes-associated economic evaluation, only 106 included social costs (14.36%), which differed from those in similar work carried out on other diseases such as Alzheimer's disease and depression, where a higher percentage was found.
- The literature review performed showed that consideration of informal care costs and/or productivity losses changed the results or conclusions in 18% of economic evaluations of diabetes (in 20 out of 110).
- However, comparisons should be made with caution, as the different types of diabetes affect completely different profiles, with respect to age, state of health and lifestyle.

Introduction

Diabetes Mellitus (DM) is a disease of high and increasing incidence and prevalence worldwide. In addition to the large number of deaths, loss of health-related quality of life and disability that DM causes directly, it also increases the probability of suffering micro and macrovascular diseases. Thus, its total effect is enormous, and its prevention and the control of related diseases are among the biggest challenges for public health and health systems throughout the world.^{1,2}

There is solid evidence of the big economic impact of DM and its associated diseases.^{3–7} The enormous economic and social burdens imposed by DM demand new ways of curbing expenditure on the related healthcare, which includes long-term care.^{8,9} It has been estimated that, in the United States, one in every seven healthcare dollars is spent on treating diabetes and its complications.^{3,10} Additionally, although in the literature there is a predominance of studies that focus on the analysis of the healthcare costs of DM, those studies that have analysed the costs from a broader perspective have identified the relevance of other social costs caused directly by DM (loss of vision, amputation of limbs) or by diseases related to it (ischemic heart disease, stroke, renal failure, etc.).^{11–13} In this sense, diabetes has been found to significantly reduce productivity at work,^{3,11–13} even necessitating an early withdrawal from the labour force,^{14,15} and leading to substantial financial losses among people with diabetes.^{16,17} Moreover, the informal care costs per person with diabetes in the United States have been estimated to range between \$1162 to \$5082 - per year, which is more than the informal care costs for other diseases, such as heart failure (\$862).^{13,18}

In recent years, several studies have tried to analyse the effect of including non-healthcare costs in economic evaluations, adopting a societal perspective instead of the more frequent perspective of the healthcare funder.^{19–23} However, none of these studies included economic evaluations of preventive programmes or treatments related to DM. The general results obtained in the previous studies indicate that (i) non-healthcare costs are only included in a small number of studies, although with significant variations depending on the disease (almost non-existent in rare diseases,²⁴ more present in Alzheimer's disease²¹); (ii) depending on the disease, the inclusion of non-healthcare costs in the analysis may produce changes in the results, and conclusions that vary from very small to very considerable changes.

The objectives of this research were, first, to verify the presence of economic evaluations that use the societal perspective in the analysis of healthcare-related interventions in the treatment or management of DM. Secondly, to study whether the inclusion of non-healthcare costs (productivity losses and/or informal care costs) can affect the results of economic evaluations and the conclusions reached by their authors.

Methods

Design

We designed a systematic review that only included original full economic evaluations of diabetes-related interventions. We used natural language and MeSH terms to build a search strategy launched in Medline using PubMed. Although we did not aim to assess which diabetes-related intervention achieved better results, we based our search strategy on the Patient, Intervention, Comparison and Outcome (PICO) framework. This frame has demonstrated a better balance between sensitivity and specificity in identifying references in systematic reviews, reducing the odds of excluding relevant papers.²⁵ The following terms were included: (“Costs and Cost Analysis” OR “cost-effectiveness” OR “cost-utility” OR “cost-benefit” OR “economic evaluation” OR “economic analysis” OR “QALY” OR “quality-adjusted life years”) AND (“Diabetes” OR “Type 2 Diabetes”). We also used diabetes-related terms (such as “diabetes”, “diabetes mellitus”, “diabetes mellitus type 2”) in the Cost-Effectiveness Analysis (CEA) Registry of Tufts University. This registry uses an algorithm, also launched in Medline, and which combines terms such as “cost-effectiveness”, “cost-

utility”, “economic evaluation”, “QALY” and “quality-adjusted life years”.^{26,27} Likewise, we avoided the loss of sensitivity (when identifying economic evaluations carried out in diabetes) which could have resulted if only PubMed had been used. Two researchers carried out the first stage of the review (screening titles and abstracts), and then the same two researchers performed a full-text review of the manuscript included after the review of titles and abstracts. We followed the PRISMA recommendations for carrying out systematic reviews.²⁸ All discrepancies were solved by another member of the team who did not participate in the review of titles and abstracts.

Inclusion Criteria

We included in the review manuscripts that fulfilled the following inclusion criteria: (i) being an original study published in a scientific journal, (ii) being an economic evaluation of any intervention related to diabetes, (iii) including informal care costs and/or productivity losses, which we referred to as social costs, (iv) using quality-adjusted life years as an outcome, (v) separating the results according to the perspective applied (healthcare payer/provider versus a societal perspective), and (vi) being written in English. Letters to the editor, reports, editorials and brief communications were excluded. The narrative and/or systematic reviews of economic evaluations were also excluded, but we reviewed the economic evaluations included in those reviews to avoid loss of sensitivity in our search strategy through cross-references. We therefore included all economic evaluations carried out on healthcare technologies used as pharmaceutical treatments, medical devices or healthcare programmes for all types of diabetes. Likewise, we included studies carried out on gestational DM, diabetes type 1 or diabetes type 2.

Data Extraction

We retrieved the following information from the studies included in the systematic review: the first author’s name and year of publication, the cost-effectiveness analysis performed (cost-effectiveness/cost-utility), the country where it was carried out and the currency used, the type of intervention considered in the evaluation, as well as the type of diabetes to which the intervention related. Different available treatments might be identified depending on diabetes-related risk factors (for example, health education programmes to tackle problems related to obesity or glucose measurement patches), the type of diabetes (pharmacological treatment, ie metformin vs insulin), or

diabetes-related complications (which range from amputations to blindness and heart attack/stroke). We also extracted the information concerning the threshold for acceptability/recommendation assumed (or stated) by the authors, the discount rates for costs and QALYs, the time horizon, the type of sensitivity analysis performed, the Incremental Cost-Utility Ratios (ICURs) resulting from the cost-effectiveness analysis and, finally, the type of costs included in the analysis. Moreover, given the scope of the systematic review, we recorded information about the method used by the authors, if explicitly identified, to estimate productivity losses and informal care costs, as well as the unit cost applied and the source from which the unit cost was taken.

Data Analysis and Cost Definitions

Costs and, hence, the costing perspectives considered in this review were defined in accordance with the System of Health Accounts methodology proposed by the Organisation for Economic Co-operation and Development (OECD) in 2000, and revised in 2011, for carrying out economic evaluations of healthcare programmes.²⁹ More precisely, the set of healthcare costs would encompass the more traditional items, such as visits to general practitioners (GP) and specialists, outpatient consultations, pharmaceuticals, hospitalisations, imaging and laboratory tests, emergency visits; but also nursing homes, community-based care, social services, out-of-pocket healthcare expenditure and the cost of travelling to be treated. According to the revised edition of the report launched by the OECD in 2011,

total long-term care consists of a range of medical/nursing care services, personal care services and assistance services that are consumed with the primary goal of alleviating pain and suffering or reducing or managing the deterioration in health status in patients with a degree of long-term dependency.

Hence, the aforementioned costs (healthcare costs in addition to the costs of social services) entailed the “healthcare payer/provider perspective” throughout the current review. On the other hand, a “societal perspective” referred to the scenario in which, additionally to the previous costs, productivity losses, defined as the economic valuation of paid worktime lost by the patients as a result of the disease, and informal care costs, defined as the economic valuation of the time allotted to care activities by a non-professional caregiver (friend or relative), were included. It should be

noted that the societal perspective should be applied not only to the costs, but also to the effects on the health of both the people who suffer from the disease and the members of their environment (relatives, friends). However, these effects are hardly ever included, and the consideration of a societal perspective is usually limited to costs.

