

Relation Between Blood Glucose and Coronary Mortality Over 33 Years in the Whitehall Study

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OBJECTIVE— Glucose intolerance is a risk factor for coronary disease, but there is uncertainty about the shape of the dose-response relationship between glucose level and risk of coronary mortality. We examined the prospective relation of 2-h postload blood glucose (2hBG) with coronary and other major causes of mortality over 33 years.

RESEARCH DESIGN AND METHODS— A 50-g oral glucose tolerance test (OGTT) was performed at baseline (1967–1969) in 17,869 male civil servants aged 40–64 years.

RESULTS— There were 3,561 coronary deaths during 451,787 person-years of observation. All-cause, cardiovascular, and respiratory mortality were elevated among participants with glucose intolerance. The hazard of coronary mortality rose from 2hBG = 4.6 mmol/l (83 mg/dl [95% CI 4.2–5.3]). The dose-response relation was best fitted by a single slope above this level, with no evidence of nonlinearity, compared with Cox models using other threshold levels, and those containing log 2hBG terms. There was no evidence for a dose-response relationship below 2hBG = 4.6 mmol/l. Between this level and 11.1 mmol/l (200 mg/dl), the age-adjusted hazard ratio was 3.62 (95% CI 2.3–5.6). The graded relationship was attenuated by 45% after adjustment for baseline coronary heart disease (CHD), BMI, systolic blood pressure, blood cholesterol, smoking, physical activity, lung function, and employment grade.

CONCLUSIONS— A threshold model with linear slope best described the dose-response relationship between postload blood glucose and CHD mortality risk.

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A raised blood glucose concentration well below the diagnostic level for type 2 diabetes is a risk factor for cardiovascular disease (CVD) mortality (1,2). The link between poor glycemic control and enhanced atherogenesis was much debated in the early 1970s (3,4), and by 1979 the intermediate category of impaired glucose tolerance was proposed explicitly to identify those at increased risk of large-vessel disease but low risk of small-vessel disease (5).

Uncertainty remains about the exact shape of the glucose–coronary heart disease (CHD) relationship and the level at which coronary mortality begins to rise

(6–8). Ten-year follow-up of 18,403 men in the Whitehall Study (2) showed among nondiabetics that CHD mortality was increased twofold above a postload glucose of 5.3 mmol/l, but below this level the degree of glycemia was not associated with coronary risk. Recent meta-analyses of observational studies have confirmed the progressive relation between glucose levels below the diabetic threshold and cardiovascular risk but have not sought to identify the level at which the risk starts to rise (1,9).

The aim of this report is to examine the nature of the dose-response relationship between a 2-h post–50-g oral glucose

tolerance test (OGTT) glucose measurement and coronary mortality over 33 years, with 451,787 person-years of follow-up. We focus in particular on the consequences of a 2-h postload blood glucose (2hBG) <5.3 mmol/l (95 mg/dl), immediately below the previously defined lower limit of glucose intolerance (2). In addition to the detailed analysis of 3,561 CHD deaths, we have examined the relation of glucose tolerance status with all-cause mortality and broad causes of death including total cardiovascular disease, stroke, neoplasm, and respiratory disease.

RESEARCH DESIGN AND

METHODS— In the Whitehall Study, 18,403 nonindustrial London-based male civil servants aged 40–64 years were examined between September 1967 and January 1970. The response rate was 74%. In brief, measurements included height, weight, blood pressure, six-lead electrocardiogram, lung function (forced expiratory volume in 1 s and forced vital capacity), plasma cholesterol concentration, and a glucose tolerance test (10). A self-administered questionnaire was completed regarding employment grade, smoking habits, health status, and physical activity.

After overnight fasting, participants drank a 50-g anhydrous dextrose preparation 2 h before the scheduled drawing of blood. Blood glucose concentration was measured by the ferricyanide reduction method on an autoanalyser (Technicon method N-9a). Those with self-reported diabetes did not participate in the OGTT and were excluded from analyses. Participants with 2hBG \geq 11.1 mmol/l (\geq 200 mg/dl) constituted the newly diagnosed diabetic group. Nondiabetic participants with 2hBG >95th centile (5.3–11.0 mmol/l; 96–199 mg/dl) were classified as glucose intolerant and those below this level as being normoglycemic (2). Employment grade, smoking status, and physical activity were coded as categorical variables (11). Existing baseline CHD was defined from either ischemic signs on the electrocardiogram trace, a report of severe pain across the

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Abbreviations: 2hBG, 2-h postload blood glucose; CHD, coronary heart disease; CVD, cardiovascular disease; OGTT, oral glucose tolerance test.

