# Predictors of and Longitudinal Changes in Insulin Sensitivity and Secretion Preceding Onset of Type 2 Diabetes

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**Identification of individuals at high risk of developing type 2 diabetes is a prerequisite for prevention of the disease. We therefore studied risk factors predicting type 2 diabetes in the Botnia Study in western Finland. A total of 2,115 nondiabetic individuals were prospectively followed with repeated oral glucose tolerance tests. After a median follow-up of 6 years, 127 (6%) subjects developed diabetes. A family history of diabetes (hazard ratio [HR] 2.2, $P = 0.008$), BMI (HR for comparison of values below or above the median 2.1, $P < 0.001$), waist-to-height index (2.3, $P < 0.001$), insulin resistance (2.1, $P = 0.0004$), and β-cell function adjusted for insulin resistance (2.7, $P < 0.0001$) predicted diabetes. Marked deterioration in β-cell function with modest changes in insulin sensitivity was observed during the transition to diabetes. The combination of FPG ≥5.6 mmol/l, BMI ≥30 kg/m$^2$, and family history of diabetes was a strong predictor of diabetes (3.7, $P < 0.0001$). Of note, using FPG ≥6.1 mmol/l or 2-h glucose ≥7.8 mmol/l did not significantly improve prediction of type 2 diabetes. In conclusion, a marked deterioration in β-cell function precedes the onset of type 2 diabetes. These individuals can be identified early by knowledge of FPG, BMI, and family history of diabetes. *Diabetes* 54:166–174, 2005**

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DPS, Diabetes Prevention Study; FFA, free fatty acid; FPG, fasting plasma glucose; HOMA, homeostasis model assessment; $HOMA_{IR}$, HOMA of insulin resistance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NCEP, National Cholesterol Education Program; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; ROC, receiver operator curve; WHO, World Health Organization; WHR, waist-to-hip ratio.



Type 2 diabetes is a metabolic disorder resulting from a collision between genetic and environmental factors. The disease is characterized by impaired β-cell function and insulin action, but the contribution of these defects to the pathogenesis of the disease is subject to great heterogeneity. The number of subjects with type 2 diabetes around the world is estimated to rise to 300 million by the year 2025, and this has been attributed to increased prevalence of obesity and senescence in the westernized world (1). Risk factors for type 2 diabetes seem to differ between ethnic groups. Consistent in all of them, a family history of diabetes confers an increased risk of developing type 2 diabetes, but its relative effect decreases with increasing prevalence of type 2 diabetes in the population. Low level of physical activity has been associated with risk of diabetes. The incidence of type 2 diabetes in individuals with impaired glucose tolerance can be reduced through diet and exercise (2). Clustering of other risk factors, like abdominal obesity, insulin resistance, hypertension and dyslipidemia, referred to as the dysmetabolic syndrome, confers an increased risk of type 2 diabetes (3,4), but this risk also varies with the prevalence of the individual components in the population. Glucose concentration per se is a strong predictor of the development of type 2 diabetes. Although both impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) have been shown to confer an increased risk for type 2 diabetes (5), this risk has varied widely between ethnic groups.

The Botnia study was initiated in 1990 to identify genes predisposing to type 2 diabetes. To date, the study includes ~9,000 individuals from 1,400 families in Finland and Sweden. Nondiabetic individuals from the original cohort in western Finland have been followed prospectively with repeated oral glucose tolerance tests (OGTTs) to detect progression to overt type 2 diabetes. In this study we have evaluated risk factors for the development of type 2 diabetes in 1,715 members from families with type 2 diabetes and in 400 control subjects without a family history of type 2 diabetes, followed for a median of 6 years.

## RESEARCH DESIGN AND METHODS

The Botnia Study is a family-based study aiming at the identification of genes increasing susceptibility to type 2 diabetes. Details of the study cohort and sampling strategy were presented earlier (6). In brief, subjects with type 2

TABLE 1
Clinical characteristics of the subjects according to glucose tolerance at baseline

| | NGT | | IFG-IGT | |
|---|---|---|---|---|
| | Men | Women | Men | Women |
| *n* | 638 (45) | 791 (55) | 329 (48) | 357 (52) |
| Smoking | 334/625 (53.4) | 208/777 (26.8) | 187/325 (57.5) | 70/349 (20) |
| Age (years) | 44 ± 12 | 45 ± 12* | 49 ± 12 | 51 ± 12* |
| BMI (kg/m$^2$) | 25.7 ± 3.2 | 25.0 ± 4.0† | 26.6 ± 3.1 | 27.4 ± 5.1* |
| Waist-height index (cm/m$^2$) | 29.3 ± 3.6 | 30.1 ± 4.4† | 30.9 ± 3.4 | 33.0 ± 5.0† |
| WHR | 0.93 ± 0.06 | 0.82 ± 0.07† | 0.95 ± 0.06 | 0.84 ± 0.07† |
| $HbA_{1c}$ (%) | 5.4 ± 0.5 | 5.3 ± 0.5* | 5.5 ± 0.4 | 5.5 ± 0.6 |
| Plasma glucose (mmol/l) | | | | |
| Fasting | 5.52 (5.14–5.76) | 5.31 (5.0–5.65)† | 6.22 (5.99–6.44) | 6.10 (5.65–6.33)† |
| 2-h | 5.53 (4.75–6.23) | 5.73 (5.09–6.44)† | 7.40 ± 1.54 | 8.05 ± 1.30† |
| Serum insulin (mU/l) | | | | |
| Fasting | 4.0 (3.0–5.7) | 4.0 (2.9–5.5) | 5.4 (4.0–8.3) | 5.3 (3.8–8.2)* |
| 2-h | 18.9 (11.1–30.1) | 23.8 (15.5–34.5)† | 34.1 (21.0–62.7) | 47.2 (27.4–74.1)† |
| $HOMA_{IR}$ | 0.97 (0.73–1.39) | 0.94 (0.68–1.32) | 1.47 (1.09–2.23) | 1.41 (0.96–2.21)* |
| Insulinogenic index | 11.3 (6.8–18.8) | 15.1 (9.0–27.9)† | 11.2 (6.5–19.2) | 11.8 (7.2–21.1) |
| Disposition index | 11.2 (7.0–18.5) | 15.4 (8.9–29.4)† | 7.0 (4.6–11.6) | 8.6 (5.3–14.8)* |
| Systolic blood pressure (mmHg) | 127.4 ± 15.5 | 124.4 ± 16.8† | 133.9 ± 18.0 | 135.2 ± 20.2 |
| Diastolic blood pressure (mmHg) | 78.4 ± 10.6 | 77.0 ± 9.9* | 81.6 ± 10.8 | 81.0 ± 11.3 |
| Total cholesterol (mmol/l) | 5.56 ± 1.08 | 5.44 ± 1.12* | 5.72 ± 1.16 | 5.87 ± 1.13 |
| LDL cholesterol (mmol/l) | 3.67 ± 1.04 | 3.41 ± 1.11† | 3.75 ± 1.20 | 3.78 ± 1.06 |
| HDL cholesterol (mmol/l) | 1.28 ± 0.29 | 1.51 ± 0.32† | 1.18 ± 0.25 | 1.45 ± 0.32† |
| Triglycerides (mmol/l) | 1.14 (0.88–1.55) | 0.96 (0.73–1.29)† | 1.39 (0.99–2.02) | 1.2 (0.87–1.64)† |
| FFA (mmol/l) | 577.5 (484–710.3) | 706.9 ± 184.2† | 657.5 (520–805.8) | 801.5 ± 261.3* |
| Apolipoprotein B (mg/dl) | 93.7 ± 21.0 | 85.7 ± 22.1† | 97.3 ± 22.2 | 95.3 ± 23.7* |
| Physical activity, metabolic equivalents (s/day)[3] | 7.25 (4.75–9.25) | 5.88 (3.5–8.0)† | 5.95 (3.75–8.04) | 5.0 (2.48–8.0)* |
| Physical activity level | 1.24 (1.16–1.32) | 1.21 (1.13–1.30) | 1.21 (1.12–1.29) | 1.19 (1.09–1.30) |

