High Blood Glucose Concentration Is a Risk Factor for Mortality in Middle-Aged Nondiabetic Men

20-year follow-up in the Whitehall Study, the Paris Prospective Study, and the Helsinki Policemen Study

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OBJECTIVE — To assess the association between high but nondiabetic blood glucose levels and the risk of death from all causes, coronary heart disease (CHD), cardiovascular disease, and neoplasms.

RESEARCH DESIGN AND METHODS — We studied the 20-year mortality of nondiabetic, working men, age 44–55 years, in three European cohorts known as the Whitehall Study (n = 10,025), the Paris Prospective Study (n = 6,629), and the Helsinki Policemen Study (n = 631). These men were identified by their 2-h glucose levels following an oral glucose tolerance test and by the absence of a prior diagnosis of diabetes. As the protocol for the oral glucose tolerance test and methods for measuring glucose differed between studies, mortality was analyzed according to the percentiles of the 2-h and fasting glucose distributions, using the Cox's proportional hazards model.

RESULTS — Men in the upper 20% of the 2-h glucose distributions and those in the upper 2.5% for fasting glucose had a significantly higher risk of all-cause mortality in comparison with men in the lower 80% of these distributions, with age-adjusted hazard ratios of 1.6 (95% CI 1.4–1.9) and 2.0 (1.6–2.6) for the upper 2.5%. For death from cardiovascular and CHD, men in the upper 2.5% of the 2-h and fasting glucose distributions were at higher risk, with age-adjusted hazard ratios for CHD of 1.8 (1.4–2.4) and 2.7 (1.7–4.4), respectively.

CONCLUSIONS — If early intervention aimed at lowering blood glucose concentrations can be shown to reduce mortality, it may be justified to lower the levels of both 2-h and fasting glucose, which define diabetes.

Whether high (but nondiabetic) blood glucose levels are predictive of an increased mortality from coronary heart disease (CHD) is not a new issue. It was the topic of a report in 1979 from the International Collaborative Group (1). The conclusion from this analysis was that there was no "consistent, strong and graded" association between asymptomatic hyperglycemia and CHD. Donahue and Orchard (2), reviewing the same question, concluded that glucose levels were related to CHD risk; but whether the effect was linear or threshold was not clear. The risk does not appear to be linearly related with glucose levels, but is only apparent in the upper percentiles of the glucose distribution, as reported by Jarrett (3).

We report the association of baseline 2-h and fasting blood glucose with the risk of death from all causes, cardiovascular disease, CHD, cerebrovascular disease, and neoplasms in three cohorts of nondiabetic men, age 44–55 years at baseline after a 20-year follow-up.

RESEARCH DESIGN AND METHODS

The Whitehall Study, the Paris Prospective Study, and the Helsinki Policemen Study are all cohort studies of working men, with baseline examinations at the same epoch 1967–1970, 1968–1974, 1971–1972, respectively (4–6). In this joint analysis we included nondiabetic men and for comparison, diabetic men (all men age 44–55 years), combining known and newly screened diabetic subjects detected at baseline on the basis of an oral glucose tolerance test. The Whitehall Study contributed 10,025 nondiabetic and 61 diabetic men (40 known, 21 screened), the Paris Prospective Study contributed 6,629 nondiabetic and 279 diabetic men (154 known, 125 screened), and the Helsinki Policemen Study contributed 631 nondiabetic and 24 diabetic men (14 known, 10 screened). The nondiabetic men all had data on 2-h glucose levels following an oral glucose tolerance test (as well as on fasting glucose for the men from Helsinki and Paris), age, BMI, systolic and diastolic blood pressures (sBP, dBP), hypertensive treatment, baseline cardiovascular disease, total cholesterol level, smoking habits, and administrative "grade" in the organization. Cardiovascular disease was defined by clinical diagnosis and by electrocardiogram (ECG) abnormalities.

The protocol for the oral glucose tolerance test differed between studies. In the Whitehall Study, subjects were screened as nondiabetic if the 2-h capillary whole-blood glucose following a 50-g oral glucose load was <11.0 mmol/l; glucose was assayed using the ferricyanide-reduction

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Abbreviations: CHD, coronary heart disease; dBP, diastolic blood pressure; ICD, *International Classification of Diseases*; sBP, systolic blood pressure.

Table 1—*Characteristics of nondiabetic men age 44–55 years, in the Whitehall, Paris Prospective, and Helsinki Policemen studies*

	Whitehall	Paris Prospective	Helsinki Policemen
n	10,025	6,629	631
Age (years)	49.4 ± 3.3	48.5 ± 2.0	49.7 ± 3.0
BMI (kg/m²)	24.7 ± 2.9	25.9 ± 3.2	26.7 ± 3.1
sBP (mmHg)	134 ± 20	143 ± 20	139 ± 19
dBP (mmHg)	84 ± 13	81 ± 13	88 ± 11
0-h blood glucose (mmol/l)	—	5.6 ± 0.6	4.9 ± 0.5
2-h blood glucose (mmol/l)	4.2 ± 0.7	5.6 ± 1.6	4.5 ± 1.3
Cholesterol (mmol/l)	5.1 ± 1.2	5.6 ± 1.1	6.4 ± 1.2
Cardiovascular disease	13	2	26
Treated for hypertension	1	4	6
Smoking			
Never	23	16	21
Ex	37	20	35
Current	40	64	44
Administrative grade			
High	6	17	9
Mid-level	76	77	29
Low	18	5	62

Data are means ± SD or %.

method (Technicon method N-9a). In the Paris Prospective Study, a 75-g oral glucose load was used, and men screened as nondiabetic had 2-h plasma venous glucose <11.1 mmol/l, as analyzed by the potassium ferricyanide method (Technicon N-2b). In the Helsinki Policemen Study, the glucose load used was either 75 or 90 g, depending on body surface area (11% received 90 g); men with a venous whole-blood concentration <10 mmol/l were screened as nondiabetic. The *o*-toluidine method was used for glucose analysis.