We recorded a change in the conclusions when the decision about the adoption of a new technology was modified as a result of the inclusion of the social costs. For instance, from the healthcare perspective, the ICUR was above the threshold value, so the assessed technology was not recommended. But when social costs were included, the ICUR was modified so that it lay below the corresponding threshold. On the other hand, a change in results was identified when social costs were introduced and (i) ICUR fell below the threshold (the previous case referred to); (ii) the intervention became cost-saving (although it was previously already cost effective, but had a positive ICUR). It is important to stress that a significant change in the results may not change the conclusions of the analysis. For example, an intervention assessed with a favourable ICUR from the healthcare perspective would be recommended. If the inclusion of social costs made the ratio significantly more favourable (or even dominant), there would have been a change in the result of the economic evaluation, but the recommendation would not have been altered, as the evaluated intervention would have already been recommended from the healthcare perspective.

Results

The search strategy launched in PubMed retrieved 7421 potential references to be included in the review. In the CEA registry, we retrieved nearly 500 references. After removing the duplicates, we screened 7857 records obtained from PubMed and the CEA registry. [Figure 1](#) includes the PRISMA flowchart explaining the numbers at each stage of the systematic review. Briefly, we found 691 economic evaluations of healthcare-related technologies, of which only 47 (6.8%) fulfilled all the inclusion criteria. The main reason for exclusion was not including social costs ([Figure 1](#), $n=632$; 91.5%). 31 additional manuscripts considered social costs, but either it was not possible to extract the ICURs from both perspectives or the costs analysis was not reported separately. Finally, 28 studies did not include QALYs as an outcome.

Description of the Studies Included

The majority of the studies included in the review were carried out in Europe ($n=31$, 66%).^{30–60} In North America, 12 additional studies were carried out (25.5%)^{61–72} and only 4 studies took place in Asian countries ($n=4$; 8.5%).^{73–76} A pharmaceutical intervention was the diabetes-related intervention being assessed in the largest number of studies ($n=18$; 38.3%),^{30,33,35–38,41,42,48–53,56,57,59–61,71–73} followed by healthcare educational or behavioural programmes (including physical advisory and nutritional programmes).^{31,32,34,39,43,45–47,54,63,65,67,76} Only one study assessed a surgical intervention aimed at treating painful diabetic peripheral neuropathy using Spinal Cord Stimulation (SCS).⁵⁵ With respect to the time horizon of the economic evaluations performed, lifetime was the most prevalent one, as it was considered in 21 studies (45%).^{30,31,37,40–42,44,48–53,56,57,59,66–68,71,75} Shorter time horizons (of one year or less) were found in 10 of the 47 studies included in the review.^{32–34,36,39,46,47,55,58,73}

Regarding the social costs included in the studies, informal care costs were included in 13 studies,^{34,39,43,46,47,54,55,61,62,64,66,68,71} whereas the economic evaluation of productivity losses was included in most of them ($n=45$) (see [Table 1](#)). Moreover, of the 13 studies that considered informal care costs, the authors of 11 of them additionally included productivity losses, both these social costs being considered in this review together.^{34,39,43,46,47,54,55,61,66,68,71} Hence, informal care costs were only included in 2 studies,^{62,64} whereas productivity losses costs were individually included in 34 references. So, productivity losses were included much more frequently than informal care costs in the economic evaluation of diabetes-related healthcare interventions.

The method most frequently used to estimate productivity losses was the human capital approach. The friction cost method was applied in five studies,^{31,34,46,55,58} but only two studies explicitly indicated the length of the friction period. de Wit et al³⁴ used 84 days and Oostdam et al.⁴⁶ 154 calendar days and an elasticity correction factor of 0.8. Moreover, five studies included not only the loss of production due to absenteeism but also those losses attributable to presenteeism.^{33,34,47,63,68} de Salas-Cansado et al³³ directly asked the participants in the study about the patient's self-perceived average productivity at work (determined as 0–100% productivity). The authors then applied a formula to estimate the number of Lost Workday Equivalents. On the

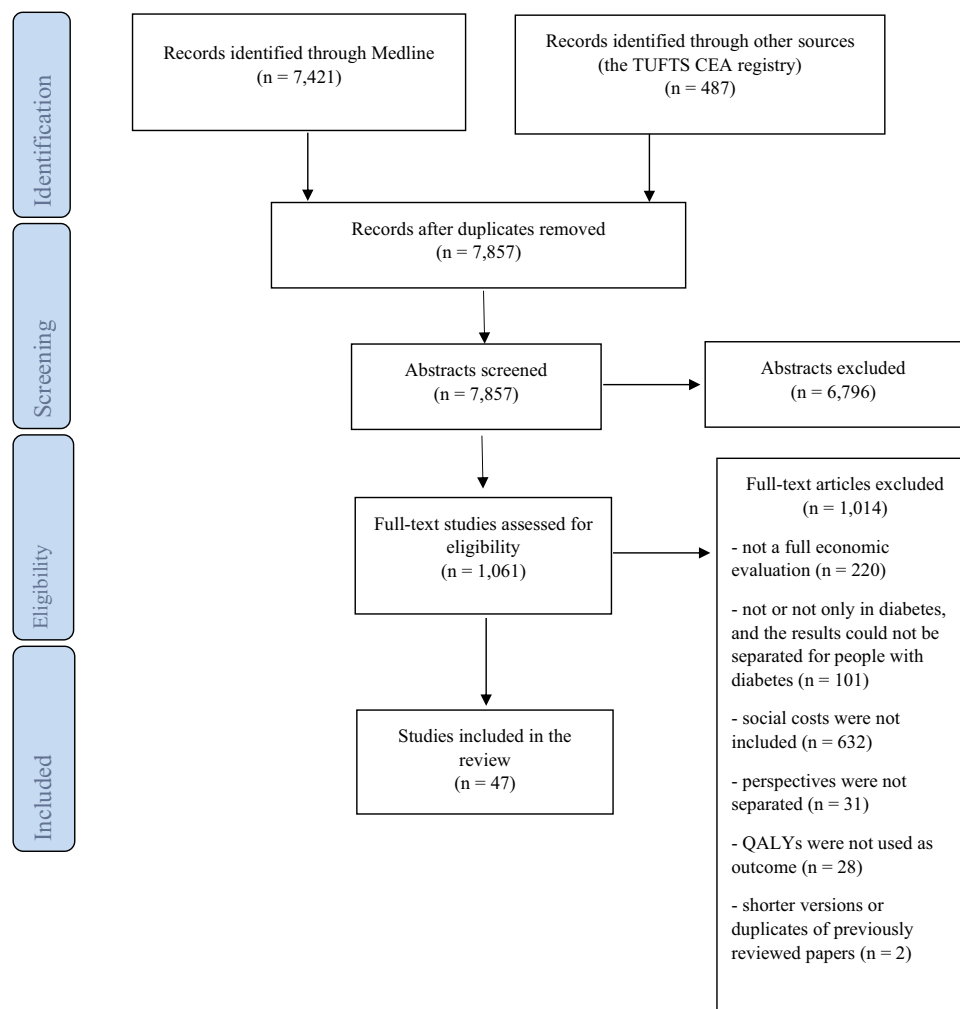


Figure 1 PRISMA flowchart of the search strategy.

other hand, Eddy et al⁶³ used the Quality of Well-being Index to estimate decreased productivity at work. In four of the articles the authors did not state the method applied for assessing productivity losses.^{48,66,71,73}

The informal care costs were estimated mainly by using the opportunity cost method (n=6),^{39,43,54,55,62,68} and only one study also used the good proxy method to assess the time of informal care.⁵⁴ The method used to estimate informal care costs was not reported in seven studies.^{34,46,47,61,64,66,71} Table 1 provides a further detailed description of the studies included in the review.