Data are *n* (%), means ± SD, or median (interquartile range). *P* values for the comparison of men and women within each group of glucose tolerance are adjusted for differences in age and BMI. *$P < 0.05$; †$P < 0.0001$.

diabetes from the area of five health care centers in western Finland were invited to participate together with their family members. An OGTT was performed for subjects with fasting blood glucose <10 mmol/l. Nondiabetic subjects, either family members of type 2 diabetic patients or control subjects (spouses without first- or second-degree family history of diabetes) aged between 18 and 70 years, were invited to prospective visits every 2–3 years. Members from families with maturity-onset diabetes of the young were followed separately and were excluded from the present study. During 1990–2002, 1,715 subjects with a family history of diabetes and 400 control subjects participated in at least two OGTT tests, with a median follow-up of 6 years (range 2–12 years). Of them, 1,429 had normal glucose tolerance (NGT), and 686 had IFG and/or IGT at the baseline examination. Glucose tolerance was classified according to the current World Health Organization (WHO) criteria, with IFG defined as fasting plasma glucose (FPG) ≥6.1 mmol/l (7). All participants gave informed consent, and the local ethics committee approved the study.

**Anthropometric and metabolic measurements.** As explained in detail elsewhere (6), we measured the subjects' weight, height, waist and hip circumference, fat-free mass (Futrex, Gaithersburg, MD), and blood pressure (mean of two recordings). BMI was calculated as weight (kg) divided by height squared (m$^2$), waist-to-hip ratio (WHR) as waist divided by hip circumference, and the waist-height index as waist circumference (cm) divided by height squared (m$^2$). All subjects participated in a 75-g OGTT after a 12-h overnight fast. Fasting blood samples were drawn for the measurement of serum total cholesterol, HDL cholesterol, triglyceride, apolipoprotein B, and free fatty acid (FFA) concentrations, and they were drawn at −10, 0, 30, 60, and 120 min for the measurement of plasma glucose and serum insulin. Insulin resistance was estimated as the homeostasis model assessment (HOMA) of insulin resistance ($HOMA_{IR}$; calculated as fasting serum insulin × FPG/22.5) and β-cell function as the ratio of incremental insulin ($\Delta I_{30}$) to glucose ($\Delta G_{30}$) responses during the first 30 min of the OGTT ($\Delta I/\Delta G = I_{30} - I_0/G_{30} - G_0$), also called the insulinogenic index. The disposition index was used to adjust insulin secretion for the degree of insulin resistance (insulinogenic index/$HOMA_{IR}$).

At the baseline examination, a structured questionnaire was used to collect data on smoking habits and physical activity during work, on the way to work, and during leisure time (8). The physical activity data were converted into metabolic units, and the physical activity level was calculated. The dysmetabolic syndrome was defined using either WHO (7) or National Cholesterol Education Program (NCEP) criteria (9).

**Assays.** We measured the concentration of plasma glucose with a glucose oxidase method (glucose analyzer; Beckman Instruments, Fullerton, CA) and serum insulin by an enzyme immunoassay (Dako, Cambridgeshire, U.K.) with an interassay coefficient of variation of 7.5. Serum total cholesterol, HDL cholesterol, and triglyceride concentrations were measured on a Cobas Mira analyzer (Hoffman LaRoche, Basel, Switzerland), and the LDL cholesterol concentration was calculated using the Friedewald formula. The serum concentration of apolipoprotein B was measured by immunochemical assay (Orion Diagnostica, Espoo, Finland) and that of FFAs by an enzymatic colorimetric method (Wako Chemicals, Neuss, Germany).

**Statistical analyses.** Normally distributed continuous variables are presented as the means ± SD and nonnormally distributed values as median and interquartile range. ANCOVA was used to compare group means of continuous variables (which, if necessary, were logarithmically transformed) and $\chi^2$ test (Fisher's exact test) for comparison of group frequencies. The age at onset of type 2 diabetes was analyzed with the Cox proportional hazards model. Data were treated as left truncated and right censored. The covariate measurements were made at entry time. All survival analyses were performed with a robust variance estimate to adjust for within-family dependence. Univariate and multivariate Cox analyses on the effects of risk factors for type 2 diabetes were performed stratified by sex and adjusted for BMI (as a continuous covariate), except for BMI, waist-height index, WHR, and any combination of risk factors for type 2 diabetes that included BMI. Individuals with missing data for any of the covariates were excluded from the analyses. The numbers needed to screen to identify one future case of diabetes in "test-positive" individuals were calculated as the inverse of the estimated prevalence of undiagnosed diabetes in the risk groups.

