



Changes in Mortality in People With IGT Before and After the Onset of Diabetes During the 23-Year Follow-up of the Da Qing Diabetes Prevention Study

Diabetes Care 2016;39:1550–1555 | DOI: 10.2337/dc16-0429

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OBJECTIVE

People with impaired glucose tolerance (IGT) have increased risk of mortality and a high risk of progression to diabetes, but the extent that the excess mortality is associated with IGT per se or is the result of subsequent diabetes is unclear.

RESEARCH DESIGN AND METHODS

We compared mortality before and after the development of diabetes among 542 persons with IGT initially who participated in a 6-year lifestyle diabetes prevention trial and were followed-up from 1986 to 2009.

RESULTS

During the 23-year follow-up, 174 (32.1%) died, with an overall death rate of 15.9/1,000 person-years. The majority of deaths (74.7%; 130 of 174) occurred after progression to type 2 diabetes, with age-adjusted death rates of 11.1/1,000 person-years (95% CI 8.2–12.0) before and 19.4/1,000 person-years (95% CI 11.9–23.3) after the development of type 2 diabetes. The cumulative mortality was 37.8% (95% CI 33.1–42.2%) in participants who developed type 2 diabetes during first 10 years of follow-up, 28.6% (95% CI 21.6–35.0%) in those who progressed to type 2 diabetes in 10–20 years, and 13.9% (95% CI 7.0–20.3%) in those who did not develop to type 2 diabetes within 20 years. Time-dependent multivariate Cox proportional hazards analyses, with adjustment for baseline age, sex, intervention, and other potential confounding risk factors, showed that the development of type 2 diabetes was associated with a 73% higher risk of death (hazard ratio 1.73 [95% CI 1.18–2.52]).

CONCLUSIONS

As elsewhere, IGT is associated with increased risk of mortality in China, but much of this excess risk is attributable to the development of type 2 diabetes.

In 2010–2011, an estimated 92–113 million adults in China had diabetes, and approximately 100 million others had impaired glucose tolerance (IGT), placing them at high risk of developing the disease (1,2). While excess risk for death among people with diabetes is well-documented in Western populations and in some Asian populations (3–9), IGT also predicts excess mortality (10–18). Most studies of mortality in people with IGT have had relatively short-term follow-up and lack follow-up evaluations to

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Received 26 February 2016 and accepted 27 May 2016.

This article contains Supplementary Data online at <http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc16-0429/-/DC1>.

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determine whether they subsequently developed diabetes. The extent that the excess mortality is attributable to IGT itself or is attributable to diabetes, which develops in many with IGT, is controversial (14,16,17).

Qiao et al. (16) examined this question in a Finnish population and concluded that IGT is an independent risk predictor for all-cause mortality and that the excess risk in people with IGT cannot be explained by the subsequent development of overt diabetes. However, two other studies, also with follow-up to identify incident diabetes, concluded that the excess mortality in those with impaired fasting glucose (IFG) and IGT occurs primarily among those who developed type 2 diabetes, and that the risk increases with increasing duration of type 2 diabetes (14,17). Understanding the extent to which IGT itself or the subsequent development of type 2 diabetes influences excess mortality has important implications for the design, conduct, and utility of diabetes prevention programs.

This study is an epidemiological analysis of the 23-year follow-up study of participants with IGT from the Da Qing Diabetes Prevention Study to examine the extent to which IGT alone and the subsequent development of diabetes influence mortality.

RESEARCH DESIGN AND METHODS

Study Design and Participants

The details of the design of the Da Qing Diabetes Prevention Study and related follow-up studies have been reported previously (19–22). Briefly, in 1986, based on results of oral glucose tolerance tests (OGTTs) classified by 1985 World Health Organization (WHO) criteria, 576 adults (312 men and 264 women) with IGT were randomized by clinic to either a control group or one of three lifestyle intervention groups (diet, exercise, diet plus exercise). Participants were examined at baseline and at 2 years, 4 years, and 6 years after randomization. We subsequently conducted follow-up studies in 2006 and 2009, 20 and 23 years after randomization, respectively, to determine the incidence of diabetes, diabetes-related complications, mortality, and causes of death. Follow-up data were obtained for 542 (94%) of the original participants. Mortality in an age- and sex-matched cohort of 519 people (282 men and 237 women) who participated in the diabetes and IGT screening

but had normal glucose tolerance (NGT), defined as 2-h plasma glucose <6.7 mmol, were used for comparison.

Institutional review boards at WHO and the China-Japan Friendship Hospital approved the studies. Surviving participants and proxies for deceased participants gave written informed consent for the follow-up studies.

