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ORIGINAL RESEARCH

Is Lipid a Missing Link Between Renal Function and Diabetes Risk? Insights from a Mediation Analysis Based on the Cohort Study

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Purpose: Both renal function impairment and lipid abnormalities are recognized risk factors for diabetes. However, the potential mediating role of lipid parameters in the relationship between renal function and diabetes risk remains unexplored. This study aimed to investigate whether and to what extent lipid parameters mediate the association between renal function and diabetes risk.

Patients and Methods: We conducted a cohort study including adults from 32 sites across 11 Chinese cities between 2010 and 2016. Renal function was assessed by estimated glomerular filtration rate (eGFR). Lipid parameters included triglyceride glucose (TyG), triglyceride glucose- body mass index (TyG-BMI), triglyceride/ high-density lipoprotein cholesterol (TG/HDL-c), and atherogenic index of plasma (AIP). Cox proportional hazards models were used to examine the relationship between eGFR and diabetes risk. Subgroup analyses were performed to identify potential effect modifiers. Mediation analyses quantified the proportion of eGFR's effect on diabetes risk mediated through each lipid parameter.

Results: Among 115,488 participants (54.07% male, mean age 44.12 ± 12.95 years) followed for 3.10 ± 0.95 years, 2659 (2.30%) developed diabetes. After multivariable adjustment, higher eGFR was inversely associated with diabetes risk (HR=0.98, 95% CI: 0.98–0.98). This association was more pronounced in females, participants <60 years, those with BMI <25 kg/m², SBP <140 mmHg, non-smokers, non-drinkers, ALT <40 U/L, and AST <40 U/L. Mediation analyses revealed that TyG, TyG-BMI, TG/HDL-c, and AIP mediated 23.14%, 21.05%, 3.54%, and 12.49% of the eGFR-diabetes relationship, respectively.

Conclusion: Reduced renal function, as indicated by lower eGFR, is associated with increased diabetes risk. This relationship is partially mediated through lipid metabolism pathways, suggesting lipid may represent a missing link between renal function and diabetes risk.

Keywords: renal function, estimated glomerular filtration rate, diabetes, lipid, mediation

Introduction

Diabetes, a chronic metabolic disorder, disrupts glucose metabolism and affects multiple organ systems.[1] Recent projection models indicate that, due to the lipid disorders epidemic,[2] an astounding 1.31 billion individuals globally are anticipated to develop diabetes by 2050,[3] with increasing prevalence among younger populations.[4] Established risk factors include sex, age, family history, lifestyle factors (smoking, alcohol consumption), liver enzymes, renal function, and metabolic conditions (obesity, hypertension, dyslipidemia).[1–4] Early risk detection and intervention are essential for disease prevention and management.

The estimated glomerular filtration rate (eGFR) serves as a critical indicator of renal function and predicts renal and metabolic outcomes across diverse populations.[5–7] Reduced eGFR not only reflects kidney damage but may contribute to diabetes development through impaired insulin clearance, chronic inflammation, and uremic toxin accumulation that disrupts

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insulin signaling pathways.[8,9] Multiple studies have demonstrated associations between decreased eGFR and elevated diabetes risk.[8–12] Moreover, hyperfiltration in early diabetes can accelerate nephropathy through glomerular capillary hypertension and endothelial damage.[13]

Diabetic nephropathy is a common complication of diabetes and results from direct hyperglycemic injury, renin angiotensin system activation, and oxidative stress.[13–15] Dyslipidemia exacerbates these pathological processes through lipotoxicity, inflammation, and metabolic dysregulation.[15–18] This relationship between renal injury and diabetes is further complicated by characteristic interrelated abnormalities in lipoproteins and plasma lipids seen in diabetes. While gold-standard insulin resistance (IR) assessments like hyperinsulinemic-euglycemic clamp tests exist, their clinical utility is limited by complexity and cost.[19,20] Therefore, alternative lipid-based markers provide more practical IR indicators that effectively balance atherogenic and anti-atherogenic profiles,[21] including the triglyceride/high-density lipoprotein cholesterol (TG/HDL-c) ratio, atherogenic index of plasma (AIP), triglyceride glucose index (TyG), and triglyceride glucose body-mass index (TyG-BMI).[22–25] Importantly, these lipid parameters closely correlate with cardiovascular and diabetes events.[26–29]

Although both eGFR and lipid parameters are independently associated with diabetes risk, the potential mediating role of lipid parameters in the relationship between renal function and diabetes risk remains unexplored. This study investigated how lipid parameters might mediate the association between eGFR and diabetes risk.

Materials and Methods

Data Source and Study Population

The dataset was obtained from DATADRYAD (www.datadryad.org), generously shared by Chen et al.[30] The original data comes from their published study (https://doi.org/10.5061/dryad.ft8750v). This open-access repository allows for the creation of derivative works, sharing, adaptation, and modification of the dataset.[30] This study was approved by the Rich Healthcare Group Review Board and the institutional ethics committee waived informed consent for this retrospective study.

Based on the study design and data requirements, our inclusion criteria were: (1) adults aged ≥20 years; (2) completion of at least two health examinations between 2010 and 2016 at Rich Healthcare Group facilities distributed across 11 cities and 32 districts in China. We excluded participants who presented with: (1) missing baseline data for height, sex, weight, or fasting plasma glucose (FPG); (2) extreme BMI values (<15 or >55 kg/m²); (3) follow-up intervals <2 years; (4) diabetes at baseline; (5) uncertain diabetes status during follow-up; (6) missing baseline eGFR, TG, or HDL-c values; or (7) outlier eGFR levels. After applying these screening criteria sequentially (Figure 1), our final analytical cohort comprised 115,488 participants.

