Journal of the Endocrine Society, 2023, **7**, 1–10
https://doi.org/10.1210/jendso/bvad069
Advance access publication 1 June 2023
Clinical Research Article

Estimated Glucose Disposal Rate Predicts Renal Progression in Type 2 Diabetes Mellitus: A Retrospective Cohort Study

Juan Peng,[1] Aimei Li,[1] Liangqingqing Yin,[1] Qi Yang,[1] Jinting Pan,[1] and Bin Yi[1]

[1]Department of Nephrology, The Third Xiangya Hospital, Central South University, Changsha, Hunan 410013, China

Correspondence: Bin Yi, MD, PhD, Department of Nephrology, The Third Xiangya Hospital, Central South University, 138 Tongzipo Road, Changsha, 410013, China. Email: yibin2008@csu.edu.cn.

Abstract

Context: Insulin resistance is a feature of type 2 diabetes mellitus (T2DM). The estimated glucose disposal rate (eGDR), a validated marker for insulin resistance, is associated with complications of diabetes, but few studies have explored the relationship between eGDR and renal outcomes in T2DM.

Objective: This study investigated the value of eGDR in predicting renal progression in T2DM.

Methods: A total of 956 T2DM patients with a baseline estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m^2 and 5 years of follow-up were enrolled. Primary outcomes were rapid eGFR decline, eGFR <60 mL/min/1.73 m^2, and composite renal endpoint consisting of 50% eGFR decline, doubling of serum creatinine, or end-stage renal disease. A continuous scale with restricted cubic spline curves and a generalized linear model were applied to evaluate the associations between eGDR and primary outcomes.

Results: Rapid eGFR decline was experienced by 23.95% of patients, 21.97% with eGFR <60 mL/min/1.73 m^2, and 12.13% with the composite renal endpoint. The eGDR showed a relationship with follow-up eGFR and percentage change in eGFR ($P < .001$). An eGDR <6.34 mg/kg/min was an independent risk factor for rapid eGFR decline, eGFR < 60 mL/min/1.73 m^2, or the composite renal endpoint($P < .05$). Compared with eGDR of 5.65~6.91 mg/kg/min, eGDR levels >8.33 mg/kg/min decreased the risk of rapid eGFR decline by 75%, eGFR < 60 mL/min/1.73 m^2 by 60%, and the composite renal endpoint by 61%. Subgroup analysis was performed by sex, age, and diabetes duration, which showed that eGDR was associated with primary outcomes.

Conclusion: Lower eGDR is a predictive factor for renal deterioration in T2DM patients.

Key Words: type 2 diabetes mellitus, estimated glucose disposal rate, estimated glomerular filtration rate

Abbreviations: BMI, body mass index; BUN, blood urea nitrogen; DKD, diabetic kidney disease; DM, diabetes mellitus; eGDR, estimated glucose disposal rate; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; FBG, fasting plasma glucose; HbA1c, glycated hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; sUA, serum uric acid; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglycerides; WC, waist circumference.

Diabetic kidney disease (DKD) is a microvascular complication of diabetes mellitus (DM) and the major cause of end-stage renal disease (ESRD), affecting approximately 20% to 40% of patients with DM [1]. Although the achievement of recommended targets for blood glucose, blood pressure, and blood lipids delays the progression of DKD to some extent, the proportion of people with ESRD caused by DM continues to increase, from 375.8 per million people in 2000 to 1016 per million people in 2015 [2, 3]. DKD also substantially increases the risk of cardiovascular events, all-cause mortality, and the economic burden on individuals and society [4, 5]. Therefore, preventing the onset and progression of DKD has become a major public health problem that needs to be solved.

Insulin resistance is defined as a reduced response of target tissues and cells to insulin stimulation. It is not only an independent risk factor for DM, but also closely related to the development and progression of DKD [6]. Insulin resistance can trigger abnormal changes in renal hemodynamics [7], accelerate renal cell apoptosis [8], lower renal tubular reabsorption [9], and damage podocyte structure and function, leading to renal injury [10]. The hyperinsulinemic-euglycemic clamp is the current gold standard test for assessing insulin resistance once it is established, but its complicated operation process and high expense make it rarely used in the clinical. Thus, many indicators have been put forth to assess islet function, such as the estimated glucose disposal rate (eGDR), homeostatic model assessment for insulin resistance, and oral glucose insulin sensitivity index [11]. The eGDR is strongly associated with the development and progression of albuminuria in patients with DM. In a retrospective cohort study on 1441 patients with type 1 DM (T1DM), eGDR <5.6 mL/kg/min after follow-up increased the risk of albuminuria in patients with T1DM [12]. This association has been further confirmed in type 2 DM (T2DM) by Giuseppe Penno et al [13]. However, data linking eGDR with decreased estimated glomerular filtration rate (eGFR) in patients with

Received: 1 November 2022. **Editorial Decision:** 22 May 2023. **Corrected and Typeset:** 9 June 2023

DM have been limited and inconsistent. One study found that neither elevated nor decreased eGDR was associated with the development of ESRD in patients with T1DM [12], but another large study confirmed that eGDR was a risk factor for decreased eGFR in patients with T2DM [13]. There has been no cohort study of eGDR and renal function in T2DM. Hence, we investigated the relationship between eGDR and eGFR and assessed the predictive value of eGDR for renal outcome events in patients with T2DM through a retrospective cohort.

Methods

Study Subjects

This study retrospectively reviewed 1083 subjects with T2DM with baseline eGFR ≥60 mL/min/1.73 m^2, aged >18 years, who came from the Third Xiangya Hospital of Central South University between January 2011 and September 2021. T2DM was diagnosed according to the World Health Organization 1999 diabetes classification and diagnostic criteria [14]. Each patient was hospitalized 2 or more times at an interval of 5 ± 0.5 years. Subjects were excluded because of the following criteria: (i) no follow-up eGFR information; (ii) urinary tract infections, malignant tumors, hereditary diseases, infectious diseases, or malignant hypertensive diseases; (iii) a recent dramatic increase in proteinuria, nephrotic syndrome, acute kidney injury, posttransplantation or other kidney diseases; and (iv) acute complications of DM or severe cardiac, pulmonary, or hepatic insufficiency. Thus, in the end, 956 participants were ultimately included in the study. The study was approved by the Ethics Committee of the Third Xiangya Hospital of Central South University (22156).

