Chapter 6

ECONOMIC EVALUATION OF A LIFESTYLE INTERVENTION IN PRIMARY CARE TO PREVENT TYPE 2 DIABETES AND CARDIOVASCULAR DISEASE

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Submitted for publication
ABSTRACT

Background
Prevention of chronic diseases in high-risk populations is important from a public health perspective, but also to contain the costs associated with these diseases.

Purpose
To determine the cost-effectiveness of a primary care lifestyle intervention from a societal perspective.

Design
Economic evaluation alongside a randomised controlled trial.

Setting/participants
Adults aged 30-50 years, who were at risk of type 2 diabetes (T2DM) and/or cardiovascular disease (CVD) were recruited from twelve general practices in The Netherlands, in 2008. They were randomised to the intervention (n=314) or control group (n=308).

Intervention
The intervention consisted of up to six face-to-face counselling sessions with a trained practice nurse, followed by 3-monthly sessions by phone. The control group received health brochures.

Main outcome measures
Costs were collected using 3-monthly retrospective questionnaires. Quality of life was measured with the EQ-5D, at baseline and after 24 months. Nine-year risk of developing T2DM and ten-year risk of CVD mortality were assessed with the ARIC and SCORE formulae, respectively. Measurements were done at baseline and after two years.

Results
Small, statistically non-significant differences in effects were found between the intervention and control group with regard to risk scores and Quality Adjusted Life Years (QALYs) gained. The mean difference in costs between the intervention and
control group was €-866 (95% confidence interval -2372; 370). The probability that the intervention was cost-effective varied from 93% at a threshold for willingness to pay of €8000 to 88% at a threshold of €80,000 per QALY.

Conclusions
A lifestyle intervention consisting of up to six face-to-face counselling sessions with a trained practice nurse followed by 3-monthly sessions by phone for adults at increased risk of T2DM and/or CVD resulted in cost savings over a two-year period. However, due to methodological uncertainty it is currently not advised to implement the intervention in Dutch general practices.
BACKGROUND
Worldwide an increased prevalence of type 2 diabetes (T2DM) and cardiovascular diseases (CVDs) has been noted over the last decades.\textsuperscript{1,2} A further rise is expected, due to an aging population and the rising prevalence of obesity. The expected increase in T2DM and CVDs is not only a medical, but also a socioeconomic problem. In most countries health care costs are rapidly rising, and the obesity epidemic plays an important role in this process.\textsuperscript{3} The development of interventions to prevent chronic diseases in high-risk populations is of utmost importance to contain these costs.

Several studies have shown that the risk of developing T2DM and associated CVDs reduces with weight loss and improved lifestyle behaviours.\textsuperscript{4} A recent review found evidence for the cost-effectiveness of diabetes prevention interventions.\textsuperscript{5} Nevertheless, as these interventions have been studied under strictly controlled conditions, there remains a need for cost-effectiveness studies of interventions addressing ‘real world’ settings. Information about the trade-off between costs and benefits of these interventions will help policy makers to decide whether it is efficient to implement and reimburse them.

The purpose of the current study is to assess the cost-effectiveness and cost-utility of a pragmatic, theory-based primary care intervention compared with providing health brochures in reducing the estimated risk for T2DM and CVD.

METHODS

Design of the study
An economic evaluation was conducted alongside a randomised controlled trial (RCT), the Hoorn Prevention Study, carried out in the Netherlands from 2008 to 2010. The economic evaluation was performed from a societal perspective. Details of the study design and the intervention have been published elsewhere.\textsuperscript{6} The study design and informed consent procedure were approved by the Medical Ethics Committee of the VU University Medical Center and all participants provided written informed consent. The trial has been registered at isrctn.org as ISRCTN59358434.
Study population and setting

The study population consisted of men and women living in several municipalities in the semi-rural region around the city of Hoorn in the Netherlands. Twelve general practitioners approached a total of 8193 of their patients, aged 30-50 without known diabetes or CVD, based on patient records. These persons were asked to measure their waist circumference with a paper tape measure that they received by regular mail. Of the 3587 responders, 921 had an increased waist-circumference (≥101 cm for men and ≥87 cm for women). These were invited for baseline measurements, of whom 772 persons attended baseline measurements that included estimation of the 9-year risk of developing T2DM, using a formula developed in the Atherosclerosis Risk In Communities (ARIC) Study, and the 10-year risk of CVD mortality, using a formula developed in the Systematic COronary Risk Evaluation (SCORE) project. For both risk scores and for each participant, age was extrapolated to 60 years. Responders with a minimum risk of 10% on one or both risk scores were eligible. A total of 150 respondents were excluded, because they were unable to communicate adequately in the Dutch language, pregnant, or diagnosed with T2DM or CVD. Finally, a total of 622 participants were randomly assigned to either the intervention group (n=314) or the control group (n=308; Figure 1).

