Association of Lipid Accumulation Product With Chronic Kidney Disease in Chinese Community Adults: A Report From the REACTION Study

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Abstract

Background: Limited studies regarding the relationship between lipid accumulation product (LAP), a novel surrogate marker of visceral adiposity, and declined estimated glomerular filtration rate (eGFR) have yielded conflicting findings, and no report has demonstrated the relationship of LAP with chronic kidney disease (CKD), defined by lower eGFR and/or the presence of albuminuria. This study aimed to estimate the possible association between LAP and CKD in Chinese community adults.

Method: This cross-sectional study, drawn from the REACTION study, included 7072 participants aged ≥40 years in Luzhou city, Sichuan Province. LAP was determined based on a combination of waist circumference (WC) and fasting triglycerides (TG). CKD was defined as eGFR <60mL/min/1.73m² and/or presence of albuminuria [urinary albumin-creatinine ratio (ACR) ≥30mg/g]. A multiple logistic regression model was performed to evaluate the possible association between LAP and CKD in Chinese community adults.

Results: Participants with CKD had significantly higher LAP, age, WC, weight, body mass index, systolic blood pressure, diastolic blood pressure, pulse pressure (PP), TG, total cholesterol (TC), fasting blood glucose, 2 h postload blood glucose, glycated hemoglobin A1C, serum creatinine, urinary ACR, prevalence of obesity, type 2 diabetes mellitus, hypertension, myocardial infarction, coronary heart disease, peripheral arterial disease, cardiovascular disease (CVD), users of hypoglycemic drugs, and lower high density lipoprotein cholesterol, eGFR, and users of drinking (P<0.01 or P<0.05). Multiple logistic regression analysis demonstrated that LAP quartiles were positively associated with an increased risk of prevalent CKD (Q2: odds rate [OR]: 1.083, 95% confidence intervals [CI] 0.850-1.381; Q3: OR: 0.961, 95% CI 0.741-1.247; Q4: OR: 1.497, 95% CI 1.139-1.966, P for trend = 0.004) even after adjustment for potential confounding factors. Stratified analysis revealed that the associations of LAP quartiles with increased risk of prevalent CKD also occurred in people who were older, women, overweight, with hypertension, normal glucose tolerance, normal PP, low-density lipoprotein cholesterol < 3.4 mmol/L, without CVD events, no smoking and drinking. Conclusions: These findings suggest that LAP is significantly associated with increased risk of prevalent CKD in Chinese community adults, and may inform both public health recommendations and clinical practice.

Background

Chronic kidney disease (CKD), a chronic condition characterized by abnormalities of kidney structural or functional loss caused by multiple factors, including genetic alterations, infection, obesity, dyslipidaemia, diabetes, and hypertension, is a leading public health problem with an increasing incidence worldwide at an annual rate of 8%, consuming up to 2% of the global health expenditure [1]. The incidence and prevalence of CKD vary within countries by ethnicity and social determinants of health.
It is estimated that CKD affects ~ 10% of the global population [2, 3], and the prevalence of CKD in 2012 was 10.8% in China with a large population [3]. CKD has been reported to be associated with increased risk of unfavourable health outcomes, such as infection, anemia, bone disease, cognitive impairment,

cancer, end-stage renal disease, atherosclerotic cardiovascular disease (CVD) event, poor health-related quality of life, hospitalization, and even cardiovascular and all-cause mortality [2, 3, 4]. However, kidney biopsy used to show definitive evidence of CKD is invasive and costly, and the current therapeutic options of CKD are very limited. Therefore, it would be of great importance if a simple, noninvasive, inexpensive, and reliable index is available for the early identification and management of individuals at high risk for CKD in clinical settings, and further effective strategies are formulated to prevent its development and progression.

Compelling data indicate that obesity plays an important role in the onset and development of CKD [3, 5, 6, 7], but the underlying mechanisms by which obesity, especially visceral obesity, affects CKD are multifactorial and are not fully understood. It has been well established that adiposity is an important risk factor for renal function decline and albuminuria [6]. Compared with subcutaneous adipose tissue, visceral adipose tissue is more strongly associated with cardiometabolic risks [5]. Visceral adipose tissue secretes several proinfammatory cytokines such as C-reactive protein (CRP), interleukine-6 (IL-6), and distinct atherogenic lipoprotein profiles, contributes to the change in adipocytokines such as adiponectin, leptin, resistin, and omentin-1, which lead to subclinical inflammation, oxidative stress, insulin resistance (IR), and endothelial dysfunction, and subsequently, induces kidney structure and function changes such as glomerular sclerosis and increased albuminuria, and ultimately result in renal dysfunction [5, 7, 8, 9]. Body mass index (BMI) is the most frequently used index in the assessment of adiposity in clinical practice, but lacks discriminatory power between lean vs. adipose tissue, or between subcutaneous and visceral fat, and also lacks the ability to track over time changes in the lipid compartment [10]. Waist circumference (WC), a practical athropometric parameter to identify central obesity, is also unable to distinguish between visceral adipose tissue and subcutaneous adipose tissue [5, 7]. In recent years, lipid accumulation product (LAP), a novel surrogate marker of visceral adiposity and an alternative continuous index of central lipid accumulation proposed by Kahn in 2005, is based on a combination of WC and fasting triglyceride (TG) levels, and reflects the anatomic and physiologic changes associated with obesity among adults [9, 10]. Given the close associations between visceral adiposity and CKD, it is plausible that the LAP might be significantly associated with CKD. However, limited studies regarding the relationship between LAP and declined estimated glomerular filtration rate (eGFR) in targeted specific populations have yielded conflicting findings [9, 11, 12, 13], and no report has demonstrated the relationship of LAP with CKD, defined by declined eGFR and/or the presence of albuminuria [urinary albumin to creatinine ratio (ACR) ≥30mg/g] [3]. It is well known that elevated urinary ACR is not only a symbol for impaired function of kidney but has also been shown to be associated with deleterious metabolic and cardiovascular consequences.

Thus, this cross-sectional study is based on a large sample of the general population in China (REACTION Study) and is aimed to explore the relationship between LAP and CKD in Chinese community adults.

