Research Article

The Cumulative Exposure to High-Sensitivity C-Reactive Protein Predicts the Risk of Chronic Kidney Diseases

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Keywords

Chronic kidney diseases · High-sensitivity C-reactive protein · Estimated glomerular filtration rate · Proteinuria · Cohort study

Abstract

Background and Objectives: This study was to characterize the association of cumulative exposure to increased high-sensitivity C-reactive protein (hs-CRP) with chronic kidney diseases (CKD). **Methods:** We included 35,194 participants with hs-CRP measured at three examinations in 2006, 2008, 2010. Participants were classified into nonexposed group (hs-CRP <3.0 mg/L in all 3 examinations), 1-exposed group (hs-CRP ≥3.0 mg/L in 1 of the 3 examinations), 2-exposed group (hs-CRP ≥3.0 mg/L in 2 of the 3 examinations), and 3-exposed group (hs-CRP ≥3.0 mg/L in 3 examinations). Cox proportional hazards models were used to assess the association of cumulative hs-CRP with incident CKD. CKD includes an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² or urinary protein positive. **Results:** The study showed the risk of CKD as the number of years of exposure to hs-CRP increases. Participants in 3-exposed group had significantly increased CKD risk with hazard ratio (HR) (95% confidence interval, CI) of 1.70 (1.49–1.93), in comparison with 1.47 (1.34–1.62) for participants in the 2-exposed group, and 1.08 (1.00–1.16) for those in the 1-exposed group ($p < 0.01$); meanwhile, the similar and significant associations were also observed for eGFR <60 mL/min/1.73

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m², proteinuria positive, in participants of the 3-exposed group in comparison with the non-exposed group, with respective HRs (95% CI) of 1.27 (1.01–1.58) and 2.27 (1.87–2.76). **Conclusions:** Cumulative exposure to hs-CRP was associated with a subsequent increased risk of CKD and was of great value to risk prediction.

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Introduction

Chronic kidney disease (CKD) is a clinical syndrome characterized by abnormality in kidney structure or function. In the United States, the prevalence of CKD as diagnosed by estimated glomerular filtration rate (eGFR) and proteinuria is 11.5% [1]. According to the Chinese Epidemiology Surveillance in 2012, CKD prevalence in Chinese adults was 10.8%, with a total case number of 120 million [2]. Elevated inflammatory markers are important risk factors for CKD [3]. In animal models, inflammation process has been proved to be essentially involved in the progression of kidney diseases [4–8]. Tonelli et al. [9] found that higher baseline C-reactive protein (CRP) would accelerate kidney function failure in CKD patients.

So far, studies on the association between CRP and CKD have generated conflicting results. Some studies reported that CRP, fibrinogen, and serum albumin were related to rapid reduction of eGFR [10, 11]. Hiramoto et al. [12] found that in CKD patients, CRP concentration was significantly associated with kidney function recession. Kugler et al. [13] found that elevated CRP significantly increased risk of CKD. However, other studies reported no association. Studies by Sarnak et al. [14] found that higher CRP was not an independent risk factor for nondiabetic kidney disease progression. Shankar et al. [15] found that increase in CRP would not result in higher CKD risk. Previous studies on the relationship between high-sensitivity CRP (hs-CRP) and CKD were mostly based on single hs-CRP measurement, whereas hs-CRP concentration is affected by many factors, such as metabolic factors (e.g., obesity, diabetes), environmental factors, and underlying infections. A single measure of hs-CRP might not accurately indicate the association between inflammatory markers and CKD. Moreover, there are few longitudinal studies using hs-CRP to predict CKD incident risk in the general population. The Kailuan Study (registration No. ChiCTR-TNC-11001489) is a cohort study on risk factors for cardiovascular diseases based on a community population. Participants received biennial health examinations on cardio health risk factors including serum creatinine (sCr), urinary protein, and hs-CRP, which enables our study to gain insight into the association between cumulative hs-CRP exposure and CKD risk.