Data Collection, Measurement, and Calculation

In the original investigation, questionnaires were used to collect basic information about family history of diabetes, smoking behaviors, and alcohol consumption. Blood pressure was measured using a standard mercury sphygmomanometer. Participants provided fasting venous blood samples after a minimum 10-hour fast. A Beckman 5800 autoanalyzer was employed to measure levels of TG, aspartate aminotransferase (AST), FPG, HDL-c, blood urea nitrogen (BUN), total cholesterol (TC), serum creatinine (Scr), low-density lipoprotein cholesterol (LDL-c), and alanine aminotransferase (ALT).

eGFR

We gathered data on eGFR at baseline and recorded it as a continuous variable. The eGFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) algorithm for "Asian Origin",[31] which was determined by Scr, sex, and age. The units for Scr and age were mg/dL and year, respectively. The unit for eGFR was mL/minute/1.73 m^2. The eGFR quartiles were determined based on the statistical distribution within our study population, dividing participants into equal quartiles.

Lipid Parameters

The lipid parameters were determined as follows:[22–25]

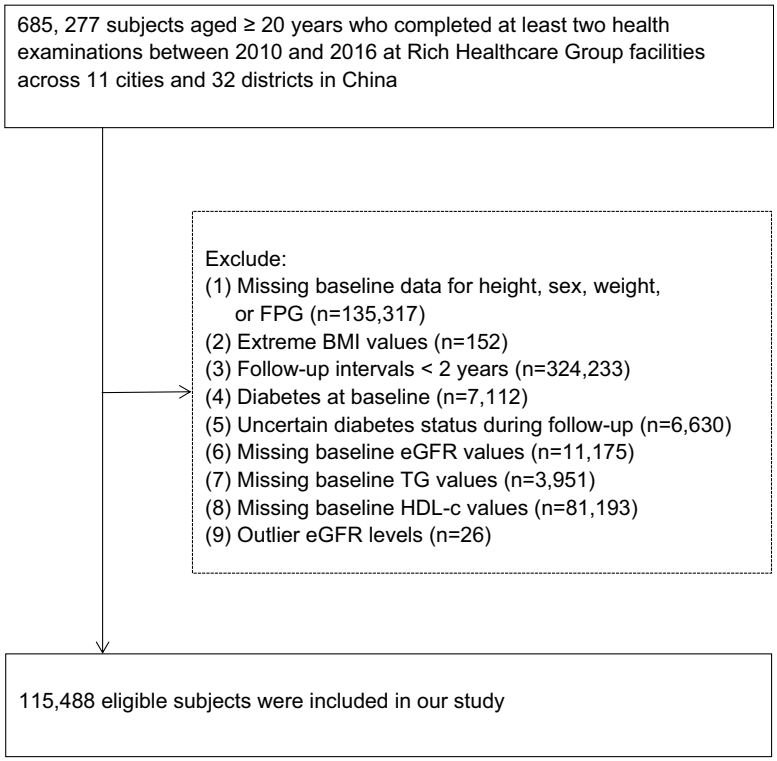

Figure 1 Flowchart of study participant selection. The initial cohort included 685,277 subjects across 11 cities and 32 regions from 2010 to 2016 in China. After applying exclusion criteria, 115,488 eligible subjects were included in our study.
Abbreviations: FPG, fasting plasma glucose; BMI, body mass index; eGFR, estimated glomerular filtration rate; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol.

$$BMI = Weight\,(kg)/Height^2\,(m)$$

$$TyG = \ln[FPG\,(mg/dL) \times TG\,(mg/dL)/2]$$

$$TyG - BMI = TyG \times BMI$$

$$TG/HDL - c = \frac{TG\,(mg/dL)}{HDL - c\,(mg/dL)}$$

$$AIP = \log_{10}\frac{TG\,(mg/dL)}{HDL - c\,(mg/dL)}$$

Diagnosis of Diabetes

Diabetes was diagnosed based on either of the following criteria: FPG ≥7.0 mmol/L or self-reported diabetes diagnosis during follow-up.[32]

Treatment of Missing Data

Missing covariate data were addressed using a multiple imputation approach. [33] Missing data were reported as quantities and percentages. The variables with missing values included DBP (16, 0.01%), ALT (329, 0.28%), drinking status (82,894, 71.77%), AST (66,474, 57.55%), SBP (16, 0.01%), smoking status (82,894, 71.77%), and BUN (1381, 1.19%). The imputation model incorporated age, sex, AST, ALT, DBP, SBP, BMI, BUN, drinking and smoking status, as well as family history of diabetes.

Statistical Analysis

Categorical data are presented as frequencies (percentages), while continuous variables are expressed as medians (interquartile ranges) or means (standard deviations). The Chi-squared test or Kruskal–Wallis *H*-test was used to compare differences across eGFR quartiles.

Confounding factors were selected based on their established relationships with the outcomes of interest or when their inclusion changed effect estimates by more than 10%.[34] After considering existing research evidence and clinical relevance,[1–4] we adjusted for the following covariates: age, DBP, LDL-c, AST, ALT, SBP, BMI, sex, family history of diabetes, BUN, drinking status, and smoking status. We developed three multivariate Cox proportional hazards regression models to investigate the association between eGFR and diabetes risk. Model I was unadjusted. Model II was adjusted for sex, age, BMI, DBP, and SBP. Model III was comprehensively adjusted for sex, age, family history of diabetes, LDL-c, AST, ALT, SBP, DBP, BUN, BMI, smoking status, and drinking status. Results were presented as hazard ratios (HRs) with 95% confidence intervals (CIs). Additionally, we conducted subgroup analyses using stratified Cox proportional hazards regression models across different population categories. To assess the potential influence of unmeasured confounding on the relationship between eGFR and diabetes risk, we calculated the E-value.[35]

The lipid parameters included TyG-BMI, TyG, TG/HDL-c, and AIP. Multivariate logistic and Cox regression analyses were used to examine the relationships between lipid parameters and eGFR, and diabetes risk, respectively. The "mediation" package in R 4.2.0 was used to perform mediation analysis, which assessed the mediating effects of lipid parameters (TyG-BMI, TyG, TG/HDL-c, and AIP) on the associations between eGFR and diabetes risk, adjusted for sex, age, DBP, SBP, ALT, AST, LDL-c, family history of diabetes, BUN, drinking status, and smoking status. The presence of a mediating effect was confirmed when all of the following conditions were met: a significant total effect, a significant indirect effect, and a positive proportion of the mediator effect.