Methods

Study population

Details of the REACTION Study design and characteristics of the study participants have been previously described elsewhere [14, 15, 16]. In brief, the REACTION Study, consisted of 193,846 participants aged ≥40 years were recruited, between 2011 and 2012 from 16 provinces, autonomous regions, or municipalities of mainland China, was led by Rui-Jin Hospital affiliated to Shanghai Jiao-Tong University School of Medicine to evaluate the association of T2DM and prediabetes with the risk of cancer in the Chinese population. This cross-sectional study, drawn from the REACTION study, only used baseline investigation data from Luzhou, Sichuan Province. A total of 10150 participants aged ≥40 years were recruited initially from May 2011 to December 2011. Participants with type 1 diabetes mellitus, liver disease, cancer, acute inflammatory or infection disease, those using lipid-lowering drugs, ACEI/ARB drugs, anti-inflammatory and anti-infective drugs, and systemic glucocorticoids, and those with incomplete demographic or clinical characteristic data were excluded. Finally, 7202 eligible participants were included in the final analysis.

The present study was conducted according to the guidelines laid out in the Declaration of Helsinki, and all procedures involving human participants were approved by the Research Ethics Committees of the Rui-Jin Hospital affiliated to the Jiao-Tong University School of Medicine, and also by the Affiliated Hospital of Southwest Medical University. All participants provided informed written consent to participate.

Data collection and measurements

Data collection was performed in local community clinics by trained study personnel according to a standard protocol at baseline. Trained study personnel used a standard questionnaire and face-to-face interviews to obtain data on participants' demographic information (age and sex), lifestyle behaviors (smoking status and alcohol intake), family and personal medical history, and medication use. Smoking statuses were classified as never, former and current smokers according to cigarette smoking habits [16]. The type and frequency of alcohol consumptions were recorded, and alcohol intake statuses were also never, former and current drinkers [15, 16]. WC, body weight and height were measured with the subject wearing light clothes without shoes, and then BMI was calculated (kg/m^2) [14, 15]. The LAP index was calculated as [WC (cm) − 65] × [triglyceride concentration (mmol/L)] for men, and [WC (cm) − 58] × [triglyceride concentration (mmol/L)] for women [9, 10]. All participants were divided into quartiles based on the LAP index: Q1, LAP < 16.20; Q2, 16.20 ≤ LAP < 28.88 ng/ml; Q3, 28.88 ≤ LAP ≤ 50.16; Q4, LAP > 50.16. Blood pressure was measured three times at 5-min intervals when participants were in a seated position for at least 5 min at rest, and the average of the three readings was calculated and used for the final analysis. Pulse pressure (PP) was calculated as systolic blood pressure (SBP)-diastolic blood pressure (DBP).

A blood draw was obtained in all individuals in the morning after an overnight fasting for at least 10 h. All participants underwent a 75-g oral glucose tolerance test (OGTT), and blood samples were collected at 0

and 2 h by the same well-trained nurses. Blood samples were centrifuged at 3500 rpm for 10 min at 4 °C and filled into 1mL aliquots and stored at -80°C until analyzed. Fasting blood glucose (FBG), 2 h postload blood glucose (PBG), glycated hemoglobin A1C (HbA1c), lipid profiles, including total cholesterol (TC), TG, high density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and creatinine (Cr) were measured according to relevant protocols and guidelines at a certified central laboratory located at the Affiliated Hospital of Southwest Medical University, which is accredited in accordance with ISO 15189.

The first morning urine specimens were collected for urinalysis. Urinary albumin concentration and creatinine were determined by chemiluminescence immunoassay, and then urinary albumin-to-creatinine ratio (ACR; mg/g creatinine) was calculated. Renal function expressed as the eGFR was calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations modified by a Japanese coefficient [2, 9].

Definition of variables

Obesity was defined as BMI ≥28 kg/m^2, and overweight was defined as 24 kg/m^2 ≤BMI <28 kg/m^2 [17]. Declined renal function was defined as eGFR <60mL/min/1.73m². CKD was defined as eGFR <60mL/min/1.73m² and/or presence of albuminuria (ACR ≥30mg/g) [3]. Participants were divided into appropriate (LDL-C< 3.4 mmol/L), borderline high (3.4mmol/L≤LDL-C< 4.1 mmol/L), and high (LDL-C≥ 4.1 mmol/L) groups based on the 2016 Chinese guideline for the management of dyslipidemia in adults [18]. According to the criteria in previously published articles [14, 15], type 2 diabetes mellitus (T2DM), prediabetes, and normal glucose tolerance (NGT) were diagnosed. Hypertension was defined as SBP ≥140 mmHg, DBP ≥ 90 mmHg, or self- reported previous diagnosis of hypertension by clinicians and taking antihypertensive drugs [9]. A brachial PP ≥63 mmHg was considered abnormal (high pulse pressure) [19, 20]. CVD events included myocardial infarction (MI), coronary heart disease (CHD), stroke, and peripheral arterial disease (PAD), and the detailed definitions have been described in previously published articles [14, 15, 18, 21].

Statistical analysis

Statistical analysis was performed with the Statistical Package for Social Sciences version 20.0 (SPSS, Chicago, IL). First, Kolmogorov-Smirnov test for normality and Levene's homogeneity of variance test was conducted. Continuous variables with a non-normal distribution are presented as median (25th percentile−75th percentile), and those with a normal distribution are expressed as the mean ±standard deviation (SD). Categorical variables are presented as numbers (percentages).

Two-group comparisons were performed with χ^2 test for categorical variables or Student's t test for normally distributed continuous variables or Mann−Whitney U test for nonparametric distributed continuous variables. The univariate logistic regression analyses were performed to determine the association of LAP and other variables with the risk of prevalent CKD in all study subjects. Then, logistic regression analysis with unadjusted and multivariate-adjusted models was performed to determine the

association between LAP quartiles and the risk of prevalent CKD. Model 1 was unadjusted. Model 2 was adjusted for age and gender. Model 3 was additionally adjusted for BMI based on Model 2. Model 4 was further adjusted for smoking, drinking and CVD events based on Model 3. Model 5 was additionally adjusted for SBP, DBP, PP, LDL-C, prevalence of T2DM, and hypoglycemic drugs based on Model 4. Odds ratios (OR) and corresponding 95% confidence intervals (CI) were calculated. Stratified analyses were conducted by the different level of gender (women and men), age (<60 and ≥60 years), BMI (normal weight, overweight, and obesity), glucose metabolism state (NGT, prediabetes, and T2DM), blood pressure (normal blood pressure and hypertension), PP (normal PP and abnormal PP), LDL-C (LDL-C< 3.4 mmol/L, 3.4≤ LDL-C <4.1 mmol/L, and LDL-C ≥ 4.1 mmol/L), prevalence of CVD events (No and Yes), current smoking status (No and Yes), and current drinking status (No and Yes). Subjects were stratified into subgroups to separately explore the relevant underlying factors which might affect the relationship between the LAP index and CKD. Meanwhile, potential interactions of the LAP index and strata variables were assessed in the logistical regression analysis after adjustment for age, sex, BMI, smoking, drinking, prevalence of T2DM and CVD events, SBP, DBP, PP, LDL-C, and hypoglycemic drugs.

