Type 2 Diabetes Prevention Programs; How Far are we?

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Abstract

Type 2 diabetes is the most costly chronic disease for both, the individual and the society. Many randomized controlled trials of structured lifestyle modification have consistently demonstrated that achieving and maintaining a healthy body weight through a combination of a change in dietary behaviors and an increase of physical activity reduces the risk of incidence of type 2 diabetes in adults at high risk. Although, their results have demonstrated the efficacy of lifestyle modification for diabetes prevention, long-term compliance with these lifestyle changes has proven difficult, however, and the benefits wane with weight regain. Small community-based programs have reported some success in modifying surrogate markers for diabetes through lifestyle intervention. The cost-effectiveness of lifestyle interventions has been examined in a number of clinical trials and computer modelling simulations. Short time-horizon studies have shown prediabetes lifestyle interventions to be cost-effective and even cost saving. Long time-horizon studies based on 10- to 30-year predictive mathematical models have used different models with different data, and have come to different conclusions about the cost-effectiveness of prediabetes lifestyle interventions. It is difficult to base a long time-horizon policy decision on predictive models when long-term randomized controlled trial data are not available to support the conclusions of those models. In conclusion, for large-scale implementation of preventive strategies, the future plan should focus on health education of the public, improving the national capacity to detect and manage non-communicable diseases and development of innovative, cost effective, and scalable methodologies.

Keywords: Community-based programs; Cost-effectiveness; Lifestyle interventions; Primary health care; Prevention; Type 2 diabetes

Abbreviations: CDQDPS: Chinese Da Qing Diabetes Prevention Study; CVD: Cardiovascular Disease; DEHKO: Development Programme for the Prevention and Care of Diabetes in Finland; DEPLAN: Diabetes in Europe – Preventing using Lifestyle, Physical Activity and Nutritional Intervention; DEPLOY: Diabetes Education and Prevention with Lifestyle intervention Offered at the Young Men's Christian Association; DPPOS: Diabetes Prevention Program Outcomes Study; DPP: Diabetes Prevention Program; DPS: Finnish Diabetes Prevention Study; FIN-D2D: National Type 2 Diabetes Prevention Programme in Finland; FINDRISC: Finnish Diabetes Risk Score; GGT: Greater Green Triangle Diabetes Prevention Project in Australia; GOAL: Good Ageing in Lahti Region Lifestyle Implementation Trial in Finland; IDF: International Diabetes Federation; IGT: Impaired Glucose Tolerance; NGR: Normal Glucose Regulation; T2D: Type2 Diabetes

Introduction

Diabetes is the one of the most common non-communicable diseases. It is the fourth or fifth leading cause of death in most high-income countries and there is substantial evidence that it is epidemic in many economically developing and newly industrialized countries. Diabetes imposes a large economic burden on individuals and families, national health systems and countries. Health expending on diabetes accounted for 11% of total health expenditure worldwide in 2013 [1-3].

The most recent estimates indicate that 8.3% of adults - 382 million people have diabetes and the number of people with the disease will increase by 55% - 592 million in less than 25 years. Type2 diabetes (T2D), which is the most common condition and a serious global health problem, accounts for 85% to 95% of all diabetes in high-income countries and may account for an even higher percentage in lower-middle-income countries. A further 316 million people or 6.9% of adults with Impaired Glucose Tolerance (IGT) are at risk from the disease as well as at increased risk from Cardiovascular Disease (CVD) – an alarming number that is set to reach 471 million by 2035. The majority of adults with IGT are under the age of 50 (153 million) and are therefore likely to spend many years at high risk [4].

In most countries diabetes has increased alongside rapid culture and social changes: ageing populations, increasing urbanization, dietary changes, reduced physical activity and unhealthy behaviors [5-7]. Population growth and prolonged life expectancy have contributed to a steady increase in the number of older people aged 60 years or over who constitute more than 11.1% of the world's population. The International Diabetes Federation (IDF) estimates the global prevalence of diabetes in people aged between 60 and 79 to be 18.6%, more than 134.6 million people, accounting for over 35% of all cases of diabetes in adults. It is important to know that one-third of all people with IGT are in this age group [4].

