Association Between Fasting Blood Glucose and All-Cause Mortality in a Rural Chinese Population: 15-Year Follow-Up Cohort Study

Nannan Cheng · Yue Zhang · Jie Yang · Jingyi Li · Lijing Ye · Ziyi Zhou ·

Zhuo Wang · Lishun Liu · Yun Song · Zhibo Yang · Guiping She · Xue Bai ·

Xiao Huang · Xiaoshu Cheng · Genfu Tang · Binyan Wang · Xianhui Qin ·

Pierre Zalloua · Fangrong Yan ⬤ · Xiping Xu

ABSTRACT

Introduction: The worldwide prevalence of diabetes has been increasing for decades; diabetes can lead to serious health problems and even death, but the effects of maintaining low fasting blood glucose (FBG) remain controversial. The purpose of this study was to investigate the relationship between FBG levels and all-cause mortality in a long-term follow-up cohort and to find a relatively safe range of FBG levels.

Methods: This study included 17,902 adults from a community-based cohort study in rural China who were prospectively followed from 2003 to 2018. Generalized estimating equations were used to evaluate the association between FBG and all-cause mortality, adjusting for per-

N. Cheng · Y. Zhang · J. Yang · J. Li · L. Ye ·
F. Yan (✉)
State Key Laboratory of Natural Medicines, Research Center of Biostatistics and Computational Pharmacy, China Pharmaceutical University, Nanjing 210009, China
e-mail: f.r.yan@163.com

Z. Zhou · Z. Wang · L. Liu · Y. Song · X. Xu (✉)
Beijing Advanced Innovation Center for Food Nutrition and Human Health, College of Food Science and Nutritional Engineering, China Agricultural University, Beijing, China
e-mail: xipingxu126@126.com

Z. Yang
Chinese Medicine Hospital of Zhaotong, Zhaotong, Yunnan, China

G. She
The Second Affiliated Hospital of Shaoyang University, Shaoyang, Hunan, China

X. Bai
The Affiliated Traditional Chinese Medicine Hospital of Southwest Medical University, Luzhou, China

X. Huang · X. Cheng
Department of Cardiovascular Medicine, Second Affiliated Hospital of Nanchang University, Nanchang, China

Y. Song · G. Tang · B. Wang
School of Health Administration, Anhui Medical University, Hefei, China

B. Wang
Shenzhen Evergreen Medical Institute, Shenzhen, China

X. Qin · X. Xu
National Clinical Research Study Center for Kidney Disease, the State Key Laboratory for Organ Failure Research; Renal Division, Nanfang Hospital, Southern Medical University, Guangzhou, China

P. Zalloua
School of Medicine, Lebanese American University, Byblos, Lebanon

tinent covariates and auto-correlations among siblings.

Results: A total of 1053 (5.9%) deaths occurred during 15 years of follow-up. There was a significant U-shaped association between all-cause mortality and FBG. Compared with the reference group (FBG of 5.6 – < 6.1 mmol/l), the risk of death among individuals with FBG levels < 5.6 mmol/l significantly increased by 38% (OR 1.34; 95% CI 1.13–1.59), while the risk of death among individuals with FBG ≥ 6.1 mmol/l or participants with a self-reported history of diabetes significantly increased by 51% (OR 1.49; 95% CI 1.20–1.85). Additionally, the U-shaped association remained steady in any stratification of risk factors.

Conclusion: Our study showed a significant U-shaped relationship between FBG levels and risk of all-cause mortality in this rural Chinese population. When FBG was within the range of 5.6 – < 6.1 mmol/l, the risk of all-cause mortality was the lowest.

Keywords: All-cause mortality; Fasting blood glucose; U-shaped relationship

Key Summary Points

This is a large cohort with a population of 17,902 and a long-term (from 2003 to 2018) follow-up.

The study found a relatively safe range of fasting blood glucose (FBG) levels in this rural Chinese population.

A significant U-shaped relationship between FBG levels and risk of all-cause mortality was found in this rural Chinese population.

The American Diabetes Association (ADA) changed the definition of impaired fasting glucose (IFG) from an FBG range of 6.1–6.9 mmol/l to 5.6–6.9 mmol/l, which may not be suitable for this rural Chinese population.

