ORIGINAL RESEARCH

Trajectories of Long-Term Normal Fasting Plasma Glucose and Risk of Coronary Heart Disease: A Prospective Cohort Study

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***Background*—**Fasting plasma glucose (FPG) levels can vary over time and its longitudinal changing patterns may predict cardiometabolic risk. We aim to identify different trajectories of FPG in those who remained normoglycemic and investigate the association between trajectory groups and coronary heart disease risk in a large prospective cohort study.

***Methods and Results*—**A total of 20 514 subjects between ages 20 and 80 years were included at baseline. All participants had maintained normal FPG throughout an average follow-up period of 5.8 years. We identified 3 distinct trajectories using a group-based trajectory model, labeled by initial value and changing pattern: low-increasing (n=12 694), high-increasing-decreasing (n=5330), and high-decreasing-increasing (n=2490). The coronary heart disease incidence density among these 3 groups (3.00, 4.05, and 3.26 per 1000 person-years, respectively) was significantly different (P=0.038). The high-increasing-decreasing group was characterized by a starting FPG of 4.80 mmol/L, and increased up to 5.42 mmol/L at age 55, then decreased thereafter. Treating the low-increasing group as the reference, the age- and sex-adjusted hazard ratio was 1.58 (95% confidence interval, 1.23–2.02) for the high-increasing-decreasing group by Cox proportional hazard regression. After adjustment for other potential confounding factors, the hazard ratio is 1.40 (95% confidence interval, 1.08–1.81). The association persisted after adjustment for baseline FPG, mean, or SD of FPG.

***Conclusions*—**Distinct trajectories of long-term normal FPG are associated with the development of coronary heart disease, which is independent of other metabolic factors including FPG levels. These findings have implications for intervention and prevention of coronary heart disease among individuals who are normoglycemic. **(*J Am Heart Assoc*. 2018;7:e007607. DOI: 10.1161/JAHA.117.007607.)**

Key Words: epidemiology • fasting plasma glucose • group-based trajectory model • proportional hazard regression • cardiovascular disease risk factors

It had been well documented that prediabetes mellitus and diabetes mellitus increase the risk of coronary heart disease (CHD).[1–3] Among the 3 indexes commonly used to diagnose diabetes mellitus—fasting plasma glucose (FPG), 2-hour PG, and hemoglobin A1C—FPG is cost-effective and widely used. Thus, the association between FPG and CHD had been extensively studied. Park et al[3] reported a J-shaped association between fasting glucose levels and cardiovascular disease risk across the full range of FPG values. It had also been demonstrated that the angiographic CHD prevalence increases with increasing FPG levels.[4] Even FPG levels within the normal range predict cardiovascular disease in the elderly population in Taiwan.[5] Similar findings have been reported in other populations.[6,7] Furthermore, Shaye et al[6] showed that FPG may help identify apparently healthy people with early metabolic abnormalities who are at increased risk for cardiovascular disease before progression to prediabetes mellitus and overt diabetes mellitus.

Most of these studies, however, used a single measurement. It is known that FPG levels vary over time and their variability may predict cardiometabolic risk. Single measurements may also preclude the examination of long-term trajectories of FPG and their relevance to the development of cardiometabolic diseases, including CHD. A life course approach using multiple FPG measurements over time may

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Clinical Perspective

What Is New?

- Three different trajectories of long-term normal fasting plasma glucose are identified, which are independently associated with the risk of coronary heart disease.

What Are the Clinical Implications?

- Individuals, even apparently healthy with normal fasting plasma glucose, should pay more attention to the longitudinal changing pattern of fasting plasma glucose level for prevention of coronary heart disease.

shed new light on FPG trajectories and their relevance to the development of CHD. Such an approach will likely provide critical information for identifying people with increased risk of development of CHD even if FPG levels are within a normal range, and has implications for prevention and intervention.

