American Journal of Epidemiology Advance Access published December 22, 2005

American Journal of Epidemiology

DOI: 10.1093/aje/kwj027

Original Contribution

The Predictive Role of Blood Glucose for Mortality in Subjects with Cardiovascular Disease

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Received for publication April 2, 2005; accepted for publication September 2, 2005.

Using the Framingham Heart Study data (United States, 1948–1978), the authors examined the association of blood glucose with 2-year all-cause, cardiovascular, and noncardiovascular mortality in subjects with documented cardiovascular disease. After adjustment for systolic blood pressure, cholesterol, body mass index, cigarette smoking, and use of antihypertensive agents, they found that glucose was a strong, independent predictor of mortality. However, the relations for men and women were qualitatively different. For men, adjusted mortality risk increased very rapidly through the normal range (from 4.12% at 3.89 mmol/liter (70 mg/dl) to 12.26% at 5.55 mmol/liter (100 mg/dl)) and was flat at 12.26% thereafter. For women, risk was flat at 3.65% through the normal range and then increased rapidly, reaching 8.34% at 6.99 mmol/liter (126 mg/d), but increased much more slowly thereafter. Exactly analogous relations held for cardiovascular mortality. For men and women combined, noncardiovascular mortality increased from 1.82% at 3.89 mmol/liter to 2.06% at 5.55 mmol/liter to 2.29% at 6.99 mmol/liter (p for trend = 0.009). These findings suggest that although 5.55 mmol/liter (normal) may be a useful mortality risk division (albeit with different implications for the two sexes), 6.99 mmol/liter (diabetic) is not, especially for men.

blood glucose; cardiovascular diseases; mortality; risk factors

Abbreviations: AIC, Akaike's Information Criterion; CVD, cardiovascular disease.

A growing body of evidence suggests that glucose may be an important predictor of mortality in patients with established cardiovascular disease (CVD) (1–7). Above-normal glucose levels below the diabetes cutpoint have been shown to carry increased mortality risk for patients in an acute phase of coronary heart disease (1–3) or undergoing percutaneous coronary intervention (5). Only a few studies have examined the role of glucose level in mortality among subjects in a chronic, stable phase of CVD (4, 6, 7). Some indicated that risk increased across the three broad categories: normal ($\leq$5.55 mmol/liter (100 mg/dl)), impaired (5.56–6.99 mmol/liter (101–126 mg/dl)), and diabetic ($>$6.99 mmol/liter ($>$126 mg/dl)) (4, 6). Recently, using the Framingham Heart Study data, Port et al. (7) showed that there was a continuous, graded relation of all-cause, cardiovascular, and noncardiovascular mortality to blood glucose for nondiabetic subjects with chronic CVD. These studies considered only men and women combined. In the present study, we used the same Framingham data as those used by Port et al. to quantitatively examine the

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mortality/glucose relations over the entire glucose range for men and women separately as well as together. Our primary goals were to determine 1) whether the relations differed for men and women and 2) whether the current normal (5.55 mmol/liter (100 mg/dl)) and diabetic (6.99 mmol/liter (126 mg/dl)) cutpoints are useful divisions for mortality risk.

MATERIALS AND METHODS

Background

The methodology of the Framingham Heart Study has been described previously (8). In brief, the target population consisted primarily of White, urban, middle-class Americans. In 1948, a sample of 5,209 subjects was selected from Framingham, Massachusetts; these subjects were given biennial examinations. The 30-year data used here contain the results for the first 15 examination cycles. The Framingham Heart Study determined blood glucose values using a sample of random (i.e., casual) whole blood using Nelson's method (9). For ease of comparison with other studies, here we state all of our results in terms of plasma equivalents (glucose) obtained by applying the following formula: plasma glucose = 1.12 × whole blood glucose (10). Glucose was not measured at examinations 5, 11, and 13.

According to Framingham classifications, CVD consisted of coronary heart disease, stroke, congestive heart failure, and intermittent claudication. Coronary heart disease consisted of myocardial infarction, coronary insufficiency, sudden death, and angina pectoris. CVD status was ascertained by direct examination by two or more Framingham physicians using a variety of techniques, as detailed by Dawber (8).

Statistical analysis

Most prospective studies, having just single initial measurements, must look long term to accrue sufficient events. However, by using the Framingham investigators' pooled logistic regression method ''PRO'' (pooling of repeated observations) (11, 12), we took full advantage of the fact that we had 15 repeated measurements of baseline variables and used all deaths that accrued over 30 years of follow-up to accurately determine 2-year risks. That method, which has close affinities with survival analysis with time-varying covariates, considers each examination as a separate ministudy and pools the observations to follow subjects anew over successive 2-year intervals until death or the end of the 30-year follow-up. We considered the pooled population of subjects who, at the time of the examination, were between ages 45 and 74 years and had a current or previous diagnosis of CVD. This pooled population was divided into six age-sex groups: 1) men aged 45–54 years, 2) men aged 55–64 years, 3) men aged 65–74 years, 4) women aged 45–54 years, 5) women aged 55–64 years, and 6) women aged 65–74 years.

All models were fitted by logistic regression using Stata 9 software (Stata Corporation, College Station, Texas). Age and sex were entered categorically, and all models were adjusted for age-sex category, systolic blood pressure, total cholesterol, body mass index, cigarette smoking, use of antihypertensive drugs, and time period (i.e., examination). Significance of terms was decided by likelihood ratio and two-sided Wald tests.

