What is the Impact of Sex on Cardiovascular Disease Risk Factors in Patients with Chronic Kidney Diseases in China: A Cross-sectional Study

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Abstract

Background: It is controversial about the sex differences in the association of chronic kidney diseases (CKD) and cardiovascular disease (CVD) risk. Thus, we examined CVD risk makers of CKD and non-CKD men and women in China, especially some “non-traditional” ones.

Methods: This cross-sectional study used 7999 participants from the China Health and Nutrition Survey in 2009. This study examined the “traditional” risk factors and of CVD, such as lipoprotein cholesterol (LDL-C), total cholesterol (TC) and non-high density lipoprotein cholesterol(non-HDL-C).Also, the “non-traditional” risk factors of CVD were calculated, such as lipoprotein (a) (Lp(a)), white blood cell (WBC) count, visceral adiposity index (VAI) and lipid accumulation product (LAP).

Results: Compared with men with CKD, higher levels of TC and LDL-C were observed in women with CKD. Furthermore, compared with men with CKD, the relative difference of WBC count was greater between women with CKD and their non-CKD ones. Meanwhile, the level of LAP and VAI of women with CKD were higher than men with CKD, which indicate the visceral obese. We also observed that the sex by CKD status interactions were statistically significant for TC, LDL-C, non-HDL-C, LAP, VAI and Lp(a) (all $p < 0.05$). After adjusted the covariates, the sex differences effect on CVD risk factors among CKD patients couldn’t be eliminated as well.

Conclusions: In CKD situation, women had greater lipid profiles and put on more visceral adiposity than men, which may indicate a higher CVD risk of women with CKD.

Background

In the previous studies, chronic kidney disease (CKD) has considered as an important public health problem and received lots of attention (1). In China, the prevalence of CKD in adults has reached 10.8%(2). Besides, cardiovascular disease (CVD) has shown an increasing incidence and it is one of the most important causes of death in patients with CKD (3). At the same time, there many risk factors for CVD and CKD is one of them (4), and the risk of CVD increases with the development of CKD (5). CVD is interrelating with kidney disease closely, which is called cardiorenal syndrome, in which one organ’s disease leads to the dysfunction of the other, ultimately causing both organ failed (6).

Recent studies demonstrated that advanced age, hypertension, diabetes, and dyslipidemia were considered as the CVD risk factors (7). Some lipid markers and inflammatory markers, including Lipoprotein (a)(Lp(a))(8) and white blood cell (WBC) count(9), were known as “non-traditional” risk factors of CVD(10). Besides, visceral adiposity index (VAI) and lipid accumulation product (LAP) were indicating the abdominal obesity and abdominal obesity was deeply related with CVD (11).Thus, VAI and LAP are considered as “non-traditional” risk factors of CVD as well(12). Due to the different living habits (13) and incidence of lipid metabolism disorder syndrome(14) between different genders, men were reported to have larger value of traditional risk factors (15), however, few researches focus on the “non-traditional” ones.

It is reported that 43.9% of CKD patients in China are men and 56.1% of them are women, indicating that there are more women patients with CKD in China(2). Population-based studies have showed that there some difference between genders of CKD epidemiology, in which CKD affected more women than men(16). Particularly, the differences between these markers mentioned above in men and women with CKD are short of research. We need to arouse the importance of the difference between different genders with CKD for CVD risk factors in order to give better treatment to CKD patients. Thus, we designed this study to explain the gender differences in CVD risk factors in CKD patients, including some “non-traditional” ones.

Methods

Participants

The data used in this study was from a database called China Health and Nutrition Survey (CHNS). This is a household-based and longitudinal survey in China. There were 8 survey rounds of CHNS and conducted in different years. Besides, the participants were from nine provinces (Heilongjiang, Liaoning, Henan, Jiangsu, Hubei, Shandong, Hunan, Guizhou and Guangxi),and more than half of China’s population is included in this study, a great difference can be found about the health status, economic development and

geography. The Lots of institutions supported this survey as mentioned in previous study(17) and all participant were provided a written informed consent (18).

Since CHNS began to collect the fasting blood in 2009, data from CHNS 2009 were used in this study. At the 2009exam, 10243 adult respondents were surveyed with 1120 did not give blood. Meanwhile, there 64 participants were pregnant and 805 participants' age was under 18, there 8254 participants with fasting blood samples finally. There also some different exclusion criteria including participants without the information of body mass index (BMI), age or waist circumference (WC) and with extreme triglycerides (TG) (> 500 mg/dl), BMI (≥ 40 kg/m^2) or high-density lipoprotein cholesterol (HDL-C) (> 100 mg/dl) values. At the same time, in order to eliminate the different effects caused by the curing of CVD risk factors on the result of this study between different genders, participants were using anti-diabetic agent, lipid-lowering agent and anti-hypertension agent were excluded as well. This analysis included 7999 participants in the end.

Measurements

The stuff of CHNS used standard protocols from the World Health Organization (WHO) to measure participants' height, weight, systolic/diastolic BP and WC. Also, they used a calibrated beam scale to measure the participants' weight with a light clothing and portable SECA stadiometer to measure height. Using an inelastic tape to measure WC at middle between the top of the exhalation ilium and the bottom of chest. BMI was equal to the value using square of height (in meters) to divide weight (in kilograms). Meanwhile, trained technicians used mercury manometers to measure BP after a rest of ten minutes three times and averaging the three readings of BP in the end.

