The Relationship Between Glucose and Incident Cardiovascular Events

A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years

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OBJECTIVE — To assess the relationship between nondiabetic glucose levels and cardiovascular risk.

RESEARCH DESIGN AND METHODS — Three independent searches using MEDLINE (1966–1996), followed by a manual search of the references from each retrieved article, were conducted by two physicians and one medical librarian. Data had to be reported in at least three quantiles or intervals so that the nature of the relationship between glucose and cardiovascular events (i.e., linear or nonlinear) could be explored, and to ensure that any incremental cardiovascular risk was consistent across quantiles or intervals.

RESULTS — Analyzed studies comprised 95,783 people (94% male) who had 3,707 cardiovascular events over 12.4 years (1,193,231 person-years). Studies reporting fasting glucose levels (n = 6), 2-h glucose levels (n = 7), 1-h glucose levels (n = 5), and casual glucose levels (n = 4) were included. The glucose load used varied from 50 to 100 g. The highest glucose interval for most studies included glucose values in the diabetic range. The relationship between glucose levels and the risk of a cardiovascular event was modeled for each study and the β-coefficients were combined. Compared with a glucose level of 4.2 mmol/l (75 mg/dl), a fasting and 2-h glucose level of 6.1 mmol/l (110 mg/dl) and 7.8 mmol/l (140 mg/dl) was associated with a relative cardiovascular event risk of 1.33 (95% CI 1.06–1.67) and 1.58 (95% CI 1.19–2.10), respectively.

CONCLUSIONS — The progressive relationship between glucose levels and cardiovascular risk extends below the diabetic threshold.

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Individuals with type 2 diabetes have a two- to fourfold increased risk of cardiovascular disease compared with nondiabetic individuals (1–3). Recent epidemiological studies suggest that in people with type 2 diabetes, cardiovascular mortality is related to the degree of hyperglycemia (4–6); one randomized controlled trial has shown that in diabetic patients, total mortality is decreased by lowering blood glucose with insulin after an acute myocardial infarction (7). Thus, in patients with type 2 diabetes, the blood glucose concentration is a continuous and possibly modifiable cardiovascular risk factor.

The glucose thresholds used to define diabetes were chosen to identify people at risk for eye and kidney diseases (8–10), without regard to the risk of cardiovascular disease. If there is a glucose threshold for cardiovascular disease, it may therefore be lower than that for diabetes or even possibly impaired glucose tolerance. We explored this possibility by doing a systematic overview and metaregression analysis of cohort studies that assessed the relationship between glucose and the incidence of cardiovascular disease.

RESEARCH DESIGN AND METHODS

— All prospective studies of the risk of cardiovascular disease according to baseline glucose determinations were sought. Three independent searches using MEDLINE (1966–1996), followed by a manual search of the references from each retrieved article, were conducted by two physicians and one medical librarian. The medical subject headings of "blood glucose" or "glucose intolerance" were combined with the heading of "coronary artery disease," "stroke," "cerebrovascular disorders," "mortality," or "heart disease," as well as "prospective study," "cohort study," or "follow-up." In addition, any other cohort studies, which reported cardiovascular disease (myocardial infarction or stroke) and mortality, were analyzed to identify additional studies in which glucose was measured at baseline.

Published studies were included if *1*) they included nondiabetic participants who were not selected on the basis of preexisting disease or health status, *2*) data were reported by quantiles (defined by tertiles, quartiles, etc.) or intervals of glucose values at baseline, and *3*) the number of fatal or nonfatal cardiovascular outcomes (sudden death, stroke, or acute myocardial infarction) and the number of people at risk within each glucose quantile or interval were prospectively recorded. Data had to be reported in at least three quantiles or intervals so that the nature of the relationship between glucose and cardiovascular events (i.e., linear or nonlinear) could be explored, and to ensure that any incremental cardiovascular risk was consistent across quantiles or intervals.

