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Review

A systematic review on costs and cost-effectiveness of screening and prevention of type 2 diabetes in women with prior gestational diabetes: Exploring uncharted territory

Amber Werbrouck [a,b,*], *Masja Schmidt* [c], *Koen Putman* [c], *Katrien Benhalima* [d], *Nick Verhaeghe* [a,c], *Lieven Annemans* [a,1], *Steven Simoens* [b,1]

[a] *Department of Public Health and Primary Care, Interuniversity Centre for Health Economics Research (I-CHER), Ghent University, De Pintelaan 185, 9000 Gent, Belgium*

[b] *Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, O&N2 bus 521, Herestraat 49, 3000 Leuven, Belgium*

[c] *Department of Public Health, Interuniversity Centre for Health Economics Research (I-CHER), Vrije Universiteit Brussel, Laarbeeklaan 103, 1090 Brussel, Belgium*

[d] *Department of Endocrinology, University Hospital Gasthuisberg, KU Leuven, Herestraat 49, 3000 Leuven, Belgium*

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ABSTRACT

Aims: Women with gestational diabetes mellitus (GDM) are more likely to develop type 2 diabetes mellitus (T2DM) as compared to women with normoglycemic pregnancies. This study aims to explore the literature on cost(-effectiveness) of screening and prevention of T2DM in women with prior GDM.

Methods: Five databases were systematically searched, inclusion criteria were: (1) women with (prior) GDM; (2) post-partum screening or prevention of T2DM; and (3) health-economic evaluations. No year limits were applied. English, Dutch, French or German publications were included. Quality was assessed using the Consensus Health Economic Criteria checklist.

Results: Two cost-effectiveness analyses and two cost analyses were found. One study evaluated nine screening strategies. Three studies evaluated one prevention strategy each: intensive diet and behavioural modification; annual counseling; and an annual dietary consultation. Methodological quality was poor. Perspectives were unclear, time horizons were too short, and no incremental analyses were performed.

Conclusion: An oral glucose tolerance test per three years leads to the lowest cost per case detected, and prevention is potentially cost-effective or cost-saving. More health economic evaluations are needed that compare all relevant alternatives, including 'doing nothing'.

* Corresponding author at: Corneel Heymanslaan 10, Building 4K3, 9000 Gent, Belgium.
E-mail address: amber.werbrouck@ugent.be (A. Werbrouck).

[1] Shared last-authorship.

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Contents

1. Introduction

The World Health Organization (WHO) estimates that globally 422 million adults had diabetes in 2014, meaning that prevalence has almost doubled since 1980 (4.7% in 1980, to 8.5% in 2014) [1]. Diabetes causes serious microvascular (e.g. retinopathy, nephropathy and peripheral neuropathy) and macrovascular complications (e.g. stroke and myocardial infarction), leading to decreased quality of life and a decreased life expectancy [1–3]. Moreover, in 2015 global costs of diabetes were estimated at US$ 1.31 trillion or 1.8% of global gross domestic product, making it one of the most expensive diseases to treat [4,5].

Diabetes mellitus type 2 (T2DM) accounts for more than 90% of all diagnosed cases [6,7]. Gestational diabetes mellitus (GDM) is a less common type of diabetes, defined as "diabetes diagnosed in the second or third trimester of pregnancy" [8]. Several recommendations for screening strategies of GDM have been developed, yet consensus is lacking [9]. Due to different screening strategies, incidence rates show large variations, from 1% to 20% globally [9–11]. Despite these difficulties, identification of GDM is important to prevent short-term adverse neonatal and maternal outcomes, such as macrosomia or pre-eclampsia [12,13]. Moreover, screening of GDM identifies a population at risk for future development of T2DM, since women with prior GDM are over seven times more likely to develop T2DM (relative risk: 7.43), compared to women with normoglycemic pregnancies [10]. Thus, identifying women with prior GDM as a specific population at risk offers unique opportunities to provide targeted prevention programs.