The follow-up period was from the date of randomization (1986) until the date of death, 31 December 2009 for those still alive, or the last date of contact for those lost to follow-up. Diabetes and IGT were defined by 1985 WHO criteria from results of the OGTT done every 2 years during the active intervention period (1986–1992) and at the 20-year and 23-year follow-up examinations, or by self-report of physician-diagnosed diabetes with evidence of elevated glucose concentrations in the medical record, or taking hypoglycemic medications, as described previously (3,19–21). The time to the development of diabetes was defined as the time from randomization to the date of diagnosis of diabetes or, for those who never developed diabetes, the date of death, date lost to follow-up or 31 December 2009. For those who progressed to diabetes, time after diagnosis of diabetes was defined as the interval from the date of diagnosis of diabetes to the date of death, date lost to follow-up, or 31 December 2009, whichever came first. Deaths were determined from death certificates, proxy interviews, and medical records.

Statistical Analysis

Data are presented as means (\pm SD) or counts (percentages). Descriptive statistics were compared between groups of participants who developed diabetes within 10 years, 10–20 years, and more than 20 years or who never developed diabetes over the 23-year follow-up period. ANOVA tests were used for normally distributed continuous variables. χ^2 tests were used for categorical variables. Death rates were calculated as the number of deaths divided by the number of person-years. Because participants had wide variations in age, time to diagnosis, age at diagnosis, and duration of diabetes, our age-adjusted death rates were calculated by the direct method using the updated age distribution of the total IGT population as the standard population. The cumulative incidence of death was computed by product-limit estimate

using the method described by Kalbfleisch and Prentice (23). To investigate the effects of IGT and of diabetes and its duration on mortality, the cohort was then divided into two subcohorts by time to onset of diabetes. In the cohort before the onset of diabetes, the time to diabetes was treated as censoring, whereas the time of onset of diabetes and corresponding age were treated as entry time and age for the cohort after the onset of diabetes. We calculated age-specific and age-adjusted all-cause death rates using updated, time-dependent analyses. In models exploring the effect of the onset of diabetes on death, a time-dependent covariate representing the status of having diabetes was used to estimate the hazard ratio associated with diabetes using an extended Cox model (24,25). The baseline covariates such as age, sex, and baseline clinical characteristics (blood pressure, smoking, cholesterol, BMI), and history of cardiovascular disease (i.e., myocardial infarction and stroke) were also included in the model. Differences were considered statistically significant if two-sided *P* values were ≤ 0.05 . Statistical analyses were conducted with SAS version 9.4 (SAS Institute, Inc., Cary, NC) (26).

RESULTS

The vital status, dates of death, and dates of onset of diabetes were determined among 542 (94.1%) of the original IGT study participants. Table 1 shows the baseline characteristics of these participants according to the time taken to develop diabetes. Participants who developed type 2 diabetes within the first 10 years of follow-up were older, had higher BMI, plasma glucose concentrations, and systolic blood pressures than those who developed it later. During 23 years of follow-up, a majority of the participants (428 of 542; 79.0%) developed type 2 diabetes, and 174 died, with an overall death rate of 15.9 per 1,000 person-years. This rate was 70% higher than that of a comparison group of similar age and sex with NGT (9.3 per 1,000 person-years) (3) (Supplementary Table 1).

Most of the deaths (130 of 174; 74.7%) in the cohort occurred after the development of diabetes. Those who developed type 2 diabetes during first 10 years of follow-up had the highest cumulative mortality (37.8%; 95% CI 33.1–42.2), followed by those who developed it after

Table 1—Baseline characteristics of participants who progressed to diabetes within 10 years, 10–20 years, and more than 20 years or never developed diabetes over the 23-year follow-up

	Time to progression to diabetes (years)			P value
	0–10 (n = 319)	10–20 (n = 118)	>20 or never (n = 105)	
Age (years)	45.9 ± 9.0	46.1 ± 9.5	41.9 ± 8.3	0.0003
Female sex, n (%)	140 (43.9)	55 (46.6)	48 (45.7)	0.88
BMI (kg/m ²)	26.5 ± 3.6	25.7 ± 3.9	24.3 ± 3.6	<0.0001
FPG (mmol/L)	5.7 ± 0.8	5.5 ± 0.8	5.3 ± 0.7	<0.0001
PG2h (mmol/L)	9.1 ± 0.9	8.9 ± 0.9	8.7 ± 0.7	<0.0001
Blood pressure				
Systolic (mmHg)	136.4 ± 24.3	130.4 ± 22.5	125.6 ± 19.4	0.0001
Diastolic (mmHg)	89.0 ± 14.2	87.0 ± 12.0	84.3 ± 12.1	0.012
Cholesterol (mmol/L)	5.0 ± 1.3	4.9 ± 1.2	4.6 ± 1.3	0.09
Smoking, n (%)	127 (39.8)	53 (44.9)	40 (38.1)	0.56
Previous CVD, n (%)	5 (1.6)	1 (0.9)	0 (0)	0.39
Death, n (%)	125 (39.2)	37 (31.4)	12 (11.4)	