Materials and Methods

Study Population

From 2006 to 2007, 11 hospitals in the Kailuan community, including Kailuan General Hospital and its affiliated hospitals, recruited and provided health examinations for current and former employees of the Kailuan Company. Hence, the health providers provided following health examinations every 2 years. We included participants who participated in the 2006–2007, 2008–2009, and 2010–2011 health examinations to observe the association between three-time hs-CRP exposure level and future CKD incidence. This study followed the Declaration of Helsinki and was approved by the Ethical Board of Kailuan General Hospital.

The inclusion criteria of this study were: those from the Kailuan Study who participated in the 2006–2007, 2008–2009, and 2010–2011 health examinations, had complete hs-CRP data, had complete sCr and urinary protein data, and consented and signed to participate in

this study. The exclusion criteria were: those who participated in the examinations but had missing hs-CRP values of either of the three times, had had CKD prior to 2010, or had missing data of sCr and urinary protein.

Assessment of Serum hs-CRP, Creatinine, and Urinary Protein

Detailed epidemiology research designs, anthropometry measurements, and related biochemical tests have been described in previous publications from our group [16]. Serum hs-CRP was quantified by an immunoturbidimetry assay (Kanto Chemical Co. Inc., Tokyo, Japan). The laboratory proficiency testing administered by the Ministry of Health from 2006 to 2009 was 100%. The reference interval was 0–5.0 mg/L, and the lower limit of detection was 0.1 mg/L, as tested by a HITACHI 7600 automated analyzer (Hitachi Ltd., Tokyo, Japan).

sCr was quantified by enzymatic method (Shanghai Mingdian Bioengineering, Shanghai, China) on a Hitachi 7600 P auto-analyzer (Hitachi Ltd., Tokyo, Japan). Both the intra- and inter-assay coefficients of variation were <10%, and linearized standard curve ranged from 44 to 106 μ mol/L. The test followed the manufacturer's recommendation and was in accordance with the Ministry of Health proficiency test. The routine urine test used urine dry chemistry and urine sediment methods (H12-MA test paper and a DIRUI-600 urine analysis system [Changchun Dirui Medical Co., Ltd., Beijing, China]). Urinary protein was tested by a semi quantitative method, where <15 mg/dL means "negative," 15–29 mg/dL mean "traces," 30–300 mg/dL means "+," 300–1,000 mg/dL means "++," and >1,000 mg/dL means "+++."

Assessment of Covariates

Smoking was defined as at least 1 cigar/day in the past 1 year. Drinking was defined as consuming 100 mL hard liquor (ethanol content >50%) daily in the past 1 year. Active physical activity was defined as ≥ 3 times/week physical exercise, with ≥ 30 min every time. Height and weight were measured by trained nurses, and body mass index (BMI) was calculated as weight (kg)/height (m^2). Hypertension was diagnosed as systolic blood pressure (SBP) ≥ 140 mm Hg or diastolic blood pressure (DBP) ≥ 90 mm Hg or using antihypertensive drugs currently. Diabetes was diagnosed as fasting blood glucose (FBG) ≥ 7.0 mmol/L or using anti-diabetic drugs currently. Hyperlipidemia was diagnosed as total cholesterol (TC) ≥ 5.2 mmol/L or triglyceride ≥ 1.7 mmol/L or low-density lipoprotein cholesterol ≥ 3.4 mmol/L or using lipid-lowering agents currently [17].

Cumulative Exposure to hs-CRP

We defined hs-CRP ≥ 3.0 mg/L as exposed to inflammation. We classified participants into 4 groups: the nonexposed group had all 3 hs-CRP measurements <3.0 mg/L, the 1-exposed group had hs-CRP ≥ 3.0 mg/L in 1 out of 3 examinations, the 2-exposed group had hs-CRP ≥ 3.0 mg/L in 2 out of 3 examinations, and the 3-exposed group had hs-CRP ≥ 3.0 mg/L in all 3 examinations.