A generalized estimating equation procedure was used to test differences in diabetes-related phenotypes over time between those who developed (converters) and those who did not develop (nonconverters) type 2 diabetes adjusted for age, BMI, a family history of diabetes, and sex. The number of visits varied between individuals, 1,372 persons had one, 392 had two, 219 had

TABLE 2
Comparison of baseline characteristics between NGT subjects who remained NGT or who developed IFG-IGT or type 2 diabetes during follow-up

| | NGT | IFG-IGT | Type 2 diabetes | *P* |
|---|---|---|---|---|
| *n* (M/F) | 1,190 (515/675) | 199 (100/99) | 40 (23/17) | |
| Age (years) | 44 ± 12 | 48 ± 12 | 51 ± 12 | <0.0001 |
| BMI (kg/m$^2$) | 25.1 ± 3.6 | 26.4 ± 3.6 | 26.4 ± 4.8 | <0.0001 |
| Waist-height index (cm/m$^2$) | 29.4 ± 4.3 | 31.1 ± 4.5 | 31.2 ± 4.3 | 0.0038 |
| WHR | 0.86 ± 0.09 | 0.89 ± 0.08 | 0.90 ± 0.07 | 0.044 |
| Plasma glucose (mmol/l) | | | | |
| Fasting | 5.42 (5.03–5.71) | 5.48 (5.20–5.71) | 5.54 (5.25–5.86) | 0.014 |
| 2-h | 5.65 (4.86–6.33) | 5.99 (5.23–6.69) | 5.76 (4.63–6.70) | 0.0008 |
| Serum insulin (mU/l) | | | | |
| Fasting | 3.87 (2.96–5.42) | 4.49 (3.26–6.27) | 4.49 (2.45–8.35) | 0.0029 |
| 2-h | 20.8 (13.0–32.1) | 25.3 (15.7–45.2) | 23.5 (9.6–56.9) | 0.0027 |
| $HOMA_{IR}$ | 0.93 (0.69–1.31) | 1.08 (0.79–1.56) | 1.12 (0.60–2.07) | 0.0008 |
| Insulinogenic index | 13.4 (7.9–24.6) | 12.9 (7.7–21.0) | 9.6 (5.9–17.0) | 0.26 |
| Disposition index | 13.8 (8.1–24.8) | 11.0 (7.2–19.6) | 5.9 (4.4–14.2) | 0.0012 |
| Systolic blood pressure (mmHg) | 124.7 ± 16.1 | 130.4 ± 16.5 | 132.7 ± 17.6 | 0.08 |
| Diastolic blood pressure (mmHg) | 76.9 ± 10.1 | 80.9 ± 10.1 | 82.5 ± 10.3 | 0.0059 |
| Total cholesterol (mmol/l) | 5.47 ± 1.10 | 5.55 ± 1.03 | 5.73 ± 1.30 | 0.38 |
| LDL cholesterol (mmol/l) | 3.52 ± 1.07 | 3.56 ± 1.12 | 3.57 ± 1.40 | 0.081 |
| HDL cholesterol (mmol/l) | 1.42 ± 0.33 | 1.35 ± 0.31 | 1.37 ± 0.37 | 0.24 |
| Triglycerides (mmol/l) | 1.01 (0.8–1.4) | 1.11 (0.87–1.46) | 1.25 (0.98–1.81) | 0.27 |
| FFA (mmol/l) | 641.0 (527.0–764.5) | 704.9 ± 182.0 | 750.2 ± 220.4 | 0.045 |
| Apolipoprotein B (mg/dl) | 88.5 ± 22.1 | 93.9 ± 21.5 | 90.5 ± 19.3 | 0.20 |
| Physical activity, metabolic equivalents (s/day$^3$) | 6.55 (4.46–8.75) | 5.75 (3.5–8.0) | 5.45 (2.49–8.99) | 0.044 |
| Physical activity level | 1.23 (1.15–1.31) | 1.22 (1.12–1.28) | 1.20 (1.09–1.31) | 0.037 |

Data are the means ± SD or median (interquartile range). *P* values (ANCOVA) were adjusted for age, sex, and BMI.

three, and 132 had four follow-up visits. The generalized estimating equation corrects for the potential problem that one person with more visits contributed more to the change over time than a person with fewer visits. In the generalized estimating equation, the standard errors were adjusted for repeated measurements in the same person with a robust variance estimator (10,11). The final measurement for converters was made at the visit when diabetes was diagnosed, and that for nonconverters was made at the last visit in the study. All statistical analyses were performed using Number Crunching Statistical Systems, version 2000 (Kaysville, UT), R software (available online at www.r-project.org), and Stata (StataCorp). Two-sided *P* values <0.05 were considered statistically significant.

## RESULTS

**Clinical characteristics at baseline and follow-up.** In total, we included 1,715 relatives of patients with type 2 diabetes and 400 control subjects without family history of diabetes (Table 1). Of 1,165 individuals with information available on parental diabetes, 43% had a diabetic mother, compared with 28% with a diabetic father ($P < 0.05$). Among the 686 subjects (32.4%), with abnormal glucose tolerance at the baseline examination, 263 (12.4%) had isolated IFG, 250 (11.8%) had isolated IGT, and 173 (8.2%) had both IFG and IGT. During the median follow-up of 6 years, 127 (6%) subjects developed diabetes. As expected, the glucose tolerance worsened more often in subjects with IFG or IGT than in subjects with NGT. Among those with NGT at baseline, 1,189 (83.2%) retained NGT, 199 (13.9%) progressed to IFG-IGT, and 41 (2.9%) developed type 2 diabetes. Of those with abnormal glucose tolerance at baseline, 379 (55.3%) converted to NGT, 221 (32.2%) retained IFG-IGT, and 86 (12.5%) progressed to type 2 diabetes.

Men had higher fasting but lower 2-h plasma glucose levels than women. Consequently, there was a significant sex difference in the occurrence of IFG and IGT; IFG was seen more often in men than in women (16.2 vs. 9.2%, $P < 0.001$), whereas IGT was more common in women than in men (13.5 vs. 9.8%, $P = 0.009$). Men had higher serum concentrations of total cholesterol, LDL cholesterol, apolipoprotein B, and triglycerides and lower concentrations of HDL cholesterol, whereas women had higher fatty acid levels than men (Table 1).

NGT subjects who converted to IGT or type 2 diabetes were older at baseline; had higher BMI, waist-height index, and plasma glucose; had lower disposition index; and were more insulin resistant than those who remained NGT (Table 2). They also had higher fasting serum FFA levels and a lower level of daily physical activity. Similarly, IFG-IGT subjects who converted to type 2 diabetes were older and had higher BMI, waist-height index, and initial glucose and insulin concentrations and lower insulinogenic and disposition indexes than those who reverted to NGT (Table 3).