Measurements of biochemical

All tested samples were collected after a more than 8-hour overnight fast. We analyzed total samples with strict quality control in a lab of Beijing. Picric acid method was used to measure serum creatinine (Scr). GODPAP method was used to measure fasting plasm glucose (FPG). Hitachi 7600 automated analyzer was used to measure all lipids parameters, including, TG, low density lipoprotein cholesterol [LDL-C] and HDL-C. The value of non-HDL-C equaled to TC minus HDL-C. Measured Lp (a) with an immunoturbidimetric method. Also, apolipoprotein B (apo B), apolipoprotein a1 (apo a1), alanine aminotransferase (ALT), uric acid (UA), fasting insulin concentration and hypersensitive C-reactive protein (hs-CRP) were measured accurately with proper methods. Details on these procedures have been described previously(17). With drawing a conclusion of data from Chinese chronic kidney disease, estimated glomerular filtration rate (eGFR) was calculated with an equation developed by adaptation of the Modification of Diet in Renal Disease (MDRD) equation: $eGFR = 175 \times Scr^{-1.234} \times age^{-0.179}$ [if female, × 0.79](19). CKD is defined as having eGFR < 60 ml/min/1.73 m^2 (20).

The LAP was calculated as LAP (18): Men: [WC (cm) − 65] × [TG (mmol/l)]; Women: [WC (cm) − 58] × [TG (mmol/l)]. And in order to avoid the nonpositive values of LAP, we eliminated men/women with WC values less than 65/58. We calculated homeostasis model assessment of insulin resistance (HOMA-IR) (21) with the formula: HOMA-IR = fasting insulin (micro-international units per milliliter) × FPG (millimoles per liter)/22.5. The triglycerides and glucose index (TyG) were calculated by the formula: TyG index(22): Ln [TG (mg/dl) × FPG (mg/dl)/2]. Also, we used the formulas to calculated VAI(23), in which men were used the formula : [WC/39.68 + (1.88 × BMI)] × (TG/1.03) × (1.31/HDL); and the formula for women was : [WC/36.58 + (1.89 × BMI)] × (TG/0.81) × (1.52/HDL).

Statistical analysis

We used SPSS software (version 25.0 for windows; SPSS, Chicago, IL, USA) to conducted the statistical analysis. And control persons were those participants who had eGFR≥60ml/min/1.73 m^2. All continuous variables were calculated as mean ± standard deviation (SD). We used two-way analysis of covariance to computed CKD status and gender as the two main effects in five tables in this study. We also conducted the statistical analysis of the association of sex × CKD interactions with CVD risk factors. A log-transformed (natural logarithm) was used in insulin to approximate normal distributions before conducting analyses. A two-sided P-value < 0.05 was regarded as statistically significant.

Results

Table 1
Non-adjusted mean levels of studied cardiovascular disease risk factors

	Men			Women			Men vs Women		
	CKD	non-CKD	P*	CKD	non-CKD	P*	P(CKD)	P(non-CKD)	P(Interaction)&
N	290	3399		327	3983				
Age(years)	66.8±0.7	49.6±0.3	< 0.001	67.1±0.7	49.4±0.2	< 0.001	0.764	0.500	0.764
BMI(kg/m^2)	23.5±0.2	23.2±0.1	0.209	23.6±0.2	23.3±0.1	0.180	0.705	0.183	0.705
WC(cm)	85.9±0.6	84.1±0.2	0.005	82.8±0.6	81.1±0.2	0.004	< 0.001	< 0.001	< 0.001
SBP(mmHg)	137.6±1.2	125.0±0.3	< 0.001	137.4±1.3	122.5±0.3	< 0.001	0.939	< 0.001	0.939
DBP(mmHg)	84.7±0.7	81.7±0.2	< 0.001	81.6±0.7	78.8±0.2	< 0.001	0.002	< 0.001	0.002
eGFR(ml/min per1.73 m^2)	51.9±0.5	84.0±0.3	< 0.001	50.7±0.5	84.4±0.2	< 0.001	0.133	0.332	0.133
TG(mmol/l)	1.7±0.1	1.6±0.0	0.070	1.8±0.1	1.4±0.0	< 0.001	0.290	< 0.001	0.135
TC(mmol/l)	4.9±0.1	4.8±0.0	0.001	5.4±0.1	4.8±0.0	< 0.001	< 0.001	< 0.001	< 0.001
HDL-C(mmol/l)	1.4±0.0	1.4±0.0	0.762	1.5±0.0	1.5±0.0	0.945	0.001	< 0.001	0.001
LDL-C(mmol/l)	3.1±0.1	2.9±0.0	0.003	3.5±0.1	3.0±0.0	< 0.001	< 0.001	0.016	< 0.001
TG/HDL	1.4±0.1	1.3±0.0	0.091	1.4±0.1	1.1±0.0	< 0.001	0.701	< 0.001	0.701
non-HDL(mmol/l)	3.6±0.1	3.4±0.0	0.001	3.9±0.1	3.4±0.0	< 0.001	< 0.001	0.589	< 0.001
Apo B(g/l)	1.0±0.0	0.9±0.0	< 0.001	1.1±0.3	0.9±0.3	< 0.001	< 0.001	0.467	< 0.001
ApoB/apo a1	0.9±0.0	0.8±0.0	0.048	0.9±0.4	0.8±0.3	< 0.001	0.235	< 0.001	0.235
FPG(mmol/l)	5.9±0.1	5.3±0.0	< 0.001	6.0±0.1	5.3±0.0	< 0.001	0.534	0.001	0.443
HbA1c (mmol/mol)	5.8±0.1	5.6±0.1	0.001	5.9±0.1	5.6±0.0	< 0.001	0.164	0.109	0.164
HOMA-IR	6.5±0.1	3.6±0.1	< 0.001	6.5±0.8	3.4±0.1	< 0.001	0.961	0.196	0.961
Insulin	1.1±0.0	1.0±0.0	< 0.001	1.1±0.0	1.0±0.0	< 0.001	0.997	0.261	0.997
TyG index	8.8±0.0	8.6±0.0	< 0.001	8.9±0.0	8.5±0.0	< 0.001	0.159	< 0.001	0.159
ALT	22.7±1.0	27.7±0.4	< 0.001	21.7±1.0	21.1±0.3	< 0.001	0.464	< 0.001	0.464
Lp (a)(mg/dl)	16.0±1.1	14.2±0.3	0.140	20.8±1.9	16.0±0.3	< 0.001	0.037	< 0.001	0.037

