Reducing Morbidity and Mortality in Type 2 Diabetes by Lifestyle intervention: 30-year observational follow-up of the Da Qing Diabetes Prevention Study

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Summary

Background Lifestyle interventions delay the onset of type 2 diabetes in people with impaired glucose tolerance (IGT), but whether this leads subsequently to fewer complications or increases longevity is uncertain. We aimed to determine the long-term effects of lifestyle intervention in people with IGT on the incidence of diabetes, its complications, and mortality.

Methods In 1986, 577 adults with IGT in Da Qing, China were randomly assigned by clinic to a control group or one of three interventions (diet, exercise, or diet plus exercise) for six years. Participants were then followed for 30 years to assess the effects of intervention on the incidence of diabetes, cardiovascular events, composite microvascular complications, cardiovascular death, and life expectancy.

Findings During the 30-year follow-up, the intervention group, compared with controls, had a median delay in diabetes-onset of 3.96 years (95% CI, 1.25 to 6.67; P=0.0042), 26% fewer cardiovascular events (hazard ratio, 0.74; 95% CI, 0.59 to 0.92; P=0.0060), 35% lower incidence of microvascular complications (hazard ratio, 0.65; 95% CI, 0.45 to 0.95; P=0.0245), 33% fewer cardiovascular disease deaths (hazard ratio, 0.67; 95% CI, 0.48 to 0.94; P=0.022), and 26% fewer all-cause deaths (hazard ratio, 0.74; 95% CI, 0.61 to 0.89; P=0.0015), and an increase of 1.44 life years (95% CI, 0.20 to 2.68; P=0.023).

Interpretation Lifestyle intervention in people with IGT delayed the onset of type 2 diabetes and reduced the incidence of cardiovascular events, microvascular complications, cardiovascular and all-cause mortality, and increased life expectancy. The study provides strong justification to continue to implement and expand use of such interventions to curb the global diabetes epidemic and its consequences.

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Introduction

A major epidemic of diabetes mellitus has occurred during the past twenty years with the world-wide prevalence rising from 150 million cases in 2000 to an estimated 425 million in 2017, with a projected increase to 629 million by 2045.1 This epidemic is currently estimated to result in some 4 million excess deaths each year. The excess mortality is mainly due to high rates of cardiovascular disease, renal disease, and infection that develop over time in patients with type 2 diabetes.2 By the mid-1980’s obesity and physical inactivity had been established as major modifiable risk factors, and people with impaired glucose tolerance (IGT) were shown to be at high risk of developing type 2 diabetes.3,4 Randomised trials were then initiated to determine if lifestyle interventions could delay onset or prevent diabetes in individuals with IGT.

The Da Qing Diabetes Prevention Study (DQDPS) was the first such trial, beginning in 1986, which after six-years intervention with diet and/or exercise, demonstrated an overall 51% reduction in diabetes incidence.5 The Finnish Diabetes Prevention Study (DPS) followed in 1993, and the Diabetes Prevention Program (DPP) in 1999, both reporting 58% reduction in type 2 diabetes incidence after approximately three years of lifestyle intervention.6,7 Reports from India and Japan also documented reduced diabetes incidence from lifestyle interventions in people with IGT.8-10 Follow-up of DQDPS, DPS and DPP showed that diabetes incidence remained lower for several years beyond the period of active intervention.11-13

Serious complications, which cause most of the excess morbidity and mortality in diabetes, occur typically ten or more years after its onset. Consequently, only long-term follow-up studies can answer the crucial question of whether lifestyle or other interventions that delay diabetes-onset subsequently reduce serious complications and attributable mortality. Despite clear evidence that lifestyle interventions reduce diabetes incidence, the findings of the 13- and 15-year follow-up studies of the DPS and DPP cast doubt on the ability of lifestyle interventions to reduce incidence of cardiovascular and microvascular complications.12,14 Here we report the findings of a 30-year follow-up of the DQDPS designed to document the protracted effects of lifestyle intervention in people with IGT on diabetes, cardiovascular events, microvascular complications, cardiovascular deaths, and life expectancy.
Research in context

Evidence before this study.

