Population-Based Incidence Rates and Risk Factors for Type 2 Diabetes in White Individuals

The Bruneck Study

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Incidence rates and risk factors for type 2 diabetes in low-risk populations are not well documented. We investigated these in white individuals who were aged 40–79 years and from the population of Bruneck, Italy. Of an age- and sex-stratified random sample of 1,000 individuals who were identified in 1990, 919 underwent an oral glucose tolerance test (OGTT) and an assessment of physiological risk factors for diabetes, including insulin resistance (homeostasis model assessment, HOMA-IR), and postchallenge insulin response (Sluiter's Index). Diabetes at baseline by fasting or 2-h OGTT plasma glucose (World Health Organization criteria, n = 82) was excluded, leaving 837 individuals who were followed for 10 years. Incident cases of diabetes were ascertained by confirmed diabetes treatment or a fasting glucose ≥7.0 mmol/l. At follow-up, 64 individuals had developed diabetes, corresponding to a population-standardized incidence rate of 7.6 per 1,000 person-years. Sex- and age-adjusted incidence rates were elevated 11-fold in individuals with impaired fasting glucose at baseline, 4-fold in those with impaired glucose tolerance, 3-fold in overweight individuals, 10-fold in obese individuals, and ~2-fold in individuals with dyslipidemia or hypertension. Incidence rates increased with increasing HOMA-IR and decreasing Sluiter's Index. As compared with normal insulin sensitivity and normal insulin response, individuals with low insulin sensitivity and low insulin response had a sevenfold higher risk of diabetes. Baseline impaired fasting glucose, BMI, HOMA-IR, and Sluiter's Index were the only independent predictors of incident diabetes in multivariate analyses. We conclude that ~1% of European white individuals aged 40–79 years develop type 2 diabetes annually and that "subdiabetic" hyperglycemia, obesity, insulin resistance, and impaired insulin response to glucose are independent predictors of diabetes. *Diabetes* 53:1782–1789, 2004

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ADA, American Diabetes Association; HOMA, homeostasis model assessment; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NFG, normal fasting glucose; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; WHO, World Health Organization.

Type 2 diabetes, by far the most common form of diabetes, is increasing at an alarming rate all over the world. Current projections estimate that the absolute number of cases worldwide may double over the next two decades, leading to a commensurate increase in the human, social, and economic costs of the disease (1). This estimate is based primarily on projections of prevalence data, because of the paucity of population-based type 2 diabetes incidence data. The heterogeneity of type 2 diabetes and its recognized polygenic basis and dependence on environmental factors all call for population-based, ethnically focused, and country/continent-specific studies of type 2 diabetes incidence.

The apparent increasing prevalence of type 2 diabetes could in part depend on methodological biases, whereby increased attention to the disorder heightens awareness, screening, and reporting; inflates successive cross-sectional prevalence estimates; and potentially inflates estimates of the true underlying incidence rate. Accurate estimation of type 2 diabetes incidence rates requires plasma glucose assessment in clearly defined population-based samples. Furthermore, comprehensive assessment of the key determinants of diabetes incidence at the population level is required to implement the most appropriate screening and prevention programs.

Many of the existing population-based incidence data that are based on plasma glucose assessment were collected in high-risk groups. These data have shown that older age, family history, obesity, and nonwhite race/ethnicity are strong and consistent determinants of type 2 diabetes (2–4). Only a few studies have examined with plasma glucose assessment low-risk population-based samples. Most of these studies are old and based on previous diagnostic criteria (4–9). Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), representing abnormal but subdiabetic levels of fasting and postchallenge glycemia, are powerful biochemical predictors of type 2 diabetes (10,11). Physiological data show that peripheral insulin resistance and pancreatic β-cell dysfunction are precursors and key determinants of type 2 diabetes (12), but evidence of these physiological traits as type 2 diabetes risk factors in low-risk, population-based samples is scant. The aims of the present study, therefore, were to define the incidence and specific risk factors for

type 2 diabetes in a population-based sample of people who were aged 40–79 years and living in Bruneck, Italy.

RESEARCH DESIGN AND METHODS

The Bruneck Study is a long-term, prospective, population-based survey of atherosclerosis and its risk factors. It is being conducted in Bruneck, a small town of ~13,500 people, located in northeastern Italy, close to the Austrian border. As reported previously (13), the baseline evaluation was performed between July and November 1990. Among the 1,000 randomly selected men and women of the 4,793 white individuals who were aged 40–79 years, 936 volunteered after the purposes and modalities of the study had been carefully presented. As 17 individuals had incomplete data collection, the sample that we used for most statistical analyses included 919 individuals. However, the analyses that included insulin assessment were performed in 888 individuals (450 men and 438 women) because 2 individuals were insulin treated and 29 individuals had no serum available for the measurement of insulin. The main clinical features of the study population and the subset with insulin available have been reported in previous publications (13,14).

