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Association of fasting plasma glucose change trajectory and risk of hypertension: a cohort study in China

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Abstract

We aimed to assess the association between fasting plasma glucose (FPG) change trajectory and incident hypertension among Chinese population. This cohort study included 11,791 adults aged 18–80 years without hypertension at first entry and who completed at least four follow-ups between 2009 and 2016. Logistic regression was used to estimate odds ratios (ORs) and 95% CIs for the association between FPG change trajectory and probability of hypertension. During a median follow-up of 5.10 years (total person–years 61,887.76), hypertension developed in 2177 participants. After adjusting for baseline potential confounders, the probability of hypertension increased with the increasing FPG change trajectory (adjusted OR (aOR) 1.22, 95% CI 1.07–1.40), bell-shape trajectory (aOR 1.15, 95% CI 1.02–1.30) and other-shape trajectory (aOR 1.13, 95% CI 1.02–1.25) which showed a higher variability of FPG compared to the decreasing group. In addition, the increasing FPG change trajectory was associated with a higher probability of hypertension compared with the decreasing group regardless of age and BMI but was only significant in males and in those with normal FPG at baseline. Our study indicates that the increasing FPG change trajectory determines the highest risk of hypertension, demonstrating the importance of maintaining low and stable levels of FPG, especially in males and in those with normal FPG.

Introduction

Hypertension and diabetes often coexist (1, 2), probably because of the common pathways to hypertension and diabetes (such as oxidative stress, stress, obesity, and insulin resistance) (3). About 66.3% of people with hypertension in America have diabetes (4). Coexistence of hypertension and diabetes can significantly increase the risk of cardiovascular disease and death (5, 6). The existence of hypertension may also indicate the likelihood of future diabetes (7, 8), while the presence of diabetes significantly increases the incidence of hypertension (9). The precursors to diabetes and hypertension remain unknown; however, a meta-analysis indicated that prediabetes was associated with an increased risk of cardiovascular disease (10). To better understand the interaction between the two diseases, we must investigate the association between fasting plasma glucose (FPG) levels and hypertension.

FPG levels are an indicator of the adequacy of basal insulin secretion and hepatic and renal insulin sensitivity

(11). Although age, sex, waist circumference, BMI, and weight changes may affect the predictive power of FPG levels for hypertension (12), FPG level is still identified as a significant risk factor for hypertension (13, 14, 15, 16). In addition, Mendelian randomization analysis of the causal association between diabetes and hypertension has shown that diabetes may cause hypertension and that this causality is irreversible (17). Although these findings all demonstrated the association between FPG levels and hypertension, previous studies were generally based on a single FPG assessment and failed to take into account the potential effect of change in FPG levels over time. Because of regression dilution, studies based on a single measure of FPG at baseline could underestimate the true association between FPG levels and hypertension risk (18). Moreover, ignoring the effect of cumulative average FPG levels may also bias the true association between FPG levels and hypertension risk.

We therefore aimed to identify patterns of FPG change trajectories over time and to investigate the possible association of FPG change trajectory and cumulative average FPG levels with hypertension risk in a Chinese cohort.

Materials and methods

Participants

This cohort analysis included adults aged 18–80 years who underwent a comprehensive health screening examination at Beijing Xiaotangshan Hospital between 2009 and 2016. The participants were all civil servants with good education who were asked by their institutions to have health examinations annually. When participants came in for their first health check-ups between 2009 and 2015, they were considered to be the baseline population. The follow-ups were conducted between 2010 and 2016, the intervals ranging from 1 to 3 years because of the diversity of participation. A total of 12,765 participants without hypertension at first entry who completed at least four follow-up visits were evaluated for eligibility. We excluded 312 adults with a history of cancer, myocardial infarction, stroke, coronary heart disease, or heart failure at baseline as well as 645 adults with missing data on FPG levels at baseline and/or during follow-up visits. Ultimately, data for 11,808 participants were retained for this analysis. We used the NCSS-PASS 15 to estimate the sample size. We assumed $\alpha = 0.05$, $1 - \beta = 0.90$. According to one study (19), the incidence rate of hypertension in the control group was 2.4% and hazard ratio (HR) was 1.95. If the ratio of exposure

group to control group is 1, the sample size should reach 2752. Considering the possibility of loss of follow-up in the cohort study, a total sample size of 3302 would be required if the sample size was extended by 20%, so the sample size of the study was deemed sufficient.

