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Correlation between conventional and unconventional lipid parameters with the risk of progression of renal function decline: insights from the China Health and Retirement Longitudinal Study 2011–2015

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ABSTRACT

Background: This study aimed to evaluate the association between conventional and unconventional lipid parameters and the risk of future chronic kidney disease (CKD) and progression of renal function decline.

Methods: Data from 4,542 participants who were free of CKD at baseline were analyzed using information from the China Health and Retirement Longitudinal Study (2011–2015). The follow-up period was four years. The primary endpoints were incident CKD and rapid progression of renal function decline. The associations between lipid parameters and the risk of CKD and rapid progression of renal function decline were assessed using restricted cubic splines (RCS) and logistic regression analysis.

Results: Logistic regression analysis showed that high-density lipoprotein cholesterol (HDL-C) was negatively associated with CKD risk, while remnant cholesterol (RC) and the atherogenic index of plasma (AIP) were positively associated. Triglycerides (TG), RC, and AIP were positively correlated with rapid renal function decline, whereas low-density lipoprotein cholesterol (LDL-C) and HDL-C were negatively correlated. Among these parameters, AIP was the most strongly associated with CKD [adjusted odds ratio (OR) (95% CI): 2.091 (1.199, 3.649), $p=0.009$] and rapid progression of renal function decline [adjusted OR (95% CI): 3.996 (2.632, 6.068), $p<0.001$].

Conclusion: LDL-C and HDL-C were negatively associated with rapid progression of renal function decline, while TG, RC, and AIP were positively associated with this outcome. Among the lipid parameters examined, AIP was the most strongly associated with CKD and rapid progression of renal function decline.

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Chronic kidney disease; renal function decline; lipid parameters; atherogenic index of plasma; remnant cholesterol

1. Introduction

Chronic kidney disease (CKD) is a significant global public health concern and a major cause of mortality and disability [1]. The global all-age mortality rate from CKD increased by 41.5% between 1990 and 2017 [1]. Given that CKD is largely preventable and treatable, early detection and management of risk factors for renal function decline may improve patient quality of life and reduce the burden on healthcare and financial systems.

According to earlier epidemiological research, dyslipidemia is linked to a decline in kidney function and may be a factor in the onset of CKD [2]. Elevate triglyceride (TG), triglyceride-rich lipoproteins (TRLs), low-density lipoprotein cholesterol (LDL-C), and decreased high-density lipoprotein cholesterol (HDL-C) are characteristic lipid abnormalities in CKD [3–7]. However, previous research findings regarding the role of lipid abnormalities in renal function decline have been inconsistent. For example, elevated levels of TG, LDL-C, and remnant cholesterol (RC), as well as reduced levels of HDL-C, have been associated with an increased risk of CKD [8–11]. Conversely, in the Chronic Renal Insufficiency Cohort study, TG, total cholesterol (TC), very-low-density lipoprotein cholesterol (VLDL-C), LDL-C, and HDL-C levels were not found to be independently associated with the progression of kidney function decline [12].

Moreover, prior studies have either categorized blood lipid status into two groups (normal or dyslipidemia) or

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examined only one or two blood lipid indicators. The dose-response relationships between conventional and unconventional blood lipid parameters and CKD or rapid progression of renal function decline have not been thoroughly and systematically investigated. Additionally, most prior research is cross-sectional, with few prospective studies. To address this gap, we aimed to prospectively examine the association between conventional and unconventional lipid parameters and the risk of future CKD and renal function decline, thereby providing a more comprehensive understanding of the role of blood lipid parameters in renal function decline.

2. Methods

2.1. Data source and study population

This study utilized data from the 2011, 2013, and 2015 waves of the China Health and Retirement Longitudinal Study (CHARLS), which included information from 17,705 individuals in the 2011 wave. CHARLS is a nationally representative longitudinal study that covers 150 counties and 450 villages across 28 provinces in mainland China. The study aims to provide a comprehensive set of micro-databases that accurately represent middle-aged and older Chinese individuals and their families. Ethical approval for the study was obtained from Peking University under the reference number IRB00001052–11015. Following the baseline survey in 2011, two follow-up surveys were conducted in 2013 and 2015. Comprehensive information on blood samples and the data resource profile has been previously published [13–15]. Participants were excluded if they lacked data on serum creatinine or serum cystatin C in either the 2011 or 2015 waves, LDL-C in the 2011 wave, body mass index (BMI) in the 2011 wave, waist circumference in the 2011 wave, or gender. Additionally, individuals with an estimated glomerular rate filtration (eGFR) of less than 60 mL/min/1.73m^2 in the 2011 wave were excluded. After these exclusions, a total of 4,542 individuals were ultimately included in the study (Figure 1).

