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Efficacy of lifestyle intervention in adults with impaired glucose tolerance with and without impaired fasting plasma glucose: a post hoc analysis of Da Qing Diabetes Prevention Outcome Study

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Abstract

Aims—The extent that pre-diabetic fasting plasma glucose (FPG) levels influence the effectiveness of lifestyle interventions in preventing type 2 diabetes (T2DM) is uncertain. We aimed to determine if the outcome of lifestyle intervention in people with impaired glucose tolerance (IGT) differs in those with normal or impaired FPG levels.

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AUTHOR CONTRIBUTIONS

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, preparation and editing the final report. J.W. 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. Y.J.C. assisted in the statistical analysis and preparation of the report. 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. P.H.B is Scientist Emeritus and received technical support from the NIDDK intramural program of the US National Institutes of Health for his work on this study. 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.

DATA AVAILABILITY STATEMENT

Data collected for this study may be shared and made available upon reasonable request to the corresponding author and subject to an approved proposal and data access agreement.

CONFLICT OF INTEREST

No potential conflicts of interest relevant to this article have been reported.

Methods—Using data from the Da Qing Diabetes Prevention Outcome Study, a 30-year follow-up of a six-year randomized trial of lifestyle intervention in 576 people with IGT, we conducted a post-hoc analysis to compare the efficacy of intervention to reduce the incidence of T2DM and its complications in those with baseline FPG <100mg/dL and FPG ≥100 mg/dL.

Results—Lifestyle intervention reduced the cumulative incidence of T2DM by 37–46% in those with baseline FPG <100mg/dL and by 47–51% in those with FPG ≥100 mg/dL. The FPG <100 mg/dL group had a lower cumulative incidence of diabetes and 6.41years median delay in its onset compared with 2.21 years delay in the FPG >100 mg/dL group. In those with FPG <100 mg/dL intervention was associated with at least as great a reduction in cardiovascular disease (CVD) and all-cause mortality as in the FPG >100 mg/dL group.

Conclusions—Lifestyle intervention reduced the incidence of T2DM in people with IGT regardless of baseline FPG levels, and in those with FPG <100 mg/dL led to a substantial delay in its onset. All persons with IGT, with normal or impaired FPG levels, may benefit from lifestyle intervention to delay its onset and mitigate the incidence of T2DM.

Keywords

lifestyle intervention; impaired glucose intolerance; impaired fasting glucose; type 2 diabetes; Da Qing Study

1 INTRODUCTION

Randomized clinical trials have consistently shown that lifestyle interventions in people with impaired glucose tolerance (IGT) reduce the incidence and delay the onset of type 2 diabetes.[1–7] Nevertheless, in translating findings from these trials to prevention programs, there has been reluctance to screen potential participants for IGT as its presence can only be determined from an oral glucose tolerance test (OGTT). More commonly fasting plasma glucose (FPG) and HbA1c measurements are now used to identify potential candidates for lifestyle intervention programs,[8] although the efficacy of lifestyle interventions in delaying the onset of type 2 diabetes and its complications among people with elevated FPG or HbA1c levels without IGT is controversial.[9] People with IGT and impaired fasting glucose (IFG)[10] or intermediate hyperglycemia[11], who have a very high risk of type 2 diabetes, may respond differently to intervention than those without IFG who have a lower risk and who are perhaps identified at an earlier stage in the development of diabetes.

The extent that the efficacy and effectiveness of lifestyle intervention in people with IGT is influenced by baseline FPG levels beyond the period of active intervention is uncertain. The US Diabetes Prevention Program (DPP) reported that lifestyle intervention over a three-year period reduced the incidence of diabetes in those with IGT and baseline FPG levels of 95–109 mg/dL by 55% from 6.4 cases/100 person-years in controls to 2.9/100 person-years, and in those with baseline FPG levels of 110–139 mg/dL by 63%, from 22.3 cases/100 person-years in controls to 8.8/100 person-years.[3] In contrast, in the Finnish Diabetes Study (DPS) lifestyle intervention over a four-year period in those with IGT and baseline FPG levels of <5.8 mmol/L (104 mg/dL) reduced the incidence of diabetes by 37% from 3.8/100 person-years in the controls to 2.4 cases/100 person-years in the intervention

group, compared with a 73% reduction in those with baseline FPG levels of 5.8–6.4 mmol/L (105–115 mg/dL) from 6.9 cases/100 person-years in controls to 2.7 cases/100 person-years in the intervention group,[12] thus suggesting that intervention may be less effective in those with lower FPG levels. While the incidence of diabetes was markedly lower in the DPS than in the DPP, both studies confirmed that lifestyle interventions in people with IGT reduce the incidence of diabetes as had been reported previously in the DQDPS.[1] Each of these studies have also subsequently reported that the overall effect of intervention on the incidence of diabetes persists for several years beyond the period of active intervention.[13–15] The present study addresses the extent that normal or impaired baseline FPG levels influenced the response to lifestyle intervention on type 2 diabetes incidence and its major complications in participants with IGT in the Da Qing Diabetes Prevention Study (DQDPS).

To determine if the efficacy of lifestyle intervention varied among subgroups of persons with IGT with normal or elevated FPG, we conducted a *post hoc* analysis of participants in the Da Qing Diabetes Prevention Outcome Study (DQDPOS). This study has shown that a six-year lifestyle intervention in people with IGT regardless of their baseline FPG levels delays the onset of type 2 diabetes, ultimately reduces the incidence of serious diabetes-related complications, and extends life expectancy.[16] For the current analysis participants were divided using the current American Diabetes Association criteria for IFG into those who had baseline FPG levels below 100 mg/dL and ≥100 mg/dL.[10] Findings in the intervention groups were compared with those of the controls with similar baseline FPG levels. We sought to determine if the efficacy of the intervention relating to onset of type 2 diabetes and its complications differed between these FPG sub-groups.