The requirement for informed consent was waived because the analysis used only routine health-screening data. The study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of Xiaotangshan Hospital (No. 202006).

Data collection

At baseline and at every follow-up, data on demographic characteristics (age and sex), smoking (currently smoking and/or having smoked at least 100 cigarettes during the lifetime), drinking (consumed alcohol 12 or more times in the last year), medical history (had a history of hypertension, type 2 diabetes mellitus (T2DM), cancer, myocardial infarction, stroke, coronary heart disease, heart failure, and so on), and use of medications (antihypertensive medication was defined as using antihypertensive drugs in the last 2 weeks; antidiabetic medication was defined as using hypoglycemic drugs currently; and antilipidemic medication was defined as using lipid-lowering drugs in the past 2 weeks) were collected through face-to-face standardized questionnaire interviews; anthropometry (height, weight, BMI, waist circumference (WC), resting heart rate (RHR), systolic and diastolic blood pressure (SBP and DBP)) measured three times in the right arm at intervals of 30 s using an electronic sphygmomanometer (HEM-770AFuzzy, Omron, Kyoto, Japan), and clinical and biochemical measures (levels of FPG, serum uric acid (UA), blood urea nitrogen (BUN), creatinine (CR), total cholesterol (TC), triglycerides (TG), HDL-C, and LDL-C) were collected by trained doctors and nurses. The details of other information collection in the study population have been previously published (20).

Definitions

Hypertension was defined against any of the following criteria: (1) self-report of a physician's diagnosis of hypertension; (2) use of anti-hypertension medication during the past 2 weeks; or (3) SBP $\geq$140 mmHg and/or DBP $\geq$90 mmHg (21).

Prehypertension was defined as SBP $\geq$120 mmHg, <139 mmHg and/or DBP $\geq$80 mmHg, <89 mmHg (21).

Impaired fasting glucose (IFG) was defined as FPG $\geq$ 6.1 and <7.0 mmol/L (22). T2DM was defined with any of the

following: (1) self-report of a physician's diagnosis of T2DM; (2) use of glucose-lowering medications during the past 2 weeks; (3) FPG level ≥ 7.0 mmol/L; (4) 2-h plasma glucose level ≥11.1 mmol/L; or (5) hemoglobin A1c level ≥ 6.5%.

Statistical analysis

We used linear regression and quadratic regression models to fit the change trajectory of FPG for each participant, then used the annual change rate of FPG, adjusted R^2 and regression coefficient for the linear regression model ($L\text{-}R_a^2$, β_L) and quadratic regression model ($Q\text{-}R_a^2$, β_Q) to determine the optimal model. According to the change trajectory, participants were divided into the following six trajectory groups: consistent (annual change rate during all visits < 1%); increasing (at least one visit with annual change rate ≥1%, $\beta_L > 0$, $L\text{-}R_a^2 > Q\text{-}R_a^2$ and $L\text{-}R_a^2 > 0$); decreasing (at least one visit with annual change rate ≥1%, $\beta_L < 0$, $L\text{-}R_a^2 > Q\text{-}R_a^2$ and $L\text{-}R_a^2 > 0$); bell shape (at least one visit with annual change rate ≥1%, $\beta_Q < 0$, $L\text{-}R_a^2 < Q\text{-}R_a^2$ and $Q\text{-}R_a^2 > 0$); U shape (at least one visit with annual change rate ≥1%, $\beta_Q > 0$, $L\text{-}R_a^2 < Q\text{-}R_a^2$ and $Q\text{-}R_a^2 > 0$); and other shape (at least one visit with annual change rate ≥1%, $L\text{-}R_a^2 < 0$ and $Q\text{-}R_a^2 < 0$). This classification resulted in 17 participants in the consistent group, so we excluded the 17 participants from the main analyses. We provided example graphs for each FPG change trajectory with data for six individuals in each category (Supplementary Fig. 1, see section on supplementary materials given at the end of this article).

We examined the cumulative average FPG level (average of all available FPG levels between 2009 and 2016), s.d. of FPG level (s.d. of all available FPG levels between 2009 and 2016), end-stage FPG level (FPG level at the last follow-up visit), and annual increasing rate of FPG level (slope of the simple linear regression model with FPG level between 2009 and 2016 as the response variable and follow-up years as the independent variable) to obtain more details. The participants were classified into three FPG level groups – <5.6, 5.6–6.1, and ≥6.1 mmol/L – according to cumulative average and end-stage FPG level. The participants were divided into four groups based on the quartiles of the s.d. (<0.19, 0.19 to <0.25, 0.25 to <0.34, and ≥0.34) and annual increasing rate (<−0.06, −0.06 to <−0.02, −0.02 to <0.03, and ≥0.03) of FPG level.

