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Low Fasting Plasma Glucose Level as a Predictor of Cardiovascular Disease and All-Cause Mortality

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Background—Although medical textbooks usually classify fasting plasma glucose <70 or 80 mg/dL (<3.89 or 4.44 mmol/L) as abnormal, the prognosis for patients with low fasting plasma glucose is unclear.

Methods and Results—We conducted prospective cohort studies among 40 069 men and women to investigate the association between fasting plasma glucose levels and cardiovascular disease and all-cause mortality. We documented a U-shaped relation between fasting plasma glucose and mortality. In addition to diabetes and impaired fasting glucose levels, low fasting plasma glucose levels were also associated with high mortality. After multivariate adjustment for age, sex, study population, ethnicity, current smoking status, high blood pressure, total cholesterol, body mass index, triglycerides, history of cardiovascular disease and cancer, and a family history of cardiovascular disease, patients with fasting plasma glucose <70 mg/dL (<3.89 mmol/L) had a 3.3-fold increased risk of cardiovascular disease mortality, and patients with fasting plasma glucose 70 to 79 mg/dL (3.89 to 4.43 mmol/L) had a 2.4-fold increased risk compared with the risk in patients with fasting plasma glucose 80 to 109 mg/dL (4.44 to 6.05 mmol/L) (tests for trend $P<0.0001$). Participants with low fasting plasma glucose levels also had increased risk of all-cause mortality (test for trend $P<0.0001$).

Conclusions—Participants with low fasting plasma glucose levels had a high risk of cardiovascular disease and all-cause mortality. (*Circulation*. 2000;101:2047-2052.)

Key Words: glucose ■ cardiovascular diseases ■ mortality

Under normal physiological conditions, plasma glucose concentration is maintained within narrow limits by a tightly regulated balance between glucose efflux from and influx into the circulation.¹ A normal plasma glucose level is important for human energy and nutrition. It is known that high fasting plasma glucose (FPG) levels and diabetes are associated with a high incidence of cardiovascular disease (CVD) and all-cause mortality.²⁻⁵ On the other hand, low plasma glucose levels may cause brain and heart problems.^{1,6} Early studies of low FPG focused on brain damage during hypoglycemia.⁶⁻⁸ Although medical textbooks usually classify FPG <70 or 80 mg/dL (<3.89 or 4.44 mmol/L) as abnormal,^{9,10} symptoms usually appear only when FPG is <50 mg/dL (<2.78 mmol/L).¹¹ There is a paucity of information about the association between low plasma glucose levels and cause-specific and all-cause mortality. In the present study, we address this issue in 2 prospective studies with a total follow-up of 350 552 person-years.

Methods

Subjects

Subjects for this study were 40 069 men and women 20 to 82 years of age at baseline (mean, 43 years) from either the Aerobics Center

Longitudinal Study (ACLS) or the San Antonio Heart Study (SAHS). The participants from the ACLS completed ≥ 1 preventive medical evaluation at the Cooper Clinic in Dallas, Tex, between 1970 and 1989. Details of the study design and population characteristics of this study are available in previous reports.^{12,13} Briefly, this is a population-based prospective study. More than 97% of the 35 140 patients are white, 78% are men, and most had white-collar or professional occupations. The baseline evaluation was performed after participants gave their informed written consent for the initial medical examination and subsequent registration in the follow-up study. Examinations followed an overnight fast of ≥ 12 hours and included personal and family health histories and a questionnaire on demographic characteristics and health habits. All procedures were administered by technicians who followed a standard manual of operations.¹² The study was reviewed and approved annually by the Institutional Review Board at the Cooper Institute for Aerobics Research.

The participants in the SAHS were randomly recruited between 1979 and 1988 from 3 types of neighborhoods: low-income barrios, middle-income transitional neighborhoods, and high-income suburbs. All men and nonpregnant women between 25 and 64 years of age residing in the selected households were considered eligible for the study. Of 4929 subjects, 62% were Mexican Americans, and 57% were women. The baseline evaluation was performed after participants gave their informed written consent for the medical examination. Examinations followed an overnight fast of ≥ 12 hours and included a questionnaire on demographic characteristics and health

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habits. Technicians who followed a standard manual of operations administered all procedures. The study was approved by the University of Texas Health Science Center Institutional Review Board, and all participants gave informed consent. Details of the study design and sampling, recruitment, and field procedures of the SAHS have been reported previously.^{4,14}