People with impaired glucose tolerance (IGT) carry a high risk of developing type 2 diabetes and are at increased risk for cardiovascular disease. We searched PubMed for systematic reviews published between Jan 1, 2014, and Dec 31, 2018, using the search terms, “lifestyle intervention”, “diabetes prevention”, “systematic review”, and “meta-analysis.” Findings from several reviews indicated dietary and physical activity lifestyle interventions can delay the onset of diabetes in people with IGT, an effect which extends up to 23 years beyond the period of active intervention. Lifestyle interventions in people with IGT can also lead to improvement in cardiovascular risk factors. Whether or not such interventions ultimately lead to delay in onset and reduction in the incidence of the micro-vascular and cardiovascular complications, and increase life expectancy remains uncertain.

Added value of this study.

This study, with much longer follow-up than any previously reported, investigates the long-term consequences of a six-year trial of lifestyle intervention in people with IGT from Da Qing, China on the development of cardiovascular events, microvascular complications and life expectancy. Thirty years after initiation the trial significant reductions in the incidence of each of these complications were found, along with continuing reduction in mortality leading to a significant increase in life expectancy. The study provides compelling evidence of the long-term benefits of lifestyle intervention in people with IGT.

Implications of all the available evidence.

The similarity of findings from several studies of the effects of lifestyle intervention in delaying the onset of type 2 diabetes in people with IGT suggests that the long-term benefits described in the present study may be generalizable to many populations. In most parts of the world, especially in lower and middle-income countries (LMIC’s) where projected increases in diabetes prevalence are greatest, and resources are limited, lifestyle interventions may offer the most practical and cost-effective way to address the ongoing diabetes epidemic. The long-term benefits reported in the present study, however, may be less likely to be observed in populations where high quality diabetes care has now led to diminishing rates of complications and mortality. Nevertheless, even in such populations lifestyle interventions in people with IGT should remain a priority as they will postpone the onset of diabetes for some years and reduce the need for otherwise more expensive care. The study provides strong justification to continue to implement and expand use of such interventions to curb the global diabetes epidemic and its consequences.
Methods

The design and methods used in the DQDPS and subsequent 20- and 23-year follow-up studies have been described previously.²⁵,¹¹,¹⁵ DQDPS was designed originally as a clinical trial to test if lifestyle modification could delay or prevent type 2 diabetes among Chinese adults with IGT. In 1986, 33 randomly selected primary care clinics in Da Qing, China screened 110,660 adults, and using 75g oral glucose tolerance tests, identified 577 aged 25-74 years with IGT.³ The clinics were then randomised to provide one of three interventions (diet, exercise, or diet plus exercise) or serve as a control. Each clinic provided the assigned intervention to participants who normally received health care at that clinic. The dietary intervention aimed to increase vegetable intake and lower alcohol and sugar intake, and the exercise intervention aimed to increase leisure time physical activity. Those overweight or obese were also encouraged to reduce calorie intake to lose bodyweight. The control clinics provided standard care to participants. Active intervention took place for six years, after which participants were informed of the trial results and subsequently received routine medical care from their usual providers.

This paper reports results of an observational study of DQDPS participants followed for up to 30 years after randomisation to compare long-term outcomes related to diabetes between those exposed to lifestyle interventions and the control group. A priori for follow-up, as there were no significant differences in diabetes incidence among the three individual intervention groups during the trial,⁵ they were combined to increase the power to detect differences in outcomes between the combined lifestyle intervention and control group.

Outcome events were ascertained in 2006, 2009 and 2016. Institutional review boards at the Chinese Centers for Disease Control and Prevention and Fuwai Hospital approved the study. Surviving participants, and proxies who served as informants for the deceased, gave written informed consent.

Data collection

For the present study, vital status on December 31, 2016 was determined. For the deceased, proxy informants, a living spouse, sibling, or child, were interviewed using standardized questionnaires and the data were then verified by review of medical records and/or death certificates. For living participants, data were collected by interview, clinical examination and medical record review by trained staff and physicians in Da Qing First Hospital. In 2016 among the 279 living participants, 24 (8.6%) were unable to attend the hospital because of ill-health and were examined at their homes, and 31 (11.1%) living outside Da Qing were interviewed by telephone and examined in local hospitals. Specific methods for data collection are described in the study protocol in the Supplementary Appendix.

Outcome events

The primary outcomes were incident diabetes, cardiovascular disease (CVD) events, a composite of microvascular complications, CVD death and life expectancy. Secondary outcomes included stroke, coronary heart disease and heart failure, and microvascular complications of retinopathy, nephropathy and neuropathy.

