Relation of Impaired Fasting and Postload Glucose With Incident Type 2 Diabetes in a Dutch Population
The Hoorn Study

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Worldwide, the prevalence of type 2 diabetes is very high and increasing. The World Health Organization (WHO) predicts that between 1995 and 2025, the worldwide prevalence of diabetes among persons aged 20 years and older will increase from 4.0% to 5.4%.1 Diabetes is associated with a high risk for microvascular and macrovascular complications and with a high risk of premature death.2,4

For prevention purposes, there is great interest in the identification of persons at high risk for developing diabetes. Therefore, several follow-up studies have been performed in nonwhite populations with a high prevalence of diabetes5-7 and among persons with impaired glucose tolerance (IGT).6,10 Edelstein et al11 reported cumulative incidences ranging from 23% to 62% in 6 prospective studies among persons with IGT, within 2 to 27 years of follow-up. The incidence was higher among the Hispanic, Mexican-American, Pima, and Nauruan populations compared with the incidence among white populations. Variables predictive of the development of diabetes in different studies were fasting and postload glucose,7,11-13 obesity,11,12 and such lifestyle variables as physical inactivity.14

However, little is known about the conversion from normal glucose tolerance (NGT) to diabetes in white persons with impaired fasting glucose (IFG) or with normal glucose levels.

Context Persons with impaired glucose tolerance (IGT) are known to have an elevated risk of developing diabetes mellitus. Less is known about diabetes risk among persons with impaired fasting glucose (IFG) or with normal glucose levels.

Objective To determine the incidence of diabetes in relation to baseline fasting and postload glucose levels and other risk factors.

Design, Setting, and Participants Population-based cohort study conducted from October 1989 to February 1992 among 1342 nondiabetic white residents of Hoorn, the Netherlands, aged 50 to 75 years at baseline, in whom fasting plasma glucose (FPG) levels and glucose levels 2 hours after a 75-g oral glucose tolerance test were measured at baseline and at follow-up in 1996-1998.

Main Outcome Measures Cumulative incidence of diabetes, defined according to the diagnostic criteria of the World Health Organization (WHO-1985 and WHO-1999) and the American Diabetes Association (ADA-1997), during a mean follow-up of 6.4 years, compared among participants with IFG, IGT, and normal glucose levels at baseline.

Results The cumulative incidence of diabetes was 6.1%, 8.3%, and 9.9% according to the WHO-1985, ADA, and WHO-1999 criteria, respectively. The cumulative incidence of diabetes (WHO-1999 criteria) for participants with both IFG and IGT was 64.5% compared with 4.5% for those with normal glucose levels at baseline. The odds ratios for diabetes (WHO-1999 criteria), adjusted for age, sex, and follow-up duration, were 10.0 (95% confidence interval [CI], 6.1-16.5), 10.9 (95% CI, 6.0-19.9), and 39.5 (95% CI, 17.0-92.1), respectively, for those having isolated IFG, isolated IGT, and both IFG and IGT. In addition to FPG and 2-hour postload glucose levels (P<.001 for both), the waist-hip ratio also was an important risk factor for developing diabetes (P=.002).

Conclusion In this study, the cumulative incidence of diabetes was strongly related to both IFG and IGT at baseline and, in particular, to the combined presence of IFG and IGT.

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METHODS

Study Population

The Hoorn Study, begun in 1989, is a population-based cohort study on glucose intolerance in a general Dutch elderly population. The study population and design have been described in detail previously.18 In summary, a random sample (n = 3553) of all inhabitants of Hoorn aged 50 to 75 years was invited to take part in the study. A total of 2540 subjects (71%) agreed to participate. After exclusion of 56 nonwhite participants, the study cohort consisted of 2484 men and women. The baseline examination took place between October 1989 and February 1992.

Between January 1996 and December 1998, a follow-up examination was carried out. Of the initial cohort, 150 persons had died and 108 had moved out of Hoorn before 1996. One hundred forty other persons were not invited because of logistic reasons. Of the remaining 2086 persons who were invited for the follow-up examination, 1513 (72.5%) participated. In the present study all analyses have been done on 1342 participants, because those who had diabetes according to any one of the diagnostic criteria at baseline or who had missing values for glucose were excluded (FIGURE).

All participants gave their written informed consent for participation in the Hoorn Study. The Ethics Committee of the University Hospital Vrije Universiteit Amsterdam approved the design of the study.

Glucose Measurements

For the measurement of FPG, a blood sample was taken after an overnight fast. Subsequently, a 75-g oral glucose tolerance test (OGTT) was administered and the plasma glucose level was measured 2 hours later (2hPG). The glucose levels were determined by a glucose dehydrogenase method (Merck, Darmstadt, Germany).

