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Cost–utility analysis of lifestyle interventions to prevent type 2 diabetes in women with prior gestational diabetes

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Background: To compare estimated costs and health outcomes of lifestyle interventions for the prevention of type 2 diabetes mellitus in women who had gestational diabetes. **Methods:** An age-specific Markov model was applied comparing costs and quality-adjusted life years (QALYs) of three alternatives: 'doing nothing'; an annual reminder system (ARS) with an awareness campaign ('ARS-awareness'); and an ARS with an intensive lifestyle intervention ('ARS-ILS'). A healthcare payer perspective was adopted, the time horizon was 30 years and the setting was Flanders (Belgium). Sensitivity analyses were performed. **Results:** 'ARS-awareness' was extendedly dominated. Per 10 000 participants, 'ARS-ILS' cost €13 210 256 more and gained 496 QALYs compared with 'doing nothing' (26 632 €/QALY), with a 63% probability of being cost effective, given a cost effectiveness threshold of 35 000 €/QALY. A scenario analysis showed that 'ARS-ILS' for 15 years only offered to women with prediabetes (compared with 'doing nothing') has an 89.5% likelihood of being dominant. **Conclusions:** 'ARS-ILS' may be the preferred intervention. However, the probability of being cost effective was low. Based on further scenario analyses, we recommend healthcare decision makers to consider the application of a more intensive alternative, focused on the highest risk profiles and with a shorter intervention duration.

Introduction

Gestational diabetes mellitus (GDM) is defined by the American Diabetes Association as diabetes diagnosed in the second or third trimester of pregnancy provided that overt diabetes early in pregnancy has been excluded.[1,2] Women with prior GDM are more than seven times as likely to develop type 2 diabetes mellitus (T2DM), compared with women with normoglycaemic values during pregnancy.[3]

Costs and consequences of T2DM could be avoided by preventive measures, as several risk factors are modifiable (e.g. overweight and obesity, unhealthy diet, physical inactivity and smoking).[4] There is an extensive body of evidence on the effectiveness of intensive lifestyle (ILS) interventions for the prevention of T2DM in a general population at risk[4,5] and in women with prior GDM.[6] Awareness campaigns could be a low-cost alternative to ILS interventions. Little is known about the effectiveness of awareness campaigns, but an American study found that being informed about increased diabetes risk was associated with increased adoption of healthy lifestyle behaviours.[7]

Evidence regarding effectiveness alone is insufficient to inform decision makers about the most efficient prevention alternatives. More information about cost effectiveness is required to justify health investments.[8] For a general population at risk, it is shown that intensive approaches to prevent T2DM are likely to be cost effective.[9] A systematic search[10] yielded only one study on cost effectiveness of prevention programmes of T2DM in women with prior GDM, which was published in 1998.[11] This study did not analyze or discuss the case of women with prior GDM in detail, and did not reflect current practice. Other studies evaluated the cost effectiveness of screening and prevention of GDM.[12–14] However, these programmes differ substantially from prevention of T2DM after GDM, in terms of goal and target population. The aim of this health-economic evaluation was to compare estimated costs and health outcomes of lifestyle interventions for the prevention of T2DM in women who had GDM in Flanders, Belgium.

Methods

Ethical approval was obtained at the University Hospital of Ghent, Belgium (B670201834861).

Model structure

A Markov decision-analytic model was constructed in Microsoft Excel® 2016, for women known for prior GDM and included five health states postpartum: normal glucose tolerance (NGT); prediabetes; T2DM without complications (T2DM_0); T2DM with complications (T2DM_C); and death (figure 1). The model considered a closed cohort that starts immediately postpartum. At that moment, every woman can either have NGT or prediabetes (women with T2DM immediately postpartum are not part of the target population for prevention of T2DM). The model structure was based on existing models for prevention of T2DM in other populations,[9] and validated by a clinical expert (KB). The setting was in Flanders (Belgium). We applied a healthcare payer perspective: direct medical

