Within-Trial Cost-Effectiveness of Lifestyle Intervention or Metformin for the Primary Prevention of Type 2 Diabetes

THE DIABETES PREVENTION PROGRAM RESEARCH GROUP*

OBJECTIVE — The Diabetes Prevention Program (DPP) demonstrated that intensive lifestyle and metformin interventions reduced the incidence of type 2 diabetes compared with a placebo intervention. The aim of this study was to assess the cost-effectiveness of the lifestyle and metformin interventions relative to the placebo intervention.

RESEARCH DESIGN AND METHODS — Analyses were performed from a health system perspective that considered direct medical costs only and a societal perspective that considered direct medical costs, direct nonmedical costs, and indirect costs. Analyses were performed with the interventions as implemented in the DPP and as they might be implemented in clinical practice.

RESULTS — The lifestyle and metformin interventions required more resources than the placebo intervention from a health system perspective, and over 3 years they cost approximately $2,250 more per participant. As implemented in the DPP and from a societal perspective, the lifestyle and metformin interventions cost $24,400 and $34,500, respectively, per case of diabetes delayed or prevented and $51,600 and $99,200 per quality-adjusted life-year (QALY) gained. As the interventions might be implemented in routine clinical practice and from a societal perspective, the lifestyle and metformin interventions cost $13,200 and $14,300, respectively, per case of diabetes delayed or prevented and $27,100 and $35,000 per QALY gained. From a health system perspective, costs per case of diabetes delayed or prevented and costs per QALY gained tended to be lower.

CONCLUSIONS — Over 3 years, the lifestyle and metformin interventions were effective and were cost-effective from the perspective of a health system and society. Both interventions are likely to be affordable in routine clinical practice, especially if implemented in a group format and with generic medication pricing.

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Intensive lifestyle and medication interventions can delay or prevent progression from impaired glucose tolerance (IGT) to type 2 diabetes (1–3). The Diabetes Prevention Program (DPP) demonstrated that compared with the placebo intervention, the intensive lifestyle intervention reduced the incidence of type 2 diabetes by 58%, and the metformin intervention reduced the incidence of type 2 diabetes by 31% over 2.8 years (3).

Previously, we have reported in detail the resources used and costs of the DPP (4). Over 3 years, the direct medical cost of identifying one person with IGT, implementing, and maintaining the interventions was $2,919 for the lifestyle intervention, $2,681 for the metformin intervention, and $218 for the placebo intervention. From a societal perspective, the total costs of the lifestyle, metformin, and placebo interventions were $27,100, $25,900, and $23,500 per person over 3 years. What is the value of the investment in these interventions? Answering this question requires a cost-effectiveness analysis that combines both costs and health outcomes (5).

In this study, we performed within-trial cost-effectiveness analyses of the DPP in order to provide payers and policy makers a quantitative assessment of the value of the lifestyle and metformin interventions. These analyses allow comparison of the DPP interventions with other interventions in health and medicine (6–8) and provide the basis for future studies of the costs and benefits of the DPP interventions over a patient's lifetime. To our knowledge, we present the most rigorous economic evaluation of a behavioral weight-control program ever reported in the literature.

RESEARCH DESIGN AND METHODS

The clinical trial

The DPP enrolled 3,234 participants with IGT who were at least 25 years of age and who had a BMI of 24 kg/m^2 or higher (22 kg/m^2 in Asian Americans). Mean age of the participants was 51 years and mean BMI was 34.0 kg/m^2. Of the participants, 68% were women and 45% were members of minority groups.

The goals for the participants assigned to the intensive lifestyle interven-

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Abbreviations: DPP, Diabetes Prevention Program; IGT, impaired glucose tolerance; NNT, number needed to treat; QALY, quality-adjusted life-year; QWB-SA, Self-Administered Quality of Well-Being Index.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

See accompanying editorial, p. 2693.

tion were to achieve and maintain a weight reduction of at least 7% of initial body weight through diet and physical activity of moderate intensity, such as brisk walking, for at least 150 min/week. A 16-lesson curriculum and subsequent individual sessions (usually monthly) and group sessions with case managers were designed to reinforce the behavioral changes.

The medication interventions (metformin and placebo) were initiated at a dose of 850 mg taken orally once a day. At 1 month, the dose of metformin or placebo was increased to 850 mg twice daily. Adherence was reinforced during individual quarterly visits with case managers. Standard lifestyle recommendations were provided through written information and an annual 20- to 30-min individual session that emphasized the importance of a healthy lifestyle (3).

