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ORIGINAL RESEARCH

# Trajectories of Fasting Plasma Glucose and Risks of Chronic Kidney Disease in a General Chinese Population: A Retrospective Study

Jian Liu[1,*], Yuhua Ma[2,*], Geping Yu[3], Weiming Wang[1]

[1]Department of Nephrology, Ruijin Hospital, Shanghai Jiao Tong University, School of Medicine, Shanghai, People's Republic of China; [2]Department of Nephrology, Traditional Chinese Medicine Hospital of Kunshan, Jiangsu, People's Republic of China; [3]Department of Nephrology, Tonglu First People's Hospital, Hangzhou, People's Republic of China

*These authors contributed equally to this work

Correspondence: Weiming Wang, Department of Nephrology, RuiJin Hospital, Shanghai Jiao Tong University, School of Medicine, Shanghai, People's Republic of China, Tel/Fax +86 021-64370045 Ext 665232, Email wwm11120@rjh.com.cn



**Aim:** To investigate the association between longitudinal changing patterns of fasting plasma glucose (FPG), and kidney function change in the general population.

**Methods:** We conducted a retrospective, longitudinal cohort study of a health examination center database in China. Subjects who had at least three visits from 2011 to 2018 with baseline eGFR ≥60 mL/min/1.73 $m^2$ were enrolled. The FPG trajectories were identified by group-based trajectory modeling (GBTM). We examined the association of eGFR slopes and FPG trajectories by Cox analysis.

**Results:** Totally, 8114 participants were identified. Three heterogeneous FBP trajectories were detected by GBTM as low-stable group (n=7294), moderate-stable group (n=657) and high-stable group (n=163). The high-stable group had lower baseline eGFR, a higher percentage of fast eGFR slope, lower HDL-c, higher LDL-c, higher cholesterol, and higher Lg(triglyceride). Cox analysis showed that the high-stable trajectory was a risk factor for fast eGFR decline (for eGFR slope <−4 mL/min per 1.73 $m^2$ per year, adjusted HR [95% CI] 1.544 [0.876, 2.722]; for eGFR slope <−5 mL/min per 1.73 $m^2$ per year, adjusted HR [95% CI] 2.117[1.100, 4.075]). Further, we analyzed a subgroup in which participants' long-term FPG was normal. We divided this subgroup into four trajectories by GBTM, and Cox analysis showed that after adjustment for other potential confounding factors, the high-stable trajectory was an independent risk factor for fast eGFR slope (for eGFR slope <−4 mL/min per 1.73 $m^2$ per year, adjusted HR [95% CI] HR 1.640[1.050, 2.561]; for eGFR slope <−5 mL/min per 1.73 $m^2$ per year, adjusted HR [95% CI] 1.818[1.018, 3.248]) in subgroup.

**Conclusion:** We found that discrete FPG trajectories were significantly associated with risk of fast eGFR slope in individuals and those with long-term normal FPG. These observations suggest the importance of early prevention of CKD among individuals who are high-glycemic and normoglycemic.

**Keywords:** fasting plasma glucose, trajectory, chronic kidney disease

## Background

The incidence of chronic kidney disease (CKD) is steadily increasing. The prevalence rate of CKD in China is 10.8%~11.8%.[1,2] High fasting plasma glucose (FPG) is a risk factor for kidney disease. On one side, it can induce diabetic nephropathy;[3,4] on the other side, high glucose influences kidney function.[5,6] Previous studies showed that people with high blood glucose had a higher incidence of kidney disease. Trajectories of FPG may be useful to identify and prevent CVD incidence early. However, most of the studies only included baseline FPG but not FPG during the follow-up period, and did not investigate longitudinal changes (ie, trajectories) of fasting plasma glucose (FPG) in relation to incidence of chronic kidney disease. Besides, although a lot of clinical trials had pointed out that the benefit of controlling glucose, they did not explore the different trajectories of the glucose and did not discuss the association of long-term normal FPG and incidence of chronic kidney disease. So, in this current study of 8114 participants, we used a group-based trajectory model (GBTM) to identify latent FPG trajectory groups and investigated the

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association between trajectory groups and CKD risk after adjusted for other potential confounding factors. Also, we investigated this association in a sub-group in which the long-term FPG of the participants was normal during the whole follow-up period.