We first examined risk associated with the three broad glucose categories: normal (≤5.55 mmol/liter (100 mg/dl)), impaired (5.56–6.99 mmol/liter (101–126 mg/dl)), and diabetic (>6.99 mmol/liter (>126 mg/dl)) for men and women separately as well as combined. We next studied risk by considering glucose as a continuous covariate. Our basic structure for continuous models was logit $= \beta\mathbf{x} + f(g)$, where $\mathbf{x}$ is a vector of covariates used for adjustments, and f is a specified (up to unknown parameters) function of glucose g. We examined the mortality/glucose relation with minimal assumptions on the shape of that relation by using the ''nine-categories'' model that assumed risk to be constant only within each of nine glucose categories (mmol/liter (mg/dl)): ≤3.89 (≤70), 3.90–4.44 (71–80), 4.45–5.00 (81–90), 5.01–5.55 (91–100), 5.56–6.11 (101–110), 6.12–6.99 (111–126), 7.00–9.71 (127–175), 9.72–12.49 (176–225), and >12.49 (>225). Specifically,

$$f(g) = \sum_{i=1}^{9} \gamma_i I_{C_i}(g),$$

$$\text{where } I_c(g) = 1 \text{ if } g \in C \text{ and } = 0 \text{ if } g \notin C.$$

That model, which was closer to the actual data than low-parameter continuous fits, was used primarily to visualize the glucose/mortality relation in more detail than provided by using just normal, impaired, and diabetic categories, and to aid in judging how well low-parameter continuous models reflected the actual data.

The Appendix gives details of the low-parameter models we considered. Included were the ''linear'' model [$f(g) = \alpha + \gamma g$]; transform models with $f(g) = \alpha + \gamma h(g)$, where h is a function of g; linear-transform models with both g and $h(g)$ as predictors [$f(g) = \alpha + \gamma_1 g + \gamma_2 h(g)$]; and, importantly, spline models with possible knots at $k_1 = 5.55$ (current normal), $k_2 = 6.11$ (previous normal), and $k_3 = 6.99$ mmol/liter (diabetic) cutpoints. These knots were chosen a priori to evaluate whether they were potentially useful as cutpoints for mortality. Low-parameter models were compared by using Akaike's Information Criterion (AIC) (13).

We examined the adequacy of the low-parameter fits by comparing the rates they predicted in the normal, impaired, and diabetic categories, and in the nine categories, with the adjusted observed rates in these categories. To facilitate visual comparison of the nine-categories model with low-parameter models, we plotted the nine-parameter model as a step function whose height was the risk in a given category and whose horizontal segments marked the location of the observations in a category; we singled out, on each segment, the location of the mean glucose level in the category.

RESULTS

Overall, for men and for women, age, systolic blood pressure, body mass index, and percentage of antihypertensive drug users tended to increase with increasing glucose level. Women had higher levels of all risk factors that we adjusted

TABLE 1. Pooled population characteristics by sex and by normal, impaired, and diabetic glucose categories, Framingham Heart Study, 1948–1978

	Women		Men		Difference	*p* value
	Observations (no.)	Mean (SD*)	Observations (no.)	Mean (SD)		
Normal (<5.55 mmol/liter) (70 mg/dl)						
Age (years)	868	62.43 (7.10)	1,200	61.28 (6.93)	1.15	<0.001
Smoker (%)	868	18.66 (38.98)	1,200	29.50 (45.62)	−10.84	<0.001
Antihypertensive drug user (%)	846	34.52 (47.57)	1,163	16.34 (36.99)	18.18	<0.001
Glucose level (mmol/liter)	868	4.81 (0.51)	1,200	4.77 (0.51)	0.05	0.078
Systolic blood pressure (mmHg)	868	151.40 (28.69)	1,200	141.07 (23.67)	10.33	<0.001
Cholesterol level (mmol/liter)	841	6.64 (1.32)	1,163	6.05 (1.11)	0.59	<0.001
Body mass index†	864	26.78 (4.85)	1,197	26.25 (3.57)	0.53	0.004
Impaired (5.55–6.99 mmol/liter) (100–126 mg/dl)						
Age (years)	505	64.32 (6.44)	607	62.95 (6.29)	1.37	<0.001
Smoker (%)	505	16.83 (37.45)	607	29.16 (45.49)	−12.33	<0.001
Antihypertensive drug user (%)	499	38.48 (48.70)	601	24.79 (43.22)	13.68	<0.001
Glucose level (mmol/liter)	505	6.10 (0.38)	607	6.15 (0.39)	−0.05	0.032
Systolic blood pressure (mmHg)	505	153.28 (29.01)	607	142.32 (22.06)	10.96	<0.001
Cholesterol level (mmol/liter)	402	6.46 (1.29)	480	5.99 (1.08)	0.46	<0.001
Body mass index	504	27.61 (5.93)	604	27.03 (3.80)	0.58	0.049
Diabetic (≥6.99 mmol/liter) (>126 mg/dl)						
Age (years)	281	64.46 (6.42)	375	63.81 (6.86)	0.65	0.215
Smoker (%)	281	22.42 (41.78)	375	23.20 (42.27)	−0.78	0.8139
Antihypertensive drug user (%)	277	45.49 (49.89)	372	26.61 (44.25)	18.87	<0.001
Glucose level (mmol/liter)	281	10.59 (4.42)	375	10.35 (4.22)	0.24	0.481
Systolic blood pressure (mmHg)	281	154.08 (27.33)	375	145.00 (22.45)	9.08	<0.001
Cholesterol level (mmol/liter)	202	6.46 (1.41)	264	5.87 (1.19)	0.60	<0.001
Body mass index	278	28.39 (6.34)	375	27.38(4.02)	1.01	0.014
All categories						
Age (years)	1,654	63.35 (6.86)	2,182	62.18 (6.82)	1.17	<0.001
Smoker (%)	1,654	18.74 (39.04)	2,182	28.32 (45.07)	−9.58	<0.001
Antihypertensive drug user (%)	1,622	37.61 (48.45)	2,136	20.51 (40.38)	17.10	<0.001
Glucose level (mmol/liter)	1,654	5.52 (2.49)	2,182	5.45 (2.41)	0.08	0.387
Systolic blood pressure (mmHg)	1,654	152.43 (28.57)	2,182	142.09 (23.06)	10.33	<0.001
Cholesterol level (mmol/liter)	1,445	6.56 (1.33)	1,907	6.01 (1.12)	0.55	<0.001
Body mass index	1,646	27.31 (5.50)	2,176	26.66 (3.74)	0.65	<0.001