The follow-up for causes of death was restricted to 20 years. In the Whitehall Study, 1.9% of the men were lost or censored during follow-up, 4.7% in the Paris Prospective Study, and 0% in the Helsinki Policemen Study.

The causes of death in the Whitehall Study were those officially certified and coded by the Office of Population Census and Surveys. In the Paris Prospective Study, until the end of 1988, information was obtained from the family and treating physicians, and the causes of death were classified after review by a medical panel; for those with missing causes and for deaths after 1989, the officially certified causes of death were used. Death certificates, autopsy reports, and hospital information were used in the Helsinki Policemen Study.

International Classification of Diseases (ICD) (revisions 8 and 9) was used for coding the causes of death (7); CHD corresponded to the codes 410–414 for the Whitehall and Helsinki Policemen Studies, but for the Paris Prospective Study, as is customary in France, additional categories were used to define CHD death: congestive heart failure (ICD code revision 8: 427.0), left ventricular failure (427.1), acute edema of lung (519.1), symptoms referable to cardiovascular and lymphatic system (782), and sudden death (795) (8,9). In all studies, cerebrovascular disease corresponded to the codes 430–438. The category cardiovascular disease included CHD and cerebrovascular disease deaths as defined above, plus the remaining ICD codes in the ICD chapter "circulatory disorders" (390–459). Neoplasms corresponded to the ICD codes 140–239. There were 0.1, 0.8, and 0% of men with unknown causes of death in the Whitehall, Paris, and Helsinki studies, respectively.

Data analysis

Survival curves were calculated, using the Kaplan-Meier method, for all causes of death and for death from CHD, according to glucose fractiles and diabetic status. Hazard ratios for the various causes of death were evaluated using Cox's proportional hazards model; they compared men in the upper percentiles of the glucose distributions with those in the lower 80%. These ratios were adjusted for age, or for age and other risk factors (BMI, sBP, hypertensive treatment, baseline cardiovascular disease, total cholesterol, smoking habits [never smoker, exsmoker, current smoker], and administrative grade [three for Paris and Helsinki, five for Whitehall]). The combined hazard ratio is a weighted average of the hazard ratios, using weights proportional to the inverse of the variance of each study hazard ratio. Data were analyzed in three centers: London, Paris, and Kuopio.

RESULTS — The men, age 44–55 years, had similar mean ages (Table 1). For the classic CHD risk factors, the men in the Paris Prospective Study had higher levels of

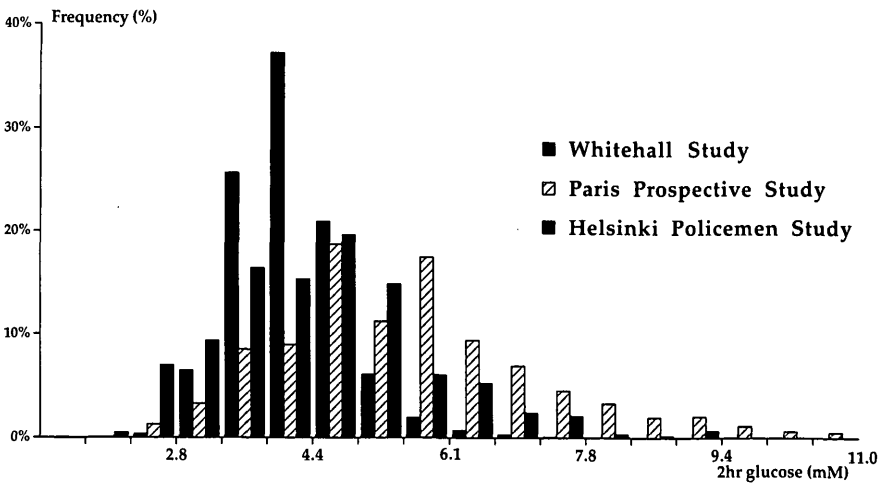

Figure 1—*Distribution of 2-h blood glucose in the three studies: the Whitehall Study, the Paris Prospective Study, the Helsinki Policemen Study. Glucose was measured in the Whitehall Study from capillary whole blood, in the Paris Prospective Study from venous plasma, and in the Helsinki Policemen Study from venous whole blood.*

Table 2—*20-year mortality from all causes, cardiovascular disease, CHD, cerebrovascular disease, and neoplasms in nondiabetic men age 44–55 years, by fractiles of 2-h blood glucose; the Whitehall, Paris Prospective, and Helsinki Policemen studies*