Intervention and control

Both groups received care as usual if needed e.g. prescription of medication in the case of severe hypertension. Additionally, a lifestyle intervention based on cognitive behavioural principles was offered to the intervention group. The intervention was aimed at improving physical activity, diet or smoking behaviour, as chosen by the participants. It consisted of written materials and up to six individual 30-minute face-to-face counselling sessions, followed by 3-monthly 15-minute sessions by phone. Counselling was done by eight practice nurses, who received 18 hours of training prior to the intervention. Coaching on the job was provided to the practice nurses halfway through the sessions and consisted of one hour individual coaching with feedback. Also, a peer supervision meeting was arranged. A full description of the intervention and its underlying principles has been published elsewhere.

The control group received existing brochures about physical activity, healthy diet and smoking cessation.
Figure 1. Participant flow

ARIC, the 9-year risk of developing T2DM; SCORE, the 10-year risk of CVD mortality
Study measures

Clinical outcome measures

Outcome measures of the cost-effectiveness analyses were the estimated risk of developing T2DM and the estimated risk of CVD mortality. The 9-year risk of developing T2DM was estimated with the risk formula derived from the ARIC Study,\(^7\) based on ethnicity, parental history of diabetes, systolic blood pressure, waist circumference, and height. The 10-year risk of CVD mortality was estimated with the formula developed by the SCORE project,\(^8\) which includes sex, smoking status, total cholesterol, and systolic blood pressure. A detailed description of the measurement of these parameters has previously been published.\(^6\)

For the cost-utility analysis, the EQ-5D was used to assess quality of life at baseline, and at 6, 12 and 24 month follow-up.\(^9\) Health utilities were estimated with the Dutch tariff.\(^10\) Quality adjusted life years (QALYs) were calculated by multiplying the utilities with the amount of time a participant spent in a particular health state. Transitions between health states were linearly interpolated.

Cost measures

Information on health care utilization, medication costs, participant costs and productivity loss was obtained through eight retrospective 3-month questionnaires provided to the participants between baseline and 24-month follow-up.

Health care utilization consisted of costs of general practitioner care, allied health care, medical specialist care and hospitalization.\(^11\) Participants’ costs concerned complementary care, over-the-counter (OTC) medication, and costs associated with improving physical activity, such as sports club memberships and sports equipment. Health care utilization and complementary care were valued with Dutch standard costs.\(^11\) When these were not available, prices reported by professional associations were used. The costs of prescribed medication were calculated using prices charged by the Royal Dutch Society for Pharmacy.\(^12\) Costs of OTC medication and sports were reported by the participants. Costs of productivity losses based on self-reported sick leave from work were estimated with the friction cost approach (friction period 154 calendar days and an elasticity of 0.8), using the mean income of the Dutch population according to age and gender.\(^11\) Cost categories and prices used in the economic evaluation are given in Table 1. Prices were adjusted for the year 2008, the year of the first measurement, using consumer price indices.\(^13\) No discounting was done for the costs in the second year.
Table 1. Price weights used for valuation of resource use, per visit unless otherwise mentioned