From July to October 1995, a first reevaluation of the cohort (5-year follow-up) was performed (15,16). Of the original population sample, 62 individuals were deceased, 1 had moved away and could not be traced, and 30 declined to participate in the follow-up study. Thus, the follow-up study was 96.5% complete among survivors (n = 826 of 856).

From September to October 2000, a further reevaluation of the cohort (10-year follow-up) was performed. In the period 1995–2000, 97 individuals were deceased, none had moved away, and 33 had incomplete data collection. Thus, this second follow-up examination was 95.5% complete among those who had participated in the first follow-up and were still alive (n = 696 of 729).

Full medical records from the hospital and general practitioners of all individuals who did not participate in the follow-up and of all individuals who died during follow-up were available for review. The protocol was approved by the Ethics Committee of the University of Verona. All participants gave an informed consent.

Clinical data. The following demographic and clinical data were collected with a standardized questionnaire: sex, age, cigarette smoking, alcohol consumption, physical activity, socioeconomic status, previous diseases, and drug prescription. BMI and blood pressure were assessed with standard techniques. Details on the methods have been reported previously (13–16).

Laboratory data. In the morning, after an overnight fast, venous blood was sampled for the measurement of plasma concentrations of glucose and serum concentrations of total and HDL cholesterol, triglycerides, urate, and insulin. A 75-g oral glucose tolerance test (OGTT) was administered to all individuals without known diabetes to establish their glucose tolerance both at baseline and at the 5-year follow-up but not at the 10-year follow-up, when only venous blood in the fasting state was sampled after an overnight fast for plasma glucose assessment. During the OGTT, blood was withdrawn at 120 min for the measurement of plasma glucose and serum insulin. Details on analytical procedures have been reported previously (13–16).

Assessment of insulin resistance and β-cell function. The degree of insulin sensitivity at baseline was estimated by the homeostasis model assessment (HOMA) (17). In a recent article, we reported on the good reliability of the HOMA in estimating insulin resistance (18). The β-cell secretory response to oral glucose load was estimated using baseline OGTT data as described by Sluiter et al. (19) and validated by Hanson et al. (20).

Diagnosis of diabetes. At baseline and at the 5-year follow-up, the presence of diabetes was established according to World Health Organization (WHO) criteria (21), i.e., when fasting glucose was ≥7 mmol/l (126 mg/dl) or when 2-h OGTT glucose was ≥11.1 mmol/l (200 mg/dl) or when the participants had a clinical diagnosis of the disease and treatment was ongoing (diet, drugs). At the 10-year follow-up, an OGTT was not performed and the diagnosis of diabetes was established with American Diabetes Association (ADA) criteria (22), i.e., when fasting glucose was ≥7 mmol/l or when the individuals had a known clinical diagnosis of the disease. In individuals who reported a known clinical diagnosis of diabetes at baseline or at the 5- or 10-year follow-up, the presence of the disease was confirmed by reviewing the medical records of their general practitioners and the files of Bruneck Hospital. No self-reported case of diabetes was accepted without a validated confirmation. Information on the finding of a diabetic fasting or postchallenge plasma glucose, as well as on the finding of an IFG or IGT condition, was given to the individual's general practitioner to allow further investigations and treatment, if necessary.

Diagnosis of other clinical conditions. At baseline, the presence of hypertension, dyslipidemia, hyperuricemia, and obesity were established as follows. Hypertension was diagnosed when systolic blood pressure was ≥140 mmHg or diastolic blood pressure was ≥90 mmHg or blood pressure treatment was ongoing. Dyslipidemia was diagnosed when triglycerides were ≥1.7 mmol/l (150 mg/dl) and/or HDL cholesterol was <1 mmol/l (40 mg/dl) in women or <0.9 mmol/l (35 mg/dl) in men. Hyperuricemia was diagnosed when serum urate was ≥416 μmol/l (7 mg/dl) in men or ≥387 μmol/l (6.5 mg/dl) in women. A BMI ranging from 25 to 30 kg/m^2 was used to define overweight; a BMI >30 kg/m^2 was used to define obesity.