All statistical analyses were conducted using R software (version 4.2.0), the rms package, MSTATA, and EmpowerStats (version 4.2). Results with two-sided P-values less than 0.05 were considered statistically significant. This study was conducted in accordance with the Declaration of Helsinki and adhered to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines.[34]

Results

Participants Characteristics

Table 1 summarizes the characteristics of the study subjects. Our study included 115,488 participants, comprising 54.07% males and 45.93% females. The average age was 44.12 ± 12.95 years, with a mean follow-up duration of 3.10 ± 0.95 years. Diabetes developed in 2659 individuals (2.30%). The eGFR quartiles were determined as follows: Q1 (30.51–98.37), Q2 (98.37–110.01), Q3 (110.01–120.10), and Q4 (120.11–158.62). From Q1 to Q4, HDL-c levels increased, as did the proportion of females, nonsmokers, and nondrinkers. However, age, AST, ALT, LDL-c, TG, TC, FPG, DBP, SBP, Scr, BMI, BUN, TG/HDL-c, TyG-BMI, TyG, and AIP all decreased from Q1 to Q4. The risk of diabetes declined across all quartiles (Table 1).

According to the Kaplan-Meier curves, the risk of diabetes decreased as eGFR increased. This analysis demonstrated that individuals with the highest eGFR exhibited the lowest risk of diabetes (Figure 2).

Associations Between eGFR and Diabetes Risk

To examine the relationship between eGFR and diabetes risk, we established three Cox proportional hazards regression models (Table 2). In Model I, each unit increase in eGFR was associated with a 3% reduction in diabetes risk (HR = 0.97, 95% CI: 0.96–0.97). In Models II and III, each unit increment in eGFR resulted in a 2% decrease in diabetes risk (HR = 0.98, 95% CI: 0.98–0.98). Furthermore, we incorporated eGFR data as categorical variables into the model. Compared to individuals in the lowest quartile (Q1), Model III showed HRs of 0.81 (95% CI: 0.74–0.89) for Q2, 0.52 (95% CI: 0.46–0.58) for Q3, and 0.32 (95% CI: 0.27–0.37) for Q4 participants (Table 2).

Table 1 Characteristics of the Study Population Stratified by eGFR Quartiles

Characteristic	Overall	eGFR Quartile				P Value
		Q1 (30.51–98.37)	Q2 (98.37–110.01)	Q3 (110.01–120.10)	Q4 (120.11–158.62)	
Participants	115488	28,852	28,878	28,881	28,877	
Age (years)	44.12 ± 12.95	54.98 ± 14.37	47.80 ± 11.08	40.62 ± 7.25	33.11 ± 4.94	<0.001
BMI (kg/m^2)	23.35 ± 3.30	24.20 ± 3.09	23.78 ± 3.17	23.20 ± 3.21	22.21 ± 3.38	<0.001
SBP (mmHg)	119.44 ± 16.67	125.82 ± 18.49	121.30 ± 16.47	116.76 ± 15.03	113.87 ± 13.81	<0.001
DBP (mmHg)	74.45 ± 10.97	77.27 ± 11.37	75.98 ± 11.01	73.56 ± 10.60	70.99 ± 9.76	<0.001
FPG (mg/dL)	89.05 ± 10.91	91.57 ± 11.32	90.05 ± 11.23	88.10 ± 10.61	86.50 ± 9.73	<0.001
TC (mg/dL)	86.25 ± 16.14	89.99 ± 16.67	88.66 ± 16.35	85.09 ± 15.35	81.28 ± 14.67	<0.001
TG (mg/dL)	19.80 (13.86–30.06)	23.40 (16.20–34.20)	21.96 (15.12–32.40)	19.08 (13.14–28.80)	16.20 (11.52–23.40)	<0.001
HDL-c (mg/dL)	24.73 ± 5.48	24.33 ± 5.37	24.52 ± 5.49	24.72 ± 5.52	25.35 ± 5.50	<0.001
LDL-c (mg/dL)	49.79 ± 12.39	52.51 ± 12.72	51.47 ± 12.61	48.95 ± 11.96	46.22 ± 11.26	<0.001
ALT (U/L)	18.10 (13.00–27.60)	19.70 (14.50–27.90)	19.60 (14.00–29.00)	18.00 (12.90–28.30)	15.40 (11.20–24.50)	<0.001
AST (U/L)	22.10 (18.20–27.48)	23.60 (19.74–28.88)	23.00 (19.00–28.18)	21.98 (18.00–27.10)	20.38 (16.98–25.36)	<0.001
Scr (mg/dL)	0.80 ± 0.17	0.96 ± 0.16	0.81 ± 0.14	0.75 ± 0.13	0.66 ± 0.12	<0.001
BUN (mg/dL)	84.34 ± 21.06	93.33 ± 21.84	86.54 ± 20.22	81.23 ± 19.39	76.26 ± 18.78	<0.001
TyG	6.82 ± 0.61	7.00 ± 0.59	6.92 ± 0.60	6.77 ± 0.61	6.59 ± 0.58	<0.001
TyG-BMI	160.16 ± 32.11	170.03 ± 30.03	165.26 ± 30.95	158.03 ± 31.36	147.30 ± 31.43	<0.001
TG/HDL-c	0.82 (0.52–1.34)	0.99 (0.64–1.54)	0.91 (0.58–1.47)	0.78 (0.50–1.29)	0.63 (0.43–1.02)	<0.001
AIP	−0.09 (−0.28–0.13)	−0.01 (−0.20–0.19)	−0.04 (−0.24–0.17)	−0.11 (−0.30–0.11)	−0.20 (−0.37–0.01)	<0.001
Final FPG (mg/dL)	92.98 ± 12.65	96.25 ± 14.24	94.28 ± 13.27	91.93 ± 11.65	89.48 ± 9.97	<0.001
Follow-up time (years)	3.10 ± 0.95	3.10 ± 0.92	3.12 ± 0.96	3.15 ± 0.97	3.04 ± 0.94	<0.001
Sex						<0.001
Male	62448 (54.07%)	19,247 (66.71%)	17,266 (59.79%)	14,954 (51.78%)	10,981 (38.03%)	
Female	53040 (45.93%)	9605 (33.29%)	11,612 (40.21%)	13,927 (48.22%)	17,896 (61.97%)	
Smoking status						<0.001
Current	19777 (17.12%)	6519 (22.59%)	6022 (20.85%)	4492 (15.55%)	2744 (9.50%)	
Ever	3993 (3.46%)	1212 (4.20%)	1086 (3.76%)	1002 (3.47%)	693 (2.40%)	
Never	91718 (79.42%)	21,121 (73.20%)	21,770 (75.39%)	23,387 (80.98%)	25,440 (88.10%)	
Drinking status						<0.001
Current	2562 (2.22%)	785 (2.72%)	757 (2.62%)	616 (2.13%)	404 (1.40%)	
Ever	16662 (14.43%)	4783 (16.58%)	4607 (15.95%)	4153 (14.38%)	3119 (10.80%)	
Never	96264 (83.35%)	23,284 (80.70%)	23,514 (81.43%)	24,112 (83.49%)	25,354 (87.80%)	