Calculation of eGFR

We estimated GFR according to the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula [18]. For women, if sCr ≤ 0.7 : $eGFR = 144 \times (sCr/0.7)^{-0.329} \times 0.993^{Age}$; if sCr >0.7: $eGFR = 144 \times (sCr/0.7)^{-1.209} \times 0.993^{Age}$. For men, if sCr ≤ 0.9 : $eGFR = 144 \times (sCr/0.9)^{-0.411} \times 0.993^{Age}$; if sCr >0.9: $eGFR = 144 \times (sCr/0.9)^{-1.209} \times 0.993^{Age}$, where the unit of sCr is in mg/dL.

Outcomes

We defined incident CKD as first occurrence of either eGFR <60 mL/min/1.73 m^2 or positive proteinuria [19]. Follow-up of each participants started at the examination date in 2010–2011 and ended at the last health examination (2014–2015) or the incidence of CKD.

Fig. 1. Study flowchart.

Statistical Analysis

Health examination data were recorded by trained staff and uploaded to Kailuan General Hospital Server. Data were analyzed in SAS 9.2 (SAS Institute, Inc., Cary, NC, USA). Quantitative variables were presented as mean $\pm$ standard deviation, using one-way analysis of variance for test of difference between groups and list significance test for pairwise comparison. Categorical variables were presented as number and percentage (%), using chi-square test for intergroup difference. We compared incidence rate of CKD across cumulative hs-CRP exposed groups and further used Cox proportional hazards model to calculate hazard ratio (HR) and 95% confidence interval (CI). All tests were two-sided, and p value <0.05 was considered as statistically significant.

To exclude confounding factors such as acute inflammation and use of lipid-lowering agents, antihypertensive drugs, or antidiabetic drugs, we excluded participants that met these criteria, respectively, and conducted sensitivity analysis in the Cox proportional hazards model.

Results

Baseline Characteristics

There were 57,927 participants who participated in the 2006–2007, 2008–2009, and 2010–2011 health examinations. 2,758 were excluded for missing hs-CRP result in either of the examinations; 12,815 were excluded for diagnosed CKD prior to 2006 and 1,506 were

Table 1. Baseline general characteristics of the 35,194 individuals selected for study

Variables	Years of exposure to cumulative hs-CRP				p value
	nonexposed (n = 19,993)	1-exposed (n = 9,522)	2-exposed (n = 3,896)	3-exposed (n = 1,783)	
Male	15,362 (77)	7,446 (78)	2,951 (76)	1,235 (69)	<0.001
Age, years	52±11	53±11	57±11	59±11	<0.001
Baseline SBP, mm Hg	124±18	126±18	130±20	132±20	<0.001
Baseline DBP, mm Hg	81±11	82±11	84±11	84±11	<0.001
BMI	24.5±3.3	25.2±3.4	25.8±3.6	26.1±3.9	<0.001
FPG, mmol/L	5.3±1.3	5.4±1.4	5.4±1.5	5.4±1.8	<0.001
TC, mmol/L	4.9±1.1	5.0±1.1	5.0±1.0	5.1±1.0	<0.001
Baseline eGFR, mL/min/1.73 m ²	86.6±20.4	86.2±22.1	86.3±19.8	86.0±19.8	0.214
Current smokers	6,683 (33.4)	3,182 (33.4)	1,020 (26.2)	415 (23.3)	<0.001
Current drinkers	3,992 (20)	1,786 (18.8)	576 (14.8)	213 (12.0)	<0.001
Physical activity	2,701 (13.5)	1,167 (12.3)	419 (10.8)	170 (9.5)	<0.001
Hypertension	5,792 (29.0)	3,385 (35.6)	1,874 (48.1)	1,008 (56.5)	<0.001
Diabetes mellitus	1,202 (6.0)	719 (7.6)	666 (17.1)	398 (22.3)	<0.001
Hyperlipidemia	8,971 (44.9)	4,857 (51.0)	2,097 (53.8)	994 (55.8)	<0.001
Antihypertensive medication	1,491 (7.5)	813 (8.5)	377 (9.7)	213 (12.0)	<0.001
Antidiabetic medication	321 (1.6)	152 (1.6)	79 (2.0)	46 (2.6)	<0.001
Lipid-lowering medication	181 (0.9)	62 (0.6)	31 (0.8)	21 (1.2)	<0.001
06hs-CRP, mg/L	0.44 (0.20–0.92)	1.00 (0.36–2.70)	3.90 (1.71–7.60)	7.00 (4.70–9.50)	<0.001
08hs-CRP, mg/L	0.91 (0.55–1.56)	2.50 (1.18–4.00)	4.30 (3.30–6.10)	5.40 (4.11–7.90)	<0.001
10hs-CRP, mg/L	0.80 (0.40–1.30)	1.66 (0.80–3.60)	3.10 (1.20–5.03)	5.70 (4.10–8.96)	<0.001