Costs and consequences of T2DM could be avoided, as it is well known that several modifiable risk factors (e.g. overweight and obesity, unhealthy diet, physical inactivity and smoking) are associated with T2DM [1]. However, substantial differences in intensity of screening and prevention programs exist. Examples of programs for T2DM with differential intensities are: screening alone [14–17], screening combined with awareness campaigns [18–20], or screening combined with intensive lifestyle or pharmaceutical interventions [21,22]. It is likely that the effectiveness of such programs will be determined by, among other factors, the intensity of the program. Regarding programs that offer screening alone, several studies assume that screening alone could lead to decreased time to detection of T2DM, which can prevent or delay complications [16,17]. Although this seems plausible, there is limited evidence on the effect of early detection on complications [14,15]. Screening programs combined with an awareness campaign are a low-cost option compared to intensive prevention programs. Evidence on the effect of awareness is scarce, but an American study found that being told of the

increased diabetes risk was associated with increased adoption of healthy lifestyle behaviors [19]. There is an extensive body of literature on the effectiveness of intensive lifestyle or pharmaceutical interventions in a general population at risk [1,23,24] as well as in women with prior GDM [21,22]. Although interventions in both target groups have been shown to be effective, these findings cannot simply be extrapolated from a general population at risk to women with a recent history of GDM. The latter are often younger than other at-risk populations, and difficulties during recruitment or low retention rates have been reported [25,26]. This could be explained by specific barriers early after child birth, as well as low risk perception [21,27].

Evidence on the effectiveness of screening and prevention of T2DM grows, but this evidence alone is often insufficient to inform decision makers about the most appropriate screening or prevention strategies. When only effectiveness would be taken into account, it is likely that costly, high-intensity programs would be most appropriate. However, such programs might generate higher costs, and should only be adopted if the expected costs are justified by the expected effects. Full health economic evaluations are needed to allow consideration of both effects and costs of different interventions, and more specifically, the ratio between these effects and costs [28]. For a population at risk for T2DM in general, several health-economic evaluations have been executed and showed that preventive approaches are likely to be cost-effective [5,17,29,30]. The cost-effectiveness of interventions for diabetes prevention has been subject to systematic reviews before [29,30]. Even though women with GDM were included as a high risk population, they were not the main focus of these reviews. Moreover, both reviews excluded partial health economic evaluations and one of the reviews focused solely on lifestyle interventions. Therefore, the aim of this study was to systematically review existing literature on costs and cost-effectiveness of screening and prevention programs of T2DM in women with prior GDM.

2. Methods

The "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) statement was followed [31]. Other guidelines, specifically focusing on the preparation of a systematic review of health economic studies, were consulted [32–34]. Methods of this systematic review were specified a priori and documented in a protocol. The protocol was reviewed by a clinical expert (KB) and is available upon request from the corresponding author.

2.1. Literature search

Five electronic databases were systematically searched. The electronic search strategy was developed for MEDLINE (via PubMed, see Appendix A) and adapted for EMBASE (via embase.com), EconLit (via ProQuest), Web of Science Core Collection (via Web Of Science) and all Cochrane databases (via the Cochrane Library). The last search was performed on July 4th, 2017. No filters (e.g. publication date or type of study) were applied.

The key concepts that were translated into search strings, were: (1) women with (prior) GDM, (2) screening or prevention, (3) T2DM, and (4) economic evaluations (e.g. cost-effectiveness analyses, cost-utility analyses and cost analyses). The latter was based on a highly sensitive and validated search filter specifically designed to identify economic evaluations [35], which was broadened for the purpose of this review to maximize sensitivity. All search strategies were evaluated by a clinical expert (KB).

2.2. Study selection

Eligibility criteria were defined a priori in the protocol using the PICOS (i.e. Population, Intervention, Comparator, Outcome and Study Design) strategy. Eligibility criteria are shown in Table 1. Studies about prevention or screening of GDM were not included, even though these studies sometimes assessed the effects of screening and prevention of GDM on the development of T2DM [36]. This systematic review focusses on postpartum screening- or prevention of T2DM, which is not within the scope of the latter studies. Moreover, the cost-effectiveness of GDM screening and treatment has been subject to a recent review [37]. Studies that were published in English, Dutch, French or German were eligible for inclusion.

Reference lists of included studies were hand searched to identify relevant articles. Systematic reviews were collected separately, as a source for supplementary references.

Two reviewers (AW; MS) screened the titles and abstracts of all records generated by the search using the web application Rayyan [38]. Full texts were retrieved for all remaining articles after this first round of screening. If the full text was not available online, the authors of the original articles were contacted via email. The second screening round on full text was performed by two reviewers (AW; KP) and reasons for exclusion were documented. For both screening rounds, reviewers were blinded from each other's decision, disagreements were resolved by discussion, and in case of any doubt a third reviewer was consulted.