	Men			Women			Men vs Women		
VAI	1.9±0.1	1.7±0.0	0.082	2.8±0.1	2.2±0.0	< 0.001	< 0.001	< 0.001	< 0.001
LAP	38.2±2.0	33.2±0.6	0.012	47.1±2.2	36.2±0.5	< 0.001	0.003	< 0.001	0.003
UA(mmol/l)	413.1±5.4	341.2±1.4	< 0.001	347.1±4.8	257.6±1.1	< 0.001	< 0.001	< 0.001	< 0.001
WBC (10^9/ml)	6.6±0.1	6.5±0.0	0.412	6.4±0.1	6.0±0.0	< 0.001	0.267	< 0.001	< 0.001
Hb(g/dl)	146.0±1.2	152.3±0.3	< 0.001	127.5±1.1	132.2±0.3	< 0.001	< 0.001	< 0.001	< 0.001
Hs-CRP (mg/l)	5.2±1.0	2.5±0.1	< 0.001	4.6±0.6	2.2±0.1	< 0.001	0.579	0.066	0.579
Ferrtin (ng/ml)	181.6±11.7	196.5±3.8	0.264	125.8±7.5	76.0±1.7	< 0.001	< 0.001	< 0.001	< 0.001

Data are mean ±standard deviation (SD)

CKD, chronic kidney disease; non-CKD, non-chronic kidney disease; BMI, Body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG: triglycerides; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; Apo B: apolipoprotein B; Lp (a), Lipoprotein (a);FPG, fasting plasma glucose; HOMA-IR: homeostasis model assessment of insulin resistance; TyG index: the product of triglycerides and fasting glucose; ALT, alanine aminotransferase; VAI: visceral adiposity index; LAP: lipid accumulation product;. UA, uric acid; WBC, white blood cell count; Hs-CRP, hypersensitive C-reactive protein.

* p value for difference between CKD and non-CKD participants

& Interaction of sex by CKD status

Table 1 showed the non-adjusted mean values of CVD risk factors of CKD status in different genders. We can found an increase of CVD risk profile, such as TG, TC, LDL-C, TG/ HDL-C, Non-HDL-C, HOMA-IR, TyG, VAI, LAP and so on, in men and women with CKD in which compared with their non-CKD participants. Meanwhile, in CKD patients, we found that the TC, LDL-C, non-HDL-C and Apo B of women were significantly higher than men. Notably, between CKD patients and non-CKD people, women were more diverse than men in terms of WBC values. In addition, women with CKD have higher level of Lp(a), VAI and LAP compared with men with CKD. There was no difference of BMI between patients with CKD compared with their non-CKD ones. Besides, compared with non-CKD men, men with CKD had a lower level of ferritin, which was opposite to women.

Table 2
Age- and BMI-adjusted mean levels of studied cardiovascular disease risk factors

	Male			Female			Male & Female		
	CKD	non-CKD	P*	CKD	non-CKD	P*	P(CKD)	P(non-CKD)	P(Interaction)
N	290	3399		327	3983				
WC(cm)	84.1±0.4	84.3±0.1	0.730	80.0±0.4	81.3±0.1	0.001	< 0.001	< 0.001	< 0.001
SBP(mmHg)	130.2±1.0	125.6±0.3	< 0.001	127.2±1.0	123.3±0.3	< 0.001	0.798	< 0.001	0.798
DBP(mmHg)	82.5±0.6	81.9±0.2	0.328	78.0±0.6	79.1±0.2	0.078	0.001	< 0.001	0.001
eGFR(ml/min per1.73 m^2)	57.1±1.0	83.6±0.3	< 0.001	58.6±0.7	83.7±0.2	< 0.001	0.134	0.395	0.134
TG(mmol/l)	1.7±0.1	1.6±0.0	0.016	1.6±0.0	1.5±0.0	0.002	0.292	< 0.001	0.292
TC(mmol/l)	4.8±0.1	4.8±0.0	0.489	5.0±0.1	4.9±0.0	0.002	< 0.001	< 0.001	< 0.001
HDL-C(mmol/l)	1.3±0.0	1.4±0.0	0.016	1.5±0.0	1.5±0.0	0.481	0.001	< 0.001	0.001
LDL-C(mmol/l)	3.0±0.1	3.0±0.0	0.542	3.2±0.1	3.0±0.0	0.001	< 0.001	0.015	< 0.001
TG/HDL	1.5±0.1	1.3±0.0	0.010	1.3±0.1	1.1±0.0	0.002	0.134	< 0.001	0.631
non-HDL(mmol/l)	3.5±0.1	3.4±0.0	0.101	3.6±0.1	3.4±0.0	0.001	< 0.001	0.417	< 0.001
Apo B(g/l)	0.9±0.0	0.9±0.0	0.088	1.0±0.0	0.9±0.0	< 0.001	< 0.001	0.331	< 0.001
ApoB/apo a1	0.9±0.0	0.9±0.0	0.156	0.9±0.0	0.8±0.0	< 0.001	0.234	< 0.001	0.234
FPG(mmol/l)	5.6±0.1	5.4±0.0	0.003	5.7±0.1	5.3±0.0	< 0.001	0.576	< 0.001	0.576
HbA1c (mmol/mol)	5.6±0.0	5.6±0.0	0.433	5.7±0.0	5.6±0.0	0.089	0.186	0.079	0.186
HOMA-IR	6.4±0.4	3.6±0.1	< 0.001	6.2±0.4	3.4±0.1	< 0.001	0.913	0.147	0.913
Insulin	1.1±0.0	1.0±0.0	< 0.001	1.1±0.0	1.0±0.0	< 0.001	0.933	0.455	0.933
TyG index	8.8±0.0	8.6±0.0	< 0.001	8.7±0.0	8.5±0.0	< 0.001	0.161	< 0.001	0.161

Data are means±SD

CKD, chronic kidney disease; non-CKD, non-chronic kidney disease; BMI, Body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG: triglycerides; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; Apo B: apolipoprotein B; Lp (a), Lipoprotein (a);FPG, fasting plasma glucose; HOMA-IR: homeostasis model assessment of insulin resistance; TyG index: the product of triglycerides and fasting glucose; ALT, alanine aminotransferase; VAI: visceral adiposity index; LAP: lipid accumulation product;. UA, uric acid; WBC, white blood cell count; Hs-CRP, hypersensitive C-reactive protein.