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

Table 1—*Characteristics of abstracted studies*

Reference	Age (years)	Men (%)	Number screened	Diabetes exclusions	Number followed	Study duration (years)	Cardiovascular deaths (*n*)	Cardiovascular events plus deaths (*n*)	Glucose method	Glucose intervals	Highest glucose interval (mmol/l)
Fasting											
Scheidt-Nave et al. (19)	40–79	43	3,458	DM Hx, BCH	3,458	14	217	217	Plasma	7	7.2–7.7
Shaten et al. (24)	35–57	100	12,866	DM meds	12,694	10.5	426	426	Serum	6	≥7.8
Yarnell et al. (29)	45–59	100	4,860	DM Hx	4,349	4	NA	209	Plasma	5	≥7.8
Schroll and Hagerup (30)	50	100	388	DM Hx	383	10	18	18	Blood	5	5.3–12.5
Ohlson et al. (31)	73	100	973	DM Hx, BCH	832	17	N/A	141	Whole blood	5	>5
Pyorala et al. (16,65)	40–59	100	1,059	DM Hx	845	10	42	42	Blood	5	5.2–15.2
2-h (dose)*											
Stamler et al. (14) (100 g)	42–58	100	1,694	DM Hx	1,694	15	166	166	Plasma	5	6.7–23.3
Pyorala et al. (16,65) (75–90 g)	40–59	100	1,059	DM Hx	845	10	42	42	Blood	5	5.6–18.5
Fuller et al. (17) (50 g)	40–64	100	18,403	DM Hx	18,106	15	915	915	Capillary	5	4.8–11.1
Balkau et al. (21) (75 g)	44–55	100	7,166	DM Hx	7,038	15.6	167	167	Blood	3	≥11.1
Da Silva et al. (25) (100 g)	40–59	100	1,499	DM Hx	1,491	5	12	12	Capillary	5	6.8–17.8
Grabauskas (33) (75 g)	45–59	100	2,455	DM Hx	2,413	10	114	114	Plasma	5	10–17.8
Tuomilehto et al. (22) (75 g)	≥40	43	1,537	NA	1,537	5	51	51	Capillary	3	≥11.1
1-h (dose)*											
Stenhouse et al. (15) (50 g)	40–59	100	3,331	DM Hx	638	11	21	21	Plasma	5	6.8–23
Donahue et al. (18) (50 g)	45–70	100	6,394	DM Hx	6,394	12	119	303	Serum	5	10.6–29.6
Vaccaro et al. (20) (50 g)	34–65	100	873	DM Hx	873	19	144	144	Plasma	5	11.7 (mean)
Reunanen et al. (27) (60–90 g)	40–59	100	3,351	DM Hx	3,267	4	64	64	Plasma	5	10.8–28.1
Pyorala et al. (16,65) (75–90 g)	40–59	100	1,059	DM Hx	845	10	42	42	Blood	5	8.0–20.3
Casual											
Perry et al. (23)	40–59	100	7,735	DM Hx, BCH	7,177	9.5	222	505	Serum	5	≥6.1
Hawthorne and Gilmour (26)	45–64	100	1,134	DM Hx	1,128	6	29	29	Whole blood	5	6.0–28.8
Cruz-Vidal et al. (28)	45–64	100	8,248	DM meds	5,445	8.25	83	83	Whole blood	5	7.8–34.2
Lund Haheim et al. (32)	40–49	100	16,172	DM Hx	16,021	18	80	80	Serum	5	≥6.2
All studies	20–84	—	112,311†	—	95,783†	12.4	3,074†	3,707†	—	—	—

BCH, biochemical criteria for diabetes using the measured glucose level; DM Hx, history of diabetes; DM meds, on diabetes medications; NA, not available. *Dose of oral glucose given; †does not include any study more than once.

Studies that were restricted to subjects with a previous diagnosis of diabetes (based on history and/or the use of hypoglycemic agents) at the time of cohort inception were excluded to allow exploration of the correlation between glucose levels and the incidence of cardiovascular disease across the range of glucose values (from nondiabetic to diabetic levels). Studies that did not give quantile or interval definitions or number of events and number of people at risk in each quantile or interval were also excluded. In

Table 2—*Calculated regression coefficients and the reported effects of glucose and insulin on cardiovascular disease*