(*Continued*)

Table 1 (Continued).

Characteristic	Overall	eGFR Quartile				P Value
		Q1 (30.51–98.37)	Q2 (98.37–110.01)	Q3 (110.01–120.10)	Q4 (120.11–158.62)	
Family history of diabetes						<0.001
No	112855 (97.72%)	28,349 (98.26%)	28,271 (97.90%)	28,069 (97.19%)	28,166 (97.54%)	
Yes	2633 (2.28%)	503 (1.74%)	607 (2.10%)	812 (2.81%)	711 (2.46%)	
Diabetes						<0.001
No	112829 (97.70%)	27,686 (95.96%)	28,038 (97.09%)	28,428 (98.43%)	28,677 (99.31%)	
Yes	2659 (2.30%)	1166 (4.04%)	840 (2.91%)	453 (1.57%)	200 (0.69%)	

Notes: Categorical data are represented as frequencies (percentages), whereas continuous variables are represented as medians (interquartile ranges) or means (standard deviations).

Abbreviations: eGFR, estimated glomerular filtration rate; TyG, triglyceride glucose; TyG-BMI, triglyceride glucose- body mass index; AIP, atherogenic index of plasma; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL-c, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; LDL-c, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; Scr, serum creatinine; BUN, blood urea nitrogen.

Subgroup Analysis

In all analyzed subgroups (Table 3), each unit increase in eGFR was consistently associated with reduced diabetes risk. The subgroup analysis revealed that this negative association between eGFR and diabetes risk was particularly pronounced among

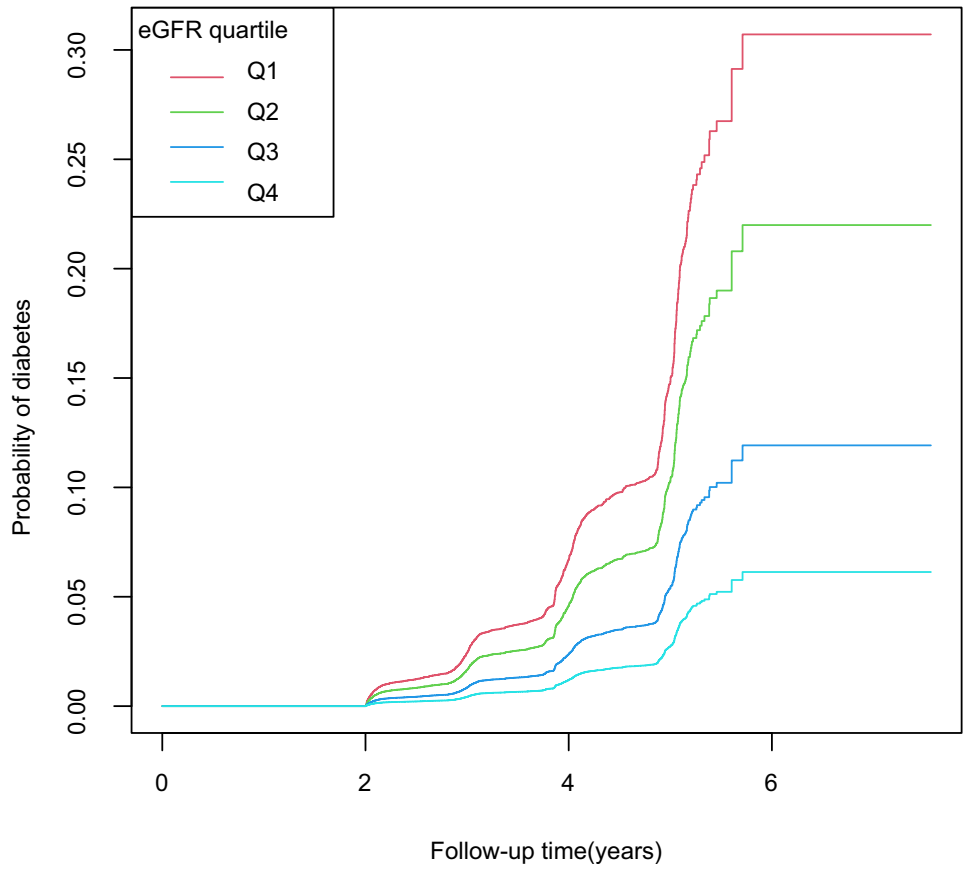

Figure 2 Kaplan-Meier curves for the probability of diabetes based on eGFR quartiles (log-rank, P<0.0001). The graph shows that participants in Q1 (lowest eGFR) had the highest probability of developing diabetes, while those in Q4 (highest eGFR) had the lowest probability.

Abbreviations: eGFR, estimated glomerular filtration rate.