Data Collection

Age, sex, height, weight, diabetes duration, and medication history (lipid-lowering drugs, antidiabetic, anticoagulant) were obtained from the electronic medical record system at each hospital stay.

All body fluid samples were analyzed at the clinical laboratory of the Third Xiangya Hospital. Serum creatinine (sCr), blood urea nitrogen (BUN), serum uric acid (sUA), fasting blood glucose (FBG), fasting serum insulin (INS), total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) were tested using automatic biochemical analyzers. Glycated hemoglobin A1c (HbA1c) was measured using high-performance liquid chromatography.

Hypertension was defined as (i) systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥90 mmHg; (ii) a self-reported history of physician-diagnosed hypertension; and/or (iii) the use of antihypertensive agents. The eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine formula (2009) [15]. The percent change in eGFR was calculated as (last eGFR − first eGFR)/first eGFR *100 [16]. Body mass index (BMI) was calculated as weight (kg)/height^2 (m). The eGDR (mg/kg/min) was calculated as eGDR = 21.158 − (0.09 × WC) − (3.407 × HT) −(0.551 × HbA1c), where WC = waist circumference (cm), HT = hypertension (yes = 1/no = 0), and HbA1c = HbA1c (%) [17]. Rapid eGFR decline was defined as an eGFR loss of >5 mL/min/1.73 m^2/year [18].

Outcomes

Primary outcomes were rapid eGFR decline, eGFR < 60 mL/min/1.73 m^2, and a composite renal endpoint consisting of 50% eGFR decline, doubling of serum creatinine or ESRD.

Statistical Analysis

Under the missing at random assumption, we first performed multiple imputations by chained equations to impute missing data for height (0.2% missing), weight (0.3% missing), WC (6.1% missing), HbA1c (3% missing), fasting serum insulin (4.9% missing), FPG (3.2% missing), sUA (1% missing), BUN (0.8% missing), HDL cholesterol (3.3% missing), LDL cholesterol (3.1% missing), TC (3.2% missing) and TG (2.9% missing). We generated 25 complete datasets for analyses. The missing at random assumption was plausible in our case, as a wide range of variables, including all variables in the substantive analysis, were included in the imputation model [19].

All statistical analyses were performed with Stata 16 and Rx64 4.1. Variables with normal distribution are presented as means ± SD. Using univariate analysis of variance was run to compare the differences between groups. Skewed distribution data are presented as median with interquartile range, and they were compared using the Kruskal-Wallis test. Restricted cubic spline linear regression analysis was used to analyze the correlations of eGDR with follow-up eGFR and percentage change in eGFR. The correlations of eGDR with the primary outcomes were evaluated by restricted cubic spline logistic regression analysis. To balance best fit and overfitting in the main splines, the number of knots, (between 3 and 7) was chosen as the one that yielded the lowest Akaike information criterion (AIC), but if different knot numbers were within 2 of each other, the lowest number of knots was chosen [20]. Furthermore, the relationships between 5 predefined eGDR levels and primary outcomes were examined by generalized linear regression models: 5 equally distributed categories of eGDR were defined by the 20th, 40th, 60th, and 80th centiles. P values <.05 were considered statistically significant.

Results

Incidence of Events

At the end of the 5 years of follow-up, among the 956 study subjects, a total of 747 (78.14%) patients experienced a decrease in eGFR, 229 (23.95%) showed rapid eGFR decline, 210 (21.97%) developed eGFR <60 mL/min/1.73 m^2, and 116 (12.13%) progressed to the composite renal endpoint. All data have been de-identified.

Baseline Clinical Characteristics by Follow-up eGFR Levels

The study subjects were divided into 2 groups: follow-up eGFR ≥60 mL/min/1.73 m^2 and eGFR <60 mL/min/1.73 m^2. The lipid, BMI, WC, FPG, history of lipid-lowering drugs use, and history of anticoagulant medication use were not significantly different between the 2 groups. Compared with the eGFR ≥60 mL/min/1.73 m^2 group, patients in the eGFR < 60 mL/min/1.73 m^2 group were older at baseline, had a longer duration of diabetes, and had higher blood pressure, HbA1c, sUA, BUN, and proportion of insulin use as well

as lower eGDR levels and proportion of oral hypoglycemic drugs (all $P < .05$) (Table 1).

Relationship Between eGDR and the Progression of Renal Function in Patients With T2DM

Correlation of eGDR with follow-up eGFR and percentage change in eGFR

Restricted cubic spline linear regression analyses showed a significant correlation between baseline eGDR and follow-up eGFR ($F = 13.4$, $P < .001$) (Fig. 1A). After adjusting for age, diabetes duration, sUA, LDL, TG, BMI, and BUN, this association remained statistically significant ($F = 10.3$, $P < .001$) (Fig. 1C). Baseline eGDR also showed a significant correlation with the percentage change in eGFR ($F = 6.7$, $P < .001$) (Fig. 1B). After correcting for the same confounding factors, its association remained significant ($F = 9.9$, $P < .001$) (Fig. 1D).

Impact of eGDR on renal outcome events

Restricted cubic spline logistic regression analyses showed that eGDR below a threshold level of 6.34 (95% CI, 6.20-6.48) mg/kg/min increased the risk of having a rapid eGFR decline (Fig. 2A), eGFR <60 mL/min/1.73 m^2(Fig. 2B) or the composite renal endpoint (Fig. 2C) in patients with T2DM, after adjusting for sex, age, diabetes duration, sUA, BUN, LDL, TG, BMI, lipid-lowering drugs, insulin, anticoagulant medication, and oral hypoglycemic drugs ($P < .05$). Furthermore, eGDR >6.34 mg/kg/min was associated with a decreased risk of the occurrence of rapid eGFR decline (Fig. 2A) or eGFR < 60 mL/min/1.73 m^2 ($P < .05$) (Fig. 2B). A value of eGDR equal to 6.34 (95% CI, 6.20-6.48) mg/kg/min may be a good cutoff point for predicting renal outcome.

Generalized linear regression models showed that compared with eGDR levels of 5.65~6.91 mg/kg/min, eGDR levels >8.33 mg/kg/min decreased the risk of rapid eGFR decline by 75%, eGFR <60 mL/min/1.73 m^2 by 60% and the composite renal endpoint by 61%, after correcting for the same confounding factors (Fig. 3).