**Individual risk factors for type 2 diabetes.** Table 4 shows estimated hazard ratios (HRs) for individual risk factors (based on Cox proportional hazard regression models comparing subjects with values above or below the median) for the development of diabetes. A family history of diabetes (HR 2.2, $P = 0.008$) and smoking (1.5, $P = 0.041$) were associated with an increased risk of type 2 diabetes. Subjects with BMI, waist-height index, WHR, or waist circumference above the median had an approximately twofold ($P = 0.0002$) increased risk of diabetes compared with those with values below the median; this effect was stronger in subjects with IFG-IGT. In general, of the different measurements of total or abdominal obesity, waist-height index was the strongest predictor of type 2 diabetes (HR 2.3, $P = 0.0002$). However, the sensitivity (77,

TABLE 3
Comparison of baseline characteristics between IFG-IGT subjects who converted to NGT, remained IFG-IGT or developed type 2 diabetes during follow-up

| | NGT | IFG-IGT | Type 2 diabetes | *P* |
|---|---|---|---|---|
| *n* (M/F) | 379 (189/190) | 221 (97/124) | 86 (43/43) | |
| Age (years) | 48 ± 12 | 53 ± 12 | 52 ± 11 | <0.0001 |
| BMI (kg/m$^2$) | 26.2 ± 4.1 | 27.4 ± 4.2 | 29.4 ± 4.2 | <0.0001 |
| Waist-height index (cm/m$^2$) | 31.1 ± 4.4 | 32.5 ± 4.1 | 34.5 ± 4.2 | 0.097 |
| WHR | 0.89 ± 0.09 | 0.89 ± 0.09 | 0.92 ± 0.1 | 0.37 |
| $HbA_{1c}$ (%) | 5.4 ± 0.5 | 5.7 ± 0.6 | 5.7 ± 0.4 | 0.0010 |
| Plasma glucose (mmol/l) | | | | |
| Fasting | 6.16 (5.76–6.38) | 6.16 (5.59–6.38) | 6.27 (5.76–6.61) | 0.22 |
| 30-min | 9.28 ± 1.49 | 9.70 ± 1.41 | 10.19 ± 1.50 | <0.0001 |
| 2-h | 7.44 ± 1.34 | 8.03 ± 1.46 | 8.29 ± 1.64 | <0.0001 |
| Serum insulin (mU/l) | | | | |
| Fasting | 4.95 (3.63–7.49) | 5.52 (3.95–8.31) | 7.27 (4.85–10.93) | 0.054 |
| 2-h | 32.2 (22.9–58.0) | 48.2 (26.8–72.1) | 60.6 (32.2–112.0) | 0.0003 |
| $HOMA_{IR}$ | 1.34 (0.96–2.03) | 1.48 (1.03–2.24) | 1.83 (1.32–3.0) | 0.043 |
| Insulinogenic index | 12.7 (7.2–20.0) | 9.8 (6.0–18.4) | 11.5 (8.1–23.5) | 0.009 |
| Disposition index | 8.6 (5.6–14.8) | 6.9 (4.3–11.4) | 5.9 (3.5–11.1) | 0.0004 |
| Systolic blood pressure (mmHg) | 130 (119–141) | 135.5 (123.1–147) | 140.0 (127–158) | 0.17 |
| Diastolic blood pressure (mmHg) | 80.2 ± 11.6 | 81.9 ± 10.2 | 84.7 ± 10.5 | 0.62 |
| Total cholesterol (mmol/l) | 5.8 ± 1.2 | 5.8 ± 1.1 | 5.8 ± 0.9 | 0.23 |
| LDL cholesterol (mmol/l) | 3.78 ± 1.15 | 3.73 ± 1.13 | 3.76 ± 1.04 | 0.051 |
| HDL cholesterol (mmol/l) | 1.34 ± 0.32 | 1.33 ± 0.32 | 1.24 ± 0.30 | 0.31 |
| Triglycerides (mmol/l) | 1.2 (0.86–1.77) | 1.35 (1.0–1.84) | 1.61 (1.05–2.07) | 0.68 |
| FFA (mmol/l) | 695.0 (547.3–875.5) | 755.4 ± 219.3 | 768.2 ± 233.2 | 0.92 |
| Apolipoprotein B (mg/dl) | 95.3 ± 23.2 | 96.7 ± 22.7 | 93.2 ± 24.5 | 0.60 |
| Physical activity, metabolic equivalents (s/day$^3$) | 5.8 (3.5–8.5) | 5.0 (2.7–7.7) | 4.8 (1.9–7.3) | 0.12 |
| Physical activity level | 1.21 (1.12–1.30) | 1.19 (1.10–1.28) | 1.17 (1.08–1.26) | 0.18 |

Data are the means ± SD or median (interquartile range). *P* values (ANCOVA) were adjusted for age, sex, and BMI.

68, 72, and 73%) and specificity (52, 51, 53, and 51%) of waist-height index, WHR, waist circumference, and BMI, respectively, were relatively similar in the prediction of type 2 diabetes. Also high triglycerides ($P = 0.039$), low HDL cholesterol ($P = 0.025$) concentrations, and high diastolic blood pressure ($P = 0.016$) were associated with a moderately increased risk of subsequent type 2 diabetes.

Both insulin resistance estimated as $HOMA_{IR}$ (HR 2.1, $P = 0.0004$) and impaired β-cell function estimated as insulinogenic index (1.5, $P = 0.039$) were predictors of type 2 diabetes. β-Cell function adjusted for the degree of insulin resistance, i.e., the disposition index (2.7, $P < 0.0001$), more than doubled the risk of type 2 diabetes, and this effect was particularly seen in subjects with NGT (HR 2.8, 95% CI 1.4–5.8, $P = 0.005$). The risk of developing diabetes increased gradually from isolated IFG (HR 2.3, $P = 0.0007$) to isolated IGT (3.5, $P < 0.0001$) and combined IFG-IGT (3.8, $P < 0.0001$) when compared with NGT.

**Combination of risk factors.** Subjects with the dysmetabolic syndrome had an approximately 3.5-fold ($P < 0.0001$) increased risk of type 2 diabetes; this risk was similar whether we used WHO or NCEP criteria (Table 4). Because assessment of the components of the dysmetabolic syndrome may be cumbersome in clinical practice, we also restricted the risk assessment to information on family history of diabetes, BMI, and FPG concentration. Individuals with a combination of a family history of diabetes, FPG ≥5.6 mmol/l, and BMI ≥30 kg/m$^2$ had a high risk of developing type 2 diabetes (HR 3.7, $P < 0.0001$ compared with those with zero, one, or two risk factors; and HR 13.0, $P < 0.0001$ compared with subjects without any risk factors) (Table 5 and Fig. 1). Using these criteria, we estimated that the number needed to screen to identify one person who will develop diabetes was six. Adding hypertension (HR 4.7, 95% CI 2.9–7.5, $P < 0.0001$) or dyslipidemia (HR 3.7, 2.1–6.6, $P < 0.0001$) to the risk factors did not significantly change the risk of developing type 2 diabetes, but the number of individuals with all five risk factors was very small ($n = 18$).