Baseline demographic characteristics are described by FPG change trajectory groups and blood pressure status at the last follow-up, with continuous variables presented as mean (s.d.) or median (interquartile range (IQR)) if not normally distributed and with categorical variables presented as frequency (%). Chi-square and Kruskal–Wallis tests were used to compare differences among groups.

Person–years of follow-up were calculated as the period between the first entry and the last confirmed follow-up or the date of diagnosis of hypertension. Because the trajectory models were fitted based on the data obtained from each follow-up, including the last follow-up, the exact follow-up time from the last follow-up of the FPG trajectory to hypertension presentation was uncertain, so multivariable logistic regression models were used to estimate odds ratios (ORs) and 95% CIs of hypertension probability attributable to FPG change trajectory, with the decreasing trajectory group as the reference. Model 1 was unadjusted, while model 2 was adjusted for age, sex, smoking, drinking, medication use, BMI, RHR, SBP, DBP, and levels of FPG, TC, TG, HDL-C, BUN, CR, and UA at baseline and follow-up. Sensitivity analysis by excluding participants with diabetes at baseline and during follow-up was used to test the robustness of our findings. We also performed subgroup analyses stratified by sex (men, women), age (<60, ≥60 years old), BMI (<24, ≥24 kg/m²), and FPG level at baseline (normal level, or IFG, or T2DM). We conducted similar analysis in the baseline prehypertension population.

All statistical analyses were performed with R 3.6.1 (R Foundation), with two-sided $P < 0.05$ considered statistically significant.

Results

A total of 11,791 participants (7386 men) were included after excluding 17 adults in the consistent group. The median age was 40 (IQR 32–48). Hypertension developed in 2177 participants during a median follow-up of 5.10 years, with an incidence density of 3.52% (2177/61,887.76 person–years). The composition of FPG change trajectories was as follows: 2053 (17.41%) were in the decreasing group; 1075 (9.12%) in the increasing group; 2462 (20.88%) in the U-shape group; 1907 (16.17%) in the bell-shape group; and 4294 (36.42%) in the other shape group. The maximum, minimum, and annual increasing rates of FPG level for the different trajectories are shown in Supplementary Table 1. Table 1 summarizes the baseline characteristics of the population included in the analysis by FPG change trajectory. Age, BMI, RHR, FPG, and serum TG levels were significantly associated with FPG change trajectory (all $P < 0.05$). Supplementary Table 2 summarizes the baseline characteristics of the study population by hypertension status at the last follow-up. Compared with normotensive participants, those with hypertension were older, had higher BMI, weight, WC, RHR, SBP, DBP, and levels of FPG, TC, TG, LDL-C, BUN, CR, and UA but lower HDL-C levels ($P < 0.001$), and more were men.

Table 1 Characteristics at baseline by fasting plasma glucose (FPG) change trajectory. Data are median (interquartile range) or mean (s.d.) unless indicated.

