Impact of low fasting plasma glucose on mortality in the general population

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Abstract
Background: While the association between hypoglycaemia and poor outcomes in diabetes is well established, it is unclear whether such an association is generalizable to those without diabetes.
Methods: A total of 8497 participants free of cardiovascular disease and diabetes from the Third National Health and Nutrition Examination Survey were included. We examined the relationship between baseline low (<80 mg/dL) and high ($\geqslant 126$ mg/dL) fasting plasma glucose compared to normal levels (80–99 mg/dL).
Results: Over a median follow-up of 14 years, 2101 deaths occurred, of which 570 were due to cardiovascular disease. In a model adjusted for sociodemographic and cardiovascular disease risk factors, individuals with low fasting plasma glucose were at increased risk of cardiovascular disease and all-cause mortality [hazard ratio = 1.79 (95% confidence interval = 1.04–3.08) and hazard ratio = 1.35 (95% confidence interval = 1.02–1.78), respectively], compared to those with normal fasting plasma glucose. These associations were stronger among men than women for both cardiovascular disease mortality and all-cause mortality.
Conclusion: Low fasting plasma glucose in individuals without diabetes is a risk factor for cardiovascular disease and all-cause mortality, especially in men.

Keywords
Low fasting plasma glucose, hypoglycaemia, cardiovascular mortality, Third National Health and Nutrition Examination Survey

Introduction

Hypoglycaemia is associated with cardiovascular disease (CVD) morbidity and mortality in individuals with diabetes.[1–3] Whether this association is generalizable to those without diabetes is unclear. It is believed that the relationship between hypoglycaemia and poor cardiovascular outcomes in diabetics is explained by the unfavourable impact of lower levels of fasting plasma glucose (FPG) on the inflammation, sympathoadrenal activation, increased platelet and neutrophil activation, endothelial function, coagulation, and inflammatory mediators or cytokines.[4–8] We hypothesized that these relationships would not be different in individuals without diabetes, and hence, those with lower levels of FPG in the general population will be at a higher risk of CVD and all-cause mortality compared to those with FPG in the normal range. We tested this hypothesis in a sample from the third National Health and Nutrition Examination Survey (NHANES-III) who did not have a history of diabetes.

Methods

The NHANES (1988 and 1994) is a periodic survey of the noninstitutionalized civilian population in the United States. Its principal aim is to determine estimates of disease prevalence and health status of children and adults.

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The structure of the NHANES-III, its components and resulting data are published elsewhere.[9] The NHANES-III study was approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board, and documented consent was obtained from participants.

For this analysis, we only considered NHANES-III participants aged 20 to 90 years with follow-up mortality data ($n = 18{,}799$). We excluded participants with a self-report history of diabetes or on antidiabetic medications, prior CVD, those who did not fast ≥8 h prior to blood sampling for FPG or missing key covariates. After exclusions ($n = 10{,}302$), 8497 participants were included in the final analysis.

Fasting blood sample was analysed for glucose using laboratory procedures as reported by NCHS.[9] We created four categories of FPG: normoglycaemia (80–99 mg/dL), hypoglycaemia (<80 mg/dL), impaired glucose tolerance (100–125 mg/dL) and hyperglycaemia (≥126 mg/dL).

All-cause mortality and CVD mortality served as outcomes for this study. The NHANES-III participants were followed up for mortality from the initial exam (1988 and 1994) through 31 December 2006. The probabilistic matching method was used to link the participants with the National Death Index and the cause of death. Name, social security number and date of birth were parts of 12 identifiers used to match the participants. The follow-up duration was defined as the period between initial examination for NHANES-III participation and 31 December 2006, or date of death, whichever occurred first.

Age, sex and race/ethnicity (non-Hispanic White, non-Hispanic Black, Mexican American and other); smoking status (never, current and former); and leisure-time physical activity were self-reported. Body mass index (BMI) was calculated from height and weight measurements. Obesity was defined as BMI ≥30 kg/m². Blood pressure (BP; mmHg) was measured while seated, using a standard mercury sphygmomanometer and up to three measurements were averaged. Blood samples were analysed for total cholesterol (TC), triglycerides (TG), using laboratory procedures as reported by the NCHS.[9] Hyperlipidaemia was defined as TC ≥200 mg/dL or TG ≥150 mg/dL or use of antihyperlipidaemic agents.

