

Is the Current Definition for Diabetes Relevant to Mortality Risk From All Causes and Cardiovascular and Noncardiovascular Diseases?

THE DECODE STUDY GROUP

ON BEHALF OF THE EUROPEAN DIABETES EPIDEMIOLOGY GROUP

OBJECTIVE — To assess the relation between fasting plasma glucose (FPG) or 2-h plasma glucose (2hPG) and mortality from all causes, cardiovascular disease (CVD), and non-CVD and to determine whether the relationship is graded or threshold.

RESEARCH DESIGN AND METHODS — Diabetes Epidemiology: Collaborative Analysis Of Diagnostic Criteria in Europe (DECODE) is a collaborative prospective study of 22 cohorts in Europe with baseline glucose measurements for 29,714 subjects aged 30–89 years who were followed-up for 11 years (329,050 person-years). Hazard ratio (HR) for death was estimated using Cox regression analysis.

RESULTS — High glucose concentrations as well as very low glucose levels were associated with increased risk of death. Compared with an FPG of 4.50–6.09 mmol/l, the multivariate-adjusted HR (95% CI) for FPG <4.50 mmol/l was 1.2 (1.0–1.4) for all-cause, 1.3 (1.0–1.8) for CVD, and 1.1 (0.9–1.4) for non-CVD mortality; the corresponding HRs for diabetes (FPG \geq 7.0 mmol/l) were 1.6 (1.4–1.8), 1.6 (1.3–1.9), and 1.6 (1.4–1.9), respectively. For a 2hPG of 3.01–4.50 mmol/l, as compared with a 2hPG of 4.51–5.50 mmol/l, the HRs were 1.1 (1.0–1.2), 1.1 (0.9–1.3), and 1.1 (1.0–1.3), respectively; the corresponding HRs for diabetes (2hPG \geq 11.1 mmol/l) were 2.0 (1.7–2.3), 1.9 (1.5–2.4), and 2.1 (1.7–2.5), respectively. The HR for previously undetected diabetes defined by 2hPG was not significantly different from that for known diabetes, which was significantly higher than that for undetected diabetes based on FPG. Subjects with a 2hPG of 10.01–11.09 mmol/l had mortality risks similar to those diabetic subjects defined by an FPG \geq 7.0 mmol/l.

CONCLUSIONS — The relation between mortality and glucose was J shaped rather than showing threshold effect at high glucose levels, except for CVD mortality and 2hPG, where the relation was graded and increasing.

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Diabetes and impaired glucose tolerance (IGT) are associated with increased mortality, particularly from cardiovascular diseases (CVDs). However, it is still unclear whether the relation between glycemia and mortality is contin-

uous over the entire range of glucose values or whether a threshold for increased mortality exists. This issue has been investigated during the last decades. In 1979, a series of studies from the International Collaborative Group (1) did not

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Additional information for this article can be found in an online appendix at <http://care.diabetesjournals.org>.

Abbreviations: 2hPG, 2-h plasma glucose; CVD, cardiovascular disease; DECODE, Diabetes Epidemiology: Collaborative Analysis Of Diagnostic Criteria in Europe; FPG, fasting plasma glucose; HR, hazard ratio; IFG, impaired fasting glycemia; IGT, impaired glucose tolerance.

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

consistently detect evidence for a threshold or graded association between asymptomatic hyperglycemia and coronary heart disease. A systematic overview and meta-regression analysis of epidemiological studies found that the progressive relation between glucose levels and CVD risk extends below the diabetic threshold in nondiabetic men (2). This analysis is based on aggregate data, and no adjustment for other risk factors was made. Subsequently, based on data from a 23-year follow-up of the Paris Prospective Study, Balkau et al. (3) reported that the relation between glucose levels and mortality was curvilinear and, in the upper levels of the glucose distributions, the risk of death progressively increased with increasing fasting and 2-h glucose concentrations. This analysis included men only. Diabetes Epidemiology: Collaborative Analysis Of Diagnostic Criteria in Europe (DECODE) is based on a large collaborative dataset (4–7) and overcomes some of the limitations of the previous attempts to evaluate the association between glucose concentration and mortality.

The aim of the present study was to assess whether the relation between fasting plasma glucose (FPG) and 2-h plasma glucose (2hPG) and the risk of mortality from all causes, CVD, and non-CVD is graded or whether a threshold effect exists. In addition, the relevance of the current definition for diabetes with regard to the prediction of mortality was addressed.

RESEARCH DESIGN AND METHODS

The study populations and the methods used to recruit the participants have been reported in our previous publications (4–7). Briefly, data on glucose concentrations at fasting and 2 h after a 75-g oral glucose tolerance test from population-based studies or large studies in occupational groups in Europe were collected and analyzed at the Diabetes and Genetic Epide-

miology Unit of the National Public Health Institute in Helsinki, Finland.