* p value for difference between CKD and non-CKD participants

& Interaction of sex by CKD status

	Male			Female			Male & Female		
ALT	26.5±1.3	27.4±0.4	0.565	21.3±1.0	21.1±0.3	0.879	0.933	< 0.001	0.458
Lp (a) (mg/dl)	14.8±1.2	14.3±0.3	0.668	19.2±1.3	16.2±0.4	0.027	0.029	< 0.001	0.029
LAP	36.2±1.6	33.4±0.4	0.085	39.8±1.5	36.8±0.4	0.063	< 0.001	< 0.001	< 0.001
VAI	1.9±0.1	1.7±0.0	0.022	2.5±0.1	2.2±0.0	0.003	< 0.001	< 0.001	< 0.001
UA(mmol/l)	422.1±5.0	340.4±1.4	< 0.001	334.3±4.0	258.7±1.1	< 0.001	< 0.001	< 0.001	< 0.001
WBC (10^9/ml)	6.7±0.1	6.5±0.0	0.049	6.6±0.1	6.0±0.0	< 0.001	0.270	< 0.001	0.270
Hb(g/dl)	149.7±1.1	152.0±0.3	0.042	127.7±1.0	132.2±0.3	< 0.001	< 0.001	< 0.001	< 0.001
Hs-CRP (mg/l)	4.6±0.4	2.6±0.1	< 0.001	3.8±0.5	2.3±0.1	0.006	0.598	0.069	0.598
Ferrtin (ng/ml)	195.5±13.2	195.3±3.7	0.990	85.8±6.0	79.3±1.6	0.300	< 0.001	< 0.001	< 0.001

Data are means±SD

CKD, chronic kidney disease; non-CKD, non-chronic kidney disease; BMI, Body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG: triglycerides; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; Apo B: apolipoprotein B; Lp (a), Lipoprotein (a);FPG, fasting plasma glucose; HOMA-IR: homeostasis model assessment of insulin resistance; TyG index: the product of triglycerides and fasting glucose; ALT, alanine aminotransferase; VAI: visceral adiposity index; LAP: lipid accumulation product;. UA, uric acid; WBC, white blood cell count; Hs-CRP, hypersensitive C-reactive protein.

* p value for difference between CKD and non-CKD participants

& Interaction of sex by CKD status

Table 3
Age-, BMI-, and HOMA-IR-adjusted mean levels of studied cardiovascular disease risk factors

	Male			Female			M&F		
	CKD	non-CKD	P*	CKD	non-CKD	P*	P(CKD)	P(non-CKD)	P(Interaction)&
N	290	3399		327	3987				
WC(cm)	84.0±0.4	84.3±0.1	0.534	79.9±0.4	81.3±0.1	< 0.001	< 0.001	< 0.001	< 0.001
SBP(mmHg)	130.1±1.0	125.6±0.3	< 0.001	126.9±1.0	123.4±0.3	0.001	0.797	< 0.001	< 0.001
DBP(mmHg)	82.6±0.6	81.9±0.2	0.295	78.0±0.6	79.1±0.2	0.060	0.001	< 0.001	< 0.001
eGFR(ml/min per1.73 m^2)	57.2±1.0	83.6±0.3	< 0.001	58.7±0.7	83.7±0.2	< 0.001	0.135	0.405	0.539
TG(mmol/l)	1.7±0.1	1.6±0.0	0.121	1.6±0.0	1.5±0.0	0.019	0.279	< 0.001	< 0.001
TC(mmol/l)	4.8±0.1	4.8±0.0	0.420	5.0±0.1	4.9±0.0	0.003	< 0.001	< 0.001	< 0.001
HDL-C(mmol/l)	1.3±0.0	1.4±0.0	0.058	1.5±0.0	1.5±0.0	0.827	0.001	< 0.001	< 0.001
LDL-C(mmol/l)	3.0±0.1	3.0±0.0	0.402	3.2±0.1	3.0±0.0	0.002	< 0.001	0.015	< 0.001
TG/HDL	1.4±0.1	1.3±0.0	0.091	1.2±0.1	1.1±0.0	0.018	0.640	< 0.001	< 0.001
non-HDL(mmol/l)	3.5±0.1	3.4±0.0	0.120	3.6±0.1	3.4±0.0	0.002	< 0.001	0.444	0.579
Apo B(g/l)	0.9±0.0	0.9±0.0	0.093	1.0±0.0	0.9±0.0	< 0.001	< 0.001	0.355	0.657
ApoB/apo a1	0.9±0.0	0.9±0.0	0.239	0.9±0.0	0.8±0.0	0.002	0.231	< 0.001	< 0.001
FPG(mmol/l)	5.4±0.1	5.4±0.0	0.631	5.6±0.1	5.3±0.0	< 0.001	0.498	0.001	0.005
HbA1c (mmol/mol)	5.5±0.1	5.6±0.0	0.068	5.6±0.0	5.6±0.0	0.604	0.167	0.123	0.298
Insulin	1.1±0.0	1.0±0.0	< 0.001	1.1±0.0	1.0±0.0	0.012	0.990	0.040	0.071
TyG index	8.7±0.0	8.6±0.0	0.017	8.6±0.0	8.6±0.0	0.006	0.135	< 0.001	< 0.001

Data are means±SD

BMI: body mass index; HOMA-IR: homeostasis model assessment of insulin resistance; CKD, chronic kidney disease; non-CKD, non-chronic kidney disease; BMI, Body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG: triglycerides; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; Apo B: apolipoprotein B; Lp (a), Lipoprotein (a);FPG, fasting plasma glucose; TyG index: the product of triglycerides and fasting glucose; ALT, alanine aminotransferase; VAI: visceral adiposity index; LAP: lipid accumulation product;. UA, uric acid; WBC, white blood cell count; Hs-CRP, hypersensitive C-reactive protein.