* SD, standard deviation.
† Weight (kg)/height $(m)^2$.

for other than smoking (table 1). There were 3,836 observations (57 percent men) and 310 deaths (70 percent men), of which 69.7 percent ($n = 216$) were cardiovascular related (table 2).

The Framingham Heart Study classified a subject as ''glucose intolerant'' at a given examination if any of the following conditions held: 1) previous or current diagnosis of diabetes, 2) definite or trace glucose in urine, and 3) plasma glucose ≥7.46 mmol/liter (134 mg/dl). A total of 15.6 percent of women and 17.4 percent of men were known to be glucose intolerant. Essentially none of the subjects were using lipid-lowering agents, and none of the non-glucose-intolerant subjects were using antihyperglycemic agents.

All-cause mortality

Men and women combined. For men and women combined, adjusted all-cause mortality rates significantly increased across the normal, impaired, and diabetic categories (figure 1). The nine-categories model suggested that risk rapidly increased through the normal or subdiabetic range and increased much more slowly thereafter (figure 2). The low-parameter fits supported this view. Single-knot spline

TABLE 2. Deaths by sex and by normal, impaired, and diabetic glucose categories,* Framingham Heart Study, 1948–1978

	Normal	Impaired	Diabetic	Total
Men (no.)				
Observations	1,200	607	375	2,182
Subjects	515	372	245	686
Cardiovascular-related deaths	74	51	35	160
Non-cardiovascular-related deaths	29	18	10	57
All deaths	103	69	45	217
Women (no.)				
Observations	868	505	281	1,654
Subjects	380	305	171	517
Cardiovascular-related deaths	24	13	19	56
Non-cardiovascular-related deaths	11	16	10	37
All deaths	35	29	29	93
Men and women (no.)				
Observations	2,068	1,112	656	3,836
Subjects	895	677	416	1,203
Cardiovascular-related deaths	98	64	54	216
Non-cardiovascular-related deaths	40	34	20	94
All deaths	138	98	74	310

* Refer to table 1 for a definition of these categories.

models with knots at 5.55 or 6.11 mmol/liter, or the two-knot spline with these knots and the right slope constrained to be 0, were AIC equivalent, optimal (appendix table 1), and predicted risks that were very close to each other (data not shown). We selected the spline with knot at 5.55 mmol/liter as our ''all-subjects spline'' model. That model was AIC superior to the linear model (appendix table 1). In the all-subjects spline model, both the left slope and the right slope were significant ($p < 0.001$ and $p = 0.050$, respectively), and there was a significant difference between them ($p = 0.001$): the left slope was 12.02 times greater than the right slope (figure 2). However, as detailed below, the relation for the sexes combined presented a biased picture of the relation for men and women individually.

Men and women separately. Surprisingly, there was a qualitative difference between the sexes in the association of glucose with mortality (figure 3). For men, there were significant differences in mortality between the normal and impaired and between the normal and diabetic categories, but no difference was found between the impaired and diabetic categories. For women, there was a large and significant difference between the impaired and diabetic categories and only a small (nonsignificant) difference between the normal and impaired categories.

Examining the relation with glucose as a continuous covariate revealed much more dramatic differences (figure 4). The nine-categories model suggested that for men, risk rose very rapidly through the normal range and then leveled off, while, remarkably, the reverse seemed true for women. For them, risk seemed unrelated to glucose until about the top of the normal range and then increased. The low-parameter models supported these impressions.

For men, the clear optimal AIC model was the single-knot spline with knot at 5.55 mmol/liter and right slope constrained to be 0. We chose that model as our ''men-spline'' model. It had a large, significant left slope ($p < 0.001$) and was vastly superior to the linear model (appendix table 1 and figure 3). According to the men-spline model, risk increased very rapidly from 4.12 percent at 3.89 mmol/liter (70 mg/dl) to 12.26 percent at 5.55 mmol/liter (100 mg/dl) and was flat at 12.26 percent thereafter (figure 3). The unconstrained spline model with knot at 5.55 mmol/liter supported the flatness to the right; in that model, there was a small, nonsignificant ($p = 0.889$), negative right slope.