2.3. Data extraction

A data extraction sheet was developed, based on an existing template [34]. The following data was extracted: (1) study identification (first author, year, title, journal); (2) funding (sources and competing interest); (3) general study characteristics (country, setting, population, interventions, comparator); (4) methods (approach (i.e. model- or trial-based), type of study, perspective, time horizon, costs, effects, analyses of uncertainty, used software); and (5) results (costs, effects, ICER, analyses of uncertainty, author's conclusions). Authors of original articles were contacted if further information was needed.

2.4. Quality assessment

Two reviewers (AW; MS) independently evaluated methodological quality of the original articles using an amended Consensus Health Economic Criteria (CHEC) checklist [39]. One adaptation of the CHEC was made, namely the inclusion of the option "not applicable". This was introduced to avoid

Table 1 – Eligibility criteria.

	Inclusion criteria	Exclusion criteria
Population	Women with (prior) GDM (according to the new definition or the old definition: "women with onset or first recognition of hyperglycemia during pregnancy")	n.a.
Intervention	Postpartum prevention or screening for T2DM	Prevention or screening for GDM
Comparator	No interventions, standard care or any other intervention	n.a.
Outcomes	All outcomes related to costs or cost-effectiveness (i.e. full or partial)	Outcomes related to effectiveness only
Context	No restrictions	n.a.
Study design	All health economic studies (model-based or trial based, full or partial)	Reports, systematic reviews, commentaries, congress abstracts, protocols, animal studies
Language	English, Dutch, French or German	

n.a.: not applicable. GDM: Gestational diabetes mellitus; T2DM: Type 2 diabetes mellitus.

underestimation of the quality of partial health economic studies. The following two interpretations were applied: (1) item 4 (time horizon), only a lifetime horizon was considered appropriate; and (2) item 12 (outcome valuation), this item was only considered applicable for cost-utility analyses considering quality-adjusted life years (QALYs). Reviewers were blinded to each other's decision, disagreements were resolved by discussion, and in case of any doubt a third reviewer (KP) was consulted.

2.5. *Synthesis of results*

Relevant items were presented in an evidence table and/or described in detail in the main text. If a statistical model was applied (even with individual data of participants for one of more input parameters), the included study was considered to be model-based. Regarding costs, for this systematic review a distinction was made between operational costs of the strategy and costs of T2DM treatment. Costs are reported in the original currencies, but in order to increase comparability across the included studies, an online application was used to convert different currencies to euros (€) (Belgium as target country, 2016 as reference year) [33,40]. If no reference year was mentioned in the original article, the publication year minus two years was imputed (a correction of two years was arbitrary chosen, since we consider it probable that data were collected at most two years before publication). Converted costs are placed between square brackets.

3. Results

The selection process is shown in Fig. 1. Starting from 1597 records, a total of four publications presenting the results of four different studies were included [41–44]. No additional records were found via reference backtracking, protocols or reviews. The reasons for exclusion, collected during the screening on full text, were: (1) Population: the studies described a population at risk for GDM; (2) Intervention: the article did not describe a screening- or prevention program; (3) Outcome: the abstract mentioned costs, but the article did not contain a cost analysis; and (4) Study design: abstract, protocol or review.

