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ORIGINAL RESEARCH

Association of different glucose traits with kidney function decline risk in a Chinese community-based population without chronic kidney disease

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Background: Chronic kidney disease (CKD) has become a major issue worldwide and hyperglycemia is known as an important risk factor responsible for CKD progression. Few studies have investigated whether fasting plasma glucose (FPG) could predict kidney function decline (KFD) risk better than postprandial plasma glucose, and vice versa. In this study, we investigated the roles of FPG and 2-hour plasma glucose (2 h-PG) in predicting KFD risk in a Chinese community-based population without baseline deterioration of kidney functions.

Methods: Subjects with normal kidney function from an atherosclerosis cohort in Beijing, China were followed up for 2.3 years. The outcome was KFD (a drop in glomerular filtration rate category accompanied by 25% or greater decline of estimated glomerular filtration rate from the baseline or a sustained decline of more than 5 mL/min/1.73 m^2/year rate).

Results: A total of 3,738 subjects were included of which, 7.7% of the subjects suffered from KFD. After covariates adjustments, both FPG (OR =1.23, $P<0.001$) and 2 h-PG (OR =1.07, $P<0.001$) were associated with KFD. Furthermore, FPG was independent of 2 h-PG to predict KFD (OR =1.26, $P<0.001$). Subgroup analyses and interaction tests including diabetes mellitus, after adjusting all covariates, revealed no significant heterogeneity among analyzed subgroups. We also found subjects with FPG level of 6.1–7.0 mmol/L and >7.0 mmol/L had 1.83 times and 2.51 times KFD risk respectively, compared to subjects with FPG level <5.6 mmol/L.

Conclusion: FPG was superior to 2 h-PG in predicting KFD in a Chinese community-based population without CKD. FPG screening may be an important measure for CKD primary prevention even in subjects with impaired fasting glucose.

Keywords: fasting plasma glucose, postprandial plasma glucose, kidney function decline, chronic kidney disease

Introduction

Chronic kidney disease (CKD) has become a major public health issue worldwide. A cross-sectional survey[1] of a nationally representative sample of Chinese adults in 2010 showed that the overall prevalence of CKD was 10.8% in China and the estimated CKD patients reached about 119.5 million. However, only 12.5% of them were aware of the condition. Thus, identifying and treating related risk factors for early stages of CKD should be an effective approach to prevent and delay its progression.[2]

Hyperglycemia has been known as a key risk factor responsible for CKD progression. Several reviews emphasized that diabetes mellitus (DM) was mainly responsible for CKD in many developed and developing countries[3,4] and also in China.[5] Fasting plasma glucose (FPG) is an important index of hyperglycemia and considered a major risk factor for microvascular complications including CKD in patients with newly

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diagnosed type 2 diabetes.[6] Postprandial blood glucose, in recent years, has been identified as a possible independent risk factor for cardiovascular disease (CVD).[7,8] Nevertheless, whether FPG and postprandial plasma glucose play different roles in predicting CKD risk still remains unclear. In addition, few studies have investigated whether FPG can predict the risk of CKD progression better than postprandial plasma glucose and vice versa.

In the present study, our objective is to elucidate the roles of FPG and 2-hour plasma glucose (2 h-PG) in predicting CKD progression defined as kidney function decline (KFD) in a Chinese community-based population without baseline deterioration of kidney function.

Research design and methods

Data collection

The subjects came from an atherosclerosis cohort in Gucheng and Pingguoyuan communities of Shijingshan district in Beijing, China.[9] In brief, the baseline survey was conducted on 9,540 residents aged ≥40 years from December 2011 to April 2012, and 5,962 of them with gene chip data were invited for a follow-up visit from May 2014 to July 2014. A total of 3,823 subjects responded onsite. There was no significant baseline characteristic difference between subjects who responded and those who did not (data not shown). We further excluded participants whose estimated glomerular filtration rate (eGFR) was below 60 mL/min/1.73 m^2 and participants without creatinine, fasting blood glucose (FBG), and 2 h-PG data. Finally, a total of 3,738 eligible participants were included in this analysis. The flowchart is provided in Figure S1, and the STROBE statement checklist in Table S1. This study was approved by the ethics committee of Peking University and Peking University First Hospital. Each participant provided a written informed consent. We adhered to the principles of the Declaration of Helsinki and the procedures were performed in accordance with institutional guidelines.