A total of 22 cohorts provided data on all-cause mortality; 20 of these provided data on cause-specific mortality. Data from 19,337 men and 10,377 women aged 30–89 years were analyzed, of whom 1,366 were previously diagnosed with diabetes. The mean duration of follow-up was 11 years, and a total of 329,050 person-years of follow-up were accumulated. Measurements of FPG and 2hPG, BMI, blood pressure, and smoking were available for all 22 cohorts, but serum cholesterol was only determined in 20 of these. Therefore, when all confounding variables were used in an analysis, only data from 20 cohorts were available ($n = 26,410$, including 1,008 known diabetic subjects). While all 20 cohorts had mortality data, only 18 had data on cause-specific mortality ($n = 25,245$, including 911 known diabetic subjects). Glucose concentrations of different blood samples were all converted to plasma glucose during the data analysis (see online appendix 1).

Vital status was recorded for each subject attending the baseline examination. Subjects who emigrated, for whom vital status could not be confirmed, were censored at the time of emigration. The follow-up was complete, from 95% in the Paris Prospective Study to 100% in most other studies (6). Fatal events were classified using the International Classification of Diseases. CVDs were defined with codes 401–448 for the eighth or ninth revisions and codes I10–I79 for the tenth revision. The diagnosis of diabetes, IGT, and impaired fasting glycemia (IFG) was made according to the World Health Organization 1999 definitions (8).

Statistical analysis

First, hazard ratios (HRs) for mortality were estimated using Cox proportional hazard models for each of the 22 cohorts separately using logarithmically transformed continuous glucose variables. The β -coefficients from the individual Cox models were then combined into an overall β -coefficient by a fixed-effects approach according to the method detailed by Fleiss (9). A fixed- rather than random-effects approach was chosen because the statistic Q for measuring study-to-study variation in effect size was not statistically different from zero (9).

As the effect size was homogeneous,

data from cohorts where all required confounding variables were available were then pooled together to increase statistical power for further calculation of the HRs by glucose intervals of width of 0.5 mmol/l. The observed HRs for FPG intervals of 0.5 mmol/l were calculated with reference to the interval centered on an FPG of 4.75 mmol/l for all-cause and non-CVD mortality and on FPG of 5.25 mmol/l for CVD mortality, where the observed mortality was the lowest. The same reference groups were also used to calculate HRs for 2hPG intervals of 0.5 mmol/l.

Adjacent glucose intervals of width of 0.5 mmol/l with similar risk for mortality were then merged to make more accurate analyses based on the wider glucose intervals. A common reference category, previously diagnosed diabetes, was used to calculate the HRs to enable a more direct comparison between FPG and 2hPG.

In previously undiagnosed diabetic subjects, both curvilinear (with linear and quadratic terms) and threshold models allowing for a change in slope around the threshold glucose value (10) were compared with the linear models using χ^2 log-likelihood tests between nested models. The Cox models used the log of glucose concentrations and were adjusted for age, sex, cohort, BMI, systolic blood pressure, cholesterol, and smoking. SPSS for Windows version 10.0 was used for all statistical analyses.

RESULTS— Overall, among the 29,714 participants of 22 cohorts, there were 4,858 all-cause deaths. For the 20 cohorts with causes of death, there were 28,549 subjects and 1,662 deaths from CVD (Table 1). Multivariate-adjusted β -coefficients for each individual cohort are shown in Fig. 1. A positive β -coefficient was observed in most of the cohorts for both the 2hPG and the FPG concentrations. The test for measuring study-to-study variation in effect size showed that there was no statistically significant heterogeneity between the studies. The Q -statistics, which tested the null hypothesis that the results among the studies were homogeneous, for 2hPG were 22.0 ($P = 0.36$) for all-cause mortality, 14.6 ($P = 0.71$) for CVD mortality, and 30.0 ($P = 0.05$) for non-CVD mortality. For FPG, these estimates were 21.2 ($P = 0.46$), 29.5 ($P = 0.05$), and 20.2 ($P = 0.37$), respectively.