Diabetes was defined by 1985 WHO criteria¹⁶ from results of 75g oral glucose tolerance tests (OGTTs) done every two years during the trial (1986–1992), self-reported physician-diagnosed diabetes, and evidence of elevated glucose levels or use of glucose lowering medication in medical records. Participants not already known to have diabetes received a 75g OGTT at the follow-up examinations, also interpreted using 1985 WHO criteria. Primary CVD events were defined as non-fatal or fatal myocardial infarction, sudden death, heart failure, or stroke, and secondary CVD events as of each of these individual components. Composite microvascular disease was defined as retinopathy, nephropathy, or neuropathy; retinopathy as a history of photocoagulation, blindness from retinal disease, or proliferative retinopathy identified at follow-up examinations, nephropathy as a history of end-stage renal disease, renal dialysis, renal transplantation, or death from chronic kidney disease,
and neuropathy as a history of lower extremity ulceration, gangrene, or amputation. Causes of death were determined from review of medical records and death certificates. The onset for each outcome was taken as its earliest date of recognition from medical records, interview, or the 2006 and 2016 examinations. Two physicians, unaware of participants’ trial assignments, independently adjudicated each outcome, with disagreements resolved by a third senior physician.

**Statistical analysis**

Although the follow-up is observational, the primary and secondary analyses were performed using intention to treat principles. Incidence was calculated as number of events divided by person-years of exposure censored at date of first recognition of the event, loss to follow-up, death or December 31, 2016, whichever came first. Time-to-first-event survival curves for each outcome were estimated by the Kaplan–Meier method, and compared between groups with log-rank tests. Cox proportional-hazards analyses, accounting for clinic assignment, were used to calculate hazard ratios to quantify between-group differences. Differences between the intervention and control groups in average number of event-free years and life expectancy were calculated from areas under the survival curves as a summation of yearly discrete survival function, and life-years gained as the difference in mean life expectancy between the groups. We fitted a parametric model with Weibull distribution to interpolate the median survival time from baseline. Median delay in onset of events and numbers needed to treat to prevent an event during follow-up were estimated from survival functions. Post hoc Cox proportional hazards analysis was used to determine if differences in the primary outcomes could be attributed to delay in diabetes-onset in the intervention group. Other secondary analyses explored changes in BMI, smoking and sex-related differences as potential explanatory variables related to differences in primary outcomes between intervention and control groups. Differences between intervention and control groups were considered statistically significant if p<0.05 in two-sided tests. SAS/STAT version 14.3 (SAS Institute, Cary, NC, USA) was used for statistical analysis.

**Role of the funding sources**

Centers for Disease Control and Prevention, Chinese Centers for Disease Control and Prevention, National Center of Cardiology & Fuwai Hospital, China-Japan Friendship Hospital, and Da Qing First Hospital were co-sponsors of the follow-up study. Scientists from these organizations were involved in the study design, collection, analysis, interpretation of the data, and writing the report. Co-authors had full access to all data in the study and final responsibility for submitting the paper for publication.

**Results**

A flowchart of the study is shown in Figure 1, and characteristics of participants at baseline and 30-year follow-up are given in Table 1. The 30-year cumulative incidence for primary outcomes in the control and intervention groups and related hazard ratios are shown in Figure 2 and numbers of events and person-years at risk for primary and secondary outcomes are given in the Supplementary appendix (Tables S1, S2). The effect of intervention in delaying the onset of primary outcome events, the average number of event-free years, and the number needed to treat to prevent each primary outcome event are shown in Table 2.

**Diabetes**

A median delay in diabetes-onset of 3.96 years (95% CI, 1.25 to 6.67; P=0.0042) in the intervention group and the lower cumulative incidence of diabetes, initially reported at the end of the six-year trial, persisted throughout follow-up (HR, 0.61; 95% CI, 0.45-0.83; 39% difference; P=0.0015) (Fig. 2A). Findings were similar in men and women (Table S5).

**CVD events**
CVD events were recorded in 195/405 (48.1%) of the intervention and 80/135 (59.3%) of the control group with cumulative incidences of 52.9% (95% CI, 47.5-57.9) and 66.5% (95% CI, 57.0-74.4) respectively (Table S1), resulting in 26% (95% CI, 8.41; P=0.0060) fewer CVD events in the intervention group (Fig. 2B). The incidence of secondary CVD outcomes was 25% lower (95% CI, 4.41; P=0.024) for stroke and of similar magnitude but not significant for CHD (27% (95% CI, -4.49; P=0.079) and heart failure (29% (95% CI, -4.52; P=0.081)) (Fig. S1).

