Lifestyle management: preventing Type 2 diabetes and cardiovascular complications

For individuals with Type 2 diabetes, cardiovascular disease is the principle cause of morbidity and mortality. Lifestyle management is recognized as being an essential part of diabetes and cardiovascular disease prevention. Meta-analyses demonstrate that lifestyle interventions, including diet and physical activity, led to a 63% reduction in diabetes incidence in those at high risk. 'Real-world' lifestyle modification programs have demonstrated encouraging improvement in risk factors for diabetes; however, the effect on diabetes incidence has not been reported. It has been demonstrated that lifestyle interventions reduce cardiovascular risk factors; however, data on long-term cardiovascular outcomes is lacking. The aim of this review is to discuss the current evidence of lifestyle interventions in the prevention of diabetes and cardiovascular disease.

KEYWORDS: cardiovascular disease ▪ diet ▪ lifestyle ▪ physical activity ▪ prevention ▪ Type 2 diabetes

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Cardiovascular disease (CVD) is the principle cause of morbidity and mortality in individuals with Type 2 diabetes mellitus (T2DM), and individuals with T2DM experience at least a twofold greater risk of CVD than the general population [1]. Impaired glucose tolerance (IGT) and impaired fasting glycemia (IFG) are also associated with an increased risk of CVD [2,3], as is the metabolic syndrome [4,5]. The prevalence of T2DM is increasing globally [6], with this increase being attributed to a 'Western lifestyle' characterized by increased energy intake and sedentary behaviors. The current burden of T2DM and its associated cardiovascular (CV) complications is already placing pressure on health systems. Prevention of these conditions is essential to ensure that the individual, social and economic impact of T2DM and CVD is minimized.

Lifestyle intervention for the prevention of T2DM

Several studies have examined the effect of a combination of diet and physical activity (PA), often referred to as a lifestyle intervention [7–12], on the development of T2DM. Recent meta-analyses of intensive lifestyle (IL) trials in people at high risk show that IL reduced the risk of T2DM by 63% compared with standard recommendations [13]. The study groups and interventions utilized are further discussed below.

Malmö study

The Malmö feasibility study examined the benefits of a 12-month IL program in men with IGT and early-stage T2DM [7]. Limitations of this study include recruitment of only men, and a non-random assignment of subjects to the intervention and control groups. IL was associated with a 59% reduction in the incidence of T2DM.

Da Qing IGT & Diabetes Study

The Da Qing IGT and Diabetes Study involved a large population-based screening program to identify people with IGT [8]. The effect of diet and PA in preventing the development of T2DM in 577 subjects aged over 25 years with IGT was examined over 6 years in 33 hospital clinics across China. Each clinic (rather than individual participants) was randomized into one of four groups: diet alone, PA alone, diet and PA, or no intervention. The diet intervention aimed to achieve 55–65% energy from carbohydrate, 25–30% from fat, increased vegetable consumption, no more than a moderate intake of alcohol and a reduction in simple sugars. For those with a body mass index (BMI) above 25 kg/m², weight loss to achieve a BMI below 25 kg/m² was targeted. The PA intervention aimed at increasing exercise by at least 1–2 'units' per day, where one unit was equivalent to 30 min of mild exercise, 20 min of moderate exercise or 10 min of strenuous exercise. Individual counseling was given and individual goals set, then subjects met in small groups weekly for 1 month, then monthly for 3 months and 3-monthly thereafter. The control group was exposed to general information about T2DM.

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At baseline, the mean age was 44–46 years, and BMI was 25–26 kg/m² across the study groups. All groups lost weight over the study period with the diet group losing 1.5 kg, the PA group losing 1.2 kg, the diet and PA group losing 5.1 kg, and the control group losing 1.3 kg. The cumulative incidence of T2DM over the 6 years of follow up was 44% in the diet group, 41% in the PA group, 46% in the diet and PA group and 68% in the control group. In comparison with the control group, significant reductions in the incidence of diabetes of 33% in the diet group, 47% in the PA group and 38% in the diet and PA group were observed. In those individuals with a BMI above 25 kg/m², all interventions significantly reduced the incidence of diabetes. In those with a BMI below 25 kg/m², a statistically significant reduction in diabetes incidence was observed in the PA-only and diet and PA groups. The diabetes incidence in the diet only group was 36.3% lower than the control group (60.0 vs 38.2%); however, this reduction failed to reach statistical significance.

A 20-year follow-up of the Da Qing IGT and Diabetes Study demonstrated that the protective effect of lifestyle modification persisted beyond the intervention period, with a cumulative incidence of diabetes in the intervention groups of 80%, compared with 93% in the control group [14]. Participants in the combined diet and PA group had a 43% lower incidence of diabetes compared with control. Those in the intervention groups compared with control had an average of 3.6 fewer years of T2DM, demonstrating that IL programs, even if not preventing T2DM completely, can at least postpone the development of this condition.