Estimates based on the pooled data

analysis revealed that the lowest HRs were in subjects with an FPG of 4.5–5.0 mmol/l for all-cause and non-CVD mortality (Figs. 2A, C, D, and F) and in subjects with an FPG of 5.0–5.5 mmol/l for CVD mortality (Fig. 2B and E). Below and above these FPG concentrations, the risk of death was higher, with the highest risks in the upper range of the FPG distribution. Combining adjacent FPG groups, the multivariate-adjusted HRs (95% CI) in comparison with an FPG of 4.50–6.09 mmol/l were, for subjects with low FPG concentrations (<4.50 mmol/l), 1.2 (1.0–1.4) for all-cause, 1.3 (1.0–1.8) for CVD, and 1.1 (0.9–1.4) for non-CVD mortality. For subjects with IFG (FPG 6.1–6.9 mmol/l) and those with previously undetected diabetes (FPG ≥ 7.0 mmol/l), the corresponding HRs were 1.1 (1.0–1.2) and 1.6 (1.4–1.8), 1.1 (1.0–1.3) and 1.6 (1.3–1.9), and 1.1 (1.0–1.2) and 1.6 (1.4–1.9), respectively. This indicates that the relation between mortality and FPG concentration followed a J-shaped curve, as depicted in Figs. 2 and 3. The curvilinear relation was superior to a linear model for all-cause ($\chi^2 = 17.7$, 1 df, $P < 0.001$) and CVD ($\chi^2 = 17.7$, 1 df, $P < 0.001$) but not for non-CVD mortality ($\chi^2 = 2.5$, 1 df, $P > 0.1$). The threshold models provided a significantly better fit to the data than the model with a linear FPG term for most of the threshold points studied (online appendix 2). The best threshold model is where the log-likelihood ratio is a maximum. For all-cause mortality, this corresponds to an FPG of 5.3 mmol/l; the β -coefficient was negative for the lower FPG concentrations and positive for concentrations higher than the threshold, a J-shaped relation. Similar relations were seen for CVD and non-CVD deaths, where the thresholds were at 5.4 and 4.5 mmol/l, respectively.

For 2hPG, the lowest mortality risk was found for glucose concentrations <3.0 mmol/l (Fig. 2). After that, the risk of death first increased and then declined slightly with increasing 2hPG concentration until the 2hPG interval centered on 4.75 mmol/l for all-cause and non-CVD mortality and on 5.25 mmol/l for CVD mortality. Thereafter, the risk of mortality increased gradually (Figs. 2 and 3). In comparison with subjects with a 2hPG of 4.51–5.50 mmol/l, the multivariate-adjusted HRs (95% CI) for low a 2hPG of 3.01–4.50 and ≤ 3.00 mmol/l were 1.1 (1.0–1.2) and 0.9 (0.7–1.1) for all-cause,

Table 1—Characteristics of subjects at baseline and the number (%) of deaths from all causes, CVD, and non-CVD

Center	N	Men (%)	Age (years)	Glucose (mmol/l)		Follow-up (maximum years)	Deaths		
				Fasting	2 h		CVD	Non-CVD	All cause
Pol-Monica, Poland	364	47	43–74	5.6 ± 1.0	7.1 ± 2.9	6.6	16 (4.4)	8 (2.2)	29 (8.0)
Oulu elderly, Finland	374	37	70–89	7.0 ± 2.3	9.5 ± 3.5	4.4	NA	NA	80 (21.4)
East and West Finland	411	100	69–89	6.1 ± 1.9	7.9 ± 3.2	8.2	106 (25.8)	108 (26.3)	214 (52.1)
Glostrup Study 1897, Denmark	415	53	70	5.9 ± 1.9	8.0 ± 4.1	27.0	204 (49.2)	193 (46.5)	402 (96.9)
Zutphen Study, the Netherlands	484	100	69–89	6.2 ± 1.8	6.6 ± 3.0	4.8	57 (11.8)	63 (13.0)	120 (24.8)
MONICA_86, Northern Sweden	553	51	30–65	5.0 ± 0.9	5.6 ± 2.1	15.0	14 (2.5)	20 (3.6)	42 (7.6)
Vantaa, Finland	609	45	64–66	5.9 ± 1.8	7.7 ± 2.5	8.1	32 (5.3)	24 (3.9)	56 (9.2)
Glostrup Study 1914, Denmark	652	54	59–61	5.9 ± 1.7	6.5 ± 3.1	19.8	130 (19.9)	155 (23.8)	286 (43.9)
MONICA_90, Northern Sweden	684	47	30–64	5.3 ± 0.6	5.4 ± 1.4	11.0	4 (0.6)	14 (2.0)	23 (3.4)
Oulu middle-aged, Finland	791	44	55	6.3 ± 1.4	7.7 ± 2.4	6.2	NA	NA	26 (3.3)
Newcastle Heart Project, U.K.	800	52	30–76	6.0 ± 1.3	6.6 ± 2.6	6.7	18 (2.3)	25 (3.1)	43 (5.4)
MONICA_94, Northern Sweden	883	48	30–74	5.3 ± 0.7	6.0 ± 2.2	7.0	11 (1.2)	9 (1.0)	29 (3.3)
Goodinge, U.K.	1,039	44	39–76	4.9 ± 0.8	5.1 ± 2.0	9.7	41 (3.9)	72 (6.9)	113 (10.9)
Glostrup Study 1936, Denmark	1,042	48	39–41	6.1 ± 0.9	8.1 ± 2.4	17.7	17 (1.6)	50 (4.8)	70 (6.7)
Hel Policemen Study, Finland	1,136	100	30–69	6.0 ± 0.8	5.6 ± 1.7	27.8	220 (19.4)	212 (18.7)	432 (38.0)
Uppsala, Sweden	1,181	100	69–73	5.8 ± 1.5	8.3 ± 4.0	4.4	18 (1.5)	22 (1.9)	40 (3.4)
Cremona Study, Italy	1,818	44	40–88	5.3 ± 1.1	5.6 ± 2.3	6.9	46 (2.5)	83 (4.6)	138 (7.6)
MONICA_92, Finland	1,929	46	39–64	5.6 ± 1.1	6.3 ± 2.3	6.0	31 (1.6)	44 (2.3)	75 (3.9)
Catalonia, Spain	2,123	43	30–89	5.9 ± 1.7	6.8 ± 2.0	3.0	19 (0.9)	25 (1.2)	44 (2.1)
Hoorn Study, the Netherlands	2,468	46	49–77	5.8 ± 1.6	6.1 ± 3.0	10.2	115 (4.7)	187 (7.6)	330 (13.4)
MONICA_87, Finland	2,798	47	32–64	5.4 ± 1.4	6.5 ± 2.6	11.0	137 (4.9)	147 (5.3)	284 (10.2)
Paris Prospective Study, France	7,160	100	44–55	5.7 ± 0.8	5.9 ± 2.2	25.3	426 (5.9)	1,556 (21.7)	1,982 (27.7)
Total	29,714	65	30–89	5.7 ± 1.3	6.4 ± 2.7	27.8	1,662 (5.8)	3,017 (10.6)	4,858 (16.3)