Statistical analysis. Individuals with diabetes at baseline by WHO criteria were excluded from all analyses. In the primary analyses, diabetes cases at the 10-year follow-up were identified by ADA criteria. In subsidiary analyses, diabetes cases at the 5-year follow-up were identified by either ADA or WHO criteria. In analysis of the 10-year incidence of diabetes, cases that were identified at the 5- and at 10-year follow-up were defined using ADA criteria and combined into a single outcome category.

Incidence rate of diabetes was calculated by standard methods (23). Individuals who died or did not join the follow-up also contributed person-years to the incidence rate calculation until death or, if alive, for the whole period. These individuals contributed diabetes cases only when there was a validated clinical diagnosis of diabetes in their medical records. Medical records of all individuals who did not participate in the follow-up and of all individuals who died during follow-up were available to identify known diabetes cases, but these individuals did not have an assessment of fasting glucose. Therefore, the incidence of diabetes in these individuals may have been underestimated. However, the person-years contributed by these subjects were only a small percentage of overall person-years, so the effect of this underestimation was very low.

The associations of demographic and behavioral variables; measures of glucose metabolism, insulin resistance, and β-cell secretion; baseline fasting glucose; and glucose tolerance categories (IFG and IGT) with incident diabetes were assessed by logistic regression analyses. The test procedure was based on maximum-likelihood estimators, and the goodness of fit of each model was assessed by the test of Hosmer and Lemeshow (24). Multivariate equations allowed for sex as well as age, family history of diabetes, smoking, alcohol, physical activity, dyslipidemia, hypertension, hyperuricemia, IGT, IFG, BMI, HOMA-IR, and Sluiter's Index at baseline. The forced entry of all these variables yielded results almost identical to those of a forward stepwise selection procedure; thus, we elected to present only data generated by fixed models.

Although there were only two time points for diabetes diagnosis (5- and 10-year follow-up), we also ran Cox proportional hazard models to account for censoring between 5 and 10 years. Cox model with fixed entry and Cox model with stepwise entry of covariates yielded results consistent and virtually identical to those of logistic regression analyses. Therefore, the results of the Cox models are not presented in this article.

Statistical analyses were performed with the SPSS-X and BMDP software. Skewed variables were $\log_e$ transformed to improve the approximation to a Gaussian distribution. Reported P values are two sided.

RESULTS

At baseline, 82 (8.9%) of 919 individuals had diabetes, as defined by WHO criteria. Seventy-four (8.0%) individuals had IFG, and 72 (7.8%) had IGT. There was some overlap between these two categories: 19 (2.1%) individuals had both IFG and IGT, 55 (5.9%) individuals had IFG and normal glucose tolerance (NGT), and 53 (5.7%) had normal fasting glucose (NFG) and IGT. The prevalence of diabetes over the age of 40 years according to WHO criteria, standardized to the structure of the population of Bruneck, was 7.2% (95% CI, 5.5–9.9), whereas the corresponding figure according to ADA criteria was 5.5% (95% CI, 4.0–7.5).

At the end of the 10-year follow-up (1990–2000), there were 64 new cases of diabetes among the 837 individuals without diabetes at baseline. The incidence was 8.2 cases per 1,000 person-years (95% CI, 6.2–10.2). The incidence standardized to the age and sex structure of the population in Bruneck was 7.6 cases per 1,000 person-years (95% CI, 5.7–9.5).

Table 1 reports incidence rates and odds ratios (ORs) for type 2 diabetes by category of candidate risk factors. The incidence, which was not significantly different in men compared with women, increased significantly across cat-

TABLE 1
Ten-year incidence rates and ORs for type 2 diabetes in various categories