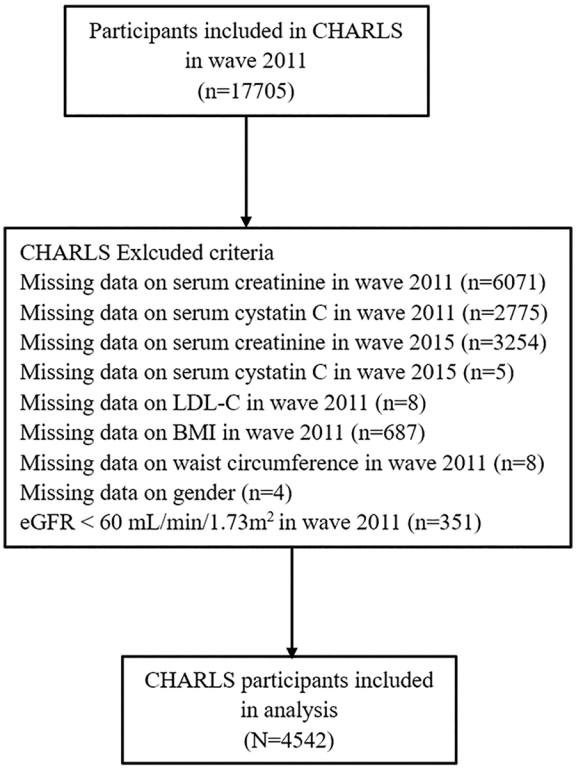

Figure 1. A detailed flow chart of participant recruitment.
LDL-C, low-density lipoprotein cholesterol; BMI, body mass index; eGFR, estimated glomerular filtration rates

2.2. Data collection and definitions

The following data was collected for this study: (1) Demographic information: age, sex, education level, and marital status; (2) Body measurements: systolic blood pressure (SBP), diastolic blood pressure (DBP), height, weight, BMI, and waist circumference; (3) Lifestyle information: smoking and drinking status; (4) Medical and medication history: including hypertension, use of antihypertensive medications, diabetes, and use of diabetes medications; (5) Laboratory tests: glycated Hemoglobin A1c (HbA1C), fasting blood glucose (FBG), TG, TC, HDL-C, LDL-C, serum creatinine (Scr), and serum cystatin C.

A BMI of ≥23 kg/m^2 was defined as overweight/obesity. Abdominal obesity was defined as a waist circumference ≥80 cm in females or ≥90 cm in males. Diabetes was defined as FBG ≥125 mg/dL, HbA1c ≥6.5%, self-reported diagnosis of diabetes, or use of insulin or oral hypoglycemic agents. Hypertension was defined as SBP ≥130 mmHg, DBP ≥80 mmHg, self-reported diagnosis of hypertension, or use of antihypertensive medications [16].

The eGFR was calculated using the creatinine-cystatin C equation developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [17]: eGFR (mL/min/1.73m^2) = $135 \times \min(Cr/\kappa, 1)^{\alpha} \times \max(Cr/\kappa, 1)^{-0.601} \times \min(Cys/0.8, 1)^{-0.375} \times \max(Cys/0.8, 1)^{-0.711} \times 0.995^{age} \times 0.969$[if female]. In this equation, Cr represents serum creatinine measured in mg/dL, and CysC represents serum cystatin C measured in mg/L. For females, κ is 0.7 and α is −0.248, while for males, κ is 0.9 and α is −0.207.

Kidney Disease Improving Global Outcomes (KDIGO) was used to categorize the phases of chronic kidney disease [16].

Non-HDL-C = TC − HDL-C; Non-HDLC/HDL-C = (TC − HDL-C)/HDL-C. RC = TC − HDL-C − LDL-C [18]. Atherogenic index of plasma (AIP) = log10[TG (mg/dL)/HDL-C(mg/dL)] [19].

2.3. Outcomes

The study's endpoints were CKD and rapid progression of renal function decline in wave 2015. CKD was defined as eGFR < 60 mL/min/1.73m^2. Rapid progression of renal function decline was defined as a mean annual decline in eGFR > 5 mL/min/1.73m [20].

2.4. Statistical analysis

The first step was to assess the normality of continuous variables. The Kolmogorov-Smirnov test (K-S test) was used to determine whether the data were normally distributed. Normally distributed data were presented as mean ± standard deviation (SD), while non-normally distributed data were presented as median with interquartile range (IQR). Categorical variables were expressed as percentages and absolute values. Differences in baseline characteristics between the CKD and non-CKD groups were evaluated using chi-square or Fisher's exact tests for categorical variables, and t-tests or Wilcoxon rank-sum tests for continuous variables.

The associations between lipid parameters and the risk of CKD, as well as rapid progression of renal function decline, were assessed using univariable and multivariable logistic regression analyses. Model 1 included only lipid parameters, while Model 2 was adjusted for biologic sex, age, education, marital status, hypertension, diabetes, BMI, smoking, and alcohol consumption. The dose-response relationships between lipid parameters and the risk of CKD were further explored using restricted cubic splines (RCS) to evaluate potential non-linear associations. Additionally, stratified analyses were performed to examine the associations between lipid parameters and rapid progression of renal function decline across different subgroups using multivariable logistic regression. These analyses were stratified by age (<65 years or ≥65 years), gender, diabetes status, hypertension status, overweight/obesity status, and abdominal obesity status.