In the current study of 20 514 participants with normal FPG levels over time, we first used a group-based trajectory model (GBTM)[8] to identify latent FPG trajectory groups and investigated the association between such trajectory group memberships and CHD risk adjusted for other potential confounding factors. As normal FPG levels may go unnoticed in clinical practice, we focused on those who had consistent normal FPG levels during the whole follow-up period.

Methods

Ethics Approval

This study protocol was approved by the ethics committee of School of Public Health, Shandong University. Written informed consent was obtained from all participants. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population and Cohort Design

A total of 34 530 participants (20–80 years old) underwent a routine health check-up at the Center for Health Management, affiliated with Jining Medical University Hospital between 2007 and 2015. Of these, 12 813 participants who were examined <3 times were excluded. We further excluded participants whose FPG level was >6.1 mmol/L on at least 1 occasion. The final sample included 20 514 participants with an average follow-up of 5.8 years and 106 231 person-years of follow-up. The average number of examinations was 5.3, and the average time interval between examinations was 1 year.

Examinations

The health check-up examinations were performed after an overnight fasting period of at least 12 hours, and all participants underwent routine anthropometric, clinical, and laboratory testing. The anthropometric measurements involved height, weight, and blood pressure. Height and weight were measured while subjects were wearing light clothing without shoes. Body mass index (BMI) was calculated as weight (kg) divided by the square of the height (m). Blood pressure, including systolic blood pressure and diastolic blood pressure, was measured on the right upper arm with participants in a sitting position after a 5-minute rest. Hypertension was defined as blood pressure ≥140/90 mm Hg or reported use of antihypertension medication.

Peripheral blood samples were obtained in the morning after a 12-hour fast to measure the following biochemical biomarkers: FPG, total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein cholesterol. The examinations of blood samples were all completed using standard protocols at the clinical laboratory of the Jining Medical University Hospital. According to the National Cholesterol Education Program Adult Treatment Panel III criteria,[9] dyslipidemia was defined as follows: (1) total cholesterol >6.20 mmol/L (240 mg/dL); (2) LDL cholesterol >4.14 mmol/L (160 mg/dL); (3) high-density lipoprotein cholesterol <1.04 mmol/L (40 mg/dL) for men or <1.30 mmol/L (50 mg/dL) for women; and (4) triglycerides >1.70 mmol/L (150 mg/dL).

Normal FPG was identified with a fasting level <6.1 mmol/L according to the *Chinese Guidelines for Prevention and Treatment of Diabetes* (2013 Edition). The long-term normal FPG was defined as the FPG level always being normal throughout the whole follow-up period. Smoking and drinking were categorized into current or noncurrent smoker and drinker. Current smoking was defined as having smoked 100 cigarettes in one's lifetime and currently smoking cigarettes. Current drinking was defined as alcohol intake more than once per month during the past 12 months. Family history of diabetes mellitus was coded as yes/no.

Outcome

The outcome was CHD. The routine health check-up database was linked to databases from the Office for Medical Insurance in Shandong Province, hospital admissions, and vital statistics from the Provincial Center for Disease control by using a unique identity number for each participant. We classified participants as having CHD if there was a record of the relevant clinical code in their medical insurance record, their linked hospital record, or their linked mortality record. We used *International Classification of Diseases, 10th revision* (*ICD-10*) clinical codes to identify cases. The *ICD-10* codes

used included I20 (angina pectoris), I21 (acute myocardial infarction), I22 (subsequent myocardial infarction), I23 (complications after myocardial infarction), I24 (other acute ischemic heart disease), and I25 (chronic ischemic heart disease). The medical insurance records were available until September 14, 2016. We used the earliest recorded date of cardiovascular disease from the 3 data sources as the outcome date.