<table>
<thead>
<tr>
<th>TYPE OF UTILIZATION</th>
<th>PRICE WEIGHT$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DIRECT HEALTHCARE COSTS</strong></td>
<td></td>
</tr>
<tr>
<td>Intervention: practice nurse</td>
<td></td>
</tr>
<tr>
<td>Face to face session</td>
<td>23.82</td>
</tr>
<tr>
<td>Phone session</td>
<td>11.91</td>
</tr>
<tr>
<td>Primary care</td>
<td></td>
</tr>
<tr>
<td>General practitioner</td>
<td>21.89$^b$</td>
</tr>
<tr>
<td>Therapists</td>
<td>24.65 – 54.33$^c$</td>
</tr>
<tr>
<td>Dietician</td>
<td>14.50</td>
</tr>
<tr>
<td>Dentist</td>
<td>18.70</td>
</tr>
<tr>
<td>Primary mental health care</td>
<td>51.86 – 134.37$^c$</td>
</tr>
<tr>
<td>Secondary care</td>
<td></td>
</tr>
<tr>
<td>Outpatient visits</td>
<td>60.68</td>
</tr>
<tr>
<td>Admission general hospital (d)</td>
<td>365.18</td>
</tr>
<tr>
<td><strong>DIRECT PATIENT COSTS</strong></td>
<td></td>
</tr>
<tr>
<td>Complementary therapists</td>
<td>25.18 – 82.30$^{c,d}$</td>
</tr>
<tr>
<td>OTC</td>
<td>as reported by patient</td>
</tr>
<tr>
<td>Sports &amp; sports equipment</td>
<td>as reported by patient</td>
</tr>
<tr>
<td><strong>INDIRECT PRODUCTIVITY LOSSES</strong></td>
<td></td>
</tr>
<tr>
<td>Sickness absence (d)</td>
<td>92 – 218$^e$</td>
</tr>
</tbody>
</table>

$^a$ Euros, corrected to the year 2008, $^b$ Price for consultation at the practice; $^c$ Range of the price weights for the different providers, $^d$ Price according to professional organisation, $^e$ Range of costs per sick leave (calendar) day, depending on age and sex
**Intervention costs**

Bottom-up micro-costing was used to estimate the cost of the intervention. Costing was based on the assumption that a total of 10,000 participants could be recruited to the intervention, and that 100 practice nurses would carry out the intervention if it would be implemented in primary care. Intervention costs consisted of fixed costs and of variable costs. The fixed costs covered costs of the development and printing of materials, training and supervision of the practice nurses, and of costs for selecting and inviting the participants. Total fixed costs per participant were £15. Variable costs per participant depended on the number of face-to-face contacts and telephone contacts that had been registered by the practice nurse. The cost price of a face-to-face session was £24, and of a phone session £12. Intervention cost per participant consisted of the total of fixed and variable costs.

**Statistical analyses**

*Multiple imputations*

Analyses were based on group allocation, regardless of actual intervention received or of adherence to the intervention, i.e. intention-to-treat analysis. In the main analysis, it was assumed that when data on follow-up telephone contacts were missing, no contacts had taken place and missing data were imputed with zero. Furthermore, missing health care costs, participant costs, sick leave days and outcomes were imputed using multiple imputation techniques. The final model included age, sex, educational level, smoking status, living alone yes/no, baseline outcome values, available midpoint (6 and 12 months) and follow-up outcome values, intervention costs and available health care costs, participant costs and sick leave days at each cost measurement. Imputations were done separately for the intervention and control group. Five different data sets were created in SPSS (version 17.0.2, Chicago, Ill) using Fully Conditional Specification and Predictive Mean Matching procedures, assuming that data were missing at random. These data sets were analysed as specified below. The estimates were pooled with methods described by Rubin. This method does not allow for an estimation of standard deviations, so the standard error of the mean (SEM) is presented to describe variability.
Main analyses
Regression analysis was used to compare outcomes between the intervention and control groups. Follow-up outcomes were adjusted for baseline values. To compare costs between groups, confidence intervals around the mean differences in costs were estimated using the bias-corrected and accelerated bootstrap method with 5000 replications. Incremental cost-effectiveness ratios (ICER) and incremental cost-utility ratios (ICUR) were estimated by dividing the difference in total costs over 24 months between the treatment groups by the difference in outcomes at 24 months. To graphically present uncertainty around the ratios, bias-corrected percentile bootstrapped cost-effect pairs (5000 replications) were plotted in cost-effectiveness planes (CE-planes). A CE-plane consists of four quadrants (see Figure 2), in which bootstrap-estimated cost-effectiveness pairs are positioned. The distribution of cost-effectiveness pairs over the four quadrants of the CE-plane is an indication of the uncertainty around the ICERs. The uncertainty of cost-effectiveness as seen in the CE-plane is translated to cost-effectiveness acceptability curves (CEACs). Whether an intervention offers value for money (i.e. is cost-effective) depends on the amount society is willing to pay for a unit in health gain, or is willing to accept in compensation for a unit in health loss: the ceiling ratio. The CEAC displays the probability that the cost per unit health effect (i.e. the ICER) lies below a certain ceiling ratio. The appropriate ceiling ratio is selected on the x-axis, the associated probability is read off the y-axis (see Figure 3).