2 MATERIAL AND METHODS

Data from the DQDPOS and the DQDPS were used for this analysis. Details of the design, methods, study population, data collection and primary outcome results from the DQDPS and DQDPOS have been described previously.[1,13,16–19]

2.1 Data collection

Briefly, in 1986, a population-based sample of 110660 adults aged ≥25 years from 33 primary care clinics in Da Qing, China were screened for IGT and diabetes.[1,19] Following a 10–12 hour fast, venous blood was drawn and plasma glucose, using a glucose oxidase method, was determined in the fasting state and at 60 and 120 minutes following ingestion of a 75g oral glucose load. Of those screened, 576 persons with IGT by 1985 WHO criteria with 2-hour venous plasma glucose levels during a 75g OGTT of 140–199 mg/dL[20] participated in the trial. They were randomized by clinic into either a control group, who received standard medical care, or to one of three lifestyle interventions: diet, exercise, or diet plus exercise for 6 years (1986–92). Participants were examined and received 75g OGTTs at baseline, 2 years, 4 years, and 6 years after randomisation. At the end of DQDPS, six years after randomisation, participants were informed of the results of the trial and asked to continue to receive health care from their usual providers.[1]

In 2006 and 2016, 20 and 30 years after randomisation, participants were retraced and followed-up to determine the long-term effects of the intervention on type 2 diabetes

incidence, diabetes-related complications, and mortality.[13,16] Among living participants data were collected by personal interview, medical chart review, and clinical examination, which included an OGTT in those not already known to have developed diabetes. For deceased participants, data were obtained from proxy interviews, and confirmed from death certificates and medical chart reviews. Follow-up data were obtained for 540 (94%) of the original participants (Figure S1). For the current analysis, participants in the original intervention and control groups were stratified by their baseline FPG levels, <100 and ≥100 mg/dL.

2.2 Outcome events

Diabetes was defined by1985 WHO criteria from results of the OGTTs done every two years during the trial (1986–1992) and the 2006 and 2016 follow-up examinations, or from self-reported physician-diagnosed diabetes, and evidence of elevated glucose levels or use of glucose lowering medication in medical records. Diabetes-related complications were analyzed using the previously reported outcome definitions (see Table 4 for definitions).

2.3 Statistical analysis

The DQDPOS was designed as an observational follow-up study to determine if the reductions in the incidence of diabetes observed in the DQDPS resulted in longer-term changes in diabetes incidence, and diabetes-related complications and mortality. As there were no significant differences in the reductions of diabetes incidence among the three individual intervention groups during the trial, based on power calculations and as pre-specified in the DQDPOS protocol, the original intervention groups were combined to increase the possibility of detecting differences attributable to the reduction in diabetes incidence on outcomes relating to complications. For the current *post hoc* analysis participants were divided according to their baseline fasting plasma glucose levels at the time of randomisation. We also analyzed the data by original intervention groups as a sensitivity analysis to assess the uniformity of the results.

The incidence of diabetes and other outcomes was calculated as number of events divided by person-years of exposure censored at date of recognition of the event, loss to follow-up, death, or December 31, 2016, whichever came first. Cumulative incidence and survival curves were estimated by the Kaplan–Meier method. Differences in the percentage of diabetes-free years and complication-free years between the intervention and control groups were determined from the survival curves. Median delay in onset of diabetes in each group was estimated from the time that the cumulative incidence reached 50%. Hazard ratios were determined using Cox proportional-hazard analyses. Numbers needed to treat to prevent a case of diabetes or complication (NNT) were calculated from the corresponding Weibull distribution survival analyses and hazard ratios.[21] We also estimated hazard ratios for diabetes incidence stratified by sex, age, body mass index (BMI), systolic blood pressure and smoking status. Differences were considered statistically significant if P was <0.05 in two-sided tests. SAS version 9.4 (SAS/STAT 14.1 Institute, Cary, NC, USA) was used for statistical analysis.

3 RESULTS

3.1 Baseline characteristics of control and intervention groups with and without IFG

Population based screening in the Da Qing population in 1986 identified 576 people with IGT who were randomized into the control or lifestyle intervention groups. Half the participants (287/576 [49.8%]) had FPG levels <100 mg/dL. For the present analysis, participants were divided into those with baseline FPG levels of <100 (n= 287) and ≥100 mg/dL (n=289) (Flow chart, Supplemental Figure S1). Their baseline characteristics are shown in Table 1.

3.2 Incidence of diabetes

The Kaplan-Meir plots show the cumulative incidence of type 2 diabetes in the control and intervention groups (Figure 1). The curves for FPG <100 mg/dL groups are shifted to the right compared with those of the FPG ≥100 mg/dL groups (P= 0.0005). This reflects a significantly lower cumulative incidence and a longer delay until the development of diabetes in the FPG <100 mg/dL group. The incidence of type 2 diabetes, absolute risk reductions, hazard ratios (HRs) and NNTs to prevent diabetes in the two FPG groups and the proportion who remained diabetes-free at the end of the trial and during follow-up are compared in Table 2. Intervention in both FPG groups was associated significant delays in diabetes onset and significant reductions in the cumulative incidence of diabetes that persisted throughout follow-up. In the FPG <100 group, the lower incidence, the longer delay in diabetes onset after randomisation, and greater time interval between diabetes onset in the intervention and controls resulted in a greater proportion remaining diabetes-free throughout the follow-up than in the FPG ≥100 group. The difference in median time to diabetes onset between the intervention and controls was 6.4 years for the FPG <100 mg/dL group compared with 2.2 years in the FPG ≥100 mg/dL groups (Table 3).