Data are n (%), mean ± SD, or mean (interquartile range). Baseline DBP, diastolic blood pressure in 2006; baseline SBP, systolic blood pressure in 2006; BMI, body mass index; hs-CRP, high-sensitivity C-reactive protein; FPG, fasting plasma glucose; TC, total cholesterol; baseline eGFR, estimated glomerular filtration rate in 2006; 06hs-CRP, high-sensitivity C-reactive protein in 2006; 08hs-CRP, high-sensitivity C-reactive protein in 2008; 10hs-CRP, high-sensitivity C-reactive protein in 2010.

Table 2. Incidence of CKD events in different hs-CRP exposure groups (per thousand persons per year)

Variables	Years of exposure to cumulative hs-CRP				p value
	nonexposed (n = 19,993)	1-exposed (n = 9,522)	2-exposed (n = 3,896)	3-exposed (n = 1,783)	
eGFR <60 mL/min/1.73 m ²	802 (10.4)	415 (11.2)	248 (17.1)	117 (17.7)	<0.01
Proteinuria positive	621 (8.0)	361 (9.7)	243 (16.8)	163 (24.9)	<0.01
CKD	1,391 (18.2)	753 (20.6)	470 (33.2)	268 (42.0)	<0.01

eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease.

excluded for incident CKD during 2006–2010 and 5,654 were excluded for missing sCr and urinary protein results. The final study population included 35,194 participants (Fig. 1). Mean age was 53 ± 11 years. There were 26,994 men (76.7%). After categorizing the study population into exposure groups (the nonexposed, 1-exposed, 2-exposed, and 3-exposed groups), we found that participants in the higher exposure groups tended to have higher age, baseline SBP, DBP, BMI, FBG, and TC. They also had higher prevalence of hypertension and diabetes. Between-group comparisons showed significant difference ($p < 0.001$, Table 1), while for baseline eGFR, between-group comparisons showed nonsignificant difference ($p = 0.214$, Table 1). In addition, we compared group average and interquartile range of hs-CRP concentration in three examinations across exposure groups ($p < 0.001$, Table 1).

Incidence of CKD in hs-CRP Exposure Groups

During an average follow-up time of 3.96 ± 0.48 years, there were 2,882 incident CKD cases, including 1,582 cases of eGFR <60 mL/min/1.73 m² and 1,388 cases of positive

Table 3. Adjusted HRs and 95% CI of cumulative hs-CRP for CKD by Cox proportional hazards models