All P-value are two-tailed, and values of less than 0.05 were considered to indicate statistical significance.

Results

Demographic and clinical characteristics of the study population The basic characteristics of the study population are summarized in Table 1. There were no significant differences in gender distribution, LDL-C, users of smokers, prevalence of overweight, prediabetes, and stroke between non-CKD and CKD groups (all P>0.05). Participants with CKD had significantly higher LAP, age, WC, weight, BMI, SBP, DBP, PP, TG, TG, FBG, PBG, HbA1c, serum Cr, urinary ACR, prevalence of obesity, T2DM, hypertension, MI, CHD, PAD, CVD events, users of hypoglycemic drugs, and lower HDL-C, eGFR, and users of drinking (P<0.01 or P<0.05; Table 1 and Figure 1). In addition, participants with eGFR <60 mL/min/1.73m² and albuminuria had significantly higher LAP compared to those with eGFR ≥60 mL/min/1.73m² and non-albuminuria, respectively (all P<0.01, Fig.1)

Table 1 Clinical and biochemical characteristics of studied population.

	Total (n=7202)	non-CKD (n=6267)	CKD (n=935)	P
Male/Female	2313/4889	2011/4265	302/633	0.898
Age (years)	58.00 (51.00−65.00)	58.00 (50.00−64.00)	62.00 (54.00−70.00)	0.000
WC (cm)	82.50 (76.00−89.00)	82.00 (76.00−89.00)	84.00 (78.00−90.30)	0.000
LAP	28.88 (16.20−50.16)	28.16 (15.81−48.36)	35.55 (19.22−63.00)	0.000
Height (cm)	156.50 (152.00−162.20)	156.80 (152.00−162.40)	156.00 (152.00−162.00)	0.057
Weight (kg)	58.10 (52.10−65.00)	58.00 (52.00−65.00)	59.00 (53.00−66.00)	0.035
BMI (kg/m^2)	23.71 (21.56−25.97)	23.63 (21.50−25.90)	24.15 (21.88−26.38)	0.000
SBP (mmHg)	122.00 (109.67−137.33)	121.33 (109.00−135.67)	130.33 (115.33−146.67)	0.000
DBP (mmHg)	75.33 (69.00−82.67)	75.00 (68.67−82.00)	77.00 (70.00−86.00)	0.000
PP (mmHg)	46.00 (38.00−57.00)	45.00 (37.00−55.00)	51.00 (40.00−64.00)	0.000
TC(mmol/L)	4.74±1.12	4.72±1.11	4.83±1.18	0.008
TG (mmol/L)	1.30 (0.92−1.91)	1.28 (0.91−1.88)	1.47 (1.03−2.14)	0.000
HDL-C (mmol/L)	1.27 (1.05−1.50)	1.27 (1.05−1.50)	1.23 (1.03−1.46)	0.002
LDL-C (mmol/L)	2.62 (2.08−3.20)	2.62 (2.07−3.09)	2.66 (2.12−3.28)	0.093
FBG (mmol/L)	5.44 (5.10−6.01)	5.42 (5.09−5.96)	5.57 (5.19−6.41)	0.000
PBG (mmol/L)	7.74 (6.33−10.32)	7.64 (6.28−10.09)	8.64 (6.88−12.17)	0.000
HbA1c (%)	5.90 (5.60−6.30)	5.90 (5.60−6.30)	6.00 (5.70−6.60)	0.000
Cr (µmol/L)	63.20 (56.70−71.33)	62.80 (56.60−70.30)	68.10 (58.40−88.80)	0.000
eGFR (mL/min/1.73 m^2)	96.46 (87.47−103.76)	96.95 (88.94−104.12)	89.99 (62.34−100.52)	0.000
Urinary ACR (mg/g)	7.74 (4.80−15.02)	6.95 (4.54−11.50)	42.05 (31.71−60.56)	0.000
Smoking habits, %		0.525		

No	6201 (86.10%)	5391 (86.02%)	810 (86.63%)	
Occasional	188 (2.61%)	155 (2.47%)	33 (3.53%)	
Regular	813 (11.29%)	721 (11.50%)	92 (9.84%)	
Drinking, %				0.020
No	5251 (72.91%)	4539 (72.43%)	712 (76.15%)	
Occasional	1442 (20.02%)	1279 (20.41%)	163 (17.43%)	
Regular	509 (7.07%)	449 (7.16%)	60 (6.42%)	
Overweight (%)	2541 (35.28%)	2190 (34.94%)	351 (37.54%)	0.121
Obesity (%)	804 (11.16%)	671 (10.71%)	133 (14.22%)	0.001
Prediabetes (%)	2010 (27.71%)	1744 (27.83%)	266 (28.45%)	0.693
T2DM (%)	1714 (23.80 %)	1391 (22.20%)	323 (34.55%)	0.000
Users of hypoglycemic drugs (%)	624 (8.66 %)	494 (7.88%)	130 (13.90%)	0.000
Hypertension (%)	2322 (32.24%)	1843 (29.41%)	479 (51.23%)	0.000
MI (%)	29 (0.40%)	21 (0.34%)	8 (0.86%)	0.019
CHD (%)	232 (3.22%)	175 (2.79%)	57 (6.10%)	0.000
Stroke (%)	38 (0.53%)	31 (0.49%)	7 (0.75%)	0.317
PAD (%)	8 (0.11 %)	3 (0.05%)	5 (0.53%)	0.000
CVD (%)	288 (4.00%)	217 (3.46%)	71 (7.59%)	0.000

Data are mean±SD. SD, standard deviation; WC, waist circumference; LAP, lipid accumulation product; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose; PBG, 2 h postload blood glucose; HbA1c, glycated hemoglobin A1c; Cr, creatinine; eGFR, estimated glomerular filtration rate; ACR, albumin-to-creatinine ratio; T2DM, type 2 diabetes mellitus; MI, myocardial infarction; CHD, coronary heart disease; PAD, peripheral arterial disease; CVD, cardiovascular disease.