Reference	Person-years	Cardiovascular events β-coefficient (95% CI)	*P* value*	Cardiovascular mortality β-coefficient (95% CI)	*P* value*	Independent effects Glucose† (*P* value)	Insulin (*P* value)
Fasting							
Scheidt-Nave et al. (19)	48,412	1.386 (0.646 to 2.126)	0.0003	1.386 (0.646 to 2.126)	0.0003	<0.02[abcdef]‡	NA
Shaten et al. (24)	133,287	0.400 (−0.227 to 1.026)	0.22	0.400 (−0.227 to 1.026)	0.22	<0.01[abcdf]§	NA
Yarnell et al. (29)	17,396	1.320 (0.451 to 2.189)	0.0055	NA	NA	NS[bcdef]	NA
Schroll and Hagerup (30)	3,830	−0.003 (−1.052 to 1.046)	0.995	−0.003 (−1.052 to 1.046)	0.995	NS[bcde]	NS
Ohlson et al. (31)	14,144	−0.339 (−2.146 to 1.469)	0.71	NA	NA	NA	NA
Pyorala et al. (16,65)	8,450	0.280 (−0.204 to 0.764)	0.27	0.280 (−0.204 to 0.764)	0.27	NS[abcde]	<0.01
All	225,519	0.606 (0.113 to 1.099)	0.016	0.531 (−0.006 to 1.067)	0.052	—	—
2-h							
Stamler et al. (14)	25,410	0.021 (−0.126 to 0.168)	0.78	0.021 (−0.126 to 0.168)	0.78	NS[abcde]	NA
Pyorala et al. (16,65)	8,450	0.392 (0.067 to 0.716)	0.023	0.392 (0.067 to 0.716)	0.023	NS[abcde]	<0.01
Fuller et al. (17)	271,590	0.792 (0.580 to 1.004)	<0.0001	0.792 (0.580 to 1.004)	<0.0001	NA	NA
Balkau et al. (21)	109,792.8	1.111 (0.407 to 1.816)	0.005	1.111 (0.407 to 1.816)	0.005	NA	<0.005
Da Silva et al. (25)	7,455	0.201 (−0.520 to 0.922)	0.59	0.201 (−0.520 to 0.922)	0.59	NS[abcde]	NA
Grabauskas (33)	24,130	0.470 (0.232 to 0.707)	0.0002	0.470 (0.232 to 0.707)	0.0002	<0.01[abcdef]	NA
Tuomilehto et al. (22)	7,685	1.095 (0.362 to 1.829)	0.005	1.095 (0.362 to 1.829)	0.005	NA	NA
All	454,512.8	0.531 (0.204 to 0.858)	0.0015	0.531 (0.204 to 0.858)	0.0015	—	—
1-h							
Stenhouse et al. (15)	7,018	0.102 (−0.305 to 0.509)	0.63	0.102 (−0.305 to 0.509)	0.63	NS[abcde]	NA
Donahue et al. (18)	76,728	0.136 (0.057 to 0.215)	0.001	0.278 (0.159 to 0.397)	<0.0001	<0.001[abcdef]	NA
Vaccaro et al. (20)	16,587	0.501 (0.207 to 0.795)	0.001	0.501 (0.207 to 0.795)	0.001	<0.05[abcdef]	NA
Reunanen et al. (27)	13,068	0.114 (−0.068 to 0.296)	0.23	0.114 (−0.068 to 0.296)	0.23	NS[abcde]	NA
Pyorala et al. (16,65)	8,450	0.499 (0.197 to 0.801)	0.002	0.499 (0.197 to 0.801)	0.002	NS[abcde]	<0.01
All	121,851	0.242 (0.084 to 0.400)	0.0013	0.287 (0.140 to 0.433)	0.0001	—	—
Casual							
Perry et al. (23)	68,181.5	0.616 (−0.148 to 1.380)	0.12	−0.255 (−1.417 to 0.907)	0.67	NA	NA
Hawthorne and Gilmour (26)	6,768	0.073 (−0.202 to 0.348)	0.61	0.073 (−0.202 to 0.348)	0.61	NS[abcde]	NA
Cruz-Vidal et al. (28)	44,921.3	0.248 (0.032 to 0.465)	0.046	0.248 (0.032 to 0.464)	0.046	NA	NA
Lund Haheim et al. (32)	288,378	1.026 (−0.935 to 2.978)	0.31	1.026 (−0.935 to 2.978)	0.31	NS[ac]	NA
All	408,248.8	0.157 (−0.092 to 0.405)	0.22	0.085 (−0.172 to 0.341)	0.52	—	—

*Goodness of fit; †*P* values are shown for studies that calculated the incremental effect of increasing glucose levels on the risk of cardiovascular or total mortality after statistical adjustment for one or more cardiovascular risk factors including [a]age, [b]blood pressure (systolic or diastolic), [c]BMI or weight, [d]lipids, [e]smoking, or [f]other risk factors. ‡The *P* value was significant in men across glucose ranges and in women for glucose values ≥6.1 mmol/l (110 mg/dl) only; §the *P* value was significant for nonsmokers. NA, not available.

studies reported in more than one publication, the most recent study that met the inclusion criteria was analyzed; when needed, data from the other publications were used to complete the database.

