

Prevalences of Diabetes and Impaired Glucose Regulation in a Danish Population

The Inter99 study

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OBJECTIVE — To determine the age- and sex-specific prevalence of impaired fasting glycemia, impaired glucose tolerance, screen-detected diabetes, and known diabetes in a Danish population aged 30–60 years and to examine the phenotype and the cardiovascular risk profile in individuals with impaired glucose regulation.

RESEARCH DESIGN AND METHODS — In the Inter99 study, 13,016 inhabitants living in Copenhagen County were invited. All participants underwent anthropometric measurements, blood samples, and a 75-g standardized oral glucose tolerance test.

RESULTS — The age-specific prevalences in men were as follows: impaired fasting glycemia: 1.4–16.3%; impaired glucose tolerance: 6.9–17.8%; screen-detected diabetes: 0.7–9.7%; and known diabetes: 0–5.8%. The corresponding figures in women were 0–5.1, 10.5–17.3, 0.6–6.3, and 0.5–9%. The prevalence of impaired glucose regulation increased with age. Among individuals with diabetes, 65.6% were previously undiagnosed; this proportion was highest in the youngest age-group (82% among 45-year-old men vs. 63% among 60-year-old men, and 70% among 45-year-old women vs. 52% among 60-year-old women). Mean BMI, waist, HbA_{1c}, systolic blood pressure, diastolic blood pressure, and total cholesterol were significantly higher ($P < 0.0001$) in the individuals with impaired glucose regulation compared with individuals with normal glucose tolerance.

CONCLUSIONS — This study revealed that the prevalence of type 2 diabetes is high and that still two out of three individuals are undiagnosed, indicating a need for more attention to the disease in society.

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The number of people with type 2 diabetes is estimated to increase rapidly within the next 25 years (1), with an estimated 42% increase in developed countries. This prediction is only based on demographic changes in the population, without considering changes

in lifestyle, and may thus represent a conservative estimate. In developed countries, the prevalence of overweight and obesity is increasing rapidly (2,3) because of reduced physical activity and overeating. This causes a rapid increase in the prevalence of diabetes (3,4). In Denmark,

the prevalence of diabetes was 12.3% among 60-year-old men and 6.8% among women in 1996, representing an increase of 58% in men and 21% in women compared with 1974–1975 (5). Several population-based studies have examined the prevalence of type 2 diabetes in northern Europe. The populations are typically ≥ 50 years of age (6,7), although in the Ely study, the population under investigation was 40–65 years old (8). Only the Hoorn (6) and Rotterdam studies (7) reported age- and sex-specific prevalences of diabetes and impaired glucose tolerance (IGT) (aged > 50 years). Among people with diabetes, at least 50% are unaware of the disease (6,9,10). People with impaired glucose regulation have an unfavorable cardiovascular risk profile compared with healthy people and therefore have a higher rate of cardiovascular disease and mortality (8,11–14). These arguments could favor implementation of screening for type 2 diabetes. Thus, the burden of diabetes in individuals < 50 years with regard to prevalence of IGT, previously undiagnosed diabetes, and known diabetes is not sufficiently illustrated. To date, no European study has examined the age- and sex-specific prevalence using the new World Health Organization (WHO) criteria from 1999. The aims of this article are to determine the age- and sex-specific prevalence of impaired fasting glycemia (IFG), IGT, screen-detected diabetes mellitus (SDM), and known diabetes mellitus (KDM) in a Danish population aged 30–60 years and to examine the phenotype and the cardiovascular risk profile in individuals with impaired glucose regulation.

RESEARCH DESIGN AND METHODS

Survey design

The Inter99 is a population-based primary prevention study on cardiovascular disease and type 2 diabetes. The study

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Abbreviations: dbP, diastolic blood pressure; FPG, fasting plasma glucose; IFG, impaired fasting glycemia; IGT, impaired glucose tolerance; KDM, known diabetes mellitus; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; PG, plasma glucose; sBP, systolic blood pressure; SDM, screen-detected diabetes mellitus; WHO, World Health Organization.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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takes place at the Research Center for Prevention and Health. The study population comprised all 61,301 individuals born in 1939–1940, 1944–1945, 1949–1950, 1954–1955, 1959–1960, 1964–1965, or 1969–1970 and living in 11 municipalities in the southwestern part of Copenhagen County. The individuals were drawn from the Civil Registration System. An age- and sex-stratified random sample comprising 13,016 individuals was drawn from the study population (15).