Statistical Analysis

All continuous variables were presented as means±SD, or medians with interquartile ranges as appropriate. Categorical data were summarized as numbers or percentages. Characteristics across different groups were compared using analysis of variance or Kruskal–Wallis tests for continuous variables and χ^2 statistics for categorical variables. We used GBTM to identify trajectory patterns of long-term normal FPG (<6.1 mmol/L for each examination).[10,11] Using R package *lcmm*,[12] trajectories of long-term normal FPG were specified as a function of participant age, with adjustment for sex. For each specification of trajectory shape, we treated FPG as the dependent variable and repeated latent class trajectory analysis by changing the number of groups from 2 to 5. A linear term for age was used to specify the random effects of the model. Then we changed the trajectory shapes (eg, linear, quadratic, and cubic) to repeat the analysis in the above stage, respectively. We determined the optimal number of groups and trajectory shapes by the following criteria: (1) improvement in the Bayesian information criterion; (2) no less than 2% membership in any single trajectory group; and (3) high posterior probabilities (>0.7).

We investigated the association between the trajectory group membership and CHD using Cox proportional hazard models, with group membership entered as an independent variable, adjusted for baseline age, sex, smoking, drinking, BMI, hypertension status, the year of the first check-up, and dyslipidemia. The proportional hazard assumption was diagnosed by Schoenfeld residuals, and the global test was not statistically significant with a *P* value of 0.13. We further adjusted for baseline FPG, the mean, and the SD of FPG calculated from repeated examinations, to explore whether the association between trajectory and CHD risk was independent of the FPG level (and variability).

Sensitive analyses were first conducted by repeating the trajectory model using different random starting values, to check the robustness of the trajectory curve. Furthermore, we calculated additional FPG measures, including the absolute or the relative difference of FPG between the last and the first examination, and the maximum of FPG levels among repeated health examinations of each participant. Then we included them in the multivariate model to confirm the robustness of the association between trajectory group membership and CHD.

Results

During the follow-up period, 361 CHD cases were identified and CHD incidence density was 3.3 per 1000 person-years. The 3 quadratic trajectories of long-term normal FPG derived from GBTM are shown in Figure – Panel A. We labeled them by the FPG value at age 20 years, followed by the increasing or decreasing pattern, group 1 (low-increasing; n=12 694, 61.88%), group 2 (high-increasing-decreasing; n=5330,

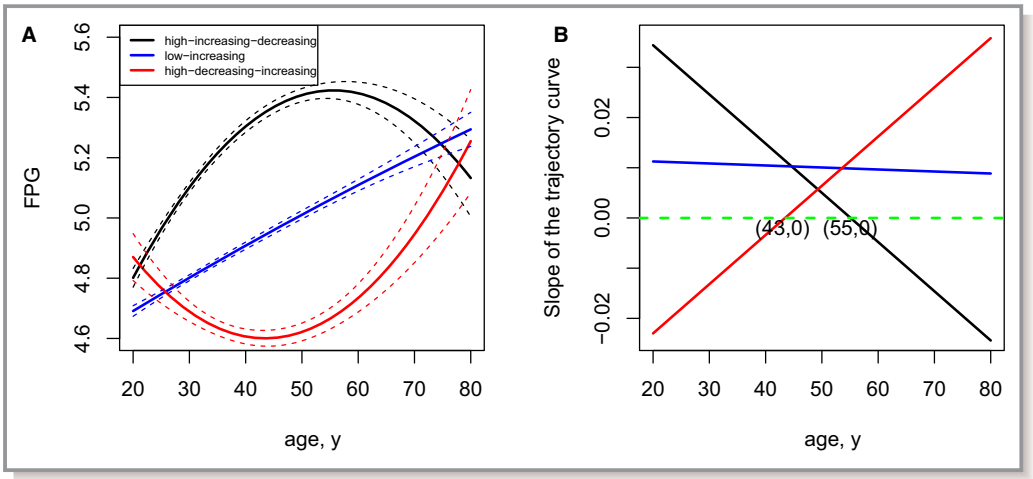

Figure. The trajectories of long-term normal fasting plasma glucose (FPG) for a hypothetical female over time. Each trajectory is represented by a different color, with dashed line representing 95% confidence intervals (A). The slope of these 3 trajectory curves is shown, and the green line represents that the slope is 0. The curve will reach the maximum or the minimum value at the age point with 0 slope (B).