Variables	eGFR <60 mL/min/ 1.73 m ² HR (95% CI)	Proteinuria positive HR (95% CI)	CKD HR (95% CI)
Model 1 ^a			
nonexposed	1	1	1
1-exposed	1.04 (0.93–1.17)	1.19 (1.05–1.36)	1.10 (1.01–1.20)
2-exposed	1.42 (1.24–1.65)	2.05 (1.77–2.38)	1.69 (1.52–1.88)
3-exposed	1.31 (1.08–1.59)	2.99 (2.51–3.57)	2.01 (1.76–2.30)
<i>p</i> _{trend}	<0.01	<0.01	<0.01
Model 2 ^b			
nonexposed	1	1	1
1-exposed	1.03 (0.92–1.16)	1.14 (1.00–1.30)	1.07 (0.98–1.17)
2-exposed	1.33 (1.15–1.55)	1.80 (1.54–2.10)	1.53 (1.37–1.71)
3-exposed	1.17 (0.95–1.44)	2.41 (2.00–2.90)	1.70 (1.48–1.96)
<i>p</i> _{trend}	<0.01	<0.01	<0.01
Model 3 ^c			
nonexposed	1	1	1
1-exposed	1.05 (0.93–1.19)	1.13 (0.99–1.28)	1.08 (0.98–1.18)
2-exposed	1.40 (1.19–1.64)	1.74 (1.48–2.04)	1.54 (1.37–1.72)
3-exposed	1.26 (1.01–1.58)	2.29 (1.88–2.78)	1.72 (1.48–1.99)
<i>p</i> _{trend}	<0.01	<0.01	<0.01

*p*_{trend}, test of trend based on median value in each category for ordinal categorical variables; hs-CRP, high-sensitivity C-reactive protein; CKD, chronic kidney diseases; HR, hazard ratio; CI, confidence interval. ^a Model 1: adjusted for age and sex. ^b Model 2: adjusted for variables in Model 1 plus baseline SBP, BMI, FPG, TC, physical activity, smoking, drinking, and treatment of antihypertensive, antidiabetic, and lipid-lowering medication. ^c Model 3: Model 2 plus hs-CRP in 2006.

proteinuria. There was a trend for higher CKD incidence rate associated with more hs-CRP exposure. The incidence rate for 1-exposed, 2-exposed, and 3-exposed cumulative hs-CRP groups were 20.6, 33.2, and 42.0 per 1,000 person-years, respectively. Incidence rates of eGFR <60 mL/min/1.73 m² and proteinuria were individually positively associated with hs-CRP exposure (*p* < 0.05, Table 2).

Cox Proportional Hazards Model for CKD Risk Factors

In the Cox proportional hazards model, we used cumulative hs-CRP exposure as explanatory variable (nonexposed group as reference) and eGFR <60 mL/min/1.73 m², proteinuria, and overall CKD as outcome, respectively. Model 1 was adjusted for sex and age, model 2 was further adjusted for baseline SBP, BMI, FBG, TC, physical activity, smoking, alcohol drinking, and use of antihypertensive, antidiabetic, and lipid-lowering drugs, based on model 1, while model 3 was further adjusted for baseline (2006) hs-CRP, based on model 2. We found that, compared to the nonexposed group, the hs-CRP 3-exposed group had higher HR of 1.26 (95% CI: 1.01–1.58) for eGFR <60 mL/min/1.73 m², 2.29 (95% CI: 1.88–2.78) for proteinuria, and 1.72 (95% CI: 1.48–1.99) for CKD (*p* for trend <0.01, Table 3).

In addition, we used baseline (2006) hs-CRP as explanatory variable and adjusted as in model 2. The HR (95% CI) was 1.02 (1.01–1.02) for proteinuria and 1.01 (1.00–1.01) for CKD; for eGFR <60 mL/min/1.73 m², the HR (95% CI) was 1.00 (0.99–1.01) (online supplementary Table S1, DOI: 10.6084/m9.figshare.9960035).