Univariate analysis of variables contributing to CKD in the study population.

Univariate analysis revealed that age, BMI, WC, LAP, SBP, DBP, PP, TG, TG, serum Cr, urinary ACR, prevalence of T2DM and CVD events, and users of hypoglycemic drugs positively correlated with the prevalence of CKD, while drinking, eGFR and HDL-C were negatively correlated with the prevalence of CKD ($P<0.01$ or $P<0.05$; Table 2).

Table 2: Clinical and biochemical characteristics of the study population.

Variables	Univariate analysis		
	B	OR (95%CI)	P-value
Gender	-0.010	0.990 (0.855-1.147)	0.898
Age	0.043	1.044 (1.037-1.052)	0.000
BMI	0.029	1.029 (1.013-1.045)	0.000
WC	0.018	1.018 (1.011-1.025)	0.000
LAP	0.005	1.005 (1.003-1.006)	0.000
SBP	0.021	1.022 (1.018-1.025)	0.000
DBP	0.021	1.022 (1.015-1.028)	0.000
PP	0.026	1.027 (1.022-1.031)	0.000
TC	0.087	1.091 (1.026-1.160)	0.005
TG	0.127	1.136 (1.087-1.187)	0.000
HDL-C	-0.302	0.740 (0.604-0.906)	0.004
LDL-C	0.070	1.072 (0.988-1.165)	0.096
Crea	0.041	1.041 (1.037-1.046)	0.000
eGFR	-0.050	0.951 (0.947-0.955)	0.000
Urinary ACR	0.188	1.207 (1.193-1.220)	0.000
Drinking	-0.173	0.841 (0.714-0.990)	0.038
Smoking	0.016	1.016 (0.830-1.244)	0.877
T2DM	0.615	1.850 (1.597-2.144)	0.000
Hypoglycemic drugs	0.635	1.887 (1.535-2.321)	0.000
CVD events	0.829	2.291 (1.736-3.023)	0.000

Beta is the standardized coefficient and measures the influence of each variable on CKD; OR is the odds ratio and refers to the risk of prevalent CKD.

Multivariable-adjusted ORs for the association of LAP quartiles with risk of prevalent CKD in the study population.

Table 3 shows the association between LAP quartiles and risk of prevalent CKD in the total population in Model 1–Model 5. As shown in Table 3, the prevalence of DPN was increased by 21.3% (95% CI 14.6–28.3%; P<0.01) per SD increase in LAP in Model 1, and such an association weakened but was still significant after further adjustment for SBP, DBP, PP, LDL-C, prevalence of T2DM, and hypoglycemic drugs in Model 5 (OR: 13.5%, 95% CI 6.3-21.1%, P<0.01). Consistently, the risk of prevalent CKD were progressively increased with increasing LAP quartiles (P for trend <0.01). When compared to participants in the lowest LAP quartile (Q1), those in the highest quartile (Q4) had significantly higher risk of prevalent CKD in Models 1–4 (P<0.01). After further adjustment for SBP, DBP, PP, LDL-C, prevalence of T2DM, and hypoglycemic drugs, the association was still significant in Model 5, indicating the stability of the relationship between LAP quartiles and increased risk of prevalent CKD (OR: 1.497, 95% CI 1.139-1.966, P<0.01).

Table 3: Association between LAP quartiles and risk of CKD in the study population

		LAP quartiles				
Variable	Per SD increase	Q1	Q2	Q3	Q4	*P* for trend
Model 1						
OR (95%CI)	1.213 (1.146-1.283)	1	1.186 (0.959-1.467)	1.333 (1.082-1.643)	2.028 (1.666-2.470)	0.000
p-value	0.000		0.117	0.007	0.000	
Model 2						
OR (95%CI)	1.203 (1.136-1.275)	1	1.113 (0.895-1.382)	1.160 (0.935-1.440)	1.731 (1.411-2.122)	0.000
p-value	0.000		0.336	0.178	0.000	
Model 3						
OR (95%CI)	1.189 (1.118-1.265)	1	1.148 (0.912-1.446)	1.120 (0.883-1.422)	1.783 (1.391-2.285)	0.000
p-value	0.000		0.239	0.350	0.000	
Model 4						
OR (95%CI)	1.187 (1.116-1.262)	1	1.154 (0.916-1.454)	1.104 (0.869-1.403)	1.773 (1.381-2.276)	0.000
p-value	0.000		0.224	0.419	0.000	

Model 5						
OR (95%CI)	1.135 (1.063-1.211)	1	1.083 (0.850-1.381)	0.961 (0.741-1.247)	1.497 (1.139-1.966)	0.004
p-value	0.000		0.518	0.766	0.004	

Data are expressed as OR (95% CI) +P value, unless stated otherwise. Model 1: unadjusted; Model 2: adjusted for gender and age; Model 3: additionally adjusted for BMI based on Model 2; Model 4: additionally adjusted for smoking, drinking, prevalence of CVD events based on Model 3; Model 5: additionally adjusted for SBP, DBP, PP, LDL-C, prevalence of T2DM, and hypoglycemic drugs based on Model 4.