The following data were extracted and tabulated from each paper (Table 1): number of subjects, subject sex and age distribution, duration of follow-up, method of glucose measurement, number and definition of glucose quantiles or intervals, number of individuals at risk in each glucose interval, and number of fatal or first nonfatal cardiovascular events in each interval. Information on whether or not the individual studies statistically adjusted estimates of the relationship between baseline glucose levels and incident cardiovascular disease for other cardiac risk factors and of the relationship between baseline insulin levels and cardiovascular disease (if measured) was also abstracted (Table 2).

To assess the impact of both fasting and postprandial glucose on the incidence of cardiovascular events, all studies were classified into four groups according to the method used for glucose measurement at baseline: *1*) fasting glucose level, *2*) 2-h post–oral glucose load glucose level, *3*) 1-h post–oral glucose load glucose level, and *4*) casual (nonfasting) glucose level.

Statistical analysis

The number of first cardiovascular events and the number of person-years of follow-up for each baseline glucose quantile or interval were tabulated within each study. The midpoint of each glucose quantile or interval was used in subsequent analyses as the baseline glucose level in that quantile; if either the lowest or highest quantile or interval did not have lower or upper boundaries (e.g., subjects with glucose levels <4.2 mmol/l or ≥6.1 mmol/1), the boundary glucose value was used (e.g., 4.2 or 6.1 mmol/l). A relative risk model using a modified Poisson regression method was used to generate three mathematical models (linear, quadratic, exponential) describing the relationship between this baseline glucose level and the relative risk of cardiovascular events during follow-up for each study. The relative risk was defined as the ratio of the cardiovascular event rate within