At present, type 1 diabetes cannot be prevented, although there is a lot of evidence that lifestyle changes can help prevent the development of T2D. Landmark clinical trials have shown than primary prevention can delay and possibly prevent the onset of diabetes in individuals at high risk [8-13]. Intensive lifestyle and pharmacological interventions reduce the rate of progression to T2D in people with IGT. The results of the prevention trials seemed that the interventions to change dietary
habits and increase physical activity are the most effective strategies, representing the first steps of T2D prevention programs, while the effect of pharmacological interventions decreased after intervention was terminated [13-18]. Encouraged by these results, there have been many attempts to translate the prevention trials into community-based programs [8,19-21]. In this review, results from long-term follow-up of diabetes prevention and the outcomes of community-based interventions in "real world" settings will be presented. Furthermore, it will provide evidence-based data on the cost-effectiveness of primary prevention of diabetes at the long-term clinical and community-based level. Finally, this review will also focus on older adults as there is a profound lack of clinical trials, although little evidence is showed that lifestyle interventions had greater impact in older participants.

**Long-term Follow Up of Diabetes Prevention**

Many randomized controlled trials of structured lifestyle modification have consistently demonstrated that achieving and maintaining a healthy body weight through a combination of a change in dietary behaviors and an increase of physical activity reduces the risk of incidence of T2D in adults at high risk by 42-67% [8,21]. Long-term post-intervention follow up evidence of lifestyle modification are only provided by three major clinical trials providing encouraging results (Table 1). However, no long-term follow-up of drug intervention to prevent diabetes has been published except for the Diabetes Prevention Program Outcomes Study (DPPOS).

**Finnish Diabetes Prevention Study (DPS)**

A total of 522 middle-aged individuals with IGT were randomized to an intensive lifestyle intervention group or to a control group. After 3.2 years of intervention, the relative risk reduction of T2D between lifestyle intervention and control group was 58% (p<0.001) [9]. After a median post-intervention follow up of 4 and 9 years (7 and 13