Finnish Diabetes Prevention Study

The Finnish Diabetes Prevention Study (FDPS) [9], the first properly randomized trial on the prevention of T2DM with lifestyle modifications, enrolled 523 subjects with IGT from five clinics in Finland. Subjects (aged 40–64 years, BMI: >25 kg/m^2) were randomly allocated into the intervention and control groups. The IL program aimed at: reducing body weight by at least 5%; achieving a dietary intake of less than 30% energy from fat, less than 10% energy from saturated fat and more than 15g/1000 kcal of fiber; and achieving more than 30 min of moderate-intensity PA daily. Endurance exercise was recommended; however, strength training programs were also offered. After 6 months, if weight loss was not meeting the subjects' goals, very low calorie diets (VLCD) were offered as intensive regimens or as replacements for one or two meals per day, which 48 subjects utilized. The intervention group had individual sessions weekly for 6 weeks, then 2-monthly sessions for 6 months and 3-monthly sessions thereafter. Subjects could also attend voluntary group sessions, and have supplementary phone calls and letters. The control group was advised to aim for a BMI below 25 kg/m², and received similar dietary and PA advice, but the information was not individualized.

At baseline, the mean age was 55 years, and the mean BMI was 31 kg/m² [9]. At 1 year, significant improvements in weight (weight loss 4.2 vs 0.8 kg, 4.7% body weight vs 0.9%) and waist circumference were observed in IL compared with control. At 2 years, some weight was regained in both groups, although weight loss remained significantly greater in IL compared with control groups (3.5 vs 0.8 kg), and this remained stable at 3 years (3.5 vs 0.9 kg, 4.0% body weight vs 1.1%) [15]. After 4 years of active intervention, the cumulative incidence of T2DM was significantly lower in the intervention group (11%) compared with control (23%), representing a reduction in incidence of 58% [9]. Follow-up 3 years post-intervention showed that the cumulative incidence of T2DM remained significantly lower in the intervention group (23%) compared with the control group (38%) – a risk reduction of 43% [16] – demonstrating the effectiveness of IL programs in reducing incidence of T2DM in those with IGT beyond the intervention period.

Diabetes Prevention Program

The Diabetes Prevention Program (DPP) was a large multicenter, randomized, placebo-controlled clinical trial involving an ethnically diverse population, and was designed to investigate the effect of IL programs, metformin or troglitazone treatment (troglitazone was ceased soon after commencement due to liver complications) compared with placebo in 3234 individuals with IGT [10]. Subjects (aged >25 years, BMI >24 kg/m^2 or >22 kg/m^2 if Asian) were individually randomly allocated into the intervention and control groups. The IL program was aimed at weight loss of more than 7% within 6 months, and subjects were encouraged to lose weight up to BMI 21 kg/m^2 [17]. Dietary strategies focused on reducing energy intake and fat intake to 25% energy from fat. Structured meal plans and meal-replacement products were offered to subjects. A goal of more than 150 min/week of moderate-intensity PA was set, and supervised PA sessions

were offered twice-weekly. Lifestyle PA (e.g., using stairs instead of an elevator) was encouraged, but did not contribute to the 150 min/week PA goal. The IL program was individualized and delivered by a 'lifestyle coach' (typically dietitians, exercise physiologists or health psychologists), with a set core curriculum covered in 16 sessions over 24 weeks. Individual contact continued 2-monthly, with phone contact between each visit for the remainder of the trial, as well as optional additional group sessions. The control group was given standard lifestyle recommendations and annual short individual sessions encouraging a healthy lifestyle.

At baseline, the mean age was 51 years and BMI was 34 kg/m² [10]. A total of 50% of participants in the lifestyle group met the goal of 7% weight loss within 24 weeks. At 1 year, a significantly greater weight loss was observed in the IL group (6.8 kg, 7.2% of initial weight) compared with the metformin group and placebo group [10,18]. At 2 years, some weight was regained; however, IL still had a significantly greater weight loss (5.4 kg) compared with the metformin (2.1 kg) and placebo (0.1 kg) groups. At 3 years, cumulative incidence of T2DM of 14% in IL, 22% in metformin and 29% in control groups were observed [10]. The incidence of T2DM was 58% lower in the IL group and 31% lower in the metformin group compared with control, with IL having a significantly lower incidence of T2DM compared with metformin. Meeting all IL goals resulted in an 89% lower risk of T2DM compared with those meeting no IL goals [18].