Baseline clinical characteristics	Person-years	Diabetes cases	Incidence rate/1,000 person-years (95% CI)	OR (95% CI)	*P* value
Men	3,872	32	8.3 (5.4–11.2)	1.0	NS
Women	3,972	32	8.1 (5.3–10.9)	1.0 (0.6–1.7)	
Age					
40–49 years	2,360	8	3.4 (1.1–5.7)	1.0	0.0023
50–59 years	2,098	19	9.1 (5.0–13.2)	2.8 (1.2–6.5)	
60–69 years	2,021	24	11.9 (7.2–16.6)	3.6 (1.6–8.2)	
70–79 years	1,365	13	9.5 (4.4–14.6)	2.4 (1.0–6.0)	
BMI					
<25 kg/m^2	4,401	18	4.1 (2.3–5.9)	1.0	<0.001
25–30 kg/m^2	2,878	31	10.8 (7.0–14.6)	3.4 (1.8–6.3)	
>30 kg/m^2	565	15	26.5 (13.3–39.7)	9.9 (4.5–21.4)	
No hypertension	3,221	14	4.3 (2.0–6.6)	1.0	0.011
Hypertension	4,623	50	10.8 (7.8–13.8)	2.3 (1.2–4.3)	
No dyslipidemia	5,658	40	7.1 (4.9–9.3)	1.0	0.072
Dyslipidemia	2,186	24	11.0 (6.6–15.4)	1.6 (1.0–2.8)	
Normouricemia	6,779	50	7.4 (5.4–9.4)	1.0	NS
Hyperuricemia	1,065	14	13.1 (6.3–19.9)	1.7 (0.9–3.2)	
Nonsmokers	5,913	50	8.5 (6.2–10.8)	1.0	NS
Smokers	1,931	14	7.3 (3.5–11.1)	0.9 (0.5–1.7)	
No/low alcohol	6,177	45	7.3 (5.2–9.4)	1.0	NS
Moderate/high alcohol	1,667	19	11.4 (6.3–16.5)	1.8 (0.9–3.5)	
High physical activity	1,958	20	10.2 (5.7–14.7)	0.8 (0.5–1.4)	NS
Low physical activity	5,886	44	7.5 (5.3–9.7)	1.0	
No family history of diabetes	5,499	46	8.4 (6.0–10.8)	1.0	NS
Family history of diabetes	2,345	18	7.7 (4.2–11.2)	1.0 (0.6–1.8)	
No IFG	7,174	37	5.2 (3.5–6.9)	1.0	<0.001
IFG	670	27	40.3 (25.4–55.2)	10.9 (6.1–19.4)	
No IGT	7,190	47	6.5 (4.6–8.4)	1.0	<0.001
IGT	654	17	26.0 (13.8–38.2)	4.4 (2.3–8.5)	

Unadjusted incidence rates are per 1,000 person-years. ORs and *P* values are derived from a logistic regression model adjusted for age and sex (except for the comparison between sexes, which was adjusted for age only, and the comparison between age-groups, which was adjusted for sex only).

egories of age. After adjusting for sex and age, the incidence rates were approximately threefold higher in individuals with a BMI ranging from 25 to 30 kg/m^2 (versus those with BMI <25) and was ~10-fold higher in obese individuals. When individuals were stratified according to sex, age (40–59 years or 60–79 years), and BMI (normal, overweight, obesity), the incidence rate was similar in men and women of the same age and BMI range. For instance, in lean younger men, the incidence was 1.8 and in lean younger women was 1.4 per 1,000 person-years, whereas in obese older men and women, the incidence was 22.9 and 33.3 per 1,000 person-years, respectively. An increase in BMI ≥2 kg/m^2 in the period 1990–1995 was associated with an increased risk of diabetes (OR 2.2; $P = 0.007$) as compared with a stable BMI.

The incidence rate was ~2-fold higher in individuals with hypertension (versus normotensive) and ~1.5-fold higher in individuals with dyslipidemia (versus those with normal triglycerides and HDL cholesterol). In these analyses, family history of diabetes and lifestyle factors (smoking, alcohol, and physical activity) were not significantly related to incidence (Table 1).

Ten-year incidence rates for diabetes were ~11-fold higher in individuals with IFG and NGT than in individuals with NFG and NGT. Incidence in individuals with both IFG and IGT was 20-fold higher. Individuals with IGT and NFG had an incidence fourfold higher than NFG/NGT (Table 2).

When individuals were stratified into quartiles of insulin resistance (HOMA-IR) or postchallenge insulin secretion (Sluiter's Index), the sex- and age-adjusted incidence rates of diabetes increased substantially across quartiles of HOMA-IR and decreased substantially across quartiles of

TABLE 2
Ten-year incidence and ORs for type 2 diabetes according to the category of glucose homeostasis at baseline

Baseline plasma glucose categories	Person-years	Diabetes cases	Incidence rate/1,000 person-years (95% CI)	OR (95% CI)	*P* value
NFG/NGT	6,704	29	4.3 (2.7–5.9)	1.0	
NFG/IGT	471	8	17.0 (5.3–28.7)	3.9 (1.6–9.3)	0.002
IFG/NGT	486	18	37.0 (20.2–53.8)	11.0 (5.6–21.9)	<0.001
IFG/IGT	183	9	49.2 (17.9–80.5)	20.5 (7.6–55.3)	<0.001

Unadjusted incidence rates are per 1,000 person-years. ORs and *P* values are derived from a logistic regression model adjusted for age and sex. The overall *P* value is $P < 0.001$.

