Longitudinal Change in Fasting Blood Glucose and Myocardial Infarction Risk in a Population Without Diabetes

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OBJECTIVE

To examine the change in fasting blood glucose (FBG) during repeated assessments over time and its potential impact on the risk of developing myocardial infarction (MI).

RESEARCH DESIGN AND METHODS

This prospective cohort study included 68,297 participants without diabetes (mean age 49 years) who were free of MI, stroke, and cancer prior to or in 2010 (baseline of the current analysis). FBG concentrations were measured in 2006, 2008, and 2010. The FBG trajectories during 2006–2010, the primary exposure of the current study, were identified by latent mixture modeling. Incident MI cases were confirmed via review of medical records by cardiologists.

RESULTS

We identified five discrete FBG trajectories according to FBG range and changing pattern over time: elevated-stable (*n* = 3,877), elevated-decreasing (*n* = 7,060), moderate-increasing (*n* = 10,298), moderate-stable (*n* = 40,352), and low-stable (*n* = 6,710). During 4 years of follow-up, we documented 283 incident MI cases. Relative to the moderate-stable pattern (FBG ranged from 4.9 to 5.1 mmol/L), adjusted hazard ratios (HRs) were 1.53 (95% CI 1.04, 2.26) for the elevated-stable pattern (FBG ranged from 6.1 to 6.3 mmol/L) and HR 0.61 (95% CI 0.38, 0.98) for the elevated-decreasing pattern (FBG decreased from 6.0 to 5.4 mmol/L), after adjustment for potential confounders such as age, sex, lifestyle factors, obesity, medical history, blood pressure, blood lipids, and C-reactive protein. Consistently, cumulative average and increasing rate of FBG during 2006–2010, but not a single baseline FBG, predicted future risk of MI.

CONCLUSIONS

We found that discrete FBG trajectories were significantly associated with subsequent risk of MI in individuals without diabetes. These observations suggest that long-term trajectories of FBG may be important for risk prediction of MI and possibly other macrovascular diseases.

Diabetes is a major risk factor for atherosclerosis, coronary heart disease (CHD), and premature death (1–3). It has been thought that the risk of developing myocardial infarction (MI) might already be present at glucose concentrations below the current cutoff for diabetes. Some (4–7) but not all studies (8,9) showed that higher fasting blood glucose (FBG) concentrations were associated with higher CHD risk in individuals

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without diabetes. It is worth noting that the majority of published studies (2–5) on this topic were based on a single measure of FBG, failing to take into account the potential effect of change in FBG concentrations over time. Not accounting for time-varying and cumulative average of FBG over time could bias the true relation between FBG and MI risk toward the null hypothesis. Further, although MI presents suddenly, the advanced extensive complex intramural lesions that lead to plaque rupture develop over decades. Thus, prospective studies that evaluate the effects of long-term FBG trajectory patterns on MI are essential.

Therefore, the aims of this study were to identify subgroups of individuals with similar trajectories and to compare the MI risk among participants who experienced a stably high level of FBG or a fast increase in FBG with those who maintained an ideal and stable FBG level. We prospectively examined the potential impact of FBG trajectories, based on repeated longitudinal assessments of FBG over 4 years, on the risk of developing MI in over 68,000 adults without diabetes. In secondary analyses, we also examined whether a single measure of FBG at baseline and cumulative average, annual increasing rate, and variability of FBG concentrations in the preceding 4 years were associated with future risk of MI.

RESEARCH DESIGN AND METHODS

Study Design and Population

The Kailuan study is a prospective cohort study designed to investigate the risk factors for common noncommunicable diseases (10–13). In brief, all 155,418 active and retired employees aged 18 years or older of the Kailuan Group, Tangshan, China, were invited to participate in 2006. A total of 101,510 participants (81,110 men and 20,400 women, aged 18–98 years) agreed to participate and completed the first survey from June 2006 to October 2007 (referred to as the 2006 survey here). There were no significant demographic differences between those who agreed to participate in the study and those who declined to join except for a variation in sex distribution (79.9% of participants were men, whereas 85.9% of all Kailuan Group employees were men). All participants underwent questionnaire assessments, physical examinations, and laboratory tests in the 11 hospitals responsible for the health care of the Kailuan community. These participants were followed biennially to update their status on the aforementioned parameters.