Predictive value of eGDR and components in renal outcome events

Whether the effect of eGDR on renal outcome events was driven by its components (HbA1c, WC, and hypertension) was explored. Table 2 shows the odds ratio (OR) and Akaike information criterion (AIC) values for renal outcome events calculated for eGDR and its components. Levels of eGDR, HbA1c, and hypertension were risk factors for all renal outcome events. The predictive value of eGDR for the occurrence of eGFR <60 mL/min/1.73 m^2 and the composite renal endpoint was superior to WC and HbA1c and was similar to hypertension (Table 2).

Table 1. Study subjects grouped by follow-up eGFR

Variable	eGFR (mL/min/1.73 m^2)		*P* value
	≥ 60	<60	
N	746	210	
Age (year)	56.28 ± 11.69	62.26 ± 11.41	.001
Male (n, %)	481(64.48%)	133(63.33%)	.890
DD (years)	6(2-10)	10(5-15)	.001
BMI (kg/m^2)	24.83(22.96-26.84)	24.22(22.27-26.67)	.061
WC (cm)	90(85-97)	90(84-98)	.894
SBP (mmHg)	130(121-140)	136(125-150)	.001
DBP (mmHg)	78(73-84)	79(73-84)	.776
TC (mmol/L)	4.72(4.05-5.43)	4.59(3.79-5.28)	.103
TG (mmol/L)	1.67(1.11-2.73)	1.61(1.03-2.56)	.201
HDL-C (mmol/L)	1.15(0.98-1.38)	1.15(0.95-1.4)	.605
LDL-C (mmol/L)	2.4(1.9-2.95)	2.33(1.8-2.9)	.252
FPG (mmol/L)	7.84(6.29-9.89)	7.74(6.1-10.13)	.737
INS (mU/L)	7.6(4.16-12.79)	7.58(4.1-13.27)	.931
HbA1c (%)	8.5(7.2-10.3)	9(7.4-11)	.038
eGDR (mg/kg/min)	6.55(4.87-8.08)	5.55(4.01-6.99)	.001
BUN (mmol/L)	5.14(4.32-6.22)	5.9(4.92-7.71)	.001
sUA (umol/L)	290(238-347)	325.5(269-400)	.001
eGFR (mL/min/1.73 m^2)	92.41(79.71-103.21)	40.98(18.99-50.26)	.001
Lipid-lowering drugs (n, %)	344(46.11%)	112(53.33%)	.064
Insulin (n, %)	651(87.27%)	200(95.23%)	.001
Oral hypoglycemic drugs (n, %)	697(93.43%)	182(86.67%)	.001
Anticoagulant medication (n, %)	151(20.24%)	53(25.24%)	.118

Abbreviations: BMI, body mass index; BUN, blood urea nitrogen; DBP, diastolic blood pressure; DD, diabetes duration; eGDR, estimated glucose disposal rate; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; INS, fasting serum insulin; LDL, low-density lipoprotein; SBP, systolic blood pressure; sUA, serum uric acid, TC, total cholesterol; TG, triglycerides; WC, waist circumference.

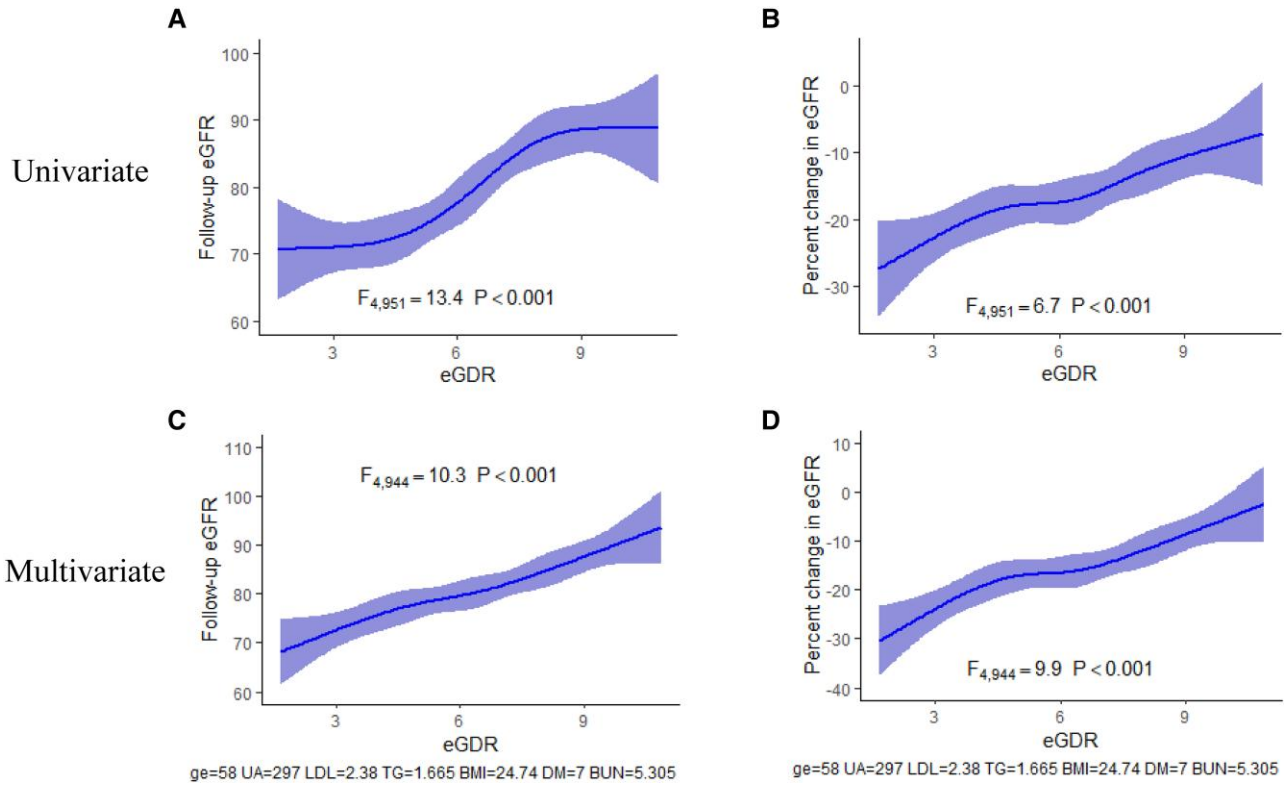

Figure 1. Correlation of eGDR with follow-up eGFR and percent change in eGFR. A, univariate restricted cubic spline linear regression with 3 knots analysis of eGDR and follow-up eGFR. B, Multivariate restricted cubic spline linear regression with 3 knots analysis of eGDR and follow-up eGFR. C, univariate restricted cubic spline linear regression with 3 knots analysis of eGDR and percent change in eGFR. D, Multivariate restricted cubic spline linear regression with 3 knots analysis of eGDR and percent change in eGFR. Analyses were adjusted for age, diabetes duration, sUA, LDL, TG, BMI, and BUN. $P < .05$ was considered statistically significant. The shaded areas represent the 95% CI for the spline model.

