OBJECTIVE — To explore the potential long-term health and economic consequences of lifestyle interventions for diabetic patients.

RESEARCH DESIGN AND METHODS — A literature search was performed to identify interventions for diabetic patients in which lifestyle issues were addressed. We selected recent (2003–2008), randomized controlled trials with a minimum follow-up of 12 months. The long-term outcomes for these interventions, if implemented in the Dutch diabetic population, were simulated with a computer-based model. Costs and effects were discounted at, respectively, 4 and 1.5% annually. A lifelong time horizon was applied. Probabilistic sensitivity analyses were performed, taking account of variability in intervention costs and (long-term) treatment effects.

RESULTS — Seven trials with 147–5,145 participants met our predefined criteria. All interventions improved cardiovascular risk factors at ≥1 year follow-up and were projected to reduce cardiovascular morbidity over lifetime. The interventions resulted in an average gain of 0.01–0.14 quality-adjusted life-years (QALYs) per participant. Health benefits were generally achieved at reasonable costs (€50,000/QALY). A self-management education program (X-PERT) and physical activity counseling achieved the best results with ≥0.10 QALYs gained and ≥99% probability to be very cost-effective (€20,000/QALY).

CONCLUSIONS — Implementation of lifestyle interventions would probably yield important health benefits at reasonable costs. However, essential evidence for long-term maintenance of health benefits was limited. Future research should be focused on long-term effectiveness and multiple treatment strategies should be compared to determine incremental costs and benefits of one over the other.

Comparing with lifestyle interventions for persons at high risk for diabetes, the long-term health and economic consequences of lifestyle interventions for diabetic patients are relatively unknown (1). This fact is noteworthy, because diabetic patients have a high risk for cardiovascular complications and, therefore, improving lifestyle is also worthwhile in this population. Furthermore, optimal management of lifestyle issues, often addressed within the context of self-management programs, is increasingly acknowledged as being an essential part of diabetes treatment and is incorporated in most national standards of care (2). Additional knowledge about long-term effects of these interventions is required for identification of the most successful strategies. Because the common aim of self-management, education, diets, lifestyle and exercise interventions is to reduce cardiovascular risk through lifestyle modification, we will refer to all of them as lifestyle interventions.

Trials are generally too short to capture the long-term benefits of an intervention, and epidemiological modeling can be used to fill this gap. By combining available evidence from different sources, modeling enables predictions of future outcomes and can be regarded as a valuable tool in addition to long-term trials. However, there is an important difference between modeling pharmaceutical and lifestyle interventions. With pharmaceutical interventions, the assumption is that if you keep taking the drug, you keep getting the benefits. If you stop the drug, you lose the benefits but the costs of the intervention cease. With lifestyle interventions, the costs are up-front costs and long-term outcomes are substantially affected by the extent to which health benefits are sustained after the intervention has stopped. Therefore, modeling lifestyle interventions requires explicit assumptions about how lifestyle changes are sustained over time (3,4).

The aim of our study was to explore the long-term outcomes of lifestyle interventions for diabetic patients. We used a computer-based simulation model to project long-term health benefits and cost-effectiveness, assuming implementation in the Dutch diabetic population.

RESEARCH DESIGN AND METHODS

Selection of trials

A literature search was performed to identify randomized controlled trials of patient-centered interventions in persons with type 2 diabetes, in which lifestyle issues (at least nutrition and/or exercise) were addressed. Inclusion criteria were recent publication (2003–2008), large trial (n >150), a minimum follow-up of 12 months, mainly Caucasian population, risk factor outcomes reported (weight, BMI, physical activity, smoking, diet, glycemic control, lipids, and/or blood pressure), and sufficient information to be able to calculate intervention costs. In addition, we searched for studies that provided quantitative information about long-term maintenance of health.
Lifestyle interventions for diabetic patients

benefits achieved through lifestyle interventions. Selection criteria for these studies as well as the methods for determining long-term maintenance estimates are described in the supplementary data (available in an online appendix at http://care.diabetesjournals.org/cgi/content/full/dc09-0363/DC1).