DIGITAL FEATURES

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INTRODUCTION

The total number of deaths worldwide has been increasing for decades; in 1950, there were 43.7 million deaths in the world, while by 2017, that number had increased to 55.9 million [1]. According to the National Bureau of Statistics, China's death rate in 2014 was 7.16% and in 2017 was 7.11% [2]. However, with the increase in total population and the gradual acceleration of aging of the population, the number of deaths in China continues to increase, and the burden of death will likely be greatly aggravated.

With the improvement of people's living standards, diabetes has gradually become one of the most important public health challenges in the twenty-first century. For the past few decades, the global prevalence of diabetes has increased; according to the International Diabetes Federation (IDF) 2019 report, an estimated 463 million people worldwide have diabetes, and by 2045 the number will be 700 million [3, 4]. Many epidemiologic studies have confirmed diabetes mellitus (DM) as a recognized risk factor for all-cause mortality [5, 6]. An article reported that the number of global deaths due to diabetes in 2000 was estimated at 2.9 million, accounting for 5.2% of all deaths [7]. Additionally, of all countries, China has the largest number of people suffering from diabetes [8].

In 1997, the American Diabetes Association (ADA) introduced the concept of impaired fasting glucose (IFG), a type of pre-diabetes defined by a patient's FBG range [9]. Many studies have found that IFG is associated with increased all-cause mortality [10–12]. In 2003, to better identify the individual risks of future DM and reduce its disease burden, the ADA changed the definition of IFG from an FBG range of 6.1–6.9 mmol/l to 5.6–6.9 mmol/l [13].

However, this change has caused much controversy, with some studies suggesting that the new IFG definition is related to increased all-cause mortality [11, 14], while other studies showed no such association [10, 12, 15]. Determining the appropriate cut-points for fasting blood glucose and finding a relatively "safe range" of fasting blood glucose to minimize mortality will help inform the public and clinical actions to prevent deaths caused by hyperglycemia or hypoglycemia. Our study combined the two standards of IFG defined by the ADA; FBG was analyzed as a categorical variable (< 5.6, $5.6 – < 6.1$, and ≥ 6.1 mmol/l).

The purpose of our study was to investigate the relationship between fasting blood glucose levels and all-cause mortality in a Chinese rural population and to identify a relatively 'safe range' for fasting blood glucose levels. Our study is based on a rural Chinese population of low socioeconomic status. The results of the study may provide evidence for rural areas or low-nutrient populations in China.

METHODS

Participants

The study participants were all part of an original cohort of a previously conducted study on osteoporosis, who were enrolled in 2003 in Anqing, Anhui Province, in Eastern China. Anqing is located in the southwest of Anhui Province, with a current population of 6.1 million, 90% of which are rural residents. The livelihoods of most are based on agriculture, and their economic level is relatively backward [16]. All participates were from a family of at least three siblings. Exclusion criteria included chronic infections, renal failure, history of type 1 diabetes mellitus, rickets or other metabolic bone diseases, chronic glucocorticoid use, and thyrotoxicosis. Premenopausal women who were uncertain of their pregnancy status at the time of enrollment were also excluded. All participants provided written informed consent and underwent a questionnaire survey at baseline, administered by professionally trained investigators, that included information on demographic data, lifestyle, and medical history. As part of the baseline study, blood pressure measurements and blood samples were obtained (as detailed below). The data supporting the findings of this study will be available from the corresponding author (Xiping Xu) on request.

The study was approved by the ethics committee of Anhui Medical University (the committee's reference number is 1005 2003-8-11). All procedures followed ethical standards. Written informed consent was obtained from each participant. The research was performed in accordance with the Helsinki Declaration of 1964 and its later amendments and applicable local laws and regulations.