Effect of Including Social Costs on the Results and Conclusions of the Economic Evaluations Performed

From the 47 studies included in the review, it was possible to obtain 110 cost-utility analyses/estimations, as one

study could perform more than one economic evaluation, as was the case of de Wit et al³⁴ and Haig et al.⁶⁶ All these estimations are provided in [Table A1](#) with more detail from the [Appendix](#). Table 2 shows the twenty ICUR estimations (18.2%) from seventeen studies where we observed changes in results or authors' conclusions after consideration of the social costs.

The conclusions of the economic evaluation changed in 8 estimations from 7 studies^{32,40,51,52,55,62,63} when the societal perspective was considered. The inclusion of social costs in most cases (estimations number 18, 37, 41, 44 and 104) led to the intervention becoming cost-effective. Hence, the ICUR from the assessed intervention was above the threshold value from the healthcare payer's perspective and, once social costs were considered, the ICUR fell below the corresponding threshold. However, there were 2 additional estimations where the opposite change in conclusions was observed (estimations numbers

Table 1 Descriptive Information on the Selected Studies (n = 47)

First Author & Publication Year	Diabetes Type	Intervention Type	Country and Currency	Discount Rate (Costs/Outcomes)	Time Horizon	Costs Included	Method Used for Calculating Social Costs
Broekhuizen (2018) ³²	Gestational diabetes mellitus	Health education or behaviour	United Kingdom, Ireland, Austria, Poland, Italy, Spain, Denmark, Belgium, and the Netherlands (2012€)	n.a./n.a.	48 weeks	Healthcare costs: primary and secondary healthcare, medication, travel costs Social costs: productivity losses	Productivity losses: human capital approach (paid time - absenteeism)
De Wit (2018) ³⁴	Diabetes mellitus type 1 or type 2	Health education or behaviour	The Netherlands (2015€)	n.a./n.a.	6 months	Healthcare costs: hospital admissions, outpatient visits and calls, emergency room visits, ambulance transfers, medication and medical supply usage Social costs: productivity losses and informal care	Productivity losses: friction cost method (paid - absenteeism and presenteeism - and unpaid work) Informal care: n. a.
Ericsson (2018) ³⁵	Diabetes mellitus type 2	Pharmaceutical	Sweden (2015SEKs)	3%; 3%	40 years	Healthcare costs: anti-hyperglycaemic treatment and other treatment costs, diabetes-related complications Social costs: productivity losses	Productivity losses: human capital approach (paid time - absenteeism)
Breeze (2017) ³¹	Diabetes	Health education or behaviour	UK (2014/15 £)	1.5%, 1.5%	Lifetime	Healthcare costs: direct health care costs, intervention and HbA1c testing costs Social costs: productivity losses	Productivity losses: friction cost approach (paid time - absenteeism)
Jendel (2017) ⁴⁰	Diabetes mellitus type 1	Medical device/ pharmaceutical	Sweden (2015SEKs)	3%; 3%	Lifetime	Healthcare costs: intervention costs (insulin sensor), self-monitoring of blood glucose strips, diabetes-related complications Social costs: productivity losses	Productivity losses: human capital approach (paid time - absenteeism)

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Table 1 (Continued).

First Author & Publication Year	Diabetes Type	Intervention Type	Country and Currency	Discount Rate (Costs/ Outcomes)	Time Horizon	Costs Included	Method Used for Calculating Social Costs
Landstedt-Hallin (2017) ⁴⁴	Diabetes mellitus type 1	Medical device/ pharmaceutical	Sweden (2015SEKs)	3%; 3%	Lifetime	Healthcare costs: direct health care costs financed by tax payments and co-payments Social costs: productivity losses	Productivity losses: human capital approach (paid time - absenteeism)
Roze (2017) ⁴⁹	Diabetes mellitus type 1	Medical device	Denmark (2015DKK)	3%; 3%	Lifetime	Healthcare costs: direct medical costs due to diabetes-related complications, intervention costs (blood glucose self-testing) Social costs: productivity losses	Productivity losses: human capital approach (paid time - absenteeism)
Slangen (2017) ⁵⁵	Diabetes mellitus type 2	Surgical	Netherlands (2012€)	4%; 1.5%	12 months	Healthcare costs: specialist doctor, surgery, laboratory tests, revisions, paramedical visits, follow-up visits, medication, inpatient admission costs Social costs: productivity losses and informal care costs	Productivity losses: friction cost method (paid time - absenteeism) Informal care: opportunity cost method
Farshchi (2016) ⁷³	Diabetes mellitus type 2	Pharmaceutical	Iran (2012US \$)	n.a/n.a.	48 weeks	Healthcare costs: laboratory, medications, clinician visits, inpatient, non-medical costs Social costs: productivity losses	Productivity losses: n.a.
Haig (2016) ⁶⁶	Diabetes mellitus type 1 or type 2	Medical procedure, pharmaceutical	Canada (2013CAN\$)	5%; 5%	Lifetime	Healthcare costs: treatment and monitoring visits, complications, treatment costs Social costs: productivity losses and informal care costs	Productivity losses: n.a. Informal care: n.a.

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Table 1 (Continued).

First Author & Publication Year	Diabetes Type	Intervention Type	Country and Currency	Discount Rate (Costs/Outcomes)	Time Horizon	Costs Included	Method Used for Calculating Social Costs
Kolu (2016) ⁴³	Diabetes mellitus type 2	Health education intervention	Finland (2015 €)	Not specified	7 years	Healthcare costs: primary care doctor, specialist doctor, nursing, physiotherapist, medication, inpatient admission costs Social costs: productivity losses and informal care costs	Productivity losses: human capital approach (paid time - absenteeism costs) Informal care: opportunity cost method (paid time)
Lian (2016) ⁷⁴	Diabetes	Screening	China (2009HK\$)	3.5%; 3.5%	n.a.	Healthcare costs: staff time costs, co-payment intervention cost, capital costs, follow-up and treatment costs Social costs: productivity losses	Productivity losses: human capital approach (paid time - absenteeism)
Nguyen (2016) ⁷⁵	Diabetes mellitus type 2	Screening	Singapore (2015 Singapore\$)	3%; 3%	Lifetime	Healthcare costs: screening, follow-up visits, laser treatment, transportation costs Social costs: productivity losses	Productivity losses: human capital approach (paid time - absenteeism)
Roussel (2016) ⁴⁸	Diabetes mellitus type 2	Pharmaceutical	France (2013 €)	3%; 3%	Lifetime	Healthcare costs: diabetes medications, self-monitoring of blood glucose, concomitant medications and diabetes-related complications costs Social costs: productivity losses	Productivity losses: n.a. (paid time - absenteeism)
Roze (2016) ⁵³	Diabetes mellitus type 1	Medical device, pharmaceutical	United Kingdom (2013£)	3.5%; 1.5%	Lifetime	Healthcare costs: treatment costs (strips, lancets, transmitter and glucose sensors) and diabetes-related complication costs Social costs: productivity losses	Productivity losses: human capital approach (paid time - absenteeism)

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Table 1 (Continued).

