Progression to Impaired Glucose Regulation and Diabetes in the Population-Based Inter99 Study

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OBJECTIVE — The purpose of this study was to estimate the progression rates to impaired glucose regulation (impaired fasting glucose or impaired glucose tolerance) and diabetes in the Danish population–based Inter99 study and in a high-risk subpopulation, separately.

RESEARCH DESIGN AND METHODS — From a population-based primary prevention study, the Inter99 study, 4,615 individuals without diabetes at baseline and with relevant follow-up data were divided into a low- and a high-risk group based on a risk estimate of ischemic heart disease or the presence of risk factors (smoking, hypertension, hypercholesterolemia, obesity, or impaired glucose tolerance). High-risk individuals (57.1%) were examined with an oral glucose tolerance test at 1 and 3 years, and all of the participants were reexamined at the 5-year follow-up. Person-years at risk were calculated. Progression rates to impaired glucose regulation and diabetes were estimated directly from baseline to the 5-year follow-up for all the participants and from baseline through the 1- and 3- to 5-year follow-up examinations for the high-risk individuals, separately.

RESULTS — In the combined low- and high-risk group, 2.1 individuals per 100 person-years progressed from normal glucose tolerance (NGT) to impaired glucose regulation or diabetes. Among high-risk individuals, 5.8 per 100 person-years with NGT progressed to impaired glucose regulation or diabetes, and 4.9 per 100 person-years progressed from impaired glucose regulation to diabetes.

CONCLUSIONS — Progression rates to impaired glucose regulation using the current World Health Organization classification criteria were calculated for the first time in a large European population-based study. The progression rates to diabetes show the same pattern as seen in the few similar European studies.

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Estimates of the future burden of diabetes in different populations require accurate progression rates from population-based studies. New incidence studies are needed because of the increasing prevalence of diabetes, the change in risk factors over time, and the introduction of new diagnostic criteria. Previous incidence studies on Caucasians of European origin have used older definitions of diabetes (1–4), have ascertained new cases by registries (5) or primary care records (6), or have only used fasting plasma glucose (FPG) for the diagnosis of diabetes (7,8).

Few population-based studies, using the current World Health Organization (WHO) classification criteria (9), have calculated progression rates from normal glucose tolerance (NGT) or impaired glucose regulation (impaired fasting glucose [IFG] and impaired glucose tolerance [IGT]) to diabetes in Caucasians of European origin (10–14). None of the European studies have calculated progression rates to impaired glucose regulation (10,11,13), and none of these studies are from the Nordic countries. Because of the heterogeneity of type 2 diabetes and its recognized polygenic basis and dependence on environmental factors, there is a need for population-based, ethnically focused, and country/continent-specific studies of type 2 diabetes incidence (7).

Impaired glucose regulation refers to a metabolic state between normal glucose homeostasis and diabetes (9). Although individuals with isolated IFG (i-IFG) are characterized by hepatic insulin resistance, individuals with isolated IGT (i-IGT) are predominantly characterized by muscle insulin resistance (15). i-IFG and i-IGT are parallel states that may progress to the combined state IFG-IGT or to diabetes. Prospective studies have shown higher progression rates from IFG-IGT to diabetes compared with the progression from i-IFG or i-IGT to diabetes (5,10,16). Therefore, in this study we present the progression rates to and from the isolated states of impaired glucose regulation (i-IFG or i-IGT) as well as the combined state (IFG-IGT). Furthermore, we hypothesize that individuals with IFG-IGT will progress to diabetes at a higher rate than individuals with i-IFG or i-IGT.

The aim of this study was to estimate the progression rates to impaired glucose regulation and diabetes in the Danish population–based Inter99 study and in a high-risk subpopulation, separately. In addition, our aim was to study the associations between progression rates from i-IFG, i-IGT, or IFG-IGT to diabetes.

RESEARCH DESIGN AND METHODS

— The Inter99 study is a population-based primary prevention study on cardiovascular disease and type 2 diabetes. The study population comprised all 61,301 individuals born in 1939–1940, 1944–1945, 1949–1950,

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1954–1955, 1959–1960, 1964–1965, and 1969–1970 living in 11 municipalities in the southwestern part of Copenhagen County, Denmark, on 2 December 1998. From the study population, an age- and sex-stratified random sample comprising 13,016 individuals was drawn. The sample was a priori randomized into two groups comprising 90% (group A: high-intensity intervention) and 10% (group B: low-intensity intervention) (17).

