2 Prevention of Type 2 Diabetes

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Abstract

The numbers of people with type 2 diabetes are rising rapidly around the world, making it imperative to develop and introduce methods of preventing the condition. A series of clinical trials over the last decade has shown conclusively that lifestyle interventions focusing on physical activity, diet, and weight loss can reduce the risk of developing type 2 diabetes by approximately 60%. Trials examining pharmaceutical interventions have shown that metformin, acarbose, and glitazones also reduce the risk of developing diabetes, but have shown no benefit of ACE inhibitors. Although uncertainty remains about the widespread use of pharmaceutical agents for diabetes prevention, programmes to implement lifestyle changes in those at high risk of developing type 2 diabetes now need to be put in place.

Key words: Type 2 diabetes; Lifestyle intervention; Physical activity; Diet.

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INTRODUCTION

Over recent decades, type 2 diabetes has become a major public health threat. As its prevalence has risen, it has become an increasingly important cause of cardiovascular disease (CVD), renal failure, visual loss and lower limb amputation. In many developed countries, its rising prevalence threatens to reverse the declines in cardiovascular mortality witnessed over the last 40–50 years, whilst in developing countries diabetes is one of the key factors in the switch from communicable to non-communicable diseases.

The most recent data suggest that there are currently 246 million adults with diabetes worldwide (at least 90% of this is type 2 diabetes), and that this will rise to 380 million individuals by the year 2025 *(1)* (Fig. 1). Although some of the increase in numbers of individuals with type 2 diabetes is due to the ageing of the population, lifestyle change has also played a major role in increasing the risk of type 2 diabetes. At a population level, the link with lifestyle is demonstrated by the approximately fourfold higher prevalence of diabetes among South Asians living in urbanised settings in the UK *(2)*, Mauritius *(3)* and India *(4)*, compared with those living in rural India *(5)*. Longitudinal studies have demonstrated that reduced physical activity and certain dietary aspects are risk factors for the development of type 2 diabetes *(6–8)*, while O'Dea has shown that when Australian aboriginals (who are among the populations with the greatest risk for and prevalence of type 2 diabetes) revert from a westernized lifestyle to a traditional hunter-gatherer lifestyle, they rapidly show profound metabolic improvement *(9)*.

The accumulating observational evidence linking both physical activity and diet to type 2 diabetes led to the belief that it would be possible to prevent type 2 diabetes with lifestyle change and, potentially, with glucose-lowering drugs. The rising tide of type 2 diabetes and the personal, social and societal impact of diabetic complications has made it imperative that all avenues of diabetes prevention are explored, and the last few years have seen the results of a number of major trials of diabetes prevention published.

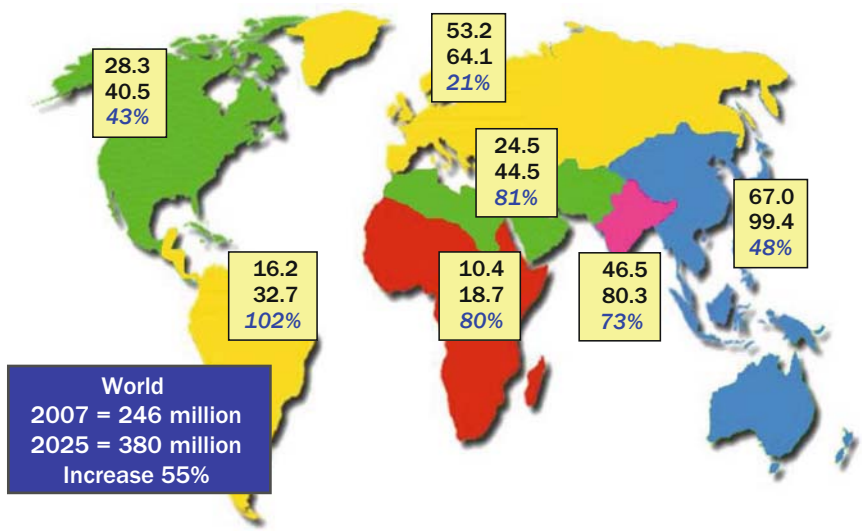

Fig. 1. The predicted global distribution and increase of diabetes: 2007–2025. The estimate is based on expected growth and ageing of the population *(1)*. The *upper* and *middle* figures represent the numbers of adults aged 20–79 (in millions) with diabetes for 2007 and 2025, respectively. The *lower* figures represent the percentage increase in numbers between 2007 and 2025.

This chapter will review the findings from the major diabetes prevention trials, with a focus mainly on those using lifestyle interventions, but will also describe the results of the pharmaceutical trials.