All statistical analyses were conducted using R software (version 4.3.2) and SPSS software (version 21.0). A two-tailed P-value of less than 0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

Among the 4,542 participants in the current study, 44.91% were male, with a median age of 59 years (interquartile range [IQR]: 52–65 years). Over the four-year follow-up period, 3.02% of individuals developed CKD, and 4.67% of patients had rapid progression of renal function decline. The baseline characteristics of the participants in the CKD and non-CKD groups are presented in Table 1. Compared to those in the non-CKD group, participants in the CKD group were more likely to be older and female, less likely to consume alcohol, and had lower levels of education and marital status. They were also more likely to have hypertension, lower HDL-C and

Table 1. Baseline characteristics in CKD and non-CKD groups.

Characteristic	Total N = 4542	Non-CKD N = 4405	CKD N = 137	P-value
Age, years	59 (52, 65)	58 (52, 65)	68 (62, 74)	<0.001
Sex				0.045
Male, n(%)	2,040 (44.91)	1,990 (45.18)	50 (36.50)	
Female, n(%)	2,502 (55.09)	2,415 (54.82)	87 (63.50)	
Ever smoke, n(%)	1,707 (37.58)	1,661 (37.71)	46 (33.58)	0.371
Ever drink, n(%)	1,452 (31.97)	1,424 (32.33)	28 (20.44)	0.004
Educational level				<0.001
Below primary school, n(%)	2,209 (48.65)	2,121 (48.16)	88 (64.23)	
Primary school, n(%)	1,056 (23.25)	1,024 (23.25)	32 (23.36)	
Middle school, n(%)	874 (19.25)	859 (19.50)	15 (10.95)	
High school or above, n(%)	402 (8.85)	400 (9.08)	2 (1.46)	
Marital status				0.023
Married, n(%)	4,002 (88.11)	3,890 (88.31)	112 (81.75)	
Other, n(%)	540 (11.89)	515 (11.69)	25 (18.25)	
Hypertension, n(%)	2,544 (56.01)	2,441 (55.41)	103 (75.18)	<0.001
Diabetes, n(%)	649 (14.29)	624 (14.17)	25 (18.25)	0.214
BMI, kg/m^2	23.20 (20.95, 25.89)	23.19 (20.95, 25.84)	23.46 (20.71, 26.99)	0.287
Waist circumference, cm	84.60 (78.00, 92.00)	84.50 (78.00, 92.00)	87.40 (79.10, 97.60)	0.002
SBP, mmHg	127 (114, 142)	127 (114, 141)	137.50 (125, 153)	<0.001
FBG, mg/dl	102.42 (94.50, 112.68)	102.42 (94.50, 112.50)	101.88 (93.24, 115.56)	0.726
HBA1C,%	5.10 (4.90, 5.40)	5.10 (4.90, 5.40)	5.10 (4.90, 5.50)	0.338
TC, mg/dl	190.79 (167.01, 215.72)	190.98 (167.01, 215.34)	188.66 (164.69, 27.66)	0.940
TG, mg/dl	105.32 (74.34, 155.76)	105.32 (74.34, 154.88)	126.56 (87.61, 176.12)	0.002
HDL-C, mg/dl	49.10 (40.59, 59.92)	49.10 (40.59, 59.92)	46.00 (36.73, 58.76)	0.016
LDL-C, mg/dl	114.43 (92.78, 136.86)	114.43 (93.17, 136.86)	115.21 (91.24, 138.40)	0.879
RC, mg/dl	19.72 (11.98, 32.09)	19.72 (11.98, 31.70)	25.90 (13.53, 40.59)	0.006
Non-HDL-C, mg/dl	138.98 (115.59, 164.69)	138.79 (115.59, 164.69)	144.20 (117.53, 172.04)	0.251
TC/HDL-C	3.82 (3.09, 4.78)	3.82 (3.08, 4.77)	4.08 (3.19, 5.34)	0.028
TG/HDL-C	2.14 (1.32, 3.58)	2.12 (1.32, 3.55)	2.65 (1.46, 4.50)	0.001
Non-HDL-C/HDL-C	2.82 (2.09, 3.78)	2.82 (2.08, 3.77)	3.08 (2.19, 4.34)	0.028
LDL-C/HDL-C	2.32 (1,76, 2.98)	2.32 (1.76, 2.97)	2.37 (1.82, 3.19)	0.150
AIP	0.33 (0.12, 0.55)	0.33 (0.12, 0.55)	0.42 (0.16, 0.65)	0.001
Baseline eGFR, mL/min/1.73m^2	87.64 (77.24, 98.50)	88.15 (77.72, 98.76)	72.58 (66.15, 82.97)	<0.001

Continuous variables are presented as mean ± SD if normally distributed, and median (IQR) if not normally distributed; categorical variables are presented as the number of patients (%).

BMI, body mass index; SBP, systolic blood pressure; FBG, fasting blood glucose; HbA1C, glycosylated hemoglobin; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein cholesterol; RC, remnant cholesterol; Non-HDL-C, non-high-density lipoprotein cholesterol; AIP, atherogenic index of plasma; eGFR, estimated glomerular filtration rates.

eGFR, and higher waist circumference, SBP, TG, RC, TC/HDL-C, TG/HDL-C, and AIP ($p < 0.05$).