Effect of eGDR on renal outcome events after risk factor stratification

Age, sex, and diabetes duration are risk factors for renal function decline in people with T2DM. So, we further stratified the analysis by age, sex, and diabetes duration. After controlling for potential confounders, in T2DM patients aged <65 years, with DM <10 years, and among women, eGDR was significantly associated with rapid eGFR decline, eGFR <60 mL/min/1.73 m^2, and the composite renal endpoint ($P < .05$). In the counterparts of each of those subgroups, eGDR was also significantly associated with rapid eGFR decline ($P < .05$). A higher cutoff point for eGDR exerted a renoprotective effect in T2DM patients with age <65 years, patients with DM <10 years, and men (age ≥65 years vs age <65 years 5.73 (95% CI, 5.66-5.80) vs 6.65 (95% CI, 6.53-6.77); diabetes duration ≥10 years vs diabetes duration <10 years 6.00 (95% CI, 5.92-6.08) vs 6.53 (95% CI, 6.42-6.65); female vs male 6.03 (95% CI, 5.94-6.12) vs 6.52 (95% CI, 6.32-6.72) (Fig. 4A-4F, Fig. 5A-5F, Fig. 6A-6F).

Cutoff point for eGDR to predict renal outcome events

The receiver operating characteristic (ROC) curve based on the optimized Euclidean distance method [21] was drawn to validate the cutoff values of eGDR for predicting renal outcomes. We found that the cutoffs obtained by this method were similar to those obtained with restricted cubic splines (Table 3).

Discussion

In this study, we found that baseline eGDR showed a significant nonlinear correlation with the percent change in eGFR and the follow-up eGFR. A value of eGDR <6.34 mg/kg/min was an independent risk factor for renal outcome events in patients with T2DM. In addition, the predictive value of eGDR for the occurrence of eGFR <60 mL/min/1.73 m^2 and the composite renal endpoint was superior to that of HbA1c and WC and was similar to hypertension. These results suggest that lower eGDR can predict renal function progression in type 2 diabetic patients.

eGDR is one of the main indicators of the response to insulin resistance and is significantly associated with the glucose disposal rate measured with a euglycemic-hyperinsulinemic clamp [13]. In the present research, we identified that patients with a follow-up eGFR <60 mL/min/1.73 m^2 had significantly lower eGDR levels than those with eGFR ≥60 mL/min/1.73 m^2, in line with the conclusions of other studies [22–25]. Bombelli et al recruited 15 773 patients with T2DM treated at 19 Italian diabetes clinics and found that patients with lower eGDR were more likely to have lower eGFR [13]. Hence, we further analyzed the correlation between baseline eGDR and the percentage change in eGFR and the follow-up eGFR and found that baseline eGDR was significantly associated with both. This suggests that eGDR may predict changes in eGFR levels in patients with T2DM.

Notably, after controlling for numerous confounders, an eGDR cutoff point associated with renal outcome was found.