### Table 1: Long-term follow-up of diabetes prevention programs.

| Study        | Subjects                                                                 | Intervention                                                                                     | Relative Risk Reduction of T2D/ mean duration of intervention | Relative Risk Reduction of T2D/ mean duration of follow-up |
|--------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|
| DPS          | 522 individuals mean age 55 ± 7 years, and mean BMI 31.2 ± 4.5 kg/m² with IGT | 1. Control group: general advice about healthy lifestyle at baseline.                           | 58% (p<0.001) Compared with control group / 3.2 years         | 42% (p<0.0001) Compared with control group / a median post-intervention follow up of 4 years (7 from baseline) |
|              |                                                                          | 2. Intervention group: Individualized lifestyle intervention included 7 face-to-face counseling |                                                                | 38% (p<0.001) Compared with control group / a median post-intervention follow up of 9 years (13 years from baseline) |
|              |                                                                          | sessions with nutritionist during the first year and every 3 months thereafter. Intervention goals: body weight reduction of ≥ 5%, total fat intake <30% of energy, saturated fat intake <10% of energy, fibre intake of ≥15g/1000kcal and moderate exercise for ≥ 30/day |                                                                |                                                                |
| CDQDPS       | 577 people mean age 45 ± 9.1 years and mean BMI 25.6 ± 3.8kg/m² with IGT   | 1. Control group: general advice about healthy lifestyle at baseline.                           | 33% of dietary group (p<0.03)                                 |                                                                |
|              |                                                                          | 2. Dietary intervention: individual counseling+ compliance evaluation by physician/nurse every 3 months + small groups weekly for 1 month, monthly for 3 months and every 3 month thereafter. Intervention goals: weight reduction aiming at <24 kg/m², 55-65% of energy carbohydrate, 25-30% of energy fat and 10-15% of energy protein. Increase vegetables, decrease alcohol and sugar. | 47% of exercise group (p<0.0005)                              |                                                                |
|              |                                                                          | 3. Exercise intervention: physical activity by at least 30 minutes of moderate activities and 20 minutes of vigorous activities daily | 38% diet + exercise group (p<0.005)                             |                                                                |
|              |                                                                          | 4. Diet+Exercise intervention: diet-plus- exercise combined intervention                          |                                                                |                                                                |
| DPP          | 3234 US adults mean age 50.6 ± 10.7 years and mean BMI 34 ± 6.7 kg/m² with IGT | 1. Placebo group: general advice about healthy lifestyle at baseline.                           | 58% of lifestyle group (p<0.01)                               |                                                                |
|              |                                                                          | 2. Intervention group: 16 face-to-face counseling sessions with registered dietitian during the first 24 weeks and every 2 months thereafter. Intervention goals: ≥ 7% weight loss, total fat intake <25% of energy, energy reduction of 500-1000 kcal/day and 150 min of more per week of moderate-intense physical activity | 31% of metformin (p<0.01)                                   |                                                                |
|              |                                                                          | 3. Metformin intervention: 850 mg twice per day                                                  |                                                                |                                                                |
|              |                                                                          |                                                                                               |                                                                |                                                                |
| DPPOS post-intervention ongoing observational follow-up to the DPP | 2766 DPP participants mean age 55.2 ± 10.3 years and mean BMI 32.7 ± 6.6 kg/m² | all three groups of DPP were offered group-implemented lifestyle intervention with registered dietitian | 34% of lifestyle group (p<0.001)                               |                                                                |
|              |                                                                          | metformin treatment was continued in the original metformin group                              |                                                                |                                                                |
|              |                                                                          | the original lifestyle intervention group was offered additional lifestyle support             |                                                                |                                                                |

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years from baseline), the relative risk were 42% ($p=0.0001$) and 38% ($p<0.001$) respectively [22]. Body weight reductions from baseline to years 1 and 3 were 4.5 ± 5 kg and 3.5 ± 5.1 kg ($p<0.0001$) respectively in the intervention group and 1.0 ± 3.7 kg and 0.9 ± 5.4 kg ($p<0.0001$) in the control group [9]. Body weight increased gradually in the course of follow-up in the both groups. However, a statistically significant difference between the study groups prevailed ($p=0.006$ at year 10) [22]. Finally, it is important to be mentioned that lifestyle intervention among person with IGT did not decrease CVD morbidity during the first 10 years of follow up [23].

### Chinese Da Qing Diabetes Prevention Study, (CDQDPS)

Cluster randomization was used to allocate 577 people with IGT attending 33 participating clinics to diet alone, exercise alone, diet-plus-exercise combined or no intervention [24]. After 6 years intervention, the relative risk reduction of T2D in the diet alone, exercise alone, diet-plus-exercise combined intervention groups were 33% ($p<0.03$), 47% ($p<0.0005$) and 38% ($p<0.005$) respectively. Compared with control participants, those in the combined lifestyle intervention groups had a 43% ($p<0.01$) lower incidence of T2D over the 20 year follow-up [11]. Finally, a 23-year follow-up study indicates that the 6-year lifestyle intervention programme for Chinese people with IGT can reduce incidence of CVD and all-cause mortality. Specifically, cumulative incidence of CVD mortality was 11.9% in the intervention group versus 19.6% in the control group ($p=0.033$) and all-cause mortality was 28.1% versus 38.4% ($p=0.049$) [25].

### Diabetes Prevention Program Outcomes Study, (DPPOS)

The DPPOS is a post-intervention ongoing observational follow-up to the US Diabetes Prevention Program (DPP), one of the largest randomized controlled clinical trials to date.