Association of LAP quartiles with increased risk of prevalent CKD in stratified analysis

Stratified analysis was performed to verify the stability of the relationship between LAP quartiles and CKD. Table 4 shows the association between LAP quartiles and increased risk of prevalent CKD in the subgroups. In women, ≥60 years, overweight, NGT, normal PP, LDL-C < 3.4 mmol/L, hypertension, without CVD events, no drinking and smoking, the risks of prevalent CKD were progressively increased with increasing LAP quartiles (P for trend <0.01 or P for trend <0.05). Specifically, in women, compared to the lowest LAP quartile (Q1), the odd of increased risk of prevalent CKD in the highest quartile (Q4) was significantly higher, even after adjustment for gender, age, BMI, smoking, drinking, SBP, DBP, PP, LDL-C, prevalence of T2DM and CVD events, and hypoglycemic drugs, as shown in Table 4 (OR: 1.461, 95% CI 1.040-2.053, P = 0.029). However, in men, no significant association between LAP quartiles and increased risk of prevalent CKD was observed after multivariable adjustment (P>0.05). Significant associations of LAP quartiles with increased risk of prevalent CKD were also observed in participants who were overweight (OR: 1.473, 95% CI 1.072-2.023, P=0.017), participants with NGT (OR: 1.694, 95% CI 1.115-2.573, P = 0.013), normal PP (OR: 1.545, 95% CI 1.131-2.111, P = 0.006), LDL-C < 3.4 mmol/L (OR: 1.505, 95% CI 1.116-2.029, P = 0.007), and those without CVD events (OR: 1.476, 95% CI 1.119-1.948, P = 0.006). To further investigate the association of LAP quartiles with increased risk of prevalent CKD, stratified analysis was performed based on drinking and smoking status, and similar results were observed. When compared to Q1, participants with no drinking in Q4, were more likely to have increased risk of prevalent CKD (OR: 1.450, 95% CI 1.051-2.000, P = 0.023). Moreover, participants with no smoking in Q4 exhibited the significant association with increased risk of prevalent CKD compared with those in Q1 (OR: 1.455,

95% CI 1.083-1.954, P = 0.013). However, there was no significant relationship between LAP quartiles and increased risk of prevalent CKD among participants with drinking or smoking (all P >0.05).

Table 4: Association between LAP quartiles and increased risk of CKD in different participants

	LAP quartiles					
	Q1	Q2	Q3	Q4		
Variable	OR (95%CI) P-value	OR (95%CI) P-value	OR (95%CI) P-value	OR (95%CI) P-value	P for trend	P for interaction
Gender						0.518
Men	1	1.259 (0.844-1.879) 0.259	0.911 (0.583-1.423) 0.682	1.471 (0.905-2.393) 0.120	0.210	
Women	1	0.984 (0.723-1.341) 0.920	0.993 (0.718-1.373) 0.964	1.461 (1.040-2.053) 0.029	0.006	
Age, years						0.532
<60	1	1.098 (0.783-1.539) 0.587	1.069 (0.731-1.562) 0.732	1.621 (1.084-2.423) 0.019	0.050	
≥60	1	1.070 (0.750-1.527) 0.708	0.929 (0.642-1.344) 0.695	1.422 (0.966-2.094) 0.074	0.015	
BMI status						0.429
Normal	1	1.098 (0.829-1.454)	0.917 (0.650-1.293)	1.290 (0.862-1.929)	0.487	

		0.513	0.621	0.216	
Overweight	1	1.112 (0.861-1.436) 0.416	0.994 (0.744-1.329) 0.969	1.473 (1.072-2.023) 0.017	0.002
Obesity	1	1.498 (0.097-23.145) 0.772	4.512 (0.419-48.557) 0.214	2.100 (0.245-17.984) 0.498	0.123
Glucose metabolism status					0.637
NGT	1	0.869 (0.624-1.209) 0.404	0.921 (0.632-1.343) 0.670	1.694 (1.115-2.573) 0.013	0.020
Prediabetes	1	1.499 (0.906-2.479) 0.115	1.107 (0.650-1.885) 0.708	1.691 (0.951-3.007) 0.073	0.589
T2DM	1	1.191 (0.667-2.128) 0.555	0.859 (0.494-1.493) 0.590	1.379 (0.798-2.381) 0.249	0.249
Blood pressure status					0.000
Normal	1	1.064 (0.795-1.424) 0.678	0.936 (0.675-1.299) 0.694	1.567 (1.087-2.258)	0.066

				0.016	
Hypertension	1	1.121 (0.716-1.755) 0.618	1.056 (0.667-1.671) 0.817	1.427 (0.908-2.243) 0.123	0.035
PP status					0.012
Normal	1	1.068 (0.815-1.399) 0.632	0.956 (0.710-1.287) 0.766	1.545 (1.131-2.111) 0.006	0.013
Abnormal	1	1.159 (0.659-2.038) 0.608	0.927 (0.526-1.635) 0.794	1.234 (0.683-2.228) 0.486	0.182
LDL-C, mmol/L					0.137
< 3.4	1	1.178 (0.907-1.531) 0.219	1.054 (0.792-1.404) 0.718	1.505 (1.116-2.029) 0.007	0.014
≥3.4, <4.1	1	0.624 (0.267-1.461) 0.277	0.784 (0.353-1.744) 0.551	1.923 (0.791-4.674) 0.149	0.061
≥ 4.1	1	0.326 (0.078-1.359) 0.124	0.216 (0.052-0.899) 0.035	0.883 (0.253-3.081) 0.845	0.674

CVD events						0.653
No	1	1.068 (0.834-1.367) 0.605	0.922 (0.707-1.203) 0.550	1.476 (1.119-1.948) 0.006	0.006	
Yes	1	3.527 (0.700-17.777) 0.127	2.314 (0.675-7.928) 0.182	2.199 (0.436-11.086) 0.340	0.166	
Current drinking status						0.416
No	1	1.013 (0.758-1.353) 0.933	0.912 (0.672-1.238) 0.554	1.450 (1.051-2.000) 0.023	0.004	
Yes	1	1.226 (0.778-1.932) 0.381	1.069 (0.637-1.7963) 0.800	1.471 (0.858-2.524) 0.161	0.583	
Current smoking status						0.644
No	1	1.082 (0.832-1.408) 0.556	1.021 (0.770-1.356) 0.883	1.455 (1.083-1.954) 0.013	0.004	
Yes	1	0.992 (0.515-1.909) 0.980	0.705 (0.355-1.399) 0.317	1.850 (0.850-4.028) 0.121	0.493	

Data are expressed as OR (95% CI) +P value, unless stated otherwise. Adjusted for sex, age, BMI, smoking, drinking, CVD events, SBP, DBP, PP, LDL-C, prevalence of T2DM, and hypoglycemic drugs.