* p value for difference between CKD and non-CKD participants

& Interaction of sex by CKD status

	Male			Female			M&F		
ALT	26.3±1.3	27.4±0.4	0.464	21.1±1.0	21.1±0.3	0.971	0.460	< 0.001	< 0.001
Lp (a) (mg/dl)	14.9±1.2	14.3±0.3	0.636	19.1±1.3	16.2±0.4	0.036	0.029	< 0.001	< 0.001
LAP	34.9±1.6	33.5±0.4	0.380	38.5±1.5	36.9±0.4	0.320	< 0.001	< 0.001	< 0.001
VAI	1.8±0.1	1.7±0.0	0.165	2.4±0.1	2.2±0.0	0.032	< 0.001	< 0.001	< 0.001
UA(mmol/l)	421.4±5.1	340.5±1.4	< 0.001	332.7±4.1	258.8±1.1	< 0.001	< 0.001	< 0.001	< 0.001
WBC (10^9/ml)	6.7±0.1	6.5±0.0	0.088	6.5±0.1	6.0±0.0	< 0.001	0.273	< 0.001	< 0.001
Hb(g/dl)	149.4±1.1	152.0±0.3	0.024	127.4±1.0	132.2±0.3	< 0.001	< 0.001	< 0.001	< 0.001
Hs-CRP (mg/l)	4.5±0.5	2.6±0.1	< 0.001	3.5±0.5	2.3±0.1	0.024	0.603	0.078	0.069
Ferrtin (ng/ml)	193.3±13.3	195.5±3.7	0.873	83.5±6.0	79.5±1.6	0.531	< 0.001	< 0.001	< 0.001

Data are means±SD

BMI: body mass index; HOMA-IR: homeostasis model assessment of insulin resistance; CKD, chronic kidney disease; non-CKD, non-chronic kidney disease; BMI, Body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG: triglycerides; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; Apo B: apolipoprotein B; Lp (a), Lipoprotein (a);FPG, fasting plasma glucose; TyG index: the product of triglycerides and fasting glucose; ALT, alanine aminotransferase; VAI: visceral adiposity index; LAP: lipid accumulation product;. UA, uric acid; WBC, white blood cell count; Hs-CRP, hypersensitive C-reactive protein.

* p value for difference between CKD and non-CKD participants

& Interaction of sex by CKD status

Since CKD is related with age and CVD is related with BMI, then we adjusted age and BMI in Table 2. As the table showed, the mean levels of TC, LDL-C, Non-HDL-C and Apo B of women with CKD were greater than men with CKD under the adjusted of age and BMI. Besides, the differences of WBC between women with CKD and non-CKD ones were more striking than men. Moreover, compared with men with CKD, women with CKD have higher level of Lp(a), VAI and LAP. However, there was little statistical evidence about sex heterogeneity in the association of CKD with TG, TG/HDL, Apo B/apo a1, FPG, HbA1c, HOMA-IR, TyG, ALT and hs-CRP. Also, we observed some interactions between sex with CKD status with statistically significant in some CVD risk factors, such as TC, HDL-C, LDL-C, non-HDL-C, Lp (a), LAP and VAI(all p values < 0.05). After further adjustment for HOMA-IR, there was a little change between women with CKD and men with CKD about the difference of these risk factors (Table 3).

Table 4
Age- and VAI-adjusted mean levels of studied cardiovascular disease risk factors

	Male			Female			M&F		
	CKD	non-CKD	P*	CKD	non-CKD	P*	P(CKD)	P(non-CKD)	P(Interaction)&
N	290	3399		327	3987				
BMI(kg/m^2)	23.3±0.2	23.3±0.1	0.701	22.9±0.2	23.4±0.1	0.012	0.082	0.005	0.001
WC(cm)	84.2±0.6	84.3±0.2	0.844	78.9±0.5	81.4±0.1	< 0.001	< 0.001	< 0.001	< 0.001
SBP(mmHg)	130.3±1.0	125.6±0.3	< 0.001	126.4±1.0	123.4±0.3	0.004	0.358	< 0.001	< 0.001
DBP(mmHg)	82.5±0.7	81.9±0.2	0.331	77.5±0.6	79.2±0.2	0.012	< 0.001	< 0.001	< 0.001
eGFR(ml/min per1.73 m^2)	57.2±1.0	83.6±0.3	< 0.001	58.6±0.7	83.7±0.2	< 0.001	0.122	0.259	0.244
TG(mmol/l)	1.6±0.0	1.6±0.0	0.418	1.5±0.0	1.5±0.0	0.206	< 0.001	< 0.001	< 0.001
TC(mmol/l)	4.8±0.1	4.8±0.0	0.590	5.0±0.1	4.9±0.0	0.010	< 0.001	0.014	< 0.001
HDL-C(mmol/l)	1.3±0.0	1.4±0.0	0.139	1.5±0.0	1.5±0.0	0.251	< 0.001	< 0.001	< 0.001
LDL-C(mmol/l)	3.0±0.1	3.0±0.0	0.358	3.2±0.1	3.0±0.0	0.002	< 0.001	0.003	< 0.001
TG/HDL	1.3±0.0	1.3±0.0	0.124	1.1±0.0	1.1±0.0	0.127	< 0.001	< 0.001	< 0.001
non-HDL(mmol/l)	3.5±0.1	3.4±0.0	0.283	3.5±0.1	3.4±0.0	0.016	0.016	< 0.001	< 0.001
Apo B(g/l)	0.9±0.0	0.9±0.0	0.178	1.0±0.0	0.9±0.0	< 0.001	0.012	< 0.001	0.004
ApoB/apo a1	0.9±0.0	0.9±0.0	0.342	0.8±0.0	0.8±0.0	0.014	0.215	< 0.001	< 0.001
FPG(mmol/l)	5.6±0.1	5.4±0.0	0.009	5.7±0.1	5.3±0.0	< 0.001	0.362	< 0.001	< 0.001
HbA1c (mmol/mol)	5.6±0.0	5.6±0.0	0.359	5.7±0.1	5.6±0.0	0.293	0.779	0.002	0.004
Insulin	1.1±0.0	1.0±0.0	< 0.001	1.1±0.0	1.0±0.0	< 0.001	0.067	0.060	0.017
HOMA-IR	6.3±0.4	3.6±0.1	< 0.001	6.0±0.4	3.4±0.0	< 0.001	0.228	0.002	0.001