Costs

We have summarized the direct medical costs, direct nonmedical costs, and indirect costs associated with the DPP interventions over 3 years (4). In estimating direct medical costs, we considered the costs associated with identifying individuals with IGT, implementing and maintaining the DPP interventions, side effects of the interventions, and medical care outside the DPP (4). The latter included the costs of hospital, emergency room, urgent care, and outpatient services; telephone calls to health care providers; and prescription medications. In estimating direct nonmedical costs, we considered the value of the time that participants spent traveling to and attending appointments and the time they spent exercising, shopping, and cooking; the cost of exercise classes, exercise equipment, food, and food preparation items; and the cost of transportation (4). In estimating the costs arising from lost productivity (indirect costs), we assessed costs arising from being absent from work or usual activity due to DPP visits, illness, injury, and premature mortality (4). We summarized the costs of the lifestyle, metformin, and placebo interventions and calculated the costs of the lifestyle and metformin interventions relative to the placebo intervention and the costs of the lifestyle intervention relative to the metformin intervention from the perspectives of a large health system and society (4).

Outcomes

We assessed outcomes in usual clinical terms, that is, as cases of diabetes prevented during the trial and in terms of quality-adjusted life-years (QALYs) (5). Cost-effectiveness analyses were performed by applying incremental cost estimates from the health system and societal perspectives to the number needed to treat (NNT). The NNT is a measure of treatment effectiveness. It is the number of people who would need to be treated with a specific intervention for a given period of time to prevent one case of diabetes. NNT is calculated as 1 divided by the absolute risk reduction, i.e., the difference in risk between the experimental and control groups in a clinical trial (5). A time period of 3 years was used for these analyses. Because the closing date for the data (31 July 2001) was different from that used previously (31 March 2001), the NNTs used here differ slightly from those reported previously (3).

Cost utility was performed by comparing costs to outcomes expressed in terms of QALYs (5). QALYs measure the length of life adjusted for the quality of life. Mathematically, QALYs are calculated as the sum of the product of the number of years of life and the quality of life in each of those years. The numerical value assigned to quality of life reflects the public's judgement of the desirability of the outcome and is called a health utility. By convention, health utilities are placed on a continuum where perfect health is assigned a value of 1.0 and health judged equivalent to death is assigned a value of 0.0.

Health utilities

We assessed health utilities from the perspective of the general public using the Self-Administered Quality of Well-Being Index (QWB-SA). The QWB is a generic quality of life instrument that has been widely used in clinical trials to evaluate medical and surgical therapies (9–14). The QWB-SA was administered to DPP participants annually.

Perspective

In our analyses, we followed the recommendations of the Panel on Cost-Effectiveness in Health in Medicine (5). In all analyses from the perspective of a health system, we included only direct medical costs. In analyses from the perspective of society, we included direct medical costs, direct nonmedical costs, and indirect costs to estimate the cost per case of diabetes prevented during the trial; we included only direct medical costs and direct nonmedical costs to estimate the cost per QALYs gained (5).

Analyses

First, we performed the analyses based on the design, cost, and clinical effectiveness of the interventions as implemented in the DPP. We then assessed cost-effectiveness by age and evaluated the impact of plausible changes in both costs and outcomes on cost-effectiveness. Finally, we assessed cost-effectiveness with the interventions as they might be implemented in routine clinical practice. A recent randomized clinical trial (15) demonstrated that a behavioral weight loss program administered in a closed group of 8–12 participants was more effective than an individually administered lifestyle intervention. Another study (16) found that individual and group therapies resulted in equivalent initial weight loss but that group therapy had better long-term results. Indeed, most studies on behavioral treatment of obesity use group-based models of care (17). Thus, we recalculated resource utilization and costs for the lifestyle intervention assuming that the core curriculum, supervised activity sessions, and lifestyle group sessions were administered as closed groups of 10 participants and that direct medical costs were reduced accordingly. We assumed that individual monthly counseling and adherence sessions were conducted as they were in the DPP. We further assumed that direct medical costs, direct nonmedical costs, and indirect costs were not otherwise affected and that treatment effectiveness was not changed.

Similarly, the Food and Drug Administration has recently approved generic metformin. It is likely that generic metformin will be substantially less expensive than Glucophage. Thus, we recalculated the cost of the metformin intervention using generic metformin priced at 25% the cost of Glucophage. We further assumed that there were no other changes in the individual quarterly counseling and adherence sessions or in the direct medical costs, direct nonmedical costs, or indirect costs of the metformin intervention or in treatment effectiveness.