LIFESTYLE INTERVENTION STUDIES

A number of small, generally short-term, studies involving participants with various degrees of impaired glucose regulation were reported in the 1980s and 1990s *(10–12)*. Most of them had problems with design. Generally, however, these studies showed a benefit of healthy (or traditional) lifestyle on improving or delaying deterioration of glucose tolerance.

There have now been six large controlled and longer-term trials examining the effect of lifestyle changes on the progression from impaired glucose tolerance (IGT) to type 2 diabetes. The main lifestyle intervention targets were body weight, diet and physical activity. The intervention methods used to modify lifestyle varied between the studies as socio-cultural issues and the available facilities and personnel differed. Although there remained some methodological problems with the first two of these trials *(13, 14)*, the others were classical randomised controlled trials and provided a high level of evidence on the benefits of lifestyle change.

THE MALMÖ STUDY

This feasibility study examined the benefits of diet and exercise in 217 middle-aged men in MalmO with IGT *(13)*. The subjects chose whether they would be in the intervention or reference groups (in ratio 3:1). Thus, the subjects were not randomly assigned to the study groups and this diminishes the ability to generalise the results. The treatment group received detailed dietary advice and support within an exercise program while the other group received standard medical care according to requirements. Neither group received any form of anti-diabetic drug. Over a period of 5 years, the treated subjects significantly reduced and maintained weight loss (body mass index, BMI, fell 2.5% in the intervention group and rose 0.5% in the reference group). In addition, the estimated maximal oxygen uptake (a measure of physical fitness) increased by 10% in the intervention subjects, while it decreased by 5% in the control men. In the treated group 10.6% developed type 2 diabetes vs. 28.6% of the reference subjects. The relative risk reduction (RRR) in the incidence in the intervention group was 59% and the absolute risk reduction (ARR) was 17% points. Although the progression to diabetes in the reference group of Swedish men was lower than would be predicted from the observational studies (which may have been due to a relatively low BMI), this study demonstrated the feasibility of carrying out a diet and exercise program for 5 years among volunteers, and suggested that such a program might have significant benefits in the prevention of type 2 diabetes.

THE DA QING STUDY

The Da Qing IGT and Diabetes Study, published in 1997, involved a large population-based screening program to identify people with IGT *(14)*. The effect of exercise and diet in preventing the development of type 2 diabetes in 577 subjects with IGT was examined over 6 years in 33 hospital clinics across China. There were four intervention groups; diet alone, exercise alone, diet–exercise combined or no intervention. Randomisation into these groups was undertaken on a clinic rather than an individual basis. For dietary intervention, the participants were recommended a high-carbohydrate and low-fat diet and encouraged to reduce weight if BMI was $\geq$25 kg/m^2 aiming at 23 kg/m^2. Group sessions were organised weekly for the first month, monthly for 3 months and then three monthly. For the clinics assigned physical exercise, counselling sessions were arranged at a similar frequency. The

participants were encouraged to increase their level of leisure-time physical activity by at least 1–2 'units'/day. One unit was defined as 30 min slow walking, 10 min slow running or 5 min swimming.

The annual risk of progressing to type 2 diabetes from IGT in this population was reduced from 15.7% in the control group to 8% in the three intervention groups. The cumulative 6-year incidence of type 2 diabetes in the three intervention groups was 41–46% compared with 68% in the control group. The reported changes in risk factor patterns were modest. There was an approximate 1 kg/m^2 reduction of BMI in subjects with baseline BMI >25 kg/m^2 with no change in BMI for the lean subjects. The estimated changes in habitual dietary nutrient intakes were small and non-significant between groups. Thus, it appears that neither weight change nor even diet were the major determinants of the outcome. Physical activity and possibly subtle qualitative changes in diet played a key role.

There is a major methodological limitation in this study as allocation to intervention group was based on clinic (cluster) rather than the individual subject randomisation. Individual data analysis must, therefore, be interpreted with caution. The study subjects were relatively lean (mean BMI 25.8 kg/m^2) compared with subjects with IGT from other ethnic groups, and the progression from IGT to diabetes was high (over 10% per year in the control group) compared with findings in observational studies. These issues make it difficult to generalise the conclusions. Furthermore, the similarity in outcomes for the three different intervention groups was somewhat surprising, as it suggested that there was no benefit in combining diet and exercise over pursuing either one individually. Thus, like the MalmO study, the Da Qing study was suggestive of the benefits of lifestyle intervention, but not conclusive.

THE FINNISH DIABETES PREVENTION STUDY

The Finnish Diabetes Prevention Study (FDPS) *(15)*, the first properly controlled trial on prevention of type 2 diabetes with lifestyle modification (diet and exercise) alone, enrolled 523 subjects with IGT from five clinics in Finland between 1993 and 1998. Subjects (age 40–64 years, BMI over 25 kg/m^2) were individually randomly allocated into the intervention and control groups with stratification according to centre, gender and severity of IGT.