Sensitivity analyses
Sensitivity analyses were conducted to test the robustness of the results. In the first sensitivity analysis the costs for the second year were discounted with 4% and QALYs achieved in this year were discounted with 1.5%, in line with Dutch guidelines. In the second sensitivity analysis the productivity losses were valued with the human capital method. In the third sensitivity analysis the costs for sports were excluded. In the fourth sensitivity analysis, missing data for follow-up phone calls (which in the main analysis were assumed to be zero) were multiply imputed. The final sensitivity analysis was restricted to participants with complete cost and effect data, i.e., complete case analysis (CCA). Participants who developed CVD or T2DM during the study (n=9) or became pregnant (n=7), and participants who had died (n=1) were excluded from all analyses.
Analyses were performed with R version 2.10.1.
Figure 2. Cost-effectiveness plane for Quality Adjusted Life Years gained

Northeast quadrant of the CE-plane: the intervention is more effective and more costly than usual care.  Southeast quadrant of the CE-plane: the intervention is more effective and less costly than usual care.  Southwest quadrant of the CE-plane: the intervention is less effective and less costly than usual care.  Northwest quadrant of the CE-plane: the intervention is less effective and more costly than usual care.

Figure 3. Cost-effectiveness acceptability curve for QALYs gained
RESULTS

Participant flow and baseline characteristics

The participant flow is presented in Figure 1. On average, 64% of the cost questionnaires were fully completed and returned. Data on the number of face-to-face and phone counselling sessions, necessary to calculate the intervention costs, were complete for 174/314 (55%). As a consequence, 36 to 45% of the cost data were imputed, as was 22 to 26% of the outcome data.

Baseline characteristics are given in Table 2.

Table 2. Baseline characteristics of all randomised participants

<table>
<thead>
<tr>
<th></th>
<th>CONTROL GROUP N=308</th>
<th>INTERVENTION GROUP N=314</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female [n (%)]</td>
<td>185 (60.1)</td>
<td>178 (56.7)</td>
</tr>
<tr>
<td>Age [mean (SD), (y)]</td>
<td>43.4 (5.5)</td>
<td>43.6 (5.1)</td>
</tr>
</tbody>
</table>
| LEVEL OF EDUCATION [N(%)]
  ≤Primary                 | 103 (33.6)           | 101 (32.5)               |
  Secondary                | 145 (47.1)           | 141 (44.9)               |
  College, university      | 59 (19.2)            | 69 (22.0)                |
| Paid job [n (%)]         | 269 (87.9)           | 262 (85.6)               |
| Smoking [n (%)]          | 54 (17.5)            | 74 (23.9)                |
| ARIC [mean (SD)], % risk | 18.8 (8.5)           | 19.0 (7.8)               |
| SCORE [mean (SD)], % risk| 3.8 (2.9)            | 4.0 (3.0)                |
| Health utility [mean (SD)] | 0.90 (0.13)       | 0.88 (0.16)              |

a n=617, b n=612, c n=619, d n=612
ARIC, the 9-year risk of developing T2DM; SCORE, the 10-year risk of CVD mortality

Intervention compliance

The mean number of face-to-face counselling sessions after multiple imputation was 2.4 (SEM 0.08). The mean number of follow-up phone sessions was 2.3 (SEM 0.2).
Outcomes
Table 3 lists the outcomes of the study with regard to 9-year risk for development of T2DM (ARIC), 10-year risk for of CVD mortality (SCORE) and the QALYs achieved after two years in each group, based on the imputed samples. Both groups improved their risk for T2DM and CVD, but only minimal and statistically non-significant differences between the groups were found. Changes in CVD-risk and QALYs achieved were in favour of the intervention group.