We excluded from all of the analyses the costs of the research component of the

Table 1—*Summary of total and incremental costs of the lifestyle, metformin, and placebo interventions in year-2000 U.S. dollars*

	Lifestyle	Metformin	Placebo	Lifestyle vs. placebo	Metformin vs. placebo	Lifestyle vs. metformin
Direct medical costs						
Case finding	139	139	139	0	0	0
Intervention	2,780	2,542	79	2,701	2,463	238
Care outside DPP	4,579	4,739	5,011	−432	−272	−160
Total costs from health system perspective	7,498	7,420	5,229	2,269	2,191	78
Direct nonmedical costs	17,137	15,683	15,692	1,445	−9	1,455
Indirect costs	2,430	2,834	2,604	−174	230	−404
Total costs from societal perspective	27,065	25,937	23,525	3,540	2,412	1,128

DPP, including the resources used for recruitment, data collection, and surveillance of outcomes beyond those recommended for routine clinical practice (4). All costs were expressed as year-2000 U.S. dollars (4). Analyses were performed with a 3-year time horizon, the average length of follow-up within the DPP. Initial analyses were performed without discounting. Subsequently, where noted, both cost and health outcomes were converted to net present value using a 3% discount rate (5). All calculations were performed using exact values. Results in the abstract and text were rounded to the nearest $100, and results in the tables were rounded to the nearest dollar.

RESULTS

Costs

Table 1 summarizes the costs of the interventions. From a health system perspective, both the lifestyle and metformin interventions were more expensive than the placebo intervention: $2,300 and $2,200 more over 3 years (4). The direct medical cost of the lifestyle intervention was approximately $100 more than the metformin intervention. From a societal perspective, the lifestyle intervention cost $3,500 more than the placebo intervention, and the metformin intervention cost $2,400 more than the placebo intervention over 3 years (4). From a societal perspective, the lifestyle intervention cost $1,100 more than the metformin intervention over 3 years. This reflected both the greater direct nonmedical costs of the lifestyle intervention relative to the metformin intervention ($1,500) and the lesser indirect costs of the lifestyle intervention relative to the metformin intervention (−$400).

Health utilities

In general, participants randomized to the lifestyle and metformin interventions reported fewer symptoms and better functioning than participants randomized to the placebo intervention. Over the first 3 years of the DPP, there were three deaths in the lifestyle intervention group, six deaths in the metformin intervention group, and five deaths in the placebo intervention group (1.023, 2.029, and 1.689 deaths/1,000 person-years, respectively). Table 2 shows the mean health utility scores by treatment group and treatment year after accounting for mortality. Participants randomized to the lifestyle and metformin intervention groups accrued 0.072 and 0.022 more QALYs over 3 years than participants randomized to the placebo intervention group. Participants randomized to the lifestyle intervention accrued 0.050 more QALYs over 3 years than participants randomized to the metformin intervention.

Cost per case of diabetes prevented during the trial

The DPP demonstrated that relative to the placebo intervention, 6.9 participants with IGT would need to be treated with the lifestyle intervention and 14.3 participants would need to be treated with the metformin intervention for 3 years to delay or prevent one case of diabetes. Thus, from the perspective of a health system and relative to the placebo intervention, the lifestyle intervention cost $15,700 and the metformin intervention cost $31,300 per case of diabetes prevented during the trial (Table 3). From the perspective of society and relative to the placebo intervention, the lifestyle intervention cost $24,400 and the metformin intervention cost $34,500 per case of diabetes prevented during the trial (Table

Table 2—*Health utility scores and QALYs gained by treatment group and year*

	Utility scores			QALYs gained		
	Lifestyle	Metformin	Placebo	Lifestyle vs. placebo	Metformin vs. placebo	Lifestyle vs. metformin
Year						
1	0.703 ± 0.118	0.687 ± 0.119	0.686 ± 0.121	0.017	0.001	0.016
2	0.695 ± 0.122	0.680 ± 0.123	0675 ± 0.122	0.020	0.005	0.015
3	0.692 ± 0.125	0.673 ± 0.117	0.657 ± 0.125	0.035	0.016	0.019
Total				0.072	0.022	0.050

Data are means ± SD.

Table 3—*Cost of DPP interventions over 3 years per case of diabetes prevented during the trial and per QALY gained*