The participants were invited for a health screening program, a personal risk assessment, and health counseling. Baseline data were collected from March 1999 until January 2001.

Survey procedure

Participants filled in a questionnaire in advance. After an overnight fast, the participants underwent various procedures including anthropometric measurements, blood samples, and a standard 75-g oral glucose tolerance test (OGTT) (75 g anhydrous glucose in 250 ml water). Participants with known diabetes did not have an OGTT, but fasting plasma glucose (FPG) was measured. Plasma glucose was sampled in a heparin-NaF tube. The samples were put on ice immediately and centrifuged within 30 min. The glucose was analyzed using the hexokinase/glucose-6-phosphate dehydrogenase (Boehringer Mannheim). HbA_{1c} was taken in a capillary tube and analyzed by the principles of an ion-exchange high-performance liquid chromatography Bio-Rad variant. Serum cholesterol was determined using enzymatic techniques (Boehringer Mannheim). Two blood pressures were measured with the patient in the lying position using a standard mercury sphygmomanometer with an appropriate cuff size after at least a 5-min rest. The mean of the two blood pressures was calculated. Weight and height were measured with the participants wearing indoor clothes without shoes. Waist circumference was measured midway between the lower rib margin and iliac crest. BMI was defined as weight in kilograms divided by height in meters squared.

Definitions

The questionnaire contained information on various diseases, including diabetes, family history of diabetes, and cardiovascular risk factors. Glucose tolerance was

classified according to the 1999 WHO criteria (16). Participants with self-reported diabetes were classified as KDM. Individuals not reporting having diabetes and who had an FPG ≥ 7.0 mmol/l or a 2-h plasma glucose (PG) ≥ 11.1 mmol/l were diagnosed as having SDM. Those without KDM and with FPG < 7.0 mmol/l and 2-h PG ≥ 7.8 mmol/l but < 11.1 mmol/l were diagnosed with IGT. IFG was defined as an FPG ≥ 6.1 mmol/l but < 7.0 mmol/l and 2-h PG < 7.8 mmol/l. Normal glucose tolerance (NGT) was defined as an FPG < 6.1 mmol/l and 2-h PG < 7.8 mmol/l. BMI < 25.0 kg/m² was defined as normal, overweight was defined as a BMI between 25.0 and 29.9 kg/m², and obesity was defined as a BMI ≥ 30.0 kg/m². Using a standardized questionnaire (17), where information on leisure physical activity comprised four categories, leisure physical activity was graded as follows: 1) sedentary (reading, watching TV, etc.), 2) moderately active, minor strenuous exercise at least 4 h per week (walking/bicycling), 3) strenuous exercise at least 3 h per week (sports or other strenuous activities), and 4) regular hard physical training for competition. Because of the low numbers in the classes with the highest level of physical activity, the two highest classes (3 and 4) were merged together in the analysis. Smoking habits were graded as daily smoker, occasional smoker, ex-smoker, and never smoker. Family history of diabetes was defined as having either a parent or a sibling with diabetes.

All participants gave a written consent before taking part in the survey. The protocol was in accordance with the Helsinki declaration and approved by the local ethical committee.

Statistical analysis

Statistical analyses were carried out using SAS version 8.2 (SAS Institute, Cary, NC). Means and 95% CIs were calculated for the continuous variables. Means were standardized to age 50 years. Means for the continuous variables in the different groups were compared in a general linear model with age and glucose tolerance as independent variables. Proportions for categorical variables were standardized to age 50 years and compared using a generalized linear model with age and glucose tolerance as independent variables. Approximate CIs for physical activity were estimated by bootstrapping (18).