For women, the two-knot spline models with left slopes equal to 0 were equivalent AIC optimal models, were AIC superior to the linear model (appendix table 1), and provided risk predictions that were very close to each other (data not shown). The various equivalent possibilities for women pointed to a relation in which risk was unrelated to glucose until some point between 5.55 and 6.99 mmol/liter; then, risk first increased very rapidly and then increased at a much diminished rate thereafter. The equivalences also indicated that data were insufficient to further refine the shape of the relation in the above-normal range beyond asserting that risk increase rate in the impaired range was significantly greater than in the diabetes range or to further isolate at what point the increase in risk between 5.55 and 6.99 mmol/liter began.

We selected the spline with knots at 5.55 and 6.99 mmol/liter as our ''women-spline'' model, which conservatively

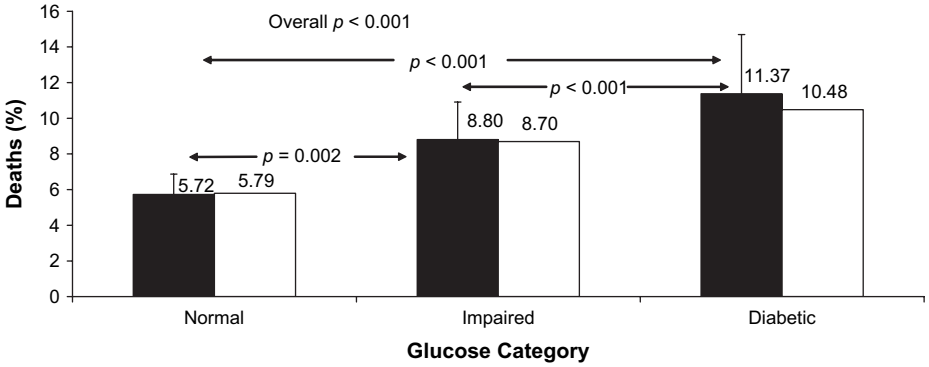

FIGURE 1. Adjusted 2-year death rates/100 for men and women combined, by normal, impaired, and diabetic glucose categories, Framingham Heart Study, 1948–1978. (Refer to the Materials and Methods section of the text for adjustment details.) The black bars give the adjusted all-cause mortality rates in each category, together with their 95% confidence intervals. The *p* values are Holm adjusted for multiple testing. The white bars show the rates predicted in these categories from an optimal spline model. The rates predicted in the three glucose categories by the spline model were quite close to those observed.

allowed risk increase to begin at the lowest value and rapid increase to continue to the highest value. It showed that for women, risk was flat at 3.65 percent for a glucose level of 5.55 mmol/liter, then it increased rapidly through the impaired range (reaching 8.34 percent at 6.99 mmol/liter) and increased much more slowly thereafter (figure 3). In the women-spline model, the middle slope was significant ($p = 0.008$) and the difference between the middle and right slopes was significant ($p = 0.033$), with the middle slope being 9.34 times as large as the right slope. The right slope was positive and nearly significant ($p = 0.112$). The unrestricted spline with these knots supported the lack of association of risk with glucose in the normal range. In that model, the left slope was very small, negative, and nonsignificant ($p = 0.857$). Rates predicted above the diabetes cutpoint should be considered cautiously because of a lack of data.

The interval of constancy in the mortality/glucose relation for men cannot be attributed to lack of data. Indeed, for men, the numbers of observations and deaths in the above-normal range were greater than those for women (table 2). Similarly, in the normal range, there were only 38 percent more observations for men than for women, which is insufficient to account for the dramatic difference between men and women observed in this range.

Cardiovascular and noncardiovascular mortality

We separately examined cardiovascular and noncardiovascular mortality by using the same methods as for all-cause

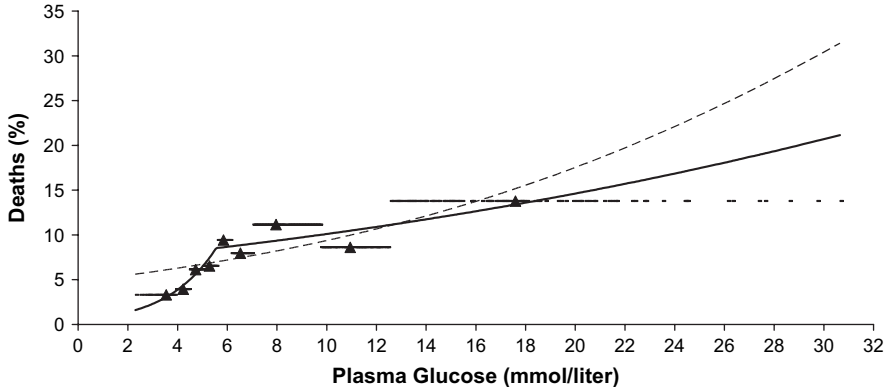

FIGURE 2. Adjusted 2-year rates of death from all causes for men and women combined, by glucose level, predicted by three models, Framingham Heart Study, 1948–1978. Linear model (dashed curve); spline model with knot at 5.55 mmol/liter (solid curve). The horizontal dashed intervals are fits from the nine-categories model, the segments of which mark points where there is at least one observation; the black triangles on each interval mark the location of mean glucose in that category. (Refer to the Materials and Methods section of the text for further information.) The spline model provides a considerably better explanation of the mortality risk than the linear model and shows that mortality rates rise quickly over the normal range and then rise much more slowly thereafter.