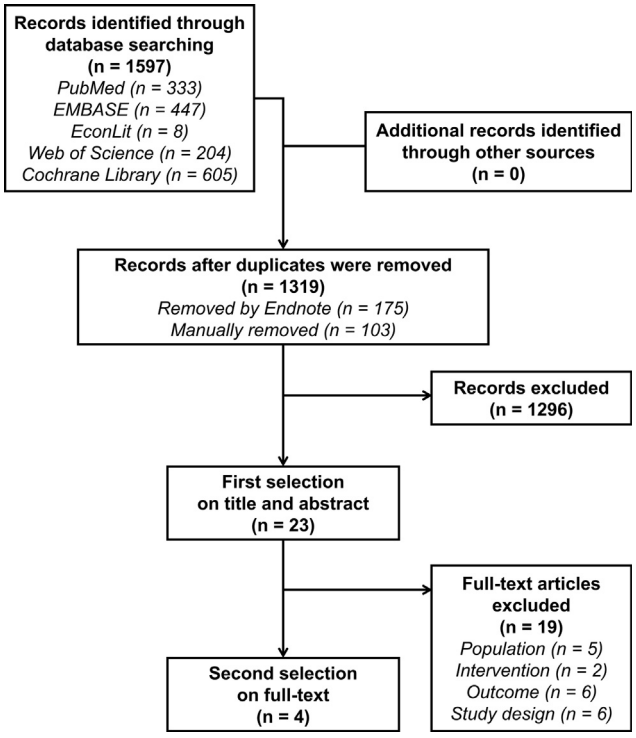

Fig. 1 – Flow diagram of the selection process. n: number.

3.1. *Study characteristics*

For the identified studies, the characteristics across a number of key study variables are summarized in Table 2.

3.1.1. Study designs

Two studies were conducted in the United States of America (USA) [41,42], one in Australia [43], and one in Bulgaria [44]. Two studies performed a cost-effectiveness analysis, namely a cost-per-case-detected analysis [42] and a cost-per-life-year-gained analysis [43]. The two other studies were categorized as cost analyses [41,44]. The American cost analysis simulated costs for the number of people affected by the intervention and – though not defined as such by the original article – can be considered a budget impact analysis [41]. The second cost analysis, a Bulgarian study also calculated disability-adjusted life years (DALYs); however, these were described as "indirect costs" [44]. Therefore, the study can best be categorized as a cost analysis. Only the American budget impact analysis [41] justified their choice of time horizon by referring to three studies [45–47] (published in 1964, 1972, 1987) which indicated that 50% of women with GDM will develop T2DM within 10 years. Nevertheless, this data could have been extrapolated over a longer time period, so this is still no clear justification for the chosen time horizon of 10 years. The discount rate was 5% in three studies [41,43,44], although for one of these studies it was not clear whether or not consequences were discounted [44]. In the American cost-per-case-detected analysis no discount rate was reported, neither for costs nor for consequences [42].

3.1.2. Populations

No study described the diagnostic criteria that were applied for GDM. One study excluded women with a positive oral glucose tolerance test (OGTT) at six weeks postpartum, because the authors argued that this test result was indicative of undiagnosed diabetes prior to pregnancy [42]. One study also targeted other populations such as (seriously) obese, overweight or high-risk adults, but these results were not included in our systematic review [43]. The Bulgarian cost analysis also considered costs and effects for treatment of type 1 diabetes mellitus, however only results of T2DM were included in our systematic review [44].

3.1.3. Screening and prevention strategies

None of the studies combined screening- and prevention strategies. The American cost-per-case-detected analysis evaluated nine strategies to screen for T2DM in women with prior GDM [42], while the three other studies evaluated prevention strategies [41,43,44]. Costs and effects of a comparator (e.g. no screening or prevention) were never reported, and consequently no incremental analyses were reported.

In the study assessing screening strategies, three different diagnostic strategies – each on an annual basis, every two years or every three years – were considered. Diagnostic strategies were 2-hour 75-gram OGTT, fasting plasma glucose (FPG) and HbA1C. The strategies including cut-off scores, sensitivity and specificity are described in detail in the original article.

Regarding prevention, the three studies evaluated one prevention strategy each for T2DM in women with prior GDM [41,43,44]. Prevention strategies were: intensive diet and behavioural modification [43]; a hypothetical intervention including annual follow-up by counseling (i.e. cognitive reinforcement to maintain long-term behavioural changes) and an annual dietary consultation [41]; and a prevention program by an endocrinologist – one to three times per year, depending on disease severity – including advice of dietary regimen, reduction of body weight, lifestyle alternation and optional metformin therapy (the latter was only added for women with a body mass index (BMI) higher than 25 kg/m^2) [44]. Additional details about timing, duration or frequency were not reported in the original articles, and could not be retrieved from additional sources (references, appendices, etc.).