First Author & Publication Year	Diabetes Type	Intervention Type	Country and Currency	Discount Rate (Costs/ Outcomes)	Time Horizon	Costs Included	Method Used for Calculating Social Costs
Roze (2016) ⁵²	Diabetes mellitus type 1	Medical device, pharmaceutical	France (2014 €)	4%; 4%	Lifetime	Healthcare costs: treatment costs (strips, lancets, transmitter and glucose sensors) and diabetes-related complication costs Social costs: productivity losses	Productivity losses: human capital approach (paid time - absenteeism)
Roze (2016) ⁵⁰	Diabetes mellitus type 1	Pharmaceutical	Netherlands (2013€)	4%; 1.5%	Lifetime	Healthcare costs: treatment costs (strips, lancets, transmitter and glucose sensors) and diabetes-related complication costs Social costs: productivity losses	Productivity losses: human capital approach (paid time - absenteeism)
Brown (2015) ⁶¹	Diabetes mellitus type 1 or type 2	Pharmaceutical	US (2012US\$)	3%; 3%	14 years	Healthcare costs: disease management and treatment costs, complications and adverse events costs, insurer costs Social costs: productivity losses and informal care costs	Productivity losses: human capital approach (paid time)
Cutino (2015) ⁶²	Diabetes mellitus type 1 or type 2	Medical device	US (2014US\$)	Not specified	15 years	Healthcare costs: study drug costs, administration and monitoring costs, concomitant treatments, adverse events Social costs: informal care costs	Informal care: opportunity costs (paid time)
Huetson (2015) ³⁸	Diabetes mellitus type 2	Pharmaceutical	Norway (2012NOKs)	4%; 4%	45 years	Healthcare costs: disease management and treatment costs, complications costs Social costs: productivity losses	Productivity losses: human capital approach (paid time)

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Table 1 (Continued).

First Author & Publication Year	Diabetes Type	Intervention Type	Country and Currency	Discount Rate (Costs/Outcomes)	Time Horizon	Costs Included	Method Used for Calculating Social Costs
Roze (2015) ⁵¹	Diabetes mellitus type 1	Medical device	Sweden (2011SEKs)	3%; 3%	Lifetime	Healthcare costs: intervention costs and diabetes-related complications costs (cardiovascular, renal, acute events, eye disease and other) Social costs: productivity losses	Productivity losses: human capital approach (paid time - absenteeism)
Kiadaliri (2014) ⁴²	Diabetes mellitus type 2	Pharmaceutical	Sweden (2014SEKs)	n.a/n.a.	Lifetime	Healthcare costs: drugs, self-monitoring blood glucose test strips and lancets, diabetes-related complications costs, treatment side effects costs Social costs: productivity losses	Productivity losses: human capital approach
Png (2014) ⁷⁶	Diabetes mellitus type 2 and prediabetes	Health education or behaviour - Pharmaceutical	Singapore (2012US\$)	3%; 3%	3 years	Healthcare costs: outpatient care, laboratory tests and medications Social costs: productivity losses	Productivity losses: human capital approach (paid time - absenteeism)
Steen-Carlsson & Persson (2014) ⁵⁷	Diabetes mellitus type 2	Pharmaceutical	Sweden (2013SEKs)	n.a/n.a.	Lifetime	Healthcare costs: preventive treatment, micro- and macrovascular complications costs Social costs: productivity losses	Productivity losses: human capital approach

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Table 1 (Continued).

First Author & Publication Year	Diabetes Type	Intervention Type	Country and Currency	Discount Rate (Costs/Outcomes)	Time Horizon	Costs Included	Method Used for Calculating Social Costs
Tsiachristas (2014) ⁵⁸	Diabetes mellitus type 2	Management program intervention	Netherlands (2012€)	n.a/n.a.	12 months	Healthcare costs: GP, nurse practitioner, nurse, dietician, physiotherapist, podiatrist, lifestyle coach, medical specialists in outpatient clinics etc., hospital admissions and admission days, and medication use Social costs: productivity losses	Productivity losses: friction cost method (paid time - absenteeism)
Ericsson (2013) ³⁶	Diabetes mellitus type 1 or type 2	Pharmaceutical	Sweden (2012 SEKs)	n.a/n.a.	1 year	Healthcare costs: insulin costs, needles, self-monitoring blood glucose test strips and lancets costs, general practitioner (GP) visit, GP home visit, and emergency department visit Social costs: productivity losses	Productivity losses: human capital approach (paid time - absenteeism)
Saha (2013) ⁵⁴	Diabetes	Physical exercise plus nutritional recommendations	Sweden (2012US\$)	3%; 3%	85 years	Health care costs: medical treatment costs, costs for institutional health care, pharmaceuticals Social costs: productivity losses and informal care costs	Productivity losses: human capital approach (paid time due to morbidity) Informal care: opportunity cost method (non-paid time) and replacement cost method
De Salas-Cansado (2012) ³³	Diabetes	Pharmaceutical	Spain (2006€)	n.a/n.a.	12 weeks	Healthcare costs: drug and non-drug treatments, medical visits, hospitalizations and diagnostic tests Social costs: productivity losses	Productivity losses: human capital approach (paid time - absenteeism and presenteeism)

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Table 1 (Continued).

First Author & Publication Year	Diabetes Type	Intervention Type	Country and Currency	Discount Rate (Costs/Outcomes)	Time Horizon	Costs Included	Method Used for Calculating Social Costs
Kamble (2012) ⁶⁹	Diabetes mellitus type 1	Medical device	United States (2010US\$)	3%; 3%	60 years	Healthcare costs: costs of glucose meters and test strips, lancets, insulin, and provider time to obtain annual treatment costs, costs of insulin pumps, transmitters, sensors, insertion devices and other pump suppliers Social costs: productivity losses	Productivity losses: human capital approach (paid time - absenteeism)
Oostdam (2012) ⁴⁶	Gestational diabetes	Non-pharmaceutical (exercise intervention)	Netherlands (2009€)	n.a/n.a.	32 weeks	Healthcare costs: visits to healthcare providers, medication Social costs: productivity losses and informal care costs	Productivity losses: human capital approach (paid time - absenteeism) and friction cost method (paid time - absenteeism) Informal care: n. a.
Smith-Palmer (2012) ⁵⁶	Diabetes mellitus type 2	Pharmaceutical	Sweden (2010SEKs)	3%; 3%	Lifetime (40 years)	Healthcare costs: diabetes-related complications costs, medications, self-monitoring blood glucose tests costs, treatment costs Social costs: productivity losses	Productivity losses: human capital approach
Greeley (2011) ⁶⁴	Diabetes mellitus type 1	Screening	United States (2008US\$)	3%; 3%	10, 20 and 30 years	Healthcare costs: medications, test strips, complications costs Social costs: informal care costs	Informal care: n. a. (paid time)

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Table 1 (Continued).

First Author & Publication Year	Diabetes Type	Intervention Type	Country and Currency	Discount Rate (Costs/ Outcomes)	Time Horizon	Costs Included	Method Used for Calculating Social Costs
Kasteng (2011) ⁴¹	Diabetes mellitus type 1 or type 2	Pharmaceutical	Sweden (2009SEKs)	3%; 3%	Lifetime	Healthcare costs: intervention drug costs, complications costs Social costs: productivity losses	Productivity losses: human capital approach (paid time - absenteeism)
Kuo (2011) ⁷⁰	Diabetes mellitus type 1 or type 2	Care delivery	United States (2010US\$)	3%; 3%	20 years	Healthcare costs: endocrinologist, registered/certified nurse or diabetes educator, exercise physiologist, medical assistant, rotated staff, laboratory tests, physician office hours, complications costs Social costs: productivity losses	Productivity losses: human capital approach (paid time)
Patel (2011) ⁴⁷	Diabetes mellitus type 1	Health education or behaviour	United Kingdom (2006£)	n.a/n.a.	1 year	Healthcare costs: hospital inpatient and outpatient services, primary care services, other community-based services, social services, medications, insulin-related equipment, other equipment and adaptations and intervention costs Social costs: productivity losses and informal care costs	Productivity losses: n.a. (paid time - absenteeism and presenteeism - and non-paid time) Informal care: n.a.
Valentine (2011) ⁶⁰	Diabetes mellitus type 2	Pharmaceutical	Switzerland (2008€)	3%; 3%	Lifetime	Healthcare costs: medications and treatment costs, complications costs Social costs: productivity losses	Productivity losses: human capital approach (paid time - absenteeism)

(Continued)

Table 1 (Continued).