Table 2 Associations Between eGFR and Diabetes Risk

Exposure	Model I HR (95% CI) P value	Model II HR (95% CI) P value	Model III HR (95% CI) P value
eGFR	0.97 (0.96, 0.97) <0.0001	0.98 (0.98, 0.98) <0.0001	0.98 (0.98, 0.98) <0.0001
eGFR quartile			
Q1	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Q2	0.68 (0.62, 0.74) <0.0001	0.82 (0.75, 0.90) <0.0001	0.81 (0.74, 0.89) <0.0001
Q3	0.35 (0.31, 0.39) <0.0001	0.52 (0.46, 0.58) <0.0001	0.52 (0.46, 0.58) <0.0001
Q4	0.17 (0.15, 0.20) <0.0001	0.31 (0.27, 0.37) <0.0001	0.32 (0.27, 0.37) <0.0001
P for trend	<0.0001	<0.0001	<0.0001

Notes: Model I was unadjusted. Model II was adjusted for sex, age, BMI, DBP, and SBP. Model III was adjusted for sex, age, DBP, family history of diabetes, LDL-c, AST, ALT, SBP, BMI, BUN, smoking status, and drinking status.
Abbreviations: eGFR, estimated glomerular filtration rate; BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDL-c, low-density lipoprotein cholesterol; BUN, blood urea nitrogen; HR, hazard ratio; CI, confidence interval.

females, individuals with BMI<25 kg/m², those younger than 60 years, participants with SBP<140 mmHg, non-smokers, non-drinkers, individuals with ALT<40 U/L, and those with AST<40 U/L (Table 3).

We utilized the E-value to assess the robustness of our findings against potential unmeasured confounders. Our results remained consistent unless there was an unmeasured confounder with an HR greater than 1.16.

Table 3 The Impact of eGFR on Diabetes in Subgroups

Characteristic	No of Participants	HR (95% CI)	P Value	P for Interaction
Sex				<0.0001
Male	62448	0.98 (0.97, 0.98)	<0.0001	
Female	53040	0.96 (0.95, 0.96)	<0.0001	
Age (years)				0.0005
<60	98,634	0.97 (0.97, 0.98)	<0.0001	
≥ 60	16,854	0.99 (0.99, 1.00)	0.0183	
BMI (kg/m^2)				<0.0001
<25	81,353	0.96 (0.96, 0.96)	<0.0001	
≥ 25	34,135	0.98 (0.98, 0.98)	<0.0001	
SBP (mmHg)				<0.0001
<140	102,777	0.97 (0.96, 0.97)	<0.0001	
≥ 140	12,711	0.99 (0.98, 0.99)	<0.0001	
Smoking status				0.0075
Current	19777	0.98 (0.98, 0.99)	<0.0001	
Ever	3993	0.98 (0.97, 0.99)	<0.0001	
Never	91718	0.96 (0.96, 0.96)	<0.0001	

(*Continued*)

Table 3 (Continued).

Characteristic	No of Participants	HR (95% CI)	P Value	P for Interaction
Drinking status				0.0352
Current	2562	0.98 (0.97, 1.00)	0.0092	
Ever	16662	0.98 (0.97, 0.98)	<0.0001	
Never	96264	0.96 (0.96, 0.97)	<0.0001	
Family history of diabetes				0.1587
No	112855	0.97 (0.96, 0.97)	<0.0001	
Yes	2633	0.98 (0.96, 0.99)	0.0002	
ALT (U/L)				0.0210
≤ 40	102,733	0.96 (0.96, 0.96)	<0.0001	
>40	12,755	0.98 (0.98, 0.99)	<0.0001	
AST (U/L)				0.0237
≤ 40	109,977	0.96 (0.96, 0.97)	<0.0001	
> 40	5511	0.98 (0.98, 0.99)	<0.0001	

Notes: Above model was adjusted for sex, age, DBP, family history of diabetes, LDL-c, AST, ALT, SBP, BMI, BUN, smoking status, and drinking status. The stratification variable was not adjusted in the model.
Abbreviations: eGFR, estimated glomerular filtration rate; BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDL-c, low-density lipoprotein cholesterol; BUN, blood urea nitrogen; HR, hazard ratio; CI, confidence interval.

Associations of Lipid Parameters with eGFR and Diabetes Risk

Table 4 demonstrates the correlations between eGFR and lipid parameters after multivariate regression analysis. eGFR was inversely associated with TyG (β=−0.005, 95% CI: −0.005 to −0.005, P<0.00001), TyG-BMI (β=−0.241, 95% CI: −0.251 to −0.230, P<0.00001), TG/HDL-c (β=−0.004, 95% CI: −0.005 to −0.004, P<0.00001), and AIP (β=−0.002, 95% CI: −0.002 to −0.002, P<0.00001). (Table 4).

Cox regression models examining the association between lipid parameters and diabetes risk are presented in Table 5. TyG (HR=2.93, 95% CI: 2.77–3.11), TyG-BMI (HR=1.02, 95% CI: 1.02–1.02), TG/HDL-c (HR=1.19, 95% CI: 1.17–1.21), and AIP (HR=3.69, 95% CI: 3.25–4.19) all showed positive associations with diabetes risk (Table 5).

Table 4 The Associations Between eGFR and Lipid Parameters

	Model I β (95% CI) P Value	Model II β (95% CI) P Value	Model III β (95% CI) P Value
TyG	−0.010 (−0.010, −0.009) <0.00001	−0.005 (−0.005, −0.005) <0.00001	−0.005 (−0.005, −0.005) <0.00001
TyG-BMI	−0.533 (−0.545, −0.522) <0.00001	−0.246 (−0.256, −0.235) <0.00001	−0.241 (−0.251, −0.230) <0.00001
TG/HDL-c	−0.009 (−0.009, −0.009) <0.00001	−0.004 (−0.004, −0.003) <0.00001	−0.004 (−0.005, −0.004) <0.00001
AIP	−0.004 (−0.004, −0.004) <0.00001	−0.002 (−0.002, −0.002) <0.00001	−0.002 (−0.002, −0.002) <0.00001

Notes: Model I was unadjusted. Model II was adjusted for sex, age, DBP, and SBP. Model III was adjusted for sex, age, DBP, SBP, family history of diabetes, LDL-c, AST, ALT, BUN, smoking status, and drinking status.
Abbreviations: eGFR, estimated glomerular filtration rate; TyG, triglyceride glucose; TyG-BMI, triglyceride glucose- body mass index; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; AIP, atherogenic index of plasma; DBP, diastolic blood pressure; SBP, systolic blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDL-c, low-density lipoprotein cholesterol; BUN, blood urea nitrogen; CI, confidence interval.