3.1.4. Cost data

All four studies considered direct medical costs. Regarding operational costs, in the Australian study total program costs per case were reported (A$ 2500 [€ 2425.24]), without further details about type of costs included [43]. The three other studies included costs of consultations (dietician, general practitioner or medical specialists) and laboratory tests. The latter varied from US$ 2 [€ 2.76] [41] to US$ 17.99 [€ 17.99] [42]. The study that applied drug therapy for prevention of T2DM for women with a BMI higher than 25 kg/m^2 included costs of metformin (€52.5 [€ 59.29] per case) [44]. Only one study also considered administrative costs (US$ 15.96 [€ 15.96] per hour of secretary time and US$ 1 [€ 1] per mailing) [42]. The budget impact analysis did not include physician visits because it was assumed that counseling would occur at semiannual contraceptive or yearly gynecological evaluations [41]. The same type of assumption was also made for the American cost-per-case-detected analysis, where only 75% of the initial visit was charged [42]. Only one study reported costs of T2DM treatment and follow up [44]. In this study, annual costs per case (incl. consultations and laboratory costs) were dependent on disease severity: € 98.9 [€ 111.7] for good metabolic control (HbA1C less than 7%), € 122.1 [€ 137.9] for satisfactory metabolic control (HbA1C between 7 and 8%), and € 241.8 [€ 273.1] for poor metabolic control (HbA1C larger than 8%) [44].

3.1.5. T2DM incidence and T2DM reduction

Regarding T2DM incidence, one of the cost analyses reported development of T2DM in 7 out of 30 (23.3%) women with prior GDM within two years of follow-up, using own data [44]. Two other studies referred to previous literature, giving an incidence of 6.7% to 8% per year within this population [41,42]. One study did not mention incidence rates [43]. Regarding T2DM reduction (due to the prevention strategy), the cost-per-life-year-gained analysis assumed a risk reduction of 50% and a 33% success rate (i.e. any sustained weight loss of 1 kg or more), without justification or mentioning sources for these percentages [43]. In the American budget impact analysis, a 10% reduction of new cases of T2DM was assumed, simulating an intervention with "limited effectiveness" based on literature of interventions towards other populations. No justification for this percentage was provided [41].

3.1.6. Sensitivity analyses

Several input parameters are uncertain in economic modelling and hence sensitivity analyses are crucial in health

Table 2 – Characteristics of the included studies.

	Screening and/or prevention?	Country	Health-economic properties	Included strategies	Main outcome(s) and results [€, 2016]	Conclusion	Quality assessment
Kim et al. [27]	Screening	USA	Type: CEA Model: n.m. Horizon: 12 Y Cycle length: n.m. Perspective: n.m. Currency: US$ Reference Y: 2005	9 strategies: (1) 75 g 2 h OGTT, (2) FPG, or (3) A1C; Every 1Y, 2Y or 3Y Compared to: No screening	Costs per case detected: OGTT/3Y:US$ 388 [€ 388] OGTT/2Y: US$ 502 [€ 502] OGTT/Y: US$ 860 [€ 860] FPG/3Y: US$ 895 [€ 895] FPG/2Y: US$ 924 [€ 924] A1C/3Y: US$ 1018 [€ 1018] A1C/2Y: US$ 1047 [€ 1047] FPG/Y: US$ 1145 [€ 1145] A1C/Y: US$ 1288 [€ 1288]	Lowest cost per case detected: OGTT every 3Y	10/18
Gregory et al. [41]	Prevention	USA	Type: cost anal. (budget impact) Model: Markov Horizon: 10 Y Cycle length: 1Y Perspective: n.m. Currency: US$ Reference Y: 1990	Annual counseling and dietary consultation Compared to: No prevention	Net savings: US$ 31.9 million [€ 44.0 million]	Cost-saving	6/15
Segal et al. [43]	Prevention	AUS	Type: CEA Model: Markov Horizon: 25 Y Cycle length: 5Y Perspective: n.m. Currency: A$ Reference Y: n.m.	Intensive diet and behavioral modification Compared to: Control cohort	Costs per life year gained: A$ 1200 to A$ 2400 [€ 1164 to € 2328]	Highly cost-effective	9/18
Todorova [44]	Prevention	BGR	Type: Cost anal. Model: decision tree Horizon: 15 Y Cycle length: n.m. Perspective: health care system Currency: € Reference Y: 2003	Dietary consultation (+metformin if BMI > 25) Compared to: Late diagnosed or complicated T2DM	Costs per case: Prevention: € 12.1 [€ 13.6] (Metformin: € 52.5 [€ 59.3]) Late diagnosed or complicated T2DM: € 1097.9 [€ 565.9] DALYs:10.1 to 15.1	n.m.	6/15