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

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chest lasting ≥ 30 min, or a report of hospitalization for CVD.

Over 99% (18,245/18,403) were flagged at the National Health Service Central Registry, which notified all deaths to the end of 2002. This 33-year follow-up provides the basis for this analysis. Underlying causes of death were classified according to the ICD-8, including mortality from CHD (ICD 410–414), stroke (ICD 430–438), aortic aneurysm (ICD 441), all CVD (ICD 390–458), malignant neoplasm (ICD 140–208), and respiratory disease (ICD 460–519). Seven percent of deaths were coded using the corresponding codes of ICD-9, and the 1% of deaths occurring after September 2002 used the corresponding ICD-10 codes.

Statistical analysis

Of 18,245 men who were successfully followed-up, 86 were excluded due to missing data on cause of death, smoking, physical activity, or baseline CHD. Participants with known diabetes (114 with type 2 and 42 with type 1 diabetes) and 134 men with missing glucose measurements were also excluded, leaving 17,869 men in the analyses.

In analyses of baseline characteristics according to glucose tolerance status (normoglycemic, glucose intolerant, and new diabetic subjects), prevalence was adjusted for age using 5-year age-groups by the direct standardization method and differences between the glucose tolerance status groups tested using the Mantel-Haenszel test. For continuous baseline measures, least square means were used to present the age-adjusted means and tests of differences between the glucose tolerance status groups tested using ANOVA. Kaplan-Meier survival over follow-up in each of the three glucose tolerant groups was computed. Hazard ratios and 95% CIs were computed for the relationships of glucose tolerant groups and postload glucose with each mortality outcome using Cox's proportional hazard regression models with follow-up period as the time scale. Further analyses using Cox models were conducted to examine the best fitting shape for the CHD mortality (log hazard) versus 2hBG relationship. Likelihood ratio statistics measured the increase in CHD variation explained by each model, and models were compared using χ^2 tests.

Multiply adjusted hazard ratios were computed using age, BMI, forced expiratory volume in 1 s, forced vital capacity,

Table 1—Baseline characteristics in relation to glucose tolerance status

	Normoglycemia (< 5.3 mmol/l)	Glucose intolerance (5.3 – 11.0 mmol/l)	New diabetes (≥ 11.1 mmol/l)
	Means \pm SE*		
Age (years)	51.4 \pm 0.1	53.2 \pm 0.2†	56.9 \pm 0.7†
BMI (kg/m ²)	24.7 \pm 0.02	25.2 \pm 0.09†	26.9 \pm 0.39†
FEV ₁ (l)	3.18 \pm 0.01	3.04 \pm 0.02†	2.84 \pm 0.09†
FVC (l)	4.05 \pm 0.01	3.87 \pm 0.02†	3.56 \pm 0.09†
Systolic blood pressure (mmHg)	135.6 \pm 0.2	141.4 \pm 0.6†	147.7 \pm 2.7†
Plasma cholesterol (mmol/l)	5.11 \pm 0.01	5.06 \pm 0.03	5.42 \pm 0.17
	Percent \pm SE*		
Physically inactive	16.0 \pm 0.3	15.1 \pm 1.1	13.7 \pm 5.7
Low work grade	23.2 \pm 0.3	28.5 \pm 1.4†	48.0 \pm 9.1†
Current cigarette smoker	41.4 \pm 0.4	40.2 \pm 1.6	29.0 \pm 6.9
Baseline CHD	13.7 \pm 0.3	18.6 \pm 1.2†	22.0 \pm 6.9
First-degree relatives with CHD‡	13.3 \pm 0.4	12.1 \pm 2.1	24.5 \pm 7.5

Total $n = 17,869$ (normoglycemia, 16,826; glucose intolerance, 987; new diabetes, 56). *Means and percents are adjusted for age (age is unadjusted). † $P < 0.001$ compared with normoglycemic group. ‡Information on first-degree relatives (parents, siblings, or children) with CHD ascertained on 6,206 participants. FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity.

systolic blood pressure, and cholesterol fitted as continuous measures and employment grade (five levels); smoking status (four levels), with additional adjustment for current number of cigarettes per day; physical activity (six levels); and baseline CHD (two levels) fitted as categorical variables. Multiple imputation was used to produce values for the 661 men with missing data for continuous covariates. Five datasets with imputed measures were generated and gave very similar regression estimates, which were averaged (12).