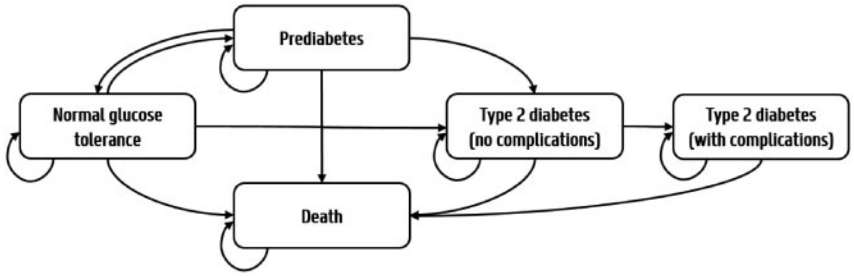

Figure 1 The boxes represent the five health states of the Markov model. Each arrow represents a transition probability from one state to another, during each cycle (1 year)

costs for the national healthcare insurance and for patients (co-payments) were included. A time horizon of 30 years was applied, the cycle length was 1 year. Discount rates were 3.0% for costs and 1.5% for health outcomes.[15]

Comparators

Three alternatives were compared: (i) 'doing nothing' (i.e. no prevention nor screening); (ii) an annual reminder system combined with an awareness campaign ('ARS-awareness'); and (iii) an annual reminder system combined with an intensive lifestyle intervention ('ARS-ILS'). In the first alternative, long-term follow-up of women with prior GDM is not part of common practice. The second alternative, 'ARS-awareness', was based on a GDM recall registry in Flanders. This programme offers a structured recall system, including an information campaign with lifestyle tips, offered by the Flemish Diabetes Association.[16] In concrete terms, women were invited to register themselves after diagnosis of GDM. When registered, they received a letter/email that summarized the recommendations regarding lifestyle changes to prevent T2DM, and a yearly reminder letter/email to undergo T2DM screening at their general practitioner. For the third alternative, 'ARS-ILS', we assumed that an ILS intervention in Flanders would include a total of 7 h of exercise coaching sessions,[17] combined with seven dietary consultations, performed each year. The latter was based on the Diabetes Prevention Program (of which evidence regarding effectiveness was used in this model, see further).[18] This successful programme aimed for weight loss/weight maintenance and a minimum level of physical activity, by means of individual coaches, self-management strategies, flexible interventions, etc.[18] In this model, expected costs for such a programme were adapted to the Flemish context.

For the base case, the alternatives were applied throughout the entire time horizon of 30 years, and for the entire start cohort (i.e. both women with NGT and women with prediabetes).

Analytic methods

Costs and quality-adjusted life years (QALYs) were calculated per 10 000 participants. Incremental cost effectiveness ratios (ICERs) were calculated by dividing the difference in costs by the difference in QALYs:

$$\text{ICER} = \frac{\text{Costs}_{\text{alternative 2}} - \text{Costs}_{\text{alternative 1}}}{\text{QALYs}_{\text{alternative 2}} - \text{QALYs}_{\text{alternative 1}}}$$

If the ICER is below a predetermined threshold, the alternative can be considered cost effective compared with another alternative. A threshold of 35 000 €/QALY was applied (100% of the gross domestic product per capita in Belgium in 2016, rounded number[19,20]). An alternative was considered dominant if it was more effective and less costly (compared with another alternative). Negative ICERs were not reported. Dominated and extendedly dominated alternatives were excluded, according to the standard methods for multiple mutually exclusive interventions.[8]

Several sensitivity analyses were performed, namely one-way sensitivity analyses, a threshold analysis, scenario analyses and probabilistic sensitivity analyses (PSAs). One-way sensitivity analyses identified the most important determinants of the model by increasing and decreasing the value of each input parameter separately by 30%. A threshold analysis for the RRR of 'ARS-awareness' was performed. Several scenario analyses were performed. PSAs (5000 iterations) are Monte Carlo simulations in which all variables are varied simultaneously, allowing to calculate the probability of being cost effective.

Health outcomes

Health outcomes were expressed in QALYs, a summary outcome measure of health, combining the impact of gains in quality of life and quantity of life (life expectancy).[8] Utilities were retrieved from regional databases, so no measurement or valuation of this preference-based outcome were performed specifically for this study.