We defined diabetes in this study according to the 1997 plasma glucose criteria of the American Diabetes Association¹⁵: (1) For impaired fasting glucose, FPG ≥ 110 mg/dL (≥ 6.11 mmol/L) but < 126 mg/dL (< 7.0 mmol/L); and (2) for diabetes, FPG ≥ 126 mg/dL (7.0 mmol/L). Subjects who did not meet this criterion but who gave a history of diabetes and reported current therapy with either oral antidiabetic agents or insulin also were considered to have diabetes. In the SAHS, participants with a 2-hour postload glucose level ≥ 200 mg/dL (11.1 mmol/L) also were considered to have diabetes. The ACLS material did not include 2-hour postload glucose data.

Primary outcome measures were CVD and all-cause mortality. The National Death Index was used to identify possible decedents in the ACLS. The National Death Index is an effective, accurate means of ascertaining deaths in the general population with a sensitivity of $\approx 96\%$ and a specificity of 100%.¹⁶ Deaths were identified and confirmed by follow-up interviews with next-of-kin in the SAHS, and vital status was ascertained for 98% of the cohort.⁴ Death certificates were obtained in both studies and coded by nosologists according to the International Classification of Diseases, 9th Edition, Revised. CVD mortality was defined as codes 390 to 459 and cancer mortality as codes 140 to 208. Only the underlying cause of death was used.

The 2 populations were pooled for analysis to increase statistical power. Data were analyzed with the SAS statistical package.¹⁷ Interaction terms between population, ethnicity, sex, and other independent variables were entered into the initial models to evaluate possible interactions; however, no significant interactions were found, and the primary analyses were on the pooled data. The adjusted mortality rates were calculated by the direct method. We used survival curves to estimate survival function against time and Log [−log (survival time)] to check proportional hazards model assumption. We used Cox proportional hazards models to estimate the association between mortality and predictor variables after adjustment for potential confounders.^{17,18} All probability values provided are for 2-sided tests, and values of $P < 0.05$ were considered statistically significant.

Results

Baseline characteristics adjusted for age, sex, ethnicity, and study population are presented in Table 1. Body mass index, total cholesterol, triglyceride, systolic blood pressure, diastolic blood pressure, exercise tolerance, fasting insulin, and 2-hour postload insulin values were lower in individuals with low FPG than in individuals with normal FPG. The prevalence of parental CVD and current smoking were higher in participants with low FPG; however, the differences for these variables were small, except for insulin level.

During an average follow-up of 8 years, there were 954 deaths, including 413 from CVD and 277 from cancer. We first stratified data by every 10 mg/dL (0.555 mmol/L) for mortality analysis. We found increased mortality in participants with diabetes and with FPG < 80 mg/dL (< 4.44 mmol/L). There were 1581 participants with diabetes, 4550 with impaired fasting glucose, and 1795 with FPG < 80 mg/dL (< 4.44 mmol/L). Among participants with low FPG, 11 had FPG < 50 mg/dL (< 2.78 mmol/L), 221 had FPG 50 to 69 mg/dL (2.78 to 3.88 mmol/L), and 1563 had FPG 70 to 79 mg/dL (3.89 to 4.43 mmol/L). Figure 1 shows the mortality rates per 1000 person-years according to FPG levels. Subjects

TABLE 1. Adjusted Baseline Characteristics of 33 658 Participants According to FPG Level

Characteristics	FPG Level, mg/dL		P (Difference Between FPG Groups)
	Low (< 80)	Normal (80–109)	
Subjects, n	1795	31 863	...
Body mass index, kg/m ²	24.7 \pm 0.1	25.9 \pm 0.02	< 0.05
Total cholesterol, mmol/L	5.28 \pm 0.03	5.45 \pm 0.01	< 0.05
HDL cholesterol,* mmol/L	1.30 \pm 0.01	1.26 \pm 0.003	< 0.05
Triglycerides, mmol/L	1.26 \pm 0.03	1.45 \pm 0.01	< 0.05
Systolic blood pressure, mm Hg	117.7 \pm 0.6	119.0 \pm 0.1	< 0.05
Diastolic blood pressure, mm Hg	77.0 \pm 0.2	78.7 \pm 0.1	< 0.05
Alcohol intake, g/wk	141.9 \pm 7.5	153.2 \pm 1.5	...
Current smoking status, %	22	18	< 0.05
History of parental CVD, %	25	23	< 0.05
History of CVD, %	7	8	...
History of cancer, %	0.7	0.9	...
Exercise tolerance, METs†	10.9 \pm 0.07	11.0 \pm 0.01	< 0.05
Uric acid,‡ mmol/L	0.34 \pm 0.01	0.34 \pm 0.01	...
GGT,‡‡ U/L	23.0 \pm 2.3	24.1 \pm 0.3	...
Fasting insulin,§ pmol/L	62.4 \pm 3.0	84.0 \pm 1.8	< 0.05
2-h insulin,§ pmol/L	442.8 \pm 20.4	570.6 \pm 13.8	< 0.05