Model input
Intervention effect was defined as a significant change in risk factor outcome for intervention participants compared with control subjects at the latest follow-up. Long-term maintenance for each risk factor was defined as the proportion of the intervention effect that could be expected to be sustained over lifetime. For each risk factor, the intervention effect was multiplied with long-term maintenance to estimate the average intervention effect over a lifetime. Calculations of intervention costs were based on publications and additional information provided by authors. We assumed that the interventions would be implemented as described, but with a minimum of two patient contacts during the first 2 years (to enhance long-term maintenance). We accounted for additional intervention costs if these requirements were not met in the original intervention.

The Chronic Diseases Model
The Chronic Diseases Model (CDM) is a Markov-type simulation model, developed at the Dutch National Institute for Public Health and the Environment. The model simulates developments for the Dutch diabetic population and is well suited to explore long-term consequences of lifestyle changes. The model combines epidemiological data to quantify the associations between multiple risk factors and chronic diseases, such as cardiovascular diseases and cancers (see supplementary Figure A1 and Table A1, available in an online appendix). The model does not include microvascular complications. Starting from baseline distributions over risk factor classes and diseases, 1-year state transitions determine future developments. State transition probability values depend on a person’s risk level, determined by age, sex, risk factor class, and prevalent disease. Estimates of the strengths of the associations between risk factors and diseases are based on international, observational studies. The CDM has previously been used to evaluate long-term outcomes for diabetes prevention and diabetes treatment and to explore the impact of lifestyle risk factors on healthy life expectancy and lifetime medical costs (5–8).

Long-term health benefits
We explored the long-term health benefits of the interventions by comparing simulated outcomes for a reference cohort and an intervention cohort. Both cohorts represented Dutch diabetic patients eligible for each specific intervention. The intervention cohort differed from the reference cohort (usual care) by an altered risk factor distribution at the start of the simulation, based upon the trial results. For example, participants in the Improving Control with Activity and Nutrition (ICAN) trial lost 2.4 kg baseline weight compared with a weight gain of 0.6 kg in control subjects, a difference of 3 kg or 2.8% of baseline weight (BMI). The long-term maintenance estimate for BMI was 35% (see RESULTS), and, consequently, ICAN participants were assumed to have an average 2.8% × 35% = 1.0% lower BMI over lifetime, compared with patients receiving usual care. We used a large Dutch diabetes database to determine how this difference affected BMI risk factor class distributions at the start of the simulation.

Once the simulation had started, the same state-specific transition probabilities were applied to both reference and intervention cohorts. Cumulative lifetime incidence of cardiovascular disease (CVD) (CVD = acute myocardial infarction + coronary heart disease + congestive heart failure + stroke) and quality-adjusted life-years (QALYs) were simulated for these cohorts as well as for 60-year-old participants.

Cost-effectiveness
Economic analyses were performed from a health care perspective. Participants were eligible Dutch diabetic patients. Intervention costs were determined by multiplying resource use with Dutch unit costs in 2007. The incremental effects on the costs of care were calculated from the model simulations as follows. All model states in the CDM were associated with health care costs, depending on age, sex, and disease state. These costs represent total medical costs, including costs for “unrelated” diseases such as dementia and mental illness (9). For each intervention, net present values of incremental costs were calculated by summing the discounted costs over all simulation years and taking the difference with the reference scenario (usual care). Cost-effectiveness ratios (CERs) were calculated as (Δ intervention costs + Δ lifetime medical costs)/Δ QALYs for each intervention. In the base-case analyses, clinical benefits and costs were discounted at 1.5 and 4%, respectively, annually, in accordance with Dutch guidelines. The simulations were run for closed cohorts, with a lifelong time horizon.

Sensitivity analyses
One-way sensitivity analyses were performed to explore the impact of discount rates, time horizon, and additional long-term intervention costs on the cost-effectiveness of the interventions. Probabilistic sensitivity analyses were performed, taking account of uncertainty in intervention effects, long-term maintenance, and intervention costs. For each intervention, 200 random, independent drawings were taken from the distributions for effect, maintenance, and costs. Intervention effect and maintenance estimates were multiplied to generate “long-term effect” estimates. We took into account the possibility that changes in lifestyle risk factors may be correlated. For example, participants with the largest increase in physical activity may also achieve the largest weight loss (10–12). Because quantitative information about all possible combinations of risk factor outcomes is limited (and sometimes inconsistent) we assumed, respectively, 0 and 100% correlation between the long-term effect estimates of all risk factors affected. To do so, the long-term effect estimates for each risk factor were ordered, before they were combined. Consequently, a low (high) effect estimate for one risk factor was combined with low (high) estimates for all other risk factors affected. For intervention costs, we considered variation in total contact time of the interventions, and we varied the number of participants in group activities.