# Methods

## Study Design and Covariates

The health examination center in Tonglu First People's hospital is one of the healthcare centers in Tonglu, which is located in the eastern area of Zhejiang Province. We conducted a retrospective, longitudinal study from January 2011 to November 2018 in this center's clinical database. Participants who were screened were identified by ID number, birthdates, and other identifiers.[7] The participants who were older than 18 years old and baseline eGFR ≥60 mL/min/1.73 $m^2$/year were included.

Blood samples were collected from the vein in the morning. All blood variables were measured using an autoanalyzer (Roche) at this central laboratory. We used the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation to calculate eGFR.[8] HUA was defined by the sex-specific criteria of serum UA >420 μmol/L in males and >360 μmol/L in females.

## Statistical Analysis

For each participant, annualized eGFR slope (mL/min per 1.73 $m^2$ per year)[9] was derived from ordinary least squares regression using all available eGFR data. A faster decrease in eGFR slope was defined as <−4 and −5 mL/min per 1.73 $m^2$ per year.

We used descriptive statistics to compare the characteristics of the cohorts stratified by quartiles. Data were checked for normal distribution by the Kolmogorov–Smirnov test. Continuous variables were described as the means (with standard deviations (SDs)) when appropriate, and nonnormally distributed variables described as medians and interquartile ranges (IQRs). Normally distributed continuous variables were compared using ANOVA, and nonnormally distributed variables were evaluated using the Kruskal–Wallis test.

GBTM, also known as Latent Class Growth Analysis, is a semi-parametric modeling method primarily used to identify classes within a population that exhibit similar developmental trajectories. GBTM can estimate the probability of each individual belonging to different trajectory groups and assign them to the trajectory group with the highest probability, thus achieving clustering of individual developmental trajectories. The FPG trajectories were identified by GBTM (Stata12, TRAJ) measures, which were used to identify subgroups of people sharing similar FPG patterns, and the model fit was assessed using the Bayesian information criterion (BIC) and predicted group proportions.[10,11] We launched a model with two to five trajectories and then compared the BIC of these models. The models with three trajectories in the total population and four trajectories in the sub-group were identified. We then compared the model in terms of functional forms. Cubic, quadratic, and linear terms were evaluated based on their statistical significance after starting with the highest polynomial (Supplement Tables S1 and S2). Cox model was used to assess the association between FPG trajectory groups and fast eGFR slope. For Cox regression, age (age <65 as ref) was divided into two groups by 65-year-old, and lipid parameters (TG, cholesterol, HDL-c, and LDL-c) were divided into four quantiles.

All analyses were performed using SPSS 20 and Stata12 (STATA Corporation, College Station, Texas). A two-sided P value <0.05 was considered statistically significant.

# Results

Altogether, 8114 patients were recruited in this study, with an age of 45.64±15.18 year-old, 61% (N=4946) of males, mean follow-up time of 5.51 years and 34,413 person-years of observations. At first observation, the UA was 350.33 ±94.27μmol/L, the FPG was 5.01±1.06mmol/L, and the eGFR were 101.37±15.23 mL/min per 1.73 $m^2$.

To decide the optimal number of subgroups, we compared BICs obtained by GBTM. Based on the BIC, average group posterior probability, the number of participants in each group and the clinical significance of the trajectories, the optimal number of subgroups was three (Supplement Table S1 and Figure 1): T1 (low-stable group, n=7294, 89.8%), T2 (moderate-stable group, n=657, 8.2%), and T3 (high-stable group, n=163, 2.0%).