Variables	Total (N = 11,791)	Decreasing (N = 2053)	Increasing (N = 1075)	U shape (N = 2462)	Bell shape (N = 1907)	Other shape (N = 4294)	P
Age (years)	40 (32–48)	40 (32–48)	40 (32–48)	41 (32–48)	39 (31–47)	40 (32–47)	0.002
Female, n (%)	4405 (37.31)	797 (38.82)	366 (34.05)	935 (37.98)	732 (38.38)	1575 (36.68)	0.061
BMI (kg/m^2)	24.45 (22.26–26.63)	24.39 (22.09–26.61)	24.80 (22.58–26.91)	24.40 (22.26–26.71)	24.43 (22.11–26.51)	24.43 (22.29–26.59)	0.008
Weight (kg)	69.63 (12.33)	69.10 (12.02)	70.85 (12.57)	69.64 (12.38)	69.26 (12.16)	69.73 (12.43)	0.450
Waist circumference (cm)	83.04 (10.14)	82.93 (10.10)	83.95 (10.13)	83.14 (10.25)	82.62 (10.04)	82.97 (10.11)	0.059
Antidiabetic medication (%)	37 (0.31)	5 (0.24)	4 (0.37)	11 (0.58)	3 (0.12)	14 (0.33)	0.001
Antilipidemic medication (%)	0 (0)	0 (0)	3 (0.15)	4 (0.16)	0 (0)	10 (0.23)	0.140
RHR (beats/min)	72 (70–80)	72 (70–80)	72 (70–81)	72 (70–80)	72 (70–80)	72 (69–80)	0.026
DBP (mmHg)	72.19 (7.72)	72.29 (7.52)	72.38 (7.60)	72.34 (7.81)	71.94 (7.85)	72.11 (7.74)	0.130
SBP (mmHg)	112.35 (11.30)	111.77 (11.14)	113.04 (11.35)	113.18 (11.52)	111.99 (11.31)	112.13 (11.20)	0.098
FPG (mmol/L)	5.16 (4.87–5.51)	5.31 (5.06–5.60)	5.00 (4.69–5.43)	5.36 (5.04–5.73)	4.95 (4.68–5.30)	5.10 (4.84–5.42)	<0.001
TC (mmol/L)	4.81 (0.92)	4.84 (0.92)	4.81 (0.89)	4.80 (0.91)	4.80 (0.92)	4.81 (0.93)	0.520
TG (mmol/L)	1.55 (1.24)	1.49 (1.13)	1.68 (1.33)	1.58 (1.37)	1.54 (1.23)	1.53 (1.18)	<0.001
LDL-C (mmol/L)	2.90 (0.74)	2.90 (0.75)	2.91 (0.71)	2.90 (0.74)	2.88 (0.73)	2.89 (0.75)	0.410
HDL-C (mmol/L)	1.36 (0.32)	1.39 (0.32)	1.33 (0.30)	1.36 (0.32)	1.36 (0.32)	1.37 (0.32)	0.270
BUN (mmol/L)	4.85 (1.28)	4.83 (1.28)	4.87 (1.27)	4.83 (1.33)	4.80 (1.21)	4.87 (1.27)	0.320
CR (μmol/L)	82.74 (14.36)	83.05 (14.15)	82.92 (14.26)	82.03 (14.87)	82.09 (14.18)	83.24 (14.24)	0.340
UA (μmol/L)	330.0 (83.39)	326.66 (82.50)	336.99 (84.72)	326.26 (82.86)	331.70 (84.44)	331.28 (83.18)	0.630

CR, creatinine; DBP, diastolic blood pressure; FPG, fasting plasma glucose; RHR, resting heart rate; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; UA, uric acid.

FPG change trajectory and risk of hypertension

In model 1, the probability of hypertension was significantly increased with the increasing FPG change trajectory (OR 1.65, 95% CI 1.49–1.82), bell-shape trajectory (OR 1.19, 95% CI 1.09–1.31), U-shape trajectory (OR 1.21, 95% CI 1.11–1.32), and other shape trajectory (OR 1.19, 95% CI 1.02–1.25) compared with decreasing FPG trajectory (Table 2). After adjusting for age, sex, smoking, drinking, medication use, BMI, RHR, SBP, DBP, and levels of FPG, TC, TG HDL-C, BUN, CR, and UA at baseline and follow-up (Model 2), the increasing, bell-shape, and other shape change trajectories remained significantly associated with probability of hypertension. Excluding participants with diabetes at baseline and follow-up did not affect the significant associations between FPG change trajectory and hypertension risk. The results between FPG trajectory and hypertension in baseline prehypertensive patients were similar to the main analysis (Supplementary Table 3).

In the subgroup analyses stratified by FPG level at baseline, the probability of hypertension associated with the increasing FPG change trajectory (adjusted OR (aOR) 1.83, 95% CI 1.44–2.32), bell-shape trajectory (aOR 1.31, 95% CI 1.06–1.62), and other shape trajectory (aOR 1.20, 95% CI 1.01–1.44), compared with the decreasing FPG trajectory, remained significant in participants with normal FPG level. The associations between FPG change trajectory and probability of hypertension, however, became non-significant in the IFG and T2DM groups (Table 3). When restricted to baseline prehypertension, the results showed a similar pattern (Supplementary Table 4).

In the subgroup analyses stratified by age, sex, and BMI, the association between the increasing FPG change trajectory and probability of hypertension was significant with male sex, age < 60 and ≥ 60 years, and BMI < 24 and BMI ≥ 24 kg/m^2 compared with the decreasing FPG change trajectory (Fig. 1). The frequency of hypertension increased with male sex, age ≥ 60 years, and BMI ≥ 24 kg/m^2 regardless of FPG change trajectory (Supplementary Table 5). Hypertension incidence by FPG change trajectory significantly differed with male sex, age < 60 and ≥ 60 years, and BMI < 24 kg/m^2 (P < 0.05).