25.98%), and group 3 (high-decreasing-increasing, n=2490, 12.14%). The low-increasing group was characterized by a gradually increasing FPG with a relatively low starting FPG of 4.69 mmol/L at age 20 years and gradually increased to up to 5.29 mmol/L at age 80 years. The high-increasing-decreasing group was characterized by a relatively higher starting FPG of 4.80 mmol/L at age 20 years, and increased to up to 5.42 at age 55 years, and decreased thereafter. The high-decreasing-increasing group was characterized by a relatively higher starting FPG of 4.87 mmol/L at age 20 years, and decreased to 4.60 mmol/L at age 43 years, and increased thereafter. As expected, the 95% confidence interval becomes relatively larger at old ages because of fewer measurements as the age increased.

To further visualize the increasing or decreasing rate, we described the slope of these 3 trajectory curves in Figure – Panel B. For the low-increasing group, the slope was almost constant, indicating a stably monotonic increasing trend in FPG levels. In fact, the quadratic term for this trajectory curve was asymptotically equal to 0 (−0.00002). For the high-increasing-decreasing group, the slope decreased to 0 around age 55 years (the age with the maximum FPG), indicating that the increasing speed gradually decreased before age 55 years. Then the absolute value of the slope became larger, indicating that the decreasing speed gradually increased after age 55 years. For the high-decreasing-increasing group, the slope increased to 0 around age 43 years (the age with the minimum FPG), indicating that the decreasing speed gradually decreased before age 43 years. Then the slope became larger, indicating the increasing speed gradually increased after age 43 years.

The baseline demographic and metabolic characteristics and outcomes of the 20 514 participants stratified by the development trajectory are displayed in Table 1. A significant difference of the CHD incidence density among these 3 groups (3.00, 4.05, and 3.26 per 1000 person-years, respectively) was observed. While all metabolic characteristics seemed to be normal since all subjects were within long-term normal FPG, participants in the high-increasing-decreasing group tended to have higher incidence density of CHD, high prevalence of family history of diabetes mellitus, lower high-density lipoprotein and elevated BMI, blood pressure, FPG, total cholesterol, LDL, and triglyceride levels. Similar findings were observed at the last health examination (Table 2).

Table 3 presents the association between the trajectory group membership and CHD using various Cox proportional hazard models. Treating the low-increasing group as the reference, the age- and sex-adjusted hazard ratio was 1.58 (95% confidence interval, 1.23–2.02) for the high-increasing-

Table 1. Descriptive Statistics for Baseline Characteristics According to Group Membership

	Group 1 (n=12 694)	Group 2 (n=5330)	Group 3 (n=2490)	*P* Value
Age, y	35.78±10.90	36.69±10.03*	40.43±8.90*	<0.001
Female, %	47.42	43.33*	38.27*	<0.001
Smoking, %	12.00	12.92	19.00*	<0.001
Drinking, %	22.83	30.68*	28.22*	<0.001
BMI, kg/m^2	23.59±3.80	24.84±4.22*	23.64±3.31	<0.001
TC, mmol/L	4.72±0.91	4.91±0.95*	4.70±0.87	<0.001
TG, mmol/L	1.04 (0.89)	1.28 (1.18)*	1.04 (0.84)	<0.001
LDL-C, mmol/L	2.72±0.73	2.84±0.75*	2.71±0.70	<0.001
HDL-C, mmol/L	1.34±0.31	1.30±0.31*	1.35±0.31	<0.001
FPG, mmol/L	4.93±0.41	5.45±0.40*	4.60±0.40*	<0.001
Dyslipidemia, %	43.14	54.80*	39.26†	<0.001
SBP, mm Hg	122.86±16.86	127.59±17.55*	121.71±16.08†	<0.001
DBP, mm Hg	76.20±12.04	79.68±12.65*	76.49±12.10	<0.001
Hypertension, %	38.29	49.34*	34.10*	<0.001
First check-up y	2011 (4)	2010 (4)†	2010 (4)*	<0.001
Diabetes mellitus family history, %	2.06	3.13*	2.21	<0.001
CHD incidence density, per 1000 person-y	3.00	4.05†	3.26	0.038

Data are presented as means±SDs, medians (interquartile ranges), or percentage. *P* values were calculated from the comparison between 3 identified groups. Group 1: low-increasing; Group 2: high-increasing-decreasing; Group 3: high-decreasing-increasing. The comparison results of CHD incidence density are obtained using Poisson regression model. BMI indicates body mass index; CHD, coronary heart disease; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.
Compared with Group 1: *P<0.001; †P<0.01.