Participant questionnaires were obtained and examinations conducted by trained research staffs according to a standard operating procedure. Their seated blood pressure was obtained using an Omron HEM-7117 electronic sphygmomanometer, and the average of three consecutive measurements was used in the analysis.

Blood samples were taken after an overnight fasting of at least 12 hours for the measurement of FPG, total cholesterol, triglycerides, and creatinine concentrations. After that, participants without history of diabetes took glucose powder (75 g) for oral glucose tolerance test (OGTT) while the others took steamed bread (100 g) instead for the measurement of 2 h-PG. All laboratory variables at baseline were measured on the Roche C8000 Automatic Analyzer.

Serum creatinine (μmol/L) at baseline was measured using the enzymatic method. Serum creatinine during revisit was measured using Jaffe's kinetic method on a Hitachi 7,180 Automatic Analyzer in the laboratory of Peking University First Hospital. Thus both, serum creatinine at baseline and revisit, were transformed into values measured by the enzymatic method.[9] Then the value of eGFR was estimated using the equation derived from the CKD Epidemiology Collaboration.[10]

Outcomes

The primary outcome was KFD which was defined according to the Kidney Disease: Improving Global Outcome (KDIGO) 2012 definition[2] is as follows: a drop in the glomerular filtration rate category (≥90 (G1), 60–89 (G2), 45–59 (G3a), 30–44 (G3b), 15–29 (G4), and <15 (G5) mL/min/1.73 m^2) accompanied by 25% or greater drop in eGFR from baseline or a sustained decline in eGFR of more than 5 mL/min/1.73 m^2/year.

Definitions

Current smoking was defined as smoking at least one cigarette per day for at least half a year. Current drinking was defined as drinking at least once per week for at least half a year. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared. Hypertension was defined as any self-reported history of hypertension and/or systolic blood pressure ≥140 mmHg and/or a diastolic blood pressure (DBP) ≥90 mmHg. DM was defined as any self-reported history of diabetes, or FPG ≥7.0 mmol/L, or 2 h-PG in OGTT ≥11.1 mmol/L. CVD was defined as any self-reported history of coronary heart disease or stroke.

Statistical analysis

Data were expressed as mean ± SD for continuous variables and percentages (%) for dichotomous variables. Normally distributed continuous variables were compared using independent *t*-test. Abnormally distributed continuous variables were expressed as median and interquartile range (IQR), and compared using Kruskal–Wallis Test. The Pearson chi-squared test was applied to all categorical variables.

Logistic regression models were used to investigate the effects of different glucose traits on the occurrence of outcomes. Covariates including age, sex, BMI, baseline

eGFR, current smoking, current drinking, total cholesterol, triglyceride, hypertension, CVD history, antihypertensive drugs, hypoglycemic drugs, and lipid-lowering drugs were selected based on previous studies showing a relation to kidney functions. To investigate the different roles of FPG and 2 h-PG in predicting KFD, they were put into the multiple regression models, first individually and then simultaneously. Furthermore, due to the strong correlation between FPG and 2 h-PG, we also compared the full regression model including both FPG and 2 h-PG with nested models with each of FPG and 2 h-PG.

Subgroup analysis examined the relationship between FPG and the risk of KFD according to age, sex, BMI, baseline eGFR, 2 h-PG, current smoking, current drinking, total cholesterol, triglyceride, hypertension, CVD, antihypertensive drugs, hypoglycemic drugs, and lipid-lowering drugs. Test for interaction in the logistic regression model was used to compare OR between the analyzed subgroups.

Moreover, the risk of microvascular complications associated with FPG indices was reported according to the glucose level.[11] So participants were divided into four groups according to FPG: FPG <5.6 mmol/L; FPG 5.6–6.0 mmol/L; FPG 6.1–6.9 mmol/L; and FPG ≥7.0 mmol/L. Multiple logistic regression models, adjusted for major confounding factors, were used to investigate the effects of different glucose groups on the occurrence of outcomes.