Demographic and clinical characteristics of the participants were compared across FPG categories using Student's analysis of variance (ANOVA) or chi-square test as appropriate.

Cox-proportional hazard analysis was used to compute hazard ratios (HRs) and 95% confidence interval (CI) of the association of FPG categories with all-cause and CVD mortality. Two incremental models were constructed. Model 1 was adjusted for age, sex and race. Model 2 was further adjusted for systolic BP, antihypertensive medications, BMI, smoking, physical activity and hyperlipidaemia.

Using a model adjusted in a similar fashion to model 2, we conducted a subgroup analysis stratified by age (using 65 years as a cut-point), sex and race (Whites vs non-Whites). Test for interaction was performed with all-cause and CVD mortality outcome.

We used a restricted cubic spline model to examine the graphical relationship between FPG and the risk for all-cause and CVD mortality to assess the potential for a non-linear association and incorporated knots at the 5th, 50th and 95th percentiles. A likelihood ratio test was computed to test for linearity on the relationship between each FPG component and mortality (all-cause and CVD mortality).

All statistical analyses were performed using with SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA), and two-sided p values were considered significant if less than 0.05.

Results

Our analysis included 8497 participants (mean age = 44 years, 53% women, 40% Whites). The baseline characteristics of the study participants stratified by FPG levels are shown in Table 1. Participants with low FPG were more likely to be younger, women, non-White, never smoker and had less prevalent CVD risk factors.

During a median follow-up of 14 years, 2101 deaths occurred of which 570 were due to CVD. Tables 2 and 3 show the results of Cox-proportional hazard analysis, compared to referent category of FPG (80–99 mg/dL), and in a model adjusted for sociodemographic and CVD risk factors, low FPG was associated with 35% increased risk of all-cause and 79% increased risk of CVD mortality [HR (95% CI): 1.35 (1.02–1.78) and 1.79 (1.04–3.08), respectively]. Diabetic range FPG was significantly associated with a 20% increased risk of all-cause mortality only ($p = 0.04$; Table 2).

In subgroup analysis, the association of low FPG was stronger among men than women for all-cause [HR (95% CI): 1.85 (1.25–2.76) vs 1.06 (0.72–1.56), respectively; interaction p value = 0.01] and CVD mortality [HR (95% CI): 4.15 (2.27–7.60) vs 0.39 (0.09–1.58), respectively; interaction p value = 0.0002; Table 4]. Low FPG also had stronger association among older participants than younger participants for all-cause mortality [HR (95% CI): 1.65 (1.09–2.49) vs 0.84 (0.58–1.22), respectively; interaction p value = 0.01; Table 4]. Moreover, men with low FPG had higher cardiovascular risk factors such as high systolic and diastolic BP as well as a history of smoking (Supplemental Table 1). The association of FPG categories with all-cause and CVD mortality was consistent by race.

The graphical representation of the risk of mortality across each FPG value is represented in Figures 1 and 2. As shown, the overall risk of all-cause and CVD mortality was high at low and high FPG values. However, when stratified by gender, only men had higher risk of all-cause and CVD mortality at low FPG values (Figure 2).

Discussion

In this analysis, we examined a population from the NHANES-III without baseline CVD and diabetes to assess

Table 1. Baseline characteristics of the study participants.