While CVD events were almost twice as frequent in men, the rate reduction associated with intervention was lower (20%; 95% CI, -6.40%) than women (31%; 95% CI, 8.49%) (Table S5). There was a median delay of 4.6 years (95% CI, 1.1 to 8.2; P=0.011) in the onset of CVD events in the intervention group, and the number needed to treat to prevent one CVD event during the 30-year interval was 9 persons (95% CI, 5.3-36) (Table 2).

Microvascular complications

The incidence of composite microvascular disease was 35% (95% CI, 5.55; P=0.025) lower in the invention group (Fig. 2C) with a cumulative incidence of 25.1% (95% CI, 20.2-30.1) in the intervention and 34.0% (95% CI, 24.5-43.8) in the control group (Table S1). The incidence of retinopathy was 40% lower (95% CI, 5.62; P=0.032) and nephropathy and neuropathy while lower in the intervention group were not significantly so (Table S2, Fig. S2).

CVD death

Mortality data and causes of death were ascertained for 540/576 (93.8%) of the original participants of whom 185/405 (45.7%) were in the intervention group and 76/135 (56.3%) in the control group (Table S3). Half of all deaths were attributed to CVD, half of which were due to stroke. The cumulative incidence of CVD death was 25.6% (95% CI, 21.1-30.4) in the intervention group and 35.2% (95% CI, 26.4-44.2) in the controls with rates that were 33% (95% CI 6.52; P=0.022) lower in the intervention group (Fig. 2D, Table S1) with lower rates of both stroke and CHD (Table S2, Fig. S1). While CVD deaths were more frequent in men than women, the rate reductions in the intervention group were greater in women than in men (Tables S5, S6). For non-CVD causes of death there were no statistically significant differences between the intervention and control groups (Table S3).

All-cause mortality and Life expectancy

All-cause death rates were 26% lower (95% CI, 11.39; P=0.0015) in the intervention group (Fig. 2E, Table S1) with significant reductions in women (41%, 95% CI, 9.62; P=0.018) but not men (15%, 95% CI, 9.34; P=0.19) (Table S5). The intervention was associated with an increase in median survival of 4.82 years (95% CI, 1.48 to 8.15; P=0.0047) and an increase in average overall survival of 1.44 years (95% CI, 0.20, to 2.68; P=0.023) longer than the controls (Table 2). The number needed to treat with lifestyle intervention to prevent one death during the 30-year interval was 10 persons (95% CI, 6 to 25; P=0.0015).

Statistically significant reductions in the incidence of all primary outcome events were found in the intervention group, which with those for the secondary outcomes, are summarized in Figure 3. Secondary analysis showed in multivariable models that correcting for time of onset of diabetes nullifies the significance of the intervention effect for each of the primary outcomes (Table S4) suggesting that much of the reduced incidence for these outcomes can be accounted for by the delay in diabetes onset in the intervention group. Further exploratory post hoc analyses were conducted to investigate possible explanations for the differences in responses to the intervention among men and women (Tables S7-S9). The three original trial intervention groups each showed similar reductions in outcome events, but which individually were not statistically significant (Table S10).
Discussion

Based on data gathered from the 20- and 23-year follow-up of the DQDPS, we have previously reported lower diabetes incidence and significant reductions in the incidence of retinopathy, CVD deaths and all-cause mortality in the lifestyle intervention group. Results from the current 30-year follow-up, now based on many more outcome events, extend and strengthen these earlier findings. For the first time we report significant reductions of 26% in CVD events, 28% in microvascular complications, which along with 33% reduction in CVD deaths, and 26% reduction in all-cause mortality, now leads to a 4.82 years increase in median survival and a mean increase of 1.44 years in life expectancy in the intervention group. These new findings further strengthen the evidence that lifestyle intervention in people with IGT reduces the incidence of serious diabetes complications and diabetes-related mortality.

Evidence from observational cohort studies links changes in dietary intake, increased physical activity and weight-loss to reduced risk of macrovascular complications in people with diabetes and IGT, but such evidence from clinical trials is limited. Trials have reported improvements in CVD risk factors, but neither the DPS, nor DPP outcome studies showed reductions in CVD events or mortality although the latter after 15-years follow-up reported a modest reduction in microvascular disease in women. The DQDPS findings are unique in that benefits of intervention were observed across a range of outcomes, including CVD events, microvascular complications, CVD deaths, and all-cause mortality. Most of these events occurred between 15 and 30 years after randomisation. The differences compared to the DPS and DPPOS seem likely to be the result of much longer follow-up that allowed enough time for development of sufficient numbers of events to permit differences in outcomes to be detected.