Responses to intervention ten years after randomisation on the incidence of type 2 diabetes in the FPG groups stratified by sex, baseline age, BMI, systolic blood pressure and smoking status are summarised in Supplemental Figure S2. The effect of intervention for each of these characteristics was similar in both groups and the effect of intervention was at least as great in those with BMI <25kg/m^2 as in participants who were overweight or had obesity, regardless of their baseline fasting glucose levels.

3.3 Incidence of diabetes-related complications

The effect of lifestyle intervention in reducing major long-term complications of type 2 diabetes among DQDPOS participants has been published previously.[16] The 30-year incidence of major diabetes complications in the two FPG groups are shown in Table 4 and Supplemental Figure S3. The cumulative incidence, absolute risk reduction and hazard rate ratios for CVD events and all-cause mortality were lower, significantly so in the FPG <100, whereas in the FPG ≥100 group these reductions were not statistically significant. In contrast, for microvascular disease there was a significant reduction incidence, absolute risk, and hazard ratio in the FPG ≥100 group, but not in the <100 group in which the incidence of microvascular disease was much lower. Outcome data for diabetes and complications in

the FPG<100 and FPG>100 groups in the three original trial interventions are shown in Supplemental Tables 1 and 2.

4 DISCUSSION

Randomized clinical trials (RCTs) have shown that lifestyle interventions are effective in postponing onset and reducing the incidence of type 2 diabetes in people with IGT. Most of the early trials were designed to establish proof-of-principle.[1–4] They were conducted in people with IGT, who were known to carry a high risk for type 2 diabetes,[22] and some had additional entry criteria, such as overweight or obesity, or elevated fasting plasma glucose levels, designed to further augment risk and minimize the follow-up time needed to determine if the interventions were successful. Only after these trials established the efficacy of lifestyle intervention to reduce type 2 diabetes incidence did questions arise about generalization of the findings to other groups without IGT but with increased risk of diabetes, such as people with isolated impaired fasting glucose (i-IFG) or elevated HbA1c.[5,7] The D-CLIP trial of lifestyle intervention for three years in 550 overweight and obese Asian Indian adults with IFG or IGT, reported reductions in the cumulative incidence of diabetes of 36% in those with IFG+IGT and 31% in those with isolated IGT, but a much lower and insignificant reduction of 12% in those with iIFG.[6] In Japan, the Zensharen study,[5] a three year trial of lifestyle intervention among 641 overweight adults with IFG (FPG 100–125mg/dL) reported a 59% reduction in diabetes incidence in the 262 participants who had IFG+IGT, but no reduction in the 379 with iIFG. Of 183 subjects with IFG+HbA1c>6.0%, regardless of the presence of IGT, a 76% (52–88%) reduction in diabetes incidence was seen, whereas there was no reduction in those with IFG and HbA1c levels of <6.0%. These studies suggest that among the many people with IFG only those who also have elevated HbA1c levels or IGT may benefit from lifestyle intervention.

To date no RCTs have demonstrated that lifestyle intervention alone reduces type 2 diabetes incidence in people with i-IFG or elevated HbA1c in the absence of IGT[23], yet these groups constitute the majority of people currently defined as having ‘prediabetes’ or ‘intermediate hyperglycaemia’.[24,25] The American Diabetes Association currently recommends FPG 100–125mg/dL, HbA1c 5.7–6.4% or 2-h PG 140–199mg/dL during 75g OGTT as criteria to identify people with prediabetes who should receive lifestyle interventions.[10] In practice, however, the 2-h glucose criterion is seldom used for screening as it necessitates the conduct of a 75g OGTT, thus resulting in failure to recognize the presence of IGT and serious underestimation of the frequency of prediabetes.[26]

Half the adult population with IGT in the Da Qing study had baseline FPG levels of <100 mg/dL, a generally similar proportion as seen in the United States and other populations.[24–26] As expected, the incidence rates and cumulative incidence of type 2 diabetes were significantly higher in those with the higher FPG levels. During follow-up the risk reductions due to intervention ranged between 37 and 46% (HRs 0.54–0.63) in the lower FPG group and 47 to 51% (HRs 0.49–0.53) in the FPG ≥100 group. Intervention, however, delayed diabetes onset for much longer in the FPG<100 group. The median delay in onset of diabetes after randomisation attributable to intervention was 2.21 years in the FPG ≥100 group compared with 6.41 years in the FPG<100 group, thereby increasing the

number of diabetes-free years experienced in the lower FPG group. For example, ten years after randomisation 56% of the FPG <100 compared with 36% of the FPG ≥100 group remained free of diabetes indicating that lifestyle intervention was a highly effective means of delaying diabetes onset, and thereby subsequently reducing the duration of diabetes experienced by participants with the lower baseline FPG levels.

We have previously reported that lifestyle intervention led to significant reductions in the incidence of serious diabetes-related complications in the DQDPOS.[16] Nevertheless, the effect of lifestyle intervention on diabetes related complications is controversial.[27] The present analysis, however, suggests that the effect of intervention on the incidence of these complications differs to some extent in those with lower and higher FPG levels. Thirty years after randomisation, intervention in the FPG <100 group was associated with reduction in CVD events, CVD deaths and all-cause mortality to a greater degree than in the FPG >100 group. For microvascular disease, the incidence in the FPG <100 group was lower, and a significant reduction attributable to intervention was seen only in the FPG >100 group in which the incidence of microvascular disease was much higher. As microvascular disease is strongly related to hyperglycaemia and diabetes duration, the lower incidence of microvascular disease in the FPG<100 group is likely attributable to their much shorter exposure to diabetes. These findings, however, suggest that the long-term benefit of intervention may be even greater in those with IGT and normal FPG levels, and strengthens the argument that people with IGT should be candidates for lifestyle interventions regardless of their FPG level.