	Cost per case of diabetes prevented (U.S. $)		Cost per QALY gained (U.S. $)	
	Health system perspective	Societal perspective	Health system perspective	Societal perspective
Lifestyle				
Comparator				
Lifestyle vs. placebo	15,655	24,426	31,512	51,582
Lifestyle vs. nothing	17,161	25,932	34,543	54,613
Personnel cost				
25% reduction	11,755	20,526	23,662	43,732
50% reduction	7,855	16,626	15,811	35,880
75% reduction	3,956	12,727	7,963	28,033
Intervention effectiveness				
10% reduction	17,243	26,904	35,013	57,313
20% reduction	18,831	29,382	39,389	64,477
Translated as group intervention	4,462	13,233	8,982	29,052
Discounting				
3% discount rate (costs and outcomes)	15,804	24,581	32,029	52,250
Metformin				
Comparator				
Metformin vs. placebo	31,338	34,489	99,611	99,171
Metformin vs. nothing	34,458	37,609	109,531	109,090
Metformin cost				
25% reduction	24,606	27,757	78,212	77,772
50% reduction	17,874	21,025	56,814	56,373
75% reduction	11,141	14,292	35,415	34,974
Intervention effectiveness				
10% reduction	34,406	37,865	110,679	110,190
20% reduction	37,693	41,483	124,514	123,964
Discounting				
3% discount rate (costs and outcomes)	31,452	34,604	102,164	101,713

3). The lifestyle intervention was more cost-effective than the metformin intervention from the perspective of both a health system and society.

Cost per QALY gained

From the perspective of a health system and compared with the placebo intervention, the lifestyle intervention cost $31,500 per QALY gained and the metformin intervention cost $99,600 per QALY gained (Table 3). From the perspective of society and compared with the placebo intervention, the lifestyle intervention cost $51,600 per QALY gained and the metformin intervention cost $99,200 per QALY gained (Table 3). The lifestyle intervention was more cost-effective than the metformin intervention from the perspective of both a health system and society.

Table 3 summarizes the results of these analyses and presents the results of sensitivity analyses demonstrating the impact of changes in the comparator, costs, intervention effectiveness, and intervention delivery on the cost-effectiveness of the interventions.

Sensitivity analyses

Lifestyle versus placebo intervention

When the lifestyle intervention was compared with no intervention, that is, neither screening for IGT nor implementing standard lifestyle recommendations, the cost of the lifestyle intervention per case of diabetes prevented during the trial increased approximately $1,500 from the perspective of a health system or society. The cost of the lifestyle intervention per case of diabetes prevented during the trial was approximately $4,300 less for individuals ≥60 years of age compared with those <45 years of age from a health system perspective and approximately $6,700 less from a societal perspective. Because 54% of the cost of the lifestyle intervention was related to the cost of DPP staff time (4), a decrease in personnel costs substantially reduced the cost of the lifestyle intervention per case of diabetes prevented during the trial. A 10 or 20% decrease in effectiveness, which might occur with greater nonadherence to the interventions (18), increased the cost of the lifestyle intervention per case of diabetes prevented during the trial. When the lifestyle intervention was implemented in a group of 10 rather than in an individual format (and personnel costs were reduced accordingly but effectiveness was not changed), the cost of the lifestyle intervention relative to the placebo intervention was reduced to $4,500 per case of diabetes prevented during the trial from the health system perspective and $13,200 per case of diabetes prevented during the trial from the societal perspective. Applying a 3% discount rate to costs and outcomes resulted in modest increases in the costs per case of diabetes prevented during the trial.

If the lifestyle intervention was compared with no intervention, the cost of the lifestyle intervention increased approximately $3,000 per QALY gained. If the lifestyle intervention was implemented in a group of 10, the cost of the lifestyle intervention compared with the placebo intervention was reduced to $9,000 per QALY gained from a health system perspective and $29,100 per QALY gained from a societal perspective.

Metformin versus placebo intervention

When the metformin intervention was compared with no intervention, the cost of the metformin intervention per case of diabetes prevented during the trial increased approximately $3,000. When stratified by age, the cost of the metformin intervention was $224,000 greater for individuals ≥60 years of age compared with those <45 years of age from a health system perspective and $247,000 greater from a societal perspective. This was due to the greater effectiveness of the intervention in younger age-groups (3). Approximately 74% of the cost of the metformin intervention was related to the cost of Glucophage (4). A 75% reduction in the cost of metformin reduced the cost of the metformin intervention per case of diabetes prevented to $11,100 from a health system perspective and $14,300 from a societal perspective. Decreases in the effectiveness of the metformin intervention and applying a 3% discount rate to costs and outcomes modestly increased the cost of the metformin intervention per case of diabetes prevented during the trial.

If the metformin intervention was compared with no intervention, the cost of the metformin intervention per QALY gained increased modestly. Reducing the cost of metformin by 75% reduced the cost per QALY gained to $35,400 from a health system perspective and $35,000 from a societal perspective.