A *P*-value of <0.05 (two-sided) was considered statistically significant for all tests. All analyses were performed using Empower(R) (www.empowerstats.com; X&Y Solutions, Inc., Boston, MA, USA) and R (http://www.R-project.org).

Results

A total of 3,738 subjects were included in the analysis. After a median 2.3-year (IQR: 2.28–2.39) follow-up, the incidence of KFD was 7.7% (289/3738). Baseline characteristics of all participants are shown according to the diabetes status (Table 1). The prevalence of DM at baseline was 23.9%. Subjects with DM significantly differed from those without DM in most variables except DBP, total cholesterol, and current smoking status.

Table 2 displays the impact of FPG and/or 2 h-PG on outcomes. In Model-1, we put either FPG or 2 h-PG in and adjust for other covariates. In Model-2, we further put FPG and 2 h-PG into the same model, and adjust by variables in Model-1 plus 2 h-PG for FPG and vice versa.

The risk of KFD was associated with both FPG and 2 h-PG in the crude model. In multiple logistic-regression analyses, every 1 mmol/L increase of FPG was associated with 23% risk of KFD (OR =1.23, 95% CI: 1.16–1.31). However, 2 h-PG was only associated with 7% risk of KFD (OR =1.07, 95% CI: 1.04–1.11) on a scale of every 1 mmol/L

Table 1 Baseline characteristics of all eligible participants

Variable	Total	Non-DM	DM	*P*-value
N	3,738	2,844	894	
Age, years	56.65±8.51	55.66±8.13	59.78±8.92	<0.001
Male, n (%)	1,339 (35.80%)	941 (33.10%)	398 (44.50%)	<0.001
BMI, kg/m^2	26.04±3.36	25.85±3.36	26.67±3.27	<0.001
SBP, mmHg	133.25±16.45	131.67±16.12	138.29±16.48	<0.001
DBP, mmHg	75.01±9.72	74.99±9.50	75.08±10.40	0.951
Total cholesterol, mmol/L	5.32±1.00	5.32±0.97	5.30±1.11	0.553
Triglycerides, mmol/L	1.30 (0.92–1.87)	1.26 (0.90–1.79)	1.47 (1.01–2.14)	<0.001[a]
FPG, mmol/L	6.15±1.76	5.51±0.51	8.18±2.59	<0.001
2 h-PG, mmol/L	8.55±4.04	6.83±1.67	14.03±4.47	<0.001
Baseline eGFR, mL/min/1.73 m^2	101.12±10.64	101.71±10.32	99.22±11.42	<0.001
Current smoking, n (%)	701 (18.80%)	518 (18.20%)	183 (20.50%)	0.132
Current drinking, n (%)	67 (1.80%)	43 (1.50%)	24 (2.70%)	0.021
Hypertension, n (%)	1,816 (48.60%)	1,217 (42.80%)	599 (67.00%)	<0.001
Cardiovascular disease, n (%)	471 (12.60%)	279 (9.80%)	192 (21.50%)	<0.001
Hypoglycemic drugs, n (%)	381 (10.20%)	0 (0.00%)	381 (43.10%)	<0.001
Antihypertensive drugs, n (%)	1,175 (31.60%)	747 (26.40%)	428 (48.10%)	<0.001
Lipid-lowering drugs, n (%)	394 (10.60%)	236 (8.40%)	158 (17.80%)	<0.001

Notes: Normally distributed continuous variables were presented as mean ± SD and compared using independent *t*-test. Abnormally distributed continuous variables were expressed as median and IQR, and [a]compared using Kruskal–Wallis Test.

Abbreviations: BMI, body mass index; DM, diabetes mellitus; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; 2 h-PG, 2-hour plasma glucose; SBP, systolic blood pressure; IQR, interquartile range.