First Author & Publication Year	Diabetes Type	Intervention Type	Country and Currency	Discount Rate (Costs/Outcomes)	Time Horizon	Costs Included	Method Used for Calculating Social Costs
Valentine (2011) ⁵⁹	Diabetes mellitus type 1	Pharmaceutical	Sweden (2006SEKs)	3%; 3%	50 years	Healthcare costs: diabetes-related complications costs, pharmacy costs Social costs: productivity losses	Productivity losses: human capital approach (paid time - absenteeism)
Huang (2010) ⁶⁸	Diabetes mellitus type 1	Diagnostic - Medical device	United States (2008US\$)	n.a./n.a.	Lifetime	Healthcare costs: intervention's technology and treatment costs, standard glucose monitoring costs, routine office visits, after-hours clinic visits, emergency room visits, 911 calls, and hospitalizations Social costs: productivity losses and informal care costs	Productivity losses: human capital approach (paid time - absenteeism and presenteeism) Informal care: opportunity cost method (paid time)
Ismail (2010) ³⁹	Diabetes mellitus type 2	Non-pharmacological intervention	United Kingdom (2005/06£)	n.a./n.a.	1 year	Healthcare costs: hospital inpatient and outpatient services, primary care services, other community-based services, social services, medications, insulin-related equipment, other equipment and adaptations and the cost of the interventions Social costs: productivity losses and informal care costs	Productivity losses: human capital approach (paid and non-paid time) Informal care: opportunity cost method (paid and non-paid time)

(Continued)

Table I (Continued).

First Author & Publication Year	Diabetes Type	Intervention Type	Country and Currency	Discount Rate (Costs/Outcomes)	Time Horizon	Costs Included	Method Used for Calculating Social Costs
Gschwend (2009) ³⁷	Diabetes mellitus type 1	Pharmaceutical	Belgium, France, Germany, Italy and Spain (2006€)	Belgium 3% costs, 1.5% benefits; France 3% both; Germany 5% both; Italy 3% both; Spain 6% both	Lifetime	Healthcare costs: diabetes-related complication costs, medication (insulin) and needles and devices for self-monitoring of blood glucose Social costs: productivity losses	Productivity losses: human capital approach
Lindgren (2007) ⁴⁵	Diabetes mellitus type 2	Health education or behaviour	Sweden (2003 €)	3%; 3%	n.a.	Healthcare costs: intervention costs, physician visits, nutritionist visits, training sessions, travel time, diabetes-related complications costs Social costs: productivity losses	Productivity losses: human capital approach (paid time - absenteeism)
Valentine (2006) ⁷²	Diabetes	Pharmaceutical	United States (2002US\$)	3%; 3%	35 years	Healthcare costs: treatment, diabetes-related complications, medication costs Social costs: productivity losses	Productivity losses: human capital approach (paid time - absenteeism)
Eddy (2005) ⁶³	Diabetes	Health education or behaviour	United States (2000US\$)	3%; 3%	30 years	Healthcare costs: hospital admissions and emergency department visits, office and clinic visits, tests and discrete procedures, medications and ongoing programs Social costs: productivity losses	Productivity losses: human capital approach (paid time - absenteeism and presenteeism)

(Continued)

Table 1 (Continued).

First Author & Publication Year	Diabetes Type	Intervention Type	Country and Currency	Discount Rate (Costs/Outcomes)	Time Horizon	Costs Included	Method Used for Calculating Social Costs
Herman (2005) ⁶⁷	Diabetes mellitus type 2	Health education intervention - Pharmaceutical	United States (2000US\$)	3%; 3%	Lifetime	Healthcare costs: intervention costs, diabetes-related complication costs, physician visits, hospitalizations Social costs: productivity losses	Productivity losses: n.a.
Rosen (2005) ⁷¹	Diabetes	Pharmaceutical	United States (2003US\$)	3%; 3%	Lifetime	Healthcare costs: intervention costs, diabetes-related complication costs, ongoing costs of care, medication costs Social costs: productivity losses and informal care costs	Productivity losses: n.a. Informal care: n.a.
The Diabetes Prevention Program Research Group (2003) ⁶⁵	Diabetes mellitus type 2	Pharmaceutical - Health education or behaviour	United States (2000US\$)	3%; 3%	3 years	Healthcare costs: intervention costs, side effects of the intervention, care outside the prevention program (hospital, emergency room, urgent care, and outpatient services; telephone calls to health care providers; and prescription medications), travel costs Social costs: productivity losses	Productivity losses: human capital approach (paid time - absenteeism)

(Continued)

Table 1 (Continued).

First Author & Publication Year	Diabetes Type	Intervention Type	Country and Currency	Discount Rate (Costs/Outcomes)	Time Horizon	Costs Included	Method Used for Calculating Social Costs
Almbrand (2000) ³⁰	Diabetes mellitus type 1 or type 2	Pharmaceutical	Sweden (1999 €)	3%; 3%	Lifetime	Healthcare costs: medication costs, hospitalizations, post-hospital discharge costs, diagnostic and monitoring procedures and tests, and outpatient visits Social costs: productivity losses	Productivity losses: human capital approach (paid time)

2 and 26). In estimation number 2,³² when social costs were considered, the assessed intervention was no longer cost-saving, as it was from the healthcare perspective. Informal care was included only in two studies^{55,62} and productivity losses in six of them. All the interventions were focused on the assessment of educational or behavioural programmes or medical devices, and the time horizons were quite similar. Most of the interventions in which the inclusion of social costs modified the conclusions were medical devices interventions,^{40,51,52,62} whereas another two were health education or behaviour programmes^{32,63} and another was a surgical procedure.⁵⁵

11 estimations from 9 studies provided changes in the ICUR results but not in the conclusions of the economic assessment.^{31,34,42,45,59–61,66,76} In 9 of them (estimations numbers 10, 15, 28, 29, 39, 51, 91, 92 and 102), the new intervention was already cost-effective (the ICUR was below the threshold) from the healthcare perspective but it dominated the comparator when the social costs were considered. Two estimations from one study reported lower QALYs in the treatment group and also lower costs when the healthcare perspective was considered, with the new intervention ICUR lying above the acceptance threshold.³⁴ When the societal approach was considered, the ICUR resulted in negative values, as the assessed intervention became dominated due to its positive incremental costs and lower health gains, against its comparator. Finally, in the results of the economic assessment, we observed one change that was the opposite of the rest when the societal perspective was considered. A novel

pharmaceutical treatment dominated the comparator treatment when the healthcare perspective was considered, but when the societal perspective was used, the intervention did not dominate the comparator, but remained cost-effective according to the threshold stated by the authors (estimation number 47⁴²).