Study parameters

All input parameters are provided in the Supplementary material. Regarding the risk of developing T2DM from NGT (transition NGT →T2DM_0, see figure 1), it is known that women with prior GDM are at increased risk to acquire T2DM. Therefore incidence rates[21] were multiplied by a relative risk (RR) of 7.43 (95% CI: 4.79–11.51),[3] adjusted to 3.78 (i.e. the original RR describes the comparison of women with GDM and women without GDM; the adjusted RR describes the comparison of women with GDM and the entire age-adjusted female population). Regarding the risk of developing prediabetes from NGT (transition NGT → prediabetes) a fixed ratio of 4.17 between the incidences of prediabetes and T2DM was assumed, based on a Flemish study.[16] Regarding the risk of developing T2DM from prediabetes (transition prediabetes →T2DM_0), two RRs were combined [i.e. a RR of 4.66 (95% CI: 2.47–6.85) for prediabetes[22] and an adjusted RR of 1.07 (95% CI: not reported)[23] for prior GDM within this population of prediabetes]. Regarding mortality rates, Flemish data[24] were multiplied by a hazard ratio for prediabetes[25] and T2DM.[26]

To simulate the effect of an intervention, transition rates were reduced by a relative risk reduction (RRR). For the effectiveness of awareness campaigns, we assumed a RRR of 11.35% (assumed 95% CI: 0.11–0.12) ('ARS-awareness'), based on a qualitative study.[7] For 'ARS-ILS', a RRR of 53% (assumed 95% CI: 0.52–0.54) was applied.[23] RRRs were only applied to the adherent group, no carry-over effect to the next cycle was assumed.

Adherence rates of 'ARS-awareness' were based on 5-year response and screening rates from a Flemish study[16] and exponentially extrapolated in Microsoft Excel® 2016 for the remaining 25 years in the model. For the base case, it was assumed that only the 'screeners' fully adhere to the programme: non-responders were also considered non-screeners, and non-screeners were considered to have the same probabilities as in the 'doing nothing' alternative. Adherence rates of 'ARS-ILS' were assumed to be 50% of the adherence rates of 'ARS-awareness'.

Table 1 Deterministic results per 10 000 participants over 30 years

	Disease costs	Intervention costs	Total costs	QALYs	Incremental costs	QALYs gained	ICER (€/QALY)
Doing nothing	€122 089 059	€0	€122 089 059	203 953			
ARS-awareness	€117 816 424	€10 797 908	€128 614 332	204 165	€6 525 273	212	30 793 €/QALY
ARS-ILS	€112 098 266	€23 201 048	€135 299 314	204 449	vs. next best alternative: €6 684 983 vs. doing nothing: €13 210 256	vs. next best alternative: 284 vs. doing nothing: 496	vs. next best alternative: 23 529 €/QALY vs. doing nothing: 26 632 €/QALY

Notes: ARS-awareness, annual reminder system combined with an awareness campaign; ARS-ILS, annual reminder system combined with an intensive lifestyle intervention; ICER, incremental cost effectiveness ratio; QALYs, quality adjusted life years.

An average utility decrement of 0.11 was applied for both diabetes without and with complications.[27] Although evidence is available that utilities differ depending on the number of complications,[28] it was preferred to use recent regional gender-specific data.[27]

Costs

Cost data, expressed in euros (€), were retrieved from the literature,[29] publically available databases,[17,30] or provided by the Flemish Diabetes Association.[31] Where needed, costs were converted to euros (Belgium, 2016, IMF purchasing power parity indices).[32] For the ARS and awareness campaign, the mean cost per person per year was calculated over the period 2009–16. Costs regarding coordination (e.g. steering board, advisory committee or attendance to conferences) and evaluation (e.g. evaluation tools or reporting to the government) were not taken into account. For the ILS, costs of the exercise coaching sessions were based on the current exercise referral programme in Flanders,[17] and costs for dietary consultations were based on current prices of private dietitians.

Assumptions

An overview of all assumptions is provided as Supplementary material. The three most important were: (i) the incidence of prediabetes could not be retrieved in the literature; therefore, it was based on the incidence of T2DM (assuming a fixed ratio between T2DM and prediabetes); (ii) a RRR of 11.35% was assumed for 'ARS-awareness'; (iii) adherence rates of 'ARS-ILS' were assumed to be 50% of the adherence rates of 'ARS-awareness'.

Results

Deterministic base case analyses

For a cost effectiveness threshold of 35 000 €/QALY, both lifestyle interventions were borderline cost effective compared with 'doing nothing', see table 1. However, 'ARS-awareness' was extendedly dominated by 'doing nothing' and 'ARS-ILS'.

Threshold analysis

A threshold analysis (a figure is provided in the Supplementary material) showed that the RRR of 'ARS-awareness' has to be greater than or equal to 10.48% in order for the intervention to be cost effective compared with doing nothing. A RRR greater than 28.95% would result in the intervention being dominant compared with doing nothing.