RESULTS

Selected trials
Seven trials fulfilled all predefined criteria. The interventions differed by scope, focus, content, intensity, and target population. Intervention duration ranged from 6 h to 24 months. The trials included were the following:

- Diabetes Education and Self Management for Ongoing and Newly Diagnosed (DESMOND): a 6-h self-management education program for
patients with newly diagnosed diabetes (n = 824) evaluated at 12 months (13)
- Beyond Good Intentions (BGI): a 12-week self-management course for patients with screen-detected diabetes (n = 196) evaluated at 12 months (14)
- Action for Health in Diabetes (Look AHEAD): a 1-year intensive lifestyle intervention for overweight patients (n = 5,145) evaluated at 12 months (15)
- Mediterranean Lifestyle Program (MLP): a 6-month lifestyle program for postmenopausal women with diabetes (n = 279) followed by two different maintenance programs, evaluated at 24 months (16)
- X-PERT: a 6-week, structured self-management education program for diabetic patients (n = 314) evaluated at 14 months (17)
- Improving Control with Activity and Nutrition (ICAN): a 1-year moderate-intensity lifestyle intervention for overweight patients (n = 147) evaluated at 12 months (18)
- Counseling for Physical Activity (CPA): a 2-year structured counseling intervention to promote physical activity (n = 340) evaluated at 24 months (10)

The selected trials, calculations of intervention costs, and characteristics of the simulated cohorts are described in supplementary Tables A2–A5 (available in an online appendix).

**Model input**

Significant reductions in risk factors were obtained in all trials (Table 1). Based on the long-term results from five other trials (supplementary data), we assumed that on average, respectively, 85, 55, and 35% of the initial effects for A1C, physical activity, and BMI (and all other risk factors) could be sustained over lifetime. We assumed slightly better maintenance for MLP and CPA, because “initial effects” in these trials were measured at 24 months follow-up. Total intervention costs, incurred over 2 years, ranged from €124 to €584 per participant (Table 1).

**Long-term health benefits**

The interventions were projected to reduce lifetime cumulative incidence of cardiovascular complications by 1–54 per 1,000 participants (Table 2). In other words, the number needed to treat to prevent one new cardiovascular complication over lifetime was 19–1,000. The relative reduction in expected lifetime CVD incidence ranged from 0.1 to 6.1%. The interventions increased life expectancy by 0.02–0.34 years and (discounted) QALYs by 0.01–0.14. For 60-year-old participants (supplementary Table A6, available in an online appendix), life expectancy increased by 0.02–0.42 years and (discounted) QALYs by 0.01–0.18. The physical activity intervention (CPA) had the largest simulated health gains. This intervention increased life expectancy of 60-year-old participants by 0.42 years, whereas average time spent with CVD complications decreased by 0.06 and 0.07 year for stroke and CHD, respectively (data not shown).

**Cost-effectiveness**

Despite prevented costs for complications, all interventions were projected to increase health care costs over a lifetime, because of increased survival (Table 2). The base-case CERs ranged from 10,000 to 39,000€/QALY (Table 3). Four interventions (BGI, X-PERT, Look AHEAD, and CPA) had average CERs <€20,000/QALY even with equal discounting of costs and effects, a 20-year time-horizon or additional lifetime intervention costs. In the probabilistic sensitivity analyses (for which details are provided in supplementary Tables A7–A9, available in an online appendix), these interventions had >85% probability to remain <€20,000/QALY (Table 3).

As expected, assuming 100% correlation between risk factor outcomes increased the variability of the simulated outcomes (supplementary Table A10, available in an online appendix). For example, for Look AHEAD, QALYs increased by 0.03–0.12 if outcomes were assumed to be independent and by 0.01–0.15 with 100% correlation. Similarly, the variability in simulated health care

<table>
<thead>
<tr>
<th>Table 1—Model input: intervention costs and intervention effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total per participant costs for the interventions*</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>DESMOND (€206)</td>
</tr>
<tr>
<td>BGI (€248)</td>
</tr>
<tr>
<td>Look AHEAD (€503)</td>
</tr>
<tr>
<td>MLP (€584)</td>
</tr>
<tr>
<td>X-PERT (€124)</td>
</tr>
<tr>
<td>ICAN (€373)</td>
</tr>
<tr>
<td>CPA (€345)</td>
</tr>
</tbody>
</table>

*Details are provided in supplementary Table A2. †This was the only nonsignificant effect that was included in the simulations. ‡Significant increase in fitness. NA, not available. SBP, systolic blood pressure.