Japanese Diabetes Prevention Trial

The Japanese Diabetes Prevention Trial recruited 458 males with IGT (80% were government employees) and randomized them to control or IL [11]. The intervention was focused on reducing BMI to 22 kg/m^2. Individualized dietary advice focused on reducing portions, reducing fat intake to less than 50 g/day, reducing alcohol intake to less than 50 g/day and limiting eating out. Moderate-intensity PA of 30–40 min/day was encouraged. The intervention was reinforced at study visits conducted every 3 months throughout the 4-year study.

At baseline, the majority of subjects were aged 50–59 years, and mean BMI was 24 kg/m^2 in both groups [11]. In the IL group, weight was 2.5 kg below baseline at 1 year, and 2.2 kg below baseline at 4 years. Weight loss from baseline was statistically significant at both time points. Weight loss at 4 years was significantly greater in IL compared with control (2.2 vs 0.4 kg). At 4 years, the cumulative incidence of T2DM was significantly lower in the IL group (3.0%) compared with control (9.3%), representing a 67% reduction in the incidence of T2DM.

Indian Diabetes Prevention Program

The Indian Diabetes Prevention Program (IDPP-1) [12] randomized Asian Indian participants aged 35–55 years with IGT into four groups: control, IL, metformin and IL plus metformin. The IL program included individualized diet and PA advice to maintain an appropriate body weight. Dietary advice encouraged subjects to avoid simple sugars and refined carbohydrates, reduce total fat to 20 g/day and restrict use of saturated fat and include more fiber-rich foods. PA advice aimed to increase PA to more than 30 min/day including occupational and transport PA. Subjects received individual advice at randomization, and then at 2 weeks by phone or letter. Monthly telephone contacts were maintained, and individual face-to-face sessions were conducted every 6 months.

The baseline mean age was 46 years, and BMI was 26 kg/m² [12]. Weight increased significantly from baseline at annual follow-up in the control group. At 3 years, small nonsignificant increases in weight, BMI and waist circumference were reported in all intervention groups [19], despite reported improvements in diet and PA in both IL groups. The cumulative incidence of T2DM was significantly lower in IL (39%), metformin (41%) and IL plus metformin (40%) groups compared with control (55%). Significant risk reductions of 29% in IL, 26% in metformin and 28% in IL plus metformin groups were seen compared with control, demonstrating that in an Indian population, IL programs can significantly reduce the incidence of progression to T2DM, even without significant weight loss.

Summary of IL trials

Evidence to date demonstrates that in those with IGT, IL interventions are effective in reducing the incidence of T2DM across a range of ethnic groups (Figure 1). Variability in the results suggests that the IL program or study populations observed may have implications for the efficacy of IL.

IL with individual counseling [9–12] appeared to be more successful than group sessions [8], although all interventions provided some individualized counseling. More frequent contacts with subjects may lead to greater weight loss, with the weight loss observed in the DPP

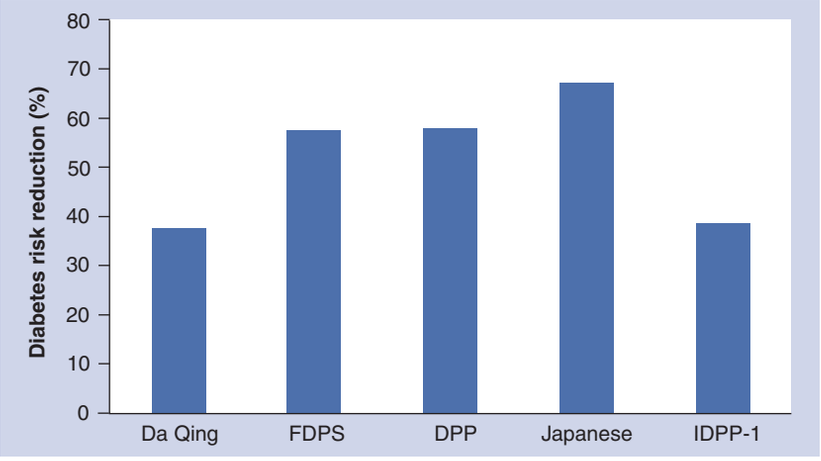

Figure 1. Diabetes risk reduction in major lifestyle intervention trials. Data show the relative risk reduction in the incidence of diabetes in the intensive lifestyle groups compared with the control groups, for each study.
Da Qing: Da Qing IGT and Diabetes Study [8]; DPP: Diabetes Prevention Program [10]; FDPS: Finnish Diabetes Prevention Study [9]; IDPP-1: Indian Diabetes Prevention Program [12]; Japanese: Japanese Diabetes Prevention Trial [11].

(6.8 kg), the FDPS (4.2 kg), Japanese (2.5 kg) and IDPP-1 (no weight change) trials being ranked in the same order as the frequency of study visits [9–12]. However, it should be noted that the more intensive intervention seen in the DPP trial (16 sessions over 24 weeks, then 2-monthly follow up) compared with the FDPS trial (6-weekly sessions, then two bi-monthly sessions, then 3-monthly sessions) did not lead to greater reductions in T2DM incidence – both being 58% [9,10].