Characteristics[a]	Fasting plasma glucose				p value[b]
	80–99 mg/dL n = 5679	<80 mg/dL n = 487	100–125 mg/dL n = 2071	≥126 mg/dL n = 260	
Fasting plasma glucose (mg/dL)	90.8 ± 5.2	76.0 ± 4.4	107.5 ± 6.3	171.3 ± 58.3	<0.0001
Glycated haemoglobin (units)	5.2 ± 0.5	5.0 ± 0.5	5.5 ± 0.5	7.4 ± 2.1	<0.0001
Age (years)	41.4 ± 17.5	33.5 ± 13.6	53.6 ± 17.7	58.5 ± 15.7	<0.0001
Men (%)	2528 (44.5%)	119 (24.4%)	1227 (59.2%)	142 (54.6%)	<0.0001
Race (%)					<0.0001
Non-Hispanic Whites	2218 (39.0%)	137 (28.1%)	900 (43.4%)	104 (40.0%)	
Non-Hispanic Blacks	1651 (29.0%)	211 (43.3%)	474 (22.8%)	71 (27.3%)	
Mexican Americans	1593 (28.0%)	123 (25.2%)	602 (29.0%)	73 (28.0%)	
Others	217 (3.8%)	16 (3.2%)	95 (4.5%)	12 (4.6%)	
Systolic blood pressure (mm Hg)	120.4 ± 17.4	112.7 ± 14.5	131.1 ± 19.3	137.1 ± 18.1	<0.0001
Diastolic blood pressure (mm Hg)	73.2 ± 10.2	68.8 ± 10.5	77.0 ± 10.5	77.7 ± 10.2	<0.0001
Antihypertensive medications (%)	366 (6.4%)	11 (2.2%)	324 (15.6%)	66 (25.3%)	<0.0001
Serum cholesterol (mg/dL)	198.4 ± 41.8	190.8 ± 40.5	214.6 ± 42.9	222.2 ± 49.9	<0.0001
Serum triglycerides (mg/dL)	120.0 ± 83.7	102.1 ± 68.9	151.5 ± 94.3	222.3 ± 157.2	<0.0001
Body mass index (kg/m^2)	26.4 ± 5.6	24.3 ± 4.8	28.3 ± 5.6	30.8 ± 6.0	<0.0001
Physical activity (MET per week)	11.2 (2.09–32.2)	10.6 (1.39–32.2)	10.4 (1.16–33.02)	7.3 (1.16–24.88)	<0.001
Ever smoker (%)	2731 (48.0%)	213 (43.7%)	1134 (54.7%)	153 (58.8%)	<0.0001

IQR: interquartile range; ANOVA: analysis of variance; MET: metabolic equivalent of task.
[a]Presented as mean ± SD or median IQR or n (%).
[b]The p value by ANOVA for continuous variables and χ^2 for categorical variables.

Table 2. Association of fasting blood glucose with all-cause mortality.

Fasting plasma glucose	Events/(1000 person-years)	Model 1		Model 2	
		HR (95% CI)	p value	HR (95% CI)	p value
80–99 mg/dL	10.9	Reference	N/A	Reference	N/A
<80 mg/dL	5.9	1.36 (1.03–1.79)	0.02	1.35 (1.02–1.77)	0.03
100–125 mg/dL	22.6	1.03 (0.94–1.13)	0.43	1.02 (0.93–1.12)	0.62
≥126 mg/dL	34.4	1.30 (1.09–1.56)	0.003	1.20 (1.00–1.45)	0.04

HR: hazard ratio; CI: confidence interval; N/A: not applicable.
Model 1 adjusted for age, sex and race. Model 2 adjusted for model 1 plus systolic blood pressure, antihypertensive medications, hyperlipidaemia, body mass index, smoking and physical activity.

Table 3. Association of fasting blood glucose with cardiovascular mortality.

Plasma glucose categories	Events (1000 person-years)	Model 1		Model 2	
		HR (95% CI)	p value	HR (95% CI)	p value
80–99 mg/dL	2.7	Reference	N/A	Reference	N/A
<80 mg/dL	1.5	1.70 (0.99–2.93)	0.05	1.75 (1.02–3.01)	0.04
100–125 mg/dL	6.8	1.16 (0.98–1.39)	0.07	1.15 (0.96–1.37)	0.12
≥126 mg/dL	9.4	1.30 (0.92–1.83)	0.13	1.22 (0.85–1.73)	0.26

HR: hazard ratio; CI: confidence interval; N/A: not applicable.
Model 1 adjusted for age, sex and race. Model 2 adjusted for model 1 plus systolic blood pressure, antihypertensive medications, hyperlipidaemia, body mass index, smoking and physical activity.

the association between low FPG and mortality, both CVD and all-cause. The key findings were as follows: (1) low FPG (<80 mg/dL) was significantly associated with increased risk of both CVD and all-cause mortality; (2) this association was stronger among males than females for both CVD and all-cause mortality; and (3) diabetic range FPG (≥126 mg/dL) was significantly associated with increased risk of all-cause mortality.