In the intervention group, subjects received advice from a nutritionist seven times during the first year and then every 3 months. The intervention goals were reduction in weight of 5% or more, total fat intake to less than 30% of energy consumed, saturated fat intake to less than 10% of energy consumed, fibre intake of at least 15 g/1,000 kcal and moderate exercise of at least 30 min/day. The subjects were individually counselled to increase their level of endurance exercise (walking, jogging, swimming, aerobic ball games, skiing). Supervised and individually tailored resistance training sessions were also offered. There were seven personal counselling sessions in the first 12 months, with three-monthly sessions thereafter. The control group subjects were given general verbal and written advice about healthy lifestyle at the beginning of the study. An oral glucose tolerance test (OGTT) was performed annually but the study end-point of type 2 diabetes was based on a confirmatory second OGTT.

After a median follow-up of 3 years, 86 cases of diabetes had developed which was about half of the 160 cases predicted for the full period of the planned 6-year study. The cumulative incidence of diabetes after 4 years was 11% in the intervention group and 23% in the control group, a reduction of 58% ($P < 0.001$) in risk of diabetes in the intervention group. The reduction in the incidence of diabetes was directly associated with changes in lifestyle (Fig. 2); none of the people (either in the intervention or in the control group) who had reached all five lifestyle targets by the 1-year visit developed diabetes.

A further publication from this study has shown the status of participants 3 years after the end of the intervention *(16)*. Although the trial intervention was no longer being provided, a significant difference in the incidence of diabetes has persisted throughout this post-intervention follow-up

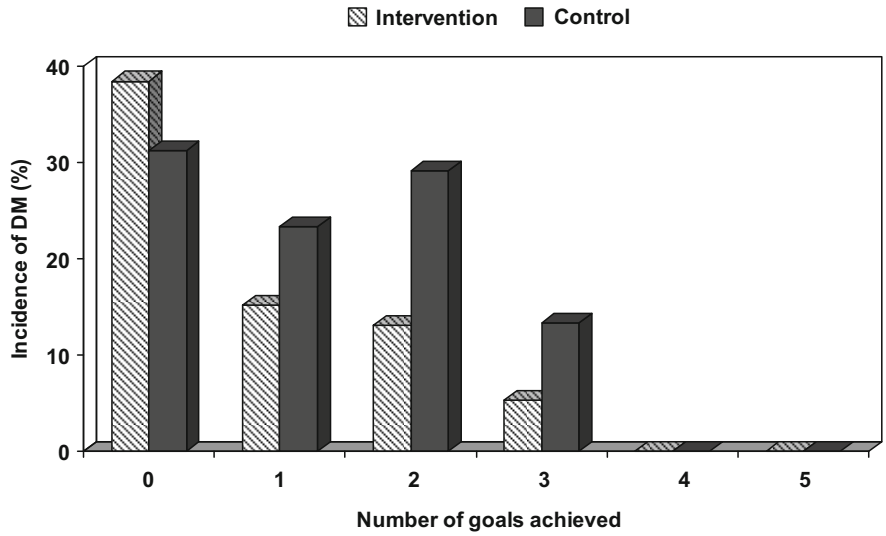

Fig. 2. Development of diabetes during the Finnish Diabetes Prevention Study (*FDPS*), according to number of intervention goals achieved *(15)*.

period, with the group originally in the lifestyle intervention arm still showing a 43% reduction in the incidence of diabetes over the lifetime of the trial. Even during the post-intervention period, the incidence of diabetes was 36% lower in the 'intervention' than the 'control' group. The mechanism of this profound 'hangover' effect remains uncertain, and some have suggested that the initial intervention produced a 'metabolic memory'. However, it seems likely that at least part of the explanation can be accounted for by the persistence of differences in lifestyle between the two groups beyond the end of the structured intervention and by the weight differences (or at least differences in fat mass) between the two groups during the intervention period. Indeed, the intervention group continued to achieve more of the lifestyle goals during the post-intervention phase than did the control group.

The study has also been analysed to determine which of the key goals was of most importance in producing the benefits *(16)*. When considered individually, achievement of each of the lifestyle goals, except the goal for saturated fat, was associated with a reduced incidence of diabetes. However, when considered together, only weight loss was significantly associated with benefits, indicating that most of the benefits of diet and exercise were mediated through weight loss. Thus, individuals who did not lose weight were unlikely to reduce their risk of developing diabetes, even if they reported that they were complying with the other lifestyle targets.