Data are means±SD

VAI: visceral adiposity index; CKD, chronic kidney disease; non-CKD, non-chronic kidney disease; BMI, Body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG: triglycerides; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; Apo B: apolipoprotein B; Lp (a), Lipoprotein (a); FPG, fasting plasma glucose; HOMA-IR: homeostasis model assessment of insulin resistance; TyG index: the product of triglycerides and fasting glucose; ALT, alanine aminotransferase; LAP: lipid accumulation product;. UA, uric acid; WBC, white blood cell count; Hs-CRP, hypersensitive C-reactive protein.

* p value for difference between CKD and non-CKD participants

& Interaction of sex by CKD status

	Male			Female			M&F		
TyG index	8.7±0.0	8.6±0.0	0.001	8.6±0.0	8.6±0.0	0.007	< 0.001	< 0.001	< 0.001
ALT	26.3±1.3	27.4±0.4	0.439	20.7±1.0	21.1±0.3	0.679	0.090	< 0.001	< 0.001
LAP	33.6±1.1	33.6±0.3	0.990	34.9±1.0	37.2±0.3	0.023	0.003	< 0.001	< 0.001
Lp (a)(mg/dl)	15.0±1.2	14.3±0.3	0.580	19.4±1.3	16.1±0.4	0.020	0.009	< 0.001	< 0.001
UA(mmol/l)	418.5±4.8	340.7±1.3	< 0.001	329.7±3.8	259.1±1.0	< 0.001	< 0.001	< 0.001	< 0.001
WBC (10^9/ml)	6.7±0.1	6.5±0.0	0.080	6.5±0.1	6.0±0.0	< 0.001	0.087	< 0.001	< 0.001
Hb(g/dl)	149.6±1.1	152.0±0.3	0.034	127.3±1.0	132.2±0.3	< 0.001	< 0.001	< 0.001	< 0.001
Hs-CRP (mg/l)	4.6±0.5	2.6±0.1	< 0.001	3.7±0.5	2.3±0.1	0.009	0.537	0.028	0.021
Ferrtin (ng/ml)	190.4±13.0	195.7±3.7	0.694	82.9±6.0	79.6±1.6	0.594	< 0.001	< 0.001	< 0.001

Data are means±SD

VAI: visceral adiposity index; CKD, chronic kidney disease; non-CKD, non-chronic kidney disease; BMI, Body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG: triglycerides; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; Apo B: apolipoprotein B; Lp (a), Lipoprotein (a); FPG, fasting plasma glucose; HOMA-IR: homeostasis model assessment of insulin resistance; TyG index: the product of triglycerides and fasting glucose; ALT, alanine aminotransferase; LAP: lipid accumulation product;. UA, uric acid; WBC, white blood cell count; Hs-CRP, hypersensitive C-reactive protein.

* p value for difference between CKD and non-CKD participants

& Interaction of sex by CKD status

Table 5
Age-, VAI-, and HOMA-IR- adjusted mean levels of studied cardiovascular disease risk factors