If we instead use FPG ≥6.1 mmol/l in combination with family history of diabetes and BMI ≥30 kg/m$^2$, the HR increases to 5.4 (95% CI 3.1–9.6, $P < 0.0001$). Notably, using 2-h glucose ≥7.8 mmol/l from the OGTT instead of FPG ≥6.1 mmol/l did not significantly improve the prediction (HR 5.0, 95% CI 2.6–9.5, $P < 0.0001$). The number needed to screen for FPG ≥6.1 mmol/l and for 2-h glucose ≥7.8 mmol/l instead of FPG ≥5.6 mmol/l was four.

Sensitivity (22, 16, and 13%), specificity (95, 97, and 98%), positive predictive value (21, 29, and 31%), and the area under the receiver operator curve (ROC) curve (74, 75, and 75%) did not significantly differ for the combinations *1*) family history of diabetes, FPG ≥5.6 mmol/l, and BMI ≥30 kg/m$^2$; *2*) family history of diabetes, FPG ≥6.1 mmol/l, and BMI ≥30 kg/m$^2$; and *3*) family history of diabetes, 2-h glucose ≥7.8 mmol/l, and BMI ≥30 kg/m$^2$, respectively. The corresponding values for IFG, IGT, and IFG and/or IGT were determined, respectively, for sensitivity (44, 49, and 68%), specificity (81, 82, and 70%), positive predictive value (13, 15, and 13%), and area under the ROC curve (63, 65, and 69%).

**Changes in insulin resistance and β-cell function over time.** Although subjects who developed diabetes (converters) were more insulin resistant already at baseline, their insulin resistance ($HOMA_{IR}$) worsened more

TABLE 4
Univariate analyses of risk factors for type 2 diabetes

| | All subjects | | Men | | Women | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | *P* | HR (95% CI) | *P* | HR (95% CI) | *P* |
| Sex (M vs. F) | 1.6 (1.1–2.2) | 0.0067 | — | — | — | — |
| Family history of diabetes | | | | | | |
| 1st degree vs. control subjects | 2.2 (1.2–4.0) | 0.0077 | 2.2 (1.1–4.5) | 0.037 | 2.3 (1.0–5.2) | 0.053 |
| 1st/2nd degree vs. control subjects | 2.1 (1.2–3.8) | 0.011 | 2.2 (1.1–4.4) | 0.037 | 2.2 (1.0–5.0) | 0.066 |
| Smoking (smokers vs. nonsmokers) | 1.5 (1.0–2.1) | 0.0405 | 1.6 (0.9–2.7) | 0.12 | 1.0 (0.5–2.0) | 0.95 |
| BMI (kg/m$^2$) | 2.1 (1.4–3.2) | 0.0002 | 1.5 (0.9–2.5) | 0.91 | 2.5 (1.3–4.6) | 0.0052 |
| Waist-height index (cm/m$^2$) | 2.3 (1.5–3.5) | 0.0002 | 1.4 (0.8–2.4) | 0.26 | 3.7 (1.8–7.7) | 0.0005 |
| WHR | 2.1 (1.5–3.0) | <0.0001 | 1.5 (0.9–2.6) | 0.091 | 2.4 (1.4–4.1) | 0.0014 |
| Waist (cm) | 2.1 (1.5–3.2) | 0.0001 | 1.9 (1.1–3.3) | 0.028 | 2.1 (1.2–3.7) | 0.015 |
| Fasting serum insulin (mU/l) | 1.8 (1.2–2.7) | 0.002 | 1.8 (1.1–3.0) | 0.020 | 1.7 (0.9–3.1) | 0.093 |
| $HOMA_{IR}$ | 2.1 (1.4–3.3) | 0.0004 | 2.0 (1.2–3.3) | 0.0081 | 2.3 (1.2–4.5) | 0.017 |
| Insulinogenic index | 1.5 (1.0–2.2) | 0.039 | 1.6 (1.0–2.6) | 0.056 | 1.2 (0.7–2.0) | 0.60 |
| Disposition index | 2.7 (1.8–4.1) | <0.0001 | 2.4 (1.4–4.3) | 0.0019 | 2.7 (1.5–5.0) | 0.0022 |
| Systolic blood pressure (mmHg) | 1.3 (0.9–1.9) | 0.23 | 1.1 (0.7–1.9) | 0.69 | 1.2 (0.6–2.2) | 0.58 |
| Diastolic blood pressure (mmHg) | 1.6 (1.1–2.2) | 0.016 | 1.4 (0.8–2.3) | 0.23 | 1.8 (1.0–3.2) | 0.058 |
| HDL cholesterol (mmol/l) | 1.5 (1.1–2.2) | 0.025 | 1.7 (1.1–2.8) | 0.027 | 1.8 (1.0–3.1) | 0.049 |
| Triglycerides (mmol/l) | 1.5 (1.0–2.2) | 0.039 | 1.0 (0.6–1.7) | 0.99 | 1.6 (0.8–3.0) | 0.19 |
| Metabolic equivalent (s/day$^3$) | 1.3 (0.8–2.0) | 0.23 | 1.3 (0.8–2.2) | 0.29 | 1.3 (0.7–2.4) | 0.46 |
| $DMS_{WHO}$ | 3.6 (2.5–5.2) | <0.0001 | 2.8 (1.7–4.6) | <0.0001 | 4.5 (2.7–7.4) | <0.0001 |
| $DMS_{NCEP}$ | 3.4 (2.4–4.9) | <0.0001 | 2.8 (1.7–4.7) | <0.0001 | 4.0 (2.4–6.7) | <0.0001 |
| Isolated IFG | 2.3 (1.4–3.7) | 0.0007 | 1.5 (0.8–3.0) | 0.24 | 3.8 (1.9–7.5) | 0.0002 |
| Isolated IGT | 3.5 (2.1–5.8) | <0.0001 | 4.4 (2.4–7.8) | <0.0001 | 2.9 (1.3–6.5) | 0.0083 |
| Combined IFG-IGT | 3.8 (2.3–6.2) | <0.0001 | 3.1 (1.6–5.8) | 0.0006 | 4.5 (2.1–9.4) | <0.0001 |
| Combined family history of diabetes and $DMS_{WHO}$ | 9.4 (3.8–23.2) | <0.0001 | 5.7 (1.8–17.8) | 0.0028 | 14.7 (3.6–60.6) | 0.0002 |
| Combined family history of diabetes and $DMS_{NCEP}$ | 8.4 (3.8–18.3) | <0.0001 | 5.9 (2.2–16.0) | 0.0005 | 10.9 (3.4–34.9) | 0.0001 |