The impact of physical activity and weight on diabetes, IGT, and IFG was determined using multiple logistic regression analysis. Glucose tolerance status was used as a dependent variable; age, sex, BMI, and leisure physical activity were used as independent variables.

RESULTS — Of the 13,016 individuals drawn from the Civil Registration System, 82 individuals were noneligible because they had died or could not be traced. Of the remaining 12,934, 6,906 (53.4%) participated in the investigation. A total of 122 individuals were excluded because of alcoholism or drug abuse ($n = 23$) or because of linguistic problems ($n = 99$), leaving 6,784 (52.5%) for analysis.

The median age for the study population was 45.1 years (range 30–60 years), and 51.3% were women. According to the WHO criteria, 374 (5.5%) could not be categorized because of either lack of all plasma glucose measurements or lack of the 2-h PG.

Figure 1 shows the age-specific prevalence of IFG, IGT, SDM, and KDM for men and women, respectively.

Diabetes

The age- and sex-specific prevalence of diabetes varied between 0.7 and 15.8%. In both sexes, the prevalence of diabetes increased with increasing age. The proportion of diabetic individuals aged 45 years who had SDM was 82% among men and 70% among women compared with 63 and 52% among 60-year-old men and women, respectively. The proportion of SDM among diabetic individuals decreased with increasing age. Men were significantly more frequently undiagnosed than women ($P = 0.03$). Of the SDM individuals, 26.6% had an FPG ≥ 7.0 mmol/l and a 2-h PG < 11.1 mmol/l, 31.2% had a 2-h PG ≥ 11.1 mmol/l but an FPG < 7.0 mmol/l, whereas 33.2% had an FPG ≥ 7.0 mmol/l and a 2-h PG ≥ 11.1 mmol/l.

In a multiple logistic regression model using diabetes as a dependent variable, the likelihood of having diabetes increased with increasing BMI, leisure physical activity, age, and sex (Table 1).

IFG and IGT

The prevalence of IFG and IGT increased with increasing age. The prevalence of IGT varied between 4.7 and 17.8% depending on age and sex. IGT was more