At both baseline and follow-up, all participants were classified in categories of glucose intolerance. In the WHO-1985 criteria, diabetes is diagnosed if FPG is 140 mg/dL (7.8 mmol/L) or greater or if 2hPG is 200 mg/dL (11.1 mmol/L) or greater,16 while by the ADA criteria, an FPG of 126 (7.0 mmol/L) or greater is sufficient.15 In the WHO-1999 criteria, these are combined and therefore diabetes is defined by an FPG level of 126 mg/dL (7.0 mmol/L) or greater or a 2hPG level of 200 mg/dL (11.1 mmol/L) or greater.17 Participants who were already treated for diabetes by insulin, hypoglycemic agents, or a physician-prescribed diet were categorized as persons with known diabetes, irrespective of their glucose levels. In case of doubt the medical information in the hospital or at the general practitioner was checked. In all analyses, known and newly diagnosed diabetes was taken together.

Impaired fasting glucose is defined as an FPG between 110 mg/dL (6.1 mmol/L) and 126 mg/dL (7.0 mmol/L).15 By WHO-1985 criteria, IGT is diagnosed if FPG is less than 140 mg/dL (7.8 mmol/L) and 2hPG is between 140 mg/dL (7.8 mmol/L) and 200 mg/dL (11.1 mmol/L).16

Other Measurements

Weight and height were measured with participants wearing light clothing only, and the body mass index (BMI) was calculated as weight divided by the square of the height (kg/m²). Waist and hip circumferences were measured and the waist-hip ratio (WHR) was defined as waist circumference divided by hip circumference.

Blood pressure was measured twice on the right arm while sitting and with a random-zero sphygmomanometer (Hawksley-Gelman, Lancing, England). The average of these 2 measurements was used for analyses. Participants were considered hypertensive if their sys-
Diastolic blood pressure was 160 mm Hg or greater, their diastolic blood pressure was 95 mm Hg or greater, or if they were using antihypertensive medica-
tion. Information on smoking habits (yes or no) and participation in sports (hours per week) was obtained by question-
naire.18

Statistical Methods
All statistical analyses were done with SPSS 9.0.19 All P values were based on 2-sided tests, and the cutoff for sta-
tistical significance was .05.

The cumulative incidence of diabetes was calculated as the number of partici-
pants who developed diabetes during the follow-up divided by the total number of those at risk at baseline. We com-
pared the 6-year cumulative incidence of diabetes between the WHO-1985, the ADA, and the WHO-1999 diagnostic cri-
teria. Furthermore, we compared the cu-
mulative incidences for combinations of normal, impaired fasting, and impaired postload glucose levels.

The follow-up duration was calcu-
lated as the time between the baseline and the follow-up measurements, and the incidence densities were calcu-
lated. Because the mean follow-up du-
ration was not equal in the categories of glucose intolerance, logistic regres-
sion adjusting for follow-up duration was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs). The ORs were also adjusted for age and sex. The Hosmer-Lemeshow goodness-of-

fit test was used to assess the overall fit of the logistic regression model.20

The OR is the ratio of the odds of 2
categories and can be interpreted as an approximation of the relative risk. In this study, odds represent the chance for conversion to diabetes relative to the chance for nonconversion to diabetes in 1 particular category. The ORs will overestimate the relative risk when the disease under study is not rare.21

To investigate which other vari-
bles were predictive of the develop-
ment of diabetes, the variables WHR (×100), BMI, hypertension, smoking, and participation in sports were added 1 by 1 into a logistic regression model including also FPG, 2hPG, age, sex, and follow-up duration as independent variables. Finally, all statistically signifi-

cant variables were included together into 1 logistic regression model.

RESULTS
The study population consisted of 610
men and 732 women with a mean age of 60.3 (SD, 6.9) years at baseline, who were followed up for 6.4 years (range, 4.4-8.1 years).

As a consequence of the definitions used, the cumulative incidence of dia-
betes was highest according to the WHO-1999 criteria: 9.9% compared with 6.1% and 8.3% according to the WHO-1985 and the ADA criteria, re-
spectively. Of the 1231 participants with NGT at baseline, 46 (3.7%) had diabetes at follow-up according to the WHO-1985 criteria. For participants with IGT the cumulative incidence was 32.4% (WHO-1985 criteria). According to the ADA criteria, the cumulative incidence was 5.0% for participants with NGT and 38.0% for those with IFG (TABLE 1).