Sensitivity analyses

Due to extended dominance of 'ARS-awareness', further sensitivity analyses are mainly focused on 'ARS-ILS'.

One-way sensitivity analyses (figure 2c) identified the four most important determinants of cost effectiveness: (i) Probability to develop T2DM for women with NGT; (ii) RRR associated with the intervention; (iii) RR to develop T2DM for women with prior GDM; and (iv) RR to develop T2DM for women who have prediabetes.

The PSA (figure 2a and b) showed limited robustness: the probability of 'ARS-ILS' to be cost effective (compared with 'doing nothing') at a threshold of 35 000 €/QALY was 63%.

Several scenario analyses for 'ARS-ILS' vs. 'doing nothing' were performed, see table 2. First, the influence of increased adherence was assessed. As expected, these scenarios resulted in lower ICERs compared with the base case, due to more QALYs gained as well as lower incremental costs. Second, a scenario in which 'ARS-ILS' was only offered to women with prediabetes was assessed. More QALYs were gained and incremental costs became negative, which means that this alternative was dominant compared with doing nothing. Third, the influence of shorter intervention durations was evaluated (total time horizon of the model remained 30 years). The shorter the intervention was applied, the lower the incremental costs and health outcomes. Lastly, a combined scenario was explored: 'ARS-ILS' was only offered to women with prediabetes and assumed to be discontinued after 15 years. This scenario was chosen arbitrarily, based on real-life feasibility. Per 10 000 participants, 'ARS-ILS' cost €8.7 million less (€6 861 528 intervention costs and €15 554 834 cost savings) and added 715 QALYs compared with 'doing nothing', i.e. the alternative was dominant. A PSA showed that—although a large dispersion was observed—the probability of being cost effective or dominant was 99.7% or 89.8%, respectively.

Discussion

In the base case analyses, both interventions appeared to be borderline cost effective compared with 'doing nothing'. 'ARS-awareness' was extendedly dominated by 'doing nothing' and 'ARS-ILS', and therefore excluded from further analyses. A scenario analysis showed that 'ARS-ILS' for 15 years only applied to women with prediabetes, compared with 'doing nothing', has a large probability of being cost-effective or even dominant. Hence, from a health-economic point of view, it could be recommended to consider the application of a more intensive intervention, yet focused on the highest risk profiles (prediabetic plus prior GDM) with a shorter intervention duration.

A systematic review[10] showed that only one study previously assessed cost effectiveness of T2DM prevention in women known with prior GDM. In this Australian cost-per-life-year-gained analysis, an intensive programme was considered highly cost effective.[11] Our results were more modest. This might be explained by more conservative assumptions, e.g. regarding adherence and probability to develop T2DM. A scenario analysis showed that the ICER was drastically decreased when more optimistic assumptions were made regarding non-responders to 'ARS-ILS' (see table 2). Hence, sufficient attention should be given to improving the adherence to such interventions. Our final scenario analyses provided results that were more in line with Segal et al.,[11] in a sense that 'ARS-ILS' is very likely