Table 2. Descriptive Statistics for Characteristics at Last Examination According to Group Membership

	Group 1 (n=12 694)	Group 2 (n=5330)	Group 3 (n=2490)	*P* Value
Age, y	39.66±11.15	40.42±10.02*	44.75±8.82*	<0.001
Female, %	47.40	43.33*	38.00*	<0.001
Smoke, %	12.00	12.93	19.00*	<0.001
Drink, %	22.83	30.68*	28.87*	<0.001
BMI, kg/m^2	24.46±6.83	25.55±5.09*	24.37±6.18	<0.001
TC, mmol/L	4.77±0.85	4.92±0.92*	4.77±0.88	<0.001
TG, mmol/L	1.04 (0.91)	1.24 (1.16)*	1.00 (0.89)	<0.001
LDL-C, mmol/L	2.79±0.71	2.89±0.75*	2.78±0.70	<0.001
HDL-C, mmol/L	1.37±0.30	1.32±0.29*	1.39±0.31‡	<0.001
FPG, mmol/L	5.02±0.40	5.58±0.34*	4.56±0.37*	<0.001
Dyslipidemia, %	38.13	49.70*	34.60†	<0.001
SBP, mm Hg	121.63±16.95	126.19±17.15*	120.23±16.18*	<0.001
DBP, mm Hg	74.74±12.12	78.19±12.55*	74.71±12.19	<0.001
Hypertension, %	38.29	49.34*	34.10*	<0.001

Data are presented as means±SDs, medians (interquartile ranges), or percentage. *P* values were calculated from the comparison between 3 identified groups. Group 1: low-increasing; Group 2: high-increasing-decreasing; Group 3: high-decreasing-increasing. BMI indicates body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.
Compared with group 1: *P<0.001; †P<0.01; ‡P<0.05.

decreasing group. After adjustment for other potential demographic and metabolic characteristics including age, sex, smoking, drinking, the year of first health check-up, family history of diabetes mellitus, BMI, hypertension status, and dyslipidemia, the group membership was still positively associated with CHD risk (hazard ratio=1.40, 95% confidence interval, 1.08–1.81). The association persisted even after adjustment for baseline FPG, mean of FPG or SD of FPG calculated from one's repeated health examinations. We have also conducted the multivariate regression analysis using continuous covariates, with hypertension replaced by systolic blood pressure and dyslipidemia by LDL cholesterol, high-density lipoprotein cholesterol, and triglycerides; the results were similar.

Discussion

In this large-scale follow-up study, we identified 3 distinct trajectories of FPG levels, within a normal range throughout the follow-up period, and disclosed the association between these trajectories and CHD risk. The phenomenon of only 3 trajectories may be partly because we limited the FPG within the normal level (3.9–6.1 mmol/L), which makes it challenging for the GBTM method to identify subtler patterns, such as zig-zag fluctuations, of trajectories. Among the 3 trajectories of long-term normal FPG levels over time, the highest CHD risk group had high FPG levels at baseline with an increasing trend until around age 55 years, followed by a decreasing trend thereafter. The associations were independent of other metabolic factors even after adjustment for baseline FPG, mean of FPG, and SD of FPG. Our study demonstrates the power of using the GBTM method to identify hidden information in repeated measurements of FPG, even within the normal range, which is hardly captured from single index of FPG. It was interesting that the FPG level decreased after age 55 years for participants in the high-increasing-decreasing group. One possible explanation was that such participants often possessed higher BMI, FPG, total cholesterol, triglycerides, LDL, and lower high-density lipoprotein at baseline, and they ought to have a higher risk for metabolic disorder. If they were still able to conduct their regular health check-up even after age 55 years, they should have been given some suggestions about lifestyle intervention from their physicians. Thus, their metabolic characteristics could be improved, and accordingly the FPG level might be a little lower than what they had been before. Further explanations should be investigated.