Given the natural history of the development of type 2 diabetes indicating that IGT usually develops before fasting glucose levels become elevated,[28] it is likely that participants with the lower FPG levels were identified and received intervention at an earlier stage in the development of the disease than those who had already developed IFG, and that the more prolonged delay in onset may be primarily the result of earlier intervention. Reports of apparent beneficial effects on disease incidence from early screening and intervention without contemporaneous controls may be attributable to ‘lead-time bias’, an issue that has confounded discussion of the value of diabetes screening for decades. In this study, however, the delay in onset and the reduction in diabetes incidence cannot be attributed to this as they resulted from a controlled randomized trial and provide solid evidence of the advantage of early detection and intervention in those with isolated IGT. Our findings, if they can be replicated, have important implications for screening for type 2 diabetes and prediabetes.

As the OGTT is not widely used to screen for those at high risk of developing type 2 diabetes, people with IGT with FPG levels of <100mg/dL or HbA1c <5.7% are unlikely to be identified as being eligible for targeted lifestyle intervention programs. Among an estimated total of 37.6% of the adult US population with prediabetes, as defined by American Diabetes Association criteria, 4.5% with FPG <100 mg/dL and HbA1c <5.7% have isolated IGT.[24] Furthermore, if only FPG>100mg/dL is used as the sole criterion to screen for prediabetes, some 41.8% of those who have IGT will not be identified as having prediabetes. Thus, many of those who may benefit from lifestyle intervention will not be identified unless OGTTs are used more widely. In the future, use of a 1-h OGTT, as an alternative way to identify people with IGT (or diabetes) may provide a more convenient

and acceptable way to identify the people with isolated IGT who could benefit from early intervention.[29,30]

'Prediabetes' or 'intermediate hyperglycemia' are terms indicative of an increased risk of diabetes presently defined as the presence of IFG, abnormal HbA1c levels, and historically by IGT. Nevertheless, there is a considerable lack of overlap among people who meet one or more of these definitions and it is likely that the pathophysiology leading to these abnormalities differs.[9,31–33] IGT is characterized mainly by peripheral insulin resistance and compensatory hyperinsulinemia, whereas IFG is mainly indicative of hepatic insulin resistance and increased hepatic glucose output.[32,34,35] Either of these abnormalities may be present in the early stages of development of type 2 diabetes, although both are often present by the time of its onset. To date no clinical trials have demonstrated that lifestyle intervention is effective in preventing diabetes in people with i-IFG or elevated HbA1c in the absence of IGT.[7] Only in people with IGT has lifestyle intervention been clearly demonstrated to delay onset and reduce the incidence of type 2 diabetes. Lifestyle interventions appear to reduce peripheral insulin resistance, an effect that is often attributed to weight loss.[35] In this study, however, and in the Indian diabetes prevention study[4] lifestyle intervention also reduced the incidence of diabetes in people with BMI <25 kg/m^2 to a similar extent as in those who were overweight or had obesity.

Strengths and limitations of the DQDPS and DQDPOS have been reviewed in detail elsewhere.[16] For this analysis the strengths are: 1) Those with IGT were identified and recruited by screening a 50% sample of the adult 1986 Da Qing population so that they constituted a representative sample of those with IGT. 2) IGT was identified by the 2-hour venous plasma glucose results from a 75g OGTT. 3) Baseline fasting glucose levels were not considered as either inclusion or exclusion criteria unless they met the 1985 WHO criteria for diabetes. 4) BMI was not considered as a selection criterion. 5) During the trial diabetes was diagnosed from OGTTs conducted at two-yearly intervals on the participants not already known to have developed diabetes. 6) After the trial, participants were traced and followed for many years after randomisation which enabled recognition of the different patterns of diabetes onset, and determination of the long-term effects of intervention on diabetes incidence. 7) Diabetes incidence was a primary event for the outcome study and was determined as systematically and as accurately as possible. 8) The lifestyle interventions employed were safe and free of any serious side-effects. 9) Loss to follow-up was minimal and incidence data were collected on 94% of the original trial participants. There are also some limitations: 1) As with any exploratory post hoc analyses the findings may be biased so that replication of the findings will be important. 2) Participants were randomised in a 1:3 ratio to control and intervention groups so that the sample sizes especially in the control groups are small. 3) The results may not be generalised to all populations as the goals, nature, intensity, and duration of lifestyle interventions used for type 2 diabetes prevention are variable. 4) Identification of people with isolated IGT requires measurement of the 2-h plasma glucose level during an OGTT which is time consuming and less convenient to measure than FPG or HbA1c levels. 5) Participants were identified based on 1985 WHO criteria which resulted in the inclusion of 35 participants with FPG 126–139 mg/dl who would have had diabetes by current criteria. 6) The study findings cannot be generalised to persons with only iIFG, or prediabetic HbA1c levels.

The present analysis illustrates that the effectiveness of an intervention cannot be judged solely based on risk reduction determined at the end of a trial especially if its effect may persist considerably longer. For example, both the DPP and the DPS reported a 58% reduction in the incidence of diabetes at the end of the active intervention period,[2,3] yet the incidence of diabetes and absolute risk reductions in the two studies were different leading to differences in estimates of the numbers needed to treat to achieve benefit. The effect of the intervention may also differ in subgroups of the target population as illustrated in the present study in which the onset of diabetes was delayed for much longer in those in the IGT population with normal fasting plasma glucose levels, a difference that could only be determined by long-term follow-up.