Data were obtained at baseline in 2003, and follow-up visits were conducted in 2014, in 2017, and at the study's conclusion in 2018. The study had a high percentage of follow-up as this rural population remained stable and homogeneous with respect to ethnicity, environmental factors, lifestyle, and dietary habits. The homogeneity and stability of the population are reflected in the fact that this is a population in rural Anqing. Most of them are Han farmers, and their diet, work, and rest are probably consistent. After excluding 335 participants who were missing fasting blood glucose data and family number at baseline, a total of 17,902 participants were included in this analysis (Fig. 1). During the follow-up period, a total of 1053 (5.9%) deaths occurred.
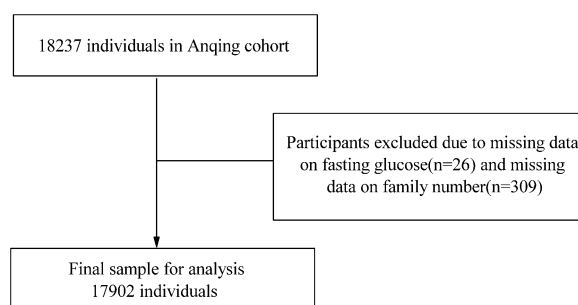
Fig. 1 Flow chart of the participants in the current study

Ascertainment of All-Cause Mortality

The study outcome was all-cause mortality. Data on all-cause mortality were obtained by telephone or through face-to-face interviews with household members.

Laboratory Assessment

At baseline, fasting blood samples were collected and stored in aliquots at $-80\,^{\circ}$C. Serum lipids and fasting blood glucose were measured enzymatically with a Cobas Integra Roche analyzer (Roche, Indianapolis, IN).

Glucose Status Classification

Type 2 diabetes mellitus was defined as either a fasting blood glucose concentration ≥ 7.0 mmol/l (126 mg/dl) or a physician's previous diagnosis of diabetes (other than during pregnancy), based on the American Diabetes Association criterion. In participants who did not have a previous diagnosis of DM, the baseline fasting blood glucose concentrations were divided into the following categories: < 5.6, ≥ 5.6 and < 6.1, and ≥ 6.1 mmol/l (< 100, ≥ 100 and < 110, and ≥ 110 mg/dl).

Statistical Analyses

Means (SD) or medians (25th percentile–75th percentile) and proportions were calculated for population characteristics by sex. Multivariable analyses were performed using generalized estimating equations (GEEs) to evaluate odds ratios (OR) and 95% confidence intervals (CIs) of all-cause mortality risk. GEEs were used to account for autocorrelations among multiple family members. In the multivariate model, we adjusted for age, sex, body mass index (BMI), smoking status, drinking status, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C). In the stratified analysis, lipids were divided into two groups by clinical cut-point, and

interactions were tested through GEE. A two-tailed $P < 0.05$ was considered to be statistically significant in all analyses. Subjects were stratified by sex, age (< 50 vs. ≥ 50 years), BMI (< 24 vs. ≥ 24 kg/m^2), smoking and drinking status (never vs. ever), TG (< 1.7 vs. ≥ 1.7 mmol/l), TC (< 5.2 vs. ≥ 5.2 mmol/l), HDL-C (< 1.04 vs. ≥ 1.04 mmol/l), SBP (< 140 vs. ≥ 140 mmHg), and DBP (< 90 vs. ≥ 90 mmHg) in additional exploratory analyses. EmpowerStats (https://www.empowerstats.com) and R software, version 3.5.1 (https://www.R-project.org/), were used for all statistical analyses.

RESULTS

Study Participants and Baseline Characteristics

Baseline characteristics of the participants according to sex are summarized in Table 1. Male participants were older and had higher blood pressure and HDL-C levels, while female participants tended to be younger and heavier with higher total cholesterol and triglyceride levels. Fasting blood glucose in the female population was significantly higher than in the male population. Within fasting blood glucose strata, age, blood pressure, BMI, TC, TG, and HDL levels were significantly higher as fasting blood glucose levels increased (Supplemental Table 1).