Table 2 Associations of different blood glucose traits and KFD according to DM status

KFD	Crude model	*P*-value	Model-1	*P*-value	Model-2	*P*-value
	OR (95% CI)		OR (95% CI)		OR (95% CI)	
Total						
FPG, mmol/L	1.21 (1.16, 1.27)	<0.001	1.23 (1.16, 1.31)	<0.001	1.26 (1.14, 1.39)	<0.001
2 h-PG, mmol/L	1.08 (1.06, 1.11)	<0.001	1.07 (1.04, 1.11)	<0.001	0.99 (0.94, 1.03)	0.562
Non-DM						
FPG, mmol/L	1.41 (1.06, 1.89)	0.019	1.46 (1.07, 1.98)	0.017	1.43 (1.04, 1.99)	0.030
2 h-PG, mmol/L	1.06 (0.97, 1.16)	0.190	1.05 (0.95, 1.16)	0.305	1.01 (0.92, 1.12)	0.783
DM						
FPG, mmol/L	1.17 (1.10, 1.25)	<0.001	1.19 (1.11, 1.28)	<0.001	1.27 (1.13, 1.42)	<0.001
2 h-PG, mmol/L	1.06 (1.02, 1.11)	0.003	1.06 (1.01, 1.10)	0.017	0.95 (0.89, 1.02)	0.136

Notes: Model-1: including either FPG or 2 h-PG, adjusted for age, sex, BMI, baseline eGFR, current smoking, current drinking, total cholesterol, triglyceride, hypertension, CVD history, antihypertensive drugs, hypoglycemic drugs, and lipid-lowering drugs. Model-2: including both the FPG and 2 h-PG, adjusted by variables in Model-1 plus 2 h-PG for FPG and FPG for 2 h-PG, respectively.

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; 2 h-PG, 2-hour plasma glucose; KFD, kidney function decline.

increase. Furthermore, when putting FPG and 2 h-PG into one model simultaneously, only the association of FPG and KFD (OR =1.26, 95% CI: 1.14–1.39) remained statistically significant.

Also, we found that the full model with FPG and 2 h-PG was significantly better than the model with 2 h-PG only ($P<0.001$) but not better than the one with FPG only ($P=0.547$).

Similar findings were observed in DM and non-DM group and there were no interactions between each glucose trait and diabetes status (*P* for interaction =0.403 for FPG and *P* for interaction =0.335 for 2 h-PG).

The relationships between KFD and different FPG level groups are shown in Table 3. Higher FPG level was associated with increased risk of KFD. Using the lowest (<5.6 mmol/L) FPG group as the control group, increased risk of KFD reached statistical significance at 1.83 times (OR =1.83, 95% CI: 1.27–2.65) in FPG level of 6.1–7.0 mmol/L group and 2.51 times (OR =2.51, 95% CI: 1.53–4.12) in FPG level of >7.0 mmol/L group, respectively.

Subgroup analyses and interaction tests are presented in Figure 1. The trends for KFD were concordant in all subgroups stratified by each adjusted variable including sex (male or female), age (<60 or ≥60-year-old), BMI (<28 or ≥28 kg/m^2), baseline eGFR (grouped by median value), 2 h-PG (<7.8 or ≥7.8 mmol/L), current smoking, current drinking, total cholesterol (<5.18 or ≥5.18 mmol/L), triglyceride (<1.70 or ≥1.70 mmol/L), hypertension, CVD, antihypertensive drugs, hypoglycemic drugs, and lipid-lowering drugs. Also, no significant interactions were observed between FBG and the modifying factors.

Discussion

The main findings of this cohort study are that FPG, independent of 2 h-PG, predicts the risk of KFD in a Chinese community-based population without CKD at baseline after 2.3-year follow-up. It is noteworthy that the risk of KFD has already significantly increased when baseline FPG ≥6.1 mmol/L.