In the current study, we identified glucose trajectory patterns using FBG concentrations in 2006, 2008, and 2010 and used the patterns to predict incident MI after 2010 (baseline of the current study, flowchart shown in Supplementary Fig. 1). We excluded 1,239 participants who did not have 2006 FBG data and 14,755 participants without 2008 and 2010 FBG data. Those participants who were excluded from the current analyses due to missing FBG data were older (58.4 vs. 50.7 years, $P < 0.001$) and more likely to be men (88.6 vs. 78.5%, $P < 0.001$) but had similar future MI risk (age- and sex-adjusted hazard ratio (HR) 1.12 [95% CI 0.98, 1.30]), relative to those with completed FBG data. We further excluded 12,993 participants with diabetes (defined as a self-reported physician-diagnosis history, currently treated with insulin or oral hypoglycemic agents, or an FBG concentration $\geq$7.0 mmol/L); 3,621 participants with MI, stroke, or cancer in or prior to 2010; and 605 participants who died during 2006 to 2010. The trajectories of FBG data and their association with future MI risk were examined among the remaining 68,297 participants.

This investigation was in accordance with the guidelines of the Declaration of Helsinki and was approved by the ethics committees of the Kailuan Medical Group, Kailuan Group, and the Brigham and Women's Hospital, Boston. All the participants gave their written informed consent.

Assessment of Incident MI

The outcome was the first occurrence of MI, either the first nonfatal MI event or MI death without past history of MI. To retrieve potential MI cases, the survey participants were linked to the Municipal Social Insurance Institution and all 11 Kailuan hospitals' discharge registers, which covered all the Kailuan Group employees (i.e., all the Kailuan study participants). We used ICD-10 for the identification of potential MI (I21) (14). Additionally, information regarding past medical history of MI was collected by questionnaire biennially after 2006. A panel of three cardiologists reviewed the medical records of potential MI case subjects identified by the ICD code and/or questionnaire. MI was defined based on cardiac enzymes (i.e., levels of creatine kinase and troponin T or I), symptoms, electrocardiographic signs, and necropsy (15). Fatal MI, including sudden cardiac death due to cardiac arrest, was confirmed by hospital records or death certificates listing CHD or MI as the main cause of death.

Assessment of FBG

Fasting blood samples were collected in the morning after an 8- to 12-h overnight fast and transfused into vacuum tubes containing EDTA. Plasma was separated from blood immediately and stored at 4°C. Blood glucose concentration was measured 4 h after blood sample collection. An automatic analyzer (Hitachi 747; Hitachi, Tokyo, Japan) was used to measure FBG with the hexokinase/glucose-6-phosphate dehydrogenase method in 2006, 2008, and 2010 (16). The coefficient of variation using blind quality control specimens was <2.0%.

The FBG trajectories during 2006 to 2010 were the primary exposure of the current study. As secondary exposures, we examined a single measure of glucose in 2010 and cumulative average glucose (average of all available FBG concentrations during the 4-year period). We grouped participants into four categories of cumulative FBG concentrations or FBG in 2010, separately, which were based on current definitions of hypoglycemia (<4.0 mmol/L [17]), normal FBG (4.0–5.6 mmol/L [18]), and impaired fasting glucose (IFG) ($\geq$5.6 mmol/L [18] or $\geq$6.1 mmol/L [19]). We also used the annual glucose increase rate (the slope of the simple linear regression model in which FBG concentration in 2006, 2008, and 2010 was the response variable and follow-up duration [years] was the independent variable) and glucose variability (as assessed by standard division) during 2006 to 2010.