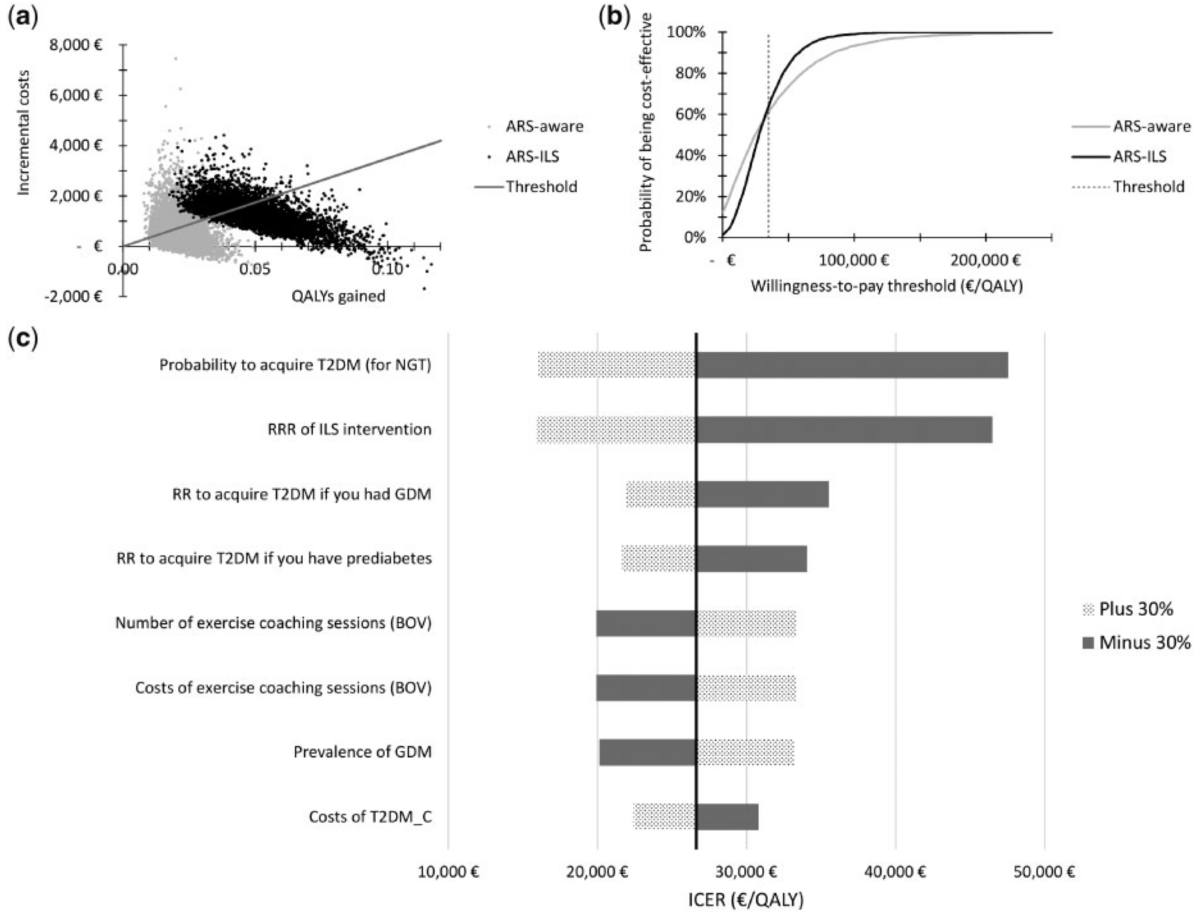

Figure 2 (a) Results of the probabilistic analyses (each intervention vs. 'doing nothing'), in which all variables are varied simultaneously. (b) Cost effectiveness acceptability curve of both interventions, vs. 'doing nothing'. (c) Tornado diagram of 'ARS-ILS' vs. 'doing nothing'. ARS-aware, annual reminder system combined with an awareness campaign; ARS-ILS, annual reminder system combined with an intensive lifestyle intervention; BOV, 'bewegen op verwijzing' (exercise coaching sessions); GDM, gestational diabetes mellitus; ICER, incremental cost effectiveness ratio; QALYs, quality-adjusted life years; RR(R), relative risk (reduction); T2DM, type 2 diabetes mellitus; T2DM_C, type 2 diabetes mellitus with complications; Threshold, cost effectiveness threshold of 35 000 €/QALY

Table 2 ICERs of the scenario analyses, for ARS-ILS vs. doing nothing

Scenarios	ICER (€/QALY)
Base case	26 632
25% of the non-responders get screened	22 630
50% of the non-responders get screened	19 976
Logarithmic extrapolation of adherence rates	23 080
Only prediabetic women get treated	Dominant
Intervention duration of 5 years[a]	29 304
Intervention duration of 10 years[a]	28 669
Intervention duration of 15 years[a]	26 670
Intervention duration of 20 years[a]	25 573
Combined scenario: only prediabetic women; 15 years	Dominant

Notes: ARS-ILS, annual reminder system combined with an intensive lifestyle intervention; ICERs, incremental cost effectiveness ratios; QALY, quality-adjusted life year.
[a]For the following years in the model, all individuals were considered to have the same transition probabilities as 'doing nothing'.

to be cost effective or even dominant when the intervention is applied for 15 years to women with prediabetes only.