Data are mean ± SD unless otherwise indicated. CVD, cardiovascular disease; FPG, fasting plasma glucose; PG2h, venous plasma glucose concentration 2 h after 75-g oral glucose load.

10–20 years (28.6%; 95% CI 21.6–35.0) and those who never developed diabetes or developed it after 20 or more years of follow-up (13.9%; 95% CI 7.0–20.3). The hazard ratios (HR) were significantly higher for those who developed diabetes in the first 10 years (HR 3.87 [95% CI 2.13–7.02]) and between 10 and 20 years (HR 2.50 [95% CI 1.30–4.81]) compared with those who did not develop diabetes or developed it later, after adjusting for age, sex, and intervention (Fig. 1).

Because the age and sex distributions of participants had wide variations in age at diagnosis of diabetes, we calculated age-adjusted death rates before and after the development of diabetes. The adjusted rates were twice as high after the development of diabetes, with rates of 11.1 per 1,000 person-years (95% CI 8.2–12.0) before and 19.4 per 1,000 person-years (95% CI 11.9–23.3) after the onset of diabetes (Table 2). Before the onset of diabetes the age-adjusted rates were only slightly higher than those in the NGT group (9.3 per 1,000 person-years; *P* = 0.32) (Supplementary Table 1). Death rates were higher after the development of diabetes than before among both women and men (Supplementary Tables 2 and 3). Cause-specific death rates before and after diabetes onset are shown in Supplementary Table 4.

Multivariate extended Cox model analysis was used to confirm the effect of the development of diabetes on mortality to assess the effects of other risk factors

and to control for the effect of the randomization to lifestyle intervention. After adjustment for age, sex, the intervention, and other potential risk factors (systolic blood pressure, smoking, cholesterol, and history of cardiovascular disease), diabetes was associated with 73% (HR 1.73 [95% CI 1.18–2.52]) increased risk of death (Table 3). This

indicates that much of the excess long-term mortality occurring in people with IGT is attributable to the development of type 2 diabetes, rather than other risk factors that are often present in those with IGT.

CONCLUSIONS

Many studies have reported excess mortality among people with IGT, but few have examined whether this is the result of the high rate of progression to diabetes, and diabetes-related mortality, or is a consequence of IGT itself. Although many studies have shown that IGT predicts increased mortality, most studies have failed to account for the possible effects of developing diabetes, thus leaving open the question of whether IGT itself is a determining risk factor for premature death or whether the excess mortality is mainly a consequence of the development of diabetes (14,16,17).

Distinguishing between these possibilities is crucial to the design and conduct of diabetes prevention programs, and ultimately their importance. If the excess mortality associated with IGT occurs mainly after the development of diabetes, then delaying or preventing the development of diabetes may be expected to lower mortality risk. Conversely, if the