Interventions also differed according to the IL goals. Interventions with weight loss goals either to a target BMI [8,11], or as a percentage of initial body weight [9,10], achieved greater reductions in T2DM incidence than interventions that did not aim for weight loss [12]. Although IL programs produced significant reductions in weight, most studies observed a weight regain 1 year into the IL program [9–11]. Greater reductions in T2DM incidence may well have been seen if initial weight loss had been maintained. While several analyses have demonstrated that weight loss was responsible for the majority of the observed reduction in T2DM incidence, a small part of the protective effect of IL appears to be independent of the effect of weight loss [9,11,18]. The lack of change in body weight reported in the IDPP-1 could mask changes in body composition that may influence progression to T2DM. Analysis of change in waist circumference rather than weight alone may be more effective in assessing this. Other than weight-loss targets, the various studies were fairly consistent in the dietary and PA targets. Among the dietary goals, only dietary fat intake appeared to be associated with reduced incidence of T2DM, with a 5% reduction in the percentage of energy from fat associated with a 25% reduced incidence of T2DM [18]. Two studies utilized VLCD or meal replacements to assist subjects in achieving the weight loss goal [9,10], although use of VLCD did not appear to reduce T2DM incidence [15]. PA goals were also fairly similar across the studies, although some studies specifically encouraged leisure time PA [10], while others included lifestyle activity such as occupational or travel-related PA [12]. Increased PA was seen to be a stronger predictor of weight loss at each subsequent year [18], which may reflect the role of exercise in maintenance of weight loss. A strong inverse correlation was observed between achieving lifestyle goals and incidence of T2DM [9,16,18].

Study groups also differed according to baseline characteristics. Baseline mean BMI varied from 24 to 34 kg/m² across the studies. In the Da Qing and Japanese studies of Asian subjects, with a baseline mean BMI of 24–26 kg/m², weight loss was achieved through IL programs, with greater reductions in T2DM than were observed in the IDPP-1 study, where weight loss was not achieved [8,11,12]. Factors other than the ability to lose weight could also have been responsible for differences in T2DM risk reduction. The DPP demonstrated that IL was effective in all included ethnic groups (55% white, 20% African–American, 16% Hispanic, 5% American–Indian and 4% Asian) [10], and weight loss reduced the incidence of T2DM across all race and ethnicity groups, regardless of baseline BMI [18]. In the DPP, IL was more effective with increasing age, with the number of subjects achieving the 7% weight-loss goal also increasing with age [20]. This greater weight loss in older participants may be due to them being more likely to achieve more than 150 min/week of PA.

It is now clear that IL is effective using a variety of strategies and across multiple ethnic groups and social conditions.

'Real-world' evidence: diabetes prevention in practice

While IL has been proven to be successful in a controlled research setting, it could be argued that results seen in highly motivated study populations using resource-intensive interventions may be very different to what is achievable in ordinary healthcare settings. Three studies of high-risk populations in Finland [21], Australia [22] and India [23] have reported interim results suggesting that IL in 'real-world' situations is effective in reducing risk factors for

T2DM including BMI [21–23] and fasting plasma glucose [23]. However, the impact on these risk factors appears to be smaller than that achieved in the setting of a randomized, controlled trial [9]. This may be due to a less intensive intervention (6–10 group or individual sessions with no individualized information) or to a somewhat less motivated study population. As no data on T2DM incidence are yet available, it is yet to be seen if the observed risk factor reduction translates to T2DM prevention. In the Development Program for the Prevention and Care of Diabetes in Finland 2000–2010 (DEHKO) [24], large scale population-based strategies for T2DM prevention incorporating nutritional interventions and increasing physical activity have been implemented; however, results of this intervention on T2DM incidence are also not yet available.

Cost–effectiveness of diabetes prevention programs

While the success of IL in the prevention of T2DM has been proven, the financial cost of intensive interventions and the possible benefit in terms of reduced healthcare costs from reduced incidence of T2DM must be considered. IL has been demonstrated to be cost-effective in developed [25–28] and developing countries [29], and appears to be more cost-effective than metformin in some populations [27], but equally cost-effective in others [29]. In addition, one argument against dietary modification is the perceived belief that healthy diets are more expensive than unhealthy diets. However, in the FDPS, dietary modification to a more healthy diet did not increase diet cost [30]. As IL programs have been demonstrated to be cost-effective, health policy should promote lifestyle modification programs for T2DM prevention.