Log likelihood ratio test and Akaike information criterion was used to calculate effect of hs-CRP indicators on CKD model fit. A multivariate model (model A) included sex, age, baseline SBP, BMI, FBG, TC, physical activity, smoking, alcohol drinking, and use of antihypertensive, antidiabetic, and lipid-lowering drugs; baseline hs-CRP or cumulative hs-CRP was then added

Table 4. Adjusted HRs and 95% CI of cumulative hs-CRP for end point events by Cox proportional hazards models (sensitive analyses)

Variables		eGFR <60 mL/min/ 1.73 m ² HR (95% CI)	Proteinuria positive HR (95% CI)	CKD HR (95% CI)
Model 4	nonexposed	1	1	1
	1-exposed	1.04 (0.91–1.19)	1.01 (0.88–1.17)	1.02 (0.92–1.13)
	2-exposed	1.23 (1.00–1.50)	1.32 (1.06–1.63)	1.27 (1.10–1.42)
	3-exposed	1.19 (0.88–1.60)	1.52 (1.15–2.04)	1.36 (1.10–1.68)
	<i>p</i> _{trend}	<0.01	<0.01	<0.01
Model 5	nonexposed	1	1	1
	1-exposed	1.04 (0.91–1.19)	1.01 (0.88–1.17)	1.02 (0.92–1.13)
	2-exposed	1.23 (1.00–1.50)	1.32 (1.06–1.63)	1.27 (1.09–1.48)
	3-exposed	1.19 (0.88–1.60)	1.53 (1.15–2.04)	1.36 (1.10–1.68)
	<i>p</i> _{trend}	<0.01	<0.01	<0.01
Model 6	nonexposed	1	1	1
	1-exposed	1.08 (0.95–1.22)	1.08 (0.93–1.25)	1.08 (0.98–1.19)
	2-exposed	1.39 (1.17–1.65)	1.76 (1.47–2.11)	1.56 (1.38–1.77)
	3-exposed	1.14 (0.87–1.48)	2.69 (2.17–3.35)	1.79 (1.51–2.12)
	<i>p</i> _{trend}	<0.01	<0.01	<0.01
Model 7	nonexposed	1	1	1
	1-exposed	1.13 (0.96–1.33)	1.09 (0.91–1.31)	1.12 (0.99–1.29)
	2-exposed	1.60 (1.29–2.00)	1.67 (1.31–2.13)	1.65 (1.39–1.95)
	3-exposed	1.11 (0.75–1.62)	2.40 (1.74–3.32)	1.70 (1.32–2.19)
	<i>p</i> _{trend}	<0.01	<0.01	<0.01

*p*_{trend}: test of trend based on median value in each category for ordinal categorical variables. CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; CKD, chronic kidney diseases; HR, hazard ratio. Model 4: Model 3 excluding the subjects with hs-CRP ≥10 mg/L during 3 examinations. Model 5: Model 3 excluding subjects under treatment of lipid-lowering medication and antihypertensive medication. Model 6: Model 3 excluding delete new-onset diabetes in 2006–2010 and people with diabetes in 2006. Model 7: Model 3 excluding delete the new high blood pressure population in 2006–2010 and having already had hypertension in 2006.

to model A. The model $-2 \log L$ was 55,767 for model A + cumulative hs-CRP and 55,776 for model A + baseline hs-CRP, with statistically significant difference ($\chi^2 = 76.4$, $p < 0.01$).

Sensitivity Analysis

In the sensitivity analyses, exclusion of the participants with hs-CRP >10 mg/L, diabetes, hypertension, and taking antihypertensive drugs, hypoglycemic agents, and lipid-lowering medication generated similar results compared to nonexposed group and cumulative hs-CRP 3-exposed group in relation to odds of having CKD or high or very high CKD risk, whereas no significant difference in HR was found for eGFR <60 mL/min/1.73 m² (Table 4).

We also have conducted several sensitive analyses between cumulative hs-CRP and chronic kidney disease among subgroup population (smokers/nonsmokers, hypertensive/non-hypertensive, diabetes mellitus/non-diabetes mellitus) (supplementary Table S2, DOI: 10.6084/m9.figshare.9960035). The results showed that, compared to the nonexposed group, the participants with cumulative hs-CRP-exposed groups had higher risk for CKD. Furthermore, the CKD risks in the population of nonsmokers, non-hypertensive, non-diabetes mellitus, and non-hyperlipidemia were much higher than in the population with smoking, hypertensive, diabetes, and hyperlipidemia ($p < 0.01$).