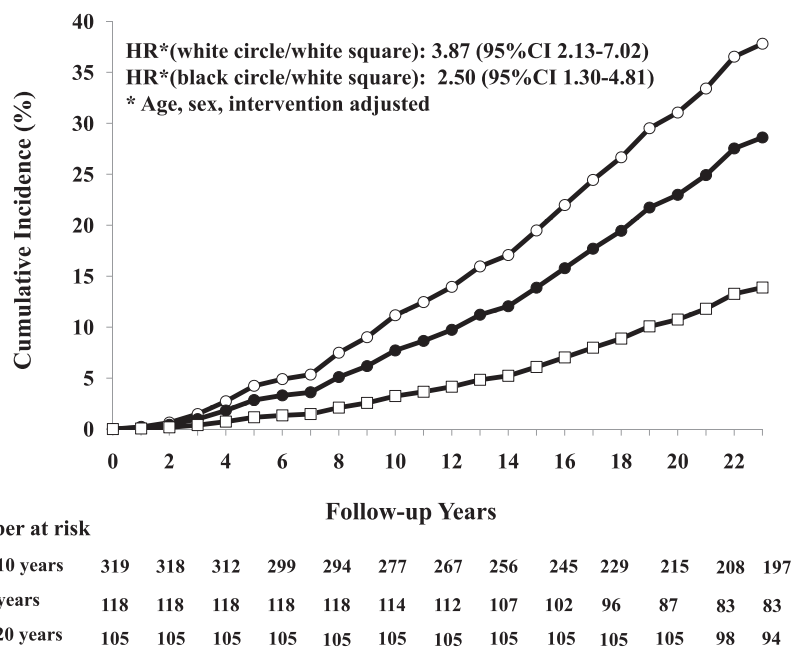


Figure 1—Age-, sex-, and intervention-adjusted cumulative incidence of death according to time to development of diabetes. The white circles represent those who developed diabetes during the first 10 years of follow-up; the black circles, those who developed diabetes between 10 and 20 years of follow-up; and the white squares, those who never developed diabetes or developed diabetes after 20 or more years of follow-up.

Table 2—Death rates (per 1,000 person-years) before and after the onset of diabetes*

	Age-group								
	25–59		60–69		≥70		All ages		Age-standardized rate†
	n/person-years	Rate	n/person-years	Rate	n/person-years	Rate	n/person-years	Rate	
Time before onset of diabetes (years)									
0–5	8/2,048	3.9	7/198	35.4	1/25	40.0	16/2,271	7.0	14.8
5–10	7/1,005	7.0	3/227	13.2	1/30	33.3	11/1,262	8.7	10.7
10–15	0/571	0.0	0/219	0.0	4/67	59.7	4/857	4.7	4.9
≥15	1/403	2.5	3/260	11.5	9/135	66.7	13/798	16.3	10.1
Total	16/4,027	4.0	13/904	14.4	15/257	58.4	44/5,188	8.5	11.1
Diabetes duration (years)									
0–5	8/1,435	5.6	18/441	40.8	9/125	72.0	35/2,001	17.5	19.9
5–10	12/985	12.2	12/546	22.0	12/140	85.7	36/1,671	21.5	20.7
10–15	7/578	12.1	11/490	22.5	14/181	77.3	32/1,249	25.6	20.1
≥15	4/269	14.9	11/369	29.8	12/204	58.8	27/842	32.1	22.3
Total	31/3,267	9.5	52/1,846	28.2	47/650	72.3	130/5,763	22.6	19.4

*Time-dependent updated age and duration groups. †Age-standardized to distribution of person-years in the total IGT group.

excess mortality is primarily associated with IGT (or IFG) and is not related to progression to type 2 diabetes, then delaying or preventing type 2 diabetes may have little or no effect in reducing excess mortality.

This is to our knowledge the first study to examine the relationship between IGT and risk for death over a prolonged follow-up period in China. During the 23-year follow-up period, 32% of IGT participants died, with cumulative mortality intermediate between those Da Qing residents with newly diagnosed type 2 diabetes (56%) and NGT (21%) (3).

Among those with IGT, the age-adjusted death rates were almost twice as high after diabetes developed as before (19.4 vs. 11.1 per 1,000 person-years). After adjustment for age, sex, and other potential risk factors, diabetes was associated with a 73% increased risk of death,

indicating that much of the excess long-term mortality associated with IGT is attributable to effects related to the development of type 2 diabetes, rather than other risk factors that are present in IGT. After adjustment for increasing age, death rates did not change significantly with increasing time to the development of type 2 diabetes and were not significantly higher than that in similarly aged persons with NGT. These findings suggest that in people with IGT, as long as the development of type 2 diabetes can be prevented or delayed, mortality can be markedly reduced. These findings provide an explanation for mortality results in the lifestyle arm of the Da Qing IGT intervention trial, which delayed the onset of type 2 diabetes and resulted in significantly reduced mortality (21). The International Diabetes Federation estimates that 415 million adults aged 20 to 79 years worldwide had diabetes in 2015. By 2040, the total

number of people with diabetes is estimated to reach 642 million (27). Widely implementing lifestyle intervention among high-risk individuals could reduce the number of people developing diabetes and the associated death. Findings from two earlier studies of mortality in people with IGT and IFG that incorporated information on the development of type 2 diabetes similarly showed no increase in mortality until people transitioned to diabetes (14,17). Our results support and strengthen these findings and indicate that, even over protracted time periods, people with IGT who do not progress to diabetes have a much lower risk of death than those of a similar age with IGT who do develop type 2 diabetes.