Table 4. Association of FPG with mortality among subgroups.

HR and 95% CI of association of FPG categories with all-cause mortality among subgroups

Subgroups	FPG	Participants	Events (%)	Hazard ratio (95% CI)	Interaction p value
Men	<80 mg/dL	119	27 (22.6%)	1.85 (1.25–2.76)	0.01
	100–125 mg/dL	1227	457 (37.2%)	0.98 (0.86–1.11)	
	≥126 mg/dL	142	77 (54.2%)	1.10 (0.86–1.40)	
Women	<80 mg/dL	368	28 (7.6%)	1.06 (0.72–1.56)	
	100–125 mg/dL	844	318 (37.6%)	1.10 (0.95–1.26)	
	≥126 mg/dL	118	58 (49.1%)	1.38 (1.04–1.83)	
White	<80 mg/dL	137	20 (14.6%)	1.43 (0.91–2.24)	0.54
	100–125 mg/dL	900	443 (49.2%)	1.07 (0.94–1.21)	
	≥126 mg/dL	104	68 (65.3%)	1.12 (0.87–1.46)	
Non-White	<80 mg/dL	350	35 (10.0%)	1.21 (0.85–1.72)	
	100–125 mg/dL	1171	332 (28.3%)	0.99 (0.86–1.14)	
	≥126 mg/dL	156	67 (42.9%)	1.28 (0.99–1.67)	
≥65 years	<80 mg/dL	26	24 (92.3%)	1.65 (1.09–2.49)	0.01
	100–125 mg/dL	640	498 (77.8%)	1.05 (0.93–1.19)	
	≥126 mg/dL	97	78 (80.4%)	1.21 (0.95–1.55)	
<65 years	<80 mg/dL	461	31 (6.7%)	0.84 (0.58–1.22)	
	100–125 mg/dL	1431	277 (19.3%)	1.30 (1.11–1.51)	
	≥126 mg/dL	163	57 (34.9%)	1.82 (1.37–2.43)	

HR and 95% CI of association of FPG categories with cardiovascular mortality among subgroups

Subgroups	FPG	Participants	Events (%)	Hazard ratio (95% CI)	Interaction p value
Men	<80 mg/dL	119	12 (10.0%)	4.15 (2.27–7.60)	0.0002
	100–125 mg/dL	1227	122 (9.9%)	0.92 (0.72–1.17)	
	≥126 mg/dL	142	25 (17.6%)	1.23 (0.80–1.92)	
Women	<80 mg/dL	368	2 (0.5%)	0.39 (0.09–1.58)	
	100–125 mg/dL	844	113 (13.3%)	1.46 (1.13–1.89)	
	≥126 mg/dL	118	12 (10.1%)	1.13 (0.62–2.06)	
White	<80 mg/dL	137	3 (2.1%)	0.83 (0.26–2.61)	0.43
	100–125 mg/dL	900	131 (14.5%)	1.14 (0.90–1.45)	
	≥126 mg/dL	104	22 (21.1%)	1.34 (0.85–2.12)	
Non-White	<80 mg/dL	350	11 (3.1%)	2.20 (1.17–4.14)	
	100–125 mg/dL	1171	104 (8.8%)	1.14 (0.87–1.50)	
	≥126 mg/dL	156	15 (9.6%)	1.10 (0.64–1.91)	
≥65 years	<80 mg/dL	26	7 (26.9%)	1.46 (0.68–3.10)	0.93
	100–125 mg/dL	640	170 (26.5%)	1.07 (0.87–1.33)	
	≥126 mg/dL	97	25 (25.7%)	1.19 (0.77–1.82)	
<65 years	<80 mg/dL	461	7 (1.5%)	1.55 (0.70–3.40)	
	100–125 mg/dL	1431	65 (4.5%)	1.68 (1.19–2.37)	
	≥126 mg/dL	163	12 (7.3%)	2.00 (1.07–3.74)	

HR: hazard ratio; CI: confidence interval; FPG: fasting plasma glucose.
Model adjusted for age, sex, race, systolic blood pressure, antihypertensive medications, hyperlipidaemia, body mass index, smoking and physical activity.
FPG 80–99 as reference.