Table 3. Pooled outcomes at baseline and two-year follow-up, after multiple imputation and adjustment for baseline values

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>INTERVENTION GROUP</th>
<th>CONTROL GROUP</th>
<th>INTERVENTION VERSUS CONTROL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=305</td>
<td>N=300</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Baseline mean (SEM)</td>
<td>Baseline mean (SEM)</td>
<td>Follow-up mean (SEM)</td>
</tr>
<tr>
<td>ARIC (%)</td>
<td>18.8 (0.4)</td>
<td>18.5 (0.5)</td>
<td>18.8 (0.5)</td>
</tr>
<tr>
<td>SCORE (%)</td>
<td>4.0 (0.2)</td>
<td>3.7 (0.2)</td>
<td>3.8 (0.2)</td>
</tr>
<tr>
<td>QALYs* achieved</td>
<td>-</td>
<td>1.80 (0.02)</td>
<td>-</td>
</tr>
</tbody>
</table>

* The maximum amount of QALYs that can be achieved in two years is 2 units.
ARIC, the 9-year risk of developing T2DM; SCORE, the 10-year risk of CVD mortality; SEM, Standard Error of the Mean; QALY, Quality Adjusted Life Year.

Costs
Mean direct and indirect costs are presented in Table 4. Total intervention costs were €98 (SEM 2.4) per participant. The majority of participant costs consisted of costs of sports and sports equipment (88%). Indirect costs of productivity losses ranged from €0 to €71,695 in the control group and €0 to €45,195 in the intervention group. Statistically significant differences in costs between the groups were not seen (Table 5). The direction of the cost-differences was consistently in favour of the intervention group. The overall cost-difference was €-866 (95% CI -2392 to 370).
Table 4. Pooled costs and cost differences in Euros between baseline and two year follow-up, after multiple imputation

<table>
<thead>
<tr>
<th></th>
<th>INTERVENTION N=305</th>
<th>CONTROL N=300</th>
<th>INTERVENTION VERSUS CONTROL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MEAN (SEM)</td>
<td>MEAN (SEM)</td>
<td>MEAN DIFFERENCE (95% CI)</td>
</tr>
<tr>
<td>HEALTHCARE</td>
<td>1016 (92)</td>
<td>1021 (107)</td>
<td>-5 (-316;272)</td>
</tr>
<tr>
<td>Intervention</td>
<td>98 (2.4)</td>
<td>0</td>
<td>98 (NA)</td>
</tr>
<tr>
<td>Other</td>
<td>918 (92)</td>
<td>1021 (107)</td>
<td>-104 (-414;173)</td>
</tr>
<tr>
<td>PARTICIPANT COSTS</td>
<td>642 (45)</td>
<td>774 (69)</td>
<td>-132 (-323;27)</td>
</tr>
<tr>
<td>PRODUCTIVITY LOSSES</td>
<td>2189 (340)</td>
<td>2918 (528)</td>
<td>-729 (-2008;285)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>3847 (388)</td>
<td>4713 (626)</td>
<td>-866 (-2400;370)</td>
</tr>
</tbody>
</table>

NA, Not Applicable; SEM, Standard Error of the Mean

Cost-effectiveness

The incremental cost-effectiveness ratio (ICER) of the 9-year risk for developing T2DM (ARIC) was -1416. The interpretation of this is as follows: 1% less decrease in risk for developing T2DM as a result of the intervention saves society €1416, compared with providing health brochures. The ICER for the 10-risk of CVD mortality (SCORE) was 6405, indicating that a 1% decrease in risk as a result of the intervention saves society €6405, compared with health brochures (Table 5). The CE-plane showed that for T2DM risk, the majority (86%) of the cost-effectiveness pairs were located in the South-West quadrant, indicating that the intervention is likely less expensive, but also less effective than providing health brochures (Table 5). Cost-effectiveness pairs for CVD risk were mostly located (74%) in the South-East quadrant, indicative of higher effectiveness at lower cost (Table 5). The CEAC for T2DM (not presented) showed that the probability of cost-effectiveness at a ceiling ratio of €0 per one per cent risk reduction was 90%, compared with providing health brochures. Thus, if society is not willing to pay in exchange for a 1% decrease in risk, or accepts compensation in exchange for a 1% increase
<table>
<thead>
<tr>
<th>Analysis</th>
<th>Sample size per group</th>
<th>ΔC (95% CI)</th>
<th>ΔE (95% CI)</th>
<th>Distribution in CE plane (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CONTROL</td>
<td>INTERVENTION</td>
<td>EUROS</td>
<td>ARIC</td>
</tr>
<tr>
<td>INTENTION TO TREAT</td>
<td>300</td>
<td>305</td>
<td>-866 (-2372,370)</td>
<td>0.6 (-0.1;1.3)</td>
</tr>
<tr>
<td>COMPLETE CASES</td>
<td>117</td>
<td>105</td>
<td>-30 (-2171,1446)</td>
<td>0.7 (-0.4;1.7)</td>
</tr>
<tr>
<td>INTENTION TO TREAT</td>
<td>300</td>
<td>305</td>
<td>-866 (-2372,370)</td>
<td>-0.1 (-0.4;0.2)</td>
</tr>
<tr>
<td>COMPLETE CASES</td>
<td>116</td>
<td>104</td>
<td>-19 (-2253,1410)</td>
<td>-0.03 (-0.34;0.29)</td>
</tr>
<tr>
<td>INTENTION TO TREAT</td>
<td>300</td>
<td>305</td>
<td>-866 (-2372,370)</td>
<td>0.02 (0.02;0.05)</td>
</tr>
<tr>
<td>COMPLETE CASES</td>
<td>114</td>
<td>98</td>
<td>110 (2004;1611)</td>
<td>0.02 (-0.02;0.06)</td>
</tr>
</tbody>
</table>