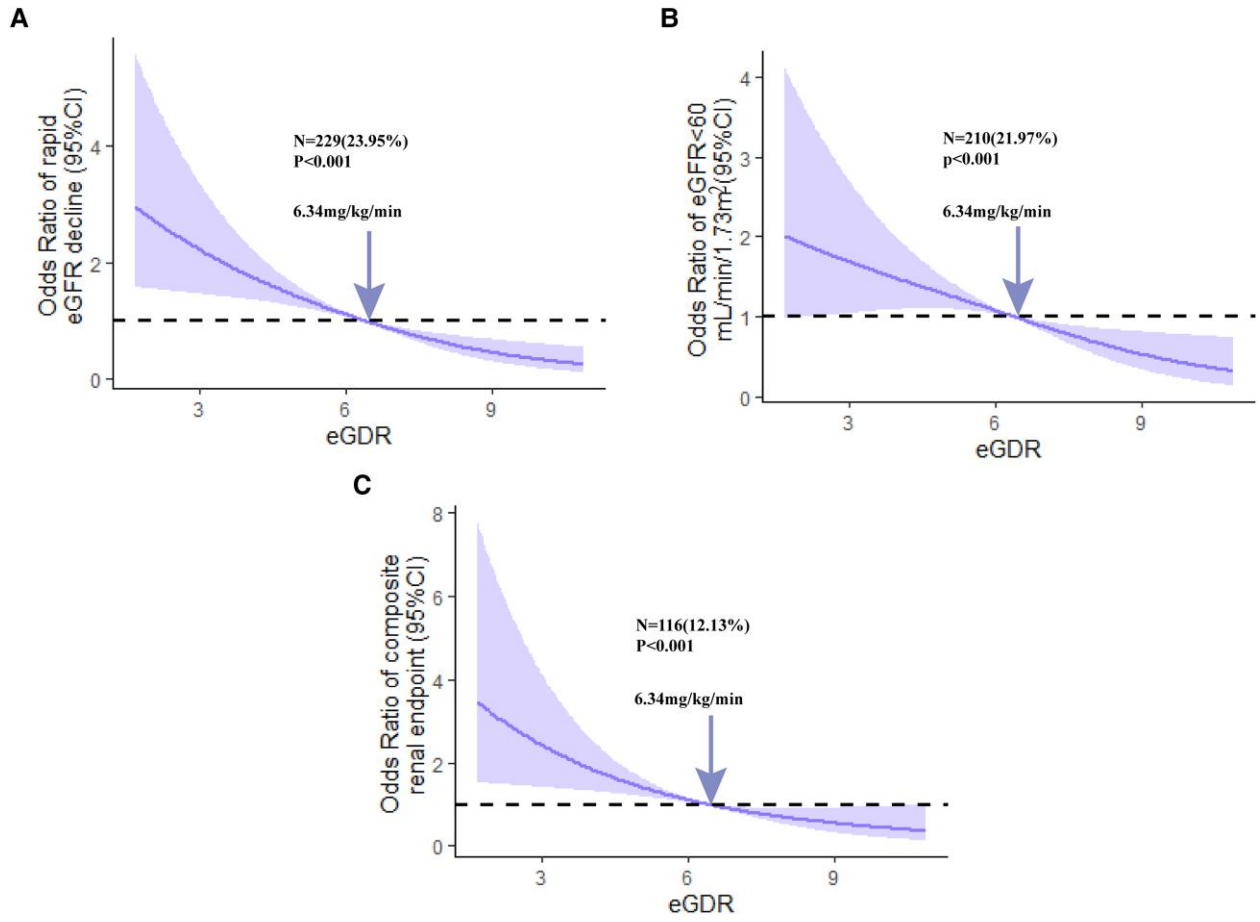

Figure 2. Multivariable adjusted odds ratios for renal outcome events according to levels of eGFR on a continuous scale in the overall population. A, Association between eGDR and rapid eGFR decline. B, Association between eGDR and eGFR <60 mL/min/1.73 m^2. C, Association between eGDR and composite endpoint. Solid purple lines are multivariable adjusted odds ratios, with shaded areas showing 95% CI derived from restricted cubic spline regressions with 3 knots. Reference lines for no association are indicated by a black dotted line at a hazard ratio of 1.0. Analyses were adjusted for age, diabetes duration, sUA, BUN, LDL, TG, BMI, lipid-lowering drugs, insulin, anticoagulant medication, and oral hypoglycemic drugs.

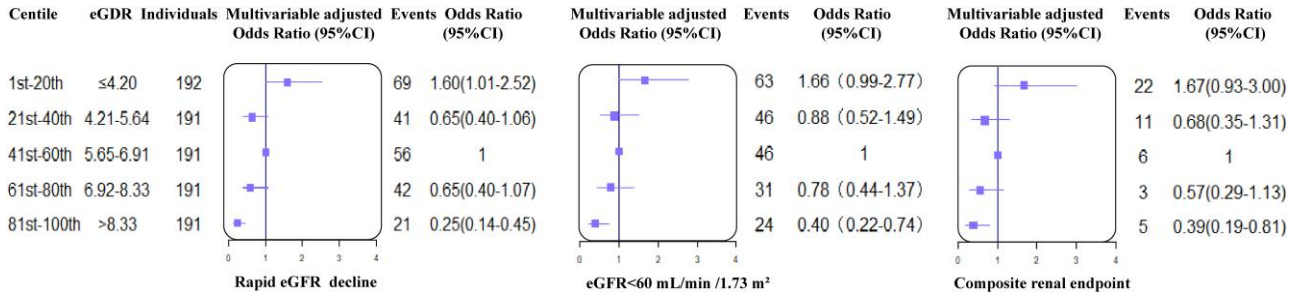

Figure 3. Sensitivity analyses of eGDR and renal outcome events.

Table 2. The effect of eGDR and components on renal outcome events

	Rapid eGFR decline			eGFR < 60 mL/min/1.73 m^2			Composite renal endpoint		
Variable	OR (95% CI)	*P*	AIC	OR (95% CI)	*P*	AIC	OR (95% CI)	*P*	AIC
eGDR	0.83 (0.77-0.88)	<.001	1025.90	0.84 (0.78-0.90)	<.001	987.04	0.85 (0.78-0.93)	<.001	607.75
HbA1c	1.28 (1.18-1.37)	<.001	1009.48	1.08 (1.01-1.16)	.024	1005.60	1.23 (1.13-1.34)	<.001	689.29
WC	1.00 (0.99-1.02)	.34	1056.54	1.00 (0.99-1.02)	.866	1010.61	0.99 (0.96-1.01)	.153	708.58
HT	1.42 (1.05-1.92)	.023	1051.41	2.14 (1.55-2.96)	<.001	988.06	1.54 (1.03-2.29)	.034	706.07

Abbreviations: AIC, Akaike information criterion; eGDR, estimated glucose disposal rate; HbA1c, hemoglobin A1c; HT, hypertension; WC, waist circumference.