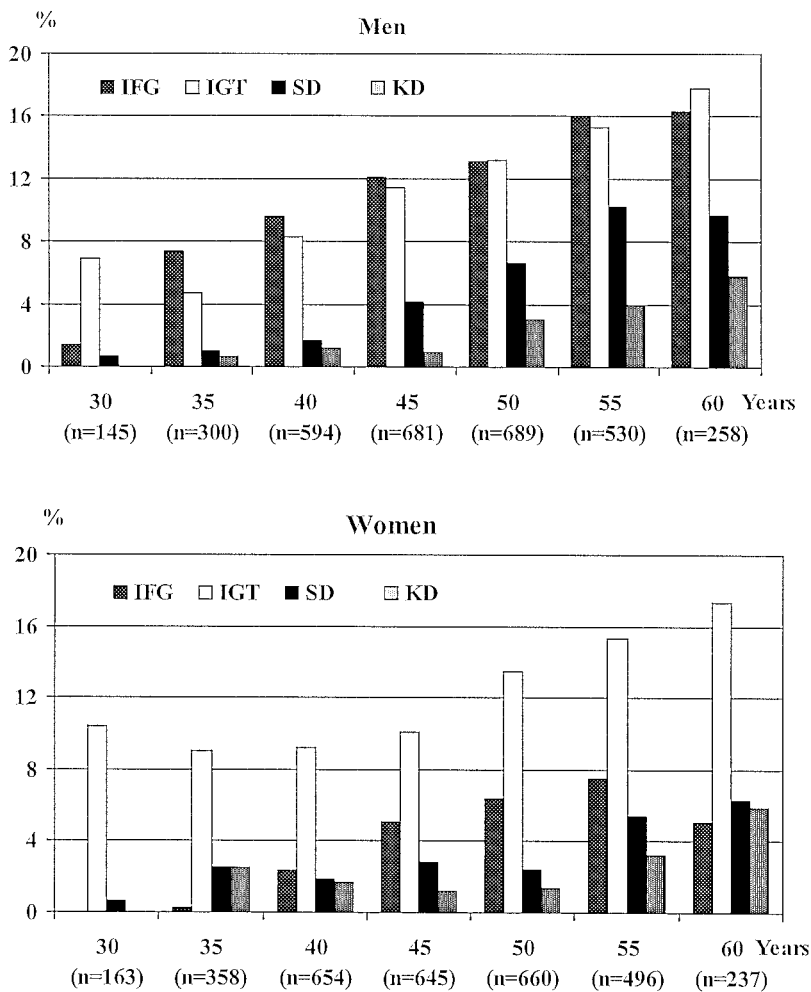


Figure 1—Age- and sex-specific prevalence of IFG, IGT, SDM, and KDM in the Inter99 study. For each age category, the total number screened is given.

frequent among young women compared with young men (9.9% among women aged 30–35 years vs. 5.8% among men aged 30–35 years). The prevalence of IFG was significantly higher in men than in women ($P < 0.0001$). In men, the prevalence of IFG was on average equal to the

prevalence of IGT, whereas in women the prevalence of IFG was $\leq 50\%$ than the prevalence of IGT.

Male sex and high BMI were significantly associated with IFG, whereas high BMI and low leisure physical activity were significantly associated with IGT (Table 1).

Table 1—Multiple logistic regression model using IFG, IGT, or diabetes as dependent variables and sex, age, BMI, and leisure physical activity as independent variables

	IFG vs. NGT	IGT vs. NGT	Diabetes vs. NGT
Men vs. women	3.0 (2.4–3.7)	1.0 (0.9–1.2)	1.7 (1.3–2.1)
Age per 5-year increase	1.4 (1.3–1.5)	1.3 (1.2–1.3)	1.6 (1.5–1.7)
BMI			
Overweight vs. normal weight	1.8 (1.4–2.2)	1.8 (1.5–2.2)	2.3 (1.7–3.2)
Obese vs. normal weight	3.4 (2.6–4.5)	4.0 (3.2–5.0)	8.3 (6.1–11.3)
Physical activity at leisure time			
Inactive vs. active	1.0 (0.7–1.4)	2.0 (1.5–2.7)	3.7 (2.4–5.7)
Moderate vs. active	1.2 (0.9–1.5)	1.6 (1.2–2.1)	2.1 (1.4–3.1)

Data are OR (95% CI).

Impaired glucose regulation

By the age of 30 years, 8.9% (95% CI 4.8–14.8) of men and 10.4% (6.2–16.2) of women had impaired glucose regulation (IFG, IGT, or diabetes). In both sexes, impaired glucose regulation increased with increasing age. By age 60 years, 49.6% (43.4–55.6) of men and 34.6% (28.6–41.0) of women had abnormal glucose tolerance.

Cardiovascular risk profile

Tables 2 and 3 shows the baseline characteristics of the population according to glucose tolerance for men and women, respectively. Age increased with deterioration in glucose intolerance ($P < 0.0001$). In both sexes, the mean BMI, waist, HbA_{1c}, systolic blood pressure (sBP), diastolic blood pressure (dBP), and total cholesterol were higher in individuals with IFG, IGT, SDM, and KDM than in individuals with NGT ($P < 0.0001$). Individuals with IGT, SDM, and KDM were less physically active than individuals with NGT and IFG ($P = 0.001$). Individuals with SDM had a higher sBP and dBP than individuals with known diabetes ($P < 0.05$), whereas HbA_{1c} was lower among individuals with SDM than among individuals with KDM ($P < 0.0001$). Furthermore, women with SDM had a higher total cholesterol than women with KDM ($P = 0.0002$). There were no differences in smoking habits between the groups.

The proportion of men with a family history of diabetes was significantly higher in individuals with IGT, SDM, and KDM than in men with NGT and IFG ($P < 0.05$), whereas no differences were seen between men with NGT and IFG. The same tendency was seen in women (Tables 2 and 3).