2-h blood glucose fractiles	Glucose mmol/l (mg/dl)	*n*	Death rate per 1,000 person-years (number of deaths)				
			All causes	Cardiovascular	CHD	Cerebrovascular	Neoplasms
Whitehall Study							
≤80th	4.56 (82)	7,923	10.60 (1,547)	5.69 (831)	4.28 (625)	0.63 (92)	3.30 (482)
80th to ≤90th	4.89 (88)	1,095	10.68 (217)	5.41 (110)	3.98 (81)	0.54 (11)	3.74 (76)
90th to ≤95th	5.22 (94)	495	11.30 (103)	7.13 (65)	5.27 (48)	0.88 (8)	2.95 (27)
95th to ≤97.5th	5.56 (100)	251	12.60 (57)	6.19 (28)	4.64 (21)	1.11 (5)	4.20 (19)
>97.5th	—	261	16.29 (74)	8.58 (39)	7.04 (32)	0.88 (4)	4.40 (20)
Total	—	10,025	10.83 (1,998)	5.82 (1,073)	4.37 (807)	0.65 (120)	3.38 (624)
Paris Prospective Study							
≤80th	6.77 (122)	5,329	11.26 (1,059)	3.41 (321)	2.14 (201)	0.57 (54)	4.87 (458)
80th to ≤90th	7.77 (140)	670	15.39 (177)	5.39 (62)	3.48 (40)	0.78 (9)	6.44 (74)
90th to ≤95th	8.66 (156)	299	19.69 (98)	5.63 (28)	4.22 (21)	1.00 (5)	9.04 (45)
95th to ≤97.5th	9.38 (169)	162	20.14 (55)	4.39 (12)	2.93 (8)	1.10 (3)	10.25 (28)
>97.5th	—	169	20.88 (57)	8.43 (23)	5.13 (14)	1.83 (5)	7.69 (21)
Total	—	6,629	12.47 (1,446)	3.85 (446)	2.45 (284)	0.66 (76)	5.40 (626)
Helsinki Policemen Study							
≤80th	5.44 (98)	509	14.60 (134)	7.26 (70)	4.05 (40)	1.29 (13)	4.25 (42)
80th to ≤90th	6.27 (113)	60	13.03 (14)	8.93 (10)	7.02 (8)	0.85 (1)	1.68 (2)
90th to ≤95th	6.77 (122)	34	30.86 (17)	20.28 (12)	12.96 (8)	2.95 (2)	2.97 (2)
95th to ≤97.5th	7.33 (132)	11	19.57 (4)	13.79 (3)	9.15 (2)	0.00 (0)	4.84 (1)
>97.5th	—	17	22.37 (6)	14.06 (4)	10.14 (3)	3.04 (1)	6.18 (2)
Total	—	631	15.52 (175)	8.35 (99)	5.02 (61)	1.36 (17)	4.00 (49)

Table 3—*Age-adjusted hazard ratios for various causes of death, according to 2-h blood glucose fractiles; the Whitehall, Paris Prospective, and Helsinki Policemen studies*

	Fractiles				
	Minimum to 80th	80th to 90th	90th to 95th	95th to 97.5th	97.5th to maximum
All causes					
Whitehall	1	1.01 (0.88–1.16)	1.05 (0.86–1.28)	1.14 (0.87–1.48)	1.44 (1.14–1.82)
Paris	1	1.37 (1.17–1.61)	1.76 (1.43–2.17)	1.81 (1.38–2.38)	1.90 (1.46–2.48)
Helsinki	1	0.86 (0.50–1.50)	1.97 (1.19–3.27)	1.38 (0.51–3.72)	1.80 (0.79–4.08)
Combined	1	1.15 (1.03–1.27)	1.38 (1.21–1.59)	1.43 (1.18–1.72)	1.63 (1.38 –1.94)
Cardiovascular disease					
Whitehall	1	0.95 (0.78–1.16)	1.23 (0.96–1.58)	1.04 (0.71–1.51)	1.41 (1.02–1.94)
Paris	1	1.58 (1.20–2.07)	1.65 (1.12–2.43)	1.30 (0.73–2.31)	2.53 (1.65–3.86)
Helsinki	1	1.20 (0.62–2.33)	2.59 (1.40–4.78)	1.93 (0.61–6.12)	2.16 (0.79–5.95)
Combined	1	1.14 (0.97–1.33)	1.44 (1.18–1.76)	1.15 (0.85–1.56)	1.77 (1.38–2.26)
CHD					
Whitehall	1	0.93 (0.74–1.18)	1.21 (0.90–1.62)	1.03 (0.67–1.59)	1.53 (1.08–2.19)
Paris	1	1.62 (1.15–2.28)	1.97 (1.26–3.09)	1.37 (0.68–2.79)	2.44 (1.42–4.20)
Helsinki	1	1.71 (0.80–3.66)	3.01 (1.41–6.46)	3.29 (0.55–9.46)	2.64 (0.81–8.53)
Combined	1	1.14 (0.95–1.37)	1.50 (1.19–1.90)	1.17 (0.82–1.67)	1.81 (1.36–2.41)
Cerebrovascular disease					
Whitehall	1	0.86 (0.46–1.61)	1.35 (0.66–2.79)	1.64 (0.67–4.03)	1.28 (0.47–3.48)
Paris	1	1.36 (0.67–2.75)	1.75 (0.70–4.37)	1.92 (0.60–6.14)	3.26 (1.30–8.15)
Helsinki	1	0.62 (0.08–4.75)	1.91 (0.43–8.51)	0	2.52 (0.33–19.29)
Combined	1	1.02 (0.65–1.61)	1.54 (0.91–2.62)	—	2.16 (1.14–4.11)
Neoplasms					
Whitehall	1	1.14 (0.89–1.45)	0.88 (0.60–1.30)	1.21 (0.76–1.91)	1.24 (0.80–1.95)
Paris	1	1.33 (1.04–1.70)	1.88 (1.39–2.56)	2.15 (1.47–3.15)	1.63 (1.05–2.52)
Helsinki	1	0.38 (0.09–1.56)	0.62 (0.15–2.57)	1.21 (0.17–8.82)	1.49 (0.36–6.17)
Combined	1	1.21 (1.02–1.43)	1.37 (1.08–1.74)	1.69 (1.26–2.26)	1.43 (1.05–1.94)