TABLE 3
ORs for 10-year incidence of type 2 diabetes according to HOMA-IR score (insulin resistance) and Sluiter's Index (β-cell secretion)

	Person-years	Diabetes cases	Incidence rate/1,000 person-years (95% CI)	OR (95% CI)	*P* value
Baseline HOMA-IR score*					
Quartile 1†	1,695	4	2.4 (0.1–4.7)	1.0	
Quartile 2	1,687	12	7.1 (3.1–11.1)	2.9 (0.9–9.3)	0.076
Quartile 2	1,688	11	6.5 (2.7–10.3)	2.5 (0.7–8.3)	0.126
Quartile 4	1,649	32	19.4 (12.7–26.1)	8.5 (2.9–25.1)	<0.001
Baseline Sluiter's Index‡					
Quartile 1	1,666	22	13.2 (7.7–18.7)	3.0 (1.3–6.9)	0.012
Quartile 2	1,705	12	7.0 (3.0–11.0)	1.5 (0.6–3.8)	0.374
Quartile 3	1,675	17	10.1 (5.3–14.9)	2.3 (0.9–5.4)	0.066
Quartile 4†	1,673	8	4.8 (1.5–8.1)	1.0	

Unadjusted incidence rates are per 1,000 person-years. ORs and *P* values are derived from a logistic regression model adjusted for age and sex. The slightly lower number of cases with diabetes is due to missing serum for insulin measurements in a few subjects. *The overall *P* value is <0.001; †reference category; ‡overall *P* value = 0.008.

Sluiter's Index (Table 3). In particular, individuals in the top quartile of HOMA-IR (insulin-resistant individuals) had an incidence eightfold higher than those in the bottom quartile (most insulin-sensitive individuals). For Hanson's index, those in the bottom quartile (impaired insulin secretion) had an incidence threefold higher than those in the top quartile (normal insulin secretion).

When individuals were categorized according to normal or low insulin sensitivity (HOMA-IR score below or above the median, respectively) as well as normal or low insulin secretion (Sluiter's Index above or below the median, respectively), it was found that isolated insulin resistance conferred a risk of diabetes only slightly higher than isolated β-cell dysfunction (OR 5.0 vs. 3.0), whereas the combination of the two defects resulted in a risk of diabetes approximately sevenfold higher (OR 7.1; Table 4). No interaction on risk of diabetes was found between HOMA-IR score and Sluiter's Index.

In a multivariate logistic regression analysis that included various sets of covariates, the only independent predictors of diabetes at 10-year follow-up were IFG, BMI, HOMA-IR, and Sluiter's Index at baseline (Table 5). When Sluiter's Index was not allowed to enter the model, IGT status turned out to be a significant predictor of diabetes (OR, 2.6; 95% CI, 1.1–5.5; $P = 0.015$).

In a subsidiary analysis of the 5-year follow-up (1990–1995), when follow-up postchallenge glucose levels were available, 39 of the 837 individuals without diabetes at baseline according to WHO criteria developed diabetes according to the same criteria (fasting glucose ≥7 mmol/l and/or 2-h glucose ≥11.1 mmol/l). Using these criteria for diabetes, both IFG (OR 6.90; $P < 0.001$) and IGT (OR 3.63; $P = 0.009$), along with BMI but not HOMA-IR and Sluiter's Index, were independent risk factors for incident disease. When using only fasting glucose to define diabetes at 5-year follow-up, 24 individuals developed diabetes over 5 years, i.e., more than one-third fewer than by using WHO criteria, and the risk predictors of diabetes were IFG, Sluiter's Index, and BMI, thus closely matching those identified in the 10-year follow-up analysis (data not shown).

DISCUSSION

The main results of this long-term, population-based study carried out in a low-risk white community are that *1*) the incidence rate of type 2 diabetes in individuals aged 40–79 years was 7.6 per 1,000 person-years and *2*) among a variety of candidate risk factors, IFG, overweight/obesity, insulin resistance, and impaired insulin response to oral glucose independently predicted incident diabetes.