RESULTS— The associations between glucose tolerance status and baseline characteristics are shown in Table 1. Glucose intolerance and new diabetes were each associated with older age, degree of obesity, poorer lung function, and higher systolic blood pressure. Prevalent glucose intolerance and diabetes was associated with low employment grade. Glucose intolerance was linked with a higher prevalence of CHD at baseline. Family history of CHD, ascertained in 6,206 participants, was unrelated to glucose tolerance status.

Survival by baseline glucose tolerance status diverged after 5–10 years of follow-up (Fig. 1). Median survival differed by ~ 4 years between the normoglycemic and glucose intolerant groups and was 10 years less in the diabetic compared with the glucose intolerant group.

Age-adjusted hazard ratios for 33-

year mortality according to glucose tolerance status are shown in Table 2. There were 11,426 deaths from all causes, with 5,497 due to CVD (48.1%) and 3,240 due to neoplasms (28.4%). Newly diagnosed diabetic subjects had significantly increased risk of mortality from all causes, CVD, CHD, and respiratory disease. Glucose intolerance was associated with increased risk of mortality from all causes, total CVD, CHD, stroke, respiratory disease, and other non-CVD causes, excluding neoplasm.

We conducted a detailed analysis in order to identify the shape of the glucose-CHD relationship. Participants were grouped into 0.2-mmol/l intervals between 3.2 and 6.4 mmol/l, with wider groups above this level. Those with newly diagnosed diabetes (2hBG ≥ 11.1 mmol/l, $n = 56$) were excluded. The dose-response relation is displayed in Fig. 2. Four types of model were fitted, as described in Table 3, all of which showed strong associations ($P < 0.001$) of blood glucose with CHD mortality. The quadratic term for blood glucose was significant ($P = 0.002$), providing evidence of a nonlinear relationship (model C). The variation explained did not increase using log 2hBG values. The series of nonlinear threshold model generally explained more of the variation in CHD than the quadratic model (model C), the best being a threshold of 4.6 mmol/l (95% CI 4.2–5.3) (model D). Model E confirmed that there was no association below

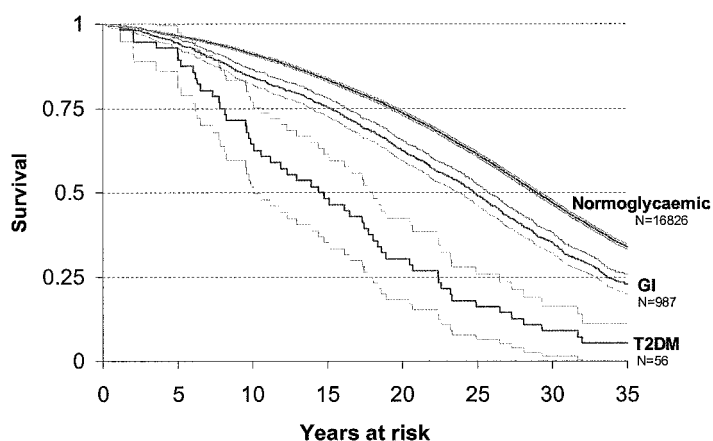


Figure 1—Survival by baseline glucose tolerance status. Age-adjusted survival and 95% CI. Glucose intolerance (GI), 5.3 ≤ 2-h glucose < 11.1 mmol/l. Newly diagnosed diabetes (T2DM), 2-h glucose ≥ 11.1 mmol/l.

2hBG = 4.6 mmol/l ($P = 0.31$). Exclusion of participants with CHD at entry to the study or CHD mortality during the first 5 years of follow-up had negligible effects on the dose-response relation.