Association between Fasting Blood Glucose and All-Cause Mortality

As shown in Fig. 2, as fasting blood glucose levels increase, the smooth curves show that after adjustment for major covariates, the risk of all-cause mortality first decreases and then increases, showing a significant U-shaped relationship between fasting blood glucose levels and risk of all-cause mortality, with a nadir at around 5.6–6.1 mmol/l. Consistent with the smooth curves, compared with the reference group (FBG of 5.6 – < 6.1 mmol/l), the odds ratios (ORs) and 95% confidence intervals

Table 1 Baseline characteristics of the study participants by sex[a]

Variables	Stratified by sex			P value
	Total	Males	Females	
N	17,902	9054	8848	
Age (years)	45.9 (7.6)	46.9 (7.7)	44.9 (7.4)	< 0.001
SBP, mmHg	121.1 (18.9)	121.7 (18.5)	120.5 (19.2)	< 0.001
DBP, mmHg	77.6 (11.6)	78.6 (11.9)	76.6 (11.3)	< 0.001
BMI, kg/m^2	21.7 (2.9)	21.3 (2.5)	22.1 (3.1)	< 0.001
Laboratory results				
Fasting glucose, mmol/l	5.5 (1.0)	5.4 (1.0)	5.5 (0.9)	0.007
Total cholesterol, mmol/l	4.4 (0.8)	4.4 (0.8)	4.4 (0.9)	< 0.001
Triglycerides, mmol/l	1.3 (0.9)	1.2 (1.0)	1.4 (0.9)	< 0.001
HDL cholesterol, mmol/l	1.4 (0.4)	1.4 (0.4)	1.4 (0.3)	< 0.001
Smoking status, n (%)				< 0.001
Never	10,440 (58.6)	1919 (21.3)	8521 (96.6)	
Former	786 (4.4)	763 (8.5)	23 (0.3)	
Current	6603 (37.0)	6328 (70.2)	275 (3.1)	
Drinking status, n (%)				< 0.001
Never	13,574 (76.2)	4982 (55.3)	8592 (97.5)	
Former	252 (1.4)	226 (2.5)	26 (0.3)	
Current	3999 (22.4)	3803 (42.2)	196 (2.2)	

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HDL* high-density lipoprotein

[a] For continuous variables, values are presented as mean (SD). For categorical variables, values are presented as n (%)

(CIs) for all-cause mortality for group 1 of the fasting blood glucose categories of < 4.75, 4.75 – < 5.6, 6.1 – < 7.0, and ≥ 7.0 mmol/l or DM were 1.31 (1.02–1.69), 1.35 (1.14–1.60), 1.34 (1.06–1.70), and 2.00 (1.45–2.76), respectively. A similar pattern was observed for group 2 when we combined the categories of fasting blood glucose into < 5.6 and ≥ 6.1. Compared with the reference group (FBG of 5.6 – < 6.1 mmol/l), the risk of death among individuals with fasting blood glucose levels < 5.6 mmol/l significantly increased by 34% (OR 1.34; 95% CI 1.13–1.59), while the risk of death among individuals with fasting blood glucose ≥ 6.1 mmol/l or participants who had a self-reported history of

diabetes significantly increased by 49% (OR 1.49; 95% CI 1.20–1.85) (Table 2). Additionally, there was a similar pattern when fasting blood glucose was divided into six equal groups (Supplemental Table 2).

Stratified Analyses on Fasting Blood Glucose and All-Cause Mortality

We further performed stratified analyses to assess the effects of FBG on all-cause mortality in various subgroups (Table 3). None of the following variables, including age, sex, BMI, SBP, DBP, smoking status, drinking status, triglycerides, total cholesterol, and high-density
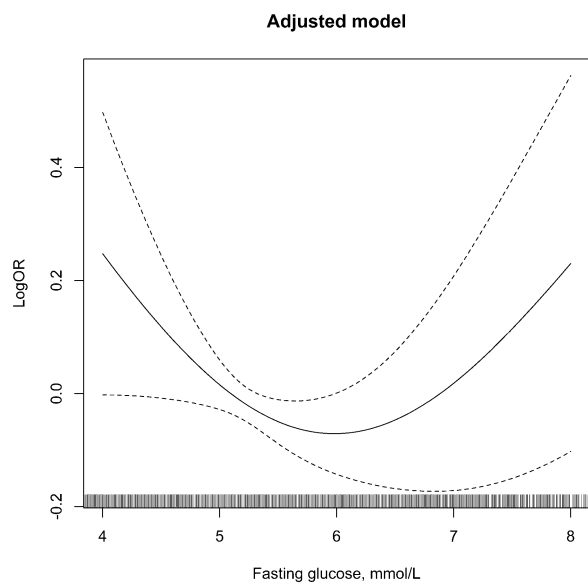
Fig. 2 Association between baseline fasting glucose and risk of all-cause mortality. Model adjusted for age, sex, systolic blood pressure, diastolic blood pressure, body mass index, total cholesterol, triglycerides, HDL cholesterol, and smoking and drinking status