Continuous variables are dichotomized into high and low values using the median as cutoff value; other comparisons are indicated. Subjects with combined risk factors are compared with those without any risk factors. All analyses except for BMI, waist-height index, and WHR were adjusted for BMI. $DMS_{NCEP}$, dysmetabolic syndrome defined using NCEP criteria; $DMS_{WHO}$, dysmetabolic syndrome defined using WHO criteria; HR, hazard ratio.

than in those who did not develop diabetes (nonconverters; increase/year 0.202 vs. 0.078, $P = 0.0025$) (Fig. 2*A*). The most marked change, though, was seen in β-cell function, with the converters showing a marked deterioration in insulinogenic index (decline/year −0.049 vs. increase/year 0.011, $P < 0.0001$) (Fig. 2*B*) and disposition index (decline/year −0.105 vs. −0.034, $P < 0.0001$) (Fig. 2*C*).

TABLE 5
The effects of combinations of risk factors for type 2 diabetes as estimated from Cox proportional hazards regression

| | HR (95% CI) |
|---|---|
| BMI | 2.9 (2.0–4.2) |
| FPG | 1.9 (1.3–2.8) |
| Combined family history of diabetes and BMI | 3.4 (2.3–5.1) |
| Combined family history of diabetes and WHR | 1.9 (1.3–2.8) |
| Combined family history of diabetes and FPG | 3.1 (2.1–4.6) |
| Combined FPG-BMI | 3.1 (2.1–4.8) |
| Combined family history of diabetes, BMI, and FPG | 3.7 (2.3–6.1) |

All effects are statistically significant at the $P < 0.0001$ level. Hazard ratio (HR) (95% CI) is for comparison of those with all risk factors to the rest of the population. Family history of diabetes refers to first-degree relatives of type 2 diabetic patients. BMI refers to BMI dichotomized as ≥30 kg/m$^2$. WHR is >0.90 in men and >0.85 in women. FPG is ≥5.6 mmol/l.

## DISCUSSION

This large prospective study clearly defined the incapacity of β-cells to compensate for insulin resistance as the key

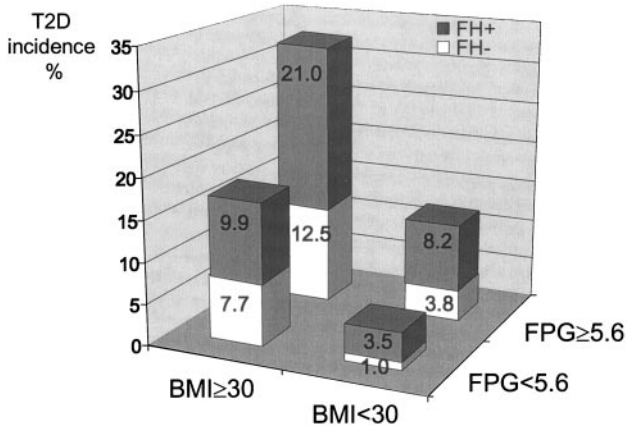


**FIG. 1. The effects of the combination of risk factors for development of type 2 diabetes (T2D). Fasting plasma glucose is in millimoles per liter. Incident diabetes was estimated as the proportion of subjects who developed diabetes during the follow-up period and who had specific risk factors (%): 26 of 124 individuals with the combination of FH+, FPG ≥5.6 mmol/l, and BMI ≥30 kg/m$^2$; 3 of 24 with FPG ≥5.6 mmol/l and BMI ≥30 kg/m$^2$; 7 of 71 with FH+ and BMI ≥30 kg/m$^2$; 52 of 638 with FH+ and FPG ≥5.6 mmol/l; 23 of 666 with FH+; 2 of 26 with BMI ≥30 kg/m$^2$; 6 of 156 with FPG ≥5.6 mmol/l; and 2 of 193 without any risk factors. The effect of the combination of FH+, FPG ≥5.6 mmol/l, and BMI ≥30 kg/m$^2$ was statistically significant at the $P < 0.001$ level compared with those with zero or one or two risk factors for the risk of type 2 diabetes.**