In contrast to the DQDPS, the DPP and DPS lifestyle interventions were designed to produce weight loss and were conducted in people with IGT with an average BMI of over 30 kg/m². Both studies concluded that weight-loss was an important factor in reducing diabetes incidence. In Da Qing, baseline BMI of participants averaged only 25.7 kg/m², and weight-loss was encouraged only in those with BMI > 25 kg/m². The interventions resulted in only small changes in BMI, suggesting that the lower diabetes incidence was mainly attributable to factors such as the changes in dietary composition and increased physical activity. Similar findings and conclusions were reported from the Indian Diabetes Prevention Programme.

Relatively greater reductions in mortality and CVD were found in Da Qing women than in men despite similar reductions in the incidence of diabetes. As the baseline prevalence of smoking was much higher in men than women (61.9% vs 17%), in secondary analyses we assessed its effect on mortality. For all-cause mortality and CVD events, both in men and women intervention was less effective in smokers (Table S7), but in the total population correction for smoking resulted only in minor changes in the apparent efficacy of the intervention (Table S8). Lower adherence to lifestyle interventions by men beyond the six-year trial, or sex differences in unmeasured confounders, may also have contributed to the more favourable intervention outcomes in women.

The effects of the intervention in DQDPS may be primarily the result of the delay in diabetes-onset, which then postponed development of complications for a similar time interval. The lower rates of complications in the intervention group, occurring mainly 15 or more years after randomisation, may be considered a metabolic ‘legacy effect’ of the delay in diabetes-onset. Another possibility is that the participants themselves or the clinics which delivered the interventions continued to practice the same strategies after the trial ended. Both the intervention and control groups received similar levels of treatment with blood pressure- and lipid-lowering agents (Table S9). The most straightforward explanation, for which we have presented supporting evidence, is that the delay in onset of diabetes itself can explain most of the postponed development of complications in the intervention group (Table S4).
Although lifestyle interventions reduce type 2 diabetes incidence in people with IGT, questions remain about how to best translate this evidence into effective public health measures.21 The long-term benefits seen in DQDPS may be more difficult to observe where high quality care has led to diminishing rates of complications and mortality.22,23 Nevertheless, in such populations lifestyle intervention in people with IGT should still remain a priority as at least it will delay diabetes onset and postpone costly care. There may also be select groups with IGT where drugs such as metformin, or weight-reducing agents are indicated to postpone the onset of diabetes.24,25 While evidence that lifestyle intervention in people with IGT reduces diabetes incidence is now unquestionable, whether such interventions reduce diabetes incidence in people with isolated impaired fasting glucose, or elevated HbA1c levels without IGT, who constitute the majority with ‘prediabetes’ as currently defined, is uncertain.10,20 In most parts of the world, however, especially in lower and middle-income countries where the projected increases in diabetes prevalence are greatest,1 and resources for diabetes care are limited, lifestyle intervention may be the most practical and cost-effective way to address the ongoing epidemic.26

Our study has several strengths and limitations. The limitations are first, the sample size is small because the original trial was designed to study diabetes incidence and not complications. Second, we were unable to perform systematic examinations at regular intervals on all participants throughout the follow-up so that the reported outcomes were limited to those which could be identified and reliably assessed from medical history and other records. Third, we lack information about adherence to lifestyle recommendations beyond the end of the trial period. Fourth, the findings apply to prevention of type 2 diabetes and its complications only in people with IGT, and may not be generalizable to other categories of ‘prediabetes’. Strengths of the study include: 1) participants were identified by population-based screening using 75g OGTTs and constitute a representative sample of the people with IGT living in Da Qing in 1986; 2) participants were randomised according to the primary care clinic to which they were pre-assigned to receive medical care, facilitating delivery of group-based interventions and reducing the likelihood of contamination between participants in the intervention and control groups; 3) little migration away from the city has occurred, thereby keeping loss to follow-up to a minimum and enabling high completion rates many years after the initial trial; 4) when the trial was initiated there was only a single referral hospital in the city which continues to provide secondary and tertiary care for many participants, thereby facilitating access to their medical records; 5) the interventions were not associated with any serious side effects or adverse reactions; and 6) although this is an observational study, the data were analyzed using intention to treat principles to minimise the likelihood of residual confounding.