Assessment of Covariates

Information on potential covariates was collected in 2006 and updated every 2 years thereafter, as detailed elsewhere (11,12,16,20). In brief, information on age, sex, smoking, alcohol intake, salt intake, physical activity, average monthly income, education level, and past self-reported medical history (e.g., hypertension, diabetes, and active treatment such as hypoglycemic agents, antihypertensive agents, lipid-lowering agents, and aspirin) was collected via questionnaire. Assessment of alcohol intake was

determined as follows: light drinker, 0.1–0.4 servings/day for women and 0.1–0.9 servings/day for men; moderate drinker, 0.5–1.5 servings/day for women and 1–2 serving/day for men; heavy drinker, >1.5 servings/day for women and >2 serving/day for men; based on 15 g of alcohol per day. Height, weight, and blood pressure were measured by trained field workers (i.e., nurses) during the surveys. BMI was calculated as weight in kilograms divided by height in meters squared. Total cholesterol, triglycerides, HDL cholesterol (HDL-c), LDL cholesterol (LDL-c), creatinine, and hs-CRP were assessed by auto analyzer (Hitachi 747; Hitachi, Tokyo, Japan) at the central laboratory of Kailuan hospital. Estimated glomerular filtration rate (eGFR) was calculated by the Chronic Kidney Disease Epidemiology Collaboration creatinine equation (21).

Statistical Analysis

All analyses were conducted using SAS version 9.3 (SAS Institute, Inc., Cary, NC). The person-time of follow-up for each participant was determined from the date when the message was collected in the 2010 survey to either the date of MI onset, death, loss to follow-up, or end of follow-up (31 December 2014), whichever came first. There were 2,439 (3.57%) participants who became lost to follow-up because of migrations or other reasons. We still included them in the analyses because they contributed person-time.

The FBG trajectories during 2006 to 2010 were identified by latent mixture modeling within the Proc Traj procedure (22,23). We used a censored normal model appropriate for continuous outcomes. Model fit was assessed using the Bayesian information criterion (BIC). We initiated a model with five trajectories and then compared the BIC to that with four, three, two, and one, respectively. The model with five patterns was identified as the best fit. We then compared the model with different functional forms. Cubic, quadratic, and linear terms were considered and evaluated based on their significance level, starting with the highest polynomial. In our final model, we had one pattern with a linear order term and four patterns with up to quadratic order terms. Cox proportional hazards model was used to investigate the association between exposures (e.g., the FBG trajectories and average FBG during 2006 to 2010) and risk of developing MI.

According to Schoenfeld residuals and log-log inspection, our models met the proportional assumption criteria. Results were adjusted for potential confounders, including age, sex, smoking, alcohol intake, education, physical activity, salt intake, income, updated use of antihypertensive and lipid-lowering agents and aspirin, average BMI, systolic blood pressure, diastolic blood pressure, eGFR, and average serum concentrations of triglycerides, HDL-c, LDL-c, and hs-CRP during 2006 to 2010. Missing data of these covariates were coded as an extra category. The moderate-stable pattern with the most participants (59.1%) was set as reference group to reach a stable model.

In a secondary analysis, we included only nonfatal MI as outcome by excluding 13 fatal MI cases. To examine whether the potential association between FBG trajectories and MI risk was due to a single measure of FBG during 2006 to 2010, we further adjusted for FBG concentrations in 2006 or 2010, one at a time. To explore whether the FBG–MI relation was explained by weight change, we conducted an analysis by adjusting for baseline BMI and annual weight change from 2006 to 2010 in the models. Likelihood ratio tests were conducted to examine statistical interactions between FBG trajectories and sex, age (<60 vs. ≥60 years), hypertension (yes vs. no), and BMI (<25 vs. ≥25 kg/m^2) in relation to MI risk, by comparing −2 log likelihood χ^2 between nested models with and without the cross-product terms.