lipoprotein cholesterol, significantly modified the association between fasting blood glucose and all-cause mortality. Compared with the reference group (FBG of 5.6 – < 6.1 mmol/l), the risk of all-cause mortality in the fasting blood glucose categories of < 5.6 mmol/l or ≥ 6.1 mmol/l increased across all stratifications by risk factors, showing a stable U-shaped relationship between fasting blood glucose levels and all-cause mortality.

DISCUSSION

In our study, FBG was analyzed categorically (< 5.6, 5.6 – < 6.1, ≥ 6.1 mmol/l). This study showed a significant U-shaped relationship between fasting blood glucose levels and risk of all-cause mortality in the study population. After adjustment for possible confounding factors, it was found that the risk of all-cause mortality was lowest when fasting blood glucose was in the level of 5.6 – < 6.1 mmol/l, suggesting that a 'safe range' for fasting blood glucose concentrations exists between 5.6

Table 2 Association between fasting glucose and all-cause mortality

Fasting glucose, mmol/l	N	Case (%)	Crude model OR (95%CI)	Adjusted model[a] OR (95%CI)	P value
Group 1[b]					
< 4.75	1987	110 (5.5)	1.11 (0.87–1.42)	1.31 (1.02–1.69)	0.035
4.75– < 5.6	10,093	590 (5.9)	1.17 (0.99–1.40)	1.35 (1.14–1.60)	< 0.001
5.6 – < 6.1	3545	178 (5.0)	Ref.	Ref.	
6.1– < 7.0	1765	120 (6.8)	1.38 (1.09–1.75)	1.34 (1.06–1.70)	0.016
≥ 7.0 or DM	512	55 (10.7)	2.28 (1.66–3.13)	2.00 (1.45–2.76)	< 0.001
Group 2[b]					
< 5.6	12,080	700 (5.8)	1.16 (0.98–1.38)	1.34 (1.13–1.59)	< 0.001
5.6 – < 6.1	3545	178 (5.0)	Ref.	Ref.	
≥ 6.1 or DM	2277	175 (7.7)	1.57 (1.27–1.95)	1.49 (1.20–1.85)	< 0.001

[a] Adjusted for age, sex, systolic blood pressure, diastolic blood pressure, body mass index, total cholesterol, triglycerides, HDL cholesterol, and smoking and drinking status
[b] Group 1: the fasting blood glucose categories of < 4.75, 4.75 – < 5.6, 5.6 – < 6.1, 6.1– < 7.0, and ≥ 7.0 mmol/l or DM; group 2: the fasting blood glucose categories of < 5.6, 5.6 – < 6.1, and ≥ 6.1 mmol/l or DM

Table 3 Association among all-cause mortality and fasting glucose, stratified by risk factors