CKD is becoming a global health burden for the general population, due to its epidemic size and constantly increasing prevalence and its potentially severe, life-threatening complications. Global deaths from kidney disease have risen by 83% since 1990.[12] Hyperglycemia is known as a

Table 3 Associations of different FPG levels and KFD

KFD	Incidence, n (%)	Crude analysis		Multiple analysis[a]	
		OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
FPG, mmol/L					
<5.6	96 (5.5)	1.0 (Ref)		1.0 (Ref)	
≥5.6, <6.1	48 (6.0)	1.09 (0.76, 1.56)	0.627	1.02 (0.71, 1.48)	0.897
≥6.1, <7.0	61 (10.6)	2.07 (1.48, 2.89)	<0.001	1.83 (1.27, 2.65)	0.001
≥7.0	84 (14.2)	2.88 (2.11, 3.92)	<0.001	2.51 (1.53, 4.12)	<0.001
P for trend			<0.001		<0.001

Notes: [a]Adjusted for age, sex, BMI, baseline eGFR, current smoking, current drinking, total cholesterol, triglyceride, hypertension, CVD history, antihypertensive drugs, hypoglycemic drugs, lipid-lowering drugs and 2 h-PG.

Abbreviations: 2 h-PG, 2-hour plasma glucose; BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; KFD, kidney function decline.