Our findings further strengthen the case for scaling up such interventions to combat the worldwide diabetes epidemic. The benefits observed are likely applicable to all individuals at high risk of type 2 diabetes especially in LMICs. Results from modelling studies also show that implementing such interventions not only improve health and prolong life but save health care resources long-term in both high and low income countries.26,27 The goal of reducing the number of persons with diabetes worldwide is likely to be best achieved through population-wide policy measures that change the environment and behaviours combined with specific lifestyle intervention programmes for high risk individuals. Scaling up lifestyle interventions requires addressing and overcoming a number of challenges, e.g. identifying the appropriate populations in which to intervene, reducing the cost of intervention etc.28 Lowering the cost of delivering the intervention may be achievable using mobile devices and trained lay community health workers which would further improve its cost-effectiveness.29

In summary, this study provides strong evidence of the effectiveness of lifestyle intervention in people with IGT in reducing not only the development of diabetes, but also of serious complications such as CVD events, microvascular complications, and excess mortality due to type 2 diabetes, and extending life expectancy. The findings support and strengthen evidence of
the benefits of lifestyle intervention and suggest that if widely applied, lifestyle intervention in people with IGT would help to curb the global diabetes epidemic and its inevitable consequences.
Contributors

Q.G. designed the study, collected data, did statistical analysis, and participated in drafting and preparation of the report. P.Z. acquired funding, designed and coordinated the study, and participated in the statistical analysis, writing and preparation of the report, and editing the final report. J.M. participated in the study design and acquiring funding, and contributed to writing the report. J.W. and Y.A participated in the study design, data collection and analysis. E.W.G acquired funding, designed the study, and contributed to the statistical analysis, writing and preparation of the report. B.Z., Y.C., X.F., H.L. and X.C. participated in the data collection. Y.J.C. assisted in the statistical analysis and preparation of the report. Y.H. participated in the study design and data collection. P.H.B. designed the study, guided the data analysis, and participated in writing, preparation and editing the final report. G.L. designed and coordinated the study, acquired funding, collected data, did statistical analysis, and participated in writing, and editing the final report.

Q.G and P.Z, as first co-authors, contributed equally to the design of the study and preparation of the report, and P.H.B and G.L, as senior co-authors, played an equal role in the design and oversight of the analysis and preparation of the report, and vouch for its findings.

Acknowledgements

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Declaration of interests

No potential conflicts of interest relevant to this article have been reported. The contents of this paper are solely the responsibility of the authors and do not necessarily represent the official positions of the Centers for Disease Control and Prevention or the National Institute of Diabetes and Digestive and Kidney Diseases.
List of Tables and Figures for main paper.

Figure 1. Flow Chart of the Study.

Table 1. Characteristics of the Control and Intervention Groups at Baseline (1986) and at the 30-year Follow-up (2016).

Figure 2. Kaplan-Meier Plot of Cumulative Incidence of Diabetes (Panel A), CVD Events (Panel B), Composite Microvascular Disease (Panel C), CVD Deaths (Panel D), and All-cause Mortality (Panel E) in the Control and Intervention Groups during the 30-year Follow-up.

Figure 3. Forest Plot of the Hazard Ratios (HR, 95% CI) for Primary and Secondary Outcome Events in the Control and Intervention Group at the 30-year Follow-up.

Table 2. Effect of Intervention on Delaying the onset of Primary Outcome Events, Numbers Needed to Treat, and Event-free Years Gained during the 30-year Follow-up.
In 1985, 110,660 persons aged 25-74 years, enrolled in 33 primary health care clinics in Da Qing, screened for diabetes and IGT

577 persons, identified by 75g OGTT as having IGT, of whom 576 had a baseline health examination
Clinics randomised to provide intervention or to serve as control clinics

Controls: 8 clinics, 138 participants
Diet only: 9 clinics, 148 participants
Exercise only: 9 clinics, 155 participants
Diet + Exercise: 7 clinics, 135 participants

Six-year trial of Lifestyle

TRIAL COMPLETED
ASSESSED FOR DIABETES:

In 1986

All participants subsequently received routine medical care from their usual

20-year follow-up

Assessed for outcomes: n=135

23-year follow-up
Assessed for outcomes: n=135

20-year follow-up

Assessed for outcomes: n=430

23-year follow-up
Assessed for outcomes: n=430

30-year follow-up
Lost to follow-up: n=3*

Review of Death certificates and medical records only.