*In the analysis ΔC= mean difference in total costs of intervention vs. control, ΔE= mean difference in outcome, ICER (ICUR) is calculated as ΔC/ΔE. In the intention to treat analysis missing data were multiply imputed. The complete cases analysis was restricted to participants with complete cost and effect data. NE: Northeast quadrant of the CE-plane: the intervention is more effective and more costly than usual care; SE: Southeast quadrant of the CE-plane: the intervention is more effective and less costly than usual care; SW: Southwest quadrant of the CE-plane: the intervention is less effective and less costly than usual care; NW: Northwest quadrant of the CE-plane: the intervention is less effective and more costly than usual care. ARIC, the 9-year risk of developing T2DM; ICER (ICUR), Incremental Cost-Effectiveness (Utility) ratio; SCORE, the 10-year risk of CVD mortality.
in risk, it is highly probable that the intervention offers value for money. The CEAC dropped when the amount that society is willing to pay or accept in compensation increased. Beyond a ceiling ratio of approximately €1500 per one per cent risk reduction, the probability that health brochures are cost-effective is higher than the probability that the lifestyle intervention is cost-effective. The probability of cost-effectiveness for CVD started at 90% at a ceiling ratio of €0 per one per cent risk reduction and fell slightly to 80% at a ceiling ratio of €10,000 per one per cent risk reduction (CEAC not presented).

**Cost-utility**
The incremental cost-utility ratio (ICUR) of €-50,273 per QALY gained was reflective of a small gain in QALYs compared with health brochures, at a reduction in societal costs (Table 5). The cost-effectiveness pairs were scattered around the plane, showing some uncertainty around the ICUR, as can be seen in Figure 2. The probability of cost-utility compared with health brochures was 90% at a ceiling ratio of €0 per additional QALY gained, reached a maximum of 93% at a ceiling ratio of €18,000 after which it reduced slightly (Figure 3).

**Sensitivity analyses**
The sensitivity analyses in which costs and QALYs were discounted, productivity losses were valued with the human capital method, the costs for sports were excluded from the participant costs, and missing number of follow-up phone calls were multiply imputed, showed similar results (data not shown). The sensitivity analysis in which only participants with complete costs and effects were included, gave different results (Table 5). The difference in societal costs virtually disappeared, but effects were similar to the main analysis. The scattering of cost-effectiveness pairs in the cost-effectiveness planes reflected the uncertainty (Table 5). The CEAC showed that for risk of T2DM that the probability of cost-effectiveness at a ceiling ratio of €0 was 50%. The CEAC for risk of CVD was around 50% at all ceiling ratios. With regard to QALYs gained, the maximum probability of cost-utility compared with health brochures was 45% at a ceiling ratio of €0 and converged to 77% at ceiling ratio of €100,000 per QALY gained.
DISCUSSION

No significant differences between the intervention and control group were found on clinical parameters, 9-year risk for developing T2DM, 10-year risk for CVD mortality or QALYs gained. Baseline health utilities were already high, which implied that there was little room for improvement in QALYs gained. Lack of effect might further be related to the low attendance to the counselling sessions. On average only 2.4 of the 6 scheduled face-to-face counselling sessions had taken place, whereas the mean number of 3-monthly phone-calls received was 2.3. These results underscore the difficulties in translating efficacious methods to interventions that are feasible and effective in a ‘real world’ setting.