Strengths and Limitations

Our study has some notable strengths, which have been described previously (3,20). 1) IGT status was determined by OGTT using uniform diagnostic procedures. 2) A total of 94% of participants were followed for up to 23 years, thereby allowing sufficient time for many to develop diabetes and for a sufficient number of deaths to provide sufficient power for this analysis. 3) Few participants were lost to follow-up, and therefore nonresponse bias is minimal.

The study also has some important limitations. 1) Beyond the 6-year intervention period of the clinical trial, glucose tolerance tests were not performed systematically at defined intervals, so the date of onset of diabetes depends mainly on clinical diagnoses, thereby limiting the accuracy of the estimates of time to development and the duration of type 2 diabetes. Delays in

Table 3—Impact of the development of diabetes on mortality

Variable (n = 542)	Hazard Ratio	95% CI	P value
Mortality (174 deaths)			
Age (years)	1.09	1.07–1.11	<0.0001
Sex (male = 1)	1.46	0.99–2.13	0.05
SBP (mmHg)	1.007	1.001–1.013	0.04
Smoking (yes = 1)	1.45	1.05–2.02	0.03
BMI (kg/m ²)	0.97	0.93–1.01	0.15
Cholesterol (mmol/L)*	1.20	0.52–2.74	0.67
Previous CVD	1.19	0.48–2.98	0.71
Intervention (yes = 1)	0.94	0.67–1.31	0.70
Diabetes status (yes = 1)†	1.73	1.18–2.52	0.01

CVD, cardiovascular disease; SBP, systolic blood pressure. *Log-transformed value. †Diabetes status as time-dependent variable.

diagnosing type 2 diabetes may have led to some overestimation of the effect of IGT and underestimation of the effect of type 2 diabetes on mortality. The lack of repeated systematic glucose measurements on participants during the follow-up after the trial also prevented any attempt to identify a specific glycaemic threshold for increased mortality. 2) We do not have updated information on risk factors, other than age and the development of type 2 diabetes, which may have influenced death rates over the course of follow-up. 3) We do not know how long participants may have had IGT when identified at the beginning of the study, so time to the development of type 2 diabetes is not synonymous with the duration of IGT, thereby limiting inferences about the possible relationship of mortality to the duration of IGT. Nevertheless, there was wide variation in the observed duration of IGT, but no evidence of differences in death rates other than those explained by increasing age and the development of diabetes. 4) The majority of participants in the IGT group received lifestyle intervention during the first 6 years of the study, which reduced the overall mortality to some extent. After adjustment for diabetes in the multivariate model, the intervention term was no longer a significant determinant, thereby indicating that the development of diabetes was the primary determinant of the increased mortality.

We conclude that most of the excess mortality associated with IGT is a consequence of the development of diabetes and that preventing progression to diabetes in people with IGT will lead to lower mortality. These findings have important implications for type 2 diabetes prevention because they provide further evidence that delaying the development of diabetes, even without a need for reversion to NGT, is likely to reduce mortality and increase longevity among people with IGT.

Conclusion

This study is to our knowledge the first long-term, population-based cohort study of mortality related to IGT in China. IGT was associated with increased risk of death, but much of the increase was the result of the subsequent development of type 2 diabetes in many of those with IGT. The results provide a strong rationale for

type 2 diabetes prevention in people with IGT because they indicate that the risk of death in people with IGT is much lower before than after the development of type 2 diabetes.

Acknowledgments. The authors thank the study participants in the original Da Qing IGT and Diabetes Study, the Da Qing Diabetes Prevention Study, and the Da Qing Diabetes Prevention Follow-up Study. The authors especially thank the late Professor Xiaoren Pan, as this study would not have been possible without his leadership in the design and implementation of the original Da Qing Diabetes Prevention Study. **Funding.** This study was supported by the National Center for Chronic Disease Prevention and Health Promotion through CDC/WHO Cooperative Agreement No. U58/CCU424123-01-02 and by the China-Japan Friendship Hospital.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. Q.G. designed the study, collected data, performed the statistical analysis, and wrote the manuscript. P.Z. coordinated and designed the study, acquired funding, performed the statistical analysis, and wrote the manuscript. J.W. and Y.A. designed the study, collected data, and performed the statistical analysis. E.W.G. and M.M.E. designed the study, acquired funding, and wrote the manuscript. H.L., B.Z., Y.S., Y.C., and S.L. collected data. W.Y. designed the study. Y.H. designed the study and collected data. P.H.B. designed the study, performed the statistical analysis, and wrote the manuscript. G.L. coordinated and designed the study, acquired funding, collected data, performed the statistical analysis, and wrote the manuscript. G.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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