Abbreviations of countries are according to the alpha-3 code of the ISO 3166-1 encoding list (AUS: Australia; BGR: Bulgaria; USA: United States of America). Costs are given in the reported currency (A$: Australian dollars; US$: United States dollars; €: euros), as well as converted to euros, between square brackets [€, 2016]. Other abbreviations; A1C: glycated hemoglobin; CEA: cost-effectiveness analysis; Cost anal.: cost analysis; DALYs: Disability-adjusted life years; FPG: fasting plasma glucose; GDM: gestational diabetes mellitus; IGT: impaired glucose tolerance; n.m.: not mentioned; OGTT: oral glucose tolerance test; Y: year(s).

economic studies. Possible types of sensitivity analyses are one-way analyses, two- or multi-way analyses, scenario analyses and probabilistic analyses [28]. All four studies only presented scenario analyses to test the impact of different input parameters on the outcome. The cost-per-case-detected analysis of Kim et al. (screening of T2DM) examined eight different scenarios [42]. The American budget impact analysis only explored variations in T2DM incidence rate and an intervention-induced T2DM reduction (i.e. effectiveness) [41]. Additionally, this study reported a break-even threshold for their model, showing that net savings started to accrue from a 5% reduction of T2DM by the intervention (base case: 10% reduction of T2DM) [41]. In the Australian cost-per-life-year-gained analysis only sensitivity to T2DM reduction (i.e. effectiveness, more specifically, success rate of the program) was reported for the program in women with prior GDM [43]. In the Bulgarian cost analysis, only sensitivity to occurrence of type 1 diabetes mellitus and T2DM, and discount rate were examined [44]. No one-way sensitivity analyses were reported in the included studies, therefore determinants of cost-effectiveness could not be identified. None of the studies reported a probabilistic sensitivity analysis.

3.2. *Quality assessment*

The methodological quality of studies is presented in Appendix B, a sum score is reported in Table 2. There were four criteria – related to consequences – that were not applicable for cost analyses [41,44]. Valuation of outcomes was not applicable for any of the studies.

All four studies showed several limitations regarding methodological quality. For all studies, the applied perspective was unclear or not reported. Also, no study applied an appropriate (i.e. lifetime) time horizon. No incremental analyses – a key aspect of health economic studies – were performed.

3.3. *Synthesis of results*

No health economic studies were found in which both screening and prevention of T2DM in women with prior GDM was evaluated.

3.3.1. *Screening strategies*

Kim et al. [27] suggested that an OGTT per three years leads to the lowest cost per case detected, compared to eight other strategies. This finding persisted in scenarios of decreased adherence to OGTT- and FPG-strategies. Determinants for cost-effectiveness of screening were not identified. Moreover, comparing strategies in terms of the cost per case detected does not provide direct information of possible health improvements, as opposed to outcomes such as quality-adjusted life years (QALYs) [28].

3.3.2. *Prevention strategies*

In the Bulgarian cost analysis, it was stated that the preventive program may save expenses of late diagnosed or complicated T2DM; however, this was not supported by data. In other words, it was not possible to draw a clear conclusion from this study [44]. Based on two other studies [41,43], there was a trend suggestive of a beneficial effect for prevention of T2DM in women with prior GDM, from the perspective of the health care system. The Australian cost-per-life-year-gained analysis, evaluating the intensive program, reported a cost of A$ 1200 [€ 1164.11] to A$ 2400 [€ 2328.23] per life year gained, which was considered highly cost-effective [43]. The American budget impact analysis concluded that preventing T2DM in women with prior GDM would be cost-saving [41]. Identification of the most cost-effective strategy was not possible because each study only considered one prevention strategy in women with prior GDM. Moreover, these two different types of prevention strategies were evaluated using different types of study designs. Determinants for cost-effectiveness of prevention were not identified. Additionally, large variations in the input parameters of the model were shown, such as estimates of T2DM reduction, costs of the strategy and costs of T2DM.