Data are ratios (95% CI).

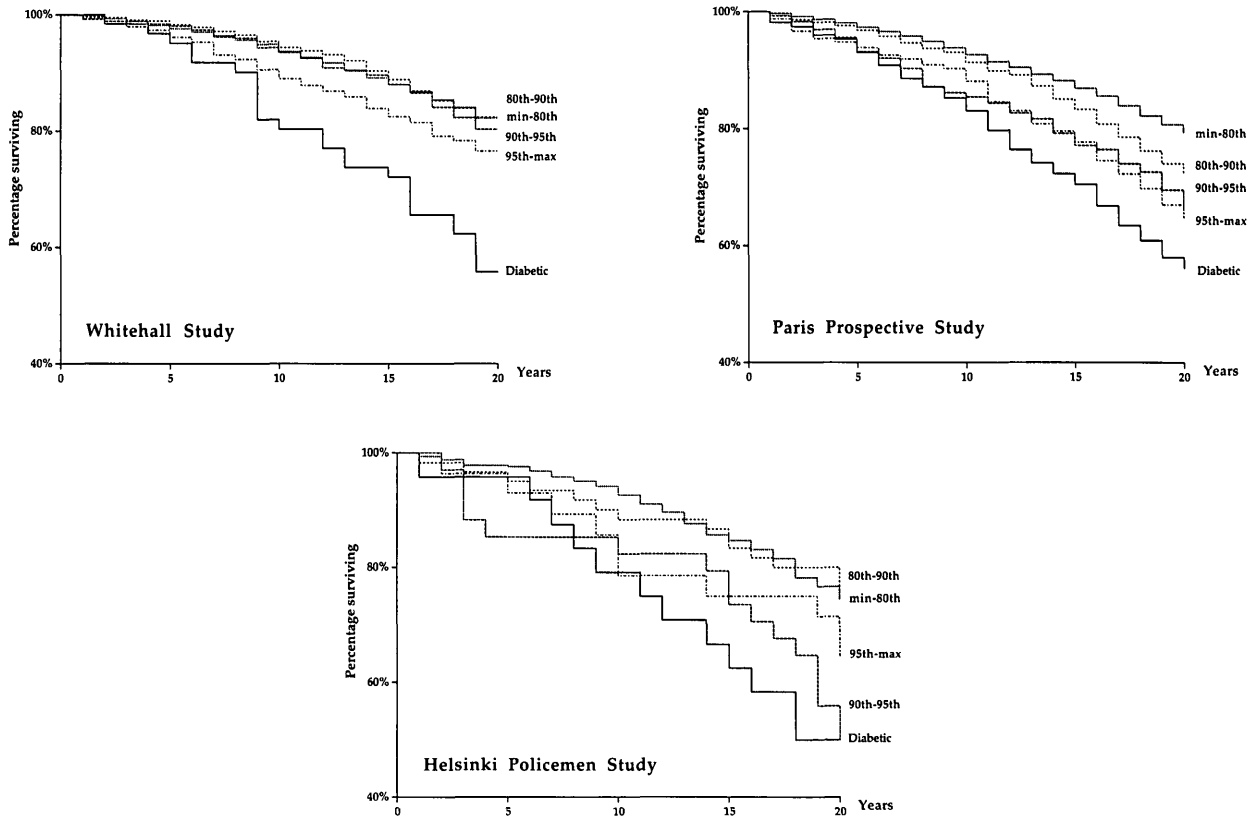

Figure 2—*Survival curves for death from all causes for nondiabetic men, by risk classes formed according to percentiles of the 2-h blood glucose concentrations: the Whitehall Study, the Paris Prospective Study, and the Helsinki Policemen Study.*