CONCLUSIONS— The Inter99 study is one of the largest population-based studies in Europe to use the OGTT and to examine the age- and sex-specific prevalences according to the new 1999 WHO diagnostic criteria. Furthermore, the Inter99 study covers the age range from 30 to 60 years. The Inter99 study revealed that diabetes is a major health problem in both men and women in Denmark and in the younger age-groups. The reported age- and sex-specific prevalences of diabetes and IGT are higher than those reported in other European studies (6,7) and those for non-Hispanic whites in the U.S. (19). This result can reflect the

Table 2—Phenotype and cardiovascular risk profile according to glucose tolerance among men

	NGT	IFG	IGT	SDM	KDM
n	2,209	380	369	167	72
Age (years)	45.1 (44.7–45.4)	48.7 (47.9–49.4)	48.9 (48.1–49.6)	51.3 (50.1–52.2)	51.8 (50.2–53.3)
BMI (kg/m ²)	26.2 (26.0–26.4)	27.7 (27.3–28.1)	28.5 (28.1–28.9)	29.9 (29.3–30.5)	29.7 (28.2–30.0)
Waist (cm)	91.8 (91.3–92.3)	96.0 (95.0–97.1)	97.6 (96.5–98.7)	101.1 (99.5–102.7)	100.1 (97.7–102.5)
HbA _{1c} (%)	5.87 (5.85–5.90)	6.00 (5.93–6.04)	5.99 (5.93–6.05)	6.73 (6.64–6.81)	8.16 (8.03–8.29)
sBP (mmHg)	132.4 (131.7–133.1)	138.6 (137.0–140.1)	142.1 (140.5–143.7)	147.9 (145.6–150.2)	143.2 (139.7–146.7)
dBP (mmHg)	84.3 (83.8–84.8)	88.1 (87.1–89.2)	90.1 (89.1–91.2)	91.4 (89.9–93.0)	88.8 (86.4–91.2)
Total cholesterol (mmol/l)	5.63 (5.58–5.68)	5.89 (5.79–6.00)	5.96 (5.86–6.07)	5.88 (5.71–6.03)	5.32 (5.08–5.57)
Family history of diabetes (%)	14.5 (13.1–16.1)	17.6 (13.9–21.8)	19.2 (15.3–23.6)	23.4 (17.2–30.5)	34.7 (23.9–46.9)
Daily smoker (%)	37.3 (35.3–49.4)	36.8 (32.0–41.9)	35.6 (30.6–40.7)	38.8 (31.3–46.7)	42.3 (30.6–54.6)
Physical activity at leisure					
Sedentary (%)	19.7 (18.0–21.5)	20.4 (17.5–24.2)	29.6 (25.6–34.1)	33.9 (27.8–39.9)	40.4 (29.3–51.7)
Moderate (%)	57.1 (55.3–58.8)	57.2 (55.2–58.8)	55.4 (52.9–57.6)	53.4 (49.9–56.5)	49.8 (41.9–55.5)
Active (%)	23.2 (21.2–25.0)	22.4 (18.9–26.0)	15.0 (12.4–17.7)	12.6 (9.9–16.2)	9.9 (6.4–15.2)

Data are age-standardized means or % (age = 50 years); 95% CIs are given in parentheses.

use of different diagnostic criteria. However, it can also reflect the impact of lifestyle changes over the last decades. The prevalences reported from Australia are similar to the prevalences in the Inter99 study (9), although there are some age differences, especially in men. In the Inter99 study, the prevalence of SDM was higher among men aged >45 years compared with Australia, where the prevalence of known diabetes was higher among men aged >55 years. Applying our age- and sex-specific prevalences to the Danish population aged 30–60 years implies that 122,000 individuals would have diabetes in 2002. The prevalence estimates for Denmark suggested by WHO (1) estimated that 85,000 individuals aged 30–60 years would have diabetes in