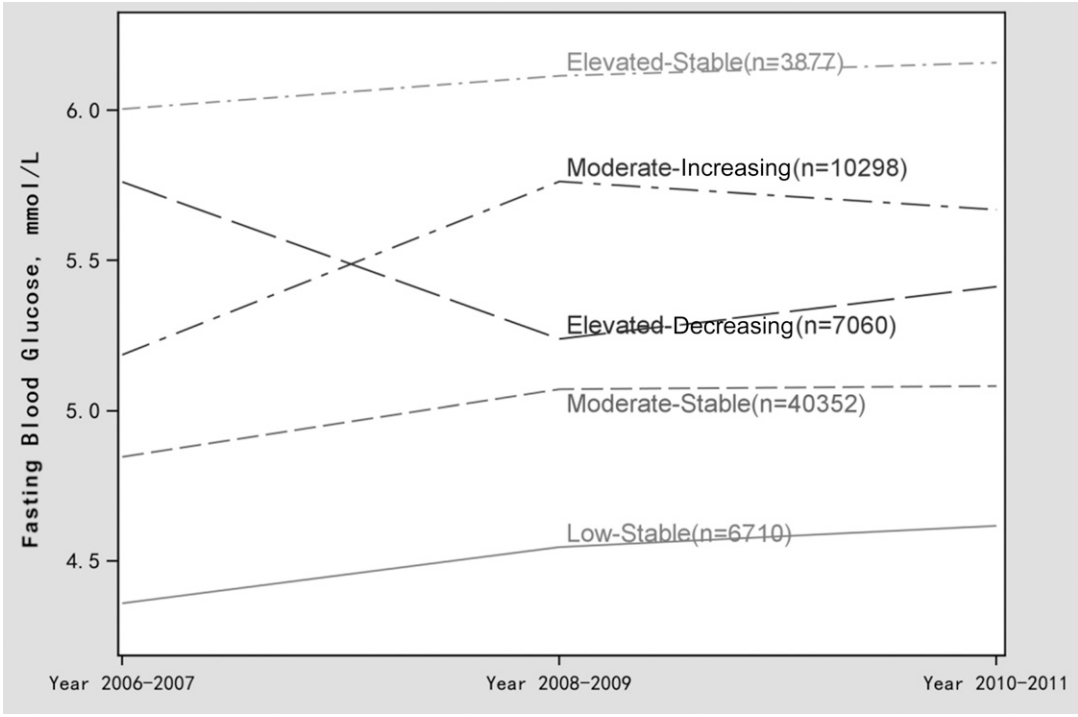

Figure 1—Trajectory of FBG during 2006–2010.

For more detailed analyses of the association between average FBG during 2006 to 2010 and subsequent MI risk, we also used restricted quadratic spline models (24) with 5 knots defined at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles of the FBG. To examine whether the potential association between high FBG and increased risk of MI was due to the higher likelihood of evolution to diabetes, we conducted a sensitivity analysis by excluding individuals who progressed to diabetes during 2010 to 2014. Because approximately one-third of the study participants worked underground in the coal mines, we conducted a sensitivity analysis after excluding these participants. Because some participants might develop other ischemic heart diseases during the follow-up, we also conducted a sensitivity analysis excluding the participants who self-reported use of aspirin and/or statins, which are routinely prescribed for all of these patients. Two-sided $P < 0.05$ was considered statistically significant in the current study.

RESULTS

We categorized the study population based on five observed discrete trajectories of FBG during 2006 to 2010 based on the FBG concentrations and changing patterns (Fig. 1): 5.7% (n = 3,877) of participants who consistently had elevated FBG concentrations (mean FBG concentrations ranged from 6.11 to 6.25 mmol/L during 2006 to 2010, referred to as "elevated-stable pattern"); 10.3% (n = 7,060) of participants who started with elevated concentrations and experienced a decrease (mean FBG concentrations decreased from 6.00 mmol/L in 2006 to 5.43 mmol/L in 2010, referred to as "elevated-decreasing pattern"); 15.1% (n = 10,298) of participants who started with moderate concentrations and experienced an increase (mean FBG concentrations increased from 5.20 mmol/L in 2006 to 5.80 mmol/L in 2010, referred to as "moderate-increasing pattern"), 59.1% (n = 40,352) of participants who maintained moderate FBG concentrations (mean FBG concentrations ranged from 4.85 to 5.08 mmol/L, referred to as "moderate-stable pattern"); and 9.8% (n = 6,710) of participants who maintained low FBG concentrations (mean FBG concentrations ranged from 4.20 to 4.47 mmol/L during 2006 to 2010, referred to as "low-stable pattern"). Individuals in the elevated-stable pattern were more likely to be men, have lower education, drink alcoholic beverages, use antihypertensive medications, and have concurrent cardiovascular risk factors (Table 1).