Discussion

In the present study, we for the first time observed that elevated LAP was positively associated with the risk of prevalent CKD, defined by declined eGFR and/or the presence of albuminuria, in Chinese community adults, and the association between LAP and CKD weakened but retained significance after controlling for confounding factors. Furthermore, stratified analysis revealed that participants with higher LAP were more likely to have increased risk of prevalent CKD than those with lower LAP, especially in women, in subjects who were older, overweight, those with hypertension, NGT, normal PP, LDL-C <3.4 mmol/L, and those without CVD events, no smoking and drinking. Therefore, early prevention and intervention are vital for CKD, and modification of the abnormal fat distribution may contribute to reduced risk of CKD and associated unfavorable health outcomes, especially in women, older subjects, and people with overweight and hypertension.

Accumulating evidence indicates that obesity and CKD have increased in parallel worldwide and are positively correlated [12], and obesity, especially visceral obesity, is an important risk factor for CKD [3, 5, 6, 7]. Visceral obesity has been reported to be associated with IR, dyslipidemia, nonalcoholic fatty liver disease, metabolic syndrome, hyperuricemia, diabetes, hypertension, and CVD events [5, 6, 8, 9], all of which are involved in the pathogenesis of CKD [3, 4, 10]. Direct measurement of visceral adipose tissue by imaging techniques, i.e. computed tomography (CT) and magnetic resonance imaging (MRI) that are considered the gold standards, is not practicable in the routine clinical practice because these imaging techniques are inaccessible, time-consuming, costly, and radioactive [7]; therefore, surrogate indices have received increasing attention for the assessment of visceral fat distribution. LAP, an emerging surrogate marker, has been suggested as an inexpensive and highly accessible index to assess the visceral adiposity distribution and reflect visceral adiposity dysfunction [9, 10]. Despite the lack of studies evaluating the association between LAP and CKD, defined by declined eGFR and/or the presence of albuminuria, there are several reports regarding the relationship between LAP and eGFR, with conflicting findings [9, 11, 12, 13]. A cross-sectional study of 4947 Korean subjects aged ≥20 years conducted by Seong et al. showed that the prevalence of declined eGFR was positively associated with the quartiles of LAP in all participants, and the positive association of prevalence of declined eGFR and LAP quartiles was observed only in men but not women, after adjusting for related variables [9]. In another study of 11,192 individuals aged ≥35 years, Dai et al. reported that LAP were significantly associated with CKD, defined by only declined eGFR, in the rural population of northeast China, and LAP can predict CKD only in women [12]. Similarly, data from an observational study from SPECT-China, which included 10,012 subjects aged ≥18 years in East China, demonstrated that LAP strongly associated with eGFR level and declined renal function and could be one of markers for predicting the risk of renal dysfunction [11]. These results are basically consistent with our study showing that

participants with CKD, declined eGFR and albuminuria had significantly higher LAP compared to those with non-CKD, declined eGFR and non-albuminuria, respectively. Moreover, we observed that elevated LAP was positively associated with the risk of prevalent CKD, and the association between LAP and CKD weakened but retained significance after controlling for confounding factors. In contrast, results from a prospective study in Iran, consisted of 6693 individuals aged ≥18 years with a mean 8.65 years of follow-up, reported that there was no statistically significant association between the quartiles of LAP and incidence of declined eGFR [13]. The discrepancies between the above mentioned studies may be due to the differences in population characteristics, races, regions, dietary habits, sample size, statistical methods, and confounding factors adjusted in the analyses. More studies are needed before conclusions can be drawn.

Notably, we found that female participants with higher LAP were more likely to have increased risk of prevalent CKD than those with lower LAP, but no statistically significant association between LAP quartiles and prevalence of CKD after adjustment for confounding factors in men, which was consistent with previous studies [12], suggesting significant gender difference in the relationship of LAP and CKD. The mechanisms underlying the gender-specific difference are unclear. We speculate that this may be due to differences in sex hormones, the distribution of fat, and lifestyles in men and women. In our study, only participants aged ≥40 years with a mean age of 58 years were included, of whom the majority of women were postmenopausal. It is well known that estrogens could regulate adipose deposition and function [9], and estrogen exerts renoprotective effects [22]. Therefore, postmenopausal females tended to deposit more abdominal visceral adipose tissue and lost estrogen renal protection partly due to the rapid decline in estrogens [5, 9]. On the other hand, males tended to be physically active and consumed more tea, especially green tea, both of which may make males have a lower distribution of abdominal fat compared to females of the same ages who were less active and consumed less tea [23, 24, 25]. It is recognized that abdominal visceral adipose tissue as a metabolically active endocrine organ is a source of various bioactive adipocytokines and inflammatory proteins such as adiponectin, visfatin, omentin-1, leptin, resistin, IL-6, tumor necrosis factor-α, CRP, and plasminogen activator inhibitor-1 [26, 27]. A growing number of studies have shown that altered cytokines levels are closely linked with change in renal hemodynamics, renal vascular damage, glomerular sclerosis, renal fibrosis, proteinuria, reduced eGFR, and CKD [6, 28, 29]. Age is an important factor for determining the prevalence of CKD, and eGFR decreased steadily as age increased [9]. In general, age is also a crucial cause of CKD-inducing diseases such as diabetes, hypertension, dyslipidemia, and hyperuricemia. In the present study, we observed a positive association between the quartiles of LAP and prevalence of CKD in subjects aged ≥60 years, and no statistically significant association in subjects aged <60 years, which was similar to a previous study [22], suggesting that age over 60 years is a strong risk factor for CKD. We also found that age, BMI, and WC were positively correlated with the prevalence of CKD in univariate analysis, and the association between the quartiles of LAP and CKD was attenuated after adjusting for gender and age in Model 2, while the association increased after further adjustment for BMI in Model 3, indicating that the risk of prevalent CKD may increase in women and subjects aged ≥60 years, and older age and women may be two stronger factors than obesity for CKD. Thus, it is of great importance to early screen for CKD among

women and subjects aged ≥60 years, and such populations should monitor the LAP early, make lifestyle changes and take necessary treatment.