The DPP was conducted in 3234 US adults with IGT. Unlike most previous studies, the cohort was diverse and included a large proportion of women (68%), ethnic and racial minorities (45%) and 20% aged 60 years or older. Participants were randomly assigned centrally to one of three interventions: intensive lifestyle; metformin 850 mg twice per day; or placebo [26]. The mean duration of intervention was 2.8 years. Compared with placebo, both lifestyle intervention and metformin group reduced T2D risk by 58% ($p<0.01$) and 31% ($p<0.01$) respectively [10].

For a median additional follow-up of 5.7 years, 2766 (mean age of 55.2 ± 10.3 years and mean BMI 32.7 ± 6.6 kg/m²) of 3150 (88%) enrolled in DPPOS. On the basis of the benefits from the intensive lifestyle intervention in DPP, all three groups of DPP were offerd group-implemented lifestyle intervention, while metformin treatment was continued in the original metformin group and the original lifestyle intervention group was offered additional lifestyle support [27].

During the 10 year follow-up since randomization to DPP, the T2D incidence rate of lifestyle group was reduced by 34% ($p<0.001$) and metformin by 18% ($p<0.001$) compared with placebo. It is important to mention that lifestyle effect was greatest in participants aged 60-85 years with a significant effect [28]. Furthermore, it should be noted that participants who were able to achieve Normal Glucose Regulation (NGR) status at least once during DPP had a 56% lower risk of diabetes during DPPOS (0.0001). Generalized mixed did demonstrate a positive effect of female sex on regression to NGR [29].

During DPP, weight loss was associated with diabetes prevention. Body weight at baseline and weight reduction during intervention was most important predictors of T2D risk. At one-year of DPP the mean weight loss of the lifestyle group participants was 7.4 kg (about 7%) of body weight, diminishing to 4.2 kg (about 4%) after 3 years [10].

During the DPPOS, the lifestyle group participants gradually regained, although still weighing 2.1 kg less than they did at randomization [27]. The metformin group lost a mean of 2.5 kg during DPP and maintained most of the weight loss. Although, during the DPPOS every age-group in the lifestyle intervention gained weight, on average, participants in both metformin and placebo group who were aged 60-85 years at DPP randomization lost weight [27,28].

Finally, although no differences in CVD events were noted after 3 years of DPP, lifestyle intervention reduced known CVD risk factors including hypertension, high triglyceride levels, low HDL levels, and small dense LDL compared with placebo and metformin therapy. During 10 years of DPPOS, assessing the association between the regression to NGR and a long-term decrease in CVD risk using the Framingham 10-year risk.

CVD risk score, the mean scores were highest in the group with IGT (16.2%), intermediate in the NGR group (15.5%), and 14.4% with diabetes (p<0.05). The lower score in the diabetes group versus other groups and a declining score in the group with IGT were probably explained by higher or increasing anti-hypertensive medication and pharmacologic therapy for dyslipidemia [30,31].

### Translating Diabetes Prevention Trials to the Public Health

Preventing diabetes is of enormous value for any nation particularly in the developing world because of the high cost of treating diabetes and its complications. However, there is less agreement with respect to the intensive and costly lifestyle intervention of the DPP and DPP [32-34]. Although, their results have demonstrated the efficacy of lifestyle modification for diabetes prevention, long-term compliance with these lifestyle changes has proven difficult, however, and the benefits wane with weight regain (Table 2).

Small community-based programs have reported some success in modifying surrogate markers for diabetes through lifestyle intervention. The Greater Green Triangle (GGT) Diabetes Prevention Project in Australia, the Diabetes Education and Prevention with Lifestyle intervention Offered at the Young Men’s Christian Association (DEPLOY) and the Good Ageing in Lahti Region (GOAL) Lifestyle Implementation Trial in Finland confirmed that short-term lifestyle modification programs can reduce risk factors for diabetes in primary care settings.