All 13,016 individuals in groups A and B were invited to a health screening program and a personal risk assessment of their absolute 10-year risk of developing ischemic heart disease (IHD) by the Copenhagen Risk Score (17). High-risk individuals were defined as individuals with an absolute risk of IHD in the upper quintile of their age and sex strata or with one or more of the following risk factors: daily smoker, systolic blood pressure ≥160 mmHg/antihypertensive therapy, total cholesterol ≥7.5 mmol/l, BMI ≥30 kg/m^2, history of diabetes, or diabetes or IGT diagnosed at baseline. Based on the personal risk estimate, each individual was offered lifestyle counseling dealing with smoking, physical activity, diet, and alcohol. High-risk individuals in group A were further offered lifestyle counseling in groups on smoking cessation or physical activity/diet with six meetings during a 4- to 6-month period, whereas high-risk individuals in group B were referred to their family physician. Baseline data were collected from March 1999 until January 2001. The Inter99 study and baseline results are described in detail elsewhere (17,18).

All high-risk individuals were reinvited at 1 and 3 years for a health examination including a new risk assessment and lifestyle counseling. If still at high risk at the reexamination, individuals in group A were again offered lifestyle counseling in groups, and individuals in group B were again referred to their family physician. All participants at baseline were reinvited at 5 years for a final health examination.

Study procedure

At each examination, the participants filled in a questionnaire on health and lifestyle in advance. In the questionnaire, nationality was divided into Danish and Other.

Height was measured without shoes to the nearest 0.5 cm, weight was measured without shoes and overcoat to the nearest 0.1 kg, and BMI was calculated as weight in kilograms divided by the square of height in meters. Waist circumference was measured to the nearest centimeter midway between the lower rib margin and the iliac crest (17,18).

After a minimum 8 h of fasting overnight, all participants without known diabetes underwent a standard oral glucose tolerance test (OGTT) (75 g anhydrous glucose in 250 ml water) at each examination. Plasma glucose was measured in the fasting state and after 120 min. Blood samples for glucose measurements were taken in heparin-sodium fluoride tubes, immediately put on ice and centrifuged, and plasma was separated within 30 min. Plasma glucose was analyzed using the hexokinase/glucose-6-phosphate dehydrogenase method (Boehringer Mannheim) (17,18).

All participants gave written informed consent before taking part in the study. The study was approved by the local ethics committee (KA 98 155) (17).

Methods and definitions

Of the 13,016 individuals invited at baseline, 82 were noneligible because they had died or could not be traced. Of the remaining 12,934 individuals, 6,906 participated in the investigation. Of these, 122 individuals were excluded because of alcoholism, drug abuse, or linguistic barriers, leaving 6,784 (52.5%) for analysis at baseline (17,18). In general, the participation rate was higher in younger women than in younger men, and it increased with increasing age until 55 years of age, after which it declined. The participation rate was identical in group A (high-intensity intervention) and group B (low-intensity intervention) (17).

Glucose tolerance status was classified according to the 1999 WHO criteria by a single OGTT (9), and IGT was divided into i-IGT and IFG-IGT. At baseline, 374 (5.5%) were nonclassifiable because of lack of either FPG or 2-h plasma glucose measurements, and 404 (6.0%) had either self-reported diabetes or diabetes diagnosed by the OGTT (18), leaving 6,006 individuals without diabetes. The high-risk group comprised 57.1% (3,429 of 6,006) at baseline.

At the 5-year follow-up, 1,975 individuals were lost to follow-up or were nonclassifiable, leaving 4,031 individuals with relevant data for the progression rates directly from baseline to 5 years. At the 1-, 3-, and 5-year follow-up examinations, 836 individuals were lost to follow-up or were nonclassifiable, resulting in 2,593 high-risk individuals with relevant data for the calculation of the progression rates in the high-risk group, separately. These analyses include all individuals with relevant follow-up data for the direct progression rates from baseline to 5 years and high-risk individuals with relevant follow-up data from 1, 3, or 5 years (n = 4,615).