4. Discussion

Considering the large body of evidence on diabetes prevention and the increased interest in studies on cost-effectiveness, it is striking that no more than four articles could be retrieved from the literature in this specific high-risk population. Two reviews already assessed the existing literature on cost-effectiveness of T2DM prevention for a general population at risk, including women with prior GDM [29,30]. However, the case of T2DM prevention in women with prior GDM was not analyzed nor discussed in detail. Moreover, as mentioned earlier, inclusion criteria were narrower. Indeed, with the exception of the Australian cost-per-life-year-gained analysis [30,43], none of the studies in this review were included. Hence, this review is of added value to these existing reviews, as it considered a broader scope of health economic evaluations (i.e. full and partial evaluations), and a broad scope of interventions within this specific high-risk population.

The included articles showed shortcomings in methodological quality. Sensitivity analyses, which are undeniably important for health economic evaluations, were very limited in the included articles. No one-way analyses or probabilistic analyses were reported. Included articles only reported sensitivity analyses – mostly scenario analyses – in which few parameters were considered. Another shortcoming was the lack of incremental analyses, which provides information of the extra cost per unit of effect. Although the included articles stated that the strategy/strategies were compared to "no screening/prevention", costs and effects of this comparator were not reported. The lack of incremental cost-effectiveness ratios impedes identification of the most cost-effective alternative. Lastly, it should be noted that the included articles applied a time horizon of 10 to 25 years. Since prevention policies aim for long-term effects, health economic evaluations in preventive policies should give

sufficient attention to a long – preferably lifetime – time horizon. In other cases, a shorter time horizon should be clearly justified. Nevertheless, the fact that all included articles were published before the publication of guidelines such as the "Consolidated Health Economic Evaluation Reporting Standards" (CHEERS) [48] might explain the low methodological quality of the studies. Deriving conclusions from these articles, which are possibly outdated, might therefore be misleading.

Although there is a clear gap in the literature regarding costs and cost-effectiveness for screening and prevention programs of T2DM in women with prior GDM, there are several articles available that could provide substantiated input for a model-based health economic evaluation. Systematic reviews are now available showing potential risk reduction for T2DM in women with (prior) GDM by several prevention strategies [21,22], as well as increased screening rates by screening strategies [20]. There has been an increased interest in health-related quality of life [2,3], which would enable the use of QALYs in a cost-utility analysis. A health economic model to evaluate screening and prevention strategies in women with prior GDM can be based on other models developed in the domain of diabetes prevention, which have already shown that prevention of T2DM for other populations at risk can be cost-effective [17,29]. In summary, there are several reasons to believe that a strategy to screen and prevent T2DM in women with prior GDM can be cost-effective, however further research is needed to permit clear conclusions to be drawn. A decision-analytic health economic model could provide a framework to combine clinical, epidemiologic and economic evidence that is now available.

Based on the included studies and their limitations, as well as general recommendations for health economic research, five recommendations for further research can be made: (1) a model-based health economic evaluation that includes different screening and prevention strategies for this particular population would offer added value to the existing evidence; (2) such a model should include a clear description of all modelled alternatives, with special attention to evidence of effectiveness for each alternative. Because current evidence is not sufficient to conclude whether or not screening or prevention is cost-effective compared to doing nothing, the comparator "doing nothing" (i.e. no screening or prevention) should be included; (3) a health economic evaluation that expresses health gain by means of QALYs is recommended in different guidelines [28,49] and would also add value to current literature; (4) sufficient attention should be given to key drivers of a model, such as T2DM reduction, costs of the strategy and costs of T2DM and its complications; uncertainty surrounding these estimates should be further explored in sensitivity analyses; and (5) there are several health economic guidelines and checklists available [39,48], which should be adhered to.

4.1. *Strengths and limitations*

Firstly, a study protocol was developed a priori, yet it was not published or registered. This might impede quality assessment of this systematic review, however the protocol is available upon request. Secondly, if studies assessed women with (prior) GDM as a subgroup without mentioning this in the title or abstract of the article, it might be possible that these studies were excluded during the first screening round. Nevertheless, to avoid this scenario, a study was screened on full text if the population was considered unclear in the title or abstract. Thirdly, because it was expected that evidence would be scarce, broad eligibility criteria were applied. This led to the inclusion of heterogeneous studies and hindered comparison. Nevertheless, the search strategy was developed to be very sensitive; hence, it is likely that this systematic review provides a complete overview of all published health economic studies of screening and prevention of T2DM in women with prior GDM.