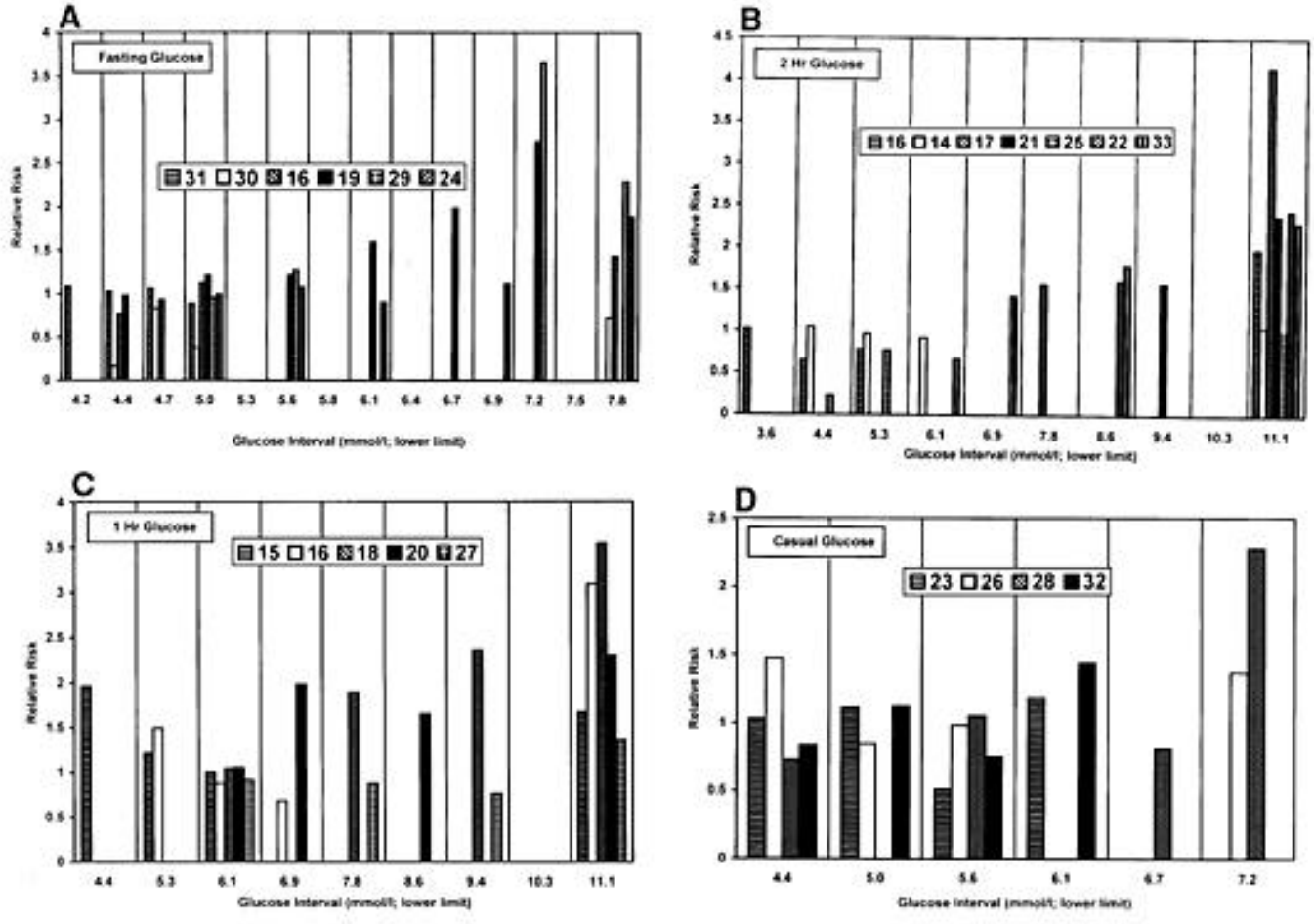

Figure 1—*The observed crude relative risk for cardiovascular events according to the midpoint of each glucose interval for every included study (compared with the lowest glucose interval) is shown. Results for studies with data that allowed calculation of the relative risk for comparable glucose values are grouped together. Four studies reported data that allowed calculation of the crude relative risks for midpoint glucose values between 4.4 and 4.7 mmol/l: studies of fasting glucose (A), studies of 2-h glucose (B), studies of 1-h glucose (C), and studies of casual glucose (D).*

each quantile or interval to the cardiovascular event rate at a blood glucose concentration of 4.2 mmol/l (75 mg/dl), at which the relative risk was set at 'one' before the papers were analyzed. The β-coefficients of each of these three models, weighted by the size of each study, were calculated for all studies in each glucose category (fasting, 2-h, 1-h, or casual). A general random effects parametric approach (11) was used to combine the individual β-coefficients into an overall β- coefficient for each glucose category. Thus, for each glucose category, three different mathematical models were generated from the combined data describing the relationship between glucose and cardiovascular disease. The degree to which each model described the combined data was assessed by comparing the sum of the deviances for studies in each category (using each model) with a χ^2 test (12). The model that provided the best fit of the combined data from studies in each glucose category (fasting, 1-h, 2-h, and casual) was then chosen for that category; statistical homogeneity was assessed according to Cochran (13).

This analysis was done for both cardiovascular mortality and for the number of first cardiovascular events. For studies that only reported cardiovascular mortality, death was considered to be the first event. Illustrative relative risks and confidence intervals at any specified glucose level represent the range within which the combined curve would fall at that glucose level.

RESULTS

— A total of 29 citations (14–42) were initially selected; 9 were excluded from the analysis (34–42). Reasons for exclusion included the following: *1*) exclusion of subjects who were not physically fit (34), *2*) a second report of a previously included study (36), *3*) nonreporting of glucose ranges within quantiles or intervals (37), *4*) division of data into <3 glucose quantiles or intervals (38,39), *5*) nonreporting of number of individuals at risk in each glucose quantile or interval (35,40,41), and *6*) nonreporting of crude cardiovascular outcomes in each glucose quantile or interval (42). The remaining 20 studies are described in Tables 1 and 2. They comprised 95,783 persons and 1,193,231 person-years of follow-up. Only four studies (18,23,29,31) reported incident cardiovascular events; 19 studies reported cardiovascular mortality data. A total of 3,707 events (3,074 cardiovascular deaths) were recorded. The mean weighted follow-up duration was 12.4 years (range 4–19 years), and 18 studies enrolled only middle-aged men.