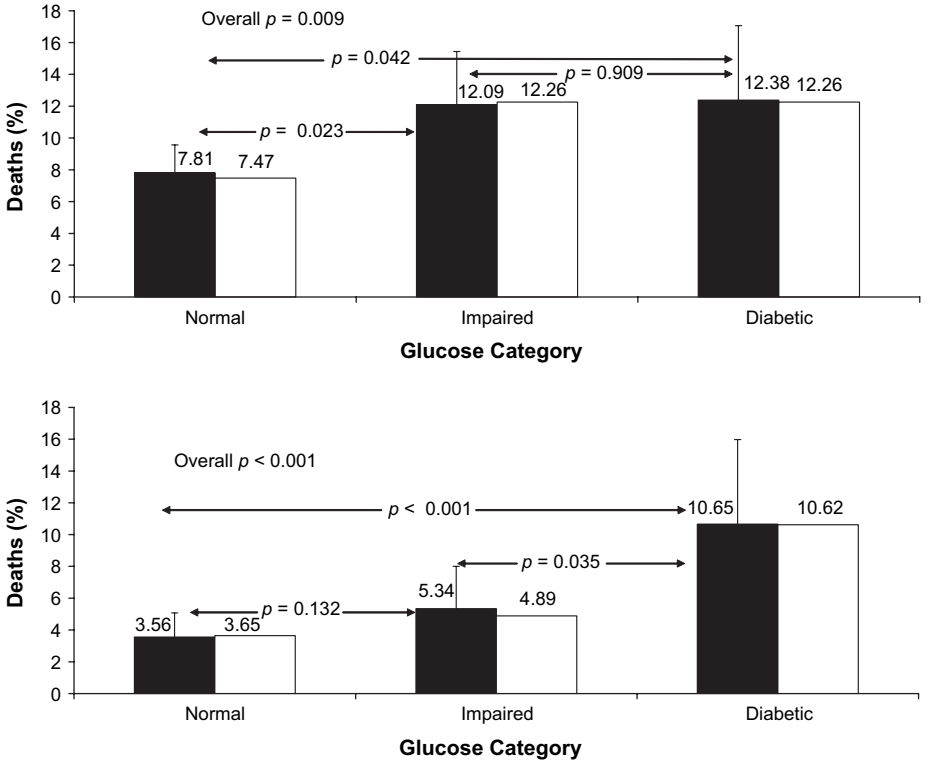

FIGURE 3. Adjusted 2-year death rates/100 for men (upper panel) and women (lower panel) separately, by normal, impaired, and diabetic glucose categories, Framingham Heart Study, 1948–1978. (Refer to the Materials and Methods section of the text for adjustment details). The black bars give the adjusted all-cause mortality rates in each category, together with their 95% confidence intervals. The *p* values are Holm adjusted for multiple testing. The white bars show the rates predicted in these categories from an optimal spline model. Comparison with figure 1 shows that the relation for men and women combined is considerably biased when applied to each sex individually.

mortality. As would be expected from the fact that 69.7 percent of the deaths were cardiovascular related, exactly analogous relations held for cardiovascular mortality as for all-cause mortality (data not shown). For non-cardiovascular-related death, data were insufficient to reliably examine the relation to glucose for men and women separately, to discriminate various models for men and women combined, or to examine risk in our nine glucose categories. Interestingly, there was evidence that noncardiovascular mortality may also be related to glucose. Table 2 gives the number of non-cardiovascular-related deaths in the normal, impaired, and diabetic categories. The adjusted non-cardiovascular-related death rates in these categories steadily increased from 1.78 percent (95 percent confidence interval: 1.28 percent, 2.49 percent) to 2.66 percent (95 percent confidence interval: 1.79 percent, 3.95 percent) to 2.96 percent (95 percent confidence interval: 1.77 percent, 4.91 percent), respectively, but the overall difference was not significant ($p = 0.148$). Examining for a linear trend, which has more power than the previous procedure to detect an increasing association, showed that, overall, there was a significant upward linear trend of noncardiovascular mortality to glucose ($p = 0.009$) in which risk increased from 1.82 percent at 3.89 mmol/liter to 2.06 percent at 5.55 mmol/liter to 2.29 percent at 6.99 mmol/liter, reaching 3.07 percent at 11.1 mmol/liter. When analysis was restricted to the nondiabetic range, for which we had very limited data, the significance of the trend deteriorated ($p = 0.097$).

Additional analyses

Adding interactions between glucose and other covariates to the models showed that no interactions were significant. None of our results on the mortality/glucose relations in the subdiabetic range materially changed when glucose-intolerant (and therefore diabetic) subjects were omitted from the analyses, and none of our findings were altered when antihypertensive drug users were omitted. The large difference in smoking between men and women (table 1) did not account for the large differences we observed between the sexes. For either sex, smoking was not significantly correlated with glucose, and the same differences between men and women persisted when the analyses were restricted to nonsmokers.