Table 5 The Associations of Lipid Parameters and Diabetes Risk

	Model I HR (95% CI) P Value	Model II HR (95% CI) P Value	Model III HR (95% CI) P Value
TyG	3.85 (3.66, 4.05) <0.0001	3.05 (2.88, 3.23) <0.0001	2.93 (2.77, 3.11) <0.0001
TyG-BMI	1.03 (1.03, 1.03) <0.0001	1.02 (1.02, 1.02) <0.0001	1.02 (1.02, 1.02) <0.0001
TG/HDL-c	1.25 (1.23, 1.26) <0.0001	1.20 (1.18, 1.22) <0.0001	1.19 (1.17, 1.21) <0.0001
AIP	6.99 (6.26, 7.82) <0.0001	4.04 (3.56, 4.57) <0.0001	3.69 (3.25, 4.19) <0.0001

Notes: Model I was unadjusted. Model II was adjusted for sex, DBP, age, and SBP. Model III was adjusted for sex, DBP, age, SBP, smoking status, family history of diabetes, LDL-c, AST, ALT, BUN, and drinking status.
Abbreviations: eGFR, estimated glomerular filtration rate; TyG, triglyceride glucose; TyG-BMI, triglyceride glucose- body mass index; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; AIP, atherogenic index of plasma; DBP, diastolic blood pressure; SBP, systolic blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDL-c, low-density lipoprotein cholesterol; BUN, blood urea nitrogen; HR, hazard ratio; CI, confidence interval.

Table 6 Analysis of the Mediation by Lipid Parameters of the Correlations Between eGFR and Diabetes Risk

	Mediation Effect (95% CI), P Value			Mediation
	Total Effect	Indirect Effect	Direct Effect	
TyG	1.24 (1.09, 1.40) <0.0001	0.29 (0.26, 0.31) <0.0001	0.96 (0.82, 1.11) <0.0001	23.14%
TyG-BMI	1.30 (1.14, 1.45) <0.0001	0.27 (0.25, 0.30) <0.0001	1.02 (0.88, 1.18) <0.0001	21.05%
TG/HDL-c	1.09 (0.95, 1.24) <0.0001	0.04 (0.03, 0.04) <0.0001	1.05(0.91, 1.21) <0.0001	3.54%
AIP	1.16 (1.02, 1.32) <0.0001	0.15 (0.13, 0.16) <0.0001	1.02 (0.88, 1.17) <0.0001	12.49%

Notes: Adjusting variables: sex, age, family history of diabetes, drinking status, smoking status, AST, ALT, LDL-c, DBP, SBP, BUN.
Abbreviations: eGFR, estimated glomerular filtration rate; TyG, triglyceride glucose; TyG-BMI, triglyceride glucose- body mass index; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; AIP, atherogenic index of plasma; DBP, diastolic blood pressure; SBP, systolic blood pressure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDL-c, low-density lipoprotein cholesterol; BUN, blood urea nitrogen; HR, hazard ratio; CI, confidence interval.

Mediating Role of Lipid Parameters

Mediation analysis revealed that TyG and TyG-BMI mediated 23.14% and 21.05% of the association between eGFR and diabetes risk, respectively. For TG/HDL-c and AIP, the mediation proportions were 3.54% and 12.49%, respectively (Table 6 and Figure 3).

Discussion

In this investigation, we discovered a negative correlation between eGFR and diabetes risk, which remained significant in the fully adjusted model. Subgroup analysis revealed a stronger association between eGFR and diabetes risk among individuals who were female, aged <60 years, with BMI <25 kg/m², SBP <140 mmHg, non-smokers, non-drinkers, and those with ALT <40 U/L and AST <40 U/L. After demonstrating the negative correlations of lipid parameters with eGFR and positive correlations with diabetes risk, we performed mediation analysis, which revealed significant roles of TG/HDL-c, TyG-BMI, TyG, and AIP in linking eGFR with diabetes risk. This suggests that lipid metabolism may be an underlying mechanism in these associations. To our knowledge, this is the first study to examine the relationship between renal function, lipid parameters, and diabetes risk.

The eGFR is widely recognized for its direct relationship with renal mass[5] and its role as a distinct indicator of cardiovascular and renal outcomes.[7] It is a critical parameter for assessing renal function, especially in individuals with diabetes. Pham et al[8] reported an increased diabetes risk in individuals with both high and low eGFR. Furthermore, Masuda et al[36] emphasized the significance of eGFR monitoring in diabetic nephropathy, using it as a screening tool for renal evaluation. Zoppini et al[37] also