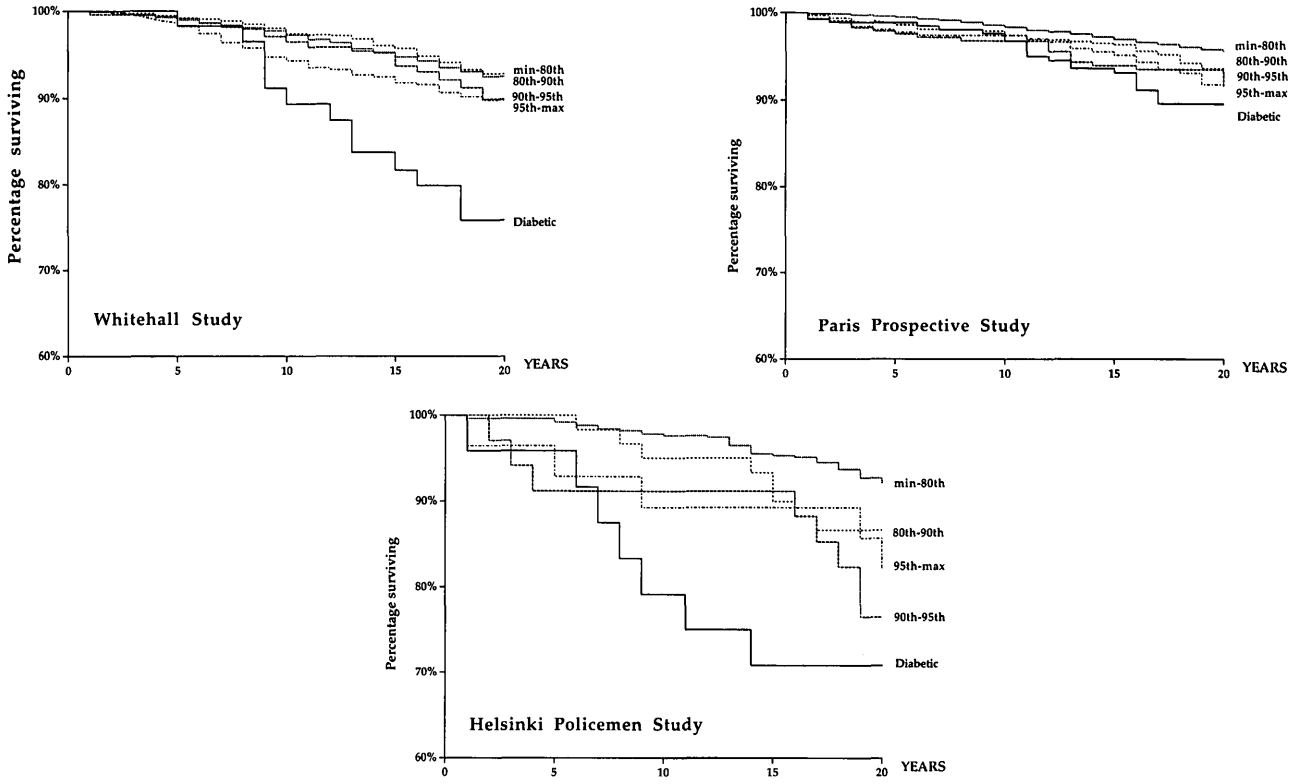

Figure 3—*Survival curves for death from CHD for nondiabetic men, by risk classes formed according to percentiles of the 2-h blood glucose concentrations: the Whitehall Study, the Paris Prospective Study, and the Helsinki Policemen Study.*

Table 4—*Hazard ratios for various causes of death, according to 2-h blood glucose fractiles, after adjustment for age, BMI, sBP, hypertensive treatment, cardiovascular disease, cholesterol concentration, smoking habits, and administrative grades; the Whitehall, Paris Prospective, and Helsinki Policemen studies*

	Fractiles				
	Minimum to 80th	80th to 90th	90th to 95th	95th to 97.5th	97.5th to maximum
All causes					
Whitehall	1	0.99 (0.86–1.14)	0.98 (0.80–1.20)	1.08 (0.83–1.41)	1.23 (0.97–1.56)
Paris	1	1.30 (1.11–1.53)	1.63 (1.32–2.01)	1.49 (1.13–1.96)	1.55 (1.18–2.03)
Helsinki	1	0.84 (0.48–1.47)	1.93 (1.13–3.30)	1.82 (0.66–5.05)	1.37 (0.59–3.14)
Combined	1	1.11 (1.00–1.23)	1.29 (1.12–1.48)	1.28 (1.06–1.54)	1.36 (1.14 –1.62)
Cardiovascular disease					
Whitehall	1	0.93 (0.76–1.13)	1.07 (0.83–1.38)	0.98 (0.67–1.42)	1.08 (0.79–1.50)
Paris	1	1.37 (1.04–1.81)	1.40 (0.95–2.07)	0.96 (0.54–1.72)	1.77 (1.15–2.73)
Helsinki	1	1.13 (0.57–2.23)	1.77 (0.91–3.43)	2.27 (0.69–7.49)	1.33 (0.48–3.74)
Combined	1	1.06 (0.91–1.24)	1.21 (0.99–1.48)	1.03 (0.76–1.40)	1.30 (1.01–1.67)
CHD					
Whitehall	1	0.91 (0.72–1.14)	1.04 (0.77–1.40)	0.96 (0.62–1.48)	1.20 (0.84–1.71)
Paris	1	1.38 (0.98–1.96)	1.66 (1.06–2.62)	1.02 (0.50–2.07)	1.69 (0.97–2.95)
Helsinki	1	1.72 (0.78–3.80)	2.42 (1.07–5.48)	3.00 (0.69–13.10)	1.69 (0.50–5.66)
Combined	1	1.06 (0.88–1.28)	1.27 (1.00–1.61)	1.04 (0.73–1.49)	1.34 (1.00–1.80)
Cerebrovascular disease					
Whitehall	1	0.84 (0.45–1.57)	1.17 (0.57–2.43)	1.63 (0.66–4.02)	0.86 (0.31–2.35)
Paris	1	1.17 (0.57–2.40)	1.48 (0.59–3.74)	1.28 (0.39–4.16)	2.13 (0.83–5.50)
Helsinki	1	0.45 (0.06–3.51)	1.33 (0.28–6.34)	0	0.97 (0.11–8.74)
Combined	1	0.94 (0.59–1.48)	1.29 (0.75–2.21)	—	1.35 (0.70–2.60)
Neoplasms					
Whitehall	1	1.14 (0.89–1.45)	0.90 (0.61–1.32)	1.21 (0.77–1.92)	1.21 (0.77–1.90)
Paris	1	1.37 (1.07–1.76)	1.90 (1.39–2.59)	1.97 (1.34–2.90)	1.49 (0.96–2.32)
Helsinki	1	0.39 (0.09–1.66)	0.78 (0.18–3.35)	2.26 (0.30–17.12)	1.36 (0.31–5.87)
Combined	1	1.23 (1.03–1.46)	1.40 (1.10–1.77)	1.62 (1.21–2.17)	1.35 (0.99–1.83)