Association of cumulative average FPG, s.d. of FPG, end-stage FPG, and annual increasing rate of FPG with risk of hypertension

Probability of hypertension was significantly associated with the cumulative average FPG levels of 5.6–6.1 and >6.1 mmol/L between 2009 and 2016 compared with FPG < 5.6 mmol/L (aOR 1.23, 95% CI 1.11–1.36, and 1.65, 95% CI 1.44–1.89, respectively; Table 4). The association was consistent with male sex (aOR 1.37, 95% CI 1.07–1.75), age <60 (aOR 1.38, 95% CI 1.08–1.76), and BMI ≥24 kg/m^2 (aOR 1.40, 95% CI 1.09–1.78) (Supplementary Table 6). Risk of hypertension increased with increased s.d. of FPG (fourth vs first quartile: aOR 1.27, 95% CI 1.08–1.50) and increased annual increasing rate of FPG (fourth vs first quartile: aOR 1.56, 95% CI 1.34–1.81) (Table 4). Probability of hypertension was higher by 60% and 92%, with 5.6–6.1 and >6.1 mmol/L end-stage FPG than lower FPG (<5.6 mmol/L) at the last follow-up. In the baseline prehypertension population, risk of hypertension increased with increased cumulative average FPG, s.d. of FPG, end-stage FPG, and annual increasing rate of FPG levels (Supplementary Table 7).

Table 2 Association between FPG change trajectory and risk of hypertension. Data are odds ratios (ORs) and 95% CIs.

	Decreasing	Increasing	U shape	Bell shape	Other shape	*P*
N (cases)	2053 (339)	1075 (253)	2462 (472)	1907 (336)	4294 (777)	
Person–years	11,224.59	5588.36	12,850.92	9501.50	22,722.39	
Incidence (per 100 person–years)	3.02	4.53	3.67	3.95	3.42	
OR (95% CI)[a]	1.00	1.65 (1.49–1.82)	1.21 (1.11–1.32)	1.19 (1.09–1.31)	1.19 (1.10–1.29)	0.190
OR (95% CI)[b]	1.00	1.22 (1.07–1.40)	0.98 (0.88–1.10)	1.15 (1.02–1.30)	1.13 (1.02–1.25)	0.460
Sensitivity analysis[c]						
N (cases)	1935 (295)	875 (176)	2167 (360)	1739 (282)	3983 (650)	
Person–years	10,547.44	4448.31	11,212.14	8594.96	20,968.28	
Incidence (per 100 person–years)	2.79	3.96	3.21	3.28	3.10	
OR (95% CI)[a]	1.00	1.42 (1.27–1.60)	1.13 (1.03–1.25)	1.17 (1.06–1.30)	1.16 (1.06–1.26)	0.120
OR (95% CI)[b]	1.00	1.31 (1.12–1.53)	1.04 (0.92–1.18)	1.22 (1.06–1.40)	1.13 (1.01–1.26)	0.550

[a]Unadjusted model. [b]Adjusted for baseline age, sex, smoking, drinking, medication use, BMI, resting heart rate, systolic blood pressure, diastolic blood pressure, fasting plasma glucose, total cholesterol, triglycerides, HDL-C, blood urea nitrogen, creatinine, and uric acid levels, and follow-up time. [c]Sensitivity analysis excluding participants with diabetes at baseline and during follow-up.

Table 3 Association between FPG change trajectory and risk of hypertension by FPG level type. Data are odds ratios (ORs) and 95% CIs.

Variables		Decreasing	Increasing	Bell shape	U shape	Other shape	P
Normal FPG	N (cases)	1891 (278)	970 (215)	1791 (295)	2154 (367)	4029 (665)	
	OR (95% CI)[a]	1.00	1.65 (1.35–2.01)	1.14 (0.96–1.37)	1.19 (1.00–1.41)	1.15 (0.99–1.34)	0.880
	OR (95% CI)[b]	1.00	1.83 (1.44–2.32)	1.31 (1.06–1.62)	1.20 (0.98–1.46)	1.20 (1.01–1.44)	0.990
IFG	N (cases)	100 (39)	72 (27)	68 (20)	176 (58)	157 (66)	
	OR (95% CI)[a]	1.00	0.94 (0.50–1.75)	0.65 (0.33–1.25)	0.77 (0.46–1.28)	1.13 (0.68–1.90)	0.760
	OR (95% CI)[b]	1.00	0.80 (0.37–1.70)	0.50 (0.22–1.09)	0.64 (0.35–1.19)	1.03 (0.56–1.93)	0.960
T2DM	N (cases)	75 (29)	66 (24)	80 (32)	173 (64)	166 (67)	
	OR (95% CI)[a]	1.00	0.91 (0.46–1.80)	1.06 (0.55–2.02)	0.93 (0.53–1.64)	1.07 (0.62–1.89)	0.770
	OR (95% CI)[b]	1.00	1.06 (0.47–2.41)	1.00 (0.47–2.13)	1.02 (0.54–1.96)	1.26 (0.67–2.42)	0.560