<table>
<thead>
<tr>
<th>Table 2—Clinical benefits and health care costs for intervention participants compared with usual care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident CVD prevented*</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>DESMOND</td>
</tr>
<tr>
<td>BGI</td>
</tr>
<tr>
<td>Look AHEAD</td>
</tr>
<tr>
<td>MLP</td>
</tr>
<tr>
<td>X-PERT</td>
</tr>
<tr>
<td>ICAN</td>
</tr>
<tr>
<td>CPA</td>
</tr>
</tbody>
</table>

*Absolute reduction in cumulative lifetime incidence of new CVD complications per 1,000 participants, expected cumulative number of new CVD complications without intervention (per 1,000 participants in the reference cohort), and in parentheses, percent relative reduction achieved through the intervention. †Discounted with 1.5% annually. ‡Discounted with 4% annually.
costs and CERs was higher if outcomes were assumed to be correlated (data not shown). The cost-effectiveness acceptability curves for the interventions, assuming correlated outcomes, are displayed in Fig. 1.

In the base-case analyses, immediate cost-savings through reduced medication use (reported for X-PERT, Look AHEAD, and ICAN) were not taken into account, and additional analyses were performed to explore the potential impact of these additional intervention benefits (Table 3). Although economic outcomes for the three interventions improved, the main results as summarized above were not substantially changed.

**CONCLUSIONS** — We showed that it is feasible to simulate long-term outcomes for different kinds of lifestyle interventions for diabetic patients. However, because of limited information about long-term maintenance of health benefits, there was substantial variability (uncertainty) in the expected long-term outcomes for each intervention. Large differences in health outcomes were also observed between interventions (0.01–0.14 QALYs gained). However, despite this variability, health gains were generally achieved at reasonable costs (€50,000/QALY). Self-management education (X-PERT) and physical activity counseling (CPA) achieved the most promising results with ≥0.10 QALYs gained per person and a very high probability of being cost-effective.

Overall, the results of the selected trials were consistent with results from several meta-analyses that generally showed 0.3–0.8% improvements in A1C and modest (1.5 kg) reductions in weight achieved through nonpharmacological diabetes interventions (2,19,20). However, we want to highlight some interesting results. First, substantial weight loss was achieved in the Look AHEAD trial. This intervention focused on weight loss, mainly through caloric restriction, and included meal replacement products and weight loss medication (12). Although substantial short-term weight loss with caloric restriction has been reported previously (21), the long-term results of Look AHEAD are awaited to see whether these weight losses are sustained. Second, the major increase in voluntary physical activity in the CPA trial (23 MET h/week, corresponding to 1 addition hour of brisk walking per day) was much larger than the average 20–60 min of additional physical activity per week generally seen in other studies (22). Although the CPA intervention combined multiple evidence-based treatment strategies to enhance physical activity, it remains to be seen whether its findings can be replicated in other settings. Finally, three trials reported a decrease in medication use, which is an important, relatively new finding, because health care utilization outcomes were not assessed in any of 21 diabetes self-management trials included in a previous review (23).

Our study has several important strengths. The large number of participants in each of the studies indicates that implementation in regular care is probably feasible. To ensure that health benefits were sustained for a reasonable period of

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**Table 3**—Results for cost-effectiveness (€/QALY): base-case and sensitivity analyses