5. Conclusion

Based on the scarce findings of this systematic review, current evidence suggests that an OGTT per three years leads to the lowest cost per case detected, and prevention could be cost-effective or cost-saving. However, there is a large literature gap regarding costs and cost-effectiveness of screening and prevention programs of T2DM in women with prior GDM. Only four studies were found and they all displayed methodological shortcomings. Moreover they were conducted between 10 and 25 years ago and as such their findings do not reflect current practice in this high-risk population. Determinants of cost-effectiveness could not be identified. Nevertheless, there are several reasons to believe that screening and prevention of T2DM in women with prior GDM could be cost-effective, and therefore future health economic research is needed.

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Conflicts of interests

The authors declare that there are no conflict of interests.

Appendix A. Search strategy in PubMed

The search strategy for MEDLINE (via PubMed) is given below. All other search strategies (EMBASE, EconLit, Web of Science and Cochrane) are available upon request.

P	1.	"Diabetes, Gestational" [Mesh]
	2.	"GDM"
	3.	(("Diabetes Mellitus"[Mesh] OR "diabetes" OR diabetic* OR "hyperglycemia" OR "hyperglycaemia") AND ("gestational" OR pregnan*))
	4.	#1 or #2 or #3
I_1	5.	"Preventive Health Services"[Mesh]
	6.	prevent* OR screen*
	7.	"Reminder Systems" [Mesh]
	8.	reminder* OR recall
	9.	"Early Diagnosis" [Mesh]
	10.	early diagnos* OR early detect*
	11.	"Risk Reduction Behavior"[Mesh]
	12.	risk reduct*
	13.	"Postpartum Period"[Mesh] OR "Postnatal Care"[Mesh]
	14.	"postpartum" OR "postnatal"
	15.	#5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
I_2	16.	"Diabetes Mellitus, Type 2"[Mesh]
	17.	"Diabetes Mellitus"[Mesh:NoExp]
	18.	(("diabetes" OR diabetic*) AND "type 2") OR "T2DM" OR "DMT2"
	19.	"Prediabetic State"[Mesh]
	20.	prediabet*
	21.	"Insulin Resistance"[Mesh]
	22.	insulin resistan* OR "hyperinsulinemia"
	23.	"Glucose Intolerance"[Mesh]
	24.	glucose intoleran* OR impaired glucose toleran* OR "impaired fasting glucose"
	25.	"Hyperglycemia"[Mesh]
	26.	"hyperglycemia" OR "hyperglycaemia"
	27.	#16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26
O	28.	"Economics"[Mesh]
	29.	"Program Evaluation/economics"[Mesh]
	30.	economic* OR pharmacoeconomic*
	31.	"cost" OR "costs" OR "costly" OR "costing"
	32.	"price" OR "prices" OR "pricing"
	33.	((expenditure* OR "expense" OR "expenses") NOT "energy")
	34.	"value for money"
	35.	"budget" OR "budgets"
	36.	"Quality-Adjusted Life Years"[Mesh]
	37.	QALY* OR (("quality adjusted" OR "quality-adjusted") AND "years")
	38.	#28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37
	39.	#4 and #15 and #27 and #38

P: Population; I: Intervention; O: Outcome; [Mesh:NoExp]: Mesh Heading without expansion; *: wildcard.

Appendix B. Quality assessment

+: Sufficient attention is given to this aspect; -: No sufficient attention is given to this aspect; n.a.: Not applicable.

		Kim et al., 2007	Gregory et al., 1993	Segal et al., 1998	Todorova et al., 2010
1	Study population	-	-	-	+
2	Competing alternatives	+	-	-	-
3	Research question	-	+	+	-
4	Study design	+	+	+	+
5	Time horizon	-	-	-	-
6	Perspective	-	-	-	-
7	Costs: identification	+	-	-	+
8	Costs: measurement	+	-	+	+
9	Costs: value	+	+	-	+
10	Outcomes: identification	+	n.a.	+	n.a.
11	Outcomes: measurement	+	n.a.	+	n.a.
12	Outcomes: value	n.a.	n.a.	n.a.	n.a.
13	Incremental analysis	-	n.a.	-	n.a.
14	Discounted	-	+	+	+
15	Sensitivity analysis	+	-	-	-
16	Conclusions	+	+	+	-
17	Generalizability	+	+	+	-
18	No conflict of interest	-	-	-	-
19	Ethics	-	-	+	-
	Sum score	10/18	6/15	9/18	6/15

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