3.2. Association between lipid parameters with risk of CKD and rapid progression of renal function decline

Table 2 presents the results of the Logistic regression analysis between conventional and unconventional lipid parameters (continuous variables) and the risk of CKD, as well as the rapid progression of renal function decline. TC and TG were not significantly associated with CKD risk; HDL-C demonstrated a significant negative association with CKD risk only in model 1; RC, TC/HDL-C, and TG/HDL-C, and non-HDL-C/HDL-C were significantly positively associated with CKD risk only in Model 1; AIP was significantly associated with increased CKD risk in both Model 1 and Model 2. Regarding rapid progression of renal function decline, significant positive associations were observed for TG, RC, non-HDL-C, TC/HDL-C, TG/HDL-C, non-HDL-C/HDL-C, LDL-C/HDL-C, and AIP in both Model 1 and Model 2; TC was significantly associated with rapid progression of renal function decline only in Model 1. Notably, among all lipid parameters, AIP was the most strongly associated with CKD [adjusted odds ratio (OR) (95% confidence interval [CI]): 2.091 (1.199, 3.649), $p = 0.009$] and rapid progression of renal function decline [adjusted OR (95% CI): 3.996 (2.632, 6.068), $p < 0.001$]. In Model 2, each 1-unit increase in AIP was associated with a 109.1% increase in the risk of CKD and a 299.6% increase in the risk of rapid progression of renal function decline.

The RCS curves revealed the following associations: HDL-C was negatively correlated with CKD (Figure 2a); RC exhibited a non-linear, J-shaped correlation with CKD (Figure 2b); AIP was positively correlated with CKD (Figure 2c). Regarding the rapid progression of renal function decline, TG was positively correlated (Figure 2d), TC exhibited a non-linear, U-shaped correlation (Figure 2e), LDL-C was negatively correlated (Figure 2f), HDL-C was negatively correlated (Figure 2g), RC was positively correlated (Figure 2h), and AIP was positively correlated (Figure 2i).

3.3. Subgroup analyses

After adjusting for all confounders, we identified significant interactions between TG and diabetes (P for interaction = 0.008) and between TG and overweight/obesity (P for interaction = 0.036) in the risk of rapid progression of renal function decline. Similarly, significant interactions were observed between RC and diabetes (P for interaction < 0.001) and between RC and overweight/obesity (P for interaction = 0.009) in the risk of rapid progression of renal function decline (Table 3). No significant interactions were found between other lipid parameters and covariates for the risk of rapid progression of renal function decline.

4. Discussion

This study prospectively assessed the relationship between conventional and unconventional lipid parameters with the risk of future CKD and progression of renal function decline in the Chinese middle-aged and elderly population. The results demonstrated significant negative relationships between HDL-C and CKD risk; positive relationships between

Table 2. Logistic regression analysis between lipid parameters and the risk of CKD and rapid progression of renal function decline.

	CKD			
	Model 1 OR (95%CI)	P value	Model 2 OR (95%CI)	P value
TC	1.000 (0.996, 1.005)	0.911	0.997 (0.992, 1.001)	0.166
TG	1.001 (1.000, 1.003)	0.062	1.001 (1.000, 1.003)	0.152
LDL-C	0.998 (0.994, 1.003)	0.529	0.995 (0.990, 1.000)	0.048
HDL-C	0.986 (0.976, 0.998)	0.021	0.988 (0.975, 1.001)	0.067
RC	1.007 (1.002, 1.013)	0.011	1.006 (1.000, 1.012)	0.061
Non-HDL-C	1.002 (0.998, 1.007)	0.303	0.998 (0.994, 1.003)	0.473
TC/HDL-C	1.131 (1.029, 1.242)	0.011	1.076 (0.960, 1.206)	0.206
TG/HDL-C	1.029 (1.000, 1.059)	0.046	1.029 (0.995, 1.065)	0.099
Non-HDL-C/HDL-C	1.131 (1.029, 1.242)	0.011	1.076 (0.960, 1.206)	0.206
LDL-C/HDL-C	1.147 (0.971, 1.356)	0.106	1.011 (0.843, 1.214)	0.902
AIP	2.194 (1.355, 3.552)	0.001	2.091 (1.199, 3.649)	0.009
	Rapid progression of renal function decline			
	Model 1 OR (95%CI)	P value	Model 2 OR (95%CI)	P value
TC	1.004 (1.001, 1.008)	0.023	1.003 (0.999, 1.006)	0.144
TG	1.004 (1.003, 1.005)	<0.001	1.003 (1.002, 1.005)	<0.001
LDL-C	0.995 (0.991, 0.999)	0.011	0.994 (0.990, 0.998)	0.004
HDL-C	0.973 (0.962, 0.983)	<0.001	0.976 (0.965, 0.987)	<0.001
RC	1.017 (1.014, 1.021)	<0.001	1.016 (1.012, 1.020)	<0.001
Non-HDL-C	1.007 (1.004, 1.011)	<0.001	1.005 (1.002, 1.009)	0.002
TC/HDL-C	1.295 (1.207, 1.389)	<0.001	1.254 (1.162, 1.353)	<0.001
TG/HDL-C	1.072 (1.051, 1.094)	<0.001	1.062 (1.040, 1.085)	<0.001
Non-HDL-C/HDL-C	1.295 (1.207, 1.389)	<0.001	1.254 (1.162, 1.353)	<0.001
LDL-C/HDL-C	1.161 (1.014, 1.329)	0.031	1.079 (0.934, 1.247)	0.299
AIP	4.534 (3.106, 6.619)	<0.001	3.996 (2.632, 6.068)	<0.001