[a]Unadjusted model. [b]Adjusted for baseline age, sex, smoking, drinking, medication use, BMI, resting heart rate, systolic blood pressure, diastolic blood pressure, fasting plasma glucose, total cholesterol, triglycerides, HDL-C, blood urea nitrogen, creatinine, and uric acid levels, and follow-up time.

Discussion

In this population-based retrospective cohort study, we assessed FPG change trajectory during follow-up for every participant. We generated five trajectory patterns of FPG level to estimate their association with risk of hypertension, observing significant associations between FPG change trajectory and risk of hypertension, especially in the subgroups of men and normal baseline FPG, and regardless of age and BMI. Higher cumulative average FPG levels, s.d. of FPG, end-stage FPG, and annual increasing rate of FPG were also significantly associated with increased hypertension risk.

In our study, 5.6–6.1 and >6.1 mmol/L cumulative average of FPG level and end-stage FPG could significantly increase the risk of hypertension. One study of 5016 adults also found FPG levels in the prediabetes range associated with a 1.95-fold (95% CI 1.43–2.52, P < 0.001) increased risk of hypertension (19). Two other studies found consistent results in individuals with diabetes and
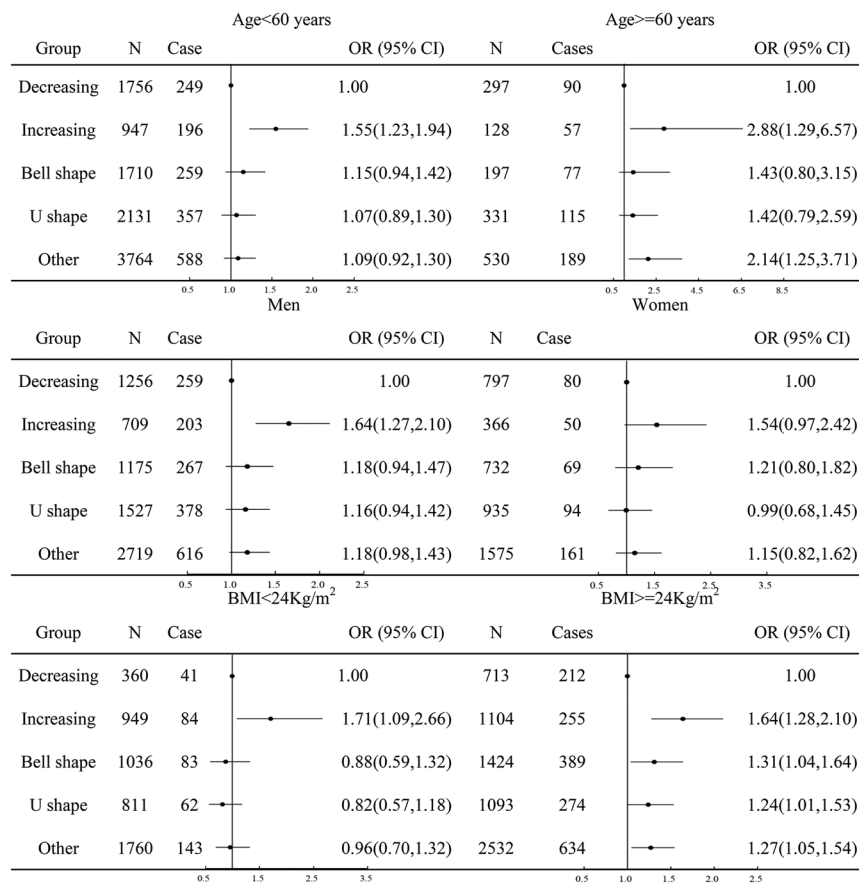

Figure 1
Probability of hypertension by fasting plasma glucose change trajectory groups stratified by sex, age, and BMI. Data are odds ratios (ORs) and 95% CIs from logistic regression, with decreasing group as the reference, after adjusting for baseline sex, age, smoking, drinking, medication use, BMI, resting heart rate, systolic blood pressure, diastolic blood pressure, fasting plasma glucose, total cholesterol, triglycerides, HDL-C, blood urea nitrogen, creatinine, and uric acid levels, and follow-up time.