In 1992

In 2006

In 2009

In 2016

30-year follow-up
Lost to follow-up: n=33*
*Most loss to follow-up (31/36) occurred between 1986-92 during the trial when some participants were relocated to a newly discovered oil field, and could no longer receive intervention or follow-up at their assigned clinics in Da Qing. In 2016, data were obtained for some participants who earlier had been reported as ‘lost to follow-up’.

Figure 1. Flow Chart of the Study.

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<thead>
<tr>
<th></th>
<th>Control</th>
<th>Intervention</th>
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<tbody>
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<td>(N=138)</td>
<td>(N=438)</td>
</tr>
<tr>
<td><strong>1986</strong></td>
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<td></td>
</tr>
<tr>
<td>Age — years</td>
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<td>44.7±9.3</td>
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<tr>
<td>Systolic</td>
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<td>131.9±24.3</td>
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<td>Diastolic</td>
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<td>87.0±14.1</td>
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<td>Total cholesterol — mmol/l</td>
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<td>5.0±1.4</td>
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<td>Fasting glucose — mmol/l</td>
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<td>2-hour glucose — mmol/l</td>
<td>9.0±0.9</td>
<td>9.0±0.9</td>
</tr>
<tr>
<td>Current smoker — no.(%)</td>
<td>69 (50.0)</td>
<td>169 (38.6)</td>
</tr>
<tr>
<td><strong>2016</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lost to follow-up — no.(%)</td>
<td>3 (2.2)</td>
<td>33 (7.5)</td>
</tr>
<tr>
<td>Characteristic</td>
<td>1986 Mean ± SD</td>
<td>2016 Mean ± SD</td>
</tr>
<tr>
<td>----------------------------------------------------</td>
<td>-----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Dead — no. (%)</td>
<td>76 (55·1)</td>
<td>185 (42·3)</td>
</tr>
<tr>
<td>Alive in 2016 — no. (%)</td>
<td>59 (42·7)</td>
<td>220 (50·2)</td>
</tr>
<tr>
<td>Age — years</td>
<td>71·8±6·9</td>
<td>70·5±6·6</td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>34 (57·6)</td>
<td>134 (60·9)</td>
</tr>
<tr>
<td>Examined — no. (%)</td>
<td>48 (81·4)</td>
<td>183 (83·2)</td>
</tr>
<tr>
<td>Body-mass index (kg/m²)</td>
<td>24·7±3·9</td>
<td>24·5±3·3</td>
</tr>
<tr>
<td>Change in BMI from 1986 to 2016 (kg/m²)</td>
<td>-1·1±3·4</td>
<td>1·2±3·3</td>
</tr>
<tr>
<td>Blood pressure — mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>143·9±19·3</td>
<td>148·1±21·2</td>
</tr>
<tr>
<td>Diastolic</td>
<td>74·2±7·4</td>
<td>77·6±10·4</td>
</tr>
<tr>
<td>Total cholesterol — mmol/l</td>
<td>4·9±0·9</td>
<td>5·0±1·4</td>
</tr>
<tr>
<td>Fasting glucose — mmol/l</td>
<td>7·8±2·8</td>
<td>7·4±2·9</td>
</tr>
<tr>
<td>2-hour glucose — mmol/l</td>
<td>11·8±3·5</td>
<td>10·1±3·5</td>
</tr>
<tr>
<td>Glycated hemoglobin — mmol/mol</td>
<td>61·6±17·6</td>
<td>60·9±18·3</td>
</tr>
<tr>
<td>Glycated hemoglobin — %</td>
<td>7·8±1·6</td>
<td>7·7±1·7</td>
</tr>
</tbody>
</table>

Plus-minus values are means ±SD

**Table 1. Characteristics of the Control and Intervention Groups at Baseline (1986) and at the 30-year Follow-up (2016).**
A. Diabetes †

![Graph showing cumulative incidence of diabetes](image)

Number at risk
Control: 128 80 48 60 24 10 4
Intervention: 128 80 48 60 24 10 4

Number at risk
Control: 128 80 48 60 24 10 4
Intervention: 128 80 48 60 24 10 4

HR: 0.61(95%CI, 0.45-0.83)
P = 0.0015

B. CVD Events ‡

![Graph showing cumulative incidence of CVD events](image)