Fasting versus random glucose

Potentially, use of random instead of fasting glucose could have introduced additional random error due to variability in time since the last meal that would compromise

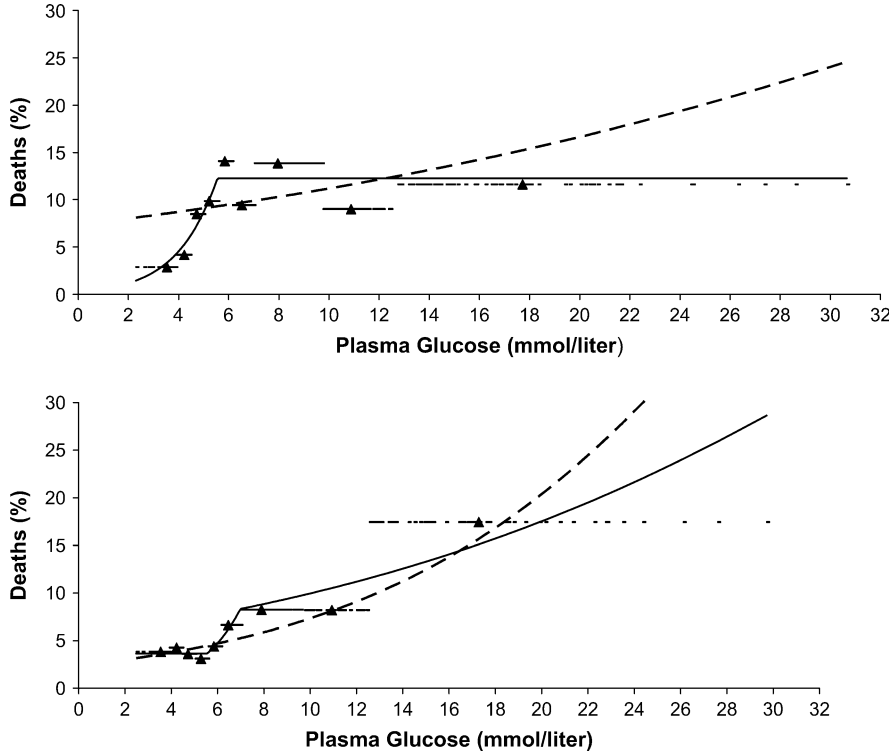

FIGURE 4. Adjusted 2-year rates of death from all causes for men (upper panel) and women (lower panel) separately, by glucose level, predicted by three models, Framingham Heart Study, 1948–1978. Linear model (dashed curve); optimal spline models (solid curve). The horizontal dashed intervals are fits from the nine-categories model, the segments of which mark points where there is at least one observation; the black triangles on each interval mark the location of mean glucose in that category. (Refer to the Materials and Methods section of the text for further information.) Compared with the spline fits, the linear fits are poor, especially for men. The relation of mortality to glucose is very different for the two sexes. For men, risk rises extremely rapidly through the normal range and is constant thereafter. For women, risk is constant through the normal range, rises rapidly through the impaired range, and then rises much more slowly thereafter. Comparison with figure 3 shows that the relation for men and women combined is very biased when applied to each sex individually.

our analyses by diluting the associations of risk with glucose. Clearly, this problem did not occur because we found very strong associations. Additionally, blood was drawn at the conclusion of many hours of examination, and one would expect that the random and fasting values would be close. Fortunately, we can verify that this was the case. Fasting glucose values were available at four of the examinations. The age- and sex-adjusted deciles of the fasting and random glucose distributions were very close (indicating that the two distributions were close), with the random ones being slightly lower. Additionally, *t* tests for the difference between random and fasting glucose for each age-sex group showed no significant differences. Thus, in our case, the use of random instead of fasting glucose had little impact on our analyses.

DISCUSSION

The Framingham data enabled us to examine the mortality/glucose relation in a population that had not yet been aggressively treated with agents known to affect CVD (e.g., statins, angiotensin-converting enzyme inhibitors) or with oral antihyperglycemic agents that might confound that relation. While our results show that glucose is a strong, independent predictor of mortality, they also unequivocally show that the mortality/glucose relations are qualitatively different for men and women. Indeed, for men, risk rises very rapidly through the normal range and is flat thereafter; for women, risk is unrelated to glucose in the normal range, then rises quickly through the impaired range and at a much slower rate thereafter (figure 4). To our knowledge, such striking differences between the sexes have not been previously reported in subjects with CVD.

Prior investigations of the mortality/glucose association in subjects with chronic CVD examined only men and women combined (4, 5, 7). Although our findings for men and women combined are in accord with the findings from these studies, they also clearly indicate that the mortality/glucose relation for men and women combined gives a biased view of the relations for either sex individually. When both sexes were considered together, the rapid rise seen through the normal range was due to the men, while the rise in the above-normal range was due to the women (figures 2 and 4).

TABLE 3. Adjusted 2-year mortality rates/100, by glucose level, predicted by the nine-categories and spline models,* Framingham Heart Study, 1948–1978