After a median follow-up of 3.9 years, we identified 283 incident MI cases. The elevated-stable FBG pattern experienced the highest future risk of developing MI among all five FBG patterns (Table 2). Relative to the moderate-stable pattern, adjusted HRs were 1.53 (95% CI 1.04, 2.26) for the elevated-stable pattern, 0.61 (95% CI 0.38, 0.98) for the elevated-decreasing pattern, 1.01 (95% CI 0.73, 1.38) for the moderate-increasing pattern, and 0.87 (95% CI 0.55, 1.37) for the low-stable pattern, after adjustment for potential confounders. Similar results were observed when we restricted to nonfatal MI cases. Further adjustment for the FBG in the 2006 or 2010 survey, for baseline BMI and weight change during 2006 to 2010, excluding participants who developed diabetes during 2010 to 2014, excluding coal-mine workers, or excluding participants who used aspirin or statins did not materially change the results (Table 2). We did not observe significant interactions between the FBG trajectories and sex, age, hypertension, and BMI in relation to MI risk (Supplementary Table 1) (P-interaction >0.2 for all).

Table 1—Basic characteristics according to the FBG trajectory patterns during 2006 to 2010 among 68,297 Kailuan participants

	Low-stable	Moderate-stable	Moderate-increasing	Elevated-decreasing	Elevated-stable
n (%)	6,710 (9.8)	40,352 (59.1)	10,298 (15.1)	7,060 (10.3)	3,877 (5.7)
Age, years	48.6	48.6	51.2	49.0	52.3
Women, %	33.2	24.7	17.2	15.8	13.1
Never smoker, %	61.0	60.7	55.3	54.5	51.5
Never alcohol intake, %	60.1	58.4	51.5	51.2	47.6
Physical activity ≥3 times/week, %	14.1	13.2	15.1	14.7	15.9
Salt intake ≥10 g/day, %	8.9	9.7	11.6	10.9	13.3
College/university, %	10.3	8.5	5.2	7.5	5.0
Average income ≥¥3,000/month, %	7.3	6.7	5.9	6.5	6.1
Use of antihypertensive agent, %	11.7	13.0	18.3	16.5	20.8
Use of lipid-lowering agents, %	1.18	1.29	1.75	1.81	1.75
Use of aspirin, %	0.76	0.60	0.77	0.64	0.64
BMI, kg/m^2†	23.9	24.7	25.4	25.1	25.7
hs-CRP, mg/mL†‡	1.22	1.01	1.11	1.04	1.18
TC, mmol/L†	4.75	4.89	5.10	5.01	5.24
TG, mmol/L†	1.33	1.53	1.75	1.71	1.92
HDL-c, mmol/L†	1.56	1.53	1.55	1.53	1.54
LDL-c, mmol/L†	2.27	2.48	2.60	2.63	2.71
SBP, mmHg†	124	127	131	131	135
DBP, mmHg†	80	82	84	84	86
eGFR, mL/min/1.73 m^2†	87.2	85.4	85.9	86.8	86.5

†Average concentrations based on measurements in 2006, 2008, and 2010. ‡Geometric mean. DBP, diastolic blood pressure; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

Consistently, we observed that higher average FBG concentrations during 2006 to 2010 were significantly associated with risk of developing MI, relative to FBG of 4.0–5.6 mmol/L (Table 3). In the restricted quadratic spline models, we observed a J-shaped relation between FBG concentrations and MI risk. When FBG concentrations were >5.7 mmol/L, the risk of MI increased sharply with an increase in FBG concentrations (Supplementary Fig. 2). In contrast, a single FBG measurement in 2010 failed to predict future MI risk. Annual increment but not variability of FBG over 4 years was significantly associated with MI risk.