Model 1 unadjusted; Model 2 adjusted for sex, age, education, marital, hypertension, diabetes, BMI, smoking, and drinking.
TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein cholesterol; RC, remnant cholesterol; Non-HDL-C, non-high-density lipoprotein cholesterol; AIP, atherogenic index of plasma; OR, odds ratio; CI, confidence interval.

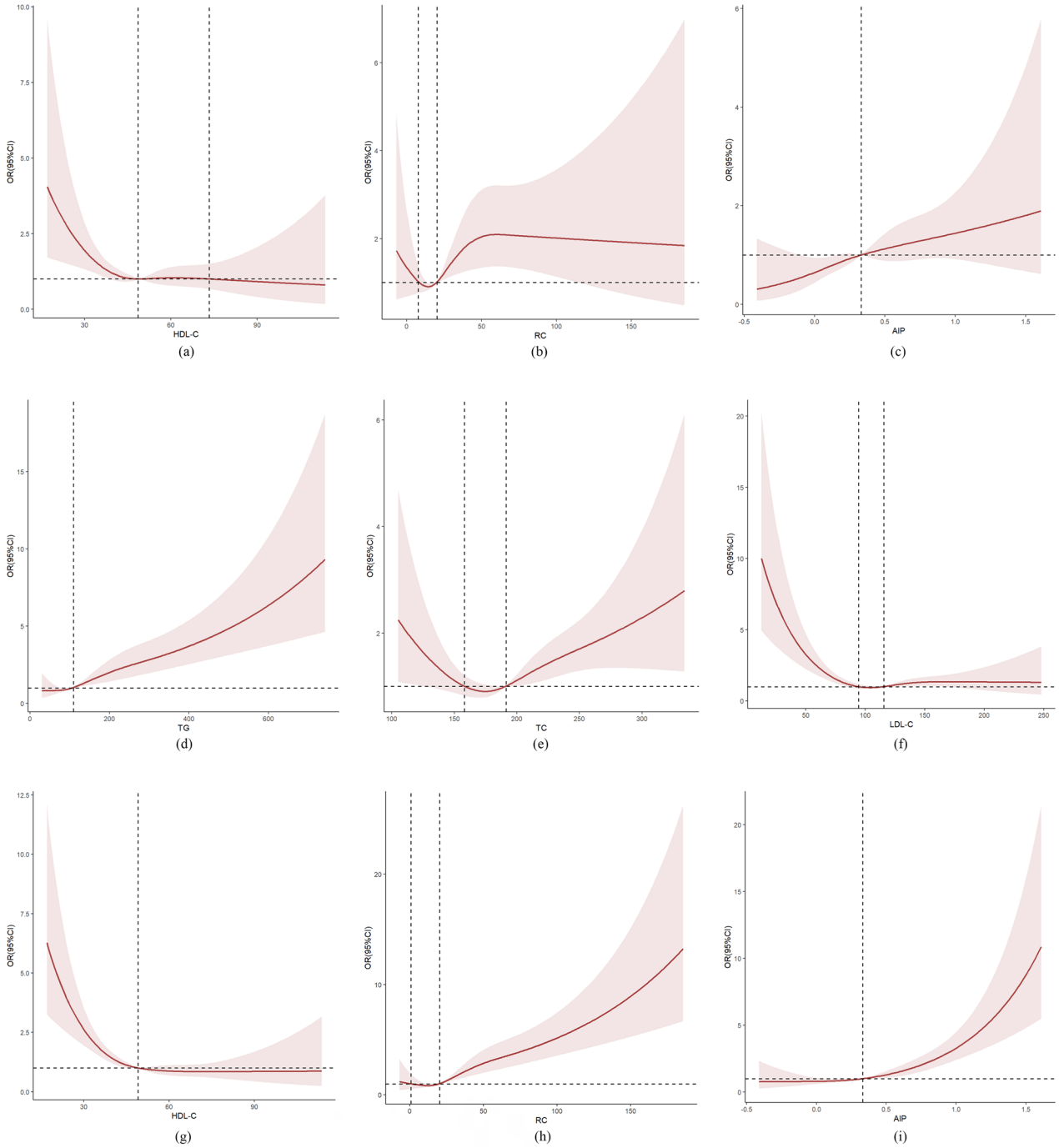

Figure 2. The RCS analysis between lipid parameters and CKD and rapid progression of renal function decline.
TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein cholesterol; RC, remnant cholesterol; AIP, atherogenic index of plasma; OR, odds ratio; CI, confidence interval
(a) The nonlinear association between HDL-C and CKD, P for overall = 0.0055, P for nonlinear = 0.0652, values of 48.579 and 73.350 were set as references (vertical dashed line); (b) The nonlinear association between RC and CKD, P for overall = 0.0068, P for nonlinear = 0.0414, values of 7.550 and 20.128 were set as references (vertical dashed lines); (c) The nonlinear association between AIP and CKD, P for overall = 0.0182, P for nonlinear = 0.5837, value of 0.331 was set as reference (vertical dashed line); (d) The nonlinear association between TG and rapid progression of renal function decline, P for overall < 0.0001, P for nonlinear = 0.0806, value of 108.857 was set as reference (vertical dashed line); (e) The nonlinear association between TC and rapid progression of renal function decline, P for overall = 0.0018, P for nonlinear = 0.0058, values of 158.053 and 191.407 were set as references (vertical dashed lines); (f) The nonlinear association between LDL-C and rapid progression of renal function decline, P for overall <0.0001, P for nonlinear < 0.0001, values of 94.261 and 115.522 were set as references (vertical dashed line); (g) The nonlinear association between HDL-C and rapid progression of renal function decline, P for overall < 0.0001, P for nonlinear = 0.0011, value of 49.065 was set as reference (vertical dashed line); (h) The nonlinear association between RC and rapid progression of renal function decline, P for overall < 0.0001, P for nonlinear = 0.0057, values of 0.778 and 20.128 were set as references (vertical dashed lines); (i) The nonlinear association between AIP and rapid progression of renal function decline, P for overall < 0.0001, P for nonlinear = 0.1124, value of 0.331 was set as reference (vertical dashed line)

Table 3. Subgroup analysis of the association between lipid parameters and the risk of rapid progression of renal function decline.

	TG		TC		LDL-C		HDL-C		RC		AIP	
