Do lifestyle interventions reduce diabetes incidence in people with isolated impaired fasting glucose?

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Gong Q et al.¹ have conducted a post hoc analysis to examine the effects of a lifestyle intervention among 576 adults with impaired glucose tolerance (IGT) in the Da Qing Diabetes Prevention Outcome Study. They divided the participants into those with impaired fasting glucose (IFG) (n=287) and those without IFG (n=289) at baseline. IFG was defined as fasting plasma glucose (FPG) ≥100 mg/dL. The intervention objectives were to increase participants’ vegetable intake, lower alcohol and sugar intake, lose weight in overweight or obese individuals by reducing total calorie intake, and increase leisure-time physical activity. The intervention reduced diabetes incidence significantly in both groups (IGT only and IGT + IFG) at the end of the 6-year intervention and throughout the 30 years of follow-up (hazard ratios [HR]: 0.49-0.63). This study's findings add to the existing literature that lifestyle interventions are effective in reducing diabetes incidence in people with IGT, regardless of the presence of IFG. However, the available evidence suggests that such interventions are not effective in those with IFG in the absence of IGT (i.e., isolated IFG).

Isolated IFG is defined as FPG 100-125 mg/dL by the American Diabetes Association and as FPG 110-125 mg/dL by the World Health Organization among those without IGT.² A recent meta-analysis of 24 studies showed that isolated IFG constitutes a substantial proportion of the glucose-defined prediabetes population (44-58% of Caucasians and 29-48% of Asians, depending on the criteria).³ The proportional prevalence of isolated IFG (ADA criteria) is much larger in certain other ethnic groups; 84% in Asian Indians, for example.⁴ Most importantly, in addition to being at high risk for developing type 2 diabetes,⁵ people with isolated IFG are also at increased risk for cardiovascular disease and all-cause mortality.⁶ Thus, it is crucial to examine the effectiveness of lifestyle interventions in those with isolated IFG.

In addition to the Da Qing study, other randomized controlled trials (RCTs) have shown that lifestyle interventions (e.g., at least 5-7% weight loss, ≥150 min of moderately intense physical activity a week, <30% of daily calorie intake from fat) can significantly reduce the incidence of type 2 diabetes in people with IGT with or without IFG.² However, it should be noted that there was heterogeneity in the components included in the intervention...
programs of these trials. Yet, the efficacy of such interventions has not been demonstrated in people with isolated IFG.\textsuperscript{2} In the Zensharen Study for Prevention of Lifestyle Diseases, an RCT conducted among 641 overweight Japanese adults with IFG, lifestyle intervention significantly reduced diabetes incidence at three years (HR: 0.56, 95% CI 0.36-0.87 vs. usual care group).\textsuperscript{7} Among these participants, the intervention was effective in the IFG + IGT group (n=262, HR: 0.41, 95% CI 0.24-0.69), but not in those with isolated IFG (n=379, HR: 1.17, 95% CI 0.50-2.74). Similarly, in the Diabetes Community Lifestyle Improvement Program (D-CLIP) from India, lifestyle intervention followed by metformin (for those who were at high-risk after four months) significantly reduced diabetes incidence in the IFG + IGT group (n=222, HR: 0.64, 95% CI 0.43-0.97) at three years, but not in people with isolated IFG (n=166, HR: 0.88, 95% CI 0.43-1.20).\textsuperscript{8} In the recent Norfolk Diabetes Prevention Study (NDPS), which was conducted at 135 general practices in England, in those with IFG (n=631), the odds ratio for diabetes incidence in the lifestyle intervention group versus usual care was 0.53 (95% CI 0.29-0.95) at two years.\textsuperscript{9} In NDPS, the IFG group almost certainly included some people with IGT, and it may well be that the reduction in diabetes incidence was driven primarily by the beneficial effect seen in those with IGT.

IGT and IFG are two distinct prediabetes phenotypes. While $\beta$-cell function is impaired in both, IGT is characterized by severe muscle insulin resistance, whereas marked hepatic insulin resistance is seen in IFG.\textsuperscript{10} Consequently, 2-hr plasma glucose on an oral glucose tolerance test (OGTT) is increased in IGT, while FPG is elevated in IFG, although both below the diabetes thresholds.\textsuperscript{11} Due to these differences in underlying abnormalities, IGT and IFG may respond differently to the same set of lifestyle interventions.

The evidence base for national diabetes prevention programs in countries such as the UK\textsuperscript{12} and USA\textsuperscript{13} comes primarily from lifestyle intervention trials conducted in people with IGT.\textsuperscript{2} However, these programs mainly use HbA1c and FPG to recruit high-risk individuals, as performing a 2-h OGTT is cumbersome. Of note, it has been consistently shown in different populations that the overlap of people with elevated HbA1c, IFG, and IGT (who can be identified only with an OGTT) is poor.\textsuperscript{14,15} Thus, using FPG alone would
fail to identify a substantial proportion of people with IGT and might result in significant numbers of people enrolling in intensive lifestyle-change programs with little chance of benefit. The use of a 1-h OGTT is likely to be more convenient and acceptable to identify people with IGT.\textsuperscript{16} Further, artificial intelligence using non-invasive imaging techniques may be a promising approach in the future to distinguish prediabetes phenotypes, given that such a strategy has been shown to predict a person's HbA1c from a retinal image alone.\textsuperscript{17} Whatever screening approaches are used, it is critical to ensure that people enrolled in lifestyle-based diabetes prevention programs are aligned with the phenotypes tested in the RCTs.

To conclude, based on the currently available evidence, it is important to recognize that lifestyle interventions may not be effective in reducing diabetes incidence in those with IFG in the absence of IGT.\textsuperscript{2,10} However, it should be noted that such evidence is based on sub-group analyses of RCTs with limited power. Thus, an individual participant meta-analysis of data from lifestyle intervention trials that included people with isolated IFG or adequately powered RCTs among people with isolated IFG is urgently needed.

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References

15. Greiner GG, Emmert-Fees KMF, Becker J, et al. Toward targeted prevention: risk factors for prediabetes defined by impaired fasting glucose, impaired glucose tolerance and
increased HbA1c in the population-based KORA study from Germany. *Acta Diabetol*. 2020;57:1481-1491.


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