For the relation above 2hBG concentrations of 4.6 mmol/l up to the diabetic threshold, the age-adjusted hazard ratio for CHD was 1.22 (95% CI 1.14–1.30) per mmol/l ($P < 0.001$) and 3.62 (2.34–5.56) for 2hBG of 11.1 mmol/l versus values below 4.6 mmol/l. Separate adjustments for family history (subsample) and total cholesterol did not change the age-adjusted relation between 2hBG and CHD mortality (data not shown). Multiple adjustment for all risk factors attenuated the slope by 45%, but it remained statistically significant ($P < 0.002$; multiply adjusted hazard ratio 1.12 (1.04–1.19) per mmol/l; 2.03 (1.31–3.16) for 11.1 vs. <4.6 mmol/l).

CONCLUSIONS—Mortality from CHD increased from a blood glucose level

of 4.6 mmol/l, but there was no evidence of an effect below this level. Above this level, a linear dose-response relation provided the best fit to the data. The Whitehall Study, involving 11,426 deaths over an extended follow-up period of 33 years, further showed that glucose intolerance (postload glucose 5.3–11.0 mmol/l) is associated with increased mortality risk from all causes, stroke, and respiratory disease but not all neoplasms (11).

By virtue of long follow-up and the large number of coronary deaths, these findings extend previous work on the relation between glucose levels and cardiovascular disease. Our findings are consistent with recent meta-analyses of postload glucose and CVD mortality that have assembled results from diverse population-based studies of nondiabetic subjects and shown the effect of glucose intolerance on risk over median follow-up of ~9–12 years (1,9). The DECODE study compared hazards between

the relatively broad diagnostic categories of impaired and normal glucose tolerance. Coutinho et al. (1) utilized a mixed outcome of fatal coronary disease and stroke, nonstandard interval data (three or five glucose quantiles) based on variable glucose loads (50–100 g), and a fixed baseline of 4.2 mmol/l (75 mg/dl) in the analysis. Consequently, the regression model was not sensitive to the nature of the epidemiologic relationship around normal glucose levels, specifically in relation to coronary causes. The Whitehall Study provides a similar volume of follow-up data, ~450,000 person-years over >3 decades of observation. It provides clear evidence that coronary mortality is raised among those with marginal postload hyperglycemia.

Tight glycemic control at or below the lower threshold of glucose intolerance might somewhat reduce the risk of macrovascular disease. The U.K. Prospective Diabetes Study trial (13) showed that intensive control of blood glucose substantially reduces microvascular complications of type 2 diabetes and the risk of myocardial infarction to a lesser degree. The observational component of the U.K. Prospective Diabetes Study showed risk reduction across a wide range of exposure to glycemia, indexed by HbA_{1c} level, for all-cause mortality, myocardial infarction, and stroke, after adjustment for major risk factors including blood pressure (14). Notwithstanding this independent effect, hyperglycemia acts in concert with other CVD risk factors, and it may be that lipid-lowering is the more effective intervention for diabetic patients (15). Here, the direct measurement of blood glucose in nondiabetic participants shows that risk of CHD is incrementally related to

Table 2—Age-adjusted hazard ratios for 33-year mortality in the Whitehall Study according to glucose tolerance status at baseline

Cause of death	Number of deaths			Glucose tolerance status		
	Normoglycemia	Glucose intolerance	Diabetes	Normoglycemia (<5.3 mmol/l) (n = 16826)	Glucose intolerance (5.3–11.0 mmol/l) (n = 987)	New diabetes (≥11.1 mmol/l) (n = 56)
				Reference group	Hazard ratio (95% CI)	Hazard ratio (95% CI)
All causes	10,639	734	53	1.0	1.27 (1.18–1.37)	2.37 (1.81–3.11)
CVD	5,090	371	36	1.0	1.33 (1.19–1.48)	3.20 (2.31–4.44)
CHD	3,286	247	28	1.0	1.36 (1.20–1.55)	3.70 (2.55–5.38)
Stroke	890	71	2	1.0	1.47 (1.16–1.88)	1.16 (0.29–4.64)
Aortic aneurysm	271	13	1	1.0	0.89 (0.51–1.54)	1.78 (0.25–12.7)
Non-CVD	5,549	363	17	1.0	1.22 (1.10–1.36)	1.53 (0.95–2.46)
Neoplasm	3,057	178	5	1.0	1.08 (0.93–1.25)	0.78 (0.32–1.86)
Respiratory disease	1,323	105	7	1.0	1.49 (1.22–1.82)	2.95 (1.40–6.21)
Other causes	1,169	80	5	1.0	1.30 (1.04–1.64)	2.36 (0.98–5.67)