Values are mean \pm SEM or percentages. METs indicates metabolic equivalents; GGT, γ -glutamyltranspeptidase. All variables were adjusted for age, sex, ethnicity, and study population. To convert values for glucose to millimoles per liter, divide by 18.01. To convert values for cholesterol to milligrams per deciliter, multiply by 38.67, and to convert triglycerides to milligrams per deciliter, multiply by 88.57. To convert values for uric acid to milligrams per deciliter, multiply by 17.14. To convert values for insulin to micro-U per milliliter, divide by 6.0.

*n=23 587.

†ACLS data only.

‡n=13 526.

§SAHS data only.

in the SAHS, which included many Mexican Americans, had a high prevalence of diabetes (8%) compared with subjects in the ACLS (3%). The prevalence of low FPG was also higher in Mexican Americans. There was a clear relation between low FPG and mortality after adjustment for age, sex, and study population. After exclusion or adjustment for history of chronic disease, the magnitude of association between low FPG and mortality did not change.

We then focused on the comparison between low FPG and normal FPG. We first performed subgroup analyses in women versus men, individuals aged ≥ 50 years versus those aged < 50 years, Mexican Americans versus non-Hispanic whites, deaths in the first 4 years versus deaths later than 4 years, and SAHS versus ACLS separately. All associations between low FPG and mortality were directionally similar in these subgroup analyses. Compared with participants without low FPG, those with low FPG had a substantially higher risk of CVD and all-cause mortality in each subgroup analysis.

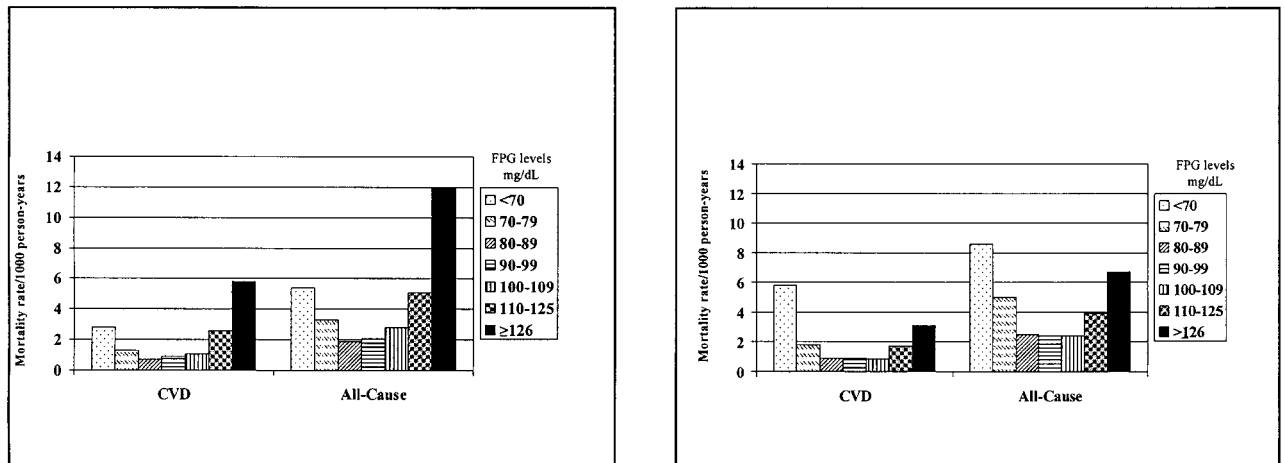


Figure 1. CVD and all-cause mortality rates per 1000 person-years, according to FPG levels. Rates in left panel are crude rates; rates in right panel are adjusted for age, sex, and population. FPG was classified as diabetes (≥ 126 mg/dL), impaired FPG (110 to 125 mg/dL), normal FPG (80 to 89, 90 to 99, and 100 to 109 mg/dL), and low FPG (70 to 79 mg/dL and <70 mg/dL). To convert values for glucose to millimoles per liter, divide by 18.01.