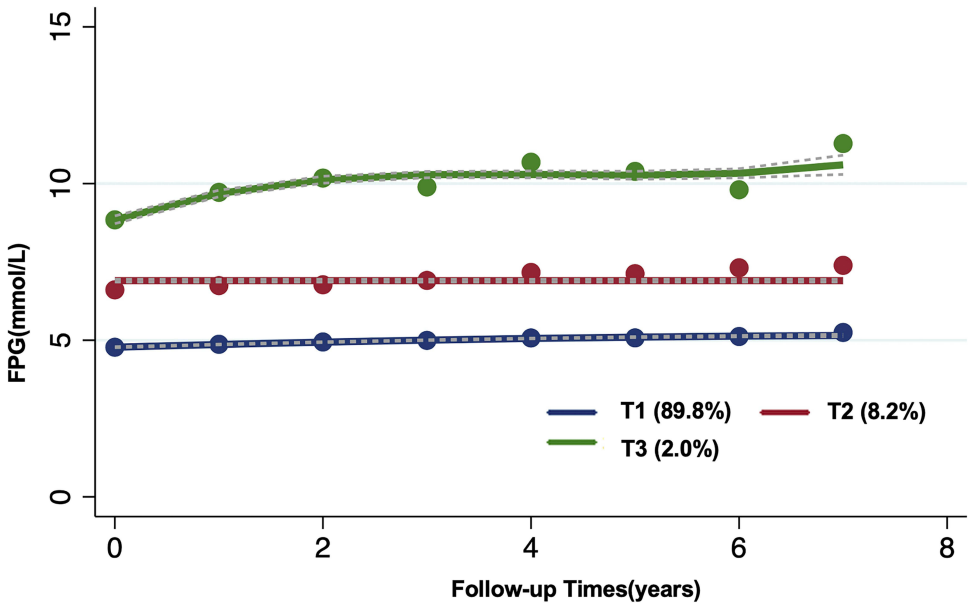


**Figure 1** The trajectories of long-term normal fasting plasma glucose by GBTM. T1, low-stable group; T2, moderate-stable group; T3, high-stable group.

The baseline characteristics, according to the trajectories of FBP, are presented in Table 1. Although the eGFR slope was almost the same in the three groups, a significant difference of the percentage of fast eGFR slope among these three groups (for eGFR slope <−4 mL/min per 1.73 $m^2$ per year, 4.4%, 6.1%, 8.0%, respectively; for eGFR slope <−5 mL/min per 1.73 $m^2$ per year, 2.5%, 3.7%, and 6.1%, respectively) was observed. We used individuals in the T1 group (low-stable group) as the reference. People in the other groups tend to be older, with a higher proportion of males. Compared with the T1 group (low-stable group), LgTG and Cholesterol were high, and the HDL-c was low in the other groups.

The number of participants who have eGFR slope <−4 mL/min per 1.73 $m^2$ per year and −5 mL/min per 1.73 $m^2$ per year were 374 and 214 irrespectively. Treating the T1 group (low-stable group) as the reference (Figure 2 and Supplement Figure 1), the T3 group experienced the highest crude risk (HR [95% CI] 1.745[1.002, 3.039]) of the eGFR slope <−4 mL/min per 1.73 $m^2$ per year. The T3 group (high-stable group) also experienced the highest risk (HR [95% CI] 1.745[1.002, 3.039]) of eGFR slope <−5 mL/min per 1.73 $m^2$ per year. After adjustment for other potential characteristics

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

| | T1 (N=7294) | T2 (N=657) | T3 (N=163) | p value |
|---|---|---|---|---|
| Age(year-old) | 44.490±15.065 | 55.930±11.993 | 55.370±12.654 | P<0.01 |
| Sex (male(%)) | 4317 (59.2%) | 492 (74.9%) | 135 (82.8%) | P<0.01 |
| FPG (mmol/L) | 4.776±0.501 | 6.634±1.487 | 8.852±2.865 | P<0.01 |
| LgTG (mmol/L) | 0.136±0.256 | 0.276±0.279 | 0.354±0.324 | P<0.01 |
| Cholesterol(mmol/L) | 4.831±0.899 | 5.105±1.076 | 5.245±1.093 | P<0.01 |
| HDL-c(mmol/L) | 1.361±0.356 | 1.244±0.344 | 1.192±0.33 | P<0.01 |
| LDL-c(mmol/L) | 2.710±0.714 | 2.846±0.786 | 2.758±0.806 | P<0.01 |
| UA (μmool/L) | 348.560±94.332 | 369.340±92.884 | 352.590±88.922 | P<0.01 |
| Scr (μmool/L) | 71.059±14.929 | 72.17±14.723 | 71.108±13.367 | 0.186 |
| baseline eGFR (mL/min per 1.73 m2) | 102.034±15.281 | 95.016±13.370 | 97.333±13.558 | P<0.01 |
| eGFR slope (mL/min per 1.73 m2 per year) | −0.548±2.156 | −0.655±2.506 | −0.563±2.771 | 0.492 |
| eGFR slope <−4 mL/min per 1.73 m2 per year (n (%)) | 321 (4.4%) | 40 (6.1%) | 13 (8.0%) | 0.017 |
| eGFR slope <−5 mL/min per 1.73 $m^2$ per year (n (%)) | 180 (2.5%) | 24 (3.7%) | 10 (6.1%) | 0.004 |

**Notes**: Continuous variables are presented as mean±standard deviation, categorical variables as n (%).
**Abbreviations**: FPG, fasting plasma glucose; TG, triglyceride; eGFR, estimated glomerular filtration rate; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; UA, uric acid; Scr, creatinine.