While it is well established that lifestyle interventions reduce the incidence of type 2 diabetes in people with IGT, this study has shown this to be true both in people with IGT with and without IFG, thereby providing a strong rationale for the early detection and implementation of lifestyle intervention in those with IGT with normal fasting glucose as well as in those with IFG. Many more people with IGT who have FPG levels of <100mg/dL may benefit from lifestyle intervention if screening for IGT were widely implemented.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Pan XR, Li GW, Hu YH, 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. 1997;20(4):537–544. [PubMed: 9096977]
2. 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. 2001;344(18):1343–1350. [PubMed: 11333990]
3. 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. 2002;346(6):393–403. [PubMed: 11832527]
4. Ramachandran A, Snehalatha C, Mary S, et al.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. 2006;49(2):289–297. [PubMed: 16391903]

5. Saito T, Watanabe M, Nishida J, et al.Lifestyle modification and prevention of type 2 diabetes in overweight Japanese with impaired fasting glucose levels: a randomized controlled trial. Arch Intern Med. 2011;171(15):1352–1360. [PubMed: 21824948]
6. Weber MB, Ranjani H, Staimez LR, et al.The Stepwise Approach to Diabetes Prevention: Results From the D-CLIP Randomized Controlled Trial. Diabetes Care. 2016;39(10):1760–1767. [PubMed: 27504014]
7. Kosaka K, Noda M, Kuzuya T. Prevention of type 2 diabetes by lifestyle intervention: a Japanese trial in IGT males. Diabetes Res Clin Pract. 2005;67(2):152–162. [PubMed: 15649575]
8. Fang M, Echouffo-Tcheugui J, Selvin E. Clinical and Public Health Implications of 2019 Endocrine Society Guidelines for Diagnosis of Diabetes in Older Adults. Diabetes Care. 2020.
9. Campbell MD, Sathish T, Zimmet PZ, et al.Benefit of lifestyle-based T2DM prevention is influenced by prediabetes phenotype. Nat Rev Endocrinol. 2020.
10. American Diabetes A. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2021. Diabetes Care. 2021;44(Suppl 1):S15–S33. [PubMed: 33298413]
11. World Health O, International Diabetes F. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia : report of a WHO/IDF consultation. In. Geneva: World Health Organization; 2006.
12. Lindstrom J, Peltonen M, Eriksson JG, et al.Determinants for the effectiveness of lifestyle intervention in the Finnish Diabetes Prevention Study. Diabetes Care. 2008;31(5):857–862. [PubMed: 18252900]
13. 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. 2008;371(9626):1783–1789. [PubMed: 18502303]
14. Diabetes Prevention Program Research G, Knowler WC, Fowler SE, et al.10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet. 2009;374(9702):1677–1686. [PubMed: 19878986]
15. 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. 2006;368(9548):1673–1679. [PubMed: 17098085]
16. Gong Q, Zhang P, Wang J, et al.Morbidity and mortality after lifestyle intervention for people with impaired glucose tolerance: 30-year results of the Da Qing Diabetes Prevention Outcome Study. Lancet Diabetes Endocrinol. 2019;7(6):452–461. [PubMed: 31036503]
17. Gong Q, Gregg EW, Wang J, et al.Long-term effects of a randomised trial of a 6-year lifestyle intervention in impaired glucose tolerance on diabetes-related microvascular complications: the China Da Qing Diabetes Prevention Outcome Study. Diabetologia. 2011;54(2):300–307. [PubMed: 21046360]
18. Li G, Zhang P, Wang J, et al.Cardiovascular mortality, all-cause mortality, and diabetes incidence after lifestyle intervention for people with impaired glucose tolerance in the Da Qing Diabetes Prevention Study: a 23-year follow-up study. Lancet Diabetes Endocrinol. 2014;2(6):474–480. [PubMed: 24731674]
19. Pan XR, Hu YH, Li GW, Liu PA, Bennett PH, Howard BV. Impaired glucose tolerance and its relationship to ECG-indicated coronary heart disease and risk factors among Chinese. Da Qing IGT and diabetes study. Diabetes Care. 1993;16(1):150–156. [PubMed: 8422770]
20. WHO Study Group. Diabetes Mellitus. Report of a WHO Study Group. Technical Report Series No. 727.Geneva: World Health Organization; 1985.
21. Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. BMJ. 1999;319(7223):1492–1495. [PubMed: 10582940]
22. Edelstein SL, Knowler WC, Bain RP, et al.Predictors of progression from impaired glucose tolerance to NIDDM: an analysis of six prospective studies. Diabetes. 1997;46(4):701–710. [PubMed: 9075814]
23. Richter B, Hemmingsen B, Metzendorf MI, Takwoingi Y. Development of type 2 diabetes mellitus in people with intermediate hyperglycaemia. Cochrane Database Syst Rev. 2018;10:CD012661.
24. James C, Bullard KM, Rolka DB, et al.Implications of alternative definitions of prediabetes for prevalence in U.S. adults. Diabetes Care. 2011;34(2):387–391. [PubMed: 21270196]

25. Schmidt MI, Bracco PA, Yudkin JS, et al.Intermediate hyperglycaemia to predict progression to type 2 diabetes (ELSA-Brasil): an occupational cohort study in Brazil. Lancet Diabetes Endocrinol. 2019;7(4):267–277. [PubMed: 30803929]

26. Meijnikman AS, De Block CEM, Dirinck E, et al.Not performing an OGTT results in significant underdiagnosis of (pre)diabetes in a high risk adult Caucasian population. Int J Obes (Lond). 2017;41(11):1615–1620. [PubMed: 28720876]

27. Nathan DM, Bennett PH, Crandall JP, et al.Does diabetes prevention translate into reduced long-term vascular complications of diabetes?Diabetologia. 2019;62(8):1319–1328. [PubMed: 31270584]