IL in prevention of CVD

While IL has unequivocally been shown to reduce the incidence of T2DM, the ultimate goal is reduction of the CVD associated with T2DM. While preventing or delaying T2DM will likely reduce CVD risk, the associated conditions of IGT, IFG and the metabolic syndrome have also been demonstrated to confer an increased CVD risk [2–5]. Therefore, maximizing CV protection through lifestyle modification may provide further benefit in this high-risk group. However, the majority of T2DM prevention trials have not been long enough to assess CV outcomes. The 20-year follow-up of the Da Qing IGT and Diabetes Study demonstrated a cumulative incidence of first CV events of 41% in the intervention group and 44% in the control group [14]. The cumulative CV mortality was 28% lower in the intervention group (12%) compared with the control group (17%), and all-cause mortality was 18% lower in the intervention group (25%) compared with the control group (29%). However, neither of these differences was statistically significant. Since the original study was not designed to examine the effects of IL on CV complications, the statistical power to detect reductions in the incidence of CVD and mortality risk was restricted. Further follow-up of other T2DM prevention trials will help to answer this question. There are no completed trials examining the impact of IL on CV outcomes in T2DM. However, results of trials from pharmacological interventions demonstrating that lowering blood pressure [31], serum cholesterol [32] and blood glucose [33] reduce CV risk, suggest the likely benefit of IL.

Holistic CV risk reduction combining IL and pharmacological intervention reduced CV events by 50% at 8 years in subjects with T2DM and microalbuminuria compared with conventional management [34,35]. Interim results of the ADDITION study, an ongoing trial of intensive target-driven lifestyle and pharmacological intervention for CV risk in subjects with screen-detected T2DM, has demonstrated improvements in CV risk factors including BMI, blood pressure, fasting glucose, and low-density lipoprotein (LDL)-cholesterol, although no improvements were seen in high-density lipoprotein (HDL)-cholesterol or triglyceride (TG) levels [36]. The Look AHEAD study, a large-scale multicenter, randomized, controlled trial focusing solely on IL programs in overweight or obese adults with T2DM, has been designed to examine the long-term effects of IL programs on the incidence of major CV events [37]. IL programs, involving group and individual sessions, are aimed at achieving and maintaining a greater than 7% weight loss through reduced dietary energy intake and increased PA. Interim results at 1 year have demonstrated significant improvements in CV risk factors including weight (weight loss 8.6% body weight vs 0.7%), HbA1c levels, blood pressure, TG levels and HDL-cholesterol, and demonstrated reduced use of medications for diabetes, hypertension and lipid-lowering compared with control [38]. Although these trials remain ongoing, data supporting the effectiveness of lifestyle modification for the reduction of CV outcomes in other populations, and for improvement in CV risk factors in people with diabetes, suggest that this approach is likely to be successful for the reduction of CV events in people with diabetes [37].

Dietary modification have been demonstrated to improve CV outcomes in those without T2DM at high risk of CV events [39]. Secondary prevention trials of dietary intervention in subjects with coronary heart disease have demonstrated that a Mediterranean diet and/or high omega 3 intake can reduce CV events, and all-cause and CV death [40–43]. Although a 10-year follow-up demonstrated a small continued CV benefit of a high fish intake, a high-fiber and low-fat consumption was not associated with any benefit of all-cause or coronary mortality [44]. Modification of dietary fat intake from saturated to mono- and poly-unsaturated fats has been demonstrated to improve lipid profiles [39]; however, long-term intervention studies with hard end points are lacking.

While studies examining the effect of IL on hard CV outcomes are ongoing, the effectiveness of lifestyle modification in improving CV risk factors in those with T2DM, IGT, IFG and the metabolic syndrome is well established in randomized, controlled trials. Interim results from the Look AHEAD study of IL programs in subjects with T2DM has shown improvements in CV risk factors as described previously. Results of studies of IL programs in subjects with IGT and/or the metabolic syndrome, and subanalyses of diabetes prevention studies, have also demonstrated improvements in CV risk factors. In subjects with IGT, IL resulted in 1.8 kg greater weight loss than control and improvements in fasting insulin, but no change in total cholesterol or TG levels [45]. In overweight or obese subjects with and without the metabolic syndrome, IL improved weight, waist circumference [46–51], blood pressure [46,48–50], total cholesterol [46], HDL-cholesterol [50,51] and TG levels [46,48–50]. In the DPP, IL programs reduced the risk of meeting metabolic syndrome criteria, while in the metformin group and placebo group this increased [52]. While total- and LDL-cholesterol in all groups were similar over the 3 years, IL programs altered the LDL phenotype, with a reduction in the smaller, denser, more atherogenic LDL particles compared with metformin and placebo [53]. Both HDL-cholesterol and TG levels were improved, and fewer participants required drug therapy for lipids in the lifestyle group compared with metformin or placebo. Similarly, in the FDPS, a reduced prevalence of the metabolic syndrome in the intervention group was seen compared with control [54]. IL led to improvements in abdominal obesity, blood pressure, fasting glucose, HDL-cholesterol and TG from baseline, while only HDL-cholesterol improved from baseline in the control group. While IL has been demonstrated to improve CV risk factors in those with IGT, IFG and the metabolic syndrome, whether these improvements in CV risk factors translate into a reduction in CV morbidity and mortality remains to be seen.