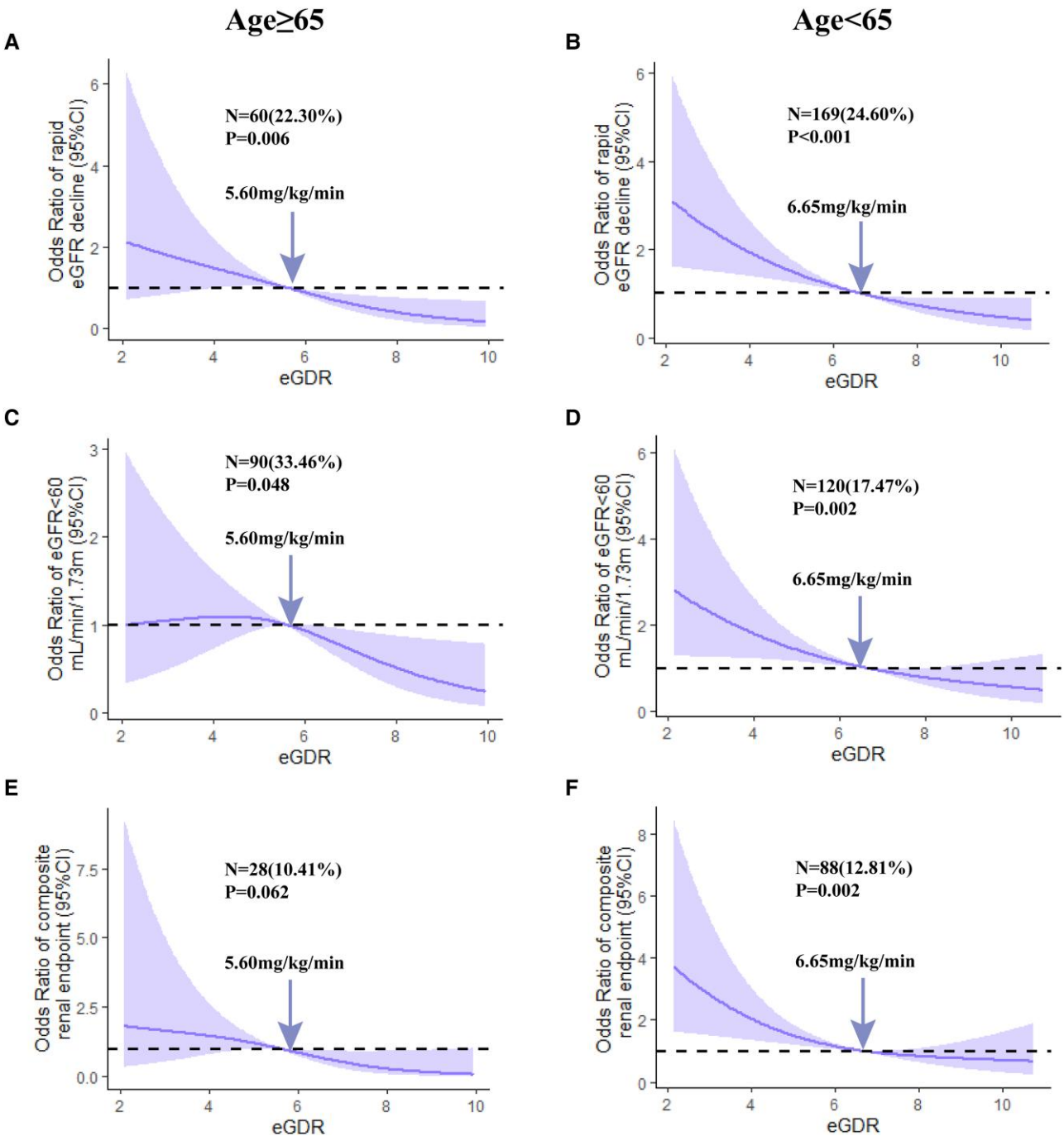

Figure 4. Multivariable adjusted odds ratios for renal outcome events according to levels of eGFR on a continuous scale after age stratification. A, Association between the eGDR and rapid eGFR decline in T2DM patients of age ≥65 years. B, Association between the eGDR and rapid eGFR decline in T2DM patients of age <65 years. C, Association between the eGDR and eGFR <60 mL/min/1.73 m^2 in T2DM patients of age ≥65 years. D, Association between the eGDR and eGFR <60 mL/min/1.73 m^2 in T2DM patients of age <65 years. E, Association between the eGDR and composite endpoint in T2DM patients of age ≥65 years. F, Association between the eGDR and composite endpoint in T2DM patients of age <65 years. Solid purple lines are multivariable adjusted odds ratios, with shaded areas showing 95% CIs derived from restricted cubic spline regressions with 3 knots. Reference lines for no association are indicated by a dotted line at a hazard ratio of 1.0. Analyses were adjusted for age, diabetes duration, sUA, BUN, LDL, TG, BMI, lipid-lowering drugs, insulin, anticoagulant medication, and oral hypoglycemic drugs.

An eGDR >6.34 mg/kg/min was a protective factor against renal outcome, but eGDR <6.34 mg/kg/min was an independent risk factor for renal outcome. Although eGDR is closely associated with complications in patients with diabetes, a specific eGDR threshold has not been defined. Nonetheless, others have reported similar relationships between the eGDR category and renal outcomes. Helliwell et al [26] recruited 2151 patients with T1DM and found that those with eGDR ≥8 mg/kg/min had the lowest prevalence of macrovascular complications (cardiovascular events), and microvascular disease (nephropathy and retinopathy), irrespective of their HbA1c levels. Those with eGDR <4 mg/kg/min had a significantly increased risk of macrovascular and microvascular complications. Similarly, Šimonienė reported [22]