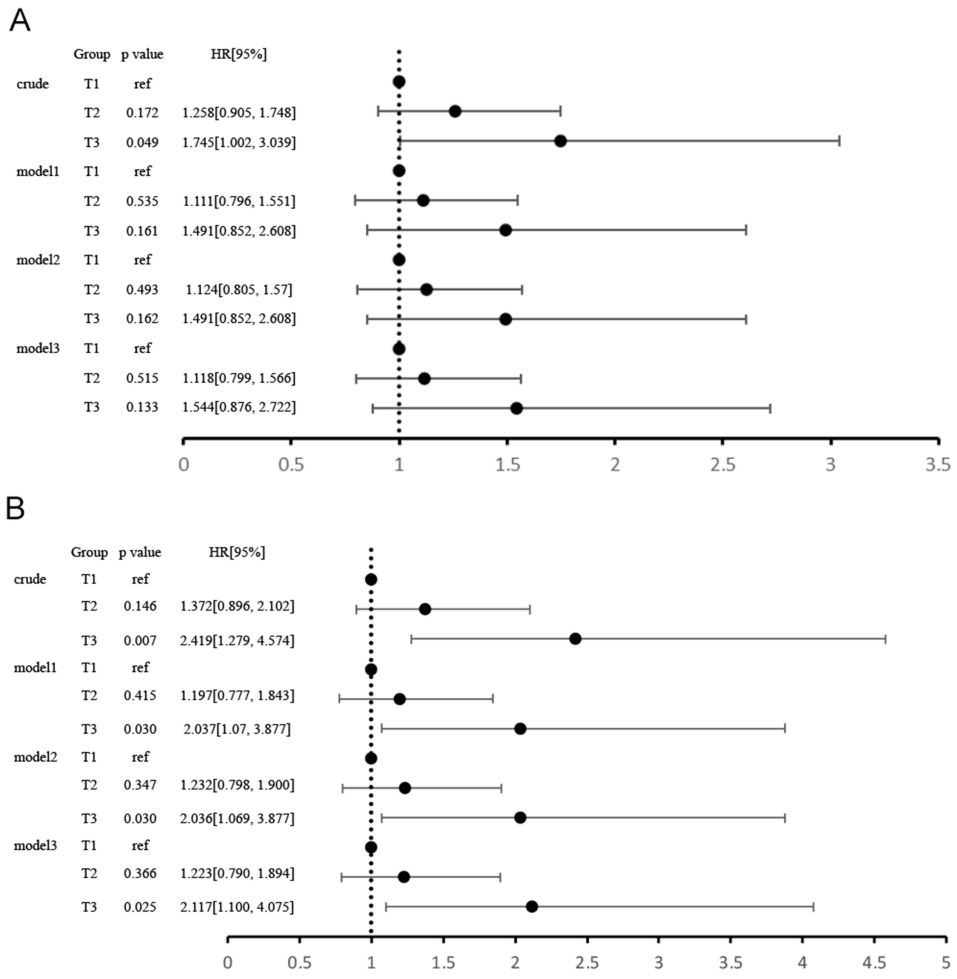


**Figure 2** The risk of fast eGFR slope in the total population. (**A**) eGFR slope <−4 mL/min per 1.73 $m^2$ per year; (**B**) eGFR slope <−5 mL/min per 1.73 $m^2$ per year model 1: adjusted for age (age<65-year-old as ref) and gender (male as ref) model 2: adjusted for age (age<65-year-old as ref), gender (male as ref) and baseline eGFR. model 3: adjusted for age (age<65-year-old as ref), gender (male as ref), baseline eGFR, HUA and lipid parameters.

including age, sex, hyperuricemia, baseline eGFR, dyslipidemia, the T3 group (high-stable group) was still positively associated with fast eGFR slope (eGFR slope <−5 mL/min per 1.73 $m^2$ per year) (HR [95% CI]2.419[1.279, 4.574]).