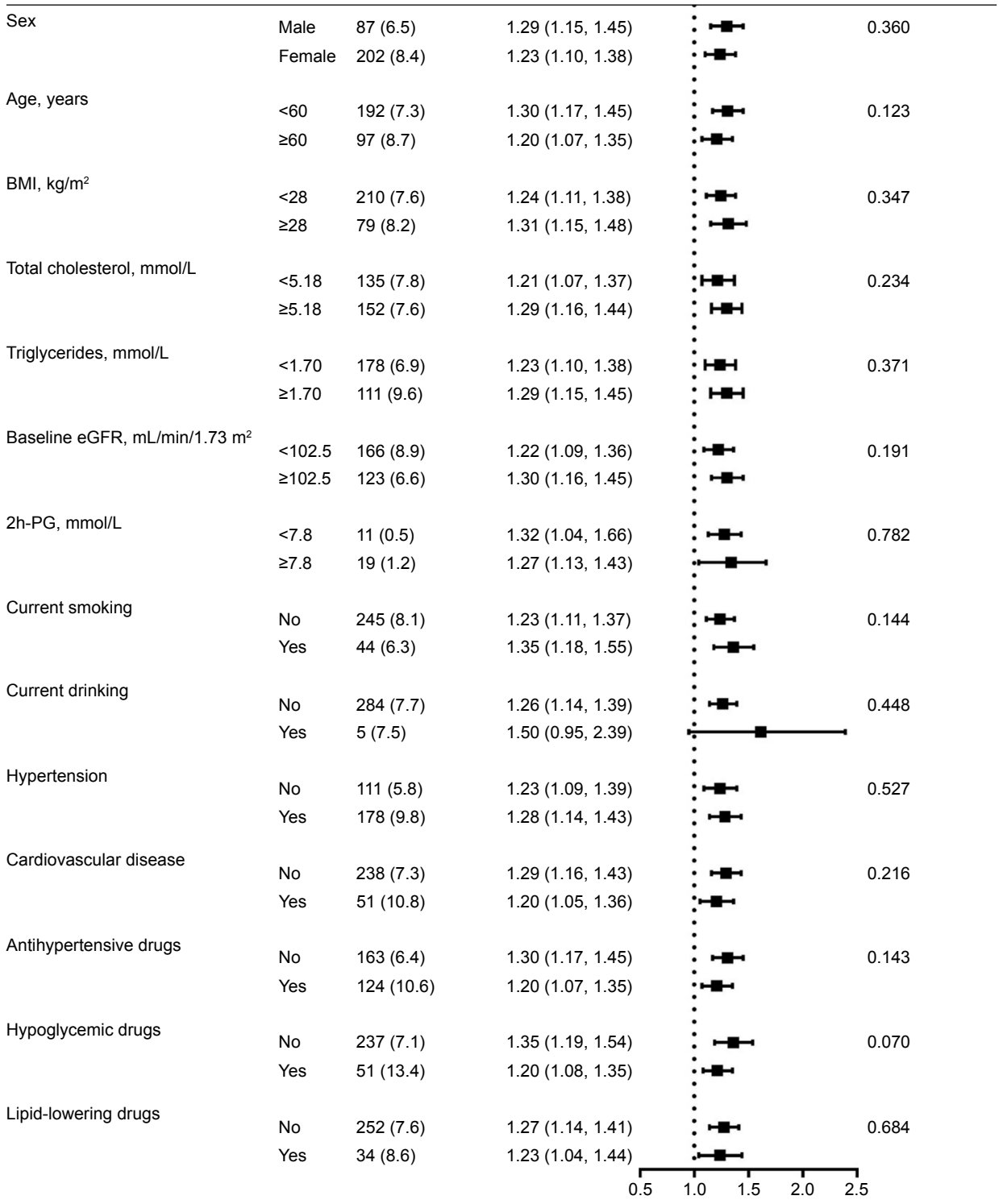

Figure 1 Subgroup analyses for the association between KFD and FPG level.
Note: Variables in the model: age, sex, BMI, baseline eGFR (grouped by median value), 2 h-PG, current smoking, current drinking, total cholesterol, triglyceride, hypertension, cardiovascular disease, antihypertensive drugs, hypoglycemic drugs, and lipid-lowering drugs.
Abbreviations: 2 h-PG, 2-hour plasma glucose; BMI, body mass index; eGFR, estimated glomerular filtration rate; KFD, kidney function decline; FPG, fasting plasma glucose.

very important factor in the deterioration of kidney function. Zhang et al[5] found CKD was more commonly related to diabetes than to glomerulonephritis in both the general population and a hospitalized urban population in China. Furthermore, both FPG and postprandial plasma glucose are commonly used parameters for evaluating glycemic status and were proven to be associated with CKD risk in previous studies.[13]

FPG was considered a risk factor for microvascular complications. The relationship between FPG and CKD, considered as one of the microvascular complications, had been reported in many cross-sectional designed studies.[14–16] It was also suggested that increasing FPG level could be a major predictor for CKD progression. Iseki et al[17] examined the relationship between FPG and end-stage renal disease (ESRD) in 78,529 screeners based on the results of community-based mass screening in Okinawa, Japan. During a 7.75-year follow-up period, a total of 133 subjects developed ESRD. The risk of ESRD development in the high-FPG group (defined as 126 mg/dL or more) was 3.098 times (95% CI, 1.738–5.525; $P<0.0001$). Consistently, our study showed that high FPG levels independently increased the risk of KFD, which is used to evaluate CKD progression, in this community-based Chinese population without CKD at baseline.

On the other hand, postprandial plasma glucose was generally considered as an important risk factor for macrovascular complications. Postprandial plasma glucose was proven to be associated with CVD events not only in cross-sectional studies[8,18] but also in cohort studies.[19] Meanwhile, postprandial plasma glucose was found to be related to CKD in an earlier study.[20] In our study, we also found that 2 h-PG was associated with KFD, one indicator for CKD progression, without adjusting FBG, which supported the speculation that postprandial plasma glucose may also play an important role in CKD.

In summary, FPG and postprandial plasma glucose were both shown to be risk factors for CKD when considered separately. However, to the best of our knowledge, few studies have investigated whether FPG could predict the risk of CKD better than 2 h-PG and vice versa. In the study, we put FPG and 2 h-PG into one multiple regression model simultaneously, and found that only the association of FPG and KFD (OR =1.26, 95% CI: 1.14–1.39) remained statistically significant after adjusting 2 h-PG. Furthermore, due to the strong correlation between FPG and 2 h-PG, we also compared the full regression model including both FPG and 2 h-PG with nested models, with each of FPG and 2 h-PG, as repeated verification. For the first time, we reported that FPG was superior to 2 h-PG in predicting the risk of KFD.

However, the precise mechanisms for the different roles of these two glucose traits in the progression of renal pathological changes are still unclear. Despite many studies concentrating on the structural changes seen in the glomerulus, abnormalities are also found in the tubulointerstitium. One explanation may be that FPG and postprandial plasma glucose may have different effects on interstitial fibrosis. Ikee et al[21] quantitatively evaluated pathological changes in the glomerulus, tubulointerstitium, and vessels in renal biopsy specimens from 23 patients with non-diabetic CKD. They demonstrated that FPG was significantly correlated with interstitial fibrosis ($r=0.532$, $P=0.009$). Meanwhile, no statistically significant correlation was found between 2 h PG and interstitial fibrosis ($r=0.081$, $P=0.71$). In fact, tubulointerstitial changes have been reported to be quite significantly correlated with renal dysfunction and prognosis.[22,23] This finding may partially explain why FPG is better in predicting KFD risk in our study.