Subgroup	OR (95%CI)	P for interaction	OR (95%CI)	P for interaction	OR (95%CI)	P for interaction	OR (95%CI)	P for interaction	OR (95%CI)	P for interaction	OR (95%CI)	P for interaction
Age(year)		0.906		0.676		0.395		0.882		0.635		0.598
<65	1.003 (1.002, 1.004)***		1.005 (1.001, 1.009)*		0.997 (0.993, 1.002)		0.980 (0.966, 0.993)**		1.015 (1.010, 1.019)***		3.408 (2.046, 5.676)***	
≥65	1.004 (1.002, 1.006)***		0.998 (0.991, 1.005)		0.988 (0.981, 0.995)**		0.970 (0.951, 0.989)**		1.019 (1.012, 1.027)***		5.842 (2.760, 12.367)***	
Gender		0.935		0.520		0.969		0.201		0.963		0.570
Male	1.004 (1.002, 1.005)***		1.005 (0.999, 1.010)		0.994 (0.988, 1.001)		0.982 (0.966, 0.998)*		1.018 (1.011, 1.024)***		4.092 (2.167, 7.727)***	
Female	1.003 (1.002, 1.005)***		1.001 (0.996, 1.006)		0.994 (0.989, 0.999)*		0.972 (0.957, 0.987)***		1.015 (1.009, 1.020)***		3.830 (2.169, 6.765)***	
Diabetes		0.008		0.782		0.617		0.998		< 0.001		0.376
No	1.005 (1.004, 1.007)***		1.003 (0.999, 1.007)		0.995 (0.990, 1.000)*		0.977 (0.965, 0.990)***		1.024 (1.018, 1.029)***		4.530 (2.712, 7.568)***	
Yes	1.003 (1.001, 1.004)***		1.001 (0.993, 1.008)		0.991 (0.984, 0.999)*		0.975 (0.953, 0.997)*		1.010 (1.004, 1.016)**		3.289 (1.582, 6.840)**	
Hypertension		0.505		0.719		0.273		0.251		0.187		0.878
No	1.004 (1.002, 1.006)***		1.003 (0.996, 1.009)		0.992 (0.984, 0.999)*		0.987 (0.970, 1.005)		1.020 (1.012, 1.028)***		3.517 (1.729, 7.151)**	
Yes	1.003 (1.002, 1.005)***		1.003 (0.999, 1.007)		0.995 (0.991, 1.000)		0.971 (0.957, 0.985)***		1.015 (1.010, 1.019)***		4.275 (2.538, 7.202)***	
Overweight/ obesity		0.036		0.304		0.640		0.120		0.009		0.136
No	1.005 (1.003, 1.006)***		1.004 (0.999, 1.010)		0.994 (0.987, 1.000)		0.984 (0.969, 0.998)*		1.022 (1.015, 1.028)***		4.396 (2.338, 8.266)***	
Yes	1.003 (1.002, 1.004)***		1.002 (0.997, 1.006)		0.994 (0.989, 1.000)*		0.967 (0.951, 0.983)***		1.014 (1.009, 1.019)***		3.839 (2.193, 6.721)***	
Abdominal obesity		0.966		0.155		0.163		0.647		0.903		0.728
No	1.004 (1.002, 1.005)***		1.003 (0.997, 1.009)		0.996 (0.989, 1.003)		0.988 (0.972, 1.003)		1.016 (1.009, 1.024)***		3.252 (1.653, 6.398)**	
Yes	1.003 (1.002, 1.005)***		1.002 (0.997, 1.006)		0.993 (0.988, 0.998)**		0.967 (0.952, 0.983)***		1.016 (1.011, 1.021)***		4.458 (2.591, 7.671)***	

Adjusted for sex, age, education, marital, hypertension, diabetes, BMI, smoking, and drinking.
'***': $p < 0.001$; '**': $p < 0.01$; '*': $p < 0.05$.
TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein cholesterol; RC, remnant cholesterol; AIP, atherogenic index of plasma; OR, odds ratio; CI, confidence interval.