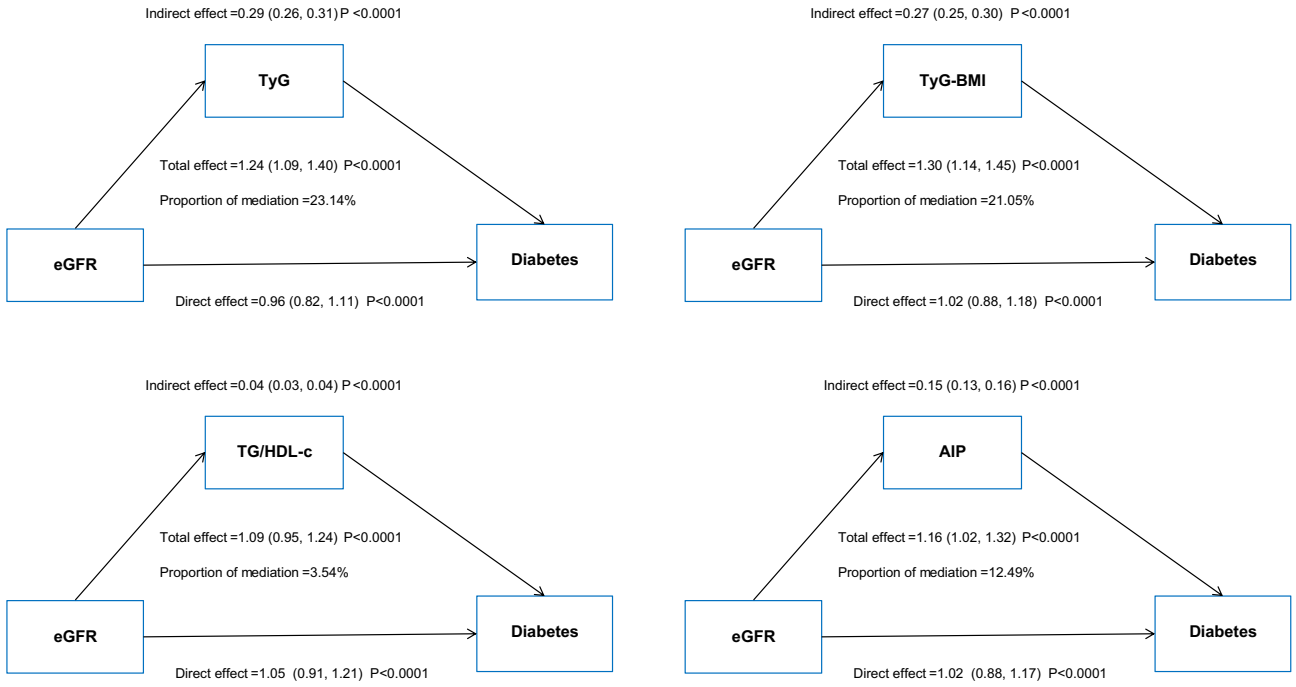

Figure 3 Mediation effect of lipid parameters (TyG, TyG-BMI, TG/HDL-c, AIP) between renal function (eGFR) and diabetes risk. The diagram illustrates the total, direct and indirect effects, with proportion of mediation for each lipid parameter: TyG (23.14%), TyG-BMI (21.05%), TG/HDL-c (3.54%), and AIP (12.49%).
Abbreviations: eGFR, estimated glomerular filtration rate; TyG, triglyceride glucose; TyG-BMI, triglyceride glucose- body mass index; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; AIP, atherogenic index of plasma.

highlighted the importance of eGFR as a widely used parameter for evaluating renal function changes in diabetes patients with preserved renal function. These studies have specifically emphasized the link between eGFR levels and diabetes risk across various ethnic groups, underscoring the impact of renal function in the pathogenesis of diabetes.[8,10–12] A retrospective cohort study found an inverse correlation between eGFR and diabetes risk (HR = 0.986, 95% CI: 0.984–0.988).[10] Our findings were consistent with this observation (HR = 0.98, 95% CI: 0.98–0.98), further supporting the inverse relationship between eGFR and diabetes risk. The distribution of eGFR in our study resulted in quartile ranges that differ from some previously published studies.[38,39] Notably, our highest quartile (Q4: 120.11–158.62 mL/min/1.73m²) includes values that may be considered hyperfiltration in clinical practice.[10] This reflects the relatively young (mean age 44.12 ± 12.95 years) and healthy baseline characteristics of our study population (individuals without diabetes at baseline) and our use of the CKD-EPI equation for Asian populations, which may yield different estimations compared to other equations.

The subgroup analysis revealed stronger negative associations between eGFR and diabetes risk among females, participants with BMI<25 kg/m², age<60 years, SBP<140 mmHg, non-smokers, non-drinkers, ALT<40 U/L, and AST<40 U/L, despite these factors not being traditional renal disease and diabetes risk factors. This seemingly paradoxical phenomenon can be explained through several mechanisms: The enhanced association in females may be related to hormonal influences, differences in body fat distribution, or heightened renal sensitivity to metabolic injury.[40,41] In individuals with lower BMI, eGFR decline may reflect non-obesity-related pathological processes such as autoimmune or inflammatory conditions rather than simple metabolic overload.[42,43] eGFR decline in younger patients may signify more severe underlying pathological states, as reduced renal function at a younger age could be associated with long-term metabolic damage or genetic factors.[44] In elderly populations, the presence of multiple comorbidities may dilute the independent effect of eGFR on diabetes risk.[45] While hypertension is both a renal disease risk factor and shares pathological mechanisms with diabetes, eGFR decline in normotensive individuals may more directly reflect renal-specific injury such as glomerulosclerosis rather than systemic metabolic dysfunction.[46] Within the "normal" BP range, eGFR decline may more sensitively reflect early vascular or endothelial dysfunction.[47] Smoking and alcohol consumption may directly damage renal and metabolic function through inflammatory or oxidative stress pathways.[48,49] In populations without these behaviors, the independent effect of eGFR

becomes more prominent. When liver enzymes are normal, the impact of the liver on insulin sensitivity is relatively minor, and renal metabolic factors such as eGFR play a more significant role in diabetes risk.[50] Simultaneously, the weakened liver-kidney interaction makes this association more pronounced in these subgroups.[51]

Our study provides strong evidence supporting adverse associations between lipid parameters and eGFR. Elevated TyG index correlates with declining renal function,[52] and TG/HDL-c ratios show a negative correlation with eGFR.[53] Our results are consistent with Oh et al,[54] who demonstrated a distinct relationship between elevated AIP and decreased eGFR, though their cross-sectional study design limited definitive causal conclusions. Deterioration of renal function exacerbates lipid disorders, while lipid disorders in turn lead to further decline in renal function.[55] Dyslipidemia induces cardiovascular dysfunction through atherosclerosis and endothelial injury, subsequently impairing renal function.[55] Hypertension plays a significant role in the relationship between lipid disorders and renal damage. When hypertension co-occurs with lipid abnormalities, it enhances vascular remodeling and cardiac hypertrophy, increasing renal vascular resistance.[56] Neuroendocrine activation and sympathetic hyperactivity cause renal vasoconstriction, elevated glomerular filtration pressure, and accelerated renal function decline.[55,56]