Incidence of diabetes. Over the period of 10 years, ~1% of white individuals who were aged 40–79 years and living in northeastern Italy (i.e., central Europe) developed type

TABLE 4
Ten-year incidence and ORs for type 2 diabetes according to the category of insulin secretion and insulin resistance at baseline

Baseline insulin sensitivity and secretion	Person-years	Diabetes cases	Incidence rate/1,000 person-years (95% CI)	OR (95% CI)	*P* value
Normal sensitivity, normal secretion	1,348	3	2.2 (0–4.7)	1.0	
Normal sensitivity, low secretion	2,034	13	6.4 (2–9–9.9)	3.0 (0.8–10.7)	0.093
Normal secretion, low sensitivity	2,000	22	11.0 (6.4–15.6)	5.0 (1.5–17.3)	0.010
Low sensitivity, low secretion	1,337	21	15.7 (9.0–22.3)	7.1 (2.1–24.4)	0.002

Unadjusted incidence rates are per 1,000 person-years. ORs and *P* values are derived from a logistic regression model adjusted for age and sex. The overall *P* value is 0.007. The slightly lower number of cases with diabetes is due to missing serum for insulin measurements in a few subjects. Normal sensitivity, HOMA-IR ≤ median; low sensitivity, HOMA-IR > median; normal secretion, Sluiter's Index ≥ median; low secretion, Sluiter's Index < median.

TABLE 5
Multivariate logistic regression analysis: factors related to 10-year incidence of diabetes

Baseline characteristics	OR (95% CI)	*P* value
Model 1*		
IFG (yes vs. no)	5.9 (3.0–11.5)	<0.001
BMI (per 1-SD unit)	1.5 (1.1–2.0)	0.004
ln HOMA-IR (per 1-SD unit)	1.7 (1.1–2.6)	0.009
ln Sluiter's Index (per 1-SD unit)	0.6 (0.4–0.9)	0.007
Model 2†		
IFG (yes vs. no)	5.5 (2.8–11.0)	<0.001
BMI (per 1-SD unit)	1.5 (1.1–2.0)	0.010
ln HOMA-IR (per 1-SD unit)	1.6 (1.1–2.5)	0.021
ln Sluiter's Index (per 1-SD unit)	0.7 (0.5–0.9)	0.047
Model 3‡		
IFG (yes vs. no)	5.7 (2.8–11.4)	<0.001
BMI (per 1-SD unit)	1.5 (1.1–2.1)	0.007
ln HOMA-IR (per 1-SD unit)	1.7 (1.1–2.5)	0.018
ln Sluiter's Index (per 1-SD unit)	0.7 (0.5–1.0)	0.050

*ORs, 95% CIs, and *P* values were derived from logistic regression analysis, which also included sex and age as covariates and were calculated for a 1-SD unit increase of continuous variables; †ORs (95% CI) and *P* values were derived from logistic regression analysis, which also included sex, age, hypertension, dyslipidemia, and IGT as covariates and were calculated for a 1-SD unit increase of continuous variables; ‡ORs and *P* values were derived from logistic regression analysis, which also included sex, age, alcohol, smoking, physical activity, family history of diabetes, hypertension, dyslipidemia, hyperuricemia, and IGT as covariates and were calculated for a 1-SD unit increase of continuous variables.

2 diabetes every year. This figure tentatively includes also those diabetic individuals who would have received a diagnosis had we performed the OGTT also at the 10-year follow-up. In fact, on the basis of the 5-year follow-up, at which we performed an OGTT, we estimate that the number of patients whose diabetes we could have diagnosed by carrying out the OGTT also at the 10-year follow-up would have been at least 30% more of all ascertained cases.

Most of the individuals who developed diabetes were older than 50 years and were overweight or obese, without any significant difference between men and women. Incidence was very low in lean individuals who were younger than 50 years (<2 cases per 1,000 patient-years) but was very high in obese older subjects (~30 cases per 1,000 person-years).

The incidence rate of type 2 diabetes that we report in the present study, which surveyed a population that was homogeneous for lifestyle, is generally higher than that reported in older studies carried out in the U.S. on low-risk populations of the same age range (4–9). In these studies, the annual incidence ranged from 2 to 8 per 1,000 person-years, but the diagnosis was based on higher glucose thresholds. In more recent American studies that were based on current diagnostic criteria and carried out in white individuals of the same age range of individuals of our study, an incidence ranging from 10 to 15 per 1,000 person-years was observed, i.e., greater than what we found in our present study (11,25–28). The finding is probably mainly due to the lower prevalence of obesity in Bruneck (<10%) as compared with the U.S. (29), but also differences in the genetic background, in the exposure to diabetogenic environmental factors, and in the demographic features of the study populations could be involved.