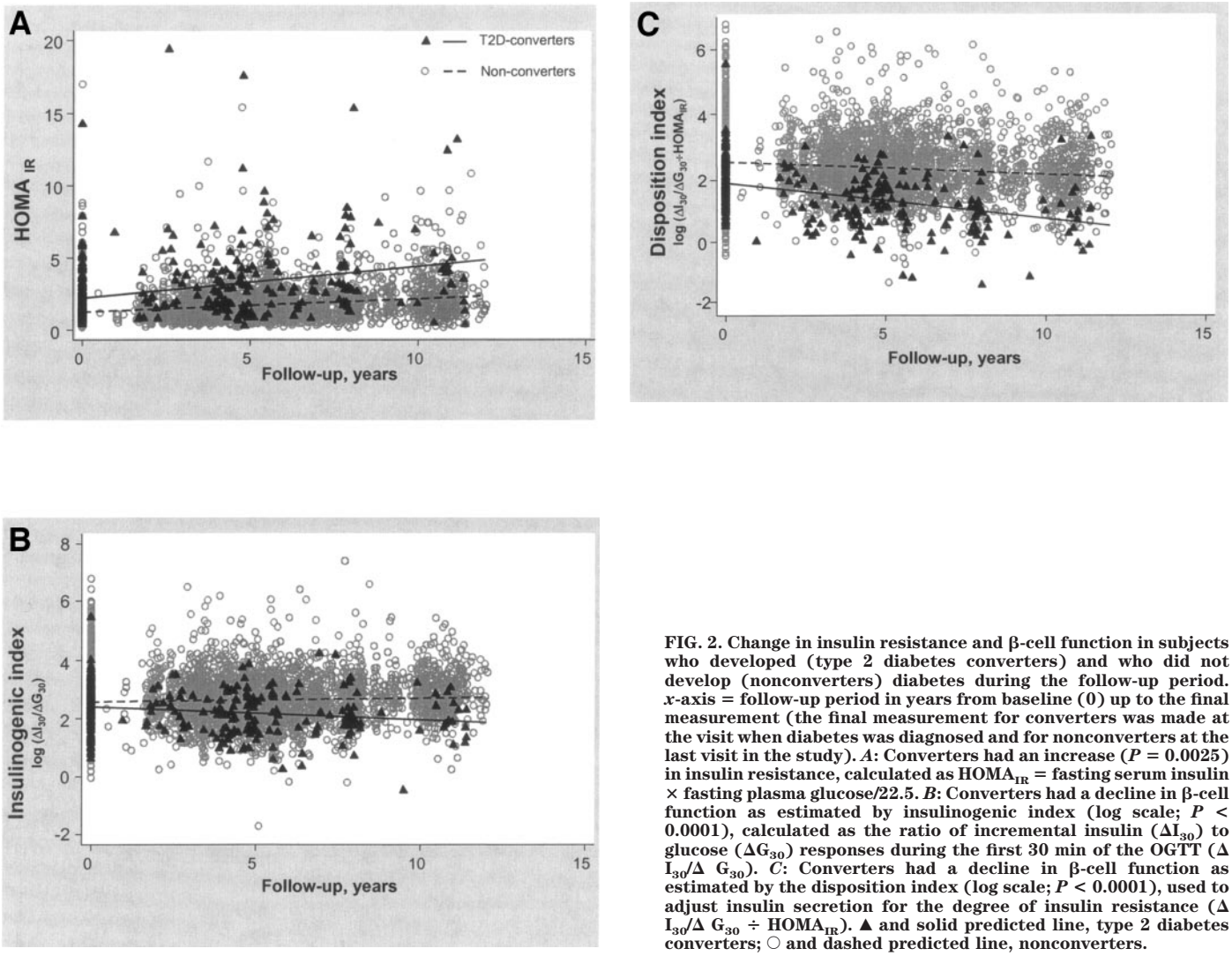


**FIG. 2. Change in insulin resistance and β-cell function in subjects who developed (type 2 diabetes converters) and who did not develop (nonconverters) diabetes during the follow-up period. *x*-axis = follow-up period in years from baseline (0) up to the final measurement (the final measurement for converters was made at the visit when diabetes was diagnosed and for nonconverters at the last visit in the study). *A*: Converters had an increase ($P = 0.0025$) in insulin resistance, calculated as $HOMA_{IR}$ = fasting serum insulin × fasting plasma glucose/22.5. *B*: Converters had a decline in β-cell function as estimated by insulinogenic index (log scale; $P < 0.0001$), calculated as the ratio of incremental insulin ($\Delta I_{30}$) to glucose ($\Delta G_{30}$) responses during the first 30 min of the OGTT ($\Delta I_{30}/\Delta G_{30}$). *C*: Converters had a decline in β-cell function as estimated by the disposition index (log scale; $P < 0.0001$), used to adjust insulin secretion for the degree of insulin resistance ($\Delta I_{30}/\Delta G_{30} \div HOMA_{IR}$). ▲ and solid predicted line, type 2 diabetes converters; ○ and dashed predicted line, nonconverters.**

defect leading to type 2 diabetes, and it provided sequential data on changes in insulin sensitivity and insulin secretion in individuals who did or did not progress to diabetes. It also demonstrated that a family history of diabetes together with features of the dysmetabolic syndrome conferred a very high risk of subsequent diabetes. A simple risk score consisting of a family history of diabetes, fasting plasma glucose ≥5.6 mmol/l, and BMI ≥30 kg/m$^2$ was a strong predictor of type 2 diabetes. Using FPG ≥6.1 mmol/l (IFG) or 2-h glucose ≥7.8 mmol/l (IGT) from the OGTT instead of FPG ≥5.6 mmol/l did not significantly improve the prediction of type 2 diabetes.

In general, the risk of progression to diabetes in the population was low, with only 2.9% of NGT and 12.5% of IFG/IGT subjects developing type 2 diabetes during the 6-year follow-up. The risk was higher in men than in women, which could be attributed to more risk factors clustering in men. In particular, men were more insulin resistant and showed more features of the dysmetabolic syndrome. In keeping with several previous studies (12), we observed a higher prevalence of IFG in men and of IGT in women. The reason for this sex difference on glucose tolerance is unclear, but the higher FFA in women compared with men could provide one explanation because FFAs are known to impair glucose metabolism (13). This hypothesis is further supported by a positive correlation between the fasting FFA concentration and the 2-h glucose value during OGTT ($R = 0.17$, $P < 0.0001$).

In keeping with the Hoorn Study (14) but in contrast to studies in Pima Indians, we did not observe a significant difference in the incidence of type 2 diabetes between individuals with IFG or IGT (9.1 vs. 12.1%, $P = 0.29$). On the whole, the rate of progression from IFG or IGT to diabetes was much lower in the Botnia Study than in the Hoorn Study (in which the 6-year cumulative incidence was 33% for IFG and 34% for IGT) or in the Pima Indians (5-year cumulative incidence 20% for IFG and 31% for IGT). The rate of progression to diabetes was also lower than in the Finnish Diabetes Prevention Study (DPS), which reported a progression rate of 23% after a 4-year follow-up period (2). This is not surprising because the IGT subjects in the DPS were somewhat older (mean age 55 ± 7 vs. 48 ± 12 years) and more obese (BMI 31 ± 5 vs. 26 ± 4 kg/m$^2$), and the IGT status was based on two OGTTs. However, in the present study most individuals had sequential OGTTs during the follow-up.

A family history of type 2 diabetes was a clear risk factor for subsequent diabetes, and the risk was not attenuated much by inclusion of second-degree relatives (HR 2.0 and 1.9). This has been a consistent finding in most studies, but

the risk has varied based on the prevalence of diabetes in the population (15), age at onset of diabetes (16), and the number of affected family members (17). When we restricted family history to affected siblings, the relative risk was 3.4-fold, which equals the sibling relative risk (λs). As reported earlier (6) and in keeping with results from other studies (18), we observed an excess maternal transmission of type 2 diabetes in the Botnia Study.