The cumulative incidence (WHO-
1999 criteria) among participants with both impaired fasting and impaired postload glucose levels was 64.5%, com-
pared with 4.5% for those with both normal fasting and normal postload glu-
cose levels. Among participants with isolated IFG or IGT, the cumulative in-
cidence of diabetes was similar (33.0% and 33.8%, respectively). However, the

mean follow-up durations were not equal in these categories. The ORs ad-
justed for follow-up duration, age, and sex were 10.0 and 10.9 for isolated IFG and IGT, respectively. The OR for par-
ticipants with both IFG and IGT relative to those with normal glucose lev-

els was very high (39.5 [95% CI, 17.0-
92.1]) (TABLE 2).

When the analyses were stratified for men and women, we observed a slightly higher cumulative incidence of dia-
betes in men than in women (10.5% vs 9.4%, respectively; WHO-1999 criteria). For participants with the combined presence of IFG and IGT the cumulative incidence was more pronounced in women (75.0%) than in men (53.3%).

In addition to fasting and postload glu-
cose levels, which were the 2 most im-
portant predictors for progression to dia-
betes (both P < .001), the WHR also was highly predictive of incident diabetes (P = .002). Of less importance, and not statistically significant, were smoking, hypertension, participation in sports, and BMI. Including the statistically significant variables into 1 model, the OR ex-
pressed per 1-SD difference was 2.32 (95% CI, 1.85-2.90) for FPG, 1.97 (95% CI, 1.59-2.44) for 2hPG, and 1.57 (95% CI, 1.19-2.08) for the WHR (TABLE 3).

COMMENT
In this prospective cohort study of a white population, 64.5% of the participants who had both impaired fasting

| Table 1. Six-Year Cumulative Incidence of Diabetes According to WHO-1985 and ADA Diagnostic Criteria* |
|-----------------|-----------------|-----------------|
| Baseline Category | Cutoff Values, FPG/2hPG, mg/dL | No. | Diabetes at Follow-up, No. (%)† |
|-----------------|-----------------|-----------------|
| WHO-1985 NGT | <126/<140† | 1231 | 46 (3.7) |
| IGT | <126/140-200† | 111 | 36 (32.4) |
| Total | | 1342 | 82 (6.1) |
| ADA NFG | <110§ | 1205 | 60 (5.0) |
| IFG | 110-126§ | 137 | 52 (38.0) |
| Total | | 1342 | 112 (8.3) |

*WHO indicates World Health Organization; ADA, American Diabetes Association; FPG, fasting plasma glucose; 2hPG, 2-hour postload glucose; NGT, normal glucose tolerance; IGT, impaired glucose tolerance; NFG, normal fasting glu-
cose; IFG, impaired fasting glucose. To convert mg/dL to mmol/L, multiply mg/dL by 0.05551.
†Cutoff level for FPG is 126 mg/dL, because all analyses were carried out in the 1342 subjects who did not have dia-
betes according to any of the diagnostic criteria at baseline.
‡Cutoff values for WHO-1985 are FPG ≥140 mg/dL or 2hPG ≥200 mg/dL; for ADA, FPG ≥126 mg/dL.
§Cutoff levels for FPG only.
and impaired postload glucose levels at baseline progressed to diabetes (WHO-1999 criteria) during the 6-year follow-up. Of those with normal fasting and postload glucose levels at baseline, 4.5% had diabetes at the follow-up examination. To our knowledge, this is the first large prospective study among whites that reports on the cumulative incidence of type 2 diabetes according to WHO-1985, ADA, and WHO-1999 diagnostic criteria.

The baseline cohort (n = 2484) of the Hoorn Study was a random sample of the population of the municipality of Hoorn, aged 50 to 75 years. The present analyses have been done in 1342 participants who did not have diabetes according to any 1 of the diagnostic criteria at baseline and who did not have missing values for glucose. Of the 2086 persons who were invited for the follow-up examination, 1513 participated and 573 did not. As is frequently observed in population studies, the participants were more healthy. The participants were younger (60.6 vs 63.2 years), less hypertensive (28.2% vs 34.8%), had a lower WHR (0.89 vs 0.9), and a more favorable lipid profile at baseline. Furthermore, they had lower baseline FPG levels (101.8 mg/dL [5.65 mmol/L] vs 105.5 mg/dL [5.85 mmol/L]), lower 2hPG levels (106.5 mg/dL [5.981 mmol/L] vs 112.2 mg/dL [6.23 mmol/L]), and lower glycosylated hemoglobin values (5.4% vs 5.6%). Therefore, we may have underestimated the true cumulative incidence of diabetes in the general population.

Because of ongoing follow-up studies, persons with IGT were first invited for the follow-up measurements. This resulted in an unequal distribution over the categories for the mean follow-up duration, with persons with the highest risks for progression to diabetes having the shortest follow-up duration. In a logistic regression model we therefore adjusted for follow-up duration.