Figures 2 and 3 show the dispersion of the costs and QALYs of the 110 economic evaluation estimations included, according to the perspective applied. Both figures show the economic evaluation results of the assessed interventions, reporting the incremental health gains measured in QALYs in the horizontal axis and the incremental costs in the vertical axis. The dots located in the upper-right quadrant represent those interventions with higher costs than their comparator but with gains in health results (better HRQoL) as well. Moreover, two frequently used reference values of cost-effectiveness thresholds (30,000 and 50,000 euros per QALY) are also provided, which are represented by the two blue diagonals. If dots were above those thresholds mean the interventions that would not be implemented since, when being compared with their comparator, their ICUR is higher than the threshold considered as a reference of willing to pay by the healthcare provider/society. Conversely, any dot below those lines denotes a healthcare intervention that would be indeed implemented. Although minor differences might be observed, there seems to be a higher number of dots below the X axis (lower incremental costs) in Figure 3, which represents the societal perspective, than in Figure 2, which corresponds to the healthcare perspective.

Table 2 Incremental Costs, QALYs and ICURs from the Healthcare Payer/Provider and the Societal Perspective in the Estimations That Changed Results or Conclusions After the Inclusion of Social Costs

Estimation Number	Authors and Publication Year	Healthcare Payer/Provider Perspective				Societal Perspective				Perspectives Comparison Do the Conclusions Change? (YES/NO)	Threshold Value
		ΔCosts	ΔQALYs	ICUR (Cost/QALY)	Authors' Conclusions	ΔCosts	ΔQALYs	ICUR (Cost/QALY)	Authors' Conclusions		
2	Broekhuizen et al (2018) ³²	-23	-0.003	7667	The intervention is more cost-effective than usual care	653	-0.003	-241,959	The intervention is dominated by usual care	YES	€10,000-24,400
4	de Wit et al (2018) ³⁴	-197	-0.0008	247,388	The intervention is less cost-effective than usual care	708	-0.0008	-888,936	HypoAware is dominated by usual care	NO, but when social costs are included, the intervention is dominated	€20,000
5	de Wit et al (2018) ³⁴	-197	-0.001	23,130	The intervention is less cost-effective than usual care	708	-0.001	-83,112	The intervention is dominated by usual care	NO, but when social costs are included, the intervention is dominated	€20,000
10	Breeze et al (2017) ³¹	0	0.0001	0	The intervention is more cost-effective than doing nothing	-0.02	0.0001	-200	The intervention dominates doing nothing	NO, but when social costs are included, the intervention becomes cost-saving	£20,000
15	Breeze et al (2017) ³¹	0	0.0001	0	The intervention is more cost-effective than doing nothing	-0.01	0.0001	-100	The intervention dominates doing nothing	NO, but when social costs are included, the intervention becomes cost-saving	£20,000
18	Jendel et al (2017) ⁴⁰	350,484	1.067	328,476	The intervention is more cost-effective than the comparator	268,899	1.067	252,014	The intervention is more cost-effective than the comparator	YES	SEKs 300,000

26	Slangen et al (2017) ⁵⁵	16,569	0.22	75,314	The intervention is more cost-effective than the comparator	21,226	0.22	96,481	The intervention is less cost-effective than the comparator	YES	€80,000
28	Haig et al (2016) ⁶⁶	9849	0.4	24,494	The intervention is more cost-effective than the comparator	-18,993	0.4	-47,483	The intervention dominates the comparator	NO, but when social costs are included, the intervention becomes cost-saving	CAN\$ 50,000
29	Haig et al (2016) ⁶⁶	11,471	0.32	36,414	The intervention is more cost-effective than the comparator	-11,114	0.32	-34,731	The intervention dominates the comparator	NO, but when social costs are included, the intervention becomes cost-saving	CAN\$ 50,000
37	Roze et al (2016) ⁵²	35,801	1.187	30,163	The intervention is less cost-effective than the comparator	31,884	1.187	26,863	The intervention is more cost-effective than the comparator	YES	€30,000
39	Brown et al (2015) ⁶¹	56,366	0.9981	56,445	The intervention is more cost-effective than the comparator for threshold values > \$56,500	-30,807	0.9981	-30,866	The intervention dominates the comparator	NO, but when social costs are included, the intervention becomes cost-saving	\$50,000–100,000
40	Cutino et al (2015) ⁶²	18,880	0.1288	146,584	The intervention is less cost-effective than the comparator	5015	0.1288	38,948	The intervention is more cost-effective than the comparator	YES	\$50,000
41	Cutino et al (2015) ⁶²	13,548	0.1288	105,186	The intervention is less cost-effective than the comparator	-1367	0.1288	-10,613	The intervention dominates the comparator	YES	\$50,000
44	Roze et al (2015) ⁵¹	415,106	0.76	545,005	The intervention is less cost-effective than the comparator	279,962	0.76	367,571	The intervention is more cost-effective than the comparator	YES	SEKs 500,000

(Continued)

Table 2 (Continued).

Estimation Number	Healthcare Payer/Provider Perspective				Societal Perspective				Perspectives Comparison Do the Conclusions Change? (YES/NO)	Threshold Value	
	Authors and Publication Year	Δ Costs	Δ QALYs	ICUR (Cost/QALY)	Authors' Conclusions	Δ Costs	Δ QALYs	ICUR (Cost/QALY)			Authors' Conclusions
47	Kiadaliri (2014) ⁴²	-1912	0.15	-12,747	The intervention dominates the comparator	5936	0.15	39,573	The intervention is more cost-effective than the comparator	NO, but when social costs are included, the intervention is no longer costs-saving	SEKs 500,000
51	Png et al (2014) ⁷⁶	281	0.01	21,065	The intervention is more cost-effective than the comparator	-19,915	0.01	-1,991,500	The intervention dominates the comparator	NO, but when social costs are included, the intervention becomes cost-saving	\$53,000
91	Valentine et al (2011) ⁶⁰	1023	0.15	6820	The intervention is more cost-effective than the comparator	-346	0.15	-2307	The intervention is more cost-effective than the comparator	NO, but when social costs are included, the intervention becomes cost-saving	€40,000-60,000
92	Valentine et al (2011) ⁵⁹	26,144	0.53	49,328	The intervention is more cost-effective than the comparator	-80,113	0.53	-151,157	The intervention is more cost-effective than the comparator	NO, but when social costs are included, the intervention becomes cost-saving	SEKs 100,000-400,000
102	Lindgren et al (2007) ⁴⁵	1673	0.2	8365	The intervention is more cost-effective than the comparator	-1853	0.2	-9265	The intervention dominates the comparator	NO, but when social costs are included, the intervention becomes cost-saving	Not determined
104	Eddy et al (2005) ⁶³	22,737	0.159	143,000	The intervention is less cost-effective than the comparator	9969	0.159	62,698	The intervention is more cost-effective than the comparator	YES	\$100,000

Note: Δ Stands for incremental.