RC and AIP and CKD risk; significant positive correlations between TG, RC, non-HDL-C, TC/HDL-C, TG/HDL-C, non-HDL-C/HDL-C, LDL-C/HDL-C, and AIP and rapid progression of renal function decline; significant negative correlations between LDL-C and HDL-C and rapid progression of renal function decline. Among all lipid parameters, AIP was the most strongly associated with CKD and rapid progression of renal function decline. Each 1-unit increase in AIP was associated with a 109.1% increase in CKD risk and a 299.6% increase in the risk of rapid progression of renal function decline. The RCS curve revealed the following associations: HDL-C was negatively correlated with CKD; RC exhibited a non-linear, J-shaped correlation with CKD; AIP was positively correlated with CKD. Regarding rapid progression of renal function decline, TG was positively correlated, TC exhibited a non-linear, U-shaped correlation, LDL-C was negatively correlated, HDL-C was negatively correlated, RC was positively correlated, and AIP was positively correlated. Subgroup analyses suggested significant interactions between TG and diabetes, TG and overweight/obesity, RC and diabetes, and RC and overweight/obesity in the risk of rapid progression of renal function decline.

Lipids play a complex role in the etiology and development of CKD, with renal damage and dysfunction potentially exacerbated by dysregulated lipid metabolism. Lipid accumulation can trigger inflammation, the production of reactive oxygen species (ROS), and the generation of endogenous electrical stress within renal cells, leading to glomerular and tubulointerstitial damage [21]. Key cellular constituents of the glomerulus, including podocytes, endothelial cells, and mesangial cells, are highly susceptible to lipotoxic injury, which may result in structural changes, functional impairment, and ultimately glomerular dysfunction [22]. The glomerular endothelium is a crucial component of the glomerular filtration barrier. Studies have shown that lipotoxicity can induce mitochondrial dysfunction in renal cells, including glomerular endothelial cells in mice fed a high-fat diet [23]. Podocytes, which are terminally differentiated cells and an essential part of the glomerular filtration barrier, are also vulnerable to dysfunction from excessive lipid intake. Individuals with CKD and underlying obesity exhibit reduced podocyte mass and abnormalities in podocyte foot processes [24]. Mesangial cells, which provide structural support and produce extracellular matrix to regulate the glomerular filtration rate, are similarly affected by lipid exposure, contributing to their malfunction in CKD [22]. The renal tubules are essential for processing glomerular filtrate. Evidence suggests that dysregulated lipid metabolism and subsequent lipid accumulation within renal tubular cells contribute to tubular injury, inflammation, and fibrosis [25].

Mendelian randomization analysis indicated that a 1 mmol/L increase in the genetically predicted blood TG level was associated with a 5% higher risk of CKD [26]. In a study of 283 individuals with new-onset type 2 diabetes mellitus, controlling TG levels was found to delay renal function decline in the early stages of diabetic kidney disease, and reversing hypertriglyceridemia may mitigate prior risks [27]. A retrospective analysis of young to middle-aged working males without diabetes or hypertension revealed that elevated LDL-C levels are associated with incident CKD and eGFR decline [10]. Low HDL-C levels have been linked to a significantly higher risk of microalbuminuria and macroalbuminuria in a study of 11,140 individuals with type 2 diabetes [28]. Another study of patients with type 2 diabetes-related CKD indicated that low HDL-C levels are associated with rapid progression of renal function decline [20]. However, in a large cohort of patients with CKD, TC, TG, VLDL-C, LDL-C, and HDL-C were not independently associated with CKD progression [12]. In contrast, our study found that LDL-C and HDL-C were negatively correlated with rapid progression of renal function decline, while TG were positively correlated with rapid progression of renal function decline in the Chinese middle-aged and elderly population. These discrepancies across studies may be attributed to differences in sample size, measurement methods, population characteristics, and the presence of confounding variables in the analyses.

Our study demonstrated significant negative correlations between LDL-C and rapid progression of renal function decline. Compared to those in the non-CKD group, participants in the CKD group generally exhibited more severe pre-existing health conditions. They were more likely to be older and female, and had lower levels of education and marital status. They were also more likely to have hypertension, lower HDL-C and eGFR, and higher waist circumference, SBP, TG, and RC. In CKD, TC and LDL-C, are usually within their normal ranges or even low [3]. This pattern may be driven by the effects of inflammation and/or malnutrition on cholesterol homeostasis, which could explain the inverse association between LDL-C and CKD [6]. Mouse studies have indicated that inflammation can alter cholesterol production, uptake, and redistribution in circulation and tissues [29]. This phenomenon may also be associated with statin use. Patients with CKD have a higher propensity for statin use. Some studies based on larger populations or longer follow-up periods suggest that statin use may have potential effects on kidney function. For example, a meta-analysis of 2,067,639 patients aged 40 years or older who were newly treated with statins found that current users of high-potency statins were 34% more likely to be hospitalized with acute kidney injury (AKI) within 120 days of starting treatment [30]. Similarly, in a study of 128,140 elderly new statin users, there was a graded, independent association between statin intensity and the risk of hospitalization for AKI over a median follow-up period of 4.6 years [31].