The DEPLOY study aimed to deliver a formal, group-based adaptation of the DPP lifestyle intervention. Among 92 overweight adults with abnormal glucose metabolism, the 46 participants (mean age of 60.1 ± 10.5 years and mean BMI 30.8 ± 5.1 kg/m²) in the intervention arm participated in the new DPP assembled into 16 classroom-style meetings of 8-12 people over 16-20 weeks. At the control group 46 participants (mean age of 56.5 ± 9.7 years and mean BMI 32 ± 4.8 kg/m²) were offered information about existing wellness programs to help participants achieve modest weight loss through gradual lifestyle changes. After 6 months, compared to baseline levels, BMI was reduced by 1.0 ± 5.1 kg/m² in the intervention group and 1.0 ± 5.1 kg/m² in the control group [9]. Body weight increased gradually in the course of follow-up in the both groups. However, a statistically significant difference between the study groups prevailed ($p=0.006$ at year 10) [22]. Finally, it is important to be mentioned that lifestyle intervention among person with IGT did not decrease CVD morbidity during the first 10 years of follow up [23].

### Table 2: Weight loss of intervention group over the diabetes prevention programs.

| Study          | 1st year | 2nd year | 3rd year | 4th year | 5th year | 10th year |
|----------------|----------|----------|----------|----------|----------|-----------|
| DPP            | 4.5      | 4        | 3.5      | 2.9      | 2.5      | 0.9       |
| DPP-DPPOS      | 7.4      | 5.6      | 4.2      | 3.2      | 2.6      | 1.9       |
body weight decreased by 6% in intervention participants and 2% in control participants \(p<0.001\). This equated to a mean weight loss of 5.7 kg for intervention participants and 1.8 kg for controls. Intervention participants also had greater changes in total cholesterol \(p<0.001\). These differences were sustained after 12 months [35,36].

In the Finland, 352 middle-aged participants (mean age of 58.5 ± 4 years and mean BMI 32.3 ± 4.9 kg/m²) with elevated T2D risk were recruited from the health care centres in Finland. The GOAL intervention included six group counselling sessions implemented lifestyle objectives derived from DPS. At 12 months, only 20% of participants achieved at least four of five keys lifestyle outcomes and physical activity and weight loss goals were achieved significantly less frequently [37].

The Australian GGT intervention study included 237 individuals (mean age of 56.7 ± 8.7 years and mean BMI 33.5 ± 5.9 kg/m²) 40-75 years of age with moderate or high risk of developing T2D. A structured group programme with six 90 minute group-sessions delivered during an eight month period by trained nurses in Australian primary health care. The intervention model used in the study was based on the diabetes prevention project in the Finnish GOAL study. At 12 months participants’ mean weight reduced by 2.52 kg. Between baseline and 12 months, statistically significant improvements were observed in participants’ mean clinical indicators except systolic blood pressure. 75% of participants experienced some weight reduction and 68% experienced weight reduction [38,39].

While early results from these are encouraging, the samples were small and largely self-selected, follow-up was short, the interventions remained relatively intensive and many studies lacked formal comparison. Furthermore, the low level of participation in the community-based diabetes risk-screening events suggests that a range of different approaches may be needed to engage people who are at risk for diabetes.

The design of effective ‘real world’ models for implementing the DPP and DPS lifestyle intervention requires a collaborative effort that balances fidelity to the design with additional incentives, communications and organizational elements that predispose, enable and reinforce behavioural changes in both practitioners and patients and that optimize reach, adoption and implementation and effectiveness, minimize cost and improve sustainability for capable community partners.

The current challenge is to translate evidence of the trials and the small community-based programs into cost-effective large scale community-wide programs. There is increasing acknowledgement that the best way to do this is through studies which have an explicit focus on generalisation and feasibility and which report information on contextual variables such as representativeness, reach, implementation and adaption, costs and other outcomes important to policy makers [21,40,41].

Finland is one of the first countries to implement a large-scale diabetes prevention strategy, The Development Programme for the Prevention and Care of Diabetes in Finland 2000-2010 (DEHKO) includes a population strategy aimed at nutritional interventions and increased physical activity in the entire nation, an individualised strategy for those at high risk, and a programme of early detection and management for people with T2D [42].