THE DIABETES PREVENTION PROGRAM

Recently, but prematurely completed, the Diabetes Prevention Program (DPP) (the data safety and monitoring board-advised closure) was a large multi-centre, randomised and placebo-controlled clinical trial carried out in the USA *(17)*. It involved an ethnically diverse population and was designed to investigate the effect of very aggressive lifestyle intervention (and metformin and troglitazone to be discussed below) in IGT patients. The study included 2,161 (in lifestyle and placebo arms) high-risk individuals with IGT and a fasting plasma glucose over 5.5 mmol/L. Special educators ('case managers' who were not regular health personnel) primarily carried out the lifestyle intervention in DPP. The lifestyle intervention involved a 16-session structured core curriculum

within the first 24 weeks after randomisation, with sessions occurring approximately monthly for the remainder of the trial. The focus of the dietary intervention was initially on reducing total fat intake but later calorie balance was introduced with a goal to achieve and maintain a weight loss of at least 7%. A physical activity target was set of ~700-kcal/week expenditure (this equalled ~150 min of moderate physical activity, such as brisk walking, every week). Clinical centres also offered voluntary-supervised activity sessions.

In the DPP, of the participants assigned to intensive lifestyle intervention, 74% achieved the study goal of ≥150 min of activity per week at 24 weeks and at the 1-year visit the mean weight loss was 7 kg (about 7% of baseline weight). With intensive lifestyle intervention there was a 58% RRR in progression to type 2 diabetes compared with the placebo group. The lifestyle intervention was effective over a range of age, BMI and racial or ethnic subgroups.

In an analysis of those in the intensive lifestyle arm of the study *(18)*, increased physical activity and reduced percent of fat in the diet predicted weight loss, but only weight loss was independently associated with a reduced incidence of diabetes. For every kilogram of weight loss, there was a 16% reduction in the risk of developing diabetes. Thus, like the FDPS, this study also showed that dietary and exercise goals are important in achieving weight loss, but unless weight loss is achieved, the risks of developing diabetes do not alter.

THE INDIAN DIABETES PREVENTION PROGRAME

The Indian Diabetes Prevention Programe *(19)* randomised 531 Asian Indian participants with IGT (79% men) into four groups – control, lifestyle modification, metformin and lifestyle plus metformin. The lifestyle intervention included both physical activity and dietary advice. Participants in the lifestyle groups were advised to walk briskly for at least 30 min daily, and those who were already achieving this goal at recruitment were encouraged to maintain their activity level. Dietary advice included avoidance of simple sugars and refined carbohydrates, fat intake not to exceed 20 g/day and an increase in fibre-rich food. Direct face-to-face counselling sessions were undertaken at baseline and every 6 months during the study, with telephone contact maintained monthly.

Over 3 years of follow-up, the cumulative incidence of diabetes was 55% in the control group, and was 39.3% in the lifestyle group. Thus, the RRR attributable to the lifestyle intervention was 28.5%, while the ARR was 15.7% points. There was no additive benefit of combining lifestyle with metformin – with the cumulative incidence of diabetes of 39.5% in this group being almost identical to that in the lifestyle alone group. Despite the more modest RRR than in some of the other studies, the high absolute conversion rate to diabetes meant that the number of individuals needed to treat over 3 years to prevent one case of diabetes was only 6.4 for the lifestyle intervention.

It is unclear exactly why the benefits of lifestyle intervention were smaller in this Indian population than in the US, Finnish and Chinese studies. However, there are a number of possible explanations. First, there were fewer face-to-face lifestyle counselling sessions in the Indian study, and this may have diminished the capacity to deliver an intensive lifestyle programe. Indeed, body weight hardly changed in the lifestyle group, and change in the body weight was not correlated with change in the plasma glucose. Second, the Indian population was described as being ‘already physically active and were on a diet similar to that prescribed’ at baseline. Thus, the lifestyle differences during the study (i.e. resulting from the intervention) between the lifestyle and control groups may not have been as great as in the other studies. Third, it is possible that ethnic differences in response to intervention may play a role, although the small number of Asians (4.4%) in the American DPP responded as well as other ethnic groups in that study. Finally, the Indian study population was younger and leaner (mean BMI 26 kg/m^2) than the American and Finnish populations.

JAPANESE DIABETES PREVENTION TRIAL

The Japanese diabetes prevention trial recruited 458 males with IGT (80% were government employees), and randomised them to a control or intensive lifestyle intervention in a 4:1 ratio *(20)*. The intervention was focused on reducing BMI to 22 kg/m^2. Dietary targets were individualised and targeted portion size, fat intake (advised to be <50 g daily), alcohol intake and limited eating out. A physical activity target of 30–40 min of moderate activity/day was set, and was being achieved by 15% of participants at baseline. The intervention was reinforced at study visits conducted every 2–3 months throughout the study.