To calculate the crude progression rates in this study, the Inter99 study was analyzed as if it were a cohort study. Participants in the low-risk group were only examined at baseline and at the 5-year follow-up. Hence, when we calculated the overall progression rates in the Inter99 study for both the high-risk and the low-risk groups combined, only information from baseline and the 5-year follow-up was used. Incident cases were defined as individuals with newly detected i-IFG, i-IGT, IFG-IGT, or diabetes/self-reported diabetes at the 5-year examination.

Progression rates for the high-risk group were calculated separately, and all information on glucose tolerance status from the 1-, 3-, and 5-year follow-up examinations was used. Incident cases were defined as individuals with newly detected i-IFG, i-IGT, IFG-IGT, or diabetes/self-reported diabetes at the 1-, 3-, or 5-year examinations. Diabetes is considered an absorbing state. Thus, individuals with known diabetes were not offered an OGTT at subsequent examinations. Individuals without diabetes may change glucose tolerance status between the examinations. Hence, an individual may progress to different states of glucose intolerance at different time points and thereby be included in more than one of the subanalyses. In this study we did not look at regression in glucose tolerance status during follow-up.

Statistical analysis

Statistical analyses were performed using SAS (version 9.1; SAS Institute, Cary, NC). Exact 95% CIs were calculated for proportions. Proportions were compared between groups using χ^2 tests. The Wilcoxon signed-rank test was used to compare means of continuous variables.

Progression rates were estimated by dividing the number of outcomes by person-years at risk using interval-censoring (19). Years at risk were calculated as the time difference between date of entry and date of exit. Date of entry was the date of the baseline examination. For individuals progressing to a relevant outcome, the date of exit was set at the midpoint be-

Table 1—*Clinical characteristics of the participants with relevant follow-up data according to glucose tolerance status at baseline*

	NGT	i-IFG	i-IGT	IFG-IGT	Total
n (% of total)	3,599 ± 78.0	414 ± 9.0	433 ± 9.4	169 ± 3.7	4,615
Men (%)	48.0 (46.4–49.7)	74.4 (69.9–78.5)*	42.7 (38.0–47.5)†	69.8 (62.3–76.6)*	50.7 (49.3–52.2)
Danish nationality (%)	96.1 (95.5–96.8)	97.8 (95.9–99.0)	91.8 (88.7–94.2)‡	97.0 (93.2–99.0)	95.9 (95.3–96.5)
Age (years)	45.7 ± 7.7	49.3 ± 6.9*	48.1 ± 7.8*	50.0 ± 6.8*	46.4 ± 7.7
BMI (kg/m²)	25.5 ± 4.0	27.7 ± 4.5*	27.7 ± 5.2*	29.2 ± 4.9*	26.0 ± 4.3
Waist circumference (cm)	84.3 ± 12.1	93.6 ± 11.7*	89.4 ± 14.2*	96.2 ± 11.9*	86.1 ± 12.7
High-risk group (%)	48.1 (46.5–49.7)	62.8 (57.9–67.5)*	100 (99.2–100)*	100 (97.8–100)*	56.2 (54.7–57.6)
Absolute risk of IHD in upper quintile of age and sex strata (%)	12.3 (11.3–13.5)	15.2 (11.9–19.0)	17.3 (13.9–21.2)†	19.5 (13.8–26.3)†	13.3 (12.4–14.3)

Data are proportions (95% CI) or means ± SD, unless otherwise indicated. *$P < 0.0001$ compared with NGT. †$P < 0.05$ compared with NGT. ‡$P = 0.0001$ compared with NGT.

tween the baseline examination and the first examination, where the outcome was identified. This was to account for the fact that progressors will have converted at an unknown time somewhere between their date of entry and exit. For nonprogressors, the date of exit was set at the date of their last recorded OGTT. Rate ratios were estimated as the ratio between two progression rates.

RESULTS — Table 1 shows the clinical characteristics of the study participants according to glucose tolerance status at baseline. A total of 13.3% had an absolute risk of IHD in the upper quintile of their age and sex strata, and 56.2% were defined as being at high risk.