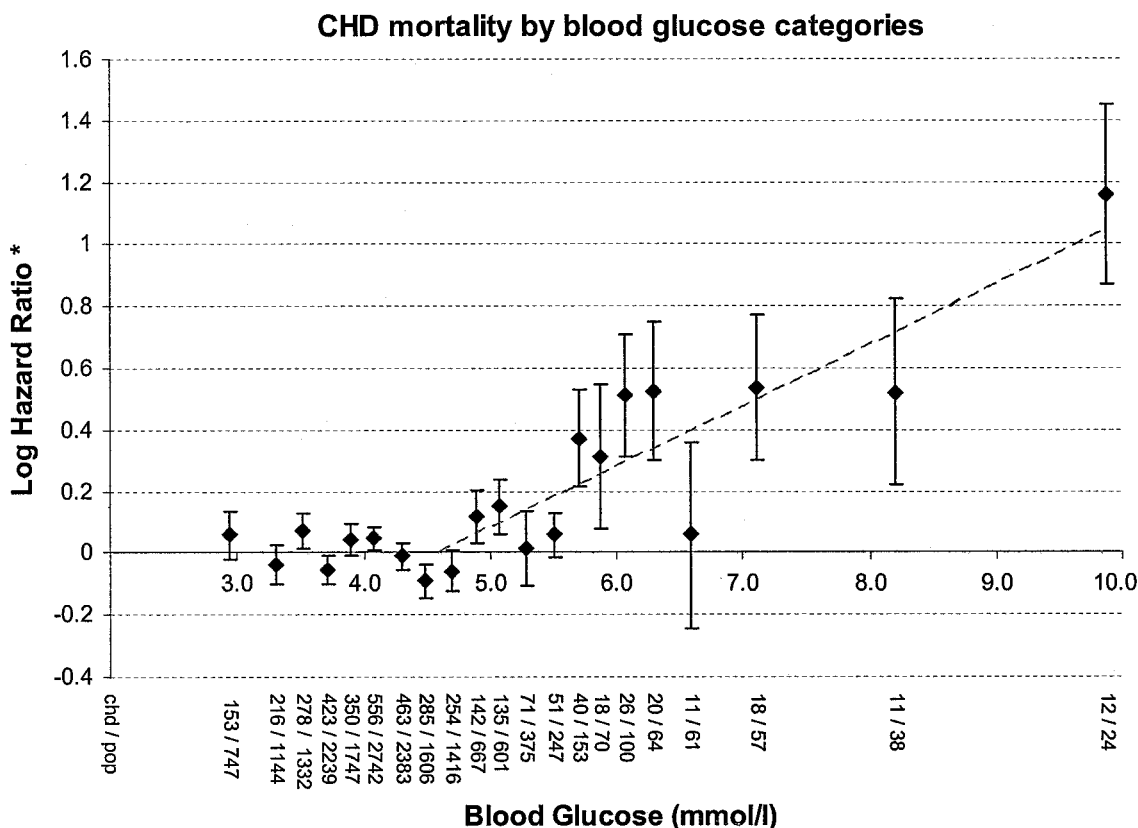


Figure 2—Coronary heart disease mortality by blood glucose category (log hazard and error bars showing SE). Blood glucose is grouped: <3.2, 0.2 mmol/l intervals from 3.2–6.3, 6.4–6.7, 6.8–7.5, 7.6–8.9, and 9.0–11.0. *The log hazard ratio is relative to baseline group of all men below a blood glucose of 4.6 mmol/l.

postload levels as low as 4.6–5.0 mmol/l. At present, extrapolation of the benefit of medical therapy from diabetic to near-normal levels of glucose lacks trial evidence. A healthy diet and sufficient physical activity are likely to be cardioprotective in part through their effects on glycaemic control (16).

Several mechanisms may account for the link between elevated glucose level and CHD risk. A raised glucose level at baseline may indicate emerging insulin resistance and a downward trajectory in glycaemic control, with increased risk of glucose intolerance, diabetes, and CHD in subsequent years (2,17). Related risk factors, particularly hypertension and an atherogenic lipoprotein profile, tend to develop in parallel with insulin resistance (18). Other pathways include oxidative stress and formation of advanced glycation end products that accelerate atherosclerosis when blood glucose is only slightly raised (19). A further indirect mechanism involves common antecedents of hyperglycemia and CHD such as poor early growth (20). Adjusting for conventional risk factors, existing baseline CHD and socioeconomic position (21) in

the present study reduced the size of the glucose-CHD association by 45%. This is evidence of a causal role for glycemia in CHD etiology. It is also consistent with an element of confounding and with risk-factor clustering of the metabolic syndrome type (22,23).