The primary strategy of the Finnish National T2D Prevention Programme (FIN-D2D) was a ‘high-risk strategy’ aiming at preventing diabetes and reducing cardiovascular risk factor levels among high-risk individuals in daily routines in healthcare centres and occupational healthcare outpatient clinics. The aim of the ‘high-risk strategy’ was first to identify individuals aged 18-87 years at elevated risk of developing type 2 diabetes and to support their lifestyle changes required to reduce their future risk. Altogether, 400 primary healthcare centres or occupational healthcare clinics were involved in the programme. To identify high-risk individuals for type 2 diabetes, the modified Finnish Diabetes Risk Score (FINDRISC, scoring ≥ 15) was used. Intervention visits were either individual counselling visits or group sessions, at which the intervention visit form was filled. The frequency of intervention visits varied between health centres depending on local circumstances and resources, and the total number of intervention visits was recorded [43].

During the one-year follow-up, 17.5% of the subjects lost ≥ 5% weight. On average this meant an 8.5 kg \(p<0.001\) reduction in weight, a 3.0 kg/m² \(p<0.001\) reduction in BMI and a 6.6 cm \(p<0.001\) reduction in waist circumference. During the follow-up, 16.8% of the subjects lost 2.5–4.9% weight and 46.1% maintained weight. Only 19.6% of the subjects gained 2.5% weight. Men were as successful as women in losing weight. Weight loss was on average 1.3 kg \(p<0.0001\) in 919 men (mean age of 56.0 ± 9.9 years and mean BMI 30.9 ± 3.6 kg/m²) and 1.1 kg \(p<0.0001\) in 1879 women (mean age of 54.0 ± 10.7 years and mean BMI 31.6 ± 5.4 kg/m²). 9.6% of the men reported both an increase in physical activity and improved dietary pattern, 4.1% an increase in physical activity, 39.3% an increase in improved dietary pattern, while 47.0% reported no lifestyle changes. Corresponding numbers for women were 14.2%, 3.8%, 39.2% and 42.7%. Those who increased their activity decreased their weight by 3.6 kg \(p<0.001\), BMI by 1.27 kg/m² \(p<0.001\) and waist circumference by 3.6 cm \(p<0.001\) more than those who did not increase their activity. Those who increased their physical activity also reported more changes in their diet, but the main results remained either statistically significant or borderline significant after adjustment for the number of intervention visits and after the adjustment for dietary change [44,45].

Estimated 10-year risk for CVD events decreased 3.5% in men and 1.5% in women reporting an increase in physical activity and improvement in diet, compared to an increase of 0.15% in men \(p<0.001\) and decrease of 0.43% \(p=0.027\), between groups in women with no lifestyle changes [46].

The relationship between weight loss and incidence of diabetes was almost stepwise. The relative risk of diabetes was only 0.31 (95% CI 0.16 – 0.59; \(p<0.001\)), which translates to 69% risk reduction in the group who lost 5% weight compared with the group who maintained weight. The relative risk was 0.72 (0.46–1.13, risk reduction of 29%; \(p<0.001\)) in the group who lost 2.5– 4.9% weight and 1.10 (95% CI 0.77–1.58, risk increase 10%; \(p<0.001\)) in the group who gained 2.5% compared with the group who maintained weight. This unexpected reduction in the risk of diabetes emphasizes that moderate weight loss in this very high-risk group representing early converters is especially effective in reducing risk of diabetes or at least postponing diabetes. Longer follow-up is needed to see whether this effect will last over time [44].