CONCLUSIONS

In this prospective study of ~68,000 adults without diabetes, we observed heterogeneous FBG trajectories over a 4-year span. Individuals in the elevated-stable pattern, as compared with those in the stable and low FBG patterns, had a higher risk for MI during 4 years of follow-up, even after adjustment for a single FBG measurement. Consistently higher cumulative average glucose concentrations over 4 years were also associated with higher subsequent MI risk. These findings have important public health value as they link glucose homeostasis in individuals without diabetes with macrovascular disease and major cardiovascular complications. The strength of our analyses lies in our large population-based cohort and repeated assessment of FBG. We also adjusted for cumulative average BMI, blood pressure, lipid profiles, and hs-CRP concentrations based on three assessments of these biomarkers over 4 years, as well as other cardiovascular risk factors, which may reduce unmeasured residual confounding greatly.

The present analyses showed that participants with stable and high FBG concentrations, which fall in the range of IFG (25), had a higher risk of developing MI relative to their counterparts with lower FBG. Previous studies, which were generally based on a single FBG assessment, generated inconsistent results regarding the association between IFG and MI risk. For example, a prospective study that included more than 1 million Koreans demonstrated that fasting glucose levels of 6.1–6.9 mmol/L were significantly associated with increased risk of MI in men and women, after adjustment for age,

Table 2—Adjusted HRs and 95% CIs for risk of MI according to the FBG trajectory patterns during 2006 to 2010 among 68,297 Kailuan participants

	Low-stable	Moderate-stable	Moderate-increasing	Elevated-decreasing	Elevated-stable
Cases, *n* (person-years)	22 (25,318)	159 (152,454)	51 (38,196)	19 (26,189)	32 (13,966)
Incidence rate, per 1,000 person-years	0.87	1.04	1.34	0.73	2.29
Age- and sex-adjusted	0.84 (0.53, 1.31)	1.00	1.11 (0.81, 1.52)	0.67 (0.42, 1.08)	1.79 (1.23, 2.62)
Multivariate model 1	0.80 (0.51, 1.25)	1.00	1.13 (0.82, 1.54)	0.68 (0.42, 1.09)	1.87 (1.28, 2.74)
Multivariate model 2	0.87 (0.55, 1.37)	1.00	1.01 (0.73, 1.38)	0.61 (0.38, 0.98)	1.53 (1.04, 2.26)
Nonfatal MI*	0.90 (0.57, 1.41)	1.00	0.91 (0.65, 1.28)	0.60 (0.36, 0.97)	1.52 (1.03, 2.26)
Sensitivity analysis					
Further adjustment for FBG in 2006*	0.84 (0.52, 1.36)	1.00	1.08 (0.77, 1.51)	0.94 (0.46, 1.92)	2.31 (1.23, 4.37)
Further adjustment for FBG in 2010*	0.86 (0.52, 1.42)	1.00	0.99 (0.67, 1.46)	0.59 (0.36, 0.97)	1.57 (0.94, 2.64)
Adjustment for baseline BMI and annual weight change from 2006 to 2010*†	0.87 (0.55, 1.36)	1.00	1.00 (0.73, 1.37)	0.61 (0.38, 0.99)	1.54 (1.04, 2.26)
Excluding participants who developed diabetes during follow-up*	0.86 (0.55, 1.35)	1.00	1.07 (0.78, 1.47)	0.60 (0.37, 0.98)	1.49 (0.98, 2.28)
Excluding 20,751 coal-mine workers*	0.78 (0.44, 1.37)	1.00	1.18 (0.81, 1.72)	0.50 (0.26, 0.95)	1.62 (1.02, 2.60)
Excluding participants who used aspirin and/or statins*	0.83 (0.52, 1.34)	1.00	0.98 (0.71, 1.36)	0.63 (0.39, 1.02)	1.52 (1.03, 2.25)