Number at risk
Control: 128 80 48 60 24 10 4
Intervention: 128 80 48 60 24 10 4

Number at risk
Control: 128 80 48 60 24 10 4
Intervention: 128 80 48 60 24 10 4

HR: 0.74(95%CI, 0.58-0.92)
P = 0.006

C. Composite Microvascular Disease §

![Graph showing cumulative incidence of composite microvascular disease](image)

Number at risk
Control: 128 80 48 60 24 10 4
Intervention: 128 80 48 60 24 10 4

Number at risk
Control: 128 80 48 60 24 10 4
Intervention: 128 80 48 60 24 10 4

D. CVD Deaths ¶

![Graph showing cumulative incidence of CVD deaths](image)

Number at risk
Control: 128 80 48 60 24 10 4
Intervention: 128 80 48 60 24 10 4

Number at risk
Control: 128 80 48 60 24 10 4
Intervention: 128 80 48 60 24 10 4

HR: 0.67(95%CI, 0.48-0.94)
P = 0.022

E. All-cause Mortality

![Graph showing cumulative incidence of all-cause mortality](image)

Number at risk
Control: 128 80 48 60 24 10 4
Intervention: 128 80 48 60 24 10 4

Number at risk
Control: 128 80 48 60 24 10 4
Intervention: 128 80 48 60 24 10 4

HR: 0.74(95%CI, 0.61-0.89)
P = 0.0013

‡ CVD events defined as the first occurrence of non-fatal or fatal CVD deaths.

¶ All-cause mortality includes both CVD and non-CVD deaths.

* HR: Hazard Ratio (intervention/control) P value from Cox proportional hazard models, controlled for clinic randomisation.

† Diabetes defined from results of oral glucose tolerance test done every 2 years during the trial (1986–1992), and in 2006 or 2016 at the follow-up examinations, or from self-reported physician-diagnosed diabetes with evidence of elevated glucose levels in the medical record, or receiving hypoglycemic medications.
Figure 2. Kaplan-Meier Plot of Cumulative Incidence of Diabetes (Panel A), CVD Events (Panel B), Composite Microvascular Disease (Panel C), CVD Deaths (Panel D), and All-cause Mortality (Panel E) in the Control and Intervention Groups during the 30-year Follow-up.
Figure 3. Forest Plot of the Hazard Ratios (HR, 95% CI) for Primary and Secondary Outcome Events in the Control and Intervention Groups at the 30-year Follow-up.

The reference category is control group. *HR: Hazard Ratios from proportional hazard models controlled for clinic randomisation.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Median Delay in Years</th>
<th>P value</th>
<th>Average Number of Event-free Years</th>
<th>P value</th>
<th>Number Needed to Treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>3.96 (1.25-6.67)</td>
<td>0.0042</td>
<td>4.07 (1.46-6.68)</td>
<td>0.0022</td>
<td>10 (7-23)</td>
</tr>
<tr>
<td>CVD Events *</td>
<td>4.64 (1.05-8.22)</td>
<td>0.011</td>
<td>1.77 (0.18-3.36)</td>
<td>0.029</td>
<td>9 (5-36)</td>
</tr>
<tr>
<td>Composite Microvascular Disease †</td>
<td>5.17 (-0.56-10.90)</td>
<td>0.077</td>
<td>0.96 (-0.12-2.03)</td>
<td>0.080</td>
<td>10 (5-193)</td>
</tr>
<tr>
<td>CVD Deaths ‡</td>
<td>7.25 (-0.18-14.67)</td>
<td>0.056</td>
<td>1.06 (-0.10-2.23)</td>
<td>0.074</td>
<td>10 (5-72)</td>
</tr>
<tr>
<td>All-cause Mortality</td>
<td>4.82 (1.48-8.15)</td>
<td>0.0047</td>
<td>1.44 (0.20-2.68)**</td>
<td>0.023</td>
<td>10 (6-25)</td>
</tr>
</tbody>
</table>

* CVD events defined as non-fatal or fatal cardiovascular disease (coronary heart disease-myocardial infarction or sudden death), heart failure, or stroke.
† Composite microvascular disease defined as the first recognition of retinopathy, nephropathy or neuropathy.
‡ CVD deaths are fatal CVD events
** Average increase in life-expectancy

Table 2. Effect of Intervention on Delaying the onset of Primary Outcome Events, Event-free Years Gained, and Numbers Needed to Treat during the 30-year Follow-up.
References


List of Tables and Figures for main paper.

Figure 1. Flow Chart of the Study.

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