Furthermore, our data revealed that the risk of KFD has already significantly increased when FPG ≥6.1 mmol/L. Consistently, Nang et al[11] have also found that the prevalence of CKD gradually increased in relation to higher FPG level, even beginning at level below the existing diagnostic threshold for DM of 7.0 mmol/L. This association persisted after adjustment for age, gender, ethnic group, and hypertension. They also pointed out that lowering the cutoff point for the diagnosis of diabetes from 7.0 to 6.0 mmol/L may increase the sensitivity for detecting kidney complications such as albuminuria and/or eGFR <60 mL/min/1.73 m^2. In our study, the risk of KFD was also graded relative to FPG levels. Increasing KFD risk reached statistical significance from FPG level of 6.1 mmol/L, which supports the idea of lowering the FPG threshold from 7.0 to 6.1 mmol/L may be appropriate for CKD primary prevention.

Our study had several limitations. First, there was no data of proteinuria at baseline in this cohort. According to KDIGO guidelines, some of the patients may have CKD if they have albuminuria, in this case especially those with DM. However, albuminuria index including albumin-creatinine ratio and urine protein measurement was not examined at baseline, so we could not exclude the possible influence of albuminuria in our analysis. Nevertheless, we mainly focused on the change of kidney function evaluated by eGFR in this study. Also, no significant heterogeneity was found in subgroup analysis according to diabetes, and the main result did not significantly change in the analysis of patients without DM and those with DM but not on hypoglycemic treatment. Second, only two time-points were examined. The slope of eGFR based on more time-point data would enhance the accuracy of kidney end point. However, similar methods using two time-points of creatinine measurements to determine the kidney end point can be found in previous studies.[24,25] Third, it may bring questions when we put FPG and 2 h-PG into one model, as FPG and 2 h-PG are closely correlated. Nonetheless, we used likelihood ratio test to

analysis the effects of different models, which consistently indicated FPG was a better predictor of KFD.

Conclusion

Our study demonstrates that FPG is independent and superior to 2 h-PG in predicting the risk of KFD in a Chinese community-based population without CKD. FPG screening monitored conveniently and continuously, could be an important and convenient measurement for CKD primary prevention even in subjects with impaired fasting glucose.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