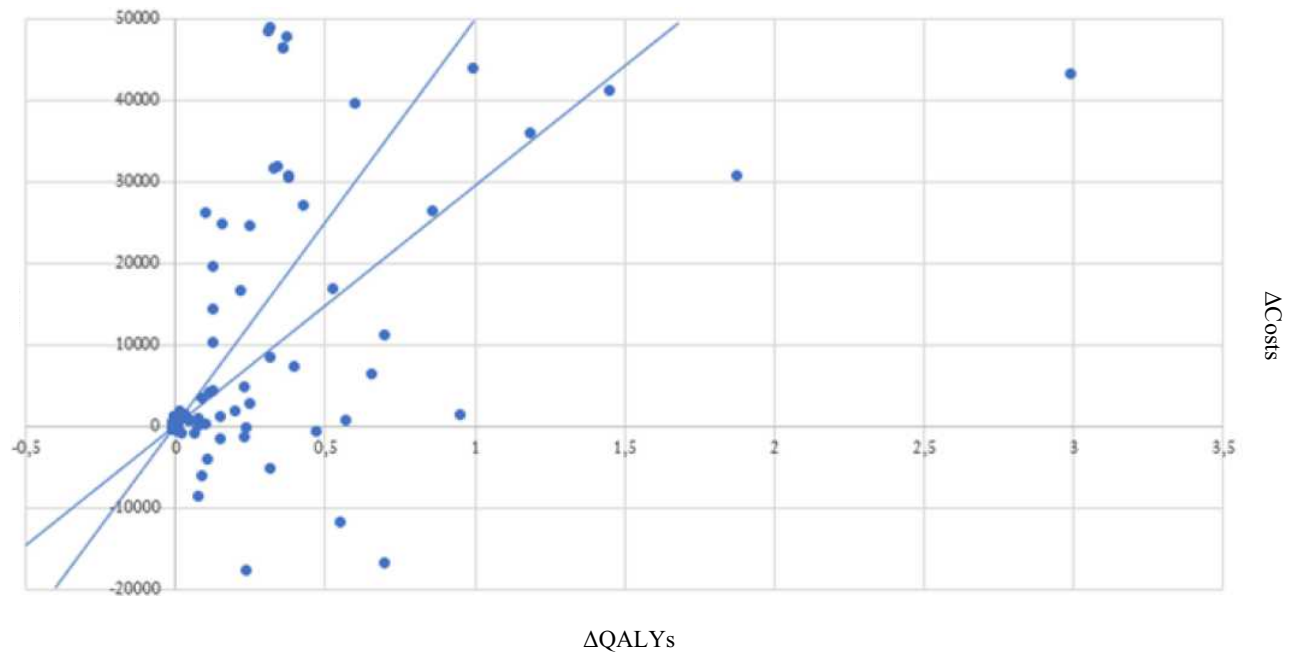


Figure 2 Incremental Cost-Utility Ratios from the healthcare perspective. For ease of comparison, results are shown in additional euros per additional QALY, applying the euro-currency exchange rates of the year of each record. The values were not updated to any base year since the efficiency thresholds applied as a usual reference are usually kept constant over several years. In this sense, and to facilitate the interpretation of the results of both panels, two vectors were drawn with the values of €30,000/QALY and €50,000/QALY since they are frequently cited thresholds in the economic evaluation literature.

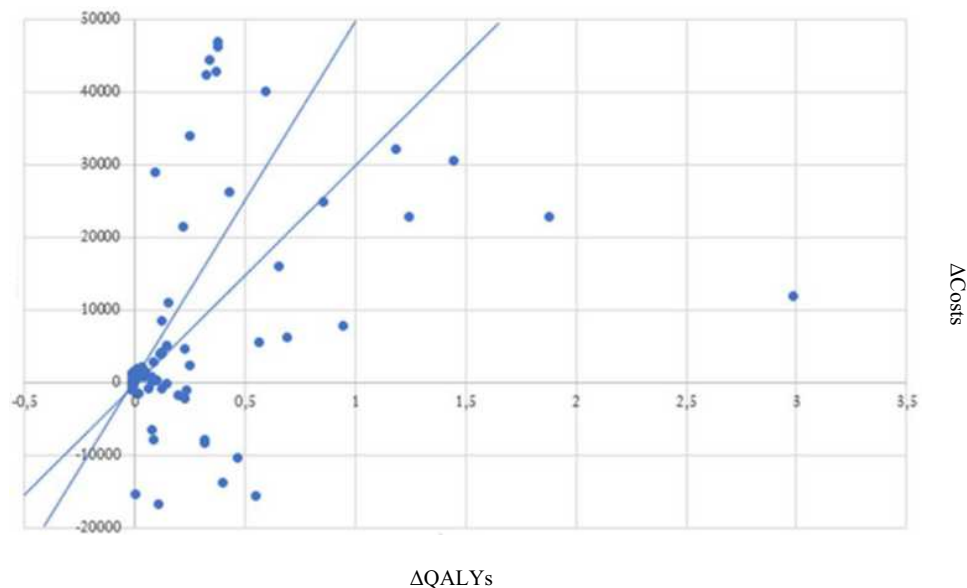


Figure 3 Incremental Cost-Utility Ratios from the societal perspective. For ease of comparison, results are shown in additional euros per additional QALY, applying the euro-currency exchange rates of the year of each record. The values were not updated to any base year since the efficiency thresholds applied as a usual reference are usually kept constant over several years. In this sense, and to facilitate the interpretation of the results of both panels, two vectors were drawn with the values of €30,000/QALY and €50,000/QALY since they are frequently cited thresholds in the economic evaluation literature.

Discussion

Although many studies have systematically reviewed economic evaluations of diabetes-related interventions, our analysis builds on the existing literature by assessing the

key role that social costs potentially play in the decision-making processes in diabetes-related healthcare technologies. Our findings showed that, of the 738 records that consisted of a full diabetes-associated economic

evaluation, only 106 included social costs (14.36%), from which 47 articles were finally selected in accordance with our inclusion criteria. An increasing number of national guidelines accept or even recommend the inclusion of a double perspective (societal perspective in addition to the healthcare payer/provider or the third-party payer perspective) as this obtains complementary results.^{77–83} However, of the forty-seven articles selected in our review, only sixteen applied both perspectives as the main viewpoints of the analyses. Moreover, our findings regarding the inclusion of social costs in all those articles that described an economic evaluation differed from those in similar work carried out on other diseases⁸⁴ such as Alzheimer's disease,²¹ where the proportion of social costs in economic evaluations reached more than two-thirds, and depression, where the figure was 42%.²³ By contrast, for DM the percentage of economic evaluation studies which included social costs was close to that in the case of rare diseases, where it was only 11%.²⁴

Moreover, from the 47 selected articles, 45 (96%) included productivity losses whereas only 13 (28%) included informal care costs. The scarce inclusion of informal care costs in diabetes-related economic evaluations and cost-of-illness studies has also been supported in the literature, which shows that only two articles from the 141 potential records in a recent review included informal care costs in the case of diabetes. Another recent review of economic evaluations carried out from 2013 to 2015 on several therapeutic areas, in which diabetes was not included, showed that the inclusion of informal care was limited (61 out of 484 potential records), but relevant, changing the conclusion of the economic evaluation or leading to cost savings. However, that review found that productivity losses and informal care costs were included in 86% and 23% respectively of the identified articles on musculoskeletal disorders or dysfunction, 94% and 47% respectively in the case of mental health problems, and 60% and 20% respectively in the case of infectious diseases.⁸⁴ These figures point towards a lack of consensus in health technology assessment with respect to the costs which should be included,⁸⁵ regardless of the therapeutic area analysed. On the other hand, the greater presence of productivity losses compared to informal care may be showing a bias in favour of reflecting costs that affect people of working age and against reflecting other costs that are related to older people. While it is true that the inclusion of labour losses has a greater tradition in the field

of economic evaluation in general, and in the economic evaluation of healthcare interventions in particular, most people with diabetes are older people who are outside the labour market. Instead, according to most international studies,^{86–88} the non-professional or informal care which they receive is usually provided by their closest affective environment, more precisely, by their partner or their daughter. This means that a significant percentage of caregivers are not part of the labour force either. However, the opportunity cost incurred by caregivers represents a significant proportion of the social cost of diseases and should therefore be taken into account. On the other hand, current trends indicate that in the coming decades an important part of this informal care will be replaced or complemented by long-term professional care,^{89,90} which will have an important effect on public and household budgets.