<table>
<thead>
<tr>
<th></th>
<th>Lifetime DC 1.5–4</th>
<th>Lifetime DC 0–0</th>
<th>Lifetime DC 3–3</th>
<th>20 years</th>
<th>Additional costs*</th>
<th>% below €20,000†‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>DESMOND</td>
<td>32,000</td>
<td>35,000</td>
<td>43,000</td>
<td>39,000</td>
<td>62,000</td>
<td>5.0/9.0</td>
</tr>
<tr>
<td>BGI</td>
<td>12,000</td>
<td>18,000</td>
<td>17,000</td>
<td>9,000</td>
<td>19,000</td>
<td>91.5/86.0</td>
</tr>
<tr>
<td>Look AHEAD</td>
<td>12,000</td>
<td>19,000</td>
<td>18,000</td>
<td>11,000</td>
<td>16,000</td>
<td>98.5/90.5</td>
</tr>
<tr>
<td>MLP</td>
<td>33,000</td>
<td>35,000</td>
<td>43,000</td>
<td>38,000</td>
<td>46,000</td>
<td>1.0/2.5</td>
</tr>
<tr>
<td>X-PERT</td>
<td>10,000</td>
<td>17,000</td>
<td>15,000</td>
<td>8,000</td>
<td>13,000</td>
<td>100/100</td>
</tr>
<tr>
<td>ICAN</td>
<td>39,000</td>
<td>38,000</td>
<td>52,000</td>
<td>52,000</td>
<td>68,000</td>
<td>4.0/NA</td>
</tr>
<tr>
<td>CPA</td>
<td>10,000</td>
<td>18,000</td>
<td>15,000</td>
<td>8,000</td>
<td>12,000</td>
<td>100/99.5</td>
</tr>
<tr>
<td>Look AHEAD§</td>
<td>11,000</td>
<td>18,000</td>
<td>16,000</td>
<td>9,000</td>
<td>15,000</td>
<td>99/55</td>
</tr>
<tr>
<td>X-PERT§</td>
<td>9,000</td>
<td>16,000</td>
<td>13,000</td>
<td>6,000</td>
<td>12,000</td>
<td>100/100</td>
</tr>
<tr>
<td>ICAN§</td>
<td>30,000</td>
<td>30,000</td>
<td>39,000</td>
<td>38,000</td>
<td>59,000</td>
<td>16.0/NA</td>
</tr>
</tbody>
</table>

*Assuming one additional 30-min individual contact (€27) per year for the remaining lifetime, starting from year 3. †Independent intervention effects for affected risk factors. ‡Dependent intervention effects for affected risk factors (100% correlation). §Assuming an average €100 per patient reduction in lifetime health care costs due to reduced medication use. DC, annual discount rates for effects and costs; NA, not available, just one risk factor affected.
time, we only used intervention effects that were measured at least 12 months after the start of the intervention. In addition, we required interventions to be continued (with at least two counseling sessions) in the second year. Long-term maintenance estimates were based on the best evidence available, and the impact of uncertainty in these estimates was explored in extensive sensitivity analyses. Finally, because changes in various lifestyle habits may go together, we considered the impact of correlated outcomes (10, 11).

Some methodological issues should be considered. Our simulations were based on randomized trial results, and it may be difficult to replicate these findings in daily practice. On the other hand, there are some reasons to believe that our health benefits might be underestimated. First, only risk factors included in the model could be used and consequently reported improvements in waist circumference, diastolic blood pressure, lipids, fitness, and psychosocial outcomes were not taken into account. Second, our model does not include microvascular complications. Although long-term health outcomes and health care costs are determined mainly by macrovascular diabetes complications, excluding microvascular disease results in an underestimation of health benefits, especially for improved glycemic control. Finally, enhanced standard care was provided to control subjects in three trials (13, 15, 17), and for these interventions we may have underestimated the effects in relation to the assumed resources used. On the other hand, large variations also exist in the extent to which lifestyle issues are currently addressed in Dutch usual care.

Because promotion of a healthy lifestyle is already acknowledged as an essential part of diabetes treatment, the question is no longer whether lifestyle issues should be addressed but rather how to find the most (cost) effective strategies for specific groups of patients. For example, Look AHEAD and ICAN were both directed to overweight diabetic patients. Although Look AHEAD seemed to dominate ICAN (larger health benefits and lower CER), these trials used different inclusion criteria and outcome measures and, therefore, results could not be properly compared. In addition, favorable efficacy and cost-effectiveness are not sufficient and potential reach, effectiveness, adoption, implementation, and maintenance issues of interventions should also be addressed (24). Because numerous factors influence the effectiveness of lifestyle interventions, standardized descriptions of intervention components are required to identify successful strategies and to enhance replication and implementation in regular care (23, 25).

We showed that lifestyle interventions can probably improve long-term health of diabetic patients at reasonable costs. Future research should be focused on long-term maintenance of health benefits achieved through lifestyle interventions and should directly compare multiple treatment strategies to determine incremental costs and benefits of one over the other. Because the potential benefits of successful lifestyle interventions are huge, we should be investing much more in gathering this valuable information.

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References

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