Glucose level (mmol/liter)	Observations (no.)	Deaths (no.)	Mean glucose level (mmol/liter)	Crude rate (%)	Nine-categories model (%)	Lower bound (%)†	Upper bound (%)†	Spline model (%)‡
				Men				
≤3.89	64	3	3.56	4.69	2.87	0.71	10.89	3.41
3.90–4.44	234	11	4.21	4.70	4.15	2.27	7.47	5.22
4.45– 5.00	470	43	4.74	9.15	8.48	6.27	11.39	7.37
5.01–5.55	432	46	5.28	10.65	9.84	7.28	13.17	10.29
5.56–6.11	326	46	5.83	14.11	14.08	10.39	18.81	12.26
6.12–6.99	281	23	6.51	8.19	9.43	5.99	14.52	12.26
7.00–9.71	242	29	7.99	11.98	13.86	9.10	20.54	12.26
9.72–12.49	60	5	10.89	8.33	9.00	3.39	21.82	12.26
>12.49	73	11	17.73	15.07	11.61	5.82	21.81	12.26
Total	2,182	217	5.45	9.95				
				Women				
≤3.89	44	2	3.57	4.55	3.84	0.93	14.47	3.65
3.90–4.44	148	7	4.20	4.73	4.26	1.99	8.90	3.65
4.45–5.00	319	13	4.74	4.08	3.60	2.01	6.35	3.65
5.01–5.55	357	13	5.28	3.64	3.11	1.75	5.47	3.65
5.56–6.11	285	12	5.81	4.21	4.40	2.47	7.71	4.21
6.12–6.99	220	17	6.48	7.73	6.64	3.71	11.60	6.14
7.00–9.71	175	17	7.91	9.71	8.24	4.37	15.01	8.79
9.72–12.49	39	3	10.94	7.69	8.20	2.53	23.55	10.52
>12.49	67	9	17.37	13.43	17.44	9.17	30.65	15.11
Total	1,654	93	5.52	5.62				
				Men and women				
≤3.89	108	5	3.56	4.63	3.30	1.23	8.56	3.10
3.90–4.44	382	18	4.20	4.71	3.94	2.45	6.27	4.32
4.45–5.00	789	56	4.74	7.10	6.12	4.65	8.01	5.67
5.01–5.55	789	59	5.28	7.48	6.53	4.98	8.52	7.42
5.56–6.11	611	58	5.82	9.49	9.42	7.18	12.28	8.61
6.12–6.99	501	40	6.49	7.98	7.95	5.56	11.25	8.83
7.00–9.71	417	46	7.96	11.03	11.16	7.85	15.63	9.34
9.72–12.49	99	8	10.91	8.08	8.61	4.10	17.19	10.47
>12.49	140	20	17.56	14.29	13.78	8.61	21.32	13.32
Total	3,836	310	5.48	8.08				

* Refer to the Materials and Methods section of the text for more information on these models.

† Lower bound or upper bound of the 95% confidence interval for the nine-categories rates.

‡ For men, knot at 5.55 mmol/liter and right slope = 0; for women, knots at 5.55 and 6.99 mmol/liter and left slope = 0; for men and women, knot at 5.55 mmol/liter.

Although speculations have been advanced on how glucose affects mortality, this mechanism remains basically unknown. Glucose may have direct harmful effects on vascular endothelium or atherosclerotic plaque, mediated by nonenzymatic glycosylation of apolipoproteins and clotting factors, increased oxidative stress, and activation of the polyol pathway (14). Alternatively, insulin may be the factor that worsens CVD, with elevated glucose levels driving compensatory hyperinsulinemia (15). The dramatic increases in mortality risk observed with glucose levels in the subdiabetic range are in accord with the concept that much cardiovascular risk accrues before overt diabetes develops, because the prediabetic state is characterized by inflammation and endothelial dysfunction (16, 17). Why the relations should be so different for the two sexes is unknown and needs further study.

We caution that our spline models attempt to capture smooth curvilinear relations of mortality to glucose, albeit somewhat artificially, by piecewise-linear approximations and should not be interpreted too literally. In particular,

the knots, and the abrupt changes at them, are artifacts of the model, and the knots do not necessarily represent ''thresholds'' of any sort. Despite their shortcomings, the adjusted rates predicted by the spline models in each of the normal, impaired, and diabetic categories, as well as the nine categories, were in good agreement with the adjusted observed rates in these categories (figure 1 and table 3).

There are some limitations to our investigation. Our findings may not apply to subjects in racial and socioeconomic groups different from those in the Framingham population (mostly White, middle class) or to subjects younger or older (aged <45 or >74 years, respectively) than those in our population. We were unable to assess the roles of insulin, high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglycerides, and glycosylated hemoglobin (HbA_{1c}) because these factors were not measured in the Framingham Heart Study. Data were insufficient to examine the mortality/glucose relation separately for various types of CVD.

Our findings might partially explain why clinical trials of glucose lowering in diabetic subjects, such as the Diabetes Control and Complications Trial (18), the United Kingdom Prospective Diabetes Study (19), and others, have not definitively demonstrated mortality reduction with glucose lowering; in these trials, the intensive control groups achieved mean HbA_{1c} values of only about 7 percent, which corresponds to a glucose level of 9.6 mmol/liter (172 mg/dl) (20). According to our results, such reductions would have no effect for men and only a very small effect for women.

Strictly speaking, our findings apply to only those diabetic subjects with recognized CVD; however, it is reasonable to assume that they apply to all diabetics because most probably have substantial (but as yet unrecognized) CVD (21). Thus, our findings underscore the need for aggressive glucose-lowering trials that aim at reductions well into the normal range, especially for men. Only such trials can determine whether the strong mortality/glucose associations reported here are causal.

In conclusion, our study revealed possible, strong gender-based differences in the association between blood glucose levels and mortality. Findings indicate that the diabetic cutpoint (6.99 mmol/liter) does not provide a useful mortality risk division, especially for men, although the normal cutpoint (5.55 mmol/liter) may be a useful division, albeit with quite different implications, for men than women. These findings suggest that future studies are needed to examine gender differences with regard to the prediabetic state, the development of diabetes, and CVD.

ACKNOWLEDGMENTS

The authors are indebted to the National Institutes of Health (Bethesda, Maryland) for providing the Framingham data.