Prior reports on the relationship between low FPG and poor outcomes in nondiabetics have focused mainly on all-cause mortality, and those that focused on CVD outcomes showed inconsistent results.[4,10–14] This inconsistency could be explained by lack of racial diversity, lack of representation of both sexes or using different definitions of hypoglycaemia. By filling these gaps in our study, our findings provide strong evidence of the relationship between low FPG and CVD mortality in the general population in the absence of diabetes. Studies in the diabetic population, conversely, have shown a more consistent association between low FPG and increased risk of both CVD mortality[1–3,5] and all-cause mortality.[15–17] Our findings regarding all-cause mortality and its associated increased risk with diabetic range FPG are in agreement with findings from studies conducted on both diabetic and nondiabetic
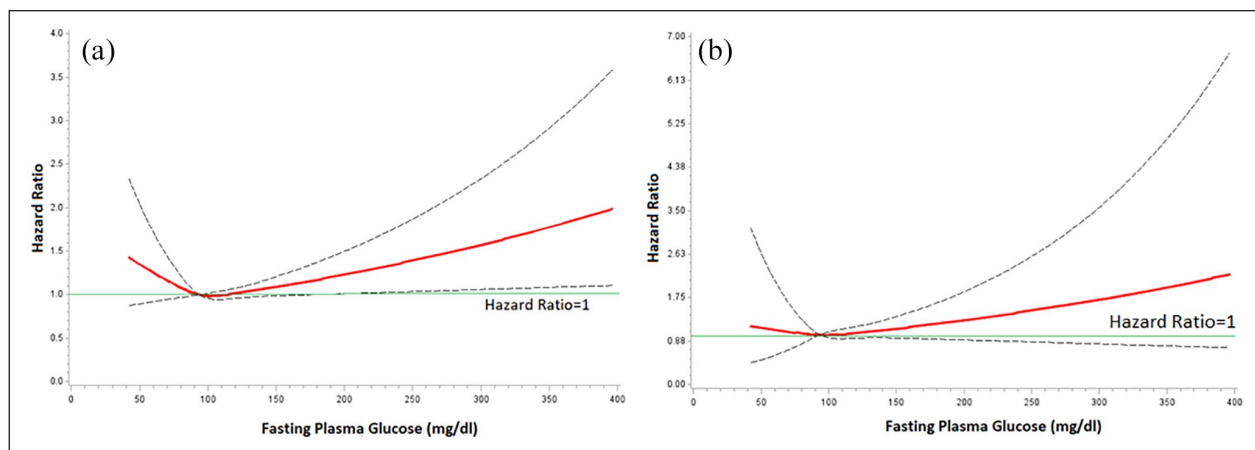
Figure 1. Risk of all-cause and CVD mortality by FPG:[a] (a) and (b) show restricted cubic spline of all-cause mortality and CVD mortality, respectively.
CVD: cardiovascular disease; FPG: fasting plasma glucose.
[a]Each hazard ratio was generated with a median value of FPG of 93.6 mg/dL as a reference and was adjusted for age, sex, race, systolic blood pressure, antihypertensive medications, hyperlipidaemia, body mass index, smoking and physical activity.
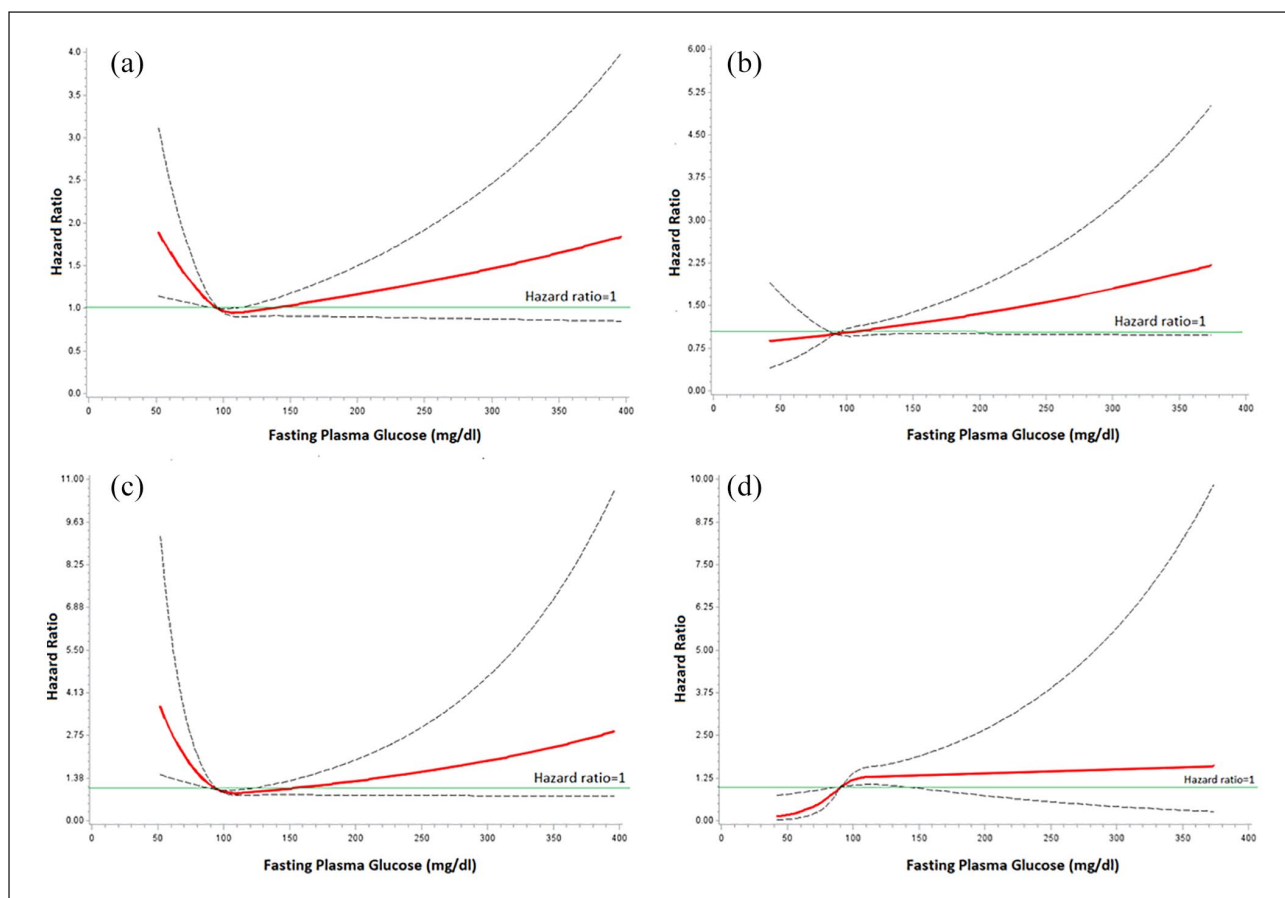