Discussion

This study showed that incidence of CKD and proteinuria was positively associated with cumulative hs-CRP exposure. Incidence rate of CKD and proteinuria in the cumulative hs-CRP 3-exposed group was twice and three times higher, respectively, compared to that of the nonexposed group. A trend for higher incidence rate of eGFR <60 mL/min/1.73 m² with increased hs-CRP exposure was also identified. Previous study found that in a metabolically healthy obese (MHO) population, during 3.9 years of follow-up, CKD incidence in the MHO/hs-CRP ≥ 0.2 mg/L group (10.3%) was significantly greater than that of the MHO/hs-CRP <0.2 mg/L group (6.5%) [20]. Hemmelgarn et al. [21] found that, compared to patients with lowered eGFR but negative urinary protein, patients characterized by severe proteinuria but normal eGFR had much worse clinical outcomes. By comparing incidence rate in a prospective cohort, we found that higher cumulative hs-CRP exposure status was significantly associated with higher incidence rate of CKD, especially proteinuria. This association was more consistent for proteinuria and kidney damage.

Moreover, we found that cumulative exposure to high hs-CRP was a risk factor for kidney damage. Compared to the nonexposed group, the 3-exposed group had a 0.72 times higher risk of CKD; for proteinuria, the risk was 1.29 times higher and for eGFR <60 mL/min/1.73 m², 0.26 times higher. More exposure to high hs-CRP was positively associated with higher risk of kidney damage and proteinuria. The study by Stuveling et al. [22] found that in nondiabetic population, higher CRP concentration was strongly related with lower eGFR (odds ratio = 1.9; 95% CI: 1.3–2.9). Other studies reported that in older populations, high CRP concentration was associated with higher sCr, lower eGFR, and higher CKD risk [10, 23, 24]. Meanwhile, a previous study also found no association between baseline hs-CRP and incident CKD [15]. However, these studies were mostly focused on a single measure of hs-CRP, without considering the fluctuation and cumulative effect of hs-CRP across a long time span. Therefore, this study is more informative in studying the association between cumulative measures of hs-CRP and incident CKD.

Due to the large sample size and relatively long follow-up period, to test the stability of our models, we used log likelihood ratio test and Akaike information criterion to compare model fitness of hs-CRP markers. The result showed that after adjustment for baseline hs-CRP, adding cumulative exposure to hs-CRP into the model generated better prediction. To minimize confounding factors such as acute inflammation, infectious disease, hypertension, diabetes, and medication, we excluded participants with these clinical features and found even higher risk for kidney damage, with a 70% higher risk of the 3-exposed group compared to nonexposure. Kugler et al. [13], in a historical prospective study on the association between CRP and CKD, found that higher CRP was positively associated with CKD risk, and this prediction value was more significant in population with diabetes, hypertension, and eGFR between 60 and 90 mL/min/1.73 m². However, these findings were not in concordance with our result. We had conducted several sensitive analyses between cumulative hs-CRP and CKD among subgroup population, and it was found that the CKD risks in the population of nonsmokers, non-hypertensive, non-diabetes mellitus, and non-hyperlipidemia were much higher. In Kugler et al.'s research [13], where CRP values for each subject were calculated as a mean for all visits, some of the data was retrospectively analyzed and was prone to bias. Our Kailuan Study consists of longitudinal studies in general population. So it is much more meaningful to monitor hs-CRP in healthy population in order to decrease the CKD risk. We look forward to more prospective cohort studies for further validation.