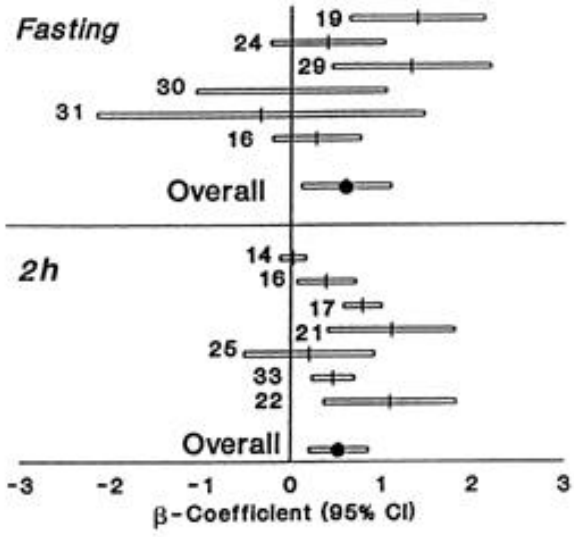

Figure 2—*The β-coefficients generated from the exponential model of the data of each study and the combined β-coefficient for fasting and 2-h postprandial glucose values are displayed.*

Of the included studies, six reported fasting glucose levels, seven studies reported 2-h glucose levels, five studies reported 1-h glucose levels, and four studies reported casual glucose levels (Table 1). The glucose doses used in the glucose tolerance tests varied from 50 to 100 g. Most studies reported events according to five baseline glucose quantiles or intervals. The highest glucose interval for most studies included glucose values in the diabetic range. The observed relative risks for cardiovascular events according to the midpoint of each glucose interval in the individual studies is graphically displayed in Fig. 1.

An analysis of the three different regression models (linear, quadratic, exponential) that were generated from the studies in each of the four glucose categories revealed that the exponential model provided the best fit for the combined data from the studies in each of the four categories (*P* homogeneity >0.5), regardless of whether cardiovascular mortality or cardiovascular events (including mortality) were analyzed. Therefore, this model was used for subsequent analyses (Table 2).

Using this model, nine of the included studies (Table 2) showed a strong relationship between glucose quantile and the risk of cardiovascular events ($P \leq 0.01$). The combined data for each glucose category (Fig. 2) showed a consistent relationship ($P < 0.02$). Using the modeled curves illustrated in Fig. 3, compared with the reference fasting glucose of 4.2 mmol/l (75 mg/dl), a fasting glucose of 6.1 mmol/l (110 mg/dl, the threshold value for the classification of impaired fasting glucose [10]) was associated with a relative risk of cardiovascular events of 1.33 (95% CI 1.06–1.67); a 2-h glucose of 7.8 mmol/l (140 mg/dl, the threshold value for impaired glucose tolerance) was associated with a relative risk of cardiovascular events of 1.58 (95% CI 1.19–2.10).

To determine if the observed glucose–cardiovascular disease relationship was due to the inclusion of subjects with undiagnosed diabetes in the top quantile or interval, the analysis was repeated without the data from this interval for those citations reporting fasting and 2-h glucose data, in which removal of the top interval removed most subjects with glucose levels above the diabetic threshold but retained subjects with glucose levels at or below this threshold. Therefore, only citations reporting fasting glucose data in which the upper limit of the second highest interval was between 6.1 and 7.8 mmol/l and citations reporting 2-h glucose data in which the upper limit of the second highest interval was between 7.8 and 11.1 mmol/l were included in this analysis. This analysis showed that with removal of data from the top glucose interval, the exponential relationship was maintained, there was a suggestive trend ($P = 0.056$) between fasting glucose and cardiovascular events, and there was a significant relationship between 2-h glucose ($P = 0.00064$) and cardiovascular events (Table 3).

Because individual subject data were not available for this analysis, the risk of a cardiovascular event with increasing glucose levels could not be adjusted for the presence or absence of other cardiovascular risk factors. Such an adjustment, however, was originally reported in 14 of the 20 studies included. Of these studies, five showed a significant effect of glucose even after adjusting for one or more of age, blood pressure, BMI, weight, lipid levels, or smoking habits (Table 2).