Glaxo-Smith Kline Pharmaceutical (Clifton, New Jersey), Merck Pharmaceutical (Rahway, New Jersey), Takeda Pharmaceutical (Deerfield, Illinois), Novartis Pharmaceutical (East Hanover, New Jersey), and Boehringer Ingelheim Pharmaceutical (Ridgefield, Connecticut) provided research grant support to Dr. Hsueh.

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APPENDIX

The general form for a spline model was $f(g) = \alpha + \gamma_1 g + \gamma_2 \max(0, g - k_1) + \gamma_3 \max(0, g - k_2) + \gamma_4 \max(0, g - k_3)$, where one or more of the $\gamma_1, \ldots, \gamma_4$ can be 0 and constraints may be placed to force the right-most slope (*R)* or left-most slope (*L*) to be 0. We specify a particular spline as spl(knot1, knot2, . . .; restrictions). For example, spl(5.55,6.99; $R = 0$) is the spline with knots at 5.55 and 6.99 mmol/liter and the restriction that the right-most slope = 0; spl(5.55,6.99) is the spline with these knots and no slope restrictions.

AIC is defined as $-2\text{ll} + 2p$, where ll is the log likelihood of the model and p the total number of parameters (including intercept). Judged by AIC, the optimal model is the one with the smallest AIC. Models within 1 of the optimal model were considered equivalent to it. Appendix table 1 gives the formulas and AIC of the models we considered.

APPENDIX TABLE 1. Log likelihood and AIC* of models considered

Model	Men and women			Men			Women		
	ll(model)*	df	AIC	ll(model)	df	AIC	ll(model)	df	AIC
Linear [$f(g) = \alpha + \gamma g$]	−886.318	13	1,798.64	−593.38	10	1,206.77	−287.08	10	594.16
Linear with sex-glucose interaction	−884.605	14	1,797.21						
Equilibrium [$f(g) = \alpha + \gamma(g/1 + g)$]	−882.251	13	1,790.50	−590.41	10	1,200.82	−286.71	10	593.42
Log [$f(g) = \alpha + \gamma \ln(g)$]	−883.775	13	1,793.55	−591.81	10	1,203.63	−286.42	10	592.85
Sqrt [$f(g) = \alpha + \gamma\sqrt{g}$]	−885.044	13	1,796.09	−592.69	10	1,205.38	−286.61	10	593.21
Quad [$f(g) = \alpha + \gamma_1 g + \gamma_2 g^2$]	−884.796	14	1,797.59	−592.18	11	1,206.36	−286.55	11	595.10
Lin_log [$f(g) = \alpha + \gamma_1 g + \gamma_2 \ln(g)$]	−882.469	14	1,792.94	−589.48	11	1,200.97	−286.42	11	594.84
Lin_sqrt [$f(g) = \alpha + \gamma_1 g + \gamma_2\sqrt{g}$]	−883.071	14	1,794.14	−590.23	11	1,202.47	−286.42	11	594.84
Spl(5.55)	−880.816	14	1,789.63†,‡	−585.82	11	1,193.64	−287.00	11	596.01
Spl(6.11)	−880.708	14	1,789.42†	−587.07	11	1,196.14	−286.63	11	595.26
Spl(6.99)	−881.303	14	1,790.61	−588.68	11	1,199.36	−286.14	11	594.28
Spl(5.55,6.11)	−880.621	15	1,791.24	−585.69	12	1,195.39	−285.22	12	594.45
Spl(5.55,6.99)	−880.581	15	1,791.16	−585.73	12	1,195.46	−285.17	12	594.35
Spl(6.11,6.99)	−880.708	15	1,791.42	−586.65	12	1,197.30	−285.60	12	595.20
Spl((5.55,6.11,6.99)	−880.579	16	1,793.16	−585.69	13	1,197.39	−285.07	13	596.13
Spl(5.55; $R = 0$)	−882.554	13	1,791.11	−585.83	10	1,191.66†,‡	−292.16	10	604.32
Spl(6.11; $R = 0$)	−881.607	13	1,789.21†	−587.16	10	1,194.31	−290.35	10	600.70
Spl(6.99; $R = 0$)	−881.576	13	1,789.15†	−588.91	10	1,197.81	−288.19	10	596.38
Spl(5.55,6.11; $R = 0$)	−881.607	14	1,791.21	−585.70	11	1,193.40	−287.50	11	596.99
Spl(5.55,6.11; $R = 0$)	−881.164	14	1,790.33	−585.74	11	1,193.49	−286.28	11	594.57
Spl(6.11,6.99; $R = 0$)	−881.319	14	1,790.64	−586.67	11	1,195.34	−286.69	11	595.39
Spl(5.55; $L = 0$)	−888.099	13	1,802.20	−594.35	10	1,208.70	−287.36	10	594.73
Spl(6.11; $L = 0$)	−888.711	13	1,803.42	−594.52	10	1,209.05	−287.84	10	595.67
Spl(6.99; $L = 0$)	−889.323	13	1,804.65	−594.65	10	1209.30	−288.47	10	596.94
Spl(5.55,6.11; $L = 0$)	−884.338	14	1,796.68	−592.33	11	1,206.66	−285.31	11	592.61†
Spl(5.55,6.99; $L = 0$)	−885.066	14	1,798.13	−593.00	11	1207.99	−285.19	11	592.38†,‡
SSpl(6.11,6.99; $L = 0$)	−886.45	14	1,800.90	−593.75	11	1,209.51	−285.75	11	593.49†

* AIC, Akaike Information Criterion; ll(model), log-likelihood of the model.
† Model with optimal AIC.
‡ The model selected.