Table 4　Risk of hypertension by cumulative average and s.d. of FPG level between 2009 and 2016, end-stage FPG level, and annual increasing rate of FPG level between 2009 and 2016.

	Cumulative average FPG level between 2009 and 2016		
	N (cases)	OR (95% CI)[a]	OR (95% CI)[b]
Range (mmol/L)			
<5.6	9863 (1481)	1.00	1.00
5.6–6.1	1000 (326)	2.55 (2.37–2.75)	1.23 (1.11–1.36)
>6.1	928 (370)	3.46 (3.22–3.72)	1.65 (1.44–1.89)
P_{trend}		<0.001	<0.001
	s.d. of FPG level between 2009 and 2016		
	N (cases)	OR (95% CI)[a]	OR (95% CI)[b]
Range			
<0.19	2983 (410)	1.00	1.00
0.19 to <0.25	2726 (436)	1.19 (1.03–1.38)	1.05 (0.89–1.25)
0.25 to <0.34	3177 (559)	1.34 (1.17–1.54)	1.12 (0.95–1.32)
≥0.34	2905 (772)	2.27 (1.99–2.60)	1.27 (1.08–1.50)
P_{trend}		<0.001	0.003
	End-stage FPG level		
	N (cases)	OR (95% CI)[a]	OR (95% CI)[b]
Range (mmol/L)			
<5.6	9661 (1429)	1.00	1.00
5.6–6.1	1061 (332)	2.62 (2.28–3.02)	1.60 (1.30–1.98)
>6.1	1069 (416)	3.66 (3.20–4.20)	1.92 (1.42–2.59)
P_{trend}		<0.001	<0.001
	Annual increasing rate of FPG level between 2009 and 2016		
	N (cases)	OR (95% CI)[a]	OR (95% CI)[b]
Range			
<−0.06	3201 (552)	1.00	1.00
−0.06 to <−0.02	2564 (444)	1.01 (0.88–1.15)	1.28 (1.08–1.51)
−0.02 to <0.03	2930 (472)	0.92 (0.81–1.05)	1.19 (1.01–1.40)
≥0.03	3096 (709)	1.43 (1.26–1.61)	1.56 (1.34–1.81)
P_{trend}		<0.001	<0.001

[a]Unadjusted model. [b]Adjusted for baseline age, sex, smoking, drinking, medication use, BMI, RHR, SBP, DBP, FPG, TC, TG, HDL-C, BUN, CR, and UA levels, and follow-up time.

BUN, blood urea nitrogen; CR, creatinine; DBP, diastolic blood pressure; FPG, fasting plasma glucose; OR, odds ratio; RHR, resting heart rate; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; UA, uric acid.

non-diabetes (9, 23). Although a case–control study with a unique population of 612 aging individuals with benign prostatic hyperplasia found a non-significant correlation between IFG or T2DM and hypertension (24), these findings may suggest that regular monitoring of FPG levels among individuals with IFG (5.6–6.9 mmol/L) (25) is of significance for public health and clinical practice given that these individuals generally do not receive treatment (26). This is particularly important given that lifestyle interventions could effectively lower FPG levels (27).

The development of hypertension is affected more by the progression of FPG level than by the FPG level at a specific time (24); however, studies of the dynamic change of FPG level and hypertension risk are not common. A Korean study (28) found that the progression of blood glucose status significantly affected the development of hypertension compared with baseline blood glucose levels: individuals with progression to prediabetes and T2DM

showed 1.41- and 1.77-fold increased hypertension risk, respectively, consistent with our study which showed the increasing FPG change trajectory significantly associated with 65% increased probability of hypertension compared with the decreasing group. The previous study (28), however, converted blood glucose into categorical variables (normoglycemia, prediabetes, and diabetes) which failed to reflect the dynamic changes in blood glucose levels in the process. We fitted all FPG levels measured during follow-up into linear regression and quadratic regression models and found hypertension risk significantly increased with increasing, bell-shape, and other-shape change trajectories compared with the decreasing trajectory in both the general population and in baseline prehypertension population. The significant association may be explained as follows: although FPG change trajectory was bell- or other-shaped, the annual increasing rate of FPG level was significantly higher for these two groups than for the decreasing group during follow-up. The U-shaped group had a lower