Two of the three included studies (16,21) that also reported insulin levels reported a relationship with cardiovascular events (Table 2). The crude glucose data abstracted from both these studies were also consistent with a positive relationship between glucose and cardiovascular events (Table 2).

CONCLUSIONS — This systematic overview and metaregression analysis included published cohort studies of nondiabetic participants. It found a graded relationship between the initial fasting and postprandial glucose level and the subsequent 12-year occurrence of a cardiovascular event; this relationship was apparent for glucose levels that were below the diabetic threshold (Fig. 1). As fasting glucose values have the least variability, estimates of the glucose–cardiovascular event relationship based on the fasting glucose studies may be more precise than estimates based

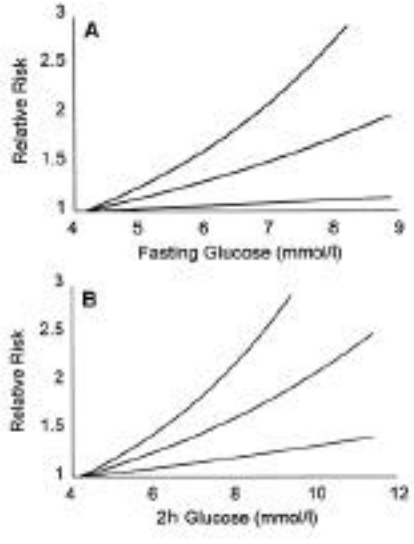

Figure 3—*The curves and 95% CIs (within which the curve lies) generated from the model and the combined β-coefficient for fasting (A), and 2-h postprandial (B) glucose values are displayed (relative risk = exp(β × (glucose – 4.2)/4.2).*

Table 3—*Calculated regression coefficients for the relationship between glucose and cardiovascular events after removal of the top glucose interval in selected studies*

Reference	Cardiovascular events β-coefficient (95% Cl)	*P* value*
Fasting		
Scheidt-Nave et al. (19)	1.203 (0.328 to 2.079)	0.007
Shaten et al. (24)	0.083 (−0.660 to 0.826)	0.827
Yarnell et al. (29)	1.346 (0.245 to 2.448)	0.023
All	0.817 (−0.020 to 1.655)	0.056
2-h		
Balkau et al. (21)	1.157 (0.029 to 2.284)	0.057
Grabauskas et al. (33)	0.970 (0.251 to 1.688)	0.008
Tuomilehto et al. (22)	1.128 (−1.530 to 3.785)	0.432
All	1.029 (0.438 to 1.620)	0.0006

*Goodness of fit.

on combining studies that used different glucose loads and times of glucose sampling. Nevertheless, the fact that the analyses of studies, which measured fasting, 2-h postprandial, 1-h postprandial, and casual glucose levels, yielded consistent patterns suggests that these findings are robust.

A number of factors support the conclusion that an elevated glucose level below the diabetic cutoff is associated with cardiovascular disease. First, the glucose cutoffs that define diabetes (fasting and 2-h post-glucose load values of 7.0 and 11.1 mmol/l, respectively) were chosen to identify people at risk for eye and kidney diseases (10,43–45), without regard to the risk for cardiovascular disease. Thus there is no a priori reason for this threshold to have any special significance with respect to the risk of cardiovascular disease. This is also true for the glucose cutoff values for impaired glucose tolerance (2-h post-glucose load value of 7.8–11.1 mmol/l), which were not originally defined on the basis of identifying people at higher cardiovascular risk (8). Second, longitudinal studies demonstrate that among patients with established diabetes, the risk of cardiovascular disease and mortality increases as the ambient glucose level increases (4–6). Several prospective studies that included nondiabetic people, but that did not satisfy all the criteria for inclusion in this metaregression analysis, also showed a similar relationship in the nondiabetic range (34,37,40–42,46,47). Third, recently published analyses of data from four of the studies included in this summary also showed a progressive relationship between glucose levels below the diabetic threshold and subsequent cardiovascular events (48–50). Fourth, cross-sectional epidemiological studies that included both diabetic and nondiabetic patients also suggested a progressive relationship between glucose levels and the prevalence of cardiovascular disease (51). Fifth, this analysis is consistent with a recent case-control study of subjects with an acute myocardial infarction, in which a progressive relationship between glucose levels and the odds of a myocardial infarction (independent of lipid levels, smoking, abdominal obesity, and insulin levels) persisted even after excluding patients with diabetes and impaired glucose tolerance (52).