For example, age- and sex-adjusted relative risks (with 95% CIs) associated with low FPG were 2.1 (1.2 to 3.8) for CVD mortality and 2.1 (1.4 to 2.8) for all-cause mortality in the ACLS data. Age- and sex-adjusted relative risks (with 95% CIs) were 3.4 (1.6 to 7.1) for CVD mortality and 1.7 (1.0 to 3.0) for all-cause mortality in the SAHS data. Age- and sex-adjusted relative risks (with 95% CIs) associated with low FPG were 2.3 (1.4 to 3.8) for CVD mortality and 2.2 (1.5 to 2.9) for all-cause mortality in the non-Hispanic whites. Age- and sex-adjusted relative risks (with 95% CIs) were 3.1 (1.4 to 6.8) for CVD mortality and 1.6 (0.8 to 3.0) for all-cause mortality in Mexican Americans. The interactions between study or ethnicity and low FPG on mortality were not statistically significant. No significant differences for CVD and all-cause mortality were found between nondiabetics with low FPG and diabetics.

We used Kaplan-Meier curves to test for differences in mortality rates between participants with low glucose and

those with normal glucose. There were strong associations between low FPG and CVD and all-cause mortality (Figure 2). Both Wilcoxon and log-rank tests were highly significant for CVD and all-cause mortality ($P < 0.0001$). Log ($-\log$ [survival function]) estimates were approximately parallel across the low FPG group and normal glucose group (figure not shown).

Table 2 shows the association between low FPG and CVD, cancer, deaths other than cancer or CVD, and all-cause mortality. Participants with low FPG had substantially higher CVD, all-cause, and other mortality. The relation between low FPG and cancer mortality was weak and nonsignificant. Additional adjustments by multivariate analyses and exclusion of persons with chronic diseases did not alter these associations. For example, the multivariate-adjusted relative risks (with 95% CIs) of low FPG for CVD and all-cause mortality were 2.7 (1.7 to 4.3) and 2.0 (1.5 to 2.6) in all study subjects, 2.7 (1.5 to 4.7) and 2.0 (1.4 to 2.9) in restricting

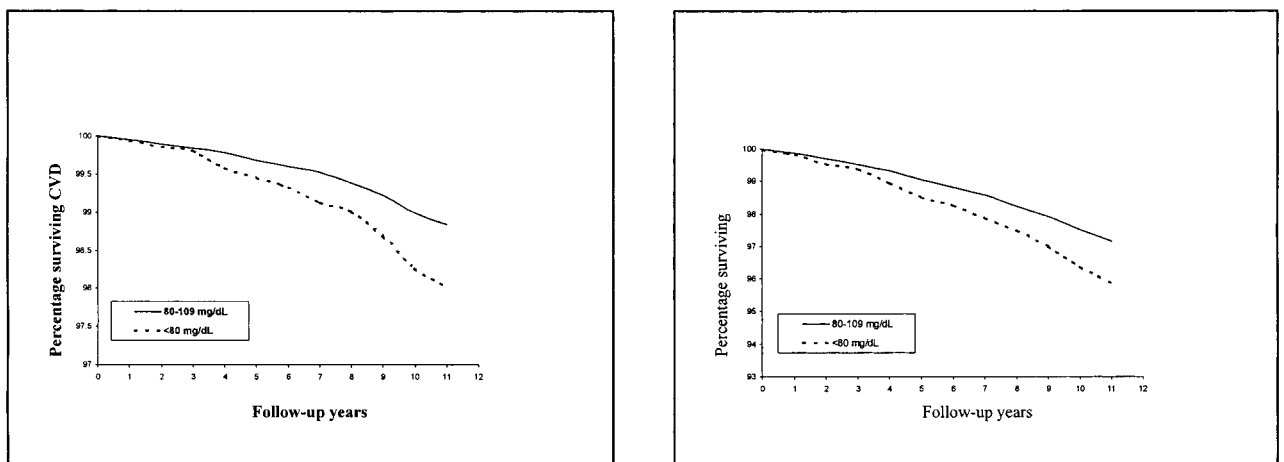


Figure 2. Kaplan-Meier survival curves of CVD mortality and all-cause mortality for participants with low (<80 mg/dL) FPG ($n=1795$, 50 all-cause deaths and 21 CVD deaths) and participants with normal (80 to 109 mg/dL) FPG ($n=31\,863$, 571 all-cause deaths and 206 CVD deaths). The 2 groups were significantly different ($P < 0.0001$). To convert values for glucose to millimoles per liter, divide by 18.01.