Although encouraging first results of the first large-scale diabetes prevention strategy, it must be noted that only 50% of the total cohort had any follow-up data. The first loss to follow-up occurred after screening; only 78% of the screened high-risk subjects had an OGTT. The second loss to follow-up occurred after the OGTT. Only 69% of subjects who had an OGTT at baseline had any follow-up data. These data reflect a real-life setting and the difficulty in following up on patients in primary healthcare settings [44-47].
The Diabetes in Europe – Preventing using Lifestyle, Physical Activity and Nutritional Intervention (DE-PLAN) project is another large-scale diabetes prevention initiative, which aims to develop community-based T2D prevention programmes for individuals at high risk in each local project centre across Europe [48-50].

The national programs such as the FIN-D2D, the Singapore Diabetes Prevention Programme and the Cameron Diabetes Prevention Plan initiated by the government should be taken as model endeavours to formulate strategies to promote and implement community health programs [43,51,52].

Cost-effectiveness of Diabetes Prevention

The increasing health and economic burden of T2D has made preventing the disease a public health priority. Implementation of diabetes prevention interventions in real-life settings requires a comprehensive evaluation approach. In most countries health care costs are rapidly rising, and the obesity epidemic plays an important role in this process. Several studies have shown that the risk of developing T2D and associated CVD reduces with weight loss and improved lifestyle behaviours [8-13]. The cost-effectiveness of lifestyle interventions has been examined in a number of clinical trials and computer modelling simulations. Although pharmacological interventions have also been shown to prevent diabetes, the cost effectiveness and risk-benefit ratio are less clear [32-34,53-63].

The 10-year, within trial, intention-to-treat economic analysis of the DPP/DPPOS demonstrates that lifestyle, when compared with placebo, is cost-effective, and metformin is marginally cost-saving. Even when compared with metformin, lifestyle was cost-effective from both a health system and societal perspective [64]. Follow-up of the DPP cohort for 10 years after randomization showed that lifestyle intervention for people older than 65 years with prediabetes can prevent many cases of diabetes. Prediabetes lifestyle interventions for relatively healthy people aged 65 years or older seem to be highly cost-effective and possibly cost saving to a health care insurance payer, although evidence is little [65-67].

Another analysis indicates that, compared with no prevention program, the DPP lifestyle program would reduce a high-risk person’s 30-year chances of getting diabetes from about 72% to 61%, the chances of a serious complication from about 38% to 30%, and the chances of dying of a complication of diabetes from about 13.5% to 11.2%. Metformin would deliver about one third the long-term health benefits achievable by immediate lifestyle modification [68].

Furthermore, modelling studies for diabetes prevention which encompass a screening stage indicate that screening for T2D and IGT, with appropriate intervention for those with IGT, in an above average risk, overweight and obese, population aged 55 and older with systolic blood pressure ≥130 mmHg, seems to be cost effective. The cost effectiveness of a policy of universal screening for undiagnosed T2D alone, which offered no intervention to those with IGT, is still uncertain, since its high cost effectiveness ratio was primarily attributable to the small gain in health benefit [60-63,69,70-77].

Cost-effectiveness analyses of lifestyle interventions are more complicated than evaluations of treatment where all important health effects can be expected to manifest in the short term. Their results are dependent, in part, on trial data as well as mathematical models. Short time-horizon studies have shown prediabetes lifestyle interventions to be cost-effective and even cost saving. Long time-horizon studies based on 10 to 30 year predictive mathematical models have used different models with different data, and have come to different conclusions about the cost-effectiveness of prediabetes lifestyle interventions [54-56,68-77]. Predictive models are useful, but they also have limitations. It is difficult to base a long time-horizon policy decision on predictive models when long-term randomized controlled trial data are not available to support the conclusions of those models.