Data are ratios (95% CI).

sBP and were more often current smokers. The baseline rate of cardiovascular disease was much lower in the Paris Prospective Study than in the two other studies.

Because of the different methods used in the three studies (the Whitehall Study measured glucose from capillary whole blood, the Paris Prospective Study from venous plasma, and the Helsinki Policemen Study from venous whole blood, and also the biochemical methods differed), the distribution of the 2-h glucose concentrations differed (Fig. 1); the levels in the Whitehall Study were, however, lower than in the other two studies, even considering the effect of the type of blood sample and the lower glucose load used in the oral glucose tolerance test.

After a 20-year follow-up, the Helsinki Policemen Study had the highest death rates of the three studies for all of the causes of death documented here, with the exception of death by neoplasms (Table 2). In the two larger studies, there was a gradual increase in all-cause death rates with increasing 2-h glucose.

With regard to all causes of death, the nondiabetic men had a better survival rate than the diabetic men (Fig. 2). In the Whitehall Study, the nondiabetic men in the upper 5% of the 2-h glucose distribution had a lower survival rate than the other subjects over the last 15 years of follow-up. In the Paris Prospective Study, there was a trend for decreasing survival over the fractile groups, and in the Helsinki Policemen Study, the curves were not regular because of the small number of deaths. For CHD death, the nondiabetic men had a better survival (Fig. 3); in the Whitehall Study, the nondiabetic men in the upper 10% of the glucose distribution tended to have a lower survival than those in the lower 90%, in contrast to the Paris Prospective and Helsinki Policemen studies, where the survival for the upper 20% of men appeared to be lower.

Using Cox's proportional hazards model to adjust for the small differences in the age distribution between the glucose levels in these cohorts, the men from Paris in the upper fractiles of the 2-h glucose distribution had relatively high hazard ratios for death from all causes in comparison with the two other studies (Table 3). The combined hazard ratio from the three studies was significantly higher in the final 20% of the 2-h glucose distribution, and this result remained after adjusting for other risk factors (Table 4). For cardiovascular disease, CHD, and cerebrovascular disease, there was a convincing increase in risk only in the final 2.5% of the glucose distribution. There was a suggestion, however, that the risk may be increased in the upper 10% of the glucose distribution, but this increase was not consistent across these high glucose levels. Death from neoplasms was more common in the Paris Prospective Study, where they carried a high-risk ratio; for the combined analyses, all glucose classes above the 80th percentile had a significantly greater risk than those below, even after adjustment for risk factors.

Data on fasting glucose levels were only available in the Paris Prospective and

Table 5—*20-year mortality from all causes, cardiovascular disease, CHD, cerebrovascular disease, and neoplasms in nondiabetic men age 44–55 years, by fractiles of fasting blood glucose; the Paris Prospective and Helsinki Policemen studies*