To further explore the association of FGB trajectories and fast eGFR slope in a sub-group of participants who maintained normal FPG throughout follow-up. We divided this sub-group into four trajectories as the methods mentioned above (Supplement Table S2 and Figure 3): Sub-T1 (low-stable group, n=1443, 21.7%), Sub-T2 (moderate-stable group, n=4002, 51.2%), Sub-T3 (moderate-increasing group, n=1511, 21.4%), and Sub-T4 (high-stable group, n=396, 5.7%).

When the Sub-T1 group (low-stable group) was set as the reference, participants in the other groups tend to be older, with a higher proportion of males. Compared with the Sub-T1 group (low-stable group), LgTG, uric acid, LDL-c, and cholesterol were high, the HDL-c, and baseline eGFR were low in the other groups (Table 2). In the Cox proportional hazard models, the Sub-T4 group (high-stable group) had highest risk for the fast eGFR slope (for eGFR slope <−4 mL/min per 1.73 $m^2$ per year, HR [95% CI] HR 1.640[1.050, 2.561]; for eGFR slope <−5 mL/min per 1.73 $m^2$ per year, HR [95% CI] 1.818[1.018, 3.248]) (Figure 4 and Supplement Figure 1).

## Discussion

The major findings in this longitudinal study with relatively large individuals were as follows. We found that the long-term high-stable trajectory of FPG associated with the development of chronic kidney disease. In FPG normal subgroup, persistent high FPG was significantly associated with the development of CKD, independent of traditional CKD risk

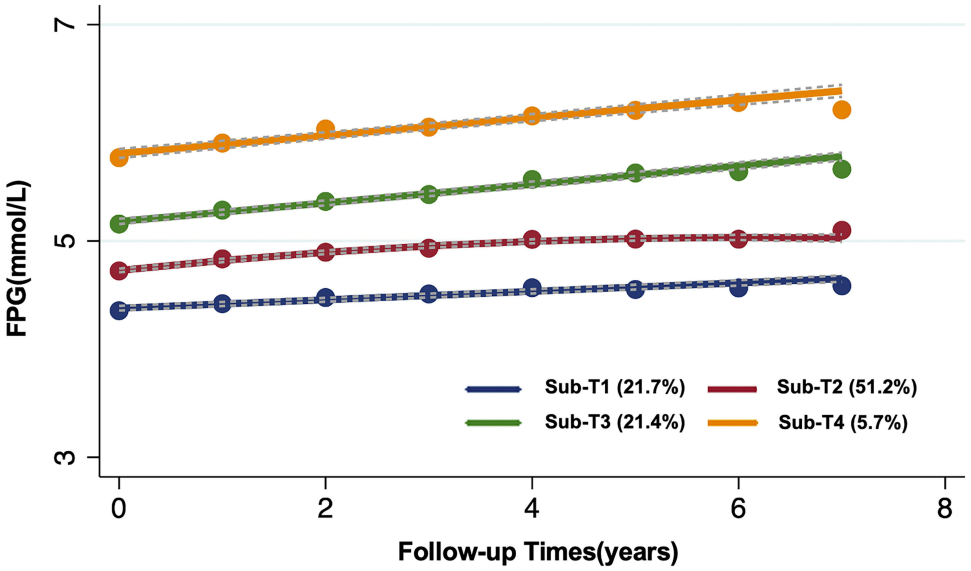


**Figure 3** The trajectories of long-term normal fasting plasma glucose in sub-group by GBTM. Sub-T1, low-stable group; Sub-T2, moderate-stable group; Sub-T3, moderate-increasing group; Sub-T4, high-stable group.

factors. This is the first and relatively large population-based study to evaluate the association between FPG trajectories and the development of CKD.

Previous studies showed that diabetes was a major cause of kidney disease, and diabetic kidney disease develops in almost 40% type 2 diabetes mellitus. Our result showed that the persistent high-stable FPG was a risk factor of CKD. This adds to the results of prior cross-sectional studies demonstrating that alterations of glucose metabolism associate with the development of CKD. Uncontrolled diabetes increased in risk for microvascular complications. Randomized clinical trials have provided evidence that strict glycemic control reduces the microvascular complications of diabetes and also has a favorable effect on cardiovascular outcomes especially in T2DM like the United Kingdom Prospective Diabetes Study,[12,13] The Action to Control Cardiovascular Risk in Diabetes (ACCORD), Control Cardiovascular Risk in Diabetes study,[14] Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled

**Table 2** Descriptive Statistics for Baseline Characteristics According to Group Membership in Sub-Group

| | Sub-T1 (N=1443) | Sub-T2 (N=4002) | Sub-T3 (N=1511) | Sub-T4 (N=396) | p value |
|---|---|---|---|---|---|
| Age (year-old) | 38.860±13.655 | 43.3±14.993 | 50.980±13.75 | 55.380±12.922 | <0.001 |
| Sex (male, %) | 851 (59%) | 2253 (56.3%) | 978 (64.7%) | 278 (70.2%) | <0.001 |
| FPG (mmol/L) | 4.300±0.365 | 4.730±0.349 | 5.189±0.409 | 5.806±0.512 | <0.001 |
| LgTG (mmol/L) | 0.082±0.242 | 0.121±0.247 | 0.199±0.271 | 0.235±0.259 | <0.001 |
| Cholesterol (mmol/L) | 4.674±0.83 | 4.807±0.885 | 5.001±0.949 | 5.022±0.915 | <0.001 |
| HDL-c (mmol/L) | 1.399±0.369 | 1.372±0.352 | 1.318±0.351 | 1.280±0.347 | <0.001 |
| LDL-c (mmol/L) | 2.604±0.657 | 2.698±0.698 | 2.814±0.776 | 2.842±0.715 | <0.001 |
| UA (μmool/L) | 339.567±91.913 | 342.876±93.325 | 364.961±95.865 | 378.393±93.967 | <0.001 |
| Scr (μmool/L) | 71.812±15.017 | 70.493±15.01 | 71.496±14.824 | 72.348±13.656 | 0.003 |
| Baseline eGFR (mL/min per 1.73 $m^2$) | 105.396±15.05 | 103.023±15.359 | 97.643±14.344 | 94.711±12.589 | <0.001 |
| eGFR slope (mL/min per 1.73 $m^2$ per year) | −0.604±2.092 | −0.489±2.144 | −0.638±2.19 | −0.697±2.602 | 0.041 |
| eGFR slope <−4 mL/min per 1.73 $m^2$ per year (n (%)) | 63 (4.4%) | 156 (3.9%) | 80 (5.3%) | 31 (7.8%) | 0.001 |
| eGFR slope <−5 mL/min per 1.73 $m^2$ per year (n (%)) | 36 (2.5%) | 93 (2.3%) | 41 (2.7%) | 19 (4.8%) | 0.030 |

**Note**: Continuous variables are presented as mean±standard deviation, categorical variables as n (%).
**Abbreviations**: FPG, fasting plasma glucose; TG, triglyceride; eGFR, estimated glomerular filtration rate; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; UA, uric acid; Scr, creatinine.