Figure 2. Risk of all-cause and CVD mortality by FPG among men and women:[a] (a) and (b) show restricted cubic spline of all-cause mortality among men and women, respectively, and (c) and (d) show restricted cubic spline of CVD mortality among men and women, respectively.
CVD: cardiovascular disease; FPG: fasting plasma glucose.
[a]Each hazard ratio was generated with a median value of FPG of 96 mg/dL for men and 91.2 mg/dL for women as reference and was adjusted for age, sex, race, systolic blood pressure, antihypertensive medications, hyperlipidaemia, body mass index, smoking and physical activity.

populations.[11,18,19] It remains unclear, however, whether prevention of hypoglycaemia in those without diabetes reverses such risk.

The stronger association between low levels of FPG and mortality in men versus women, which we observed in our study, is intriguing. Little literature could be found regarding FPG and its association with mortality by sex. However, one Asian cohort study showed an association between increased risk of all-cause mortality and low FPG in men only.[20] Although we cannot provide an explanation for such finding, sex differences in CVD and its risk factors are not surprising.

The potential mechanism by which hypoglycaemia is linked to CVD and all-cause mortality remains unclear and is made complicated by its activation of multiple complex pathways.[4,5] For instance, as plasma glucose drops below its designated threshold, the brain promotes the secretion of glucagon and increases the sympathoadrenal response.[4] As a result, epinephrine and norepinephrine are released along with stress hormones such as adrenocorticotrophic hormone (ACTH) and glucocorticoids. Furthermore, hypoglycaemia indirectly influences the release of inflammatory cytokines, which include C-reactive protein, interleukins and endothelin-1, among others. Such activation of systemic inflammation can bring about changes in coagulation and cause endothelial injury.[6,7] Moreover, increased levels of catecholamines induce a hypercoagulable state by activating platelets and the fibrinolytic systems.[8] Catecholamines also directly affect cardiac myocytes and cause them to become calcium overloaded, which can lead to prolongation of the corrected QT (QTc) interval in conjunction with catecholamine-induced hypokalaemia. Furthermore, sympathetic stimulation of the heart directly increases cardiac contractility and heart rate, which in turn increases cardiac demand and risk of cardiac ischaemia.[21,22] These systemic changes increase the risk of cardiovascular events, such as fatal ventricular arrhythmias.[22] Hypoglycaemia also impairs autonomic function by decreasing cardiac vagal baroreflex sensitivity as a result of sympathoadrenal activation.[23] Such physiologic responses can occur in the absences of symptoms commonly experienced during hypoglycaemia. This is especially likely in the setting of recurrent hypoglycaemic episodes, which lead to central nervous system adaptation and hypoglycaemia unawareness. As the brain adapts to recurrent hypoglycaemia, it produces symptoms of hypoglycaemia at even lower plasma glucose concentrations which can further exacerbate episodes of asymptomatic hypoglycaemia, contributing to CVD and mortality.[4]

Our findings suggest that low FPG is a risk factor for CVD and all-cause mortality in nondiabetics. Low FPG should be taken into account along with diabetic range FPG to properly identify individuals at risk of CVD and all-cause mortality. That is to say, a narrower window of FPG may need to be identified to minimize CVD risk and reduce mortality in both the diabetic and nondiabetic populations. Some of the inconsistencies in previous reports regarding the association between CVD mortality and low FPG may be explained by the lack of mortality stratification by sex. Future studies aimed to more clearly identify the mechanism by which hypoglycaemia is associated with increased risk of CVD and all-cause mortality are needed. Furthermore, studies incorporating low FPG in CVD risk-prediction models may help to ascertain the utility of low FPG in identifying individuals at greater risk of coronary artery disease and cardiac arrhythmias. Lastly, studies of low FPG may help to elucidate whether avoidance of hypoglycaemia directly impacts rates of CVD and all-cause mortality.

Limitations in our study include the possibility of residual confounding despite adjusting for potential confounders given the study design. Furthermore, overall health and mortality may have been influenced by changes in participant health behaviours over the long follow-up duration. Also, we did not find an association of hyperglycaemia with CVD mortality in our study, a finding contrary to previous literature; however, it is likely due to lack of power to detect such association as small number of participants ($n=260$) belonged to hyperglycaemic category. Finally, reliance on the National Death Index to identify the cause of death could have led to differential misclassification. The strengths of our study include long duration of follow-up and large sample size from a community-based population. These strengths enabled us to show that low FPG is a strong risk factor for both CVD and all-cause mortality in the nondiabetic population. These findings add to the potential of FPG screening in seemingly healthy individuals to identify those at increased risk of CVD and all-cause mortality.

Declaration of conflicting interests

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Supplemental material

Supplemental material for this article is available online.

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