Data are means ± SD or n (%) unless otherwise indicated. NA, not available.

1.1 (0.9–1.3) and 0.6 (0.4–1.0) for CVD, and 1.1 (1.0–1.3) and 1.0 (0.8–1.3) for non-CVD mortality. The corresponding HRs for subjects with IGT (2hPG 7.8–11.0 mmol/l) and those with previously undetected diabetes (2hPG ≥11.1 mmol/l) were 1.5 (1.3–1.7) and 2.0 (1.7–2.3), 1.4 (1.2–1.7) and 1.9 (1.5–2.4), and 1.6 (1.4–1.8) and 2.1 (1.7–2.5), respectively. The curvilinear model was highly significant for all-cause ($\chi^2 = 23.4$, 1 df, $P < 0.001$) and non-CVD mortality ($\chi^2 = 17.4$, 1 df, $P < 0.001$) and of borderline significance for CVD mortality ($\chi^2 = 4.3$, 1 df, $P < 0.05$). Thus, there was a J-shaped relation for all-cause and non-CVD mortality, but not for CVD mortality. The threshold models for all-cause and non-CVD mortality differed significantly from the linear model at most of the cutoff points measured (online appendix 2), and the threshold 2hPG concentrations were 5.4 and 5.1 mmol/l, respectively. Again, the negative and positive slopes around the threshold point are indicative of a J-shaped relation. For CVD mortality, the log-likelihood ratio did not have a unique maximum; thus, a threshold model was not appropriate (online appendix 2). Compared with the cur-

vilinear and threshold models, a linear model of 2hPG (in the logarithm) was better.

By taking previously diagnosed diabetes as the comparison category, the HRs for both FPG and 2hPG could be compared directly (Fig. 3A–C). For all-cause, CVD, and non-CVD mortality, the HRs for subjects with 2hPG >10.0 mmol/l (including undetected diabetic subjects and those at the upper range of IGT) were not significantly different from those for the known diabetic patients. For subjects with diabetes diagnosed on the basis of an FPG ≥7.0 mmol/l, all-cause and CVD mortality were significantly lower than for the subjects with known diabetes, whereas for non-CVD mortality, there was no difference. The subjects diagnosed as diabetic by 2hPG had a 10% higher HR than those diagnosed by FPG for all-cause and non-CVD mortality (Figs. 3A–C). The HRs for subjects with IGT were higher than those for subjects with IFG.

CONCLUSIONS— All analyses suggested that there is a J-shaped relation between mortality and glucose concentrations for both FPG and 2hPG, except for the relation between 2hPG and CVD

mortality, where the relation is graded and increasing. That high fasting and 2hPG concentrations are associated with increased risk of mortality is now unequivocally confirmed, while an association between low FPG and 2hPG concentrations and mortality has only been reported in two earlier studies. A J-shaped relationship between all-cause mortality and FPG and 2hPG has been reported in the Paris Prospective Study (3), which was also included in our present collaborative analysis. A U.S. study (11) showed that the age- and sex-adjusted mortality rates were higher in subjects with an FPG <4.4 mmol/l than in those with IFG and diabetes. Compared with subjects with normal FPG (4.40–6.09 mmol/l), multivariate-adjusted HR in subjects with an FPG <4.4 mmol/l was 2.0 (95% CI 1.5–2.6) for all-cause mortality and 2.7 (1.7–4.3) for CVD mortality. In our study population, subjects with a very low FPG concentration were younger, had lower BMI, cholesterol, and blood pressure, and were more often nonsmokers compared with the subjects with higher FPG concentrations. This was consistent with the observation from the U.S. study (11). A low