As expected, obesity was an independent predictor of diabetes, but its relative role was stronger in IFG-IGT than in NGT subjects. Several previous studies have shown that BMI or measures of abdominal obesity, i.e., waist-to-hip ratio, predict subsequent diabetes (19–22). In keeping with an earlier report (20), both WHR and BMI independently predicted type 2 diabetes in our study, whereas waist circumference could replace BMI in the prediction of type 2 diabetes. We also used waist circumference divided by height squared (6,23) as a measure of abdominal obesity because measurements of height are usually more reliable than measurements of hip circumference. The waist-height index also correlates significantly better than WHR with insulin-stimulated glucose uptake and with $HOMA_{IR}$ in the present study ($R = 0.43$ and $R = 0.25$, $P < 0.0001$). There is also a strong correlation between abdominal obesity and hepatic steatosis and insulin resistance (24,25), but it is still an open question as to whether abdominal obesity leads to insulin resistance or vice versa. It has also been debated whether the culprit is intra-abdominal or subcutaneous abdominal fat; Weyer et al. (26) showed that enlarged subcutaneous abdominal adipocyte size is an independent predictor of type 2 diabetes in Pima Indians. The importance of the link between abdominal obesity and insulin resistance was emphasized by a recent study showing that an exercise-induced decrease in visceral obesity and an increase in aerobic capacity resulted in enhanced insulin sensitivity (27). However, obesity cannot explain all of the influence of insulin resistance on type 2 diabetes risk because $HOMA_{IR}$ adjusted for BMI was still an independent predictor of diabetes.

As previously reported, insulin resistance and impaired β-cell function were independent predictors of diabetes (21,22,28–30). A new finding was that the disposition index, i.e., β-cell function adjusted for the degree of insulin resistance, was the strongest metabolic predictor of subsequent diabetes, with an overall HR of 2.7 in all subjects and 2.8 in NGT subjects. These data thus clearly demonstrate that the inability of the β-cells to compensate for the degree of insulin resistance represents the key defect leading to type 2 diabetes. The reason that the disposition index appeared to be a better predictor of type 2 diabetes in subjects with NGT than in subjects with IFG-IGT may be because we used the HOMA index as an approximation of insulin resistance. The fasting plasma glucose included in the equation of the HOMA index seems to attenuate the correlation between HOMA and clamp-derived measures of insulin sensitivity, particularly in individuals with IFG (31). As a consequence, the predictive value of HOMA or the disposition index was lowest in individuals with isolated IFG (HR 0.96, 95% CI 0.4–2.3, $P = 0.93$; and 1.3, 0.5–3.3, $P = 0.56$).

We also provide the largest dataset to date on longitudinal changes in insulin sensitivity and β-cell function in individuals who developed subsequent type 2 diabetes. The findings are in complete agreement with changes observed in 17 Pima Indians who developed diabetes (29) over a 5-year follow-up period indicating that both changes in insulin sensitivity and β-cell function precede onset of diabetes. One caveat in the interpretation of the data could be that the majority of the converters had already developed diabetes at the final assessment of insulin secretion, and thus the decline in insulin secretion could be secondary to glucose toxicity (32). This is unlikely because subjects who developed type 2 diabetes still showed a progressive decline in insulin secretion adjusted for the degree of insulin resistance, i.e., the disposition index ($P = 0.0007$), when we replaced the final visit in 124 converters by the previous visit ($n = 60$). The data, however, contrast with data from Joslin suggesting that, primarily, deterioration of insulin sensitivity ($S_i$ measured during a frequently sampled intravenous glucose tolerance test) and glucose effectiveness ($S_g$) precede diabetes (33). Of note, the subjects in the latter study were obese offspring of two diabetic parents, whereas in the Botnia Study a family history was defined as a parent or sibling with diabetes. Taken together, these data should therefore be able to put an end to debate as to whether insulin resistance or a defect in β-cell function characterize progression to type 2 diabetes (34): both defects characterize the natural history of type 2 diabetes.

Also, elevated triglyceride and low HDL cholesterol concentrations as well as elevated diastolic blood pressure predicted diabetes after adjustment for BMI and age. However, the relative risk associated with these individual risk factors was lower than that associated with BMI or the waist-height index. The situation markedly changed when we considered them together as the clustering of risk factors defined as the dysmetabolic syndrome (7,9).

Although the dysmetabolic syndrome has been considered a risk factor for cardiovascular disease rather than for diabetes (35,36), two recent studies showed that the dysmetabolic syndrome was associated with an increased risk of subsequent diabetes in nondiabetic subjects (3,4). In keeping with Laaksonen et al. (3), but in contrast to Lorenzo et al. (4), in our study there was no difference between the WHO or NCEP definitions (3.6- and 3.4-fold) in predicting type 2 diabetes. It should be noted that both studies used a truncated WHO definition leaving out 2-h glucose.

Given the complexity of these definitions for clinical practice, we also tested the predictive value of a simplified risk score including only a family history of diabetes, BMI $\geq 30$ kg/m$^2$, and fasting plasma glucose $\geq 5.6$ mmol/l. This simplified risk score predicted type 2 diabetes with a high HR (3.7, $P < 0.0001$). Although one can expect that glucose by itself should predict hyperglycemia, the prediction was already strong at supranormal increases in FPG when this was seen in combination with a family history of diabetes and BMI $\geq 30$ kg/m$^2$. As seen from the ROC curve areas, the predictive values of the different glucose cutoffs were quite similar. We therefore propose to use the nonnormal fasting plasma glucose $>5.5$ mmol/l for the clinical prediction of type 2 diabetes.

Although the prevalence of test-positive individuals us-

ing this model is lower than for IFG and IGT (6.5 vs. 12.4 and 11.8%), which, in turn, results in lower sensitivity (22 vs. 44 and 49%), this model has a higher positive predictive value (21 vs. 13 and 15%) and a greater area under the ROC curve (74 vs. 63 and 66%) compared with those for IFG and IGT.

In keeping with our findings, a previous study (4) showed that an increase in FPG >5.4 mmol/l was associated with increased risk of type 2 diabetes, particularly when combined with features of the metabolic syndrome. In addition, Stern et al. (37) proposed that a multivariable model including family history of diabetes and multiple continuous variables was a better predictor of type 2 diabetes than 2-h glucose alone. Moreover adding 2-h glucose to their model did not significantly improve the prediction. The Stern model had a better area under the ROC curve for prediction of diabetes than our simple triad model (83.4 vs. 74%), but the use of multiple continuous variables may be difficult in clinical practice.

These findings should have important implications for the screening of diabetes. Individuals at high risk for subsequent type 2 diabetes can be identified without expensive and labor-intensive OGTTs when screening is restricted to individuals with a family history of type 2 diabetes, fasting plasma glucose ≥5.6 mmol/l, and BMI ≥30 kg/m$^2$. Using these criteria, six individuals must be screened to identify one person who will develop diabetes. Because the inability of the islets to compensate for the degree of insulin resistance represents the key defect leading to type 2 diabetes, interventions focused on both defects may be needed to prevent type 2 diabetes.

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