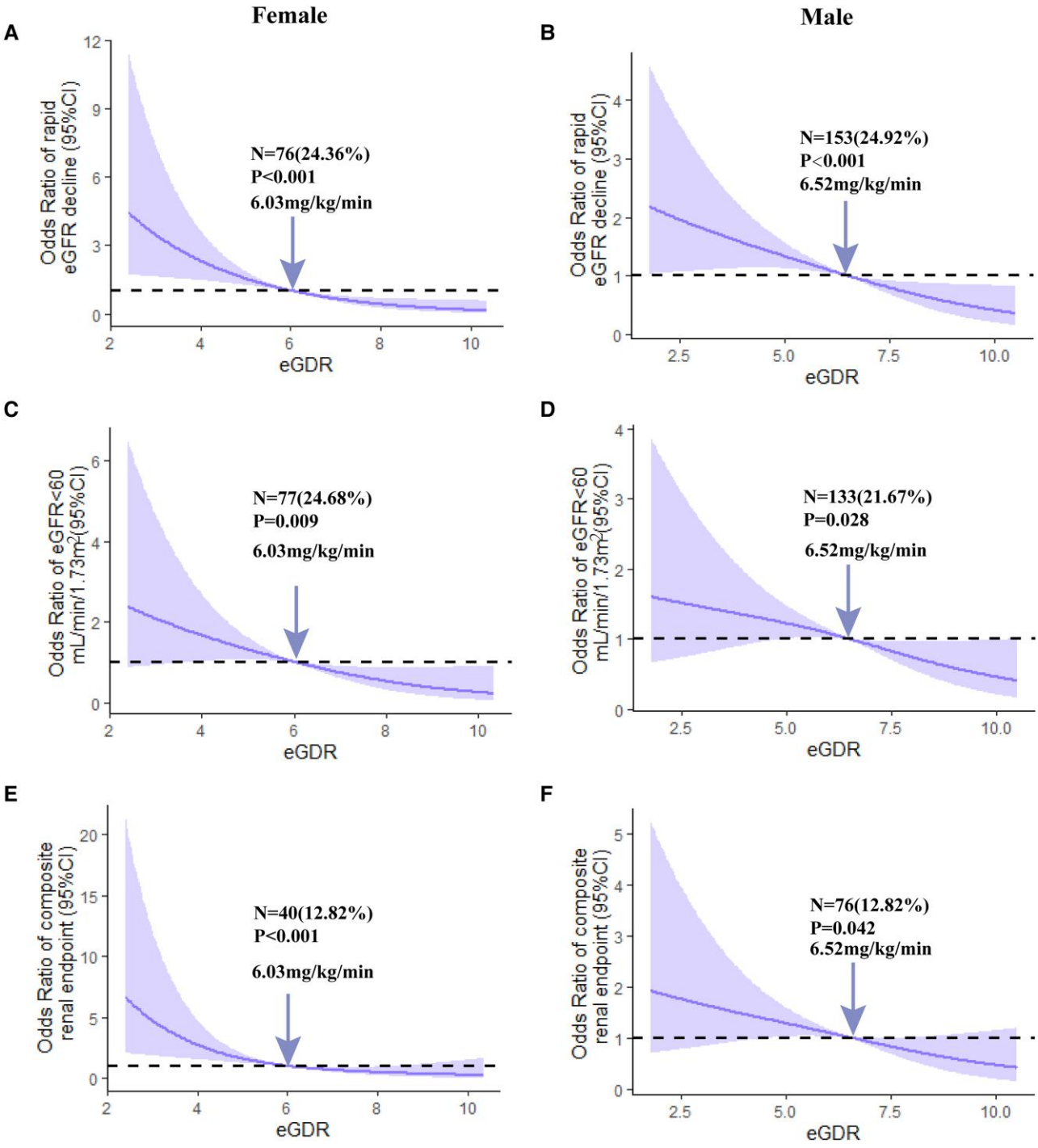

Figure 5. Multivariable adjusted odds ratios for renal outcome events according to levels of eGFR on a continuous scale after gender stratification. A, Association between the eGDR and rapid eGFR decline in female participants. B, Association between the eGDR and rapid eGFR decline in male participants. C, Association between the eGDR and eGFR <60 mL/min/1.73 m^2 in female participants. D, Association between the eGDR and eGFR <60 mL/min/1.73 m^2 in male participants. E, Association between the eGDR and composite endpoint in female participants. F, Association between the eGDR and composite endpoint in male participants. Solid purple lines are multivariable adjusted odds ratios, with shaded areas showing 95% CIs derived from restricted cubic spline regressions with 3 knots. Reference lines for no association are indicated by a dotted line at a hazard ratio of 1.0. Analyses were adjusted for age, diabetes duration, sUA, BUN, LDL, TG, BMI, lipid-lowering drugs, insulin, anticoagulant medication, and oral hypoglycemic drugs.

that when eGDR was less than 6.4 mg/kg/min, diabetic microvascular complications occurred significantly more often. Giuseppe Penno et al [13] confirmed that eGDR in the lowest quintile (<4.14 mg/kg/min) was significantly associated with micro- and macroalbuminuria, worse eGFR category, and the nonalbuminuric DKD phenotype in patients with T2DM. Whereas, Mao et al [12] followed up 1441 patients with T1DM and found that whether eGDR levels were greater than 5.6 mg/kg/min was not associated with ESRD. Their study population with T1DM was relatively young (average