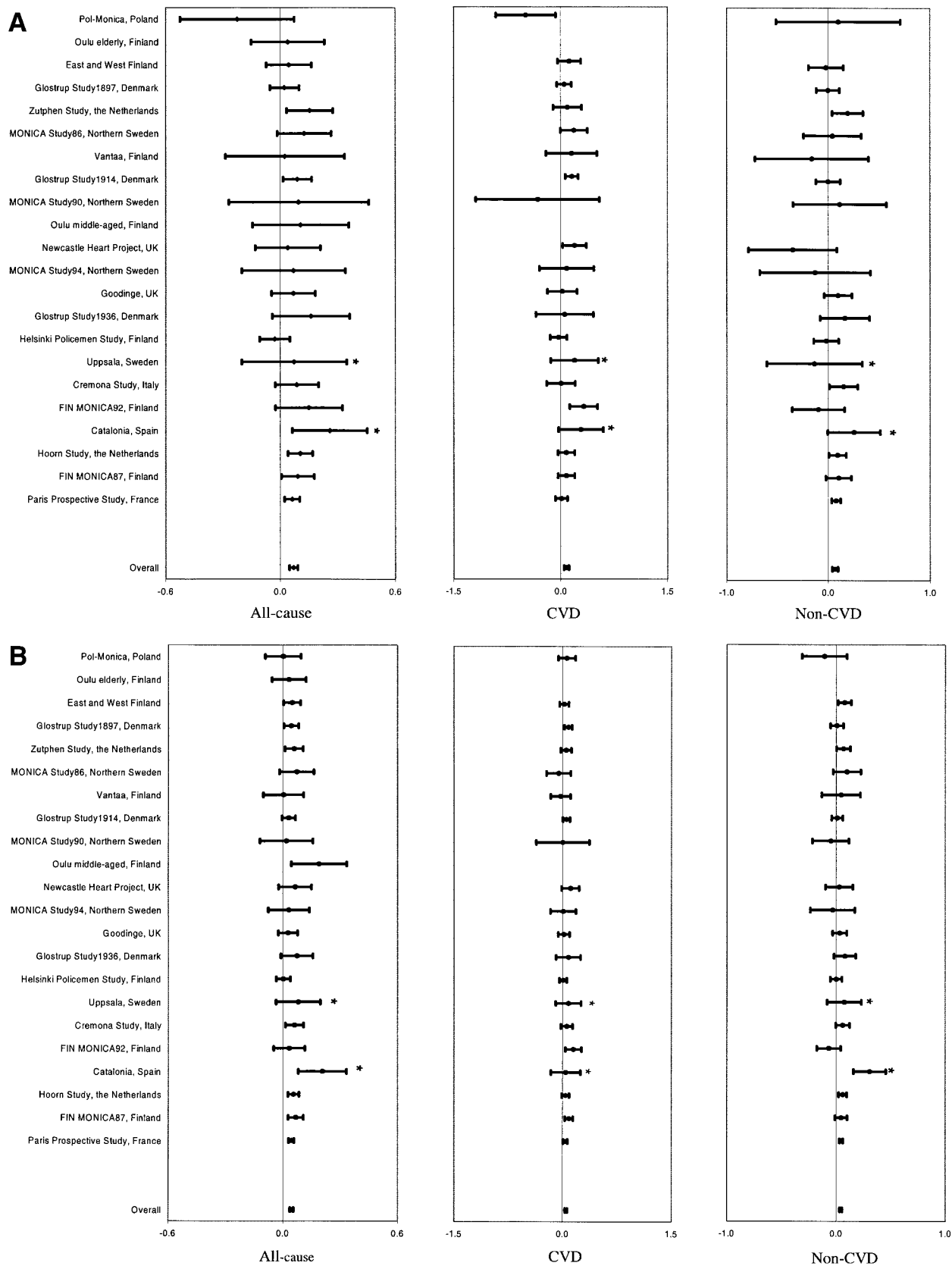
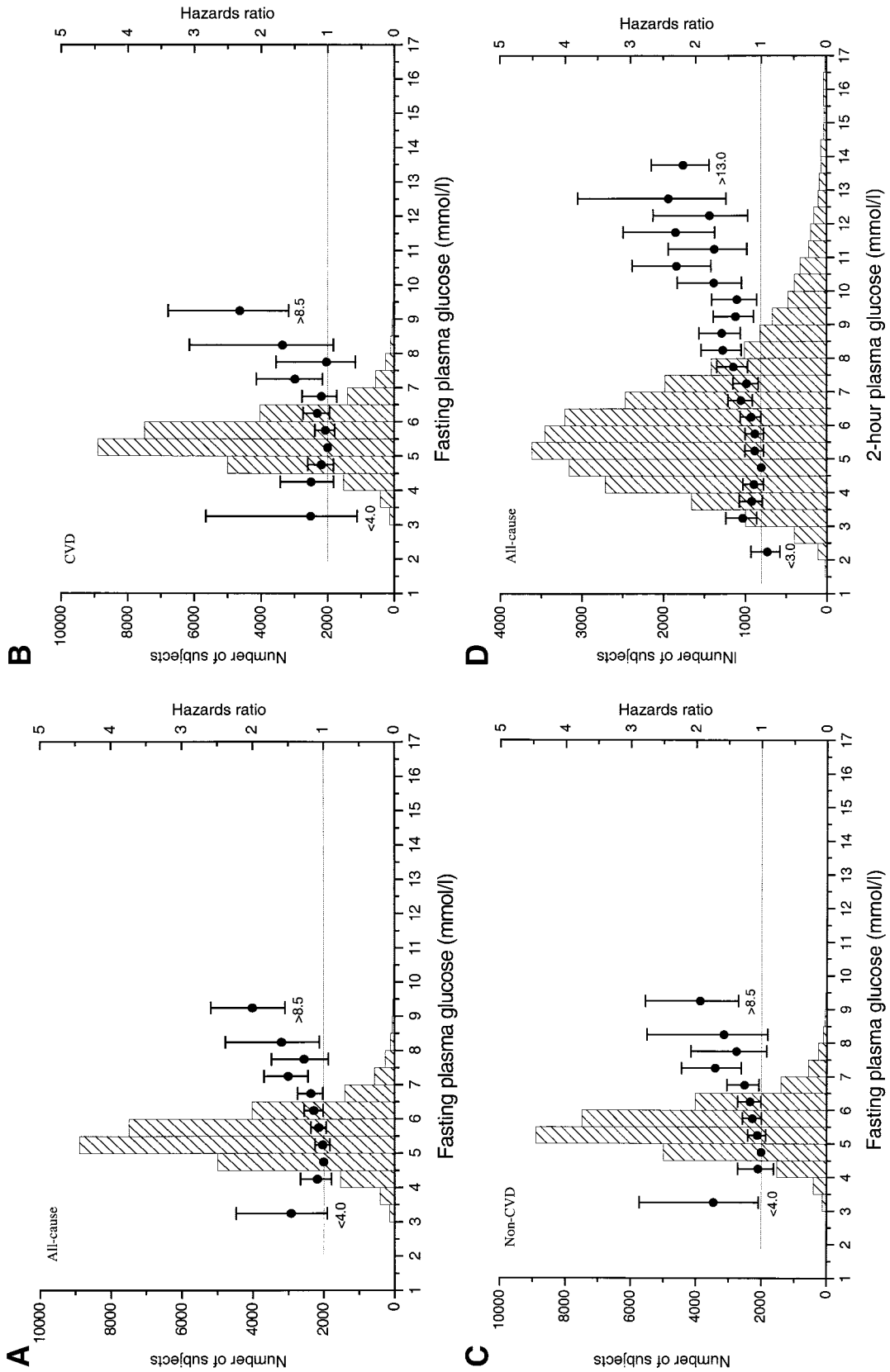