Conclusion & future perspective

Interventions based on lifestyle recommendations to improve diet and PA are effective in reducing the incidence of diabetes in those with IGT and are cost effective. 'Real-world' implementation of T2DM prevention programs with less intensive group programs appear to be successful at achieving lifestyle modification goals, although this appears be less so than intensive clinical trials. Ongoing studies will determine the effectiveness of 'real-world' interventions in preventing T2DM. A key challenge over the

Executive summary

Intensive lifestyle intervention for prevention of Type 2 diabetes mellitus

- Meta-analyses incorporating studies of intensive lifestyle (IL) interventions, including diet and physical activity, showed a 63% reduction in diabetes incidence in those at high risk.
- Weight loss accounts for most of the reduction in diabetes incidence; however, a small reduction in diabetes incidence independent of weight loss has been observed.
- In Asian Indian populations, reductions in diabetes risk may be achievable with relatively little weight loss.

'Real world' evidence: diabetes prevention in practice

- 'Real world' IL programs have shown improvement in diabetes risk factors; however, the effect on diabetes incidence has not been reported.

Cost–effectiveness of diabetes prevention programs

- IL has been shown to be cost-effective in developed and developing countries, and health policy should promote lifestyle modification programs for Type 2 diabetes mellitus prevention.

Intensive lifestyle interventions in the prevention of cardiovascular disease

- IL intervention has been shown to reduce cardiovascular risk factors in those with Type 2 diabetes mellitus, impaired glucose tolerance and impaired fasting glycemia, and obese individuals with and without the metabolic syndrome. However, data on the effects of lifestyle intervention on clinical cardiovascular outcomes are lacking.

coming decade will be to apply lifestyle intervention at a population level, with all of the social and regulatory change this will require. While IL has demonstrated improvements in CV risk factors in those with T2DM, IGT, IFG, metabolic syndrome and obese populations, it remains to be seen as to whether or not these improvements in risk factors translate to reductions in CV outcomes.

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Bibliography

1 Fox CS, Coady S, Sorlie PD *et al.*: Trends in cardiovascular complications of diabetes. *JAMA* 292(20), 2495–2499 (2004).

2 Saydah SH, Loria CM, Eberhardt MS, Brancati FL: Subclinical states of glucose intolerance and risk of death in the U.S. *Diabetes Care* 24(3), 447–453 (2001).

3 Hu FB, Stampfer MJ, Haffner SM, Solomon CG, Willett WC, Manson JE: Elevated risk of cardiovascular disease prior to clinical diagnosis of Type 2 diabetes. *Diabetes Care* 25(7), 1129–1134 (2002).

4 Gami AS, Witt BJ, Howard DE *et al.*: Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. *J. Am. Coll. Cardiol.* 49(4), 403–414 (2007).

5 Lakka HM, Laaksonen DE, Lakka TA *et al.*: The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 288(21), 2709–2716 (2002).

6 Sicree R, Shaw JE, Zimmet PZ: Diabetes and impaired glucose tolerance. In: *Diabetes Atlas*. Gan D (Ed.), International Diabetes Federation, Brussels, Belgium, 10–149 (2006).

7 Eriksson KF, Lindgarde F: Prevention of Type 2 (non-insulin-dependent) diabetes mellitus by diet and physical exercise. The 6-year Malmo feasibility study. *Diabetologia* 34(12), 891–898 (1991).

8 Pan X, Li G, Hu Y *et al.*: Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance: The Da Qing IGT and Diabetes Study. *Diabetes Care* 20, 537–544 (1997).

9 Tuomilehto J, Lindstrom J, Eriksson JG *et al.*: Prevention of Type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N. Engl. J. Med.* 344(18), 1343–1350 (2001).

10 Knowler WC, Barrett-Connor E, Fowler SE *et al.*: Reduction in the incidence of Type 2 diabetes with lifestyle intervention or metformin. *N. Engl. J. Med.* 346(6), 393–403 (2002).

11 Kosaka K, Noda M, Kuzuya T: Prevention of Type 2 diabetes by lifestyle intervention: a Japanese trial in IGT males. *Diabetes Res. Clin. Pract.* 67(2), 152–162 (2005).

12 Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V: The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent Type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). *Diabetologia* 49(2), 289–297 (2006).