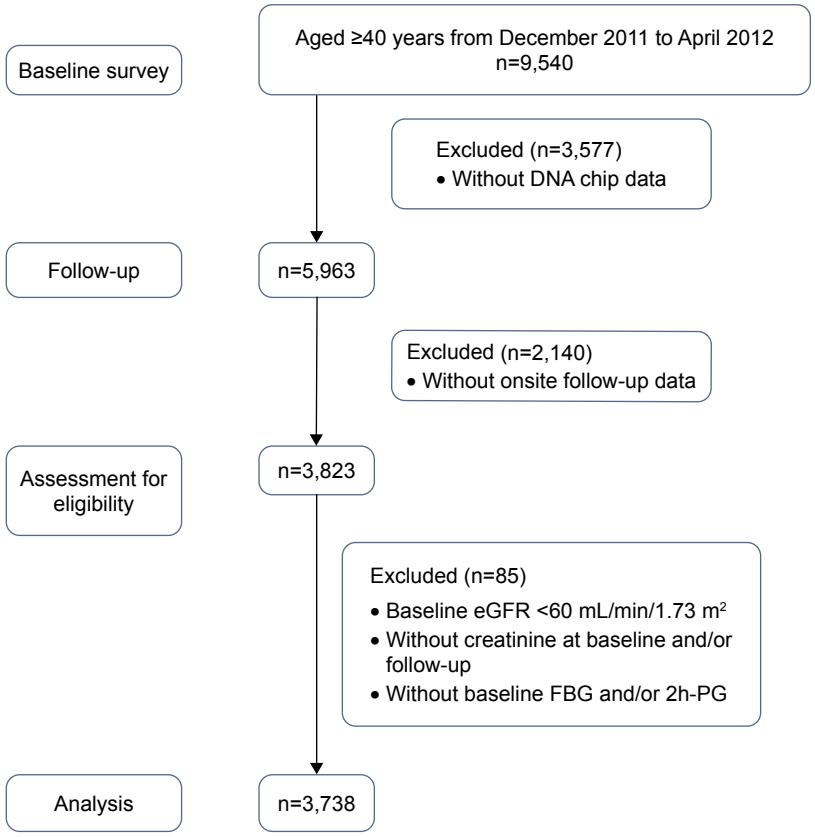

Figure S1 CONSORT flow diagram.
Abbreviations: 2 h-PG, 2-hour plasma glucose; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose.

Table S1 STROBE Statement-checklist of items that should be included in reports of observational studies

	Item no	Recommendation	Page no	Relevant text from manuscript
Title and abstract	1	a) Indicate the study's design with a commonly used term in the title or the abstract	1	1–2
		b) Provide in the abstract an informative and balanced summary of what was done and what was found	2	35–48
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3	55–70
Objectives	3	State specific objectives, including any pre-specified hypotheses	3	71–73
Methods				
Study design	4	Present key elements of study design early in the paper	3	76
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3–4	76–80
Participants	6	a) *Cohort study* – Give the eligibility criteria and the sources and methods of selection of participants. Describe methods of follow-up *Case–control study* – Give the eligibility criteria, the sources and methods of case ascertainment, and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* – Give the eligibility criteria and the sources and methods of selection of participants b) *Cohort study* – For matched studies, give matching criteria and number of exposed and unexposed *Case–control study* – For matched studies, give matching criteria and the number of controls per case	3–4	76–85

(*Continued*)

Table S1 (*Continued*)

	Item no	Recommendation	Page no	Relevant text from manuscript
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3–5	76–119
Data sources/ measurement	8[a]	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	3–4	76–104
Bias	9	Describe any efforts to address potential sources of bias	5	121–139
Study size	10	Explain how the study size was arrived at		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5	121–139
Statistical methods	12	a) Describe all statistical methods, including those used to control for confounding	5	121–144
		b) Describe any methods used to examine subgroups and interactions	5	135–139
		c) Explain how missing data were addressed	3	80–81
		d) *Cohort study* – If applicable, explain how loss to follow-up was addressed *Case–control study* – If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* – If applicable, describe analytical methods taking account of sampling strategy	3	77–80
		e) Describe any sensitivity analyses	6	164–165
Results				
Participants	13[a]	a) Report numbers of individuals at each stage of study – eg, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed	3–4	77–84
		b) Give reasons for non-participation at each stage	3–4	76–84
		c) Consider use of a flow diagram		
Descriptive data	14[a]	a) Give characteristics of study participants (eg, demographic, clinical, social), information on exposures, and potential confounders	6	149–153
		b) Indicate number of participants with missing data for each variable of interest	3–4	78–84
		c) *Cohort study* – Summarize follow-up time (eg, average and total amount)	6	149–150
Outcome data	15[a]	*Cohort study* – Report numbers of outcome events or summary measures over time *Case–control study* – Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* – Report numbers of outcome events or summary measures	6	150–152
Main results	16	a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% CI). Make clear which confounders were adjusted for and why they were included	6	154–168
		b) Report category boundaries when continuous variables were categorized	6	150–151
		c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		
Other analyses	17	Report other analyses done – eg, analyses of subgroups and interactions and sensitivity analyses	6–7	166–180
Discussion				
Key results	18	Summarize key results with reference to study objectives	7	182–185
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9	245–260
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7–9	186–260
Generalizability	21	Discuss the generalizability (external validity) of the study results	9	242–244
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	10	270–272

Notes: [a]Gives information separately for cases and controls in case–control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies. An explanation and elaboration article discusses each checklist item and gives a methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Websites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.