The second purpose of the literature review was to assess whether the inclusion of social costs changed the conclusions regarding the adoption of the evaluated intervention. The conclusions were modified in eight out of the 110 estimations resulting from the 47 articles (7%): six of them switched from being non-cost-effective from the healthcare payer/provider perspective to cost-effective when social costs were included. The results obtained were similar to those of other diseases such as Alzheimer's, in which the inclusion of social costs altered the conclusions in 11% of the economic evaluations included²¹ but differed from the case of expensive drugs, where the change in the conclusions affected more than one third of the analyses.²⁰ Some characteristics are shared among the studies whose conclusions changed after the inclusion of social costs and hence could be key drivers in the modification of conclusions: i) only productivity losses were entered as social costs,^{40,51,52,63} using the human capital approach for their valuation and with absenteeism being included in all of them;⁶³ ii) the authors applied longer time horizons (from fifteen years to lifetime); iii) they were interventions targeting individuals with type 1 diabetes; and iv) the type of intervention, which in most cases was a medical device.^{40,51,52}

Furthermore, without leading to a change in conclusions but providing them with additional support, nine estimations became dominant when social costs were included (estimation numbers 10, 15, 28, 29, 39, 51, 91, 92 and 102). The savings were almost negligible in two of these estimations (numbers 10 and 15), but in the other seven, cost savings were observed when the societal

perspective was used. Moreover, these seven studies shared some common patterns: i) all of them referred to a pharmaceutical intervention among individuals with DM type 2; ii) longer time horizons, most of which were life-time; and iii) productivity losses due to absenteeism, using the human capital approach for their valuation. A recent review of economic evaluations of different types of insulin, one of the main drugs used by people with diabetes, showed that its cost-effectiveness among individuals with type 2 diabetes was inconclusive.^{91–93} However, only in those studies where the authors performed the economic evaluation from a societal perspective (three from a total of the forty-three studies included), were the interventions dominant,^{36,94,95} highlighting the significant and favourable economic impact of including social costs in these interventions.

We also detected changes in the final conclusion but in the opposite way. This was the case of the results obtained in estimations 4 and 5, in which de Wit et al³⁴ assessed a health education or behaviour programme for people with DM type 1 or 2 during a six-month period. The results showed that when both productivity losses and informal care costs were included, the intervention was no longer cost-saving, whereas from the healthcare perspective, it was. These results, in addition to the two aforementioned studies that changed the conclusions from cost-effective to non-cost-effective⁵⁵ or dominated,³² point towards a significant long-term effect on incremental costs from the introduction of social costs in the context of diabetes-related interventions.

Some limitations should be mentioned, especially in connection with methodological questions, which limit the comparability of studies. First, we may have missed some references due to our search strategy and the databases where it was launched. In this connection, we tried to avoid bias by using more than one dataset, and we aimed to retrieve economic evaluations using a cost-utility design by searching on both Medline and the CEA registry of Tufts University. The joint use of both literature databases can be explained by the following reasons: Medline contains more than 25 million references to journal articles about life sciences with a concentration on biomedicine, as well as the health-technology assessments (HTA) published in scientific journals. Although other literature databases could have been used, other previous works have shown that very few additional economic evaluations are found in databases other than Medline, while a number of papers may in fact be lost in other databases if substituted

for Medline.^{96–99} In order to avoid loss of sensitivity in our search strategy, we also used the Cost-Effectiveness Analysis (CEA) Registry of Tufts University, which uses an algorithm also launched in Medline plus a systematic review process in which only cost-utility analyses are included.^{26,100} By using both sources, Medline and the CEA Registry, we were able to retrieve scientific papers that fulfilled our inclusion criteria. Secondly, it should be noted that we do not intend to perform again or re-interpret the economic evaluations included in the review, but, instead, we took into account the information provided by the original authors (ie the acceptability proposed after threshold) and their interpretations of the results. However, as [Table A1](#) shows, such cost-effectiveness threshold values and conclusions might not be implicit and might be subject to debate. Thirdly, the comparability of studies related to the valuation of social costs might be compromised since no homogeneous methodology was observed among the studies included. For instance, with respect to the thirteen studies that included informal care costs, only six of them explicitly stated the method used to value informal care, the opportunity cost method being used in all of them, and both the opportunity cost and the replacement cost methods being used in one study.⁵⁴ Moreover, only three of the studies provided the unit cost applied, and instead of this, the information provided by the others ranged from hourly wages^{39,55} to monthly costs, adjusted by age.⁶² Regarding productivity losses, from the forty-five included studies, four did not specify the method applied, and when mentioning the technique used, thirty-two reported that they had applied the human capital approach to value productivity losses, four had used the friction cost method^{31,34,55,58} and one of them had used both.⁴⁶ Of those using the friction cost approach, only one study provided detailed information about the length of the friction period (84 days) and the attribution of gender-specific incomes.³⁴ From the productivity loss components, time paid for absenteeism was valued in twenty-six works, and absenteeism and presenteeism in three articles.^{33,63,68} Unpaid time was additionally included with paid time in three studies.^{34,39,47}

We conclude by pointing out that despite the burden that social costs impose on diabetes, there is still a lack of evidence about the consequences of excluding them from economic evaluations of interventions targeting people with diabetes. The literature review performed shed new light on cost-utility analyses involving the assessment of diabetes-related interventions that include social costs,

showing that consideration of informal care costs and/or productivity losses changed the results or conclusions in 18% of economic evaluations of diabetes (in 20 out of 110). Moreover, the inclusion of productivity losses in most of the selected articles (96%) and of informal care costs in almost one third of them signals the burden that diabetes imposes on its sufferers, limiting their ability to work^{11,13–15} or requiring a greater need for care.^{13,101,102} However, comparisons should be made with caution, as the different types of diabetes affect completely different profiles, with respect to age, state of health, healthcare use and lifestyle.¹⁰³ While type 1 DM (5–10% of all diabetes) usually starts in childhood or early adulthood and usually cannot be prevented, type 2 DM (90–95% of all diabetes) is commonly developed during adulthood and old age and can be prevented or delayed by healthy lifestyles.^{104,105} Those different patient profiles should promote a change in the type of social costs included and their effect on the adoption of new healthcare technologies, as this literature review has shown. In view of the increasing worldwide prevalence of diabetes that is expected in the coming years, mainly of type 2 diabetes in older populations,¹⁰⁶ and the fact that policymakers may need to balance the impact of new healthcare interventions on health budgets, incident cases of diabetes and equity of healthcare provision, the findings obtained here might be of help in directing the appropriate interventions to the right diabetes populations within their scope. In this sense, considering the age group mainly affected by type 2 DM and its associated complications, which might impair their functional status and might result in a greater need for care, further research should take into account the inclusion of additional informal care costs in the analysis. This would help to bring new evidence closer to real clinical practice and would therefore help to provide policymakers with relevant and accurate information that would consider the effect of ageing on social services and non-formal resources aimed at fighting dependence in the performance of activities of daily living.

Moreover, since comparisons of current cost-utility analyses are challenging because of the various alternatives and methodologies used, further improvement is required, particularly in relation to explanations of the perspectives applied in the analysis, to the methodology applied to perform the economic evaluation and to the sources of utility and costs (especially in those studies where a lifetime is used, and a mathematical model is applied to simulate the progress of the illness). The

inclusion of all types of costs and health effects from a societal perspective could serve as more detailed information to ease decision-making by policymakers, leading to a more efficient and equitable design of diabetes-related programmes and interventions which could eventually be implemented.

Data Sharing Statement

All data generated or analysed during this study are included in this published article (and its [Appendix](#)).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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