



# Good news from the Da Qing Diabetes Prevention Outcome Study—healthy lifestyles result in long-term cardiovascular benefits

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Type 2 diabetes (T2D) has been considered as a heterogeneous disease with a strong genetic background (1,2). Nevertheless, overweight and obesity along with sedentary lifestyles explain to large extent the current epidemic of T2D. Disease is usually preceded by impaired glucose tolerance or elevated values of fasting plasma glucose. Heterogeneity depends on the impact of hundreds of genetic variants that impair, in concert with lifestyle and possibly with some poorly known environmental factors, insulin secretion capacity or insulin action in the body ultimately leading to overt diabetes (1-4). In 2017, the worldwide prevalence of diabetes was estimated to be 425 million, and the prevalence is increasing in most nations, in particular in many low and middle-income countries (3). Actions to prevent T2D was proposed already over 30 years ago (5). Actually, the Da Qing Diabetes Prevention Study, a cluster randomized study carried out in 33 Chinese clinics started already in 1986. This study included 577 individuals with impaired glucose tolerance (IGT) aged on an average 45–47 years. The average BMI was 24.5–24.7 kg/m<sup>2</sup>. First results from this study were reported in 1997, and the message was clear: there was a remarkable reduction in the incidence of T2D in people with IGT randomized by clinic into the diet, diet and exercise or exercise alone clinics as compared to those study participants randomized into the control clinics. However, no significant differences in the incidence of diabetes were

observed between three lifestyle intervention groups (6). Combining the intervention groups, the relative risk reduction of T2D was approximately 40% when compared to the control group. Some years later, both the Finnish Diabetes Prevention Study DPS (7) and the American Diabetes Prevention Program DPP (8) showed 58 % reduction in the risk of T2D in obese people with IGT (the average BMI in the Finnish DPS and American DPP was 31 and 34 kg/m<sup>2</sup>, respectively), who were individually randomized into the intervention (combining healthy dietary choices, weight reduction and physical activity) or control groups. After these three trials, several other lifestyle interventions have been published that confirm the results from earlier lifestyle intervention studies. Furthermore, the effects of lifestyle changes have been reported to last even for decade(s) after stopping active intervention (9) that suggests a strong legacy effect on disturbed glucose metabolism which has been thought to be progressive with time. On the contrary, the effects of lifestyle changes on cardiovascular morbidity and mortality in these intervention trials have remained unresolved (10), and only the Da Qing Diabetes Prevention Outcome Study has suggested beneficial effects on cardiovascular complications after 23 years of follow-up (11).

On the 25<sup>th</sup> April this year, we got good news from the Da Qing Diabetes Prevention Outcome Study when 30-year results were published in the *Lancet Diabetes &*

*Endocrinology* (12). Besides significant long-term reduction in the incidence of diabetes, there were significant reductions in all cause deaths (26%), cardiovascular disease (CVD) deaths (33%), total CVD events (26%) and composite microvascular diseases (35%) in the combined intervention groups as compared to the control group. Furthermore, the incidence of any retinopathy was 40 % lower in the combined intervention group. The mean increase in life expectancy in the intervention individuals was 1.44 years. Among the originally 577 individuals participating in the study, only 36 were lost to follow-up. Based on the detailed analyses, the authors concluded that the delay of diabetes was the main explanatory factor for lower incidence of vascular complications (12). An interesting finding was that women responded better than men to the intervention in terms of different complications, even if no gender differences were found in the incidence of diabetes. Frequent smoking could partly explain the smaller intervention effects in men. The results of this important study also suggest that it takes some 15 years before any beneficial intervention effects on morbidity or mortality can be found by lifestyle changes.

These results are unique since in the large Diabetes Prevention Program Outcome Study (DPPOS) no significant differences were found in macrovascular complications between the original intervention and control groups after 14 years of follow-up, but coronary artery calcifications were more severe in those who developed diabetes as compared to those who did not (13). No significant differences in the composite microvascular complications were observed in DPPOS either, albeit a modest decrease in women was found (14). Furthermore, recent results from the DPPOS show that regression to normoglycemia in IGT individuals was associated with 22% lower incidence of aggregate microvascular diseases (15). In line with DPPOS results, in the Finnish DPS no significant differences were found in CVD morbidity or mortality between the individuals randomized into the intervention and control groups (16), but in both groups the cardiovascular events were particularly low as compared to IGT individuals screened from a population based study (16). Good news are that early retinopathy based on fundus photographs was lower in the earlier intervention group than in the control group in a Finnish DPS sub-study (adjusted OR 0.52; 0.28–0.97,  $P=0.039$ ) (17). Interestingly, elevated triglycerides were consistently associated with early retinal changes.

The key question is why only the Da Qing Diabetes

Prevention Outcome Study observed beneficial effects on morbidity and CVD and total mortality, although all the three long-term follow studies found roughly similar preventive effect on the incidence of T2D in intervention groups after over 10 years of follow-up. Besides a longer follow-up in the Chinese study, the age difference could explain these findings; in the Chinese study, the mean age was 45–47 years while it was over 50 years in the DPP and Finnish DPS at the outset of the studies. Furthermore, BMI was markedly lower in the Chinese study than in the DPP and the Finnish DPS. Other explanations for divergent results could be genetic differences with regard to T2D and possibly CVD risk. Furthermore, possible differences in the intensiveness to manage cardiovascular diseases due to the health care resources available could have had impact on total and CVD mortality. Smoking was particularly common in the Chinese study (at baseline 62 % in men and 17% in women), whereas the respective figures in DPP and Finnish DPS were 6 and 7%. Statin users were quite uncommon at baseline in all three studies (4–6%), but approximately 40% to 63% were reported to use statin during the follow-up in all three study cohorts (12,13) (DPS: personal communication, Jaana Lindström). It is of note that ACE inhibitors and angiotensin receptor blockers became in common use as antihypertensive drugs in 1990's which also may modify the long-term results. Another interesting difference between Da Qing study and Finnish DPS and DPP is the incidence of stroke that was much higher in Chinese people.

In the Da Qing follow-up study, success in the prevention of diabetes was associated with the lower risk of late complications suggesting that long-term hyperglycemia per se could play a role in the prevention of both micro- and macrovascular complications (12), in line with the results from the UKPDS Study (18). However, both in DPP and Finnish DPS preventive effect of lifestyle changes was even greater (58%) at the end of active intervention phase, and about the same (30–40%) after the long-term follow-up over 10 years time period. An important explanation for divergent results could be marked differences in obesity between the Chinese study and the Finnish DPS and DPP: despite significant decrease in BMI and body weight during the intervention phase, the study participants in DPP and DPS remained on an average obese, and obesity per se may have an effect on later morbidity as the Look AHEAD post-hoc analyses suggest; in that post-hoc study, lower CVD morbidity was linked to marked weight loss in patients

with T2D (19). After all, recent results from the Da Qing Diabetes Prevention Outcome Study strongly suggest that besides prevention of T2D in the long-term, lifestyle intervention may also have significant preventive effect on CVD morbidity and mortality and microvascular diseases. Not surprisingly, current evidence in terms of lifestyle effects seems to be stronger with regard to microvascular complications that are closely related to hyperglycemia. Finally, lifestyle modifications tend to work regardless of genetic and ethnic background or heterogeneity of T2D.

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## Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

*Ethical Statement:* The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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