28. Saad MF, Knowler WC, Pettitt DJ, Nelson RG, Mott DM, Bennett PH. Sequential changes in serum insulin concentration during development of non-insulin-dependent diabetes. Lancet. 1989;1(8651):1356–1359. [PubMed: 2567374]

29. Bergman M, Manco M, Sesti G, et al.Petition to replace current OGTT criteria for diagnosing prediabetes with the 1-hour post-load plasma glucose>/=155mg/dl (8.6mmol/L). Diabetes Res Clin Pract. 2018;146:18–33. [PubMed: 30273707]

30. Paddock E, Hohenadel MG, Piaggi P, et al.One-hour and two-hour postload plasma glucose concentrations are comparable predictors of type 2 diabetes mellitus in Southwestern Native Americans. Diabetologia. 2017;60(9):1704–1711. [PubMed: 28664298]

31. Zimmet P, Alberti KG, Magliano DJ, Bennett PH. Diabetes mellitus statistics on prevalence and mortality: facts and fallacies. Nat Rev Endocrinol. 2016;12(10):616–622. [PubMed: 27388988]

32. Li Y, Feng D, Esangbedo IC, et al.Insulin resistance, beta-cell function, adipokine profiles and cardiometabolic risk factors among Chinese youth with isolated impaired fasting glucose versus impaired glucose tolerance: the BCAMS study. BMJ Open Diabetes Res Care. 2020;8(í).

33. Lee CMY, Colagiuri S, Woodward M, et al.Comparing different definitions of prediabetes with subsequent risk of diabetes: an individual participant data meta-analysis involving 76 513 individuals and 8208 cases of incident diabetes. BMJ Open Diabetes Res Care. 2019;7(1):e000794.

34. Lillioja S, Mott DM, Spraul M, et al.Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent diabetes mellitus. Prospective studies of Pima Indians. N Engl J Med. 1993;329(27):1988–1992. [PubMed: 8247074]

35. Nathan DM, Davidson MB, DeFronzo RA, et al.Impaired fasting glucose and impaired glucose tolerance: implications for care. Diabetes Care. 2007;30(3):753–759. [PubMed: 17327355]

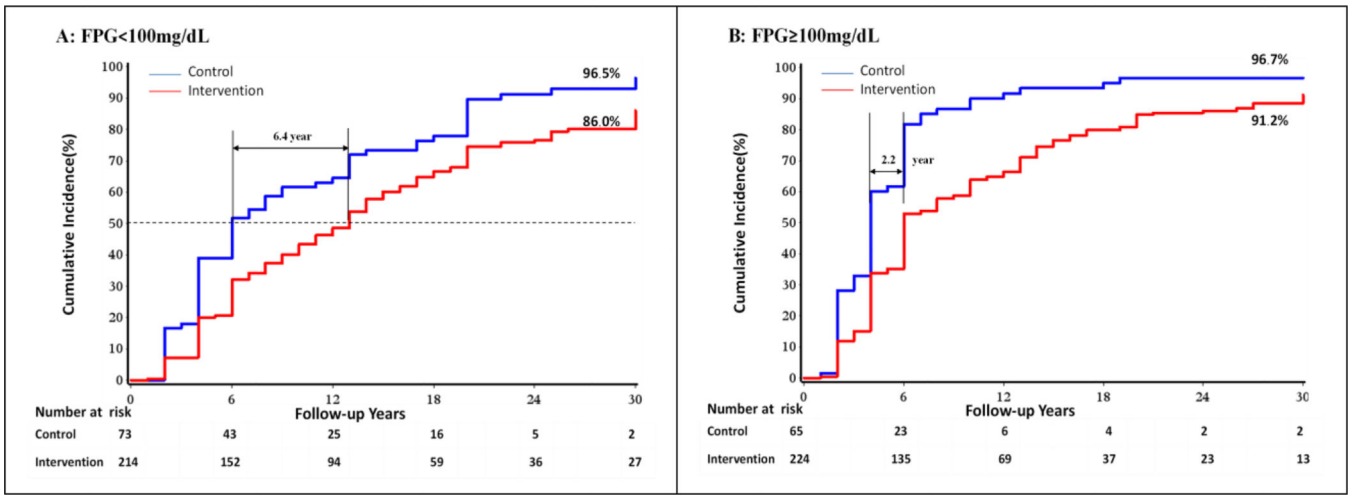

Figure 1. Kaplan-Meier plots of cumulative incidence of diabetes in control and intervention groups with FPG of <100 (Panel A), and ≥100 mg/dL (Panel B).

Abbreviations: FPG, fasting plasma glucose.

Median delay is the time from randomisation to the point at which the cumulative incidence of diabetes reaches 50%.

The difference in median delay between the control and intervention arms for the FPG <100mg/dL group was 6.4 years, and 2.2 years for the FPG ≥100mg/dL group.

Table 1.

Baseline characteristics of intervention groups and corresponding control groups with FPG levels of <100 mg/dL and ≥100 mg/dL.