TABLE 2. Relative Risk (95% CI) of Low FPG for All-Cause, CVD, and Cancer Mortality (Group With Normal Glucose as Reference)

	Relative Risk (95% CI)	
	Adjusted for Age, Sex, and Population	Multivariate Adjustment*
All-cause	1.9 (1.4–2.6)	2.0 (1.5–2.6)
CVD	2.4 (1.5–3.8)	2.7 (1.7–4.3)
Cancer	1.2 (0.6–2.3)	1.2 (0.6–2.2)
Other†	2.2 (1.3–3.6)	2.2 (1.3–3.5)

*Adjusted for baseline age, sex, population, ethnicity, body mass index, triglycerides, high blood pressure, total cholesterol, parental CVD, history of CVD and cancer, current smoking status, and examination years.

†Includes all non-CVD and noncancer deaths.

events after 4 years of follow-up, and 2.7 (1.6 to 4.5) and 2.1 (1.5 to 2.9) in individuals without a history of CVD and cancer. Among 21 participants who died from CVD in the low FPG group, 52% of the deaths were due to acute myocardial infarction, 19% were due to cerebrovascular hemorrhage, and 10% were due to cardiac arrest. Because of the small number of cerebrovascular disease deaths in the low FPG group, no significant association between low FPG and cerebrovascular disease was detected.

To investigate the possible dose-response relation of low FPG levels to mortality, we classified those with low FPG into <70 mg/dL (<3.89 mmol/L) and 70 to 79 mg/dL (3.89 to 4.43 mmol/L) groups (Table 3). We found an inverse gradient ($P<0.0001$) for CVD and all-cause mortality across FPG categories in analyses adjusted for age, sex, and study population. Other models included adjustment for age, sex, study population, ethnicity, current smoking status, high blood pressure, total cholesterol, body mass index, triglycerides, history of CVD and cancer,

TABLE 3. Relative Risk (95% CI) of CVD and All-Cause Mortality, According to FPG Levels

FPG Level	Relative Risk (95% CI)	
	CVD	All-Cause
Adjusted for age, sex, and population		
<70 mg/dL	3.2 (1.3–7.8)	2.3 (1.2–4.4)
70–79 mg/dL	1.9 (1.1–3.2)	1.7 (1.2–2.4)
Normal FPG (80–109 mg/dL)	1.0	1.0
Tests for trend	$P<0.0001$	$P<0.0001$
Multivariate-adjusted*		
<70 mg/dL	3.3 (1.3–8.0)	2.4 (1.3–4.5)
70–79 mg/dL	2.0 (1.2–3.4)	1.8 (1.3–2.5)
Normal FPG (80–109 mg/dL)	1.0	1.0
Tests for trend	$P<0.0001$	$P<0.0001$

*Adjusted for baseline age, sex, population, ethnicity, body mass index, triglycerides, high blood pressure, total cholesterol, parental CVD, history of CVD and cancer, current smoking status, and examination years. To convert values for glucose to millimoles per liter, divide by 18.01.

and a family history of CVD. In the fully adjusted model, those with FPG <70 mg/dL (<3.89 mmol/L) had a 3.3-fold increased risk of CVD mortality, and those with FPG 70 to 79 mg/dL (3.89 to 4.43 mmol/L) had a 2.0-fold increased risk compared with patients with FPG 80 to 109 mg/dL (4.44 to 6.05 mmol/L) (test for trend $P<0.0001$). In similar analyses, those with FPG <70 mg/dL (<3.89 mmol/L) had a 2.4-fold increased risk of all-cause mortality, and those with FPG 70 to 79 mg/dL (3.89 to 4.43 mmol/L) had a 1.8-fold increased risk (test for trend $P<0.0001$). Low FPG was associated with low body mass index (<18.5), low cholesterol level, low diastolic blood pressure, and current smoking. However, the association between low FPG and mortality remained the same after adjustment for or excluding these risk factors. Low FPG was not associated with ex-drinkers or nondrinkers in the data.