	FPG < 5.6 mmol/l		FPG 5.6–6.1 mmol/l		FPG ≥ 6.1 mmol/l or DM		P for interaction
	Events (%)	OR (95%CI)	Events (%)	OR (95%CI)	Events (%)	OR (95%CI)	
Sex							0.88
Female	209 (3.6)	1.42 (1.05–1.92)	54 (3.0)	Ref.	60 (5.0)	1.45 (1.00–2.11)	
Male	491 (7.9)	1.31 (1.06–1.61)	124 (7.1)	Ref.	115 (10.7)	1.52 (1.16–1.99)	
Age (years)							0.19
< 50	329 (3.8)	1.61 (1.21–2.15)	56 (2.5)	Ref.	58 (4.3)	1.72 (1.18–2.49)	
≥ 50	371 (10.9)	1.15 (0.93–1.43)	122 (9.3)	Ref.	117 (12.6)	1.38 (1.05–1.81)	
Smoking status							0.74
Never	258 (3.7)	1.29 (1.00–1.67)	77 (3.6)	Ref.	77 (5.5)	1.38 (0.99–1.91)	
Former	58 (11.5)	1.45 (0.80–2.63)	18 (10.0)	Ref.	11 (10.8)	1.09 (0.49–2.42)	
Current	381 (8.2)	1.39 (1.09–1.77)	82 (6.8)	Ref.	85 (11.3)	1.68 (1.23–2.30)	
Drinking status							0.85
Never	465 (5.1)	1.41 (1.14–1.74)	113 (4.2)	Ref.	117 (6.8)	1.50 (1.15–1.96)	
Former	33 (20.9)	1.50 (0.71–3.15)	11 (17.5)	Ref.	7 (22.6)	1.39 (0.47–4.10)	
Current	198 (7.3)	1.17 (0.85–1.60)	53 (6.8)	Ref.	50 (9.9)	1.46 (0.97–2.18)	
Systolic blood pressure, mmHg							0.33
< 140	551 (5.2)	1.33 (1.10–1.62)	128 (4.4)	Ref.	104 (6.1)	1.34 (1.03–1.75)	
≥ 140	148 (9.6)	1.26 (0.89–1.78)	49 (8.1)	Ref.	70 (12.6)	1.73 (1.16–2.59)	
Diastolic blood pressure, mmHg							0.62
< 90	562 (5.3)	1.30 (1.08–1.58)	136 (4.6)	Ref.	123 (6.7)	1.42 (1.10–1.83)	
≥ 90	137 (9.0)	1.39 (0.96–2.02)	42 (7.1)	Ref.	51 (12.0)	1.79 (1.14–2.81)	
Total cholesterol, mmol/l							0.99
< 5.2	593 (5.7)	1.33 (1.10–1.61)	144 (4.9)	Ref.	139 (7.6)	1.51 (1.19–1.93)	
≥ 5.2	107 (6.1)	1.35 (0.89–2.07)	34 (5.5)	Ref.	36 (7.9)	1.40 (0.84–2.33)	
Triglycerides, mmol/l							0.56
< 1.7	599 (5.9)	1.41 (1.17–1.70)	141 (4.8)	Ref.	134 (7.8)	1.52 (1.19–1.94)	
≥ 1.7	101 (5.3)	1.12 (0.75–1.67)	37 (5.9)	Ref.	41 (7.5)	1.36 (0.85–2.18)	
High density lipoprotein, mmol/l							0.32
< 1.04	125 (6.1)	1.88 (1.11–3.18)	17 (3.8)	Ref.	24 (7.8)	1.81 (0.93–3.51)	
≥ 1.04	575 (5.7)	1.26 (1.05–1.52)	161 (5.2)	Ref.	151 (7.7)	1.45 (1.15–1.83)	
Body mass index, kg/m^2							0.83
< 24	609 (6.1)	1.33 (1.10–1.59)	152 (5.4)	Ref.	144 (8.2)	1.48 (1.17–1.88)	
≥ 24	90 (4.3)	1.41 (0.91–2.33)	25 (3.5)	Ref.	29 (5.7)	1.57 (0.90–2.75)	

Adjusted, if not stratified, for age, sex, systolic blood pressure, diastolic blood pressure, body mass index, total cholesterol, triglycerides, HDL cholesterol, and smoking and drinking status

and < 6.1 mmol/l. Compared with the reference group (FBG of 5.6 – < 6.1 mmol/l), the risk of death significantly increased in the groups with fasting blood glucose < 5.6 mmol/l or equal to or above 6.1 mmol/l.

The worldwide prevalence of diabetes has been increasing for decades; diabetes can lead to serious health problems and even death [3–8]. Both hypoglycemia and hyperglycemia are significantly associated with adverse outcomes [17]. However, controversy regarding the association between fasting blood glucose and all-cause mortality still exists. A prospective study of a Korean population found a J-shaped association between fasting blood glucose levels and all-cause mortality, with a nadir at around 80–94 mg/dl (4.4–5.2 mmol/l) in both men and women; both low and high fasting blood

glucose concentrations were associated with a higher risk of mortality [18]. Wändell et al. also found a similar J-shaped curve relationship between fasting glucose levels and all-cause mortality [19]. However, a study including a stratified sample of participants ($n = 17,287$) from the Women's Health Initiative (WHI) showed that a fasting blood glucose level > 100 mg/ml increased the risk for cardiovascular disease and all-cause mortality. The study found no significant association with low fasting glucose (HR 0.97; 95% CI 0.79–1.20) [20].