A higher normal FPG level has been illustrated to be associated with higher levels of arterial stiffness,[13] the severity of coronary artery calcium,[14] and the risk of cardiovascular disease.[3] On the other hand, hypoglycemia or rapid changes in plasma glucose may lead to elevations of counterregulatory hormones, such as epinephrine and norepinephrine, and these increases induce vasoconstriction and platelet aggregation.[3,15] Furthermore, there is evidence that rapidly increasing glucose concentrations, rather than gradual

Table 3. HRs and their 95% CIs from Cox model

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Group 1	Reference	Reference	Reference	Reference	Reference	Reference
Group 2	1.58 (1.23, 2.02)*	1.44 (1.13, 1.85)†	1.40 (1.08, 1.81)‡	1.36 (1.01, 1.81)‡	1.43 (1.01, 2.03)‡	1.55 (1.04, 2.30)‡
Group 3	0.93 (0.66, 1.32)	0.93 (0.66, 1.32)	0.94 (0.66, 1.34)	0.97 (0.66, 1.42)	0.92 (0.59, 1.44)	0.90 (0.59, 1.38)
Age	1.09 (1.08, 1.10)*	1.09 (1.08, 1.10)*	1.09 (1.08, 1.09)*	1.08 (1.08, 1.09)*	1.09 (1.08, 1.10)*	1.09 (1.08, 1.10)*
Sex						
Male	Reference	Reference	Reference	Reference	Reference	Reference
Female	0.63 (0.49, 0.82)*	0.82 (0.59, 1.14)	0.83 (0.59, 1.17)	0.84 (0.60, 1.18)	0.83 (0.59, 1.16)	0.90 (0.63, 1.29)
Smoking		1.63 (1.25, 2.14)*	1.63 (1.24, 2.15)*	1.64 (1.25, 2.15)*	1.63 (1.24, 2.15)*	1.53 (1.15, 2.04)†
Drinking		1.01 (0.76, 1.34)	0.96 (0.72, 1.27)	0.96 (0.72, 1.27)	0.96 (0.72, 1.28)	1.04 (0.76, 1.41)
BMI		1.06 (1.03, 1.10)*	1.05 (1.01, 1.09)‡	1.05 (1.01, 1.09)‡	1.05 (1.01, 1.09)‡	1.06 (1.02, 1.10)†
Hypertension		1.21 (0.92, 1.58)	1.20 (0.91, 1.58)	1.20 (0.91, 1.58)	1.20 (0.91, 1.59)	1.21 (0.91, 1.61)
Dyslipidemia			1.11 (0.88, 1.40)†	1.11 (0.88, 1.39)	1.11 (0.88, 1.40)	1.07 (0.84, 1.37)
First check-up y		0.99 (0.91, 1.07)	0.98 (0.91, 1.07)	0.99 (0.91, 1.07)	0.98 (0.91, 1.07)	0.98 (0.90, 1.07)
Diabetes mellitus family history		1.25 (0.71, 2.21)	1.06 (0.57, 1.97)	1.05 (0.56, 1.97)	1.06 (0.57, 1.97)	1.03 (0.54, 1.99)
FPG				1.07 (0.79, 1.45)		
Mean of FPG					0.95 (0.56, 1.62)	
SD of FPG						0.86 (0.52, 1.42)

Model 1 adjusted for baseline age and sex; Model 2 adjusted for variables in model 1 plus smoking, drinking, body mass index (BMI), hypertension, first check-up year and diabetes mellitus family history; Model 3 adjusted for variables in model 2 plus dyslipidemia; Model 4 adjusted for variables in model 3 plus fasting plasma glucose (FPG); Model 5 adjusted for variables in model 3 plus mean of FPG level (mean of FPG); Model 6 adjusted for variables in model 3 plus the SD of FPG. Group 1: low-increasing; Group 2: high-increasing-decreasing; Group 3: high-decreasing-increasing. CIs indicates confidence intervals; HRs, hazard ratios.