The glucose levels were determined only once at baseline and at follow-up. Because of the known high intra-individual variation in glucose levels, especially for postload glucose, some misclassification might have occurred when participants were categorized into glucose tolerance categories.22,23 However, we previously reported that the reproducibility of the classification in glucose tolerance categories by WHO-1985 and ADA for 1109 persons with duplicate OGTTs within 6 weeks was very similar, with k values of 0.59 and 0.61, respectively, which represent fair-to-good reproducibility.24

The incidence of diabetes was highest according to the WHO-1999 combined criteria and the lowest incidence was observed if using the WHO-1985 criteria, which is due to the higher cutoff level for FPG. However, the true incidence according to the WHO-1985 was slightly underestimated, because participants with FPG levels between 126 mg/dL (7.0 mmol/L) and 140 mg/dL (7.8 mmol/L) at baseline were excluded in the analyses. If these participants (n = 23) were included, the cumulative incidence of diabetes according to WHO-1985 criteria was 6.9% instead of 6.1%. For participants with IGT and NGT the incidences then were 35.5% and 4.1%, respectively. When only the ADA diagnostic criteria should have been used, the analyses could have been done in 1391 participants instead of 1342. Then the cumulative incidence of diabetes was 5.5% for participants with NGT and 40.8% for those with IFG, which is quite similar to the values in Table 1.

Previous studies on the incidence of diabetes were mainly performed in persons with IGT only, or in nonwhite populations with a high risk for diabetes, using the WHO-1985 diagnostic criteria. In South African persons, the incidence of diabetes was 50.4% within 4 years2 and for Pima Indians the cumulative incidence of diabetes was 62% within 7 years.11 In Kinmen, a series of islands located in the Pacific Ocean, the cumulative incidence was 8.8% per year.12 We previously reported on the 2-year cumulative incidence of diabetes in a subsample of participants with IGT in the Hoorn Study. The cumulative incidence of diabetes was 28.5% when using the mean of duplicate OGTTs for the classification in glucose tolerance categories.25

Less is known about the cumulative incidence of diabetes of persons with...
IFG. In the present study, we observed a 6-year incidence of 38%. Dinneen et al. observed a cumulative incidence of 39% within 9 years of follow-up among Olmsted County residents aged 40 years or older with baseline IFG. In a prospective study in Mauritian persons aged 25 to 74 years, 28.9% of the participants with baseline IFG progressed to diabetes in 5 years, compared with 24.4% with IGT. In a study in Italy among 1245 whites who were followed up for 11.5 years, participants with both IFG and IGT at baseline had an OR of 10.3 for developing diabetes relative to those with both NFG and NGT. The cumulative incidence of diabetes among participants with IGT only was higher than the cumulative incidence for subjects with IFG only (32.5% and 9.1%, respectively). These results are therefore only partly in line with the results of the present study: we observed a 14-fold higher risk for diabetes in subjects with both IFG and IGT, while the risks of the IGT-only and IFG-only categories were similar. However, the participants in the Italian study were younger (40–59 years) and the number of those who progressed to diabetes was in some categories quite small.

Impaired fasting glucose and IGT represent different physiologic abnormalities. The primary cause for fasting hyperglycemia is the elevated rate of basal hepatic glucose production in the presence of hyperinsulinemia, while IGT is characterized by defects in both insulin secretion and insulin sensitivity. Therefore, as demonstrated herein, when there is a combined presence of these disorders the risk for future diabetes is very high. Furthermore, we observed that the WHR, not the BMI, was an important predictor for progression to diabetes. Edelstein et al. also observed in 4 prospective studies that the WHR was consistently associated with the development of diabetes. The association between BMI and incident diabetes differed between the studies reported. Therefore, the body fat distribution may be a better predictor for progression to diabetes than the BMI.

In this study, the highest cumulative incidence of diabetes was observed for participants with both IFG and IGT at baseline. Therefore, we conclude that the cumulative incidence of diabetes among white persons aged 50 to 75 years is strongly related to both impaired fasting and impaired post-load glucose levels at baseline.

Author Contributions: Study concept and design: de Vegt, Dekker, Jager, Nijpels. Analysis and interpretation of data: de Vegt, Dekker, Kostense. Drafting of the manuscript: de Vegt, Dekker, Jagen, Kostense. Critical revision of the manuscript for important intellectual content: de Vegt, Dekker, Jagen, Kostense. Obtained funding: Dekker, Stehouwer, Nijpels, Bouter, Heine. Study supervision: Dekker, Stehouwer, Nijpels, Bouter, Heine.

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