A number of possibilities may explain the relationship between glucose levels and subsequent cardiovascular events. First, glucose may itself be causally related to atherosclerosis through a number of mechanisms including increased oxidative stress (53–55), nonenzymatic glycation of LDL, other apolipoproteins (56) and clotting factors (fibrin and antithrombin-III) (57), and advanced glycation end-product formation in the vessel wall and matrix (57,58). Second, minimally elevated glucose levels at baseline are likely to be a marker for the subsequent development of higher levels of glucose, impaired glucose tolerance, or diabetes, and it is possible that these latter conditions and not glucose elevation per se are related to cardiovascular disease. To the extent that higher baseline glucose levels are associated with even higher subsequent glucose levels and higher rates of diabetes, the risk of cardiovascular disease with baseline elevated glucose levels would be magnified over a period of 10 years. Third, glucose elevation may be confounded with some other cardiovascular risk factor(s), which (either with or without glucose) may be related to atherosclerosis. Possible candidates include hyperinsulinemia, hypertriglyceridemia, low HDL, visceral obesity, and hypertension; all are factors that tend to be higher or more common in hyperglycemic patients compared with normoglycemic patients. Indeed, the clustering of glucose intolerance, hypertension, hypertriglyceridemia, visceral obesity, hyperinsulinemia, and insulin resistance in patients with cardiovascular disease is well known and has been labeled as the insulin resistance syndrome or Syndrome X (59). Fourth, both hyperglycemia and cardiovascular disease may have common predisposing factors (60,61). Possible candidates include genetic factors, early nutritional deficiency, low birth weight, and unidentified environmental factors.

The current analyses have several limitations. First, the fact that the data from individual studies were modeled precludes explicit exclusion of a threshold glucose value below which there is no graded relationship between glucose and cardiovascular disease. Indeed, the finding that an exponential model best described the data is consistent with the possibility of both a continuous relationship and a glycemic threshold for cardiovascular disease. Nevertheless, data from the individual studies (Fig. 1) support the conclusion that if there is a threshold, it extends below the impaired glucose tolerance threshold. This is supported by the observation of a clear significant relationship between 2-h glucose and cardiovascular events (Table 3) in the subanalysis of data from nondiabetic subjects. Second, it excluded several large studies that did not present data in a way that was amenable to this analysis (35,37–42). Nevertheless, the fact that the glucose–cardiovascular disease relationship reported in these studies was similar to that observed in the present study suggests that exclusion of these studies did not introduce a material bias into our analysis. Third, the number of women included in the studies was small, thereby limiting the generalizability of the results. However, the few studies, which did include women, reported results that were consistent with the analysis as a whole. Indeed, recent epidemiological data suggests that the relationship between glucose and cardiovascular risk in women may be stronger than in men (62). Fourth, different biochemical methods were used to measure glucose levels in the various studies (Table 1), and different algorithms were used for glucose tolerance testing such

as the use of a 50- or 75-g glucose load. Such variability would tend to underestimate the true relationship between glucose levels and subsequent cardiovascular events. Finally, the original studies generally used a single measurement of glucose at baseline. Experience with multiple measures of blood pressure and cholesterol and the risk of cardiovascular disease shows that single measures underestimate the relationship between the risk factor and cardiovascular disease compared with multiple measures. It is possible therefore that the true relationship between glucose levels and subsequent cardiovascular events may be steeper than demonstrated in the current analyses.

One important limitation relates to the fact that individual patient data from the original studies were not used for these analyses. Therefore, the observed relationship between glucose and cardiovascular events is unadjusted for other cardiovascular risk factors such as age, weight, blood pressure, lipids, smoking, and hyperinsulinemia. Nevertheless, the included studies all enrolled patients within a similar age range (Table 1); many (but not all) showed a significant effect of glucose after adjustment for these other factors (Table 2) and insulin was not a consistent predictor of cardiovascular disease in the individual studies in which it was measured (Table 2) (63).

Despite these limitations, these analyses and other studies provide support for the hypothesis that nondiabetic degrees of fasting and postprandial hyperglycemia are associated with cardiovascular disease and that dysglycemia is a cardiovascular risk factor (64). They highlight the importance of studying further the role of glucose and glucose lowering on the risk of cardiovascular disease.

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