Data are HR (95% CI) unless otherwise noted. Model 1 adjusted for age (years), sex, smoking (current, past, or never), alcohol intake (never, past, light, moderate, or heavy), education (illiteracy or elementary school, middle school, or college/university), physical activity (never, sometimes, or active), average monthly income of each family member (<500, 500–3,000, or ≥¥3,000), and salt intake (≥10, 6–10, or <6 g/day). Model 2 included variables in model 1 and further adjusted for updated use of antihypertensive and lipid-lowering agents and aspirin (yes/no for each), average BMI (≥30, 25–29.9, or <25 kg/m^2), systolic blood pressure (quintile), diastolic blood pressure (quintile), eGFR (quintile), average serum concentrations of triglycerides (quintile), HDL-c (quintile), LDL-c (quintile), and hs-CRP (<1, 1–3, or ≥3 mg/mL) during 2006 to 2010. *Adjusted for factors in model 2. †Adjusted for 2006 BMI (≥30, 25–29.9, or <25 kg/m^2), annual weight gain from 2006 to 2010 (kg/year), and all variables in model except for the average BMI.

Table 3—Adjusted HRs and 95% CIs for risk of MI, according to FBG concentrations in 2010 and cumulative average, annual increase rate, and variability of FBG from 2006 to 2010

	FBG concentrations				*P*-trend*
	FBG in 2010				
Range, mmol/L	<4.00	4.00 to 5.60	5.60 to 6.10	>6.10	
Cases, *n* (person-years)	2 (3,088)	184 (185,661)	62 (45,973)	35 (21,402)	
Incidence rate, per 1,000 person-years	0.65	0.99	1.35	1.64	
HR (95% CI)†	0.60 (0.15, 2.46)	1.00	1.18 (0.88, 1.57)	1.23 (0.85, 1.77)	0.12
	Average FBG during 2006 to 2010				
Range, mmol/L	<4.00	4.00 to 5.60	5.60 to 6.10	>6.10	
Cases, *n* (person-years)	1 (1,357)	222 (210,239)	36 (35,821)	24 (8,706)	
Incidence rate, per 1,000 person-years	0.74	1.06	1.00	2.76	
HR (95% CI)†	0.57 (0.08, 4.11)	1.00	0.76 (0.53, 1.08)	1.76 (1.15, 2.71)	0.14
	Annual increasing rate of FBG during 2006 to 2010				
Range, mmol/L per year	<−0.10	−0.10 to −0.01	0.00 to 0.10	>0.10	
Cases, *n* (person-years)	58 (70,304)	20 (23,451)	37 (28,751)	168 (133,617)	
Incidence rate, per 1,000 person-years	0.82	0.85	1.29	1.26	
HR (95% CI)†	1.00	1.12 (0.67, 1.87)	1.64 (1.08, 2.47)	1.38 (1.02, 1.87)	0.04
	Standard deviation of FBG during 2006 to 2010				
Range, mmol/L	Quartile 1 (<0.23)	Quartile 2 (0.23 to 0.39)	Quartile 3 (0.40 to 0.60)	Quartile 4 (>0.60)	
Cases, *n* (person-years)	77 (62,829)	74 (64,635)	59 (64,620)	73 (64,039)	
Incidence rate, per 1,000 person-years	1.23	1.14	0.91	1.14	
HR (95% CI)†	1.00	0.93 (0.67, 1.28)	0.68 (0.48, 0.96)	0.77 (0.55, 1.06)	0.06

*For tests of trend, the median value in each category was used as a continuous variable. †Model adjusted for age (years), sex, smoking (current, past, or never), alcohol intake (never, past, light, moderate, or heavy), education (illiteracy or elementary school, middle school, or college/university), physical activity (never, sometimes, or active), average monthly income of each family member (<500, 500–3,000, or ≥¥3,000), salt intake (≥10, 6–10, or <6 g/day), updated use of antihypertensive and lipid-lowering agents and aspirin (yes/no for each), average BMI (≥30, 25–29.9, or <25 kg/m^2), systolic blood pressure (quintile), diastolic blood pressure (quintile), eGFR (quintile), average serum concentrations of triglycerides (quintile), HDL-c (quintile), LDL-c (quintile), and hs-CRP (<1, 1–3, or ≥3 mg/mL) during 2006 to 2010.