Of 6,006 individuals without diabetes at baseline, 4,615 (76.8%) were followed up. More men (50.7 vs. 44.4%, $P < 0.0001$), older individuals (46.4 vs. 43.9 years, $P < 0.0001$), more individuals with Danish nationality (95.9 vs. 3.2%, $P < 0.0001$), less individuals at high risk (56.2 vs. 60.1%, $P = 0.01$), and less individuals with an absolute risk of IHD in the upper quintile of their age and sex strata (13.3 vs. 1.1%, $P < 0.0001$) were examined at follow-up compared with individuals lost to follow-up. Individuals with follow-up information had higher waist circumference (86.1 vs. 85.4 cm, $P = 0.048$) than individuals lost to follow-up.

The progression rates from NGT and/or impaired glucose regulation to more advanced stages of impaired glucose regulation and/or diabetes are presented for all study participants (Table 2) and for the high-risk group, separately (Table 3).

As shown in Table 2, individuals with NGT progressed to impaired glucose regulation at a rate of 1.9% per year, and 0.3% per year progressed to diabetes. Of all individuals with impaired glucose regulation, 4.0% per year progressed to diabetes. The progression rates from i-IFG, i-IGT, and IFG-IGT to diabetes were 8.3, 12.7, and 31.0 times higher, respectively, than the progression rate from NGT to diabetes.

In the high-risk group (Table 3), individuals with NGT progressed to impaired glucose regulation at a rate of 5.5% per year, and 0.4% per year progressed to diabetes. The progression rate from i-IFG to IFG-IGT (4.0% per year) was one-third higher than the rate from i-IGT to IFG-IGT (2.7% per year), whereas the rate from i-IFG to diabetes was similar to the rate from i-IGT to diabetes (3.7% per year). More than 10% per year progressed from IFG-IGT to diabetes.

Table 2—*Progression rates to impaired glucose regulation and diabetes directly from baseline to 5-year follow-up in the combined low- and high-risk group*

Glucose tolerance status at baseline	*n**	Glucose tolerance status at 5-year follow-up	Outcomes (*n*)	Person-years	Rate per 100 person-years (95% CI)
NGT	3,187	i-IFG	83	16,918	0.5 (0.4–0.6)
		i-IGT	192	16,621	1.2 (1.0–1.3)
		IFG-IGT	28	17,063	0.2 (0.1–0.2)
		i-IFG, i-IGT, or IFG-IGT	303	16,328	1.9 (1.7–2.1)
		Diabetes	44	17,019	0.3 (0.2–0.3)
		i-IFG, i-IGT, IFG-IGT, or diabetes	347	16,210	2.1 (1.9–2.4)
i-IFG	359	IFG-IGT	23	1,864	1.2 (0.8–1.9)
		Diabetes	45	1,804	2.5 (1.9–3.3)
		IFG-IGT or diabetes	68	1,743	3.9 (3.1–4.9)
i-IGT	354	IFG-IGT	13	1,866	0.7 (0.4–1.2)
		Diabetes	66	1,722	3.8 (3.0–4.9)
		IFG-IGT or diabetes	79	1,688	4.7 (3.8–5.8)
IFG-IGT	131	Diabetes	52	560	9.3 (7.1–12.2)
i-IFG, i-IGT, or IFG-IGT	844	Diabetes	163	4,087	4.0 (3.4–4.7)
NGT, i-IFG, i-IGT, or IFG-IGT	4,031	Diabetes	207	21,106	1.0 (0.9–1.1)

*Number of individuals at baseline.

Table 3—*Progression rates to impaired glucose regulation and diabetes from baseline through 1- and 3-year to 5-year follow-up for individuals in the high-risk group*