Discussion

Currently, known risk factors predict $\approx 50\%$ to 60% of clinical CVD,^{19,20} and it is important to find additional predictors to improve clinical risk stratification. In the present study, we found a potential new predictor of CVD with the observation of an association between low FPG and CVD and all-cause mortality. This association was strong, independent, graded across strata of low FPG, and present in 2 separate cohort studies, the ACLS and the SAHS. To our knowledge, this is the first report on low FPG associated with CVD and all-cause mortality. Most of the previous studies categorized plasma glucose into diabetes or nondiabetes. However, a recent cohort study in men showed that crude CVD and all-cause mortality seems to be higher in patients with FPG <81 mg/dL (4.5 mmol/L), but the authors did not test this hypothesis.²¹

The most important adverse effect of hypoglycemia has been associated with brain damage.²² As an important fuel of the brain, severely low FPG may induce brain damage and dysfunction. However, there were only 11 participants with classic hypoglycemia with FPG <50 mg/dL (<2.78 mmol/L) in the present study, and the exclusion of these participants did not alter the results. ECG changes, including ectopic activity, flattening of the T wave, ST depression, ventricular tachycardia, and atrial fibrillation, have been reported in cases of low plasma glucose.^{6–8} Marques et al²³ reported alteration of ventricular repolarization with lengthening of the QT interval during insulin-induced experimental low FPG. Low plasma glucose has been suspected as the cause of high CVD mortality in diabetic patients with an unstable FPG.²⁴ It is known that >60% of adults aged 20 to 30 years have already had atherosclerosis²⁵ and that the prevalence of atherosclerosis increases as age increases.^{25,26} We hypothesize that long-term exposure to low FPG may serve as a risk factor of CVD mortality, perhaps through abnormal cardiac activity and thrombosis, especially in patients with atherosclerosis.

The relation between moderately low FPG and mortality in the present study was not confounded by preexisting chronic disease. After exclusion or adjustment for history of chronic disease, including CVD and cancer, the magnitude of asso-

ciation between low FPG and mortality did not change. Some kinds of occult cancer have been reported to be associated with symptomatic hypoglycemia^{1,27}; however, the association between low FPG and cancer mortality in our data was weak and nonsignificant. We reported that low cardiorespiratory fitness is associated with diabetes and impaired fasting glucose²⁸ and that low fitness was also somewhat associated with low FPG (Table 1). Some investigators have reported that hyperinsulinemia is a cause of hypoglycemia¹; however, compared with persons without low FPG, study participants with low FPG in the SAHS had lower fasting insulin and 2-hour postload insulin levels (Table 1). Uric acid levels also were similar in individuals with low FPG and in those with normal FPG in our data (Table 1). Heavy alcohol intake and liver diseases could be associated with liver dysfunction and hypoglycemia, but alcohol intake and γ -glutamyltranspeptidase were not higher in individuals with low FPG. When we excluded patients with a history of jaundice, hepatitis, cirrhosis, or abnormal γ -glutamyltranspeptidase, the results were unchanged. Low FPG was associated with low body mass index, low cholesterol, low diastolic blood pressure, and current smoking. Low body mass index and current smoking may partly explain low FPG; however, the association between low FPG and mortality remained the same after adjustment for these potential confounders.

Limitations

The subjects in ACLS were well educated, and >95% were white.^{12,13} The subjects in the SAHS were randomly recruited from 3 types of low-, middle-, and high-income neighborhoods, which included a large proportion of Mexican Americans.^{4,14,20} Despite the differences in characteristics, results from both populations for conventional risk factors of CVD are consistent with each other and with those from other populations.^{4,5,12,13,19,20} But whether our results also apply to African Americans and Asian Americans remains to be determined. There may be some measurement errors in the assessment of fasting plasma glucose and a small amount of patients lost to follow-up. However, it is unlikely that misclassification accounts for the observed association. It is possible that low FPG was partially due to inflammation, metabolic abnormalities, or specific diets, but we did not have data to evaluate these possibilities. Additional human studies and animal data are needed to investigate these issues.

Conclusions

The association between low FPG and CVD and all-cause mortality is clinically relevant. Actually, the higher relative risks of CVD and all-cause mortality in patients with low FPG were similar to those in patients with diabetes.^{2,4,5} Clinicians should be aware of this situation and search for special causes in cases of low FPG. Although association does not necessarily indicate cause and effect, our data suggest that low FPG itself may be a cause of high mortality risk. If our results are confirmed, low FPG could be a modifiable risk factor in nondiabetics. The optimal goals associated with FPG in diabetics taking insulin or oral antidiabetic agents might be to achieve an FPG level not <80

mg/dL. Further study is needed to explore the cause of low FPG and the association between low plasma glucose and CVD and all-cause mortality.

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