Over the 4 years that the study ran for, the cumulative incidence of diabetes was 3.0% in the intervention group and 9.3% in the control group. Thus, the intervention resulted in a RRR of 67.4% and an ARR of 6.3% points. It was noteworthy that within the control group, the cumulative incidence of diabetes varied from 14.7% among those who gained at least 1.0 kg to only 4.3% in those who lost at least 1.0 kg. The intervention group had a mean weight loss of 2.18 kg. Whilst weight loss was a major mediator of the reduced incidence, it did not explain all the benefits observed.

The lifestyle prevention trials have now provided unequivocal evidence that type 2 diabetes can be prevented (or at least delayed) in subjects with IGT. The major findings of the six studies are summarised and compared in Table 1.

The similarity of the RRR of five of the six studies is striking over a range of BMI values (**Table 1**). The near identical RRR of Malmö, FDPS and DPP is remarkable. The higher ARR in the Da Qing study was a result of the higher risk of diabetes in that study population, while the lower ARR in the Japanese study reflects the lower risks of diabetes in that population. The lesser impact of an intensive lifestyle intervention in the Indian study most likely represents the lesser intensity of the delivery of the lifestyle intervention, with face-to-face appointments only occurring every 6 months.

SURGICAL OR DRUG-INDUCED WEIGHT LOSS

As yet there are no randomised-controlled trials of surgical treatment of obesity but in a group of severely overweight subjects with IGT undergoing gastric bypass surgery, the rate of conversion over 4–6 years to type 2 diabetes after an average weight loss of 22.5 kg was 0.15/100 persons/year. This was compared to a conversion rate of 4.72/100 persons/year in an un-operated group, a 30-fold reduction in risk with this intervention *(21)*. Likewise, in the Swedish Obese Subjects (SOS) Intervention Study *(22)*, gastric surgery in very obese subjects reduced the 2-year incidence of diabetes 30-fold in

Table 1
Summary of the Findings of the Six Lifestyle Intervention Studies in People with IGT

Study	*Cohort size*	*Mean BMI (kg/m^2)*	*Duration (years)*	*RRR (%)*	*ARR (%)*	*NNT*
MalmO *(10)*	217	26.6	5	63	18	28
FDPS *(15)*	523	31.0	3	58	12	22
DPP *(17)*	2,161[a]	34.0	3	58	15	21
Da Qing *(14)*	259[a]	25.8	6	46	27	25
Indian *(19)*	269[a]	26.0	2.5	29	16	19
Japanese *(20)*	458	23.9	4	67	6	63

[a]Combined numbers for placebo and diet and exercise groups

FDPS Finnish Diabetes Prevention Study, *DPP* Diabetes Prevention Program, *IGT* impaired glucose tolerance, *BMI* body mass index, *RRR* relative risk reduction, *ARR* absolute risk reduction, *NNT* number needed to treat for 1 year to prevent one case of diabetes

grossly obese subjects (weight loss 28 kg) compared with control subjects who were receiving regular care (weight loss 0.5 kg). More recently, data on laparascopic gastric band surgery have been reported. Among 434 non-diabetic patients (BMI ≥ 35 kg/m^2), followed up over 923 patient years after the procedure, none developed diabetes *(23)*. These results suggest that severe obesity can be treated surgically and lead to a marked reduction in the incidence of diabetes.

The Xendos [Xenical (orlistat) in the prevention of diabetes in obese subjects] *(24)* trial randomised 3,305 obese participants, aged 30–60 years of whom 21% had IGT to orlistat (which leads to weight loss by reducing intestinal fat absorption) or placebo. All participants received lifestyle advice (calorie-reduced diet and exercise counselling) initially two weekly for 6 months and thereafter monthly. Over 4 years, among those with IGT, orlistat reduced the incidence of diabetes by 45% (RRR 45%, ARR 10% points). Weight reduction was 6.9 kg in the orlistat group and 4.1 kg in the placebo group. Unfortunately, there was a high drop out rate over the 4-year treatment phase in both groups; 52% in orlistat and 34% in placebo.

Both the surgical and the orlistat studies in obese subjects indicate that probably weight control alone is an efficient way to prevent the development of type 2 diabetes.

PHARMACOLOGICAL INTERVENTION STUDIES

Prior to the last few years, there were nine, generally small and poorly designed, intervention studies using oral hypoglycemic agents published that examined patients over 1–10 years. All were commenced prior to 1979 when there was no agreement on the definition of pre-diabetic states and the subjects, according to recent diagnostic criteria, were probably a mixture of early type 2 diabetes and IGT. Seven studies investigated tolbutamide, and on an intention to treat analysis, four *(25–28)* reported improvement in glucose tolerance and/or reduced incidence of type 2 diabetes while three reported no benefit *(10, 29, 30)*. However, the Malmöhus study *(10)* reported a large non-compliance rate in the tolbutamide group and found prevention of progression when analysis was based on treatment compliance. This is an intriguing observation in view of the four earlier positive studies and awaits further study. Two intervention studies with phenformin did not show benefit *(31, 32)*. Finally, two studies examined glibenclamide with mixed results *(32, 33)* and one study employing World Health Organisation (WHO) criteria examined gliclazide and reported no benefit *(34)*. All these pharmacological studies, most containing fewer than 200 subjects in each of the intervention groups, would now be regarded as significantly underpowered.