Glucose tolerance status at baseline	*n**	Glucose tolerance status at 1-, 3-, or 5-year follow-up	Outcomes (*n*)	Person-years	Rate per 100 person-years (95% CI)
NGT	1,731	i-IFG	167	7,602	2.2 (1.9–2.6)
		i-IGT	208	7,543	2.8 (2.4–3.2)
		IFG-IGT	50	7,995	0.6 (0.5–0.8)
		i-IFG, i-IGT, or IFG-IGT	384	6,939	5.5 (5.0–6.1)
		Diabetes	33	8,058	0.4 (0.3–0.6)
		i-IFG, i-IGT, IFG-IGT, or diabetes	401	6,887	5.8 (5.3–6.4)
i-IFG	260	IFG-IGT	44	1,112	4.0 (2.9–5.3)
		Diabetes	42	1,121	3.7 (2.8–5.1)
		IFG-IGT or diabetes	81	1,005	8.1 (6.5–10.0)
i-IGT	433	IFG-IGT	52	1,928	2.7 (2.1–3.5)
		Diabetes	70	1,882	3.7 (2.9–4.7)
		IFG-IGT or diabetes	111	1,737	6.4 (5.3–7.7)
IFG-IGT	169	Diabetes	63	604	10.4 (8.2–13.4)
i-IFG, i-IGT, or IFG-IGT	862	Diabetes	175	3,607	4.9 (4.2–5.6)
NGT, i-IFG, i-IGT, or IFG-IGT	2,593	Diabetes	208	11,6642	1.8 (1.6–2.0)

*Number of individuals at baseline.

CONCLUSIONS — In this large population-based study with a 5-year follow-up, we found that 2% per year of all individuals with NGT at baseline progressed to impaired glucose regulation or diabetes. Among individuals at high risk with NGT at baseline, almost 6% per year progressed to impaired glucose regulation or diabetes. This relatively higher rate of progression in the high-risk group compared with the combined group was expected, because at least one criterion for being in the high-risk group was obesity, which is a well-known risk factor for diabetes (1,7). Furthermore, the high-risk individuals were additionally reexamined at 1 and 3 years, which makes any progression in glucose tolerance status more likely to be detected and at an earlier time, thus decreasing their risk time and increasing the progression rate. On the other hand, the high-risk group was offered a relatively more intensive intervention that could underestimate the spontaneous progression rates in this group.

Among individuals with impaired glucose regulation, 4% per year in the combined low- and high-risk group and almost 5% per year in the high-risk group progressed to diabetes. All individuals with i-IGT or IFG-IGT were in the high-risk group in this study because IGT was one of the criteria for being considered at high risk. Therefore, the progression rates from i-IGT to IFG-IGT and/or diabetes and from IFG-IGT to diabetes are almost the same among all of the study participants (Table 2) and in the high-risk group (Table 3). However, the use of up to four OGTT examinations in calculating the progression rates in Table 3 makes these rates more accurate than the rates in Table 2, which only use baseline and 5-year measurements.

In the high-risk group, the progression rate from IFG-IGT to diabetes was 2.8 times higher than the progression rates from the isolated states of impaired glucose regulation, i-IFG and i-IGT, to diabetes. This was expected because the IFG-IGT group has more severe metabolic abnormalities than the isolated states (15) and therefore has an increased risk of progression to diabetes. In addition, the risk of misclassification is lower. Both FPG and 2-h plasma glucose can be randomly high, but because the classification of IFG-IGT requires both an abnormal FPG and an abnormal 2-h plasma glucose, there is a low risk of a simultaneously random high FPG and 2-h plasma glucose.

In the present follow-up study, we analyzed the Inter99 study as if it was a cohort study, but because the Inter99 study was designed as an intervention study, the rates of progression might have been higher without the intervention. However, for the high-risk group, the group-based intervention (high-intensity group A) had no additional effect beyond the individualized intervention (low-intensity group B) with respect to plasma glucose levels (C.L., D.V., Ulla Toft, Inge Tetens, O.P., T.J., K.B.-J., unpublished observations). A recent study from the Danish National Diabetes Register has shown age- and sex-specific incidence rates in the Danish population (20) that are approximately one-third of the rate of progression to diabetes in our study (1.0% per year, Table 2). This reflects an underdiagnosing of diabetes in the background population, and, therefore, we cannot estimate the total effect of the lifestyle intervention in the Inter99 population by comparing our findings with those for the background population via central registries in Denmark.

Although the Inter99 study is potentially underestimating the spontaneous progression rates because of the lifestyle intervention, we compared the rate ratios with those from the few European population-based studies that have calculated progression rates from NGT or impaired glucose regulation to diabetes in Caucasians using the current WHO classification criteria (10,11,13). These studies have not calculated progression to impaired glucose regulation. None of the studies have performed interval-censoring in the calculation of progression rates, and, thus, they have potentially underestimated their crude rates. We have chosen not to compare the high-risk group with highly selected European populations (21,22) because of different criteria for being at high risk.