	Baseline FPG <100 mg/dL			Baseline FPG ≥100 mg/dL		
	Control N=73	**Intervention N=214**	**P**	**Control N=65**	**Intervention N=224**	**P**
Age (years)	47.2 (1.1)	44.6 (0.7)	0.052	46.0 (1.1)	44.8 (0.6)	0.35
Men (n, %)	45 (61.6)	110 (51.4)	0.13	34.(52.3)	123 (54.9)	0.71
Smoking (n, %)	38 (52.1)	83 (38.8)	0.047	31.(47.7)	86 (38.4)	0.18
Plasma glucose (mg/dL)						
Fasting	88.3 (0.89)	88.8 (0.49)	0.60	111.7 (1.26)	112.3(0.67)	0.66
2-hour post load	160.7 (1.8)	157.5 (1.0)	0.12	164.4 (2.03)	165.4 (1.07)	0.65
BMI (kg/m^2)	25.6 (0.5)	25.0 (0.3)	0.25	26.7 (0.4)	26.2 (0.3)	0.36
Blood pressure (mmHg)						
Systolic	132.1 (3.4)	131.1 (1.7)	0.77	134.8 (2.7)	132.7 (1.6)	0.51
Diastolic	86.7 (2.0)	86.3 (1.0)	0.86	89.1 (1.6)	87.6 (0.9)	0.42
Total cholesterol (mmol/L)	5.2 (0.1)	5.0 (0.1)	0.20	5.1 (0.2)	5.1 (0.1)	0.89

Abbreviations: FPG, fasting plasma glucose; BMI, body mass index.

Note: values are (mean ± SE) or (n, %)

Table 2.

Diabetes incidence, Absolute risk reduction, Hazard ratios and Numbers needed to treat in control and intervention groups with baseline FPG levels of <100 or ≥100 mg/dL.

Time after randomisation		Baseline FPG <100 mg/dL		Baseline FPG ≥100 mg/dL	
		Control N= 73	Intervention N= 214	Control N= 65	Intervention N= 224
6 years	No. of cases/person-years	37/351	64/1100	51/262	113/1086
	Cases/100 person-years (95% CI)	10.54 (7.14–13.94)	5.82 (4.39–7.24)	19.47 (14.12–24.81)	10.41 (8.49–12.32)
	Cumulative incidence (%) (95% CI)	51.7 (39.4–62.6)	32.1 (25.7–38.6)	81.7 (69.2–89.5)	52.9 (45.9–59.4)
	Diabetes-free (%) (95% CI)	48.3 (37.4–60.6)	67.9 (61.4–74.3)	18.3 (10.5–30.8)	47.1 (40.6–54.1)
	Absolute risk reduction	19.6%		9.1%	
	HR (95% CI)	0.54 (0.36–0.81) P =0.003		0.50 (0.36–0.69) P <0.0001	
	Adj. HR (95% CI)	0.54 (0.36–0.82) P =0.004		0.50 (0.36–0.70) P <0.0001	
	NNT (95% CI)	5 (3–18)		4 (3–7)	
10 years	No. of cases/person-years	44/473	85/1576	56/298	135/1439
	Cases/100 person-years (95% CI)	9.30 (6.55–12.05)	5.39 (4.25–6.54)	18.79 (13.87–23.71)	9.38 (7.80–10.96)
	Cumulative incidence (%) (95% CI)	61.6 (49.1–71.9)	43.4 (36.3–50.3)	90.0 (78.5–95.5)	63.9 (56.9–70.1)
	Diabetes-free (%) (95% CI)	38.4 (28.1–50.9)	56.6 (49.7–63.7)	10.0 (4.5–21.5)	36.1 (29.9–43.1)
	Absolute risk reduction	18.2%		26.1%	
	HR (95% CI)	0.58 (0.40–0.83) P = 0.003		0.49 (0.36–0.67) P < 0.0001	
	Adj. HR (95% CI)	0.61 (0.42–0.88) P = 0.009		0.49 (0.36–0.67) P < 0.0001	
	NNT (95% CI)	5 (3–17)		4 (3–7)	
20 years	No. of cases/person-years	63/667	138/2309	60/340	175/1944
	Cases/100 person-years (95% CI)	9.45 (7.11–11.78)	5.98 (4.98–6.97)	17.65 (13.18–22.11)	9.00 (7.67–10.34)
	Cumulative incidence (%) (95% CI)	89.7 (79.2–95.0)	74.5 (67.3–80.4)	96.7 (84.9–99.3)	84.9 (78.9–89.3)
	Diabetes-free (%) (95% CI)	10.3 (5.0–21.8)	25.5 (19.6–32.7)	3.3 (0.7–15.1)	15.1 (10.7–21.1)
	Absolute risk reduction	15.2%		11.8%	
	HR (95% CI)	0.63 (0.47–0.85) P = 0.003		0.51 (0.38–0.69) P < 0.0001	
	Adj. HR (95% CI)	0.69 (0.51–0.94) P = 0.02		0.52 (0.38–0.70) P < 0.0001	
	NNT (95% CI)	7 (4–19)		7 (5–12)	
30 years	No. of cases/person-years	66/712	154/2632	60/360	183/2133
	Cases/100 person-years (95% CI)	9.27 (7.03–11.51)	5.85 (4.93–6.78)	16.67 (12.45–20.88)	8.58 (7.34–9.82)
	Cumulative incidence (%) 95% CI)	96.5 (72.0–99.6)	86.0 (79.3–90.6)	96.7 (84.9–99.3)	91.2 (85.2–94.8)
	Diabetes-free (%) (95% CI)	3.5 (0.4–28.0)	14.0 (9.4–20.7)	3.3 (0.7–15.1)	8.8 (5.2–14.8)
	Absolute risk reduction	10.5%		5.5%	
	HR (95% CI)	0.63 (0.47–0.84) P = 0.002		0.53 (0.40–0.72) P <0.0001	
	Adj. HR (95% CI)	0.68 (0.51–0.92) P = 0.01		0.54 (0.40–0.72) P <0.0001	
	NNT (95% CI)	9 (6–28)		10 (6–21)	

Abbreviations: FPG, fasting plasma glucose; CI, confidence interval; HR, hazard ratio; *Adj.HR, hazard ratio

adjusted for age, BMI and smoking; NNT, number needed to treat.

Table 3.

Median time from randomisation to cumulative incidence of diabetes reaching 50%.