Study to Prevent Noninsulin-Dependent Diabetes Mellitus Study

The Study to Prevent Noninsulin-Dependent Diabetes Mellitus (STOP–NIDDM) study *(35)*, a Canadian–European double-blind, placebo-controlled randomised trial evaluated whether acarbose (an α-glucosidase inhibitor) could prevent the development of diabetes in 1,429 high-risk subjects with IGT. After a mean of 3.3 years of follow up, but including an approximate 25% discontinuation rate on acarbose, there was a 25% reduction in progression to diabetes (based on a single OGTT) attributable to acarbose. The main results were based on an intention-to-treat analysis. The drug was effective in the different subgroups of age, gender and BMI. However, the benefit of treatment on prevention seemed to be reduced after only 3 months following cessation of active treatment.

Diabetes Prevention Program

The Diabetes Prevention Program (DPP) was initially set up to investigate individually the benefits of metformin, troglitazone (a PPARγ agonist), and diet and exercise. As a result of the increased risk

of severe liver damage and in some instances fatal hepatic toxicity caused by troglitazone, this arm was discontinued after 2 years. The DPP found that metformin reduced the risk of progression to type 2 diabetes from IGT by 31% while still taking the drug. The reduction in progression was less (24.9%) when metformin was ceased, and allowed drug washout to occur before assessing glucose tolerance *(36)*. The benefit of metformin was not seen in subjects over the age of 60 years or in those with a BMI less than 30 kg/m^2 *(17)*.

Analysis of the troglitazone arm of the study over a mean of 0.9 years showed a 75% reduction in the incidence of diabetes, with most of the benefit being due to an improvement in insulin sensitivity *(37)*.

Troglitazone in the Prevention of Diabetes

Although the troglitazone arm of DPP was discontinued, a small 5-year double-blind study involving 250 Hispanic women living in Los Angeles with a history of gestational diabetes (~70% with IGT) were randomised to either troglitazone or placebo *(38)*. Women with a history of gestational diabetes mellitus (GDM) are at a high risk for developing type 2 diabetes. Over a median follow-up period of 31 months, there was a 56% reduction in the conversion of these patients to type 2 diabetes. The average annual incidence of diabetes was 5.4% in women randomised to troglitazone and 12.1% in the placebo group ($P < 0.01$). The group of women most responsive to intervention with troglitazone was those who 3 months after randomisation showed the greatest reduction in insulin resistance and fall in insulin secretion to an intravenous glucose tolerance test. There was also evidence that the protection conferred by troglitazone against developing type 2 diabetes persisted for about 8 months after treatment ceased.

Chinese Diabetes Prevention Study

In a small multi-centre study ($n = 321$) *(39)* subjects with IGT were divided into four groups: controls who received conventional education, diet and exercise, metformin and acarbose. As in the Da Qing study, allocation into groups was not random, but took place by geographical location. Over a 3-year period 34.9%, 24.6%, 12.4%, and 6.0% of each group, respectively, progressed to diabetes. This represents a RRR of 76.8% for metformin and 87.8% for acarbose compared with the control group. The mean BMI for the three groups was ~25 kg/m^2, which in relation to metformin is inconsistent with the DPP findings, which showed no benefit of metformin in those with a BMI <30 kg/m^2.

Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication Trial

The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial is the largest of all the diabetes prevention studies, and the only one to include participants with both IGT and impaired fasting glucose (IFG). The 2 × 2 factorial design of the study allowed it to separately test whether the angiotensin converting enzyme (ACE) inhibitor, ramipril, and the PPARγ agonist, rosiglitazone, could prevent the development of diabetes. In addition to the smaller studies discussed above that showed the potential of PPARγ agonists in diabetes prevention, a significant body of evidence had suggested that ACE inhibitors might also play a role in the prevention of diabetes. In particular, the Heart Outcomes Prevention Evaluation (HOPE) study showed in post-hoc analyses that ramipril was associated with a 34% reduction in the incidence of diabetes *(40)*. HOPE, like a number of other cardiovascular studies showing similar results, was not designed to test the value of ACE inhibitors in diabetes prevention – hence, the need for a trial designed specifically to test this hypothesis. DREAM randomised 5,269 adults from 21 countries, and followed the participants for a median of 3 years. Ramipril was associated with a non-significant 9% reduction in the incidence of diabetes *(41)*, while rosiglitazone led to a highly significant 60% reduction in the development of diabetes *(42)*.