To the best of our knowledge, besides the Bruneck Study, there has been only one other population-based diabetes incidence survey carried out in Europe using blood glucose levels to define diabetes. In the Hoorn Study, De Vegt et al. (30) reported a cumulative incidence of diabetes of 8.3% over the 6.4 years of follow-up of 1,342 Dutch subjects, corresponding to an incidence rate of ~13 cases per 1,000 person-years. This is higher than in Bruneck, but compared with people in Bruneck, individuals in the Hoorn sample were older, the prevalence of overweight/obesity was higher, and diabetes was defined using both fasting plasma glucose and postchallenge glycemia. Although there have been many other European diabetes surveys, they all have relied on self-reported diabetes to define cases (31–36). Self-reported diabetes is prone to substantial underestimations of the true prevalence of diabetes, and surveillance bias (e.g., increased community awareness or diabetes in family members may increase diabetes surveillance) and confounding by indication (e.g., individuals with hypertension may be more likely to get a diabetes diagnosis as a result of medical visits and biochemical testing) may distort true underlying incidence rates. Accordingly, the incidence rate was lower in these studies than in our study and ranged from 1 to 4 cases per 1,000 person-years.

An extrapolation of our results to Italy would lead to an estimate of 250,000 new cases of type 2 diabetes per year in the decade 1990–2000 among individuals older than 40 years. This figure should be increased by ~10% if the extrapolation is extended to the entire Italian population to include also those cases that manifest at an age earlier than 40 years (37).

Although any extrapolation should be taken with great caution, our results suggest that in Europe (~800 million inhabitants), the new cases of type 2 diabetes that occurred in the period 1990–2000 might be ~3.5 million per year. This figure may be close to reality because Bruneck is located in central Europe, near one of the main routes of communication between northern and Mediterranean countries, and may be considered fairly representative of the continent.

Risk factors for type 2 diabetes. Several clinical conditions individually predicted the incident development of type 2 diabetes in our study. Many of these risk conditions, including IFG, IGT, insulin resistance, low insulin secretion in response to glucose, overweight/obesity, hypertension, and dyslipidemia, have already been reported by other investigators (2–12,25–28,30–35). However, in this analysis, we found that among many individual risk factors, only IFG, BMI, insulin resistance, and hyposecretion of insulin in the face of glucose challenge were the significant independent predictors of diabetes.

The observation that HOMA-IR and Sluiter's Index can predict diabetes provides one of the first evidences in a low-risk white population that insulin resistance and impaired insulin secretion are key abnormalities in the pathogenesis of the disease, also independently of BMI and IFG. This finding is consistent with previous investigational studies (38–41) and also with clinical trials in which chronic treatment with insulin sensitizers, such as

metformin or troglitazone, or with a short-acting insulin secretagogue, such as tolbutamide, was able to prevent diabetes in high-risk individuals (42–44). HOMA-IR is a reliable surrogate measure of whole-body insulin resistance (17), predicting both diabetes and cardiovascular disease outcomes in many epidemiological studies (45–49). Indeed, HOMA-estimated insulin resistance is strongly correlated with clamp-measured insulin sensitivity (18), and the latter mainly reflects skeletal muscle insulin sensitivity (50). Thus, one might conclude that the impaired effect of the hormone on the skeletal muscle predicts type 2 diabetes. Sluiter's Index is a reliable measure of insulin secretion that can be taken to reflect the β-cell response in the postprandial period (19,20). Thus, one might speculate that an impaired insulin secretion after the meal predicts diabetes. It is interesting that the association of both abnormalities in the same individual seems to be particularly hazardous. We found that individuals with low insulin sensitivity and low insulin secretion had a risk of diabetes sevenfold higher. Collectively, these results point out the potential of predicting type 2 diabetes from simple physiological measures and not merely from risk markers.

The finding that IFG is able to predict diabetes in addition to and independent of HOMA-IR and Sluiter's Index merits a specific comment. IFG is conceivably related to the interplay between hepatic insulin resistance and inappropriate β-cell secretion, both contributing to unrestrained glucose production (38–41). High correlations between hepatic glucose production and fasting glucose concentration have been shown previously (51). The strength of IFG to predict diabetes may be related to the key role of the liver in the pathogenesis of the disease (41). It is interesting that other investigators and ourselves have recently reported that fasting glucose and, hence, IFG is inversely related to first-phase insulin secretion (40,52). The impairment of the latter is a crucial step in the progression to diabetes (39,53). The finding that Sluiter's Index, which is a presumed marker of second-phase insulin response to glucose, and IFG, which might represent first-phase insulin secretion, are able to predict independently the progression to diabetes indicates that both phases of β-cell secretion are important in the maintenance of the normal glucose homeostasis as well as in the origin of the disease. This conclusion needs to be confirmed by specific studies in which more direct measures of first- and second-phase insulin secretion are used to predict diabetes.