	Male			Female			M&F		
	CKD	non-CKD	P*	CKD	non-CKD	P*	P(CKD)	P(non-CKD)	P(Interaction)&
N	290	3399		327	3987				
BMI(kg/m^2)	23.2±0.2	23.3±0.1	0.875	22.8±0.2	23.4±0.1	0.004	0.108	0.010	0.003
WC(cm)	83.9±0.6	84.3±0.2	0.493	78.7±0.5	81.4±0.1	0.000	< 0.001	< 0.001	< 0.001
SBP(mmHg)	130.1±1.0	125.6±0.3	< 0.001	126.2±1.0	123.4±0.3	0.009	0.357	< 0.001	< 0.001
DBP(mmHg)	82.5±0.7	81.9±0.2	0.361	77.4±0.6	79.2±0.2	0.008	< 0.001	< 0.001	< 0.001
eGFR(ml/min per1.73 m^2)	57.2±1.0	83.5±0.3	< 0.001	58.7±0.7	83.7±0.2	< 0.001	0.129	0.276	0.312
TC(mmol/l)	4.8±0.1	4.8±0.0	0.521	5.0±0.1	4.9±0.0	0.013	< 0.001	0.014	< 0.001
TG(mmol/l)	1.6±0.0	1.6±0.0	0.469	1.5±0.0	1.5±0.0	0.228	< 0.001	< 0.001	< 0.001
LDL-C(mmol/l)	3.0±0.1	3.0±0.0	0.350	3.2±0.1	3.0±0.0	0.005	< 0.001	0.002	< 0.001
HDL-C(mmol/l)	1.3±0.0	1.4±0.0	0.178	1.5±0.0	1.5±0.0	0.222	< 0.001	< 0.001	< 0.001
TG/HDL	1.3±0.0	1.3±0.0	0.140	1.2±0.0	1.1±0.0	0.081	< 0.001	< 0.001	< 0.001
non-HDL(mmol/l)	3.5±0.1	3.4±0.0	0.256	3.5±0.0	3.4±0.0	0.021	0.016	< 0.001	< 0.001
Apo B(g/l)	0.9±0.0	0.9±0.0	0.170	1.0±0.0	0.9±0.0	0.001	0.011	< 0.001	0.005
ApoB/apo a1	0.9±0.0	0.9±0.0	0.404	0.8±0.0	0.8±0.0	0.027	0.220	< 0.001	< 0.001
FPG(mmol/l)	5.4±0.1	5.4±0.0	0.781	5.5±0.1	5.3±0.0	0.001	0.664	< 0.001	< 0.001
HbA1c (mmol/mol)	5.5±0.0	5.6±0.0	0.055	5.6±0.0	5.6±0.0	0.971	0.561	0.008	0.019
Insulin	1.1±0.0	1.0±0.0	0.001	1.1±0.0	1.0±0.0	0.098	0.167	0.986	0.559
TyG index	8.7±0.0	8.6±0.0	0.043	8.6±0.0	8.6±0.0	0.118	< 0.001	< 0.001	< 0.001
ALT	26.1±1.4	27.4±0.4	0.366	20.6±1.0	21.2±0.3	0.588	0.096	< 0.001	< 0.001

Data are means±SD

VAI: visceral adiposity index; HOMA-IR: homeostasis model assessment of insulin resistance; CKD, chronic kidney disease; non-CKD, non-chronic kidney disease; BMI, Body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG: triglycerides; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; Apo B: apolipoprotein B; Lp(a), Lipoprotein (a); FPG, fasting plasma glucose; TyG index: the product of triglycerides and fasting glucose; ALT, alanine aminotransferase; LAP: lipid accumulation product;. UA, uric acid; WBC, white blood cell count; Hs-CRP, hypersensitive C-reactive protein.

* p value for difference between CKD and non-CKD participants

& Interaction of sex by CKD status

	Male			Female			M&F		
LAP	33.1±1.1	33.6±0.3	0.638	34.4±1.0	37.2±0.3	0.005	0.005	< 0.001	< 0.001
Lp (a)(mg/dl)	15.0±1.2	14.3±0.3	0.568	19.2±1.3	16.2±0.4	0.027	0.008	< 0.001	< 0.001
UA(mmol/l)	419.0±4.8	340.7±1.3	< 0.001	329.1±3.8	259.1±1.0	< 0.001	< 0.001	< 0.001	< 0.001
WBC (10^9/ml)	6.7±0.1	6.5±0.0	0.117	6.5±0.1	6.0±0.0	< 0.001	0.110	< 0.001	< 0.001
Hb(g/dl)	149.3±1.1	152.0±0.3	0.019	127.0±1.0	132.2±0.3	< 0.001	< 0.001	< 0.001	< 0.001
Hs-CRP (mg/l)	4.5±0.5	2.6±0.1	< 0.001	3.5±0.5	2.3±0.1	0.031	0.600	0.037	0.032
Ferrtin (ng/ml)	189.7±13.1	195.8±3.7	0.656	81.2±6.0	79.7±1.6	0.805	< 0.001	< 0.001	< 0.001
Data are means±SD									
VAI: visceral adiposity index; HOMA-IR: homeostasis model assessment of insulin resistance; CKD, chronic kidney disease; non-CKD, non-chronic kidney disease; BMI, Body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG: triglycerides; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; Apo B: apolipoprotein B; Lp(a), Lipoprotein (a); FPG, fasting plasma glucose; TyG index: the product of triglycerides and fasting glucose; ALT, alanine aminotransferase; LAP: lipid accumulation product;. UA, uric acid; WBC, white blood cell count; Hs-CRP, hypersensitive C-reactive protein.									
* p value for difference between CKD and non-CKD participants									
& Interaction of sex by CKD status									

The visceral adiposity has a closely relationship with metabolic disorders. Thus, Table 4 adjusted for VAI instead of BMI as a represent of visceral adiposity. Women with CKD had significantly higher levels of TC, LDL-C, non-HDL-C and Apo B than their men counterparts with CKD. The differences of WBC between women with CKD and non-CKD ones was much more significantly than men. Also, women with CKD have higher level of Lp(a) and LAP compared with men with CKD. Besides, the magnitude of differences in HbA1c, ApoB/Apo a1, FPG, Hs-CRP and WBC between different genders with CKD were less marked. The Hb of women with CKD was lower compared with men with CKD. The interactions of sex × CKD mentioned in Table 2 remained significant still. After adjusting the HOMA-IR (Table 5), the difference of these CVD factors between women with CKD and men with CKD remained essentially unchanged.

Discussion

This was a study of the differences between men and women in the comparison of traditional and “non-traditional” CVD markers in CKD patients. Compared with men, women were more likely to have an atherogenic lipid pattern and visceral obese in patients with CKD. Besides, in comparison with the non-CKD counterparts, women with CKD showed greater differences in the value of WBC than men with CKD. The sex differences effect on CVD risk factors of CKD patients and non-CKD ones can’t be eliminated considering with BMI, VAI or HOMA-IR or both.

The level of traditional lipid markers, such as TC, were found to be positively associated with an increased risk of CVD, coronary heart disease (CHD) and cardiac death (CHD plus heart failure) (24). In this research, the value of TC in women with CKD was higher than men. Previous research showed that higher level of LDL-C, non-HDL-C and Apo B indicated a higher incidence of future cardiovascular events (25). In this study, the level of LDL-C, non-HDL-C and Apo B of women with CKD were higher than men with CKD as well, which indicate a worse situation of risk factors of CVD of women with CKD. Thus, the traditional lipid markers of women may need more attention.