The benefits of rosiglitazone were seen in all the pre-specified sub-groups, but were greatest in those who were most overweight at baseline. Indeed, while the incidence of diabetes increased, as expected, with increasing adiposity in the placebo group, there was no such increase in the rosiglitazone group.

It is also important to note the side effects of rosiglitazone, which were similar to those reported in trials of the drug in people with established diabetes – weight gain, and a small, but significant, increase in risk of cardiac failure. Somewhat disappointingly, the DREAM trial failed to show even a trend towards cardiovascular benefit with either of the drugs, though it should be noted that DREAM was not designed to determine the effect on CVD, and the small number of CVD events occurring in the trial was consistent with the exclusion from the trial at baseline of anyone with a prior history of CVD. However, significant concern has subsequently developed over the safety of PPARγ agonists, with regard to CVD and to fractures. First, a meta-analysis indicated a higher risk of CVD in patients treated with rosiglitazone (ref), though an interim analysis of a large clinical trial focusing on CVD has not confirmed this (ref). Second, an excess of fractures (possibly osteoporotic) has been reported with both of the currently available PPARγ agonists (ref). Thus, the use of PPARγ agonists for diabetes prevention is not currently recommended.

DIABETES PREVENTION: REAL PREVENTION OR JUST DELAY IN ONSET?

Much debate over recent years has centred on whether any of the so-called diabetes prevention trials are actually reporting disease prevention or simply a delay in the time of disease onset. People have argued that the apparently impressive findings of the prevention of 60% of the expected cases of diabetes equates to no more than a delay in the onset of diabetes of a year or so. Within the confines of a 3-year clinical trial, a 1–2 year delay in disease development will have profound effects on the total number of people developing diabetes, but the average 50-year old, who might hope to live for another 25–30 years might be less impressed with an intervention that postpones his date of diabetes onset from his 60th to his 62nd birthday.

The term ‘prevention’ is often interpreted as meaning stopping diabetes from ever happening (although most dictionaries definitions include the meaning of hindering as well as stopping), and as such could only be shown in very long clinical trials. Of course, delaying the onset of diabetes until the individual dies of something else amounts to lifetime prevention for that individual.

Interventions that ‘fix’ a problem and genuinely prevent a disease from ever occurring are generally restricted to the arena of conditions such as infectious diseases, where vaccinations, or public health measures, such as providing clean water, have virtually eliminated a number of infections. However, for diseases such as type 2 diabetes, which appear to be strongly linked to age-related functional decline or degeneration in physiological systems, interventions that can be expected to ‘fix’ the problem seem much less likely. Specifically for type 2 diabetes, the age-related decline in beta cell function often leads to diabetes among the elderly even if they remain relatively lean.

Interestingly, although this debate could equally apply to other chronic diseases, such as CVD, it does not seem to have taken place. Thus, no one discusses whether lipid lowering with statins prevents or only delays myocardial infarction, though it is abundantly clear that a sizeable proportion of those successfully treated in the intervention arm of a statin trial will still suffer a vascular event at some time after the study ends. The results of such studies are usually reported in terms of the reduction of risk or reduction of incidence of the endpoint over the duration of the study. This would likely be a more useful way of presenting the diabetes prevention trials. The conclusion that over 3 years, a lifestyle intervention reduces the risk of developing diabetes or reduces the incidence of diabetes by 58% is a simple statement of the results, is in the same format as most other prevention studies, and describes the results of the trial without making any implications about lifetime risk. In retrospect, the use of the term ‘prevention’, though justifiably a high priority for researchers to achieve, has probably

led to unrealistic beliefs about the long-term effects of interventions among the public and to a sterile debate between healthcare professionals about the meaning of delay and prevention. A focus on describing findings in terms of risk reduction and lowering of blood glucose would be much more constructive. The real debate could then address issues such as cost-effectiveness and the implementation of the trial results into clinical practice, which will ultimately be far more important in delivering effective interventions to populations.