The independent role of BMI in predicting diabetes deserves a further comment. BMI is a surrogate index of percentage of body fat mass. It is generally held that excess fat favors the onset of the disease primarily through insulin resistance. In fact, adipose tissue is a pivotal site of insulin resistance (54) and, at the same time, a putative contributor to the pathogenesis of insulin resistance in other tissues, because it releases several molecules that affect the biological action of insulin at the level of liver and skeletal muscle (38,54). These molecules include free fatty acid, tumour necrosis factor-α, interleukin-6, resistin, adiponectin, and others (55). Moreover, lipotoxicity has been described in the β-cell (56). However, our finding that BMI predicts diabetes independently of HOMA-IR might unveil an obesity-related mechanism that is distinct from insulin resistance gauged by HOMA-IR. BMI but not HOMA-IR might reflect the magnitude of adipose tissue insulin resistance. Alternatively, BMI might reflect the independent contribution of adipose tissue to the pathogenesis of diabetes with a role that is not related to insulin resistance. The finding of BMI as an important contributor to the development of diabetes on a population basis has important prevention implications, as intervention studies that were based on weight loss programs successfully reduced the incidence of diabetes (44,57).

In contrast to IFG, IGT was not an independent predictor of diabetes. It could be argued that only fasting glucose was used to diagnose diabetes at the 10-year follow-up and that many individuals with the so-called "isolated postchallenge hyperglycemia," i.e., a form and/or stage of diabetes detectable only with the OGTT, would be expected to have IGT at baseline. In other words, the predictive power of baseline IGT would be magnified by the use of OGTT at the follow-up to diagnose diabetes and would be blunted by the use of fasting glucose only. In partial support of this conclusion are our findings based on the 5-year follow-up data, when we repeated the OGTT and the diagnosis of diabetes could also be made by OGTT criteria. In fact, the analysis that focused on 5-year incidence clearly demonstrated that IGT was an independent predictor of diabetes when WHO criteria were used but not when ADA criteria were used. An alternative hypothesis is that the collinearity between IGT and Sluiter's Index, which are both based on 2-h glucose levels, might prevent IGT to enter the predictive model. In fact, when Sluiter's Index was not included in the multivariate model that examined risk factors for 10-year diabetes incidence, IGT was a statistically significant predictor.

A major finding of the present study is that the development of a multiorgan disease such as type 2 diabetes, which is rooted in abnormalities of insulin secretion by the β-cell; in altered insulin action on liver, skeletal muscle, and adipose tissue; and in the secretory activity of the adipocytes, can be predicted by parameters that describe the function of the pancreatic β-cell (Sluiter's Index and, probably, IFG status), the effect of insulin on the liver (IFG status), the effect of the hormone on the skeletal muscle (HOMA-IR), and the size of the adipose tissue (BMI).

CONCLUSIONS

The major strengths of the our study are *1*) inclusion of both men and women of a wide age range (40–79 years); *2*) a large sample from the background population (~20% of individuals of the pertinent age); *3*) short period of enrollment at both baseline and the follow-up (2–5 months), which allowed high reproducibility of methods; *4*) high participation rate at both baseline and follow-up (>90%); *5*) long-term follow-up (10 years); *6*) diagnosis of diabetes by measuring plasma glucose; and *7*) evaluation of several candidate risk factors, including insulin resistance and insulin secretion. Moreover, in contrast to most previous studies, the study cohort was composed of white individuals. Limitations of the present study include *1*) use of a surrogate measure of insulin resistance, *2*) lack of a direct assessment of first-phase insulin secretion, and *3*) lack of OGTT data at the 10-year follow-up examination.

The first two limitations are virtually inevitable in the epidemiological setting. The lack of OGTT at the 10-year follow-up examination resulted in an underestimation of diabetes incidence. Five-year follow-up data suggest that this underestimation should be ~30%.

In conclusion, this long-term, longitudinal, population-based study provides information on the incidence rate of type 2 diabetes in a representative European community and indicates that IFG, BMI, and simple measures of insulin resistance and insulin secretion can independently predict the future development of the disease. The latter information is pivotal in identifying individuals who are at risk. Interventions to prevent diabetes might focus on improving insulin secretion and insulin resistance and/or reducing the excess of body fat. However, it is reasonable to hypothesize that a multiple-target approach might be most effective.

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