13 Orozco LJ, Buchleitner AM, Gimenez-Perez G, Roque IFM, Richter B, Mauricio D: Exercise or exercise and diet for preventing Type 2 diabetes mellitus. *Cochrane Database Syst. Rev.* 3, CD003054 (2008).

14 Li G, Zhang P, Wang J *et al.*: The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. *Lancet* 371(9626), 1783–1789 (2008).

15 Lindstrom J, Louheranta A, Mannelin M *et al.*: The Finnish Diabetes Prevention Study (DPS): Lifestyle intervention and 3-year results on diet and physical activity. *Diabetes Care* 26(12), 3230–3236 (2003).

16 Lindstrom J, Ilanne-Parikka P, Peltonen M *et al.*: Sustained reduction in the incidence of Type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. *Lancet* 368(9548), 1673–1679 (2006).

17 The Diabetes Prevention Program (DPP): description of lifestyle intervention. *Diabetes Care* 25(12), 2165–2171 (2002).

18 Hamman RF, Wing RR, Edelstein SL *et al.*: Effect of weight loss with lifestyle intervention on risk of diabetes. *Diabetes Care* 29(9), 2102–2107 (2006).

19 Snehalatha C, Mary S, Joshi VV, Ramachandran A: Beneficial effects of strategies for primary prevention of diabetes on cardiovascular risk factors: results of the Indian Diabetes Prevention Programme. *Diab. Vasc. Dis. Res.* 5(1), 25–29 (2008).

20 Crandall J, Schade D, Ma Y, *et al.*: The influence of age on the effects of lifestyle modification and metformin in prevention of diabetes. *J. Gerontol. A Biol. Sci. Med. Sci.* 61(10), 1075–1081 (2006).

21 Absetz P, Valve R, Oldenburg B, *et al.*: Type 2 diabetes prevention in the 'real world': one-year results of the GOAL Implementation Trial. *Diabetes Care* 30(10), 2465–2470 (2007).

22 Kilkkinen A, Heistaro S, Laatikainen T, *et al.*: Prevention of Type 2 diabetes in a primary health care setting. Interim results from the Greater Green Triangle (GGT) Diabetes Prevention Project. *Diabetes Res. Clin. Pract.* 76(3), 460–462 (2007).

23 Balagopal P, Kamalamma N, Patel TG, Misra R: A community-based diabetes prevention and management education program in a rural village in India. *Diabetes Care* 31(6), 1097–1104 (2008).

24 Finnish Diabetes Association: The Development Programme for the Prevention and Care of Diabetes in Finland 2000–2010. DEHKO, Tampere, Finland.

25 Palmer AJ, Roze S, Valentine WJ, Spinas GA, Shaw JE, Zimmet PZ: Intensive lifestyle changes or metformin in patients with impaired glucose tolerance: modeling the long-term health economic implications of the diabetes prevention program in Australia, France, Germany, Switzerland, and the United Kingdom. *Clin. Ther.* 26(2), 304–321 (2004).

26 Diabetes Prevention Program Research Group: Within-trial cost–effectiveness of lifestyle intervention or metformin for the primary prevention of Type 2 diabetes. *Diabetes Care* 26(9), 2518–2523 (2003).

27 Herman WH, Hoerger TJ, Brandle M *et al.*: The cost–effectiveness of lifestyle modification or metformin in preventing Type 2 diabetes in adults with impaired glucose tolerance. *Ann. Intern. Med.* 142(5), 323–332 (2005).

28 Jacobs-van der Bruggen MA, Bos G, Bemelmans WJ, Hoogenveen RT, Vijgen SM, Baan CA: Lifestyle interventions are cost-effective in people with different levels of diabetes risk: results from a modeling study. *Diabetes Care* 30(1), 128–134 (2007).

29 Ramachandran A, Snehalatha C, Yamuna A, Mary S, Ping Z: Cost–effectiveness of the interventions in the primary prevention of diabetes among Asian Indians: within-trial

results of the Indian Diabetes Prevention Programme (IDPP). *Diabetes Care* 30(10), 2548–2552 (2007).

30 Ottelin AM, Lindstrom J, Peltonen M *et al.*: Costs of a self-selected, health-promoting diet among the participants of the Finnish Diabetes Prevention Study. *Diabetes Care* 30(5), 1275–1277 (2007).

31 Patel A, MacMahon S, Chalmers J *et al.*: Intensive blood glucose control and vascular outcomes in patients with Type 2 diabetes. *N. Engl. J. Med.* 358(24), 2560–2572 (2008).

32 Collins R, Armitage J, Parish S, Sleigh P, Peto R: MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 361(9374), 2005–2016 (2003).

33 Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA: 10-year follow-up of intensive glucose control in Type 2 diabetes. *N. Engl. J. Med.* 359(15), 1577–1589 (2008).