In the Dutch Hoorn study, 1,342 white Caucasians aged 50–75 years with-

out diabetes at baseline in 1989–1992 were followed for 6.4 years. The progression rates from i-IFG, i-IGT, and IFG-IGT to diabetes were 7.3, 8.3, and 16.0 times higher, respectively, than the progression rate from NGT to diabetes (0.7 per 100 person-years) (10). These rate ratios are all lower than the similar rate ratios in our study.

In the Asturias study from Northern Spain, 630 mostly Caucasians aged 30–75 years without diabetes at baseline in 1998–1999 were followed for 6.3 years. The progression rates from i-IFG, i-IGT, and IFG-IGT to diabetes were 6.9, 4.2, and 19.0 times higher, respectively, than the progression rate from NGT to diabetes (0.5 per 100 person-years) (11). The rate ratios are all lower than the rate ratios in our study.

The British Ely study included 1,040 nondiabetic individuals aged 40–69 years of predominately white-European origin. An OGTT was performed at baseline in 1990–1992 and at the 4.5- and 10-year follow-up examinations (13). The Ely study used a lower threshold (<5.6 mmol/l) for defining NGT than that recommended by the WHO in 1999 (<6.1 mmol/l) (9), and, therefore, the rates would have been higher if the WHO definition of NGT had been used. The ratio between the rate of progression from IFG to diabetes and the rate of progression from NGT to diabetes (0.2 per 100 person-years) was 7.3, which is lower than the rate ratios comparing progression to diabetes from i-IFG or IFG-IGT and NGT in our study.

Strengths of the present population-based study include its large size with 4,615 participants at baseline with follow-up data. Furthermore, the study was initiated <10 years ago, which is important because the rates of progression in a given population change over time (23,24) because of changes in modifiable risk factors (e.g., BMI and level of physical activity) and in the demography of the population. Further strengths are the separation of impaired glucose regulation into i-IFG, i-IGT, and IFG-IGT and thereby the presentation of progression rates to and from the isolated states as well as the combined state. The multiple examinations with OGTTs in the high-risk group make the progression rates among high-risk individuals very accurate. Other strengths are the calculation of person-years at risk and the use of interval-censoring, which takes into account the fact that conversion to a more severe glucose tolerance state occurs before the time of the examination.

As mentioned above, the spontaneous progression rates may be underestimated because the Inter99 study is an intervention study. A further limitation of this study is the loss to follow-up. However, a follow-up rate of 76.8% is comparable to that for the Hoorn study (73.5%) (10), the Asturias study (75.5%) (11), and the Ely study (72%) (13). In accordance with the WHO 1999 criteria, the classification of glucose tolerance status in this epidemiological study was based on a single OGTT examination (9). Nevertheless, because of the known high intraindividual variation in plasma glucose levels, especially for postload glucose, some misclassification might have occurred when participants were categorized into glucose tolerance categories (10). Furthermore, there is an additional risk of misclassification because we did not look at regression in glucose tolerance status during follow-up. However, because there was no difference in plasma glucose between the intervention groups, we consider the risk of misclassification to be random.

The relatively low participation rate at baseline (52.5%) introduces a selection bias and weakens the possibility of generalizing the results. Nevertheless, it does not affect the validity of the progression rates in this study.

The rate ratios in our study are higher than similar rate ratios in the few other European studies, which also used the current WHO classification. This may be due to a relatively low progression rate from NGT to diabetes in the Inter99 study compared with that in the Hoorn and the Asturias study. The NGT group has a lower proportion of high-risk individuals than the other glucose tolerance groups (Table 1). Therefore, the relatively low progression rate from NGT to diabetes compared with the rates from impaired glucose regulation to diabetes cannot be attributed to an intervention effect. Although the rate ratios in our study are higher than those in the other European studies, the pattern is the same with relatively low rates of progression from NGT to diabetes, intermediate rates from i-IFG and i-IGT to diabetes, and high rates from IFG-IGT to diabetes.

In summary, we have presented for the first time progression rates to i-IFG, i-IGT, and IFG-IGT in a large European population-based study, which uses the current WHO classification criteria. Progression rates to diabetes show the same pattern as that seen in the few similar European studies.

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