POPULATION APPROACHES TO PREVENTION OF TYPE 2 DIABETES

The series of lifestyle intervention trials have shown beyond any shadow of a doubt that changes to diet and exercise patterns can markedly reduce the risk of developing diabetes. Furthermore, the findings have been applicable across a wide range of demographic groups. In addition, the results of drug trials show that there are also a number of effective pharmacological options. When attempting to translate these findings into benefits for the wider population, several questions need to be addressed. The first is to what extent the lifestyle interventions tested in the clinical trials could be effective outside a research setting. It needs to be remembered that clinical trials only recruit those volunteers who are already prepared to undertake the intervention – those who are not interested in making such changes are unlikely to volunteer, though may represent a significant proportion of the at-risk population. Furthermore, the funding and infrastructure available are far greater in a clinical trial than clinical practice or public health can offer even in the wealthiest of healthcare systems. Currently, we do not know whether the level of intervention available outside clinical trials would be effective, especially when delivered to individuals who would not have had the personal motivation to volunteer for a trial. No studies have compared different intensities of lifestyle intervention. However, the similarity of risk reduction observed in the DPP, the DPS and the Japanese study suggests that the lesser intensity of intervention applied by the two latter trials (study visits every 2–3 months) may provide as much benefit as the more intensive DPP (16 study visits in the first 6 months). The lesser risk reduction seen in the Indian study, with face-to-face study visits occurring only every 6 months, suggests that the optimal level of intervention involves more frequent lifestyle counselling, and probably requires approximately four to six face-to-face visits annually. The length and intensity of a program, the frequency of program visits and the use of self-monitoring have all been shown to be important for weight loss programs *(43)*, and, hence, are likely to be important in diabetes prevention. Studies examining different intensities of intervention, and studies designed to include all of the at-risk population (rather than just clinical trial enthusiasts) are now needed.

A second crucial issue in designing a population approach to diabetes prevention is determining the balance between targeting high-risk groups and targeting the general population. The potential impact of rolling out a high-risk approach (i.e. programs designed to reproduce clinical trial results in people with IGT) will always be limited. Reasons for this include the difficulty of identifying all those at high risk, and the fact that epidemiological studies show that over a 5-year period, ~20% of new cases of diabetes had normal glucose tolerance at baseline *(44)*. To maximise the population impact, this high-risk approach needs to be coupled with a lower intensity, but more broadly-based population-wide approach focused on weight loss, or at least on the prevention of weight gain. A small shift in the population means BMI would have profound effects on the numbers of individuals within the population developing type 2 diabetes.

The third important issue is the role of pharmacological therapy. None of the pharmacological (or lifestyle) trials reported so far have been designed to look at hard clinical end-points (such as CVD or microvascular complications). The first trial to do so will be the NAVIGATOR trial, examining the effects of valsartan and nateglinide in the prevention of diabetes and of CVD. Thus, while it is likely that lowering blood glucose in people with IGT will ultimately result in clinical benefits, this

is unproven. Given the potential financial costs of treating the 10–15% of adults who have IFG and IGT, and the risk of side-effects over the many years of drug exposure that would be required, widespread use of drugs in the attempt to prevent type 2 diabetes cannot currently be justified. However, while lifestyle change appears to be a much better option (with far fewer side-effects, and an additional beneficial impact on cardiovascular risk factors other than glucose), there are those who are unable to make substantial changes (e.g. those in whom disease or old age limit their exercise capacity), some who fail to respond to an intensive lifestyle program, and some who might be judged to be at such high risk that a combined lifestyle and pharmacological approach might be appropriate from the outset. No consensus has emerged on the role of drugs, but the two groups that would seem the most important to consider for drug therapy are those who fail to lose weight in a lifestyle program, and those who are at highest risk (probably determined by blood glucose levels – the co-occurrence of IFG and IGT in the same individual is probably a useful definition of this high-risk group). Public funding or reimbursement of the costs of such pharmacological therapy is unlikely to be widely approved, given the currently available data, but after a full explanation of the risks, benefits and costs, it would not be unreasonable for an individual with IGT or IFG to choose to pay for drug treatment.

Finally, it is becoming increasingly apparent that in order to achieve meaningful lifestyle changes across a whole population, input from outside the health sector will be required. In order to alter the obesogenic environment that is now so prevalent, changes to food labelling and taxation, education, advertising, urban planning and transport will all need to be considered. In both Finland *(45)* and Mauritius *(46)*, changes at a governmental level including public health campaigns and changes in taxation and food supply were highly successful in lowering the mean population cholesterol level. Without similar societal action directed at weight control, it is unlikely that even the best organised health system can translate the findings of clinical trials into substantial population-wide reductions in diabetes incidence.

SUMMARY

It is now abundantly clear that the risk of developing type 2 diabetes can be substantially reduced by lifestyle change and by a number of glucose-lowering drugs. Lifestyle intervention directed at fat and calorie restriction, increased dietary fibre intake, and at achieving a minimum of 30 min of moderate exercise daily is the method of choice in reducing the incidence of type 2 diabetes. The focus should be on achieving weight loss and surgery and weight loss drugs may also be appropriate. However, weight loss is achieved, the greater the reduction in weight back to a healthy level, the greater the impact on reducing the risk of developing diabetes. While pharmacological therapy is clearly able to lower blood glucose in those with IGT and IFG, the lack of information on its impact on hard clinical outcomes makes it currently unsuitable for widespread use in those with IGT and IFG.

Health systems need to develop ways of identifying those at high risk of developing diabetes, and implementing intensive lifestyle programs. This needs to be supported by societal changes that facilitate the pursuit of healthy lifestyles for everyone.

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