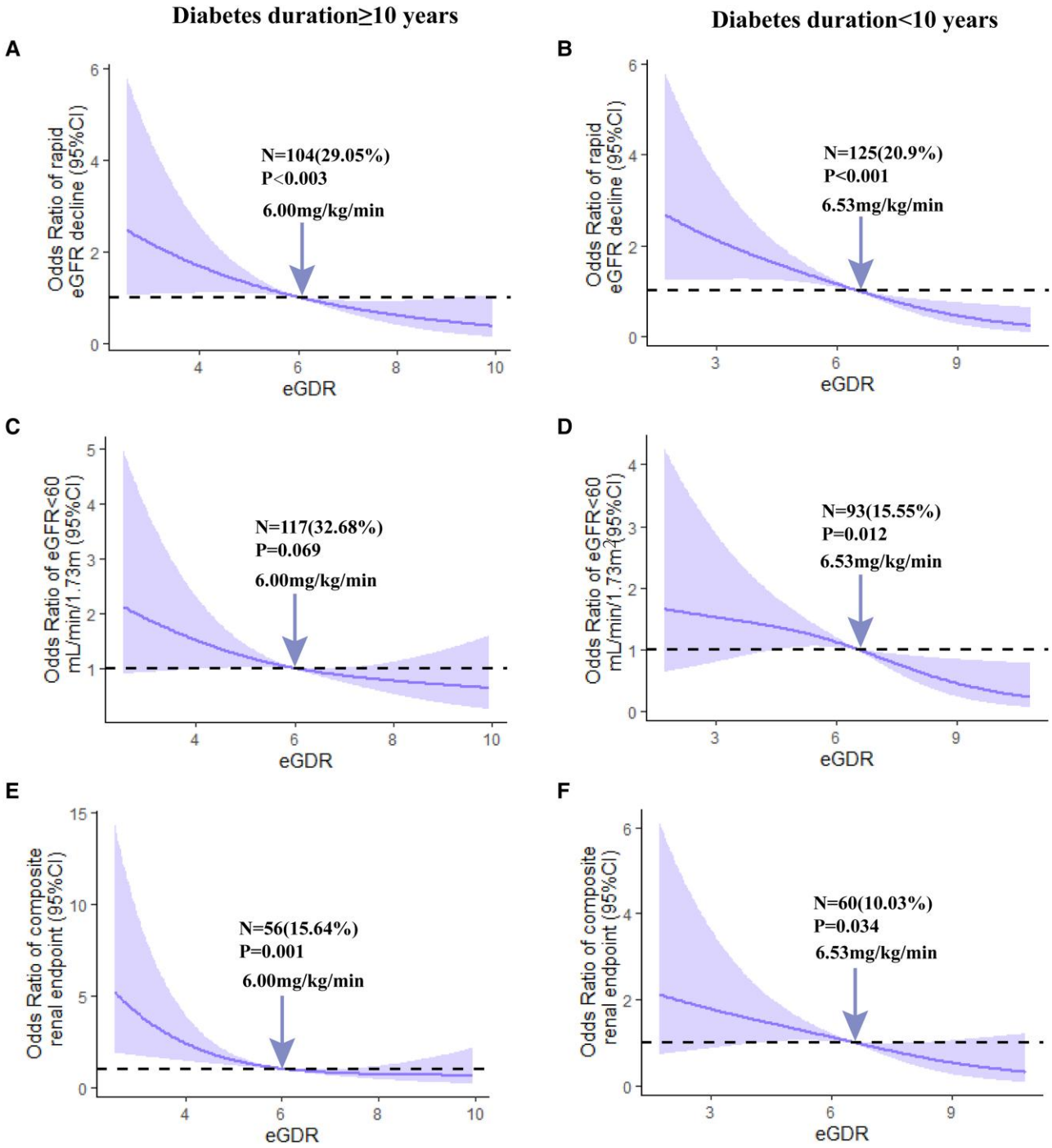

Figure 6. Multivariable adjusted odds ratios for renal outcome events according to levels of eGFR on a continuous scale after diabetes duration stratification. A, Association between the eGDR and rapid eGFR decline in T2DM patients of diabetes duration ≥10 years. B, Association between the eGDR and rapid eGFR decline in T2DM patients of diabetes duration <10 years. C, Association between the eGDR and eGFR <60 mL/min/1.73 m^2 in T2DM patients of diabetes duration ≥10 years. D, Association between the eGDR and eGFR <60 mL/min/1.73 m^2 in T2DM patients of diabetes duration <10 years. E, Association between the eGDR and composite endpoint in T2DM patients of diabetes duration ≥10 years. F, Association between the eGDR and composite endpoint in T2DM patients of diabetes duration <10 years. Solid purple lines are multivariable adjusted odds ratios, with shaded areas showing 95% CIs derived from restricted cubic spline regressions with 3 knots. Reference lines for no association are indicated by a dotted line at a hazard ratio of 1.0. Analyses were adjusted for age, diabetes duration, sUA, BUN, LDL, TG, BMI, lipid-lowering drugs, insulin, anticoagulant medication, and oral hypoglycemic drugs.

age ≤30 years), so it is not surprising that their conclusions were different. Importantly, eGDR may be superior to HbA1c and WC and was similar to hypertension in predicting renal outcome. This means that eGDR may be closely related to the progression of renal function in T2DM patients and that monitoring eGDR levels may enable early identification of renal function decline in T2DM patients.

Age, sex, and diabetes duration are risk factors for renal function decline in people with T2DM. Interestingly, there are sex-specific effects of insulin resistance. A recent study

Table 3. The cutoff point for eGDR to predict renal outcome events

		Rapid eGFR decline				eGFR < 60 mL/min/1.73 m^2				Composite renal endpoint			
	N	Cutoff	Sensitivity	Specificity	*P* value	Cutoff	Sensitivity	Specificity	*P* value	Cutoff	Sensitivity	Specificity	*P* value
All	956	6.14	57.2%	56.7%	.00026	6.38	64.8%	53.9%	1.7e-06	6.14	57.8%	54.9%	.013
Age ≥ 65	269	5.25	53.3%	57.4%	.14	5.59	55.6%	53.1%	.2	5.22	50%	56%	.55
Age < 65	687	6.62	64.5%	55.2%	8.9e-06	6.62	66.7%	54%	5.1e-05	6.14	55.7%	60.6%	.0052
Female	342	5.60	61.8%	61.3%	.00039	6.127	72.7%	54.3%	2.9e-05	5.58	65%	59.3%	.006
Male	614	6.83	64.7%	47.5%	.0087	6.63	63.9%	50.9%	.0032	6.83	63.2%	45.5%	.18
DD ≥ 10	358	5.27	49%	67.7%	.0038	6.14	59.8%	50.6%	.071	5.27	48.2%	64.9%	.071
DD < 10	598	6.38	59.2%	56.7%	.0018	6.62	74.2%	52.9%	1.5e-06	6.62	65%	50.2%	.029

Abbreviations: DD, diabetes duration; eGDR, estimated glucose disposal rate; eGFR, estimated glomerular filtration rate.

suggested that genetically predicted fasting insulin was not associated with eGFR overall in women but was correlated with lower eGFR in men [27]. Likewise, the present study found that male T2DM patients have higher eGDR cutoff points for the development of renal outcomes and may need to pay more attention to improving insulin resistance. The same findings were obtained in patients aged <65 years and in patients with a DM duration <10 years. However, the results still need to be verified by multicentric and prospective clinical research studies.

The strengths of the present research include its retrospective cohort study design and its implementation of multiple imputations for missing data, reducing the estimation bias and improving the validity of this study. However, there are also several limitations to our study that merit attention. First, eGDR is a surrogate marker of insulin resistance, but it is not as accurate as the gold standard of euglycemic-hyperinsulinemic clamp data, and the equation for eGDR was not validated among people with type 2 diabetes in China. Second, eGDR can vary with HbA1c, WC, and blood pressure, but it was only measured at baseline. Therefore, the impact of the trajectory of eGDR over time on renal function needs to be further explored. Third, although some important confounding factors were adjusted in the present study, the effect of unmeasured confounders on the study results cannot be ignored. In particular, the urine albumin-to-creatinine ratio was not measured at baseline. Fourth, although the subgroup analyses provide interesting findings requiring further study, they are post hoc in nature; therefore, the results are exploratory and hypothesis-generating. Lastly, the sample source of this study was a single center. Therefore, a large multicenter study with long-term follow-up is required to confirm the effect of eGDR on renal dysfunction in T2DM patients.

In conclusion, lower eGDR was a predictive factor for renal function progression in patients with T2DM. More attention may be needed to improve insulin resistance in patients aged <65 years, patients with diabetes mellitus duration <10 years and in men.

Acknowledgments

The authors thank all the participants for their invaluable contributions.

Funding

This study was supported by grants from the National Natural Science Foundation of China [82070759] and Natural Science Foundation of Hunan Province [2021JJ31032].

Author Contributions

J.P. and B.Y. designed the study. J.P., Q.Y., and J.T.P. collected and analyzed the data. J.P. drafted the manuscript. A.M.L. and L.Q.Q.Y. modified and verified the manuscript. B.Y. completed critical review of the article.

Disclosures

There are no potential conflicts of interest relevant to this article to report.

Ethics Committee Approval

The study was approved by the Ethics Committee of the Third Xiangya Hospital of Central South University (22156).

Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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