Several potential mechanism might explain the association between inflammation and CKD. First, epidemiology studies showed that elevated CRP concentration was associated

with atherosclerosis [25]. Atherosclerosis and glomerulosclerosis are the most common pathways for many types of kidney damage. Mesangium enlargement shares many similar characteristics as over-proliferation of pulmonary arterial smooth muscle cells [26]. CRP might reflect the inflammation process involved in glomerulosclerosis. Second, inflammatory cascade induced by macrophages and monocytes could damage tubular interstitial cells. This is a common characteristic in many non-immune kidney diseases (e.g., diabetes, hypertension, anemia, and proteinuria) [27]. Third, in human endothelial cells, CRP triggers adhesion molecules to produce interleukin 6 (IL-6) and monocyte chemoattractant protein-1 (MCP-1). These could increase inflammatory level in the plaque by attracting more monocytes and lymphocytes, which in turn induce endothelial damage, inflammation, and kidney damage. Fourth, risk factors for kidney function loss, such as obesity, smoking, hypertension, diabetes, and inadequate physical activity, are commonly associated with elevated CRP and inflammatory status [28, 29].

This study found that cumulative exposure to high hs-CRP was associated with risk of CKD. However, there are limitations to be addressed. First, this study had a relatively short follow-up time of an average 3.96 years, but since this is an ongoing cohort study with biannual examinations and follow-ups every half year, we can possibly relook at and test our results in the future. Also, urinary protein test was based on a single urine sample in a semiquantitative way instead of quantitative measure using 24-hour urine samples. This might cause misclassification of CKD. However, due to its higher sensitivity (93.3%) and specificity (91.6%) in comparison to quantitative method [30] and its easy, fast, and cheap nature, the semiquantitative method has been widely used in large-scale epidemiology studies. Second, The data of eGFR were calculated indirectly from sCr measurement during the healthy examination. The participants with abnormal level of sCr would be recommended to visit the nephrology clinic and clarified a diagnosis of chronic kidney disease by monitoring sCr level. However, we have no detailed description of acute kidney disease, this is a limitation of our study. Last but not least, participants of this study might not be representative of other populations. This finding needs to be tested in future studies.

This study highlights cumulative exposure to high hs-CRP as a risk factor for incident CKD. Controlling hs-CRP at a relatively low level could possibly reduce risk of kidney damage. Future studies should focus on the association between CRP and incidence and progression of CKD, and whether low hs-CRP exposure might predict improvement in kidney function in longitudinal cohorts. These studies might provide evidence for targeting hs-CRP as whole-body inflammatory markers for CKD prevention and treatment.

Conclusions

In a large-scale community-based prospective cohort study ($n = 35,194$), cumulative exposure to hs-CRP was associated with a subsequent increased risk of CKD and was of great value to risk prediction. This study highlights cumulative exposure to high hs-CRP as a risk factor for incident CKD.

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Statements of Ethics

Studies on human subjects were conducted in accordance with the Declaration of Helsinki. Accordingly, the authors declare that subjects have given their informed written consent and that the study protocol was approved by an appropriate ethics committee.

Disclosure Statement

All the authors declare no conflict of interest and no funding source.

Author Contributions

Jingli Gao, Xiaolan Li, Shouling Wu contributed to the conception of the study. Jingli Gao, Aitian Wang, Shouling Wu, Shuohua Chen contributed significantly to analysis and manuscript preparation. Jingli Gao, Aitian Wang, Xiaolan Li, Hualing Zhao performed the data analyses and wrote the manuscript. Junjuan Li, Jianjun Zhang, Jingtao Liang, Shouling Wu helped perform the analysis with constructive discussions.

References

- 1 Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009 May 5;150(9):604–12.
- 2 Zhang L, Wang H. Current status and challenges of chronic kidney disease in China-Enlightenment from epidemiological investigation of chronic kidney disease in China. *Chin J Integr Med*. 2012;51(7):497–8.
- 3 Fox CS, Larson MG, Leip EP, Culleton B, Wilson PW, Levy D. Predictors of new-onset kidney disease in a community-based population. *JAMA*. 2004 Feb;291(7):844–50.
- 4 Remuzzi G, Bertani T. Pathophysiology of progressive nephropathies. *N Engl J Med*. 1998 Nov;339(20):1448–56.
- 5 Bertani T, Abbate M, Zoja C, Corna D, Perico N, Ghezzi P, et al