Emerging epidemiologic studies suggested that hypertension commonly complicates CKD, and hypertension was a leading cause of incidence, prevalence, and progression of CKD [1, 3, 4, 22], which might lead to deleterious metabolic and cardiovascular consequences [3, 10]. Whether LAP is an effective maker for CKD that could be applied in the Chinese hypertensive population remains unknown. Previous studies showed that obesity is closely associated with CKD in the hypertensive population from different countries [30-33]. Lea et al. showed that metabolic syndrome associated with abdominal obesity is associated with proteinuria in hypertensive African Americans [30]. Results from the renal sub-study of the China Stroke Primary Prevention Trial (CSPPT) in China, a prospective cohort study of 12 672 hypertensive patients with over a median follow-up of 4.4 years, reported that higher BMI was significantly associated with an increased risk of CKD development in hypertensive patients with normal kidney function [31]. Similar results have been obtained from another two recent cross-sectional studies of hypertensive patients [32, 33]. Our study provided further evidence that supported the potential role of hypertension in the development of CKD, since we found that patients with CKD had significantly higher SBP and DBP, while SBP and DBP were positively correlated with the prevalence of CKD in univariate analysis. Moreover, the association between LAP quartiles and CKD was attenuated after further adjusting for blood pressure in Model 5, suggesting that hypertensive may increase the risk of prevalent CKD. Further, a stratified population study showed that participants with higher quartiles of LAP had significantly increased risk of prevalent CKD in people with hypertension, however, no correlation was found between LAP quartiles and increased risk of prevalent CKD, which also indicated that hypertension plays an important role in the development of CKD. Thus, not only modification of visceral fat distribution but also the early identification and management of established risk factors in such people are of great importance to reduce the additive risk of CKD.

Many cross-sectional and prospective studies have reported significant relationships between CKD, CVD events, diabetes, dyslipidaemia and arterial stiffness [3, 4, 19, 34], which might partially explain the association between LAP and CKD in our study. It is recognized that LDL-C is causally associated with a high risk of coronary artery disease, and high LDL-C was observationally and genetically associated with high risk of CKD in the general population [35]. There is mounting evidence that elevated PP, a surrogate measure of arterial stiffness, was demonstrated to be a well-known predictor of CVD events, such as CHD, stroke and heart failure, and cardiovascular mortality [20, 36], and also reported to be associated with increased risk of albuminuria [19] either in general or hypertensive populations. In general, patients with CKD had high prevalence of CVD, and progressive CVD and progressive declined kidney function do have a number of common risk factors [37], including hypertension and diabetes, which were the main causes of CKD. Our study provided further evidence that supported the potential role of CVD events, diabetes, dyslipidaemia and arterial stiffness in the development of CKD, since we found that patients with CKD had significantly higher CVD events and its components, including MI, CHD and PAD, blood glucose parameters (FBG, PBG, and HbA1c), prevalence of T2DM, users of hypoglycemic drugs, blood lipids parameters (TG, TG, and lower HDL-C), and PP. Moreover, the prevalence of CKD was positively correlated

with prevalence of CVD and T2DM, users of hypoglycemic drugs, TG, TG, and PP, and negatively with HDL-C in univariate analysis. Further, the association between LAP and CKD was attenuated gradually but retained significance after further adjusting for prevalence of T2DM and CVD events, hypoglycemic drugs, LDL-C, and PP and in Model 4 and Model 5, suggesting that CVD events, diabetes, dyslipidaemia and arterial stiffness may increase the risk of prevalent CKD. Unexpectedly, stratified populations study showed that significant associations between higher LAP quartiles and CKD were detected only in people who had NGT, LDL-C < 3.4 mmol/L, normal PP, and those without CVD events, however, no correlations were found between LAP quartiles and CKD in participants with prediabetes, T2DM, LDL-C ≥ 4.1 mmol/L, high pulse pressure, and CVD events. The possible reason of lacking significant associations between LAP and CKD in participants with prediabetes and T2DM, at least in part, might be due to the populations of prediabetes and T2DM may be aware of the importance of glycemic control and the improvement of fat distribution, therefore, possibly had better compliance with medical orders and more physical activities, and kept a more healthy diet habit, all of which contributed to the favorable effect of CKD. Additionally, in participants with CVD events, LDL-C ≥ 4.1 mmol/L, and high pulse pressure, no associations were also found between LAP and CKD, which may be due to that the small case numbers and large 95% Cls in certain subgroups led to the not available data or imprecise estimation. Further research in larger population is needed to verify our speculation.

Our study has several potential limitations that merit comment. First, the cross-sectional design of the current study precluded conclusions on the temporal relationship of LAP with elevated risk of CKD. Thus, further large-scale prospective studies are needed to determine the role of LAP in the early identification of CKD in Chinese adults with different characteristics. Second, imaging techniques, such as CT and MRI, are considered the gold standards for determining the extent of visceral fat area, but these imaging techniques are inaccessible, time-consuming, costly, and radioactive, and therefore are not suitable for large-scale epidemiological investigations. Instead, increasing evidence suggests that LAP is considered as a useful clinical indicator of visceral adiposity distribution and could reflect visceral adiposity dysfunction due to its inexpensiveness, accessibility and reliability. Third, despite we excluded subjects who used ACEI/ARB and lipid-lowering drugs, and after adjusting for hypoglycemic drugs in the current analysis, there is still the possibility that other medications may partially affect the association of LAP with CKD. Fourth, our study population included only middle-aged and elderly subjects in five communities of Luzhou city, located in South China, and therefore our findings may not be generalizable to participants of different ages, North China population, and other ethnic populations. More studies are needed to confirm this relationship of LAP with CKD in such populations. Fifth, although many traditional risk factors were adjusted, residual confounding variables and unmeasured factors, such as dietary factors, cannot be excluded from the current study, which may affect the exact association of LAP with CKD. Despite these limitations, the current study is not without strengths, including a large sample size, use of a standardized method at a single center, and a comprehensive adjustment for major traditional risk factors, and represented middle-aged and elderly population from different communities across Luzhou, which can raise the reliability of our findings. Moreover, our study, to our knowledge, provides first

clinical evidence on a potential link between LAP and CKD, defined by declined eGFR and/or the presence of albuminuria, in Chinese community adults.