smoking, exercise, BMI, alcohol intake, and hypertension (26). However, another large study including 652,901 Koreans reported a nonsignificant relation regarding IFG and MI risk after adjustment for CHD risk factors, including hypertension, total cholesterol, and BMI (27). Of note, in these studies, MI events were documented from medical claims data and death report data without verification, which could introduce misclassification. In the Framingham Heart Study (FHS) (*n* = 4,138), IFG was significantly associated with a higher risk of cardiovascular disease in women but not in men during 4 years of follow-up (4). To our knowledge, no prior studies have examined the potential impacts of glucose trajectories on MI risk. Because of regression dilution, studies based on a single measure of glucose at baseline could underestimate the true association between IFG and MI risk (28). This notion is further supported by the observations that high cumulative average FBG, but not a single baseline assessment, significantly predicted future MI risk in the current analyses.

A previous study (*n* = 1,428) suggested that the risk for developing cardiovascular disease was confined to individuals with IFG who subsequently developed diabetes (8). In contrast, we observed that those with the elevated-stable pattern who had fasting glucose levels within the range of IFG had the greatest risk of MI even after we excluded those who developed diabetes during the follow-up, suggesting that the observed association might not be totally explained by the development of diabetes.

Substantial evidence supports the biological plausibility of our finding (29). First, insulin resistance in the prediabetes stage could promote atherogenesis and likely contributes to the elevated risk of cardiovascular disease (30). Second, IFG is associated with some preclinical pathological changes of MI, such as arterial stiffness, arterial endothelial dysfunction, and intima-media thickening (31,32). Furthermore, individuals with prediabetes usually have some coexisting MI risk factors (e.g., dyslipidemia, hypertension, obesity, physical inactivity, procoagulant state, and inflammation) (33,34). Consistently, we also observed that the elevated-stable pattern has higher prevalence of these risk factors relative to other patterns. Additional adjustment for these conventional cardiovascular risk factors, however, did not change the significant results.

We found that for participants with average FBG concentrations of 5.7 mmol/L or higher, risk of MI increased with an increase in FBG concentrations. We also observed that decrease in FBG over time was associated with a subsequently reduced risk of MI. These findings suggest that regularly monitoring FBG among individuals with a glucose level in the range of IFG (5.6–6.9 mmol/L) is of significance for public health and clinical practice because these individuals are generally not

treated, although they may experience high future MI risk. This is particularly important given that lifestyle intervention could effectively lower glucose concentrations (35,36).

Our study has several limitations. Oral glucose tolerance testing, casual random glucose, and HbA_{1c} concentrations were not available in the Kailuan study, and some diabetes cases could be thus undiagnosed. However, we identified diabetes cases based on multiple measures of fasting glucose concentrations and self-report physician diagnosis, and the impact of underdiagnoses of diabetes on the observed association between FBG trajectory and MI risk could be small. Further, the primary aim of our study was to examine whether FBG in those without diabetes rather than diabetes diagnosis itself was associated with MI risk. Current guidelines do not recommend the routine use of oral glucose tolerance testing for diabetes screening among the general population (37). We did not collect information regarding coronary intervention for other kinds of ischemic heart disease in the current study, which could confound the observed association between FBG trajectories and MI risk. However, in the sensitivity analysis, by excluding the aspirin/statin users, we observed similar results. The current study included only Chinese adults living in the Kailuan community, and the trajectories identified in this population thus may not be generalizable to other populations. However, the biological effects of high FBG on cardiovascular health in this cohort should be the same as those among men and women in general. The homogeneous nature of our cohort could help to reduce potential confounding due to racial and health care disparities and, therefore, enhance internal validity, which is a prerequisite for the generalizability.

Conclusion

We identified five discrete FBG trajectories and found that these patterns were significantly associated with subsequent risk of developing MI in individuals without diabetes. Monitoring trajectories of FBG may provide an important approach to identify a population with higher risk of MI and help to prevent primary MI in a population without diabetes. Future research needs to explore the key risk factors that are associated with the elevated BP trajectories. Studies in populations with different racial and ethnic compositions and those that include data on HbA_{1c} are also warranted to replicate our findings.

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