34 Gaede P, Vedel P, Parving HH, Pedersen O: Intensified multifactorial intervention in patients with Type 2 diabetes mellitus and microalbuminuria: the Steno Type 2 randomised study. *Lancet* 353(9153), 617–622 (1999).

35 Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O: Multifactorial intervention and cardiovascular disease in patients with Type 2 diabetes. *N. Engl. J. Med.* 348(5), 383–393 (2003).

36 Janssen PG, Gorter KJ, Stolk RP, Rutten GE: Randomised controlled trial of intensive multifactorial treatment for cardiovascular risk in patients with screen-detected Type 2 diabetes: 1-year data from the ADDITION Netherlands study. *Br. J. Gen. Pract.* 59(558), 43–48 (2009).

37 Wadden TA, West DS, Delahanty L *et al.*: The Look AHEAD study: a description of the lifestyle intervention and the evidence supporting it. *Obesity* 14(5), 737–752 (2006).

38 Pi-Sunyer X, Blackburn G, Brancati FL *et al.*: Reduction in weight and cardiovascular disease risk factors in individuals with Type 2 diabetes: one-year results of the look AHEAD trial. *Diabetes Care* 30(6), 1374–1383 (2007).

39 Van Horn L, McCoin M, Kris-Etherton PM *et al.*: The evidence for dietary prevention and treatment of cardiovascular disease. *J. Am. Diet. Assoc.* 108(2), 287–331 (2008).

40 Burr ML, Fehily AM, Gilbert JF *et al.*: Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet* 2(8666), 757–761 (1989).

41 de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N: Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation* 99(6), 779–785 (1999).

42 Singh RB, Niaz MA, Sharma JP, Kumar R, Rastogi V, Moshiri M: Randomized, double-blind, placebo-controlled trial of fish oil and mustard oil in patients with suspected acute myocardial infarction: the Indian experiment of infarct survival – 4. *Cardiovasc. Drugs Ther.* 11(3), 485–491 (1997).

43 Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico: Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet* 354(9177), 447–455 (1999).

44 Ness AR, Hughes J, Elwood PC, Whitley E, Smith GD, Burr ML: The long-term effect of dietary advice in men with coronary disease: follow-up of the Diet and Reinfarction trial (DART). *Eur. J. Clin. Nutr.* 56(6), 512–518 (2002).

45 Oldroyd JC, Unwin NC, White M, Mathers JC, Alberti KG: Randomised controlled trial evaluating lifestyle interventions in people with impaired glucose tolerance. *Diabetes Res. Clin. Pract.* 72(2), 117–127 (2006).

46 Lien LF, Brown AJ, Ard JD *et al.*: Effects of PREMIER lifestyle modifications on participants with and without the metabolic syndrome. *Hypertension* 50(4), 609–616 (2007).

47 Elmer PJ, Obarzanek E, Vollmer WM *et al.*: Effects of comprehensive lifestyle modification on diet, weight, physical fitness, and blood pressure control: 18-month results of a randomized trial. *Ann. Intern. Med.* 144(7), 485–495 (2006).

48 Villareal DT, Miller BV, 3rd, Banks M, Fontana L, Sinacore DR, Klein S: Effect of lifestyle intervention on metabolic coronary heart disease risk factors in obese older adults. *Am. J. Clin. Nutr.* 84(6), 1317–1323 (2006).

49 Bo S, Ciccone G, Baldi C *et al.*: Effectiveness of a lifestyle intervention on metabolic syndrome. A randomized controlled trial. *J. Gen. Intern. Med.* 22(12), 1695–1703 (2007).

50 Jacobs DR, Jr, Sluik D, Rokling-Andersen MH, Anderssen SA, Drevon CA: Association of 1-y changes in diet pattern with cardiovascular disease risk factors and adipokines: results from the 1-y randomized Oslo Diet and Exercise Study. *Am. J. Clin. Nutr.* 89(2), 509–517 (2009).

51 Kukkonen-Harjula KT, Borg PT, Nenonen AM, Fogelholm MG: Effects of a weight maintenance program with or without exercise on the metabolic syndrome: a randomized trial in obese men. *Prev. Med.* 41(3–4), 784–790 (2005).

52 Orchard TJ, Temprosa M, Goldberg R *et al.*: The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. *Ann. Intern. Med.* 142(8), 611–619 (2005).

53 Ratner R, Goldberg R, Haffner S *et al.*: Impact of intensive lifestyle and metformin therapy on cardiovascular disease risk factors in the diabetes prevention program. *Diabetes Care* 28(4), 888–894 (2005).

54 Ilanne-Parikka P, Eriksson JG, Lindstrom J *et al.*: Effect of lifestyle intervention on the occurrence of metabolic syndrome and its components in the Finnish Diabetes Prevention Study. *Diabetes Care* 31(4), 805–807 (2008).