Figure 1—Individual and overall β -coefficients (plots) and 95% CIs (lines) for a 10% increase in FPG (A) and 2hPG (B) concentrations for all-cause, CVD, and non-CVD mortality in subjects without previous history of diabetes, adjusted for age, sex, BMI, systolic blood pressure, cholesterol, and smoking. *Studies where adjustment was not made for cholesterol.

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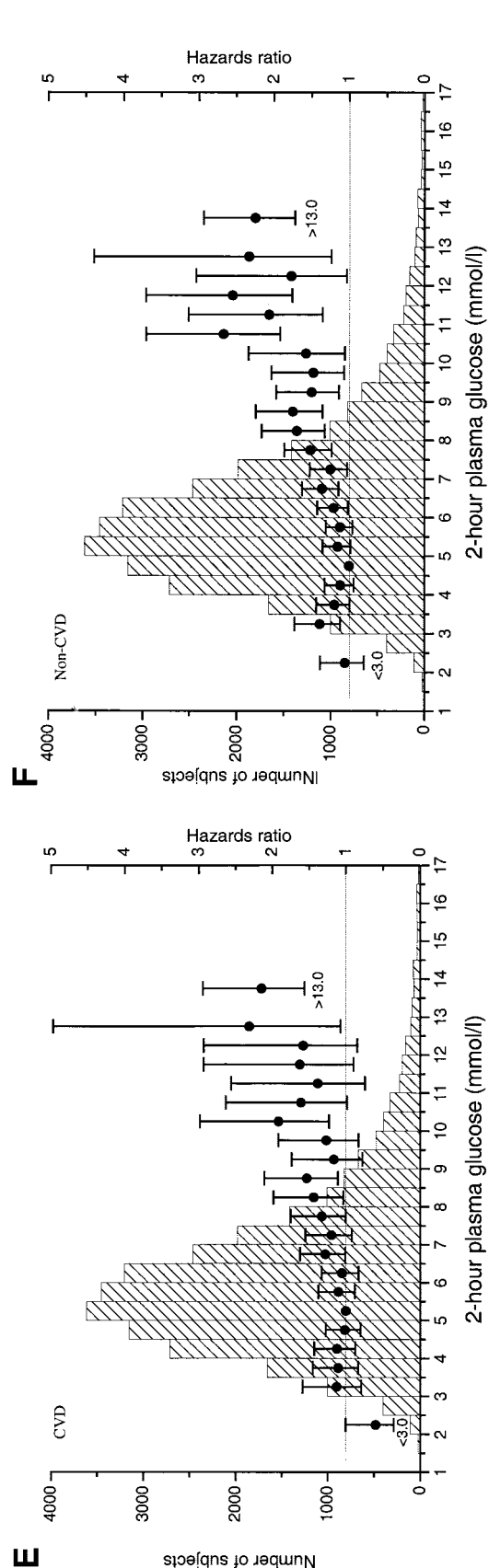