Denmark by the year 2002. This underestimation is especially distinct in the younger age-groups (35–44 years) and in the age-group of 55–60 years. This underestimation can partly be explained by the fact that the model from WHO only accounts for changes in the age and sex structure but does not include changes in obesity and physical activity due to lifestyle changes in developed countries. We found an increased risk of having diabetes in individuals who were overweight or obese compared with individuals who had a normal weight. We also found an increased risk for individuals who were moderately inactive or inactive according to leisure physical activity compared with the active individuals. In the entire Inter99 population, 39.2 and 17.6% were

either overweight or obese, respectively. Furthermore, 62% were moderately active and 22% were inactive according to leisure physical activity. These findings indicate that our population did have an unhealthy lifestyle. It is likely that this explains the difference in numbers of individuals with diabetes between our calculation and the calculation from WHO. In the U.S., the prevalence of diabetes increased by 6% from 1998 to 1999 (6.4 vs. 6.9%). The authors argued that this rapid increase must be due to lifestyle changes (3), confirming our concerns about the estimations from the WHO.

Because of the 52.5% response rate, it can be argued whether or not the responders in the Inter99 study are representative of the random sample. We have

Table 3—Phenotype and cardiovascular risk profile according to glucose tolerance among women

	NGT	IFG	IGT	SDM	KDM
n	2,526	140	382	98	67
Age (years)	45.1 (44.8–45.4)	49.8 (48.9–50.8)	47.5 (46.7–48.3)	49.2 (47.6–50.8)	49.0 (46.9–51.1)
BMI (kg/m ²)	25.2 (25.0–25.4)	28.4 (27.6–29.2)	28.0 (27.5–28.5)	30.5 (29.5–31.4)	31.0 (29.8–32.1)
Waist (cm)	79.0 (78.5–79.5)	87.6 (85.7–89.4)	86.0 (84.8–87.1)	93.6 (91.4–95.9)	96.3 (93.6–99.1)
HbA _{1c} (%)	5.78 (5.76–5.81)	6.00 (5.92–6.09)	5.87 (5.82–5.92)	6.43 (6.33–6.53)	7.96 (7.84–8.08)
sBP (mmHg)	128.2 (125.5–128.9)	134.6 (132.0–137.2)	136.7 (135.1–138.3)	142.5 (139.4–145.7)	137.4 (133.6–141.2)
dBP (mmHg)	80.8 (80.3–81.3)	85.1 (83.4–86.8)	85.3 (84.3–86.4)	88.8 (86.7–90.8)	83.8 (81.3–86.2)
Total cholesterol (mmol/l)	5.58 (5.54–5.62)	5.97 (5.81–6.12)	5.76 (5.66–5.86)	6.07 (5.88–6.27)	5.95 (5.71–6.19)
Family history of diabetes (%)	16.1 (14.7–17.6)	22.9 (16.2–30.7)	26.7 (23.3–31.4)	32.7 (23.5–42.9)	37.3 (25.8–50.0)
Daily smoker (%)	34.9 (33.0–36.8)	38.1 (30.0–46.7)	33.9 (29.1–38.9)	32.3 (23.1–42.6)	36.9 (25.3–49.8)
Physical activity at leisure					
Sedentary (%)	19.0 (17.9–21.7)	22.3 (18.3–30.0)	26.5 (23.4–32.0)	31.5 (23.4–42.4)	50.8 (37.6–63.8)
Moderate (%)	67.3 (64.8–68.4)	66.2 (61.4–67.9)	64.1 (60.1–65.9)	61.0 (52.5–65.6)	45.7 (33.8–56.3)
Active (%)	13.7 (12.1–15.2)	11.4 (8.1–14.6)	9.3 (7.4–11.6)	7.5 (5.0–11.4)	3.5 (2.1–6.3)

Data are age-standardized means or % (age = 50 years); 95% CIs are given in parentheses.

shown that the nonresponders in the Inter99 study were sicker because of contact with the somatic hospitals compared with the responders, indicating that a healthier population was showing up for examination (15).