In this study, we observed that Lp (a) of women with CKD was significantly higher than that of men with CKD. Lp (a) is one of the cardiovascular factors that have been discovered and showed significantly positively correlated with CVD in previous studies (7). Besides, apolipoprotein(a) bound to apolipoprotein B of an LDL-like particle covalently composed Lp(a) (26) and it mediates atherogenicity by using its LDL moiety. Moreover, Lp(a) can induce the proinflammatory responses as one of its normal function(27). In previous studies, androgens had a greater affection of decreasing the level of Lp(a) compared with estrogens. (28).Besides, most of the women with CKD patients are old, and mostly are in menopause (14). Thus, there is a possibility of women with CKD have a worse situation of Lp(a) compared with men with CKD and we need to promote the realization of Lp (a) in women with CKD.

WBC is also one of the newly discovered cardiovascular risk factors, which participates various stages of cardiovascular disease progression and complication(29). Oxidative stress and inflammation were the important mechanisms for WBC to be considered as a risk factor for CVD in patients with CKD(30). In our study, the value of WBC increased in both women and men with CKD. Moreover, the difference between CKD and non-CKD women was significantly higher than men. It indicated that women may get more serious processes of inflammation from non-CKD to CKD compared with men.

VAI and LAP are important markers of visceral obesity (31) and we found that the level of VAI and LAP in women with CKD were higher than men with CKD in this study. Lots of studies showed that VAI and LAP are associated with a high risk of CVD (32). The INTERHEART study had showed that VAI contributes a lot to CVD risk, evaluating the impact of obesity on CVD(33). Also, woman was found as a risk factor of abdominal obesity in the previous study(34). The specific sex-based mechanisms are still unclear(35). Simultaneously, the LAP is considered as an better index compared with BMI to recognize CVD risk as an index which describes lipid over-accumulation based on WC and fasting triglycerides (36). In this study, compared with BMI, VAI and LAP were more sensitive to reflect the change of lipid pattern in CKD patients. Thus, paying more attention to these two factors instead of BMI only in CKD patients may help doctors to get awareness of CVD risk.

The reasons of the severe condition of the risk factors of CVD of women with CKD may be the following points. Frist, previous studies have shown that autoimmune diseases, pregnancy, dialysis and transplantation lead specific challenges to women with CKD(37, 38). Second, it is not equal among men and women to access the medical care of CKD in lots of places around the world (39). Third, the lost protection of estrogen in women is also a dangerous factor for the risk of CVD in women with CKD(40). Finally, the progress of the times has made women no longer constrained by family life, but also faces more pressure from work and society, especially in China(41).This stress may increase the inflammation of women. It is important to keep the health of families, communities and populations to advocate for improving the access to medical for women (42). Therefore, more attention needed to pay to the risk factors of CVD of women with CKD to aware of the unsatisfactory condition of women with CKD.

Our study had some limitations at the same time. Firstly, it was difficult to explain whether the CKD in women will experience worse changes in visceral adiposity, some lipid profile and TyG during the process of CKD because of the cross-sectional study design. Second, since we only have the only one blood sample, the definition of CKD may not exactly as it showed. Finally, the causality between the greater relative CVD risk and these great change in the CVD risk factors among women with CKD was hard to find. However, there were also some strengths of our study, such as these data used in this study were population-based. Also, covariates of interest in this research were assessed in detail. Some non-traditional risk factors such as inflammation markers and visceral adiposity were included and they were calculated as well.

Conclusions

In summary, our study documented that CKD women had a tendency of having worse CVD risk factors than men. Increased CVD risk factors were observed in this study in both genders with CKD. CKD women had higher value of CVD risk factors than men. Moreover, the greater changes in some CVD risk factors of women with CKD compared with man were independent of important factors, such as BMI, age, visceral adiposity or HOMA-IR. These important findings may help to suggest the increased relative CVD risk in CKD women compared with men.

Abbreviations

Abbreviations	
CVD	Cardiovascular disease
CKD	Chronic kidney disease
Lp (a)	Lipoprotein (a)
WBC	White blood cell
VAI	Visceral adiposity index
LAP	Lipid accumulation product
CHNS	China Health and Nutrition Survey
BMI	Body mass index
TG	Triglycerides
HDL-C	High density lipoprotein cholesterol
WC	Waist circumference
BP	Blood pressure
WHO	World Health Organization
FPG	Fasting plasm glucose
HbA1c	Hemoglobin A1c
TG	Triglycerides
LDL-C	Low density lipoprotein cholesterol
ALT	alanine aminotransferase
UA	Uric acid
hs-CRP	Hypersensitive C-reactive protein
eGFR	Estimated glomerular filtration rate
HOMA-IR	Homeostasis model assessment of insulin resistance
TyG	triglycerides and glucose index

Declarations

Ethics approval and consent to participate:

the institutional review committees of the University of North Carolina at Chapel Hill, the National Institute of Nutrition and Food Safety, Chinese Center for Disease Control and Prevention, and the China-Japan Friendship Hospital, Ministry of Health Each approved this survey and participant provided a written informed consent

Consent for publication:

Not applicable

Availability of data and materials:

The datasets generated and/or analysed during the current study are available in the China Health and Nutrition Survey repository, https://www.cpc.unc.edu/projects/china

Competing interests:

The authors declare that they have no competing interests

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Author contributions:

ZFW and NHZ had full access to all of the data in the study and takes responsibility for the accuracy of the data analysis. SWG, GX and ZFW developed study concept and design. WZF, NHZ, RL, CYC, CD, and TTL performed the statistical analyses, and drafted the manuscript. GX and SWG obtained the funding and supervised the study.

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