Multiple studies have confirmed a significant positive correlation between lipid parameters and diabetes risk. A meta-analysis comprising 13 cohort studies demonstrated that the TyG index strongly correlates with diabetes risk (HR=2.44).[57] Research indicates that individuals with elevated TyG-BMI values face substantially increased diabetes risk.[58] Studies have also established that higher TG/HDL-c levels are significantly associated with increased diabetes risk.[59] Dyslipidemia increases diabetes risk through multiple pathophysiological mechanisms, including lipotoxic damage to pancreatic β-cells, free fatty acid-induced IR, lipid peroxidation and oxidative stress activation, and qualitative changes in lipoprotein composition leading to atherosclerosis, with these mechanisms interacting to collectively promote the onset and progression of diabetes.[60–62]

The link between renal function and diabetes risk is mediated through lipid metabolism. Possible mechanisms are as follows. Declining renal function causes mitochondrial dysfunction in tubular epithelial cells leading to impaired fatty acid β-oxidation and lipid accumulation, activates sterol regulatory element-binding protein pathways increasing renal lipid synthesis, and reduces lipoprotein lipase activity causing dyslipidemia.[17,63,64] Additionally, renal lipid accumulation releases free fatty acids that inhibit insulin signaling pathways causing systemic IR, lipotoxicity directly damages pancreatic β-cells reducing insulin secretion, while inflammation and oxidative stress induced by abnormal lipid metabolism disrupt metabolic homeostasis, further exacerbating glucose metabolism disorders and increasing diabetes risk.[15,65,66]

Our study revealed a negative correlation between eGFR and diabetes risk, with lipid parameters playing significant mediating roles. Clinically, healthcare providers should monitor diabetes risk in patients with mild renal function decline, incorporate lipid parameters (TyG, TyG-BMI, TG/HDL-c, AIP) into assessments, and focus on high-risk populations (females, BMI<25 kg/m², age<60 years, SBP<140 mmHg, non-smokers, non-drinkers, ALT<40 U/L, and AST<40 U/L). Improving lipid metabolism through lifestyle or drug interventions may reduce diabetes risk in patients with impaired renal function, especially those with lower eGFR. Our findings offer new perspectives for addressing diabetes risk through attention to renal function and lipid parameters.

To our knowledge, this study represents the first attempt to explore the mediating role of lipid parameters in the eGFR-diabetes relationship using a large-scale population-based cohort design. Building upon established associations between renal function and diabetes risk, as well as between lipid parameters and diabetes risk documented in previous literature,[10,58] we quantitatively assessed how four lipid parameters (TyG, TyG-BMI, TG/HDL-c, and AIP) mediate this relationship, with respective mediation proportions of 23.14%, 21.05%, 3.54%, and 12.49%. This approach offers mechanistic insights into the complex interplay between renal function, lipid metabolism, and diabetes risk. Additionally, our comprehensive subgroup analyses revealed stronger eGFR-diabetes associations in specific populations, providing clinically relevant stratification of risk. While the original dataset by Chen et al[30] examined BMI-diabetes relationships, our investigation addresses a distinct research question regarding the pathophysiological pathways linking renal function to diabetes risk through lipid metabolism, thereby expanding the utility of this valuable cohort data.

However, several limitations of our study warrant discussion. (1) Population specificity: Our study participants were exclusively Chinese, potentially limiting generalizability to other ethnic populations with different genetic profiles and lifestyle factors. Validation in diverse populations remains necessary to confirm our findings' universal applicability. (2) Causality

limitations: Despite our cohort design and mediation analyses suggesting mechanistic pathways, the observational nature of our study precludes definitive causal conclusions regarding the relationships between eGFR, lipid parameters, and diabetes risk. These associations should be interpreted as correlative rather than causal. (3) Residual confounding: Although we controlled for multiple confounders and calculated E-values, unmeasured factors including detailed dietary patterns, physical activity, medication use, and socioeconomic variables may still influence our results. (4) Diagnostic constraints: Our diabetes definition excluded glycated hemoglobin and impaired glucose tolerance criteria, potentially underestimating diabetes incidence.

Conclusion

The cohort study confirmed a negative relationship between renal function and diabetes risk in Chinese populations, highlighting lipid's crucial mediating role. These findings offer new insights into diabetes mechanisms, suggesting lipid metabolism as a key pathway connecting renal function to diabetes risk. Clinically, parameters like TyG, TyG-BMI, TG/HDL-c, and AIP serve as important indicators when assessing how renal function relates to diabetes risk. Future research should examine the specific mechanisms through which lipid parameters affect renal function and diabetes risk, and validate these findings across diverse populations.

Data Sharing Statement

Dryad Dataset (https://doi.org/10.5061/dryad.ft8750v) is available for free download.

Ethics Approval and Consent to Participate

This study was approved by the Rich Healthcare Group Review Board and the institutional ethics committee waived informed consent for this retrospective study. Our research adhered to the principles of the Helsinki Declaration in the following ways:

1. Confidentiality and Personal Data Protection: All data used in our study were completely de-identified before being made available on the DATADRYAD platform, ensuring participant anonymity. No personal identifiers were accessible to our research team during the analysis.
2. Data Security: Throughout our secondary analysis, we maintained strict data security protocols with access limited to authorized research personnel only.
3. Ethical Data Use: Our utilization of this dataset complies with the terms specified by DATADRYAD, which requires that all shared data adhere to ethical standards for human subject research. The dataset (https://doi.org/10.5061/dryad.ft8750v) is available under open-access terms that permit derivative analyses.
4. Scientific Integrity: Our research questions and analytical approaches were designed to maximize scientific value while respecting the original purpose of data collection and the rights of the participants.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests that might be perceived as influencing the results or interpretation of the manuscript. This includes no relevant financial interests, activities, relationships, or affiliations with any organization or entity with a financial interest in or financial conflict with the subject matter in the manuscript.

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