The reported prevalences in this article can be affected by selection bias. The Inter99 study is an ongoing intervention study, and potential participants were informed that the intervention part included an invitation to participate in a group counseling session for diet and physical activity. This type of offer could cause an overrepresentation of obese people and therefore an overestimation of obesity and diabetes. Self-reported height and weight in a reference population in the Inter99 study (15) showed a significantly lower proportion of individuals with BMI <30 kg/m² than those invited for intervention (odds ratio 0.66; 95% CI 0.59–0.75), which could consolidate the above-mentioned possibility of a selection bias. It is known, however, that self-reporters underestimate their weight and/or overestimate their height (20,21). Furthermore, individuals not motivated for lifestyle changes stay away from studies such as Inter99, including presumably the most obese individuals. It is difficult, therefore, to assess the direction of selection bias, if any.

In our study, we found a surprisingly high proportion of individuals with SDM compared with KDM. Among men, 70% were unaware of their disease (which should be compared with 61% in the Netherlands [6] and 47% in Australia [9]). In the Inter99 study, the prevalence of self-reported KDM in the responders was significantly lower compared with the responders in the reference population (2.2 vs. 3.1%). This difference was explained by a lower prevalence among men. The consequences of this bias might be, first, an underestimation of the prevalence of KDM in men and, second, an overestimation of the proportion of SDM in men. Furthermore, it is possible that our population was not truly fasting, leading to a high false prevalence of SDM; however, the proportion of individuals diagnosed based on a high fasting value and a normal 2-h PG value did not differ from other studies (22).

The proportion of women with undiagnosed diabetes was less compared with men. This sex difference can be explained by the facts: first, that we have underesti-

mated the prevalence of known diabetes among men; second, that men have less contact with their general practitioner than women (9,23); or, third, that our population has an overrepresentation of young obese women. Like other studies, we observed a high prevalence of IGT in men and women. However, in young women, the prevalence was surprisingly high (10%), eventually predicting a future rising prevalence of diabetes in younger women. The prevalence of IFG was higher in men than in women, which is similar to the AusDiab study (9). These differences could be due to differences in pathophysiology, because men could be more insulin insufficient and women could be more insulin resistant. Further analyses to answer these arguments are needed.

Our study shows that individuals with SDM have an unfavorable cardiovascular risk profile in terms of higher blood pressure, higher total cholesterol, higher BMI, and more central obesity compared with individuals with NGT. Other population-based screening studies have shown the same tendency with increasing mean blood pressure, mean cholesterol, and higher BMI, with a worsening of the glucose tolerance from normal (7–9,14,24,25). The Heart Protection Study and the Cholesterol and Recurrent Events trial have shown that medical treatment for dyslipidemia either as primary or secondary prevention reduces the number of major coronary events (26,27). Several studies have demonstrated that treatment for hypertension reduces cardiovascular events and death related to diabetes (28,29).

Because the prevalence of diabetes is high, 60% of individuals with diabetes are unaware of their disease, individuals with SDM have an unfavorable cardiovascular risk profile, and the evidence from clinical trials that individuals with known or newly diagnosed diabetes have beneficial effect of medical treatment of cardiovascular risk factors, establish that these individuals might benefit from early detection and prompt treatment of their diabetes. What is not known is whether screening for diabetes and IGT will reduce the burden of disease in society. Furthermore, disadvantages of screening are important and should be quantified. Results from the present study and the ADDITION study (30) will answer these questions.

The Da Qing study, Diabetes Preven-

tion Program, and Diabetes Prevention Study have shown that it is possible to delay the development of type 2 diabetes in individuals with IGT by lifestyle modification (31–33). We have shown that the burden of IGT is heavy also in young age-groups, indicating that action is required. If screening for IGT is implemented, development of risk scores for detection of individuals at risk of having IGT is needed, consequently reducing the number of OGTTs. Furthermore, our study supports that the estimated increase of diabetes in developed countries is underestimated. This study reveals that type 2 diabetes is a burden and that many people are still undiagnosed, indicating the need for more attention to this disease in society.

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