Figure 2—FPG (A–C) and 2hPG (D–F) distributions. HRs (●) and 95% CIs (vertical bars) for all-cause (A and D), CVD (B and E), and non-CVD (C and F) mortality according to glucose intervals of 0.5 mmol/l in subjects without previous history of diabetes, adjusted for age, sex, cohort, BMI, systolic blood pressure, cholesterol, and smoking.

BMI may be associated with a low FPG; however, an adjustment for these risk factors did not change the observed association between low FPG and mortality in the present study. The adverse effect of low FPG on mortality is not clear. It has been hypothesized that low FPG, cholesterol, and blood pressure may in some situations serve as markers of poor general health and are thereby associated with increased mortality. A curvilinear relation between the 2hPG and CVD mortality was, however, only of borderline significance when modeling with a squared term in logarithm-transformed 2hPG. The formal threshold test also indicated a graded rather than J-shaped relation between 2hPG and CVD mortality. The risk of CVD death started to increase gradually far below the cut point for diabetes. This is not entirely unexpected. An earlier report from the Whitehall Study (12) demonstrated a 1.5- to 2-fold increase in coronary heart disease and stroke mortality in men whose 2-h postload (50-g) capillary glucose was as low as 5.40 mmol/l. In addition, the current 2hPG cutoff that defined diabetes was originally adopted because it represented an optimal cutoff for separating the two components of the bimodal distribution of the 2hPG concentration in some specific populations and for identifying people with prevalent diabetic retinopathy (13,14). Therefore, there is no a priori reason for this threshold to be relevant to mortality, whether from all causes or CVD.

The present study also showed that in comparison with previously diagnosed diabetic subjects, the risk of death from all causes and CVD was similar in previously undetected diabetic individuals defined by high 2hPG concentrations, whereas it was significantly lower in those whose diabetes was defined by high FPG. This should be further examined in other populations and borne in mind when planning interventions aiming at the reduction of CVD morbidity and death. People in the upper range of IGT (10.01–11.09 mmol/l) had a similar risk of dying as those whose diabetes was defined by an FPG \geq 7.00 mmol/l. Subjects with IFG did not show an increased risk of death compared with those with normal FPG. IGT was more associated with risk of death than IFG. This provides further evidence supporting the consensus statement recently made by an international