The adoption of diabetes prevention programs by health plans and society will result in important health benefits over 10 years and represents a good value for the money spent. If the lifestyle intervention could be delivered at one-third lower cost than the intensive lifestyle interventions of the existing studies and achieve the same outcomes, it would be more cost-saving or cost-effective compared with placebo [32,55,61,70]. This might be achieved by changing the setting in which the intervention is provided. Although most large intensive lifestyle interventions seem to be cost-effective, medical nutrition therapy would be even more cost saving and/or cost-effective. Medical nutrition therapy is one form of lifestyle intervention that includes individual diet and exercise counselling and is administered by registered dieticians or other nutrition professionals. It has been shown to reduce diabetes risk factors, including body weight and blood glucose levels, and has shown success in diabetes management. The provision of medical nutrition therapy by registered dieticians or other nutrition professionals, who are experts in offering individualized nutrition counseling, will improve the quality of counseling offered to patients and alleviate the burden on physicians to provide nutrition education [65,78-84]. Although the cost of medical nutrition therapy is less than an intensive lifestyle intervention, more research is needed in the area of this form of intervention and community diabetes prevention programs to assess the effectiveness at decreasing diabetes incidence in the long term.

Many studies have methodological deficiencies since a minority of cost-effectiveness models for diabetes prevention accounted for the multivariate impacts of interventions on risk factors for T2D. While many studies mentioned above show that a health gain can be achieved by people at risk for diabetes, other analysis on reducing risk by lifestyle change did not show the expected effects and proved to be not cost-effective for health plans or a national program to implement [55,69].

Discussion

The increasing prevalence of T2D, the increase in modifiable risk factors for the disease (obesity, sedentary behaviour and poor nutritional choices), as well as the severe and costly complications which can be difficult to prevent and treat, mean that prevention is an important strategy for reducing the burden of diabetes. Improved nutritional habits like Mediterranean diet and increased physical activity are of particular importance to reduce the risk of T2D incident and to decelerate the manifestations of the disease [8,21,40,78,85-91].

Lifestyle modification has been shown to effectively reduce the risk of incident diabetes in randomised controlled trials. In addition, lifestyle modification is likely to produce beneficial other effects like reduction in risk of hypertension, hyperlipidemia, CVD and certain cancers. The main challenge is to translate this evidence into a routine community-wide setting and provide a feasible, effective and cost-effective intervention [6,8,19,21,40,41,92,93].

The key factor that reduces diabetes risk is weight loss and thus all efforts to translate the prevention trials to a community setting have focused on weight reduction. Weight regain is very common in weight loss studies that use a behaviour intervention [93-96]. Thus, it is extremely difficult to maintain weight loss, even in studies where
the intervention is still in full force and the enrollees are extremely well motivated. In addition, more evidence is needed to establish whether such intensive face-to-face individual implementation strategies are feasible in the long-term, whether group-based or remote contacts provides comparable efficacy in a more cost effective manner, and whether less-skilled personnel can deliver these same interventions [83,84,92-99]. Actually, the most successful interventions were obtained using many personnel and intensive supervision while the current practice requests less expensive, simple interventions which can be easily carried out in daily practice.

The key questions which can be addressed by all randomized controlled trials relate to the delivery, effects, costs and structure of community-based lifestyle modification programs, including key barriers and facilitators and key determinants of process and impact outcomes. Barriers in translating intensive interventions to a ‘real life’ setting include lengthy and unpleasant diagnostic testing procedures to identify pre-diabetes such as 2-hour oral glucose tolerance tests, the cost of highly educated personnel to provide the intervention and offering the intervention in locations such as single medical centres which are near to the homes of the participants [21,92-103].

Continued data from randomized controlled trials are needed to more fully understanding the long-term effects of these interventions and compare interventions with predictive models. Realistic cost-effectiveness studies of lifestyle interventions in people at risk for lifestyle-related diseases, addressing ‘real-world’ implementation, are also needed [21,104,105].

Still it is concluded that combined lifestyle interventions are likely to have great potential as a strategy to prevent diabetes. Finally, it may be more beneficial to achieve diabetes prevention by attacking the problem through national policies that reduce the overall consumption of food. In the long run, a combination of a societal and medical solution to the problem is needed [2010]. A key question which can be addressed by all randomized controlled trials is whether replication and scaling up of the randomised Finnish Diabetes Prevention Study (DPS) is a long-term strategy or metformin or metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia 49:289-297

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