Conclusions

The present study demonstrates that an increased level of LAP is significantly associated with prevalent CKD in Chinese community adults. Participants with elevated LAP are at higher risk for prevalent CKD, especially in subjects who were older, overweight, those with hypertension, NGT, normal PP, LDL-C < 3.4 mmol/L, and those without CVD events, no smoking and drinking. These findings suggest that LAP may be an easy and efficient tool for the identification of middle-aged and elderly subjects at high risk of CKD, and highlight the importance of paying more clinical attention to CKD in patients with visceral obesity to further reduce the potential risk of CKD and associated unfavorable health outcomes.

Abbreviations

CKD: Chronic kidney disease; CVD: Cardiovascular disease; CRP: C-reactive protein; IL-6: interleukine-6; IR: Insulin resistance; BMI: Body mass index; WC: Waist circumference; LAP: Lipid accumulation product; TG: Triglyceride; eGFR: Estimated glomerular filtration rate; ACR: Albumin-to-creatinine ratio; Q: Quartile; PP: Pulse pressure; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; OGTT: Oral glucose tolerance test; FBG: Fasting blood glucose; PBG: 2 h postload blood glucose; HbA1c: Glycated hemoglobin A1c; TC: Total cholesterol; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; Cr: Creatinine; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; T2DM: Type 2 diabetesmellitus; NGT: Normal glucose tolerance; MI: Myocardial infarction; CHD: Coronary heart disease; PAD: Peripheral arterial disease; SD: Standard deviation; OR: Odds ratios; CI: Confidence intervals; CT: Computed tomography; MRI: Magnetic resonance imaging; CSPPT: China Stroke Primary Prevention Trial.

Declarations

Authors' Contributions

All the authors contributed significantly to the manuscript. Pijun Yan conducted the population study, analyzed and interpreted the data, and drafted and critically revised the manuscript. Yong Xu significantly revised the draft, interpreted the data, and involved in data analyses. Ying Miao and Qian Tang conducted the study, tested the sample, collected the information and participated in data interpretation. Yuru Wu

and Xue Bai involved in data management and draft revision. QW is the PI of project, who designed the study and critically revised the manuscript. All authors read and approved the final manuscript.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The present study was conducted according to the guidelines laid out in the Declaration of Helsinki, and all procedures involving human participants were approved by the Research Ethics Committees of the Rui-Jin Hospital affiliated to the Jiao-Tong University School of Medicine, and also by the Affiliated Hospital of Southwest Medical University. All participants provided informed written consent to participate.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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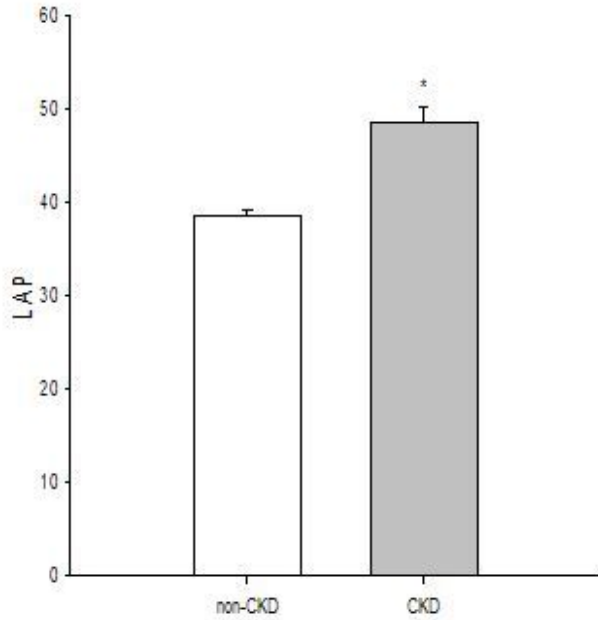
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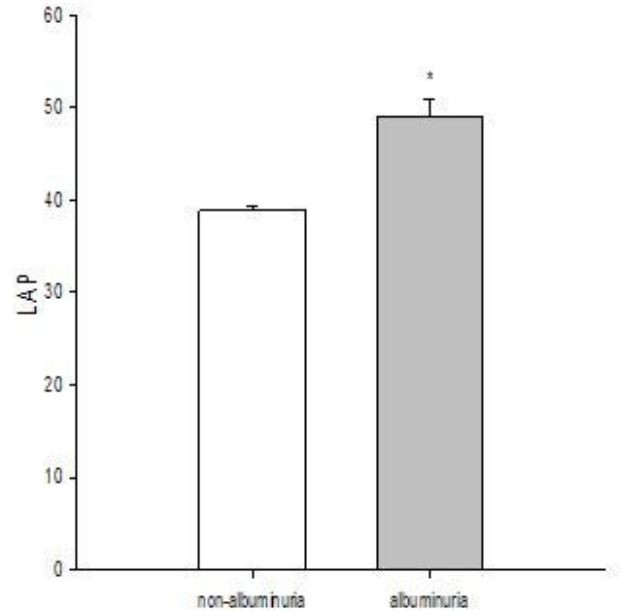
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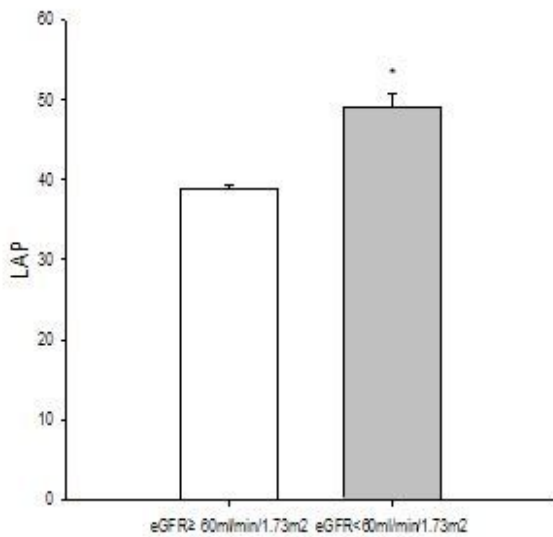
Figures

Figure 1

LAP levels in different participants. A. LAP levels between non-CKD and CKD group. B. LAP levels between non-albuminuria and albuminuria group. C. LAP levels between patients with eGFR <60 mL/min/1.73m² and eGFR ≥60 mL/min/1.73m². Vs. non-CKD group or non-albuminuria group or eGFR ≥60 mL/min/1.73m², *P<0.01