*$P<0.001$.

†$P<0.01$.

‡$P<0.05$.

increases, occur late in diabetes mellitus,[16,17] and individuals with stable FPG concentrations are less likely to develop diabetes mellitus. The "ticking clock" hypothesis proposed by Haffner et al[18] claims that the plasma glucose level should be treated as a continuous variable, and different trajectories of FPG can reflect both the FPG level and the changing pattern simultaneously. Thus, the high-risk trajectory may lead to prediabetes mellitus or diabetes mellitus, and then CHD.

Findings of the current study have several implications. Information on FPG trajectories may be helpful in understanding the role FPG plays in the development of CHD. It is known that FPG is predictive of future cardiometabolic risk. Our findings were from a sample with normal FPG levels throughout the study period, suggesting that those who remain normoglycemic may still have increased CHD risk if their FPG levels follow a certain changing pattern. Currently, those who have normal FPG levels easily go unnoticed in clinical practice. How findings in our study can be translated into clinical practice requires further follow-up studies. Perhaps we can identify a trajectory to which a given individual belongs based on the FPG measurements. Our study also demonstrates the utility of repeated routine health check-ups for improved risk assessment. It is anticipated that the models including trajectory information will have better prediction than models using only single glucose measurements. It seems relatively burdensome to use multiple examinations. However, as annual health check-ups become increasingly common, additional information from multiple examinations will be readily available.

The principal advantage of GBTM is that it does not assume a priori the existence of trajectories of a specific form, while it allows distinctive latent developmental trajectories that can be learned from the data.[8,10,11] GBTM differs from the common practice to define thresholds for FPG, as it instead focuses on the development trajectory to identify distinct, mutually exclusive groups of FPG development that may not be captured in conventional analytic approaches, providing a different one to identify those most at CHD risk. The method can theoretically integrate multiple trajectories from individuals at different ages to obtain overall trajectory parameters. Since our data included participants with an age range between 20 and 80 years, the overall FPG trajectory pattern can be described.

Strengths of this study include a large study sample size, the use of repeated measures of study variables over time, and the robustness of observed associations. Limitations of

our findings also need to be recognized. First, our outcome was determined from the medical insurance record, their linked hospital record, or their linked mortality record, rather than from research-quality disease diagnoses. Second, our data were from routine health check-ups. Findings in the current study may not be generalizable to other populations without such features. We did not have data on 2-hour PG and hemoglobin A1C, 2 markers that may follow different trajectories over time. However, they are often difficult to obtain from routine health check-ups in most developing countries, given that they are quite inconvenient and expensive. Finally, we did not have access to the drug information; one may argue that even patients with diabetes mellitus can control the FPG level to be normal through antidiabetic drugs. Nevertheless, considering that only 32.2% of diabetes mellitus patients received treatment, only 49.2% of those treated had adequate glycemic control,[19] and the proportion for long-term glycemic control should be insignificant.

Conclusions

In summary, we have identified 3 distinct trajectories of normal FPG levels and demonstrated that such trajectories are associated with the development of CHD in a large Han Chinese sample, which is independent of other metabolic factors including FPG levels. Individuals, even apparently healthy with long-term normal FPG, may be at increased risk of developing CHD if FPG levels follow a certain pattern. Future studies should address the underlying mechanisms and examine whether findings of our study can be translated into prevention and intervention measures.

Author Contributions

Drs Yuan and Xue had full access to the data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Yuan and Xue are responsible for the conception and study design. Drs Yuan, J. Liu, Sun, and Y. Liu conducted statistical analysis. Drs Yang and Wang were responsible for acquisition of data. Drs Yuan and Li were responsible for drafting of the article.

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Disclosures

None.

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