Fasting blood glucose fractiles	Glucose mmol/l (mg/dl)	*n*	Death rate per 1,000 person-years (number of deaths)				
			All causes	Cardiovascular	CHD	Cerebrovascular	Neoplasms
Paris Prospective Study							
≤80th	6.00 (108)	5,347	11.91 (1,118)	3.59 (337)	2.28 (214)	0.62 (58)	5.24 (492)
80th to ≤90th	6.33 (114)	699	13.77 (165)	4.76 (57)	3.25 (39)	0.58 (7)	5.51 (66)
90th to ≤95th	6.55 (118)	260	11.81 (55)	4.08 (19)	2.36 (11)	0.64 (3)	5.58 (26)
95th to ≤97.5th	6.88 (124)	167	16.04 (47)	3.75 (11)	2.05 (6)	1.02 (3)	6.83 (20)
>97.5th	—	156	24.03 (61)	8.67 (22)	5.51 (14)	1.97 (5)	8.67 (22)
Total	—	6,629	12.47 (1,446)	3.85 (446)	2.45 (284)	0.66 (76)	5.40 (626)
Helsinki Policemen Study							
≤80th	5.27 (95)	483	14.17 (124)	6.84 (63)	3.83 (36)	1.15 (11)	4.05 (38)
80th to ≤90th	5.50 (99)	81	19.74 (27)	13.18 (19)	6.53 (10)	2.54 (4)	3.82 (6)
90th to ≤95th	5.72 (103)	37	21.97 (14)	16. 98 (11)	13.64 (9)	2.75 (2)	4.11 (3)
95th to ≤97.5th	6.00 (108)	12	8.74 (2)	4.19 (1)	4.19 (1)	0.00 (0)	4.34 (1)
>97.5th	—	18	27.73 (8)	15.45 (5)	15.45 (5)	0.00 (0)	2.85 (1)
Total	—	631	15.52 (175)	8.35 (99)	5.02 (61)	1.36 (17)	4.00 (49)

Helsinki Policemen studies (Table 5). For all causes of death, and for death from cardiovascular disease or CHD, the upper 2.5% of the glucose distribution carried combined risk factor adjusted hazard ratios of 1.6 or higher in comparison to the lower 80% of this distribution (Table 6); these ratios were slightly higher when adjusted for age alone. There was also a higher mortality from neoplasms in this highest glucose class.

CONCLUSIONS — Among these middle-aged nondiabetic men followed up for over 20 years, those in the upper 20% of the 2-h glucose distribution were at a significantly higher risk of early death in comparison to the lower 80%, with hazard ratios increasing with glucose levels, reaching 1.4 (95% CI 1.1–1.6) for men in the upper 2.5% of this distribution, after adjustment for risk factors. In contrast, for fasting glucose, an increased risk was only evident above the 97.5th percentile, with

Table 6—*Hazard ratios for various causes of death, according to fasting glucose fractiles, after adjustment for age, BMI, sBP, hypertensive treatment, cardiovascular disease, cholesterol concentration, smoking habits, and administrative grades; the Paris Prospective and Helsinki Policemen studies*

	Fractiles				
	Minimum to 80th	80th to 90th	90th to 95th	95th to 97.5th	97.5th to maximum
All causes					
Paris	1	1.09 (0.93–1.29)	0.93 (0.71–1.22)	1.18 (0.88–1.59)	1.65 (1.26–2.15)
Helsinki	1	1.22 (0.80–1.86)	1.44 (0.81–2.54)	0.56 (0.14–2.30)	1.59 (0.76–3.33)
Combined	1	1.11 (0.95–1.29)	1.01 (0.79–1.29)	1.15 (0.86–1.53)	1.64 (1.28 –2.11)
Cardiovascular disease					
Paris	1	1.14 (0.86–1.52)	0.97 (0.61–1.54)	0.76 (0.41–1.41)	1.52 (0.97–2.38)
Helsinki	1	1.56 (0.93–2.64)	2.12 (1.08–4.14)	0.58 (0.08–1.19)	2.01 (0.78–5.13)
Combined	1	1.23 (0.95–1.57)	1.25 (0.85–1.83)	0.75 (0.42–1.34)	1.60 (1.07–2.40)
CHD					
Paris	1	1.20 (0.85–1.70)	0.85 (0.46–1.56)	0.64 (0.28–1.45)	1.42 (0.81–2.48)
Helsinki	1	1.31 (0.64–2.69)	3.20 (1.48–6.95)	1.07 (0.14–7.92)	4.48 (1.68–11.97)
Combined	1	1.22 (0.89–1.67)	1.41 (0.87–2.29)	0.69 (0.32–1.47)	1.88 (1.16–3.06)
Cerebrovascular disease					
Paris	1	0.80 (0.36–1.78)	0.91 (0.28–2.93)	1.15 (0.35–3.83)	2.11 (0.81–5.49)
Helsinki	1	1.76 (0.53–5.83)	1.34 (0.27–6.73)	0	0
Combined	1	1.02 (0.53–1.98)	1.04 (0.40–2.68)	—	—
Neoplasms					
Paris	1	1.08 (0.83–1.41)	1.08 (0.72–1.61)	1.32 (0.84–2.08)	1.68 (1.08–2.60)
Helsinki	1	0.97 (0.41–2.33)	1.02 (0.30–3.43)	0.97 (0.13–7.32)	0.49 (0.07–3.71)
Combined	1	1.07 (0.83–1.38)	1.07 (0.73–1.57)	1.30 (0.84–2.03)	1.59 (1.04–2.44)

Data are ratios (95% CI).

an adjusted hazards ratio of 1.6 (1.3–2.1).