Costs

Cost-differences were consistently in favour of the intervention albeit statistically not significant. Due to the skewed nature of the cost data, the study may have been underpowered to reach statistical significance for cost differences. The difference in total costs was mostly explained by differences in costs of productivity losses. To explore the effect of outliers on these costs, a post-hoc analysis was done. In this, the number of sick leave days was truncated at 30 days, as it is improbable that sick leave over 30 days would have been influenced by the intervention. The cost difference reduced to €-179 (95% CI -725 to 311), relative to €-866 (95% CI -2392 to 370) found in the main analysis. However, a reduction in societal costs remained.

To our knowledge, no other studies of lifestyle interventions to prevent T2DM or CVD have found immediate cost reductions as a consequence of the programme, in the absence of health effects. Some researchers have suggested that health promotion programmes have non-health benefits that are currently not measured, such as increased health literacy. These benefits may have an influence on health care use and sickness absenteeism, but this needs further exploration. The reduction in costs of personal expenses, mainly consisting of sports costs, is puzzling. Because the intervention participants were stimulated to be more physically active, higher costs were expected. All in all, the finding of cost savings in favour of the intervention cannot be easily explained.
Cost-utility
The main aim of an economic evaluation is to decide whether the treatment under scrutiny offers value for money. The ceiling ratio for QALYs gained in the Netherlands is not established, but it has been proposed to be set at €8,000 for diseases with a low burden and to €80,000 for diseases with a high burden. The burden of disease of an elevated risk for T2DM and CVD is unknown, but possibly lies at the lower end of the range. At a ceiling ratio of €8,000 per QALY gained, the probability of cost-utility of the intervention was circa 92%. At the higher end, probability of cost-utility was around 88% at a ceiling ratio of €80,000 per QALY gained. The intervention therefore has a high probability of cost-utility at all acceptable ceiling ratios. However, there is methodological uncertainty regarding this probability. The complete case analyses showed that the probability that the true cost-utility ratio falls below €80,000 is 75%. The post-hoc analysis in which the number of sick leave days was truncated at 30 days, showed a maximum probability of 70% at a ceiling ratio of €0. Thus, in these sensitivity analyses, cost-utility results were less positive. Furthermore, people generally demand larger compensations for losses compared with how much they are willing to pay for gains (willingness to pay < willingness to accept). If this aversion to lose is applicable to losses in health, a lower probability of cost-utility would have been found. Finally, as explained before, questions remain about the cause of the cost-differences. In light of these uncertainties, it is unsure if the possible benefits outweigh the efforts involved in the implementation of this new intervention. A value-of-information analysis could reveal if there is value in doing additional research.

Limitations and strengths
A limitation of the study is the amount of incomplete cost data. Intervention costs were missing for 140/314 (45%) participants, mainly because the practice nurses did not report the number of phone sessions. Data on intervention use should preferably be collected from care providers, to improve completeness of data, but this may be difficult in a primary care setting with many care providers involved. Also, 36% of the self-reported data on health care utilization, personal spending and sick leave was missing. This is comparable to other RCTs in the Netherlands with a follow-up of one year or longer, but data-completeness should be improved to increase the internal validity of these studies.
Over one-third of all cost data were imputed, using multiple imputation techniques. In multiple imputation it is assumed that unobserved data (i.e. missing costs) are (in part) dependent on the observed data (e.g. available costs). However, this assumption cannot be fully tested. Although methodological studies show that multiple imputation is preferred over complete case analyses and simple imputation methods, results from this study should be treated with some caution. Strengths of the study include the relatively long-term follow-up and the application of a randomised controlled design in a real world setting.

**Conclusion**

The lifestyle programme offered by practice nurses to adults at risk for T2DM and CVD was no more effective in reducing these risks than general health brochures. However, the intervention resulted in cost savings. A high probability of cost-utility was found at all ceiling ratios. Due to methodological uncertainty it is currently not advised to implement the intervention in Dutch general practices.