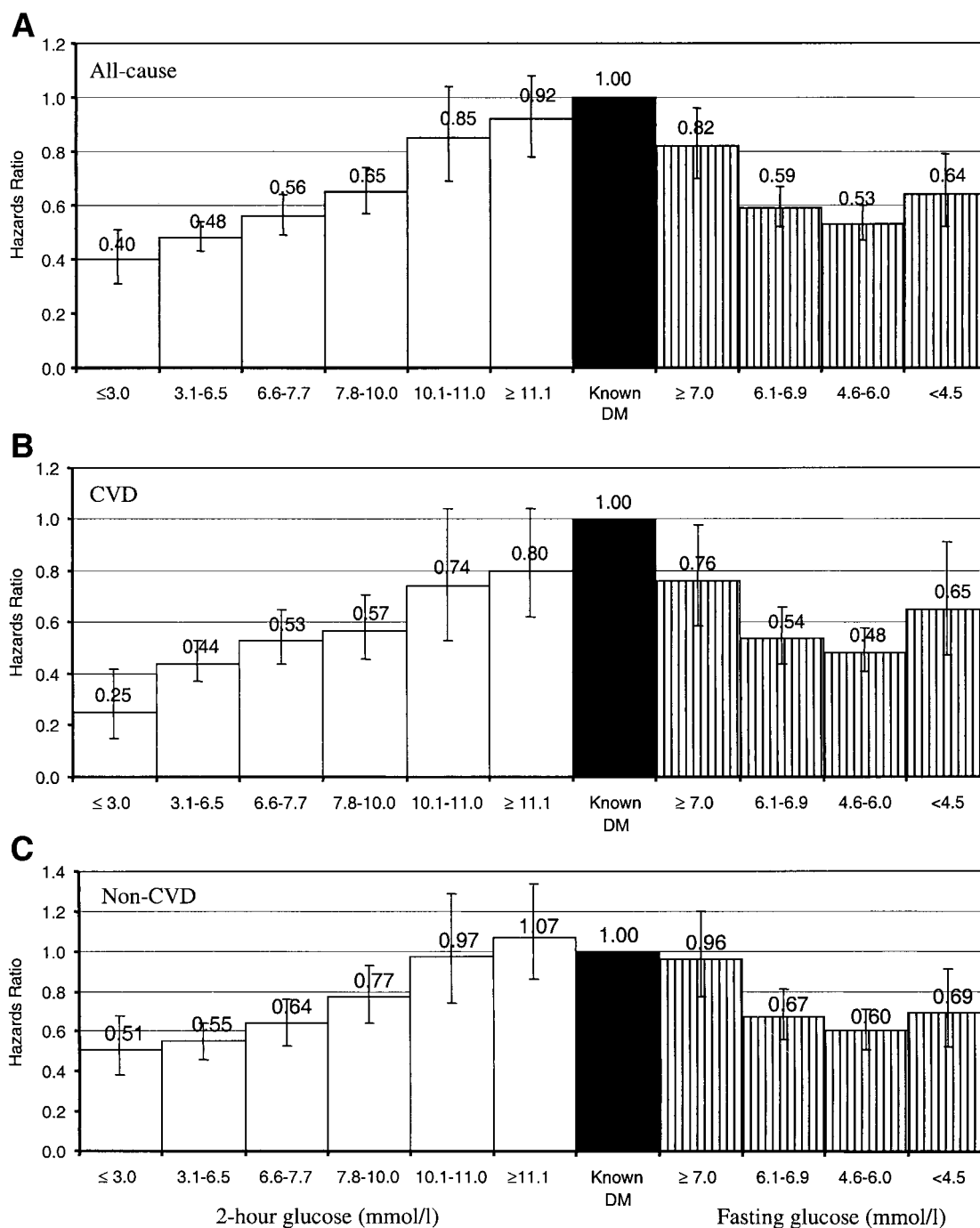


Figure 3—HRs (columns) and 95% CIs (vertical bars) for mortality from all causes (A), CVD (B), and non-CVD (C) for the FPG and 2hPG intervals using previously diagnosed diabetes as a common reference category, adjusted for age, sex, cohorts, BMI, systolic blood pressure, cholesterol, and smoking.

expert consensus workshop (15) that IFG and IGT do not represent the same disease entities and are not interchangeable. This highlights the importance of keeping the oral glucose tolerance test for the diagnosis of diabetes. This is particularly important for the elderly population because postchallenge glucose levels increase to a

much greater extent with advancing age than fasting glucose (16,17). Studies have shown that the onset of diabetes can be delayed or prevented through lifestyle intervention and treatment with oral hypoglycemic agents in subjects with IGT (18,19). It is, therefore, important to develop a sensitive screening strategy that is

both practical and predictive of individuals who will be likely to benefit from the diagnosis and prevention. The oral glucose tolerance test may be more efficient when used in high-risk populations that are identified by well-established risk factors, such as older age, obesity, hypertension, and family history of diabetes.

Identifying the high-risk population using demographic characteristics still remains a great challenge and requires more studies among different ethnic groups.

Currently, there are no internationally accepted conversion factors for glucose concentrations in the literature. The use of conversion factors in the current study may raise questions. To evaluate the potential bias caused by the transformation of glucose, we further analyzed the data from the 13 cohorts (70% of the entire study population) that used plasma glucose measurements only, and similar results were obtained. In addition, when we pooled the data from the 18 cohorts for the study of cause-specific mortality, no cohort with capillary blood glucose was included due to missing variables and the potential influence of the capillary blood glucose was therefore eliminated. Furthermore, for the results presented in Fig. 1, there is no bias due to the conversion of glucose, since a continuous glucose variable was used and the data analysis was performed for each study separately.

In conclusion, in subjects without a previous history of diabetes, there was no threshold for either fasting or 2-h post-load glucose concentration above which the risk of all-cause or CVD death increased sharply. Except for between 2hPG and CVD mortality, there was a J-shaped relation between glucose and mortality. A graded increasing relation between 2hPG and CVD mortality was observed. The risk of all-cause and CVD death for previously undetected diabetes, defined by the current cut point for 2hPG, was not different from that for known diabetic subjects, who in turn had a significantly higher risk than the subjects diagnosed as diabetic by the current FPG criteria.

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APPENDIX

Organization

The DECODE Study was undertaken in 1997 upon the initiative of the European Diabetes Epidemiology Group (Chair-

man: Knut Borch-Johnsen; Vice-chairman: Andrew Neil; Secretary: Beverley Balkau).

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U.K. The Gooding Study: John S. Yudkin, Mairi Gould, Andy Haines, and Richard W. Morris, Center for Diabetes & Cardiovascular Risk and Department of Primary Care & Population Sciences, Royal Free and University College Medical School.

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