annual increasing rate of FPG level than the two other groups, which may explain the finding of no significant association with hypertension risk in the U-shaped group (Supplementary Table 1). Glucose fluctuations are related to oxidative stress, endothelial dysfunction, and inflammation, which are traditionally associated with the pathogenesis of vascular damage (29); hence, decreasing FPG levels over time, or maintaining a stable level, is important for preventing hypertension. The results were consistent even when we excluded participants with diabetes at baseline and during follow-up. The sensitivity analysis conducted by excluding diabetes during follow-up may suggest a causal relationship between FPG change trajectory and hypertension. Hypertension could occur before diabetes with FPG level change. Our findings are important for population prevention of hypertension. Apart from monitoring of blood pressure, a focus on glucose instability is also advisable in clinical practice. Individuals should keep glucose normal and stable to prevent hypertension. Though glucose instability monitoring is not routine, we should take full advantage of managed care to facilitate such a routine collection of FPG measurement.

Despite a well-known link between age, weight changes, and blood pressure level (30), the significant association of FPG change trajectory with incident hypertension was independent of age and BMI changes in our study. In sex and FPG stratification analyses, however, FPG change trajectory was only significantly associated with risk of hypertension for males and for those with normal FPG levels at baseline. A cohort study of 9583 Chinese rural people indicated risk of hypertension increased for only females with IFG (OR 1.23, 95% CI 1.05–1.45) (31). This discordance may be explained in the following ways. First, in our study, the incidence of hypertension was lower in women (37.31%) than in men (Supplementary Table 5), which may bias the conclusions. Second, male and female estrogen levels differ, and lower endogenous estrogen levels in men than in women may lead to stronger insulin resistance (32). Insulin resistance could promote the secretion of pro-inflammatory cytokines, leading to vasculoendothelial dysfunction (33) and an increase in the systemic sympathetic tone, and may accelerate tubular reabsorption of sodium and water (34), thereby leading to high blood pressure. This disparity may make men more sensitive than women to changes in FPG levels. With IFG and diabetes, the association between FPG change trajectory and risk of hypertension was no longer significant. One possible explanation is that a high FPG level has a direct adverse effect on the cardiovascular system regardless of fluctuation in level (35). High glucose may damage the homeostasis of endothelial and smooth muscle cells by stimulating the formation of advanced glycation end products, generating reactive oxygen species and activating protein kinases, thereby promoting vascular disease (36). When progressing to IFG or diabetes, the damage to blood vessels has already occurred despite hypoglycemic treatment. Our results may suggest the importance of FPG level control in males and non-diabetic people.

Several limitations should be noted in our study. First, although we controlled for a large number of confounding factors, there is still a possibility that there are residual confounding factors such as physical activity, dietary intake, and psychological issues. Second, we did not measure fasting serum insulin, so we could not estimate the effect of insulin resistance on the association between FPG change trajectory and hypertension in IFG and T2DM participants. Third, the FPG change trajectory modeling method in our study can only reflect the change trend of FPG, not the range of FPG levels in the same trajectory group and its effect on outcome. We did however describe the FPG distribution in the FPG change trajectory groups in Supplementary Table 1. Fourth, the different intervals of follow-up may affect the modeling of the trajectory pattern, although we modeled the trajectory pattern based on at least four health examinations to improve the accuracy of modeling. Future studies are needed to confirm our findings. Fifth, the trajectory in FPG was based on baseline and each follow-up, so whether the observed trajectory pattern occurred before or after the development of hypertension at the last follow-up remains uncertain. Finally, the data for our study were sourced from medical examinations of highly educated employees that included only a low proportion of females, so the sample representativeness may be limited, requiring further research to validate our findings.

Conclusion

The increasing, bell shape, and other shape of FPG change trajectories over time were significantly associated with increased risk of hypertension. The increasing FPG change trajectory provides the highest risk of hypertension, especially in males and in those with normal FPG at baseline but regardless of age and BMI. Higher cumulative average FPG level, s.d. of FPG level, end-stage FPG, and annual increasing rate of FPG level during follow-up were significantly associated with hypertension risk. Our findings further highlight the importance of maintaining low and stable levels of FPG, especially in males and in those with normal FPG.

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