Yanhong Li et al. found a U-shaped relationship between early blood glucose concentrations and PICU mortality. When the blood glucose concentration is 110–140 mg/dl (6.1–7.8 mmol/l), the risk of all-cause mortality is the lowest [17]. The People's Republic of China-USA (PRC-USA) collaborative study also found a significant U-shaped relationship between fasting blood glucose levels and all-cause mortality, and the result of the study showed that both low (< 80 mg/dl) and high ($\geq$ 126 mg/dl) fasting blood glucose levels were significantly associated with increased risk of all-cause and cardiovascular disease mortality in the Chinese general population[21].

Our results showed that fasting blood glucose levels in this population had a significant U-shaped relationship with mortality risk and that this relationship was not affected by other risk factors; both higher and lower fasting blood glucose levels were significantly associated with increased risk of all-cause mortality, which is consistent with the results of some studies [17–19, 21]. The mechanism for the association between high fasting blood glucose levels and risk of all-cause mortality is very clear; high fasting blood glucose causes complications such as CVD and chronic kidney disease, both of which increase the risk of death [21]. While the mechanism for the relationship between low fasting blood glucose and risk of all-cause mortality is not that clear, studies have shown that hypoglycemia may be associated with low energy consumption, resulting in poor health and increased bodily susceptibility to diseases, thus increasing the risk of death [22]. Additionally, other studies have suggested that the relationship between low levels of fasting blood

glucose and all-cause mortality risk may be explained by brain damage during hypoglycemia [23]. Our study is based on a rural Chinese population, of low socioeconomic status. It may be that inadequate intake of nutrients in this population leads to an increased risk of death from malnutrition. This study provides a relatively safe fasting blood glucose range (5.6 – < 6.1 mmol/l) for the regional population in rural China, but this relatively safe fasting blood glucose range is higher than in previous studies, probably because our population generally has a low BMI, which may be caused by malnutrition. Therefore, more trials are needed to verify the results.

However, there are still several limitations to this study. First, we did not have information on specific causes of mortality. In addition, recall bias could exist. Because we conducted household or telephone interviews at follow-up visits, we failed to collect the time of death in time, resulting in the inability to use the Cox model to better predict the correlation between blood glucose and all-cause mortality. Second, we did not obtain information on patient medication usage for diabetes and/or a time variable to better predict the association between fasting blood glucose and all-cause mortality. Third, during the follow-up, we did not have complete fasting blood glucose measurements for each participant. Therefore, we could not assess the association between mean fasting blood glucose and all-cause mortality risk during follow-up. Finally, although this cohort study was designed to explore the association between fasting blood glucose and all-cause mortality, all study participants were from rural areas in Anhui Province; therefore, the findings of this study cannot be extended to a wider population.

CONCLUSION

This study showed a significant U-shaped relationship between fasting blood glucose levels and risk of all-cause mortality in a rural Chinese population. Both low and high fasting blood glucose concentrations were associated with higher mortality in this study population.

When fasting blood glucose was at the level of 5.6 – < 6.1 mmol/l, the risk of mortality was lowest, and when blood glucose was < 5.6 mmol/l or ≥ 6.1 mmol/l, the risk of death increased significantly. Controlled fasting blood glucose levels within the 5.6 – < 6.1 mmol/l range appear to be relatively safe.

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Compliance with Ethics Guidelines. The study was approved by the ethics committee of Anhui Medical University (The committee's reference number is 1005 2003–8-11). All procedures followed ethical standards. Written informed consent was obtained from each participant. The research was performed in accordance with the Helsinki Declaration of 1964 and its later amendments and applicable local laws and regulations.

Data Availability. Data described in the manuscript, code book, and analytic code will be made available from the corresponding authors on request, after the request has been submitted and formally reviewed and approved by the Ethics Committee of the Institute of Biomedicine, Anhui Medical University, Hefei, China.

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