RC is the cholesterol contained in triglyceride-rich lipoproteins (TGRL), which include very-low-density lipoproteins (VLDL) and intermediate-density lipoproteins during the fasting state, as well as chylomicron remnants during the non-fasting state [32]. A cross-sectional study showed that RC is an independent risk factor for comorbid CKD in patients with prediabetes and type 2 diabetes [33]. Another cross-sectional study from China demonstrated that RC levels were associated with CKD severity, even when traditional

lipid profiles were within target ranges in patients with type 2 diabetes [34]. In the general population, a higher RC was substantially associated with a lower eGFR [11]. Furthermore, a cross-sectional study found that RC was significantly associated with CKD, and a pre-inflammatory state, characterized by increased high-sensitivity C-reactive protein (hs-CRP) or white blood cells, partially mediated the association between RC and CKD [2]. Our study demonstrated significant positive relationships between RC and future CKD risk and rapid progression of renal function decline in the Chinese middle-aged and elderly population.

AIP is a novel biomarker that reflects the balance of pro-atherogenic and anti-atherogenic lipoproteins in the blood [35]. Compared to traditional lipid markers, AIP more accurately reflects atherogenic dyslipidemia by accounting for the interactions among various lipid components that contribute to atherosclerosis, according to several epidemiological studies [36,37]. AIP has been reported as a crucial predictor of cardiovascular disease risk and clinical outcomes [38–41]. However, studies examining the association between AIP and CKD are limited.

Subgroup analysis in this study suggested significant interactions between TG and diabetes, TG and overweight/obesity, RC and diabetes, and RC and overweight/obesity in the risk of rapid progression of renal function decline. Obesity is a significant and growing risk factor for CKD, and lipid metabolism is one of the mechanisms through which obesity promotes renal dysfunction [21]. Excess weight significantly affects kidney function through various mechanisms, including glomerular hyperfiltration, activation of the renin-angiotensin-aldosterone system (RAAS), insulin resistance, endothelial dysfunction, and lipotoxicity, also compromising kidney health through concurrent dyslipidemia [42]. A cross-sectional study involving a total of 41,085 participants with central and peripheral obesity, who were not diagnosed with CKD, had a higher risk of elevated urine albumin-to-creatinine ratio (UACR), even after adjusting for multiple factors (OR: 1.14, 95% CI: 1.07 to 1.12, $p < 0.001$) [43]. Type 2 diabetes mellitus also contributes to kidney damage through multiple pathways. Hyperglycemia induces glomerular hyperfiltration by increasing glucagon levels and promotes efferent arteriole vasoconstriction through RAAS activation, further compromising renal function [44,45]. Diabetes is associated with changes in serum lipid levels and metabolism. Diabetic dyslipidemia is the term used to describe the plasma lipoprotein profile of patients with type 2 diabetes, which consists of tiny, dense LDL particles, elevated TG, and low HDL-C [46]. Dyslipidemia may influence the onset and course of diabetic CKD [33]. Several studies of patients with type 2 diabetes showed that high TG, low HDL-C, and high RC are associated with incident CKD and eGFR decline [27,28,34].

Several limitations to this study should be acknowledged. First, because the study was observational, we could not establish a causal association between lipid parameters and the risk of future CKD or the progression of renal function decline. Second, despite our efforts to control for potential confounding variables, we could not completely rule out the influence of other unmeasured confounders. Third, given that our study focused on a Chinese population, the findings may not be generalizable to other ethnic or demographic groups. Further research is needed to validate these results in diverse populations. Fourth, the exclusion of a large number of participants due to missing primary data may have introduced selection bias, potentially affecting the representativeness of our sample.

5. Conclusion

In this study, we revealed the significant negative correlations between LDL-C and HDL-C and rapid progression of renal function decline; and significant positive correlations between TG, RC, and AIP and rapid progression of renal function decline. Among the lipid parameters, AIP is the largest risk for CKD and rapid progression of renal function decline.

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Authors' contributions

Yijing Xin: designed the study, performed the statistical analysis, and drafted and wrote the manuscript. Yanmin Yang: reviewed and revised the manuscript. Yimeng Wang, Yuyuan Shu, and Hanyang Liang performed the statistical analysis and revised the manuscript.

Declarations

Ethics approval and consent to participate

Peking University has obtained ethical approval for CHARLS (IRB00001052–11015).

Disclosure statement

No potential conflict of interest was reported by the author(s).

Availability of data and materials

The data from the China Health and Retirement Longitudinal Study is openly available at https://charls.pku.edu.cn/en/index.htm.

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