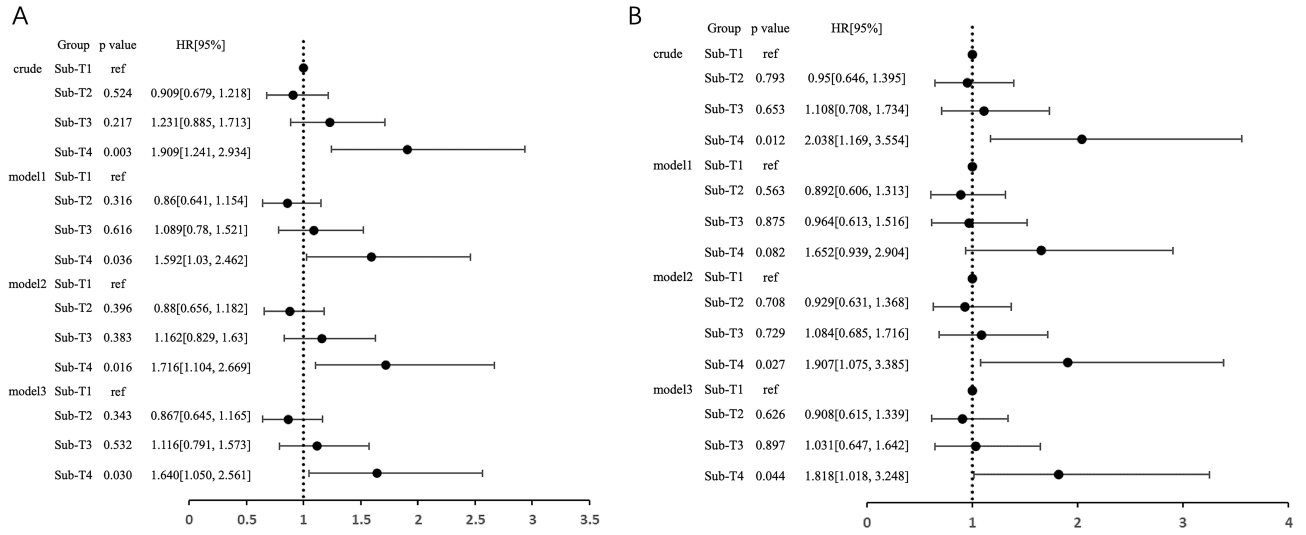


**Figure 4** The risk of fast eGFR slope in the sub-group. (**A**) eGFR slope <−4 mL/min per 1.73 m2 per year; (**B**) eGFR slope <−5 mL/min per 1.73 $m^2$ per year. model 1: adjusted for age (age<65-year-old as ref) and gender (male as ref). model 2: adjusted for age (age<65-year-old as ref), gender (male as ref) and baseline eGFR. model 3: adjusted for age (age<65-year-old as ref), gender (male as ref), baseline eGFR, HUA and lipid parameters.

Evaluation study[15] and the VA Diabetes Trial (VADT).[16] A meta-analysis of the randomized controlled trial reported that improved glycemic control is associated with a relative risk reduction of 20% of the primary renal outcome.[17]

Also, in the sub-group analysis, we found that persistent high- normal glucose was a risk factor of CKD, which indicated that persistent impaired glucose plays a role in kidney disease. Results from The Framingham Heart Study showed that pre-diabetes is associated with the development of kidney disease (2398 subjects in total).[18] Some other studies agreed with this conclusion. However, most of these studies did not include the change of glycemic status.[19,20] So, our study further indicated that long-term glycemic statues also associate with the development of CKD.

In our study, we applied the eGFR change as our end. As in our study, the baseline of eGFR was relatively high (101.37±15.23 mL/min per 1.73 $m^2$), and our subjects have at least three times of measurements and more than four years of follow-ups, we adopted fast eGFR slope as the end. The study showed that the eGFR slope is more useful in populations with higher vs lower baseline GFRs and longer durations of follow-up. Unfortunately, we did not include the UACR results, so we cannot observe the UACR end.[21]

FPG, hemoglobin A1C (HbA1c), and oral glucose tolerance test (OGTT) are indexes to evaluate the diabetes statue. However, OGTT and Hb1Ac are often difficult to obtain from routine health check-ups in most developing countries since they are quite inconvenient and expensive. So, our result showed that the FPG trajectory is a way to evaluate the CKD risk from routine health check-ups. And controlling the early stage of dysglycemia may be beneficial to kidney injury.

The strengths of this study include a large study sample size and the use of repeated measures of study variables over time. This allowed us to find subgroups based on FPG trajectories and CKD incidence by GBTM. The present study was limited by the following points. The most important limitation of our study is that the participants in this study are from a health examination center, and the lack of data on the use of medications of diabetes mellitus. We did not have data on 2-hour PG and HbA1c. Second, the outcome of the present study was based on the change of eGFR slope, and we did not include the UACR end. Third, because we included only participants with an eGFR ≥60 mL/min per 1.73 $m^2$, we cannot make conclusions about participants with an eGFR <60 mL/min per 1.73 $m^2$. Besides, this study was an observational design, which makes it impossible to infer causality between the observed associations between FPG and decreases in eGFR.

In summary, we have identified several distinct trajectories of FPG levels and demonstrated that such trajectories are associated with the development of CKD in a Chinese sample. Individuals with long-term high-normal FPG may be at increased risk of developing CKD. Future studies should address the underlying mechanisms and examine whether the findings of our study can be translated into prevention and intervention measures.

## Data Sharing Statement

The data used to support the findings of this study is available from the corresponding author upon request.

## Ethical Approval

This study was approved by the Institutional Review Board of the Ruijin Hospital, Shanghai Jiao Tong University School of Medicine (No. 201029) and was in accordance with the principles of the Helsinki Declaration II. Informed consent was waived by the ethics committee as all the data were collected after de-identification. The data were only accessible to the principal investigator, ensuring confidentiality. The information was kept confidential throughout the entire study.

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## Disclosure

The authors report no conflicts of interest in this work.

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