A number of limitations apply to this study. First, the findings are based on a 50-g OGTT, and a slightly differing dose-response relationship might be obtained with a 75-g glucose load. A 100-g glucose load produces a 2hBG ~20% higher than a 50-g load (24); however, the difference in dose-response curve resulting from a 75-g load in comparison with that used here is not predictable. Fasting glucose was not measured. Some misclassification of glucose tolerance status may thus be present, but it is unlikely to have major influence on the shape of the dose-response curve. A pooled analysis of 10 cohorts showed that 2hBG was the better predictor of all-cause and CHD mortality in population studies (9). Second, serum triglycerides and HDL cholesterol were not measured and could not be adjusted for in multivariate analysis. These lipids are potential confounders, and the resid-

ual effect of postload glycemia on CHD mortality is likely to be overestimated here (23). Third, all participants are men, predominantly of European origin, and thus the findings apply primarily to populations of this type. Fourth, an unavoidable consequence of the long follow-up period is that baseline risk factor prevalence differs from that in contemporary populations. For example, the prevalence of overweight and obesity within the relevant U.S. population group in 1999–2000 was ~70% (25) compared with 45% in this cohort. The biologic effect of glucose intolerance is likely to be similar over time, but the relevant population attributable risk may be substantially larger than our findings imply (26).

To date there has been limited evidence on the pattern of coronary mortality in relation to the upper boundary of the normal range of postload blood glucose. Over the extended follow-up period reported here, we find that CHD risk increases with post-50-g OGTT glucose in the upper fifth of the distribution. Although translation to a 75-g OGTT is problematic, our evidence is consistent with no association between 2hBG and CHD risk in the

Table 3—Increase in variation in CHD mortality explained by blood glucose

Model	Terms in fitted model	Likelihood ratio statistic (degrees of freedom); P value*†	
		Compared with age-only model	Compared with model indicated
A‡	Overall variation between blood glucose groups Age + BG (groups)	47.0 (20); P < 0.001	
B	Linear and quadratic effects using blood glucose Age + blood glucose (linear)	13.3 (1); P < 0.001	
C	Age + blood glucose (Linear) + blood glucose (quadratic) Linear effect above threshold value (no effect below threshold) Age + blood glucose ≥3.8 (linear) Age + blood glucose ≥4.0 (linear) Age + blood glucose ≥4.2 (linear) Age + blood glucose ≥4.4 (linear)	22.5 (2); P < 0.001	9.25 (1); P = 0.002 vs. model B
D	Age + blood glucose ≥4.6 (linear) Age + blood glucose ≥4.8 (linear) Age + blood glucose ≥5.0 (linear) Age + blood glucose ≥5.2 (linear) Age + blood glucose ≥5.4 (linear) Age + blood glucose ≥5.6 (linear) Linear effects above and below threshold value	28.4 (1); P < 0.001 27.6 (1); P < 0.001 25.5 (1); P < 0.001 24.6 (1); P < 0.001 22.3 (1); P < 0.001 19.9 (1); P < 0.001	5.46§ vs. model B
E	Age + blood glucose ≥4.6 (linear) + blood glucose <4.6 (linear)	29.4 (2); P < 0.001	1.04 (1); P = 0.31 vs. model D

Men with blood glucose ≥11.1 are excluded. Models compared using likelihood ratio statistics. *The likelihood ratio statistic is -2 (difference in log likelihood of two models). This estimates the increase in variation explained compared with the model specified. †Degrees of freedom for test is equal to the difference in the number of parameters between two models being compared and is given in parentheses. ‡In model A, blood glucose is grouped: <3.2; 0.2-mmol/l intervals from 3.2 to 6.3, 6.4 to 6.7, 6.8 to 7.5, 7.6 to 8.9, and 9.0 to 11.0. §Models D and C are not nested models so that the difference in the variation explained by these two models cannot be tested formally.

lower and central parts of the population distribution of postload glucose but a relatively low level at which CHD risk associated with postload glycemia begins to rise.

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