Baseline FPG <100 mg/dL			Baseline FPG ≥100 mg/dL		
Control N=73	Intervention N=214		Control N=65	Intervention N=224	
Median years (95%CI)	Median years (95%CI)	Difference (years)	Median years (95%CI)	Median years (95%CI)	Difference (years)
5.87 (3.96–9.00)	12.28 (9.99–13.99)	6.41 P <0.01	3.63 (3.06–4.00)	5.84 (5.56–7.75)	2.21 P <0.01

Abbreviations: FPG, fasting plasma glucose; CI, confidence interval.

Table 4.

Thirty-year Cumulative incidence of Major long-term outcomes, Hazard ratios and Numbers needed to treat in control and intervention groups with baseline FPG levels of <100 or ≥100 mg/dL.

Time after randomisation		Baseline FPG <100 mg/dL		Baseline FPG ≥100 mg/dL	
		Control N= 73	Intervention N= 214	Control N= 65	Intervention N= 224
CVD Events †	No. of cases/person-years	43/1433	89/4326	37/1281	106/4447
	Cases/100 person-years (95% CI)	3.0 (2.1–3.9)	2.06 (1.63–2.48)	2.89 (1.96–3.82)	2.38 (1.93–2.84)
	Cumulative Incidence (%) (95% CI)	67.6 (39.4–62.6)	49.7 (25.7–38.6)	65.1 (50.7–76.3)	56.0 (48.4–62.9)
	CVD events-free (%) (95% CI)	32.4 (37.4–40.6)	50.3 (61.4–74.3)	34.9 (23.7–49.3)	44.0 (37.1–51.6)
	Absolute risk reduction	17.9%		9.1%	
	HR (95% CI)	0.67 (0.47–0.97) P =0.03		0.80 (0.55–1.17) P =0.25	
	*Adj. HR (95% CI)	0.85 (0.59–1.24) P =0.40		0.82 (0.57–1.20) P =0.31	
	NNT (95% CI)	7 (4–118)		12 (−16–5)	
Micro-vascular Disease ‡	No. of cases/person-years	9/1581	31/4826	24/1393	45/4945
	Cases/100 person-years (95% CI)	0.57 (0.20–0.94)	0.64 (0.42–0.87)	1.72 (1.03–2.41)	0.91 (0.64–1.18)
	Cumulative Incidence (%) (95% CI)	19.8 (9.5–32.8)	21.0 (14.7–28.0)	48.1 (33.0–61.7)	29.0 (21.9–36.9)
	Microvascular disease free (%) (95% CI)	80.2 (67.2–90.5)	79.0 (72.0–85.3)	51.9 (38.3–67.0)	71.0 (63.1–78.1)
	Absolute risk reduction	−1.2%		19.1%	
	HR (95% CI)	1.05 (0.50–2.21) P = 0.89		0.49 (0.30–0.80) P =0.005	
	*Adj. HR (95% CI)	1.08 (0.50–2.30) P = 0.85		0.51 (0.31–0.84) P = 0.008	
	NNT (95% CI)	∞		5 (3–19)	
CVD Death §	No. of cases/person-years	23/1626	46/5028	17/1553	43/5212
	Cases/100 person-years (95% CI)	1.41 (0.84–1.99)	9.15 (0.65–1.18)	1.09 (0.57–1.62)	0.83 (0.58–1.07)
	Cumulative Incidence (%) (95% CI)	38.4 (25.9–50.8)	27.3 (20.8–34.3)	31.9 (19.6–44.8)	24.1 (18.0–30.7)
	CVD death-free (%) (95% CI)	61.6 (49.2–74.1)	72.7 (65.7–79.2)	68.1 (55.2–80.4)	75.9 (69.3–82.0)
	Absolute risk reduction	11.1%		7.8%	
	HR (95% CI)	0.62 (0.38–1.02) P = 0.06		0.75 (0.43–1.31) P =0.31	
	*Adj. HR (95% CI)	0.84 (0.50–1.39) P = 0.49		0.79 (0.45–1.39) P =0.41	
	NNT (95% CI)	8 (−70–4)		15 (−14–5)	
All Cause Death	No. of cases/person-years	40/1626	87/5028	36/1553	98/5212
	Cases/100 person-years (95% CI)	2.46 (1.70–3.22)	1.73 (1.37–2.09)	2.32 (1.56–3.08)	1.88 (1.51–2.25)
	Cumulative Incidence (%) (95% CI)	55.5 (43.2–66.2)	44.4 (37.4–51.3)	57.1 (43.8–68.4)	46.4 (39.5–53.0)
	Survivors (%) (95% CI)	45.5 (33.8–56.8)	55.6 (48.7–62.8)	42.9 (31.6–56.2)	53.6 (47.0–40.5)
	Absolute risk reduction	10.1%		10.7%	

Time after randomisation		Baseline FPG <100 mg/dL		Baseline FPG ≥100 mg/dL	
		Control N= 73	Intervention N= 214	Control N= 65	Intervention N= 224
	HR (95% CI)	0.68 (0.47–0.99) P = 0.04		0.81 (0.55–1.18) P =0.27	
	*Adj. HR (95% CI)	0.94 (0.65–1.38) P = 0.77		0.86 (0.59–1.26) P=0.86	
	NNT (95% CI)	7 (4–75)		13 (−16–5)	

Abbreviations: HR: Hazard Ratio; CI, confidence interval; Adj.HR, hazard ratio adjusted for age, BMI, and smoking; NNT, number needed to treat;

†CVD events defined at the first occurrence of non-fatal or fatal myocardial infarction, non-fatal or fatal stroke or sudden death, or heart failure;

‡Microvascular disease defined as the first recognition of retinopathy, nephropathy, or neuropathy;

§CVD deaths are fatal CVD events.