CONCLUSIONS — As implemented in the DPP and from a payer perspective, the lifestyle and metformin interventions cost $15,700 and $31,300, respectively, per case of diabetes delayed or prevented and $31,500 and $99,600 per QALY gained. From a societal perspective, the lifestyle and metformin interventions cost $24,400 and $34,500, respectively, per case of diabetes delayed or prevented and $51,600 and $99,200, respectively, per QALY gained. The lifestyle intervention was more cost-effective than the metformin intervention. Thus, in economic terms, the metformin intervention was dominated by the lifestyle intervention and should not be adopted if only cost-effectiveness is considered. To the extent that treatment availability, health insurance coverage, and patient and provider preferences drive clinical decision making, the metformin intervention may still be a worthwhile intervention for delaying or preventing type 2 diabetes.

Earlier research has demonstrated the effectiveness of group behavioral interventions relative to individual behavioral interventions (15,16). If the lifestyle intervention were implemented in a group of 10 participants, the cost per case of diabetes prevented during the trial and the cost per QALY gained would decrease by >70% from a health system perspective and by >40% from a societal perspective. Similarly, if the metformin intervention could be implemented with a 75% reduction in the cost of the medication by using generic metformin, the cost per case of diabetes prevented during the trial and the cost per QALY gained would decrease by ~60% from either perspective.

From the perspective of a health system or society, what is the value of delaying or preventing type 2 diabetes? From a health system perspective, delaying or preventing type 2 diabetes delays or prevents the direct medical costs of diabetes, including the costs of diabetes education and nutritional counseling, glucose monitoring, treatment, surveillance of complications, and treatment of complications (19–21). From a societal perspective, delaying or preventing diabetes reduces direct medical costs, out-of-pocket costs, and time lost from work (19). It may also improve quality of life and length of life.

The direct medical costs of diabetes are enormous. It is estimated that per capita health care expenditures for individuals with diabetes are approximately $13,400 per year, $9,700 per year more than for individuals without diabetes (estimates adjusted to year-2000 U.S. dollars) (20). These estimates probably overstate the actual initial costs of diabetes in DPP participants who developed diabetes, since they were very early in the clinical course and had few complications. The costs of diabetes increase with HbA_{1c} level and presence of complications and comorbidities (22) and would be expected to be lower for individuals with lesser degrees of hyperglycemia and for those without complications. Nevertheless, costs are 2.1 times higher in patients with new clinically diagnosed diabetes compared with individuals without diabetes, and the incremental cost of diabetes is apparent from the time of diagnosis (21). Compared with the substantial costs of diabetes, the costs per case of diabetes prevented seem quite reasonable, particularly when adjusted according to the most likely scenarios for clinical implementation.

If the treatment effects persist beyond 3 years, the costs per QALY gained of the lifestyle and metformin interventions over 3 years likely overstate the lifetime cost per QALY gained. By adopting a 3-year time horizon, the current economic analyses overestimate treatment costs and underestimate the benefits of the lifestyle and metformin interventions. The costs of both the lifestyle and metformin interventions are greatest in year 1 and decrease substantially in subsequent years (4). Much of the benefit of both the lifestyle and metformin interventions will likely occur after 3 years of follow-up. It is likely that delaying or preventing type 2 diabetes will delay or prevent the need for treatment and delay or prevent the development of complications. It may also improve survival. These will translate into a relative decrease in treatment costs and an increase in QALY gained over a lifetime, substantially reducing the cost per QALY gained. However, estimating the long-term effects of the lifestyle and metformin intervention will require modeling costs and outcome beyond the time horizon of the DPP.

The results of the within-trial cost-utility analyses provide an assessment of the value of the lifestyle and metformin interventions relative to other interventions in medicine. Even with a 3-year time horizon, the costs per QALY gained of $9,000 to $29,000 for the lifestyle intervention and $35,000 for the metformin intervention, as they are likely to be implemented in clinical practice, fall within a range generally accepted as being cost-effective (23). A recent report (24) based on a simulation model has estimated that intensive glycemic control for patients with newly diagnosed type 2 diabetes in the U.S. costs approximately $41,000 per QALY gained over a lifetime. In patients with type 2 diabetes and a total cholesterol level ≥200 mg/dl, treatment with HMG-CoA reductase inhibitors costs $52,000 per QALY gained (24). Published cost-utility ratios for interventions such as hypertension screening and therapy for asymptomatic 20-year-old men ($40,000 per QALY) are comparable (8).

In summary, this 3-year within-trial economic analysis of the DPP demonstrated that the lifestyle and metformin interventions are cost-effective. These analyses should assist health plans and policy makers in comparing the benefit of diabetes prevention to other preventive and palliative interventions. The adoption of diabetes prevention programs in health plans will likely result in important personal and member benefits at a reasonable cost and over a short period of time. Further studies are needed to define the cost-utility of these interventions over a lifetime.

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