The men from Helsinki had the highest death rate, 43% higher than the men from Whitehall and 24% higher than the men from Paris. The causes of death differed between the cohorts, with cardiovascular disease accounting for 54% of deaths in the Whitehall Study, 57% in the Helsinki Study, and 31% in the Paris Study; in all three studies, CHD was the major cause in this category, with few men dying from cerebrovascular disease. The other major cause of death was neoplasms: 31% of deaths in the Whitehall Study, 43% in the Paris Prospective Study, 28% in the Helsinki Policemen Study. These differences in causes of death may, however, be due in part to the differing methods of collecting the information and in the ascertainment and the coding of causes of death. Even with the additional causes used in the Paris Prospective Study to define CHD death, the death rate was only half that in the two other studies. The lower rate of CHD mortality in France is a well-known phenomenon, and it is not only a function of differing methods for certifying and coding causes of death: the Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) study showed that France had a lower cardiovascular mortality in comparison to its European neighbors (10).

For death from cardiovascular and CHD, there was a significantly increased risk for those above the 97.5th percentile of the glucose distributions, with hazard ratios being slightly higher for fasting than for 2-h glucose. The hazard ratios for death from neoplasms were higher in the Paris Prospective Study than in the other two studies and were significantly higher than 1.0 for most of the 2-h glucose classes above the 80th percentile, in contrast to the other two studies; the combined result follows the Paris Prospective Study. For fasting glucose, only the top 2.5% of the distribution conferred a greater risk of death from this cause in the Paris Prospective Study.

Finding an increased risk for death from CHD in the upper percentiles of the 2-h glucose distribution is not unexpected. The category "impaired glucose tolerance" was introduced by both the World Health Organization Expert Group and by the National Diabetes Data Group because of evidence from the Whitehall Study of increased rates of all-cause mortality and of mortality due to CHD (11,12).

Many of these men in the upper part of the glucose distribution were likely to convert to clinically defined diabetes during the 20-year follow-up. Thus it is possible that the observed excess mortality at the higher end of the glucose distribution may simply be a reflection of a large proportion of men who are already converting to diabetes. Similarly, for the fasting glucose levels, further, many of the men in the upper 2.5% of the distribution would now be classified as diabetic using the current American Diabetes Association criteria (13), which uses a fasting plasma glucose level of 7.0 mmol/l (126 mg/dl) as the diagnostic criterion.

In contrast to our selection of nondiabetic subjects, most other analyses of the associations between glucose levels with CHD death have included asymptomatic diabetic subjects; while these "newly screened diabetic subjects" would probably have a short duration of diabetes, they would be expected to have high rates of CHD. The Framingham Study defined nondiabetic subjects on the basis of personal history and a casual whole-blood glucose <11.1 mmol/l (14). Cardiovascular disease incidence was not related to baseline casual glucose levels in men, but in women there was a higher event rate above 7.2 mmol/l, and this linear relation remained significant after adjustment for cardiovascular risk factors. Both men and women in the Rancho Bernardo Study (nondiabetic with fasting plasma glucose <7.8 mmol/l) had increasing CHD mortality with increasing baseline fasting glucose; the relation was linear in men, but in women there was a sharp increase at 7.2 mmol/l (15). For casual glucose, the men in the British Regional Heart Study (nondiabetic with casual serum glucose <11.1 mmol/l) had an increased rate of CHD events above 6.1 mmol/l, the 80th percentile (16). Collins et al. (17) studied Indian and Melanesian Fijian men and women who were nondiabetic (2-h plasma glucose <11.1 mmol/l). The subjects who died during the 11-year follow-up had higher baseline 2-h and fasting glucose levels. The 2-h glucose was a stronger linear predictor of all-cause, cardiovascular, and coronary mortality than fasting glucose, and it remained significant after adjustment for other risk factors, except in the Melanesian men.

The relation between high glucose levels and mortality observed in our study should, however, not be interpreted without caveats as causal, that is, explained by high glucose levels. The hazard ratios have only been adjusted for the known risk factors that were available in our databases; other risk factors closely linked with high glucose levels have been identified more recently, in particular, those associated with insulin resistance (18), and, no doubt, other factors remain to be identified. Therefore, it is debatable whether the risk estimates for glucose should be adjusted for other risk factors; high glucose levels may be a marker of a cluster of other risk factors, and it has been argued that "the clock for coronary heart disease starts ticking before the onset of clinical diabetes" (19–21).

While the American Diabetes Association has accepted the new diagnostic criteria, these criteria are still currently being discussed by the International Diabetes Federation and a World Health Organization committee (13,22). The revision essentially involves lowering the limit for fasting plasma glucose from 7.8 to 7.0 mmol/l for the definition of diabetes. While the arguments for the new diagnostic criteria are mainly based on the specific complications of diabetes, namely retinopathy and nephropathy, CHD is the most frequent cause of death in type 2 diabetic patients. In fact, early mortality, no matter what the cause, is perhaps at least as relevant as morbidity from diabetic complications or mortality from causes associated with diabetes.

Nondiabetic hyperglycemia is an indicator of cardiovascular risk, but appropriate preventive action may be individual rather than generally applicable. If subjects found to be in the upper end of the fasting and 2-h blood glucose distributions are at a higher risk of early death, they should be detected and given appropriate lifestyle advice and treatment if it can be demonstrated to the subjects that lowering glucose levels reduces mortality. With regard to glycemic control, we await the results of the United Kingdom Prospective Diabetes Study (UKPDS), in particular because the entry criterion to the trial was based on two fasting plasma glucose concentrations >6.1 mmol/l, so subjects with nondiabetic but high fasting glucose levels were included (23).

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