Other characteristics of the model may have led to a more cost effective result. First, we could have applied a longer time horizon. Our model was tested for time horizons between 5 and 30 years, and a longer time horizon consistently resulted in a lower ICER. Hence, it could be expected that a time horizon beyond 30 years would result in an even lower ICER than our results are showing. However, a lifetime time horizon might have caused more uncertainty in the model and might have resulted in an overestimation of the effect of this postpartum prevention programme. Second, the broader effects or so-called collateral benefits of lifestyle interventions were not considered (effects of reduced overweight,[33] risk of cardiovascular disease,[34] mental health benefits,[35] etc.). A more complex model including other lifestyle diseases would probably result in a more cost effective result. However, this would have created additional methodological difficulties in terms of finding input for the model and/or additional assumptions. Moreover, long-term effectiveness and adherence to lifestyle interventions is unclear. Difficulties in adherence, even for short-term interventions, have been reported in this particular population.[36] Hence, assumptions (i.e. extrapolation) would influence our model even more. Third, the probability to acquire T2DM appears to be the most important determinant of cost effectiveness in our model. However, it is likely that this probability is higher in reality, due to an underestimation of incidence rates of diabetes,[4] and the used rates only taking into account diagnoses at general practices.[21] Hence, higher probabilities are very likely and would have improved the cost effectiveness of both interventions (vs. 'doing nothing').

Limitations

Four limitations were identified. First, we did not include indirect and/or non-medical costs. Nevertheless, we believe that this study explored uncharted territory, for which a healthcare payer perspective including only direct medical costs is a logical first step. Second, the one-way sensitivity analysis was performed with a fixed variation of 30% for all parameters. Although this has the advantage of being homogeneous, the results should be interpreted carefully. For each parameter, one should assess if a variation of 30% is realistic. For example the most important determinant of cost effectiveness was the probability to acquire T2DM (for NGT). As mentioned in the previous paragraph, this 30% decrease (related with the highest increase of the ICER) is unlikely. Third, the model—as any model—is a simplification of reality. For example the model did not allow for individuals to move directly from NGT to 'T2DM with complications', although T2DM is often diagnosed because of the occurrence of complications. Yet, in order to model this pathway, it would have been necessary to add another state of 'undiagnosed' T2DM, leading to large difficulties to find data to populate the model. In other words, the added value of including this state in the model would have been limited. Fourth, prediabetes is a general term for the stage between normoglycaemia and T2DM, for which different diagnostics (impaired glucose tolerance and/or impaired fasting glucose) and cut-off values exist. Unfortunately, the sources that were used in this model did not always use the same methods to identify prediabetes. This could have obscured the results of the analyses.

Implications for further research

Making assumptions is inevitable in this type of research (e.g. extrapolation to later years). However, some assumptions could be avoided in future research.

First, evidence regarding effectiveness of awareness campaigns is lacking. Therefore we made an assumption based on an American study[7] that assessed if people who are informed about their diabetes risk were more likely to adopt healthy lifestyle behaviours. The results of this study suggest that in order to be cost effective, the awareness campaign would have to decrease the risk of developing T2DM by at least 10.48%. Further research should assess whether such campaigns can effectively reduce or delay development of T2DM to that extent. Such studies should consider including a control group (a pre-post design, retrospective data, etc.).

Second, the use of different screening strategies and different criteria for diagnosis of GDM might lead to contradictory results, only because another population was assessed. Research in the field of GDM would be more consistent if there was a consensus regarding diagnostic criteria.[2]

Conclusion

Based on the base case analyses, 'ARS-ILS' may be the preferred intervention. However, the probability of being cost effective was low. A scenario analysis in which 'ARS-ILS' was only applied for 15 years to women with prediabetes resulted in a 89.5% probability of being dominant, and a 99.4% probability of being cost effective, compared with 'doing nothing'. Based on the findings of this model, we would recommend healthcare decision makers to consider the application of a more intensive intervention, focused on the highest risk profiles (prediabetic plus prior GDM) and with a shorter intervention duration.

Supplementary data

Supplementary data are available at *EURPUB* online.

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Conflicts of interest: None declared.

Key points

- An awareness campaign or an intensive lifestyle intervention were both borderline cost effective compared with doing nothing, but the probabilistic analyses showed limited robustness of these results.
- Further analyses showed that an intensive lifestyle intervention for only 15 years and only offered to women with prediabetes has a 99.4% likelihood of being cost effective, compared with 'doing nothing'.
- We recommend healthcare decision makers to consider the application of a more intensive strategy, yet focused on the highest risk profiles (women with prediabetes and prior GDM) with a shorter intervention duration.

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