The association between dyslipidemia and the incidence of chronic kidney disease in the general Zhejiang population: a retrospective study

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Research article

Keywords: Renal function, lipid profiles, epidemiology, eGFR

Posted Date: March 3rd, 2020

DOI: https://doi.org/10.21203/rs.3.rs-15778/v1

Version of Record: A version of this preprint was published on July 2nd, 2020. See the published version at https://doi.org/10.1186/s12882-020-01907-5.

Abstract

Background According to the "lipid nephrotoxicity hypothesis", there is now significant research being conducted in this area. By studying the role of hyperlipidemia in chronic kidney disease in the general Zhejiang population, we aimed to explore the correlation between changes in blood lipid levels and chronic kidney disease.

Methods We collected and analyzed clinical data from ordinary residents who participated in the annual comprehensive physical examination with no overt kidney disease in Zhejiang Provincial People's Hospital, China from January 2011 to December 2016. According to triglyceride, total cholesterol and low-density lipoprotein levels, participants were respectively divided into 4 groups. Statistical methods were used to evaluate the correlation between different blood lipid profiles and chronic kidney disease.

Results 5,183 participants were included in our study. During the six-year follow-up period, 227 participants (4.4%) developed chronic kidney disease. The odds ratio for incident chronic kidney disease was 3.14 (95%CI: 1.53–6.43) in Q3, 3.84 (95%CI: 1.90–7.76) in Q4 according to the total cholesterol group and 1.17 (95%CI: 1.04–1.32) in Q3, 1.40 (95%CI: 1.11–2.48) in Q4 according to the low-density lipoprotein group, respectively, after multivariable-adjusted analyses. According to the triglyceride grouping, the odds ratio for incident chronic kidney disease was 2.88 (95%CI: 1.29-6.43) in Q2, 2.92 (95%CI: 1.44–6.57) in Q3 and 3.08 (95%CI: 1.11–6.69) in Q4, after multivariable-adjusted analyses.

Conclusion Increased triglycerides and high levels of total cholesterol and low-density lipoprotein were independently associated with an increased likelihood of eGFR decline and development of incident chronic kidney disease in the general Zhejiang population.

Background

The prevalence of chronic kidney disease (CKD) in China and the rest of the world is increasing [1]. It has been estimated that the prevalence of CKD in China is approximately 10.8% [2]. CKD not only causes end-stage renal disease (ESRD), which requires renal replacement therapy, but also induces complications and increases mortality [3]. Therefore, risk factors for CKD should be detected early, managed and controlled, which can significantly prevent the development of CKD [4].

Due to the continuous changes in living standards and dietary habits, the incidence of dyslipidemia has increased annually. Dyslipidemia includes hypertriglyceridemia, hypercholesterolemia, lower high-density lipoproteinemia, and mixed hyperlipidemia [5]. Many studies have shown that dyslipidemia can lead to cardiovascular disease (CVD) [6, 7].

When the “Lipid Nephrotoxicity Hypothesis” was proposed in 1982, CKD was postulated as being associated with dyslipidemia [8]. Over the last few decades, this area has been continuously developed and researched [9, 10]. However, there have been conflicting results from different studies. Whether triglycerides (TG), total cholesterol (TC) and low-density lipoprotein (LDL) have any influence on the development of CKD is still unclear, and to what extent. It has not been established whether elevated blood lipid levels are an

independent risk factor for incident CKD or whether a rapid decline in annual estimated glomerular filtration rate (eGFR) in non-CKD individuals results in CKD. Furthermore, little is known on which types of blood lipids have the greatest impact on incident CKD [11–16].

In this study, the retrospective associations of serum lipid levels with progression of renal dysfunction and incident CKD were investigated in a large cohort based on annual physical examination of participants with eGFR ≥ 60 mL/min/1.73 m^2 and no basal kidney disease. In addition, we also performed an analysis of the different groupings of blood lipid types.

Methods

The study design is a retrospective observational study based on the general Chinese population. Participants were 25–85 years old, worked in Hangzhou City and participated in a comprehensive annual medical examination at the Zhejiang Provincial People's Hospital, China from January 2011 to December 2016. The baseline eGFR was ≥ 60 ml/min/1.73 m^2.

Study population

A total of 5,945 participants had complete baseline data. However, 15 of these failed to complete the follow-up examination. Then, we deleted 203 participants with incomplete data. In addition, 264 patients were excluded for previous medical history including: cardiovascular disease, cerebrovascular disease, severe liver damage, severe infection, malignancy, kidney surgery or other life-threatening illnesses. For the remaining 5463 participants, 280 individuals were excluded due to baseline eGFR < 60 ml/min/1.73 m^2. Finally, a total of 5,183 participants were selected for the research analysis (Fig. 1).

Data collection and analysis

Baseline characteristics of participants included age, gender, biochemical measurements, and medical history. Weight and height were measured while the participants were wearing lightweight clothes with no shoes. The body mass index (BMI) was calculated as the weight (kg) divided by the square of the height (m). After 15 minutes of rest, the participants were placed in a sitting position, and systolic and diastolic blood pressure (SBP/DBP) were measured using an automatic sphygmomanometer. Blood pressure (BP) was measured twice, with an interval of more than 5 minutes, then the mean value was selected. Blood samples were taken after over 12 hours of fasting overnight. We measured biomedical parameters using a biochemical automatic enzyme analyzer, including blood urea nitrogen (BUN), fasting blood glucose (FPG), TC, TG, high-density lipoprotein (HDL), LDL, and uric acid (SUA) in the Clinical Laboratory of Zhejiang Provincial People's Hospital. All covariates were measured once at baseline. All indicators were examined during follow-up. Renal function was calculated by using the formula for eGFR (ml / min / 1.73 m^2) = $186 \times SCr^{-1.154} \times age^{-0.203}$ (× 0.742, if female), which is derived from the simplified Modification of Diet in Renal Disease (MDRD) study for Chinese people [17]. According to the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline, an incident CKD event was defined as eGFR < 60 ml / min / 1.73 m^2 during follow-up. For individuals who had more than one CKD event during the follow-up period, only the first event was included in our statistical analysis.

Statistical analysis

All statistical analyses were performed using SPSS, version 23.0 (IBM, USA). All P-values were two-tailed, and $P < 0.05$ was considered to indicate statistical significance. Multivariate linear regression analysis was used to evaluate the association between blood lipid levels and eGFR changes.

Results

Baseline characteristics

The distribution of the blood lipid levels at baseline is shown in *Fig*. 2. Baseline eGFR decreased with increasing baseline TC, TG, and LDL. The baseline characteristics of the blood lipid groups are shown in *Tables* 1-3. In general, the majority of participants were middle-aged males (30.8%) . The average eGFR was 86.2 ml/min/1.73m^2. Participants in Q4 (TC> 5.38 mmol/l, TG> 1.72 mmol/l, and LDL> 3.27 mmol/l) had a higher BMI and BP, BUN, SUA and FPG levels than those in Q1 (TC ≤ 4.20 mmol/l, TG≤ 0.80 mmol/l, and LDL≤ 2.28 mmol/l). Q4 also had a higher prevalence of those who were overweight, hypertensive and had obesity, as well as a lower eGFR, than those in Q1.

A comparison of baseline characteristics of participants with and without incident CKD is shown in *Table* 4. During the 6-year follow-up period, 227 patients (4.4%) developed CKD. Participants with CKD were older and more likely to be obese, and have hyperlipidemia, hypertension or diabetes than patients without CKD.

Incidence of CKD and blood lipid levels

We compared and analyzed the relationship between blood lipid levels and incident CKD (*Table* 5, *Fig*. 3).

In the TC group, with or without adjustment, when TC was greater than 4.76 mmol/l, the likelihood of developing CKD increased commensurate with the increase in TC levels (the OR and 95% CI for the Q3 and Q4 groups were 3.22 [1.57–6.60] and 3.96 [1.97-7.99], respectively, $P < 0.01$), compared with Q1 as a reference. We also obtained the same result after adjusting in the multivariate model, but the OR was reduced (the OR and 95% CI for Q3 was 2.47 [1.075–5.66], $P < 0.05$, and in Q4 it was 2.76 [1.38-6.04], $P < 0.01$) (*Table* 5, *Fig*. 3). This indicates that high TC levels had an impact on renal dysfunction.

Similarly, in the LDL group, development of CKD increased commensurate with the increase in LDL levels (the OR and 95% CI for the Q2, Q3 and Q4 groups were 1.38 [1.08-1.84], 1.52 [1.18–2.03] and 1.88 [1.31-2.69], respectively, $P < 0.01$), compared with Q1 as a reference. However, after adjusting in the multivariable model, only the Q3 and Q4 groups were significantly different (the OR and 95% CI for the Q3 and Q4 groups were 1.17 [1.04–1.32] and 1.40 [1.11-2.48], respectively, $P < 0.05$) (*Table* 5, *Fig*. 3).

In the TG group, development of CKD increased commensurate with the increase in TG levels (the OR and 95% CI for the Q2, Q3 and Q4 groups were 3.025 [1.47-6.21], 3.15 [1.55–6.61] and 3.35 [1.64-6.83], respectively, $P < 0.01$), compared with Q1 as a reference. After we adjusted for baseline SCr, the OR decreased to 2.98 (1.50–6.11) in Q2 , 3.11 (1.49-6.325) and 3.24 (1.59–6.62) in the Q4 group, while it significantly decreased to 2.88 (1.29–6.43) in Q2, 2.92 (1.44-6.57) in Q3, and 3.08 (1.11-6.69) in Q4 after adjustment in the multivariate model (*Table* 5, *Fig*. 3).

Discussion

Before this study, we used the same data to analyze the relationship between serum uric acid and CKD in the general population, and concluded that time-mean serum uric acid is an independent risk factor for CKD [18]. Dyslipidemia and hyperuricemia are important components of the metabolic syndrome [19]. Therefore, we specifically studied the relationship between dyslipidemia and CKD.

In the current study, we found that TG, and high levels of TC and LDL were associated with the occurrence of CKD, while low TC and LDL levels were not. In particular, the primary findings of our study suggest that TG, and high levels of TC and LDL indicate a risk of progression of renal progression and renal dysfunction, even within the normal range of TG levels.

In many studies, the causal role between dyslipidemia and the occurrence and progression of CKD appears to be clear [20–22]. However, the role for the type of blood lipids seems to be conflicting in the occurrence and development of CKD. A study has shown that elevated TC, TG, and LDL are significant risk factors for an eGFR decline in apparently healthy children and adolescents [23]. Recently, Kuma et al. studied the association of dyslipidemia and eGFR reduction in 14,510 healthy people aged 20–60 years and found that elevated LDL-C i.e. exceeding 7.78 mmol/l (140 mg/dL) was a significant risk factor for development of CKD during follow-up over 5 years [24]. In 2015, a follow-up study of 1824 subjects over 5 years found that hypertriglyceridemia was associated with CKD in Japan [25]. Similarly, Tsuruya et al. conducted a prospective cohort study of 117,279 participants, including 47,373 males and 69,422 females, aged 39–74 years. This study showed that hypertriglyceridemia could lead to the progression of CKD [26]. However, Tozawa et al. found that TC and LDL were not independent risk factors for proteinuria [11] and Iseki also found that hypercholesterolemia was not an independent predictor of ESRD [27].

However, it is important to acknowledge that our research also has certain limitations. First, the participants were not selected at random. Secondly, participants who participated in the annual physical examination were very concerned about their own health. It was likely that some of the incident CKD patients did not participate in the next annual physical examination but may have been followed-up in the outpatient clinic. Finally, we cannot completely rule out all confounding factors although our adjustment in using multivariate analysis partly mitigates for this.

Conclusion

In conclusion, we found that TG, and high levels of TC and LDL are associated with decreased renal function and an increased likelihood of incident CKD development in the general population. This demonstrated that controlling elevated TG, TC, and LDL might contribute to reduced propensity of renal dysfunction. Monitoring and management of blood lipids on a regular basis, especially TG, should be considered.

Abbreviations

eGFR:estimated glomerular filtration rate; CKD: chronic kidney disease; ESRD: end-stage renal disease; CVD: cardiovascular disease; TG: triglycerides; TC: total cholesterol; LDL: low-density lipoprotein; BMI: body mass

index; SBP/DBP: systolic and diastolic blood pressure; BP: blood pressure; FPG: fasting blood glucose; HDL: high-density lipoprotein; SUA: uric acid; MDRD: Modification of Diet in Renal Disease; KDIGO: Kidney Disease: Improving Global Outcomes.

Declarations

Ethics approval and consent to participate

This study protocol was approved by the Ethics Committee of Zhejiang Provincial People's Hospital (Approval Number: KY2017019). All participants have given their written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

All data supporting the study are presented in the manuscript and available on a request to the corresponding authors of this manuscript, Qiang He.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by grants from the Natural Science Foundation of Zhejiang Province (Grant Number LZ17H050001, LY16H050005, Y18H050024), the Project of Province and the Ministry (Grant Number WKJ-ZJ-1915), the Project of Scientific Research Foundation of Chinese Medicine (Grant Number 2017ZA010□2016ZQ007). The funders had no role in study design, collection, analysis, interpretation of data, writing the report, nor in the decision to submit the report for publication.

Authors' contributions

QH and JJ designed and directed the project. XDL, MYY, MT and DNZ carried out data collection. XDL, YFZ, CRY and JJ participated in data analysis. XDL, MT and DNZ wrote the manuscript. All authors discussed the results and approved the manuscript as submitted. All authors approved the final version of the manuscript.

Acknowledgments

The authors thank Zhejinag Provical People's Hospitai for helping us during data collection.

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Tables

Table 1. Baseline characteristics of subjects by quartiles of TC.

TC（mmol/l）	Q1（£4.20） （n=1315）	Q2（>4.20（£4.76） （n=1287）	Q3（>4.76（£5.38） （n=1292）	Q4（>5.38） （n=1289）	*P* value
Age (Years)	43.14±13.79	48.64±15.11	51.02±15.20	55.59±14.46	<0.001
Male (%)	833（63.4）	809（62.9）	800（61.9）	734（56.9）	<0.001
BMI (kg/m^2)	22.54±2.95	23.12±2.94	23.48±2.95	23.84±3.11	<0.001
Overweight (24 ≤ BMI < 28) (%)	340（25.9）	418（32.5）	471（36.5）	502（38.9）	<0.001
Obesity (BMI ≥ 28) (%)	56（4.3）	64（5.0）	77（6.0）	114（8.8）	<0.001
SBP (mmHg)	120.27±16.71	124.36±17.67	126.50±18.83	130.88±19.42	<0.001
DBP (mmHg)	72.52±10.58	74.97±11.25	76.33±11.38	78.45±11.24	<0.001
TG(mmol/L)	1.08±0.76	1.28±0.85	1.49±0.96	1.87±1.27	<0.001
HDL-C (mmol/L)	1.37±0.34	1.32±0.30	1.29±0.29	1.21±0.25	<0.001
LDL-C (mmol/L)	2.03±0.38	2.55±0.34	2.98±0.37	3.67±0.67	<0.001
BUN (mmol/L)	4.79±1.07	4.98±1.13	5.07±1.19	5.15±1.13	<0.001
FPG (mmol/L)	5.08±0.65	5.20±0.81	5.26±0.80	5.41±0.99	<0.001
SCr(mmol/L)	82.26±13.48	82.75±13.91	83.03±13.61	83.13±13.88	0.371
SUA(mg/dl)	5.44±1.28	5.56±1.32	5.65±1.36	5.83±1.39	<0.001
Hypertension (%)	131（10.0）	192（14.9）	227（17.6）	299（23.1）	<0.001
Diabetes (%)	42（3.2）	53（4.0）	41（3.2）	62（4.8）	0.089
eGFR (ml/min/1.73m^2)	90.81±15.67	87.60±16.09	84.84±14.35	81.56±13.40	<0.001
Incident CKD (%)	27（2.1）	54（4.2）	43（3.3）	103（8.0）	<0.001

Table 2. Baseline characteristics of subjects by quartiles of TG.

TG（mmol/l）	Q1（£0.80） （n=1279）	Q2（>0.80（£1.16） （n=1326）	Q3（>1.16（£1.72） （n=1284）	Q4（>1.72） （n=1294）	*P* value
Age (Years)	43.79±13.81	49.46±15.83	51.79±15.47	53.18±14.37	<0.001
Male (%)	551（43.1）	764（57.6）	870（67.8）	991（76.6）	<0.001
BMI (kg/m^2)	21.53±2.54	22.68±2.76	23.81±2.93	24.95±2.74	<0.001
Overweight (24 ≤ BMI < 28) (%)	176（13.8）	384（29.0）	504（39.3）	667（51.5）	<0.001
Obesity (BMI ≥ 28) (%)	21（1.6）	34（2.6）	97（7.6）	159（12.3）	<0.001
SBP (mmHg)	117.94±16.05	123.20±18.31	127.34±18.35	133.42±17.9	<0.001
DBP (mmHg)	70.91±10.34	73.53±10.74	76.83±10.75	80.94±10.88	<0.001
TC(mmol/L)	4.39±0.79	4.71±0.83	4.99±0.92	5.23±0.93	<0.001
HDL-C (mmol/L)	1.48±0.31	1.36±0.29	1.24±0.26	1.10±0.22	<0.001
LDL-C (mmol/L)	2.45±0.64	2.79±0.70	2.94±0.79	3.04±0.76	<0.001
BUN (mmol/L)	4.95±1.20	4.97±1.15	5.01±1.12	5.06±1.09	0.052
FPG (mmol/L)	5.04±0.56	5.16±0.76	5.26±0.73	5.49±1.10	<0.001
SCr(mmol/L)	77.74±13.81	81.56±13.46	84.63±12.86	87.32±12.81	<0.001
SUA(mg/dl)	4.96±1.12	5.36±1.27	5.80±1.25	6.35±1.32	<0.001
Hypertension (%)	89（7.0）	168（12.7）	253（19.7）	339（26.2）	<0.001
Diabetes (%)	29（2.3）	39（2.9）	56（4.4）	74（5.6）	<0.001
eGFR (ml/min/1.73m^2)	92.36±16.27	86.79±14.98	83.71±13.87	82.09±13.96	<0.001
Incident CKD (%)	39（3.0）	37（2.8）	54（4.2）	97（7.5）	<0.001

Table 3. Baseline characteristics of subjects by quartiles of LDL.

LDL（mmol/l）	Q1（£2.28） （n=1321）	Q2（>2.28（£2.75） （n=1292）	Q3（>2.75（£3.27） （n=1280）	Q4（>3.27） （n=1290）	*P* value
Age (Years)	45.02±14.59	48.34±14.84	50.36±15.39	54.68±14.84	<0.001
Male (%)	745（56.4）	781（60.4）	837（65.4）	813（63.0）	<0.001
BMI (kg/m^2)	22.29±2.93	23.01±2.98	23.59±2.91	24.10±2.98	<0.001
Overweight (24 ≤ BMI < 28) (%)	318（24.1）	386（29.9）	487（38.0）	540（41.9）	<0.001
Obesity (BMI ≥ 28) (%)	49（3.7）	61（4.7）	84（6.6）	117（9.1）	<0.001
SBP (mmHg)	121.53±18.07	123.60±17.72	126.75±18.62	130.13±19.13	<0.001
DBP (mmHg)	73.26±11.35	74.38±11.00	76.52±11.34	78.11±10.95	<0.001
TC(mmol/L)	3.91±0.58	4.51±0.45	5.01±0.42	5.92±0.71	<0.001
TG (mmol/L)	1.35±1.40	1.35±0.96	1.43±0.80	1.59±0.78	<0.001
HDL-C (mmol/L)	1.31±0.34	1.30±0.32	1.28±0.29	1.29±0.26	0.065
BUN (mmol/L)	4.81±1.11	4.96±1.14	5.03±1.14	5.20±1.13	<0.001
FPG (mmol/L)	5.12±0.81	5.17±0.73	5.28±0.85	5.38±0.89	<0.001
SCr(mmol/L)	80.73±13.83	82.56±13.73	83.82±13.63	84.11±13.41	<0.001
SUA(mg/dl)	5.35±1.33	5.54±1.31	5.69±1.34	5.90±1.35	<0.001
Hypertension (%)	164（12.4）	190（14.7）	209（16.3）	286（22.2）	<0.001
Diabetes (%)	44（3.3）	40（3.1）	57（4.5）	57（4.4）	0.147
eGFR (ml/min/1.73m^2)	90.39±16.53	87.05±15.37	85.29±14.53	82.06±13.37	<0.001
Incident CKD (%)	49（3.7）	49（3.8）	42（3.3）	87（6.7）	<0.001

Table 4 Baseline characteristics of participants relative to development of CKD during the 6-year follow-up perio*d.*ΔTG, ΔTC and ΔLDL-C: ending TG/ TC/LDL minus baseline TG/ TC/LDL, respectively.

	CKD (n=227)	Without CKD (n=4956)	*P* value
Age (Years)	60.69±19.20	47.82±15.65	<0.001
Male (%)	88(38.8)	1919□38.7)	0.989
BMI (kg/m^2)	24.32±2.78	23.18±3.01	<0.001
SBP (mmHg)	139.80±20.81	124.91±18.79	<0.001
DBP (mmHg)	80.61±12.02	75.31±11.21	<0.001
TG (mmol/L)	1.71±1.29	1.42±1.11	0.001
ΔTG	0.25±0.28	0.11±0.16	<0.001
TC(mmol/L)	5.12±1.02	4.83±0.91	<0.001
ΔTC (mmol/L)	0.27±0.36	0.15±0.23	<0.001
HDL-C (mmol/L)	1.31±0.28	1.30±0.31	0.048
LDL-C (mmol/L)	2.98±0.82	2.82±0.77	<0.001
ΔLDL-C (mmol/L)	0.15±0.25	0.08±0.19	<0.001
BUN (mmol/L)	5.68±1.17	4.96±1.14	<0.001
FPG (mmol/L)	5.46±1.01	5.24±0.82	<0.001
SUA(mg/dl)	6.24±1.41	5.59±1.33	<0.001
Hypertension (%)	103(35.7)	746(16.9)	<0.001
Diabetes (%)	25(45.4)	173(15.1)	<0.001
Baseline eGFR (ml/min/1.73m^2)	68.71±7.62	87.01±15.14	<0.001
Ending eGFR (ml/min/1.73m^2)	48.75±8.76	82.38±10.99	<0.001

Table 5 Association between blood lipids and incident CKD. [1] Data adjusted for age, gender, BMI, BP, TG, HDL, LDL, BUN, FPG, SCr, SUA, hypertension, diabetes, proteinuria. [2] Data adjusted for age, gender, BMI, BP, TC, HDL, LDL, BUN, FPG, SCr, SUA, hypertension, diabetes, proteinuria. [3] Data adjusted for age, gender, BMI, BP, TC, TG, HDL, BUN, FPG, SCr, SUA, hypertension, diabetes, proteinuria. *P<0.05, **P<0.01.

	Quartiles of TC (mmol/l) OR (95% CI)				Quartiles of TG (mmol/l) OR (95% CI)				Quartiles of LDL (mmol/l) OR (95% CI)			
	£4.20	>4.20–£4.76	>4.76–£5.38	>5.38	£0.80	>0.80–£1.16	>1.16–£1.72	>1.72	£2.28	>2.28–£2.75	>2.75–£3.27	>3.27
CKD–227–4.4%–	27 –2.1–	54–4.2–	43–3.3–	103 –8.0–	39 –3.0–	37–2.8–	54–4.2–	97 –7.5–	49 –3.7–	49–3.8–	42–3.3–	87 –6.7–
Unadjusted	1.00 (-ref-)	1.844 –0.848-4.010–	3.221 –1.573-6.597–**	3.964 –1.967-7.990–**	1.00 (-ref-)	3.025 –1.474-6.208–**	3.153 –1.547-6.611–**	3.348 –1.643-6.826–**	1.00 (-ref-)	1.381 –1.079-1.840–**	1.523 –1.183-2.032–**	1.877 –1.311-2.688–**
Adjusted only for baseline creatinine	1.00 (-ref-)	1.766 –0.811-3.847–	3.137 –1.530-6.434–**	3.843 –1.904-7.756–**	1.00 (-ref-)	2.977 –1.449-6.113–**	3.111 –1.489-6.325–**	3.243 –1.588-6.624–**	1.00 (-ref-)	1.023 –0.683-1.532–	1.311 –1.099-1.700–*	1.634 –1.153-2.495–*
Adjusted[1]	1.00 (-ref-)	1.292 –0.468-3.567–	2.466 –1.075-5.657–*	2.764 –1.382-6.037–**	-	-	-	-	-	-	-	-
Adjusted[2]	-	-	-	-	1.00 (-ref-)	2.876 –1.286-6.432–**	2.923 –1.438-6.572–*	3.076 –1.112-6.687–*	-	-	-	-
Adjusted[3]	-	-	-	-	-	-	-	-	1.00 (-ref-)	0.946 –0.898-0.996–	1.172 –1.041-1.319–*	1.400 –1.111-2.476–*

Figures

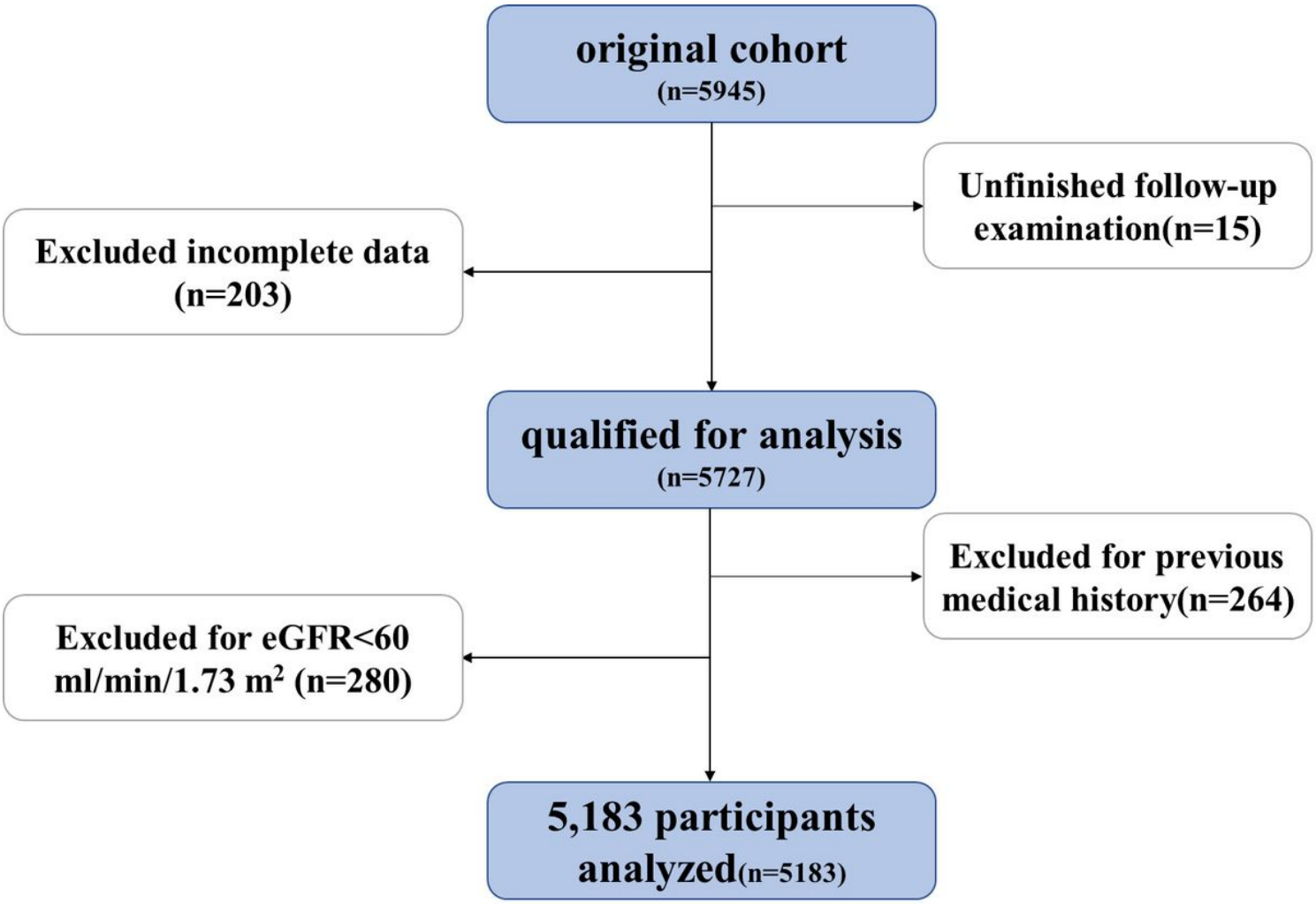

Figure 1

Flow diagram of study population.

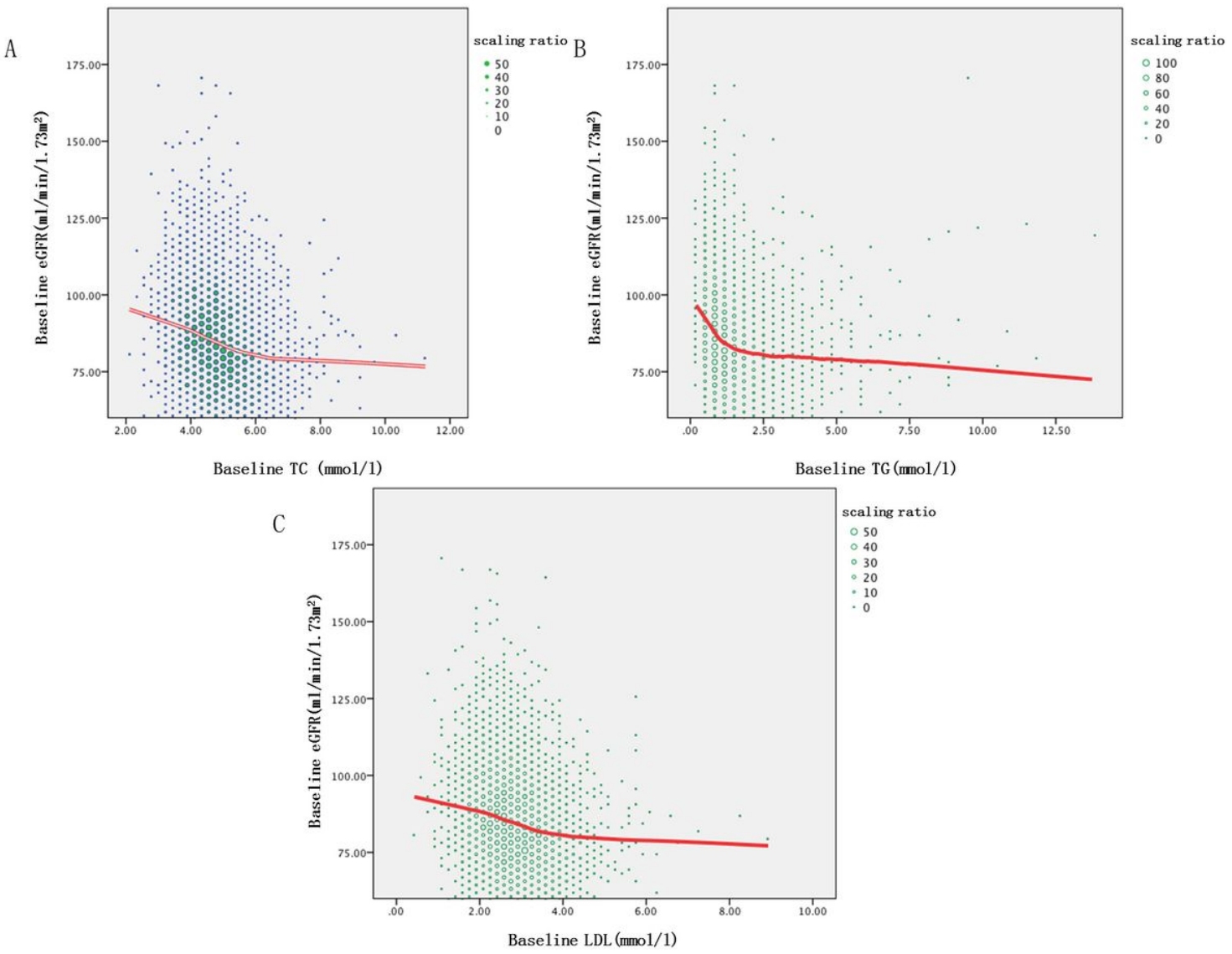

Figure 2

The relationship between blood lipid levels and eGFR at first visit. A: The relationship between baseline TC and eGFR. B: The relationship between baseline TG and eGFR. C: The relationship between baseline LDL and eGFR.

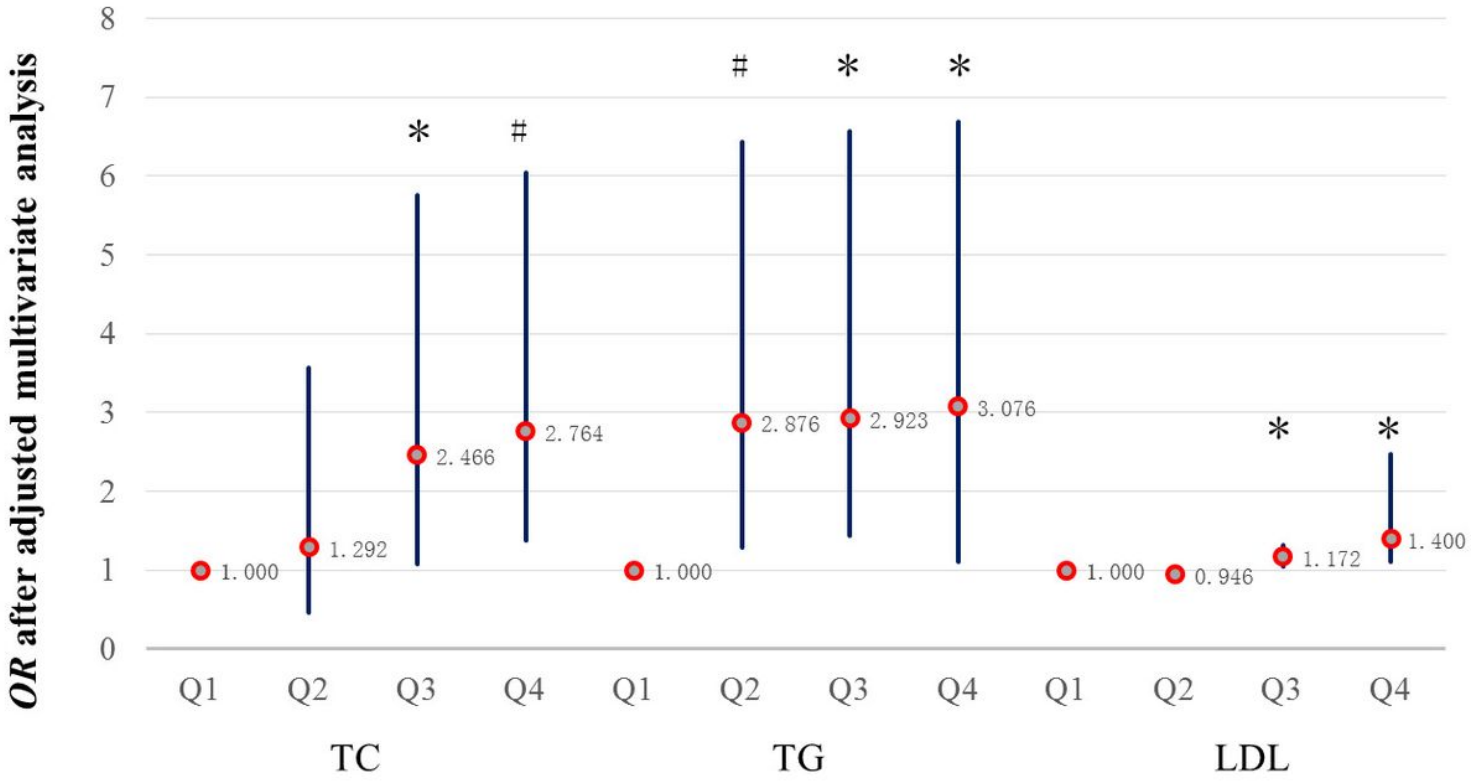

Figure 3

The relationship between blood lipid levels and OR after multivariable-adjusted analysis. A comparison of Q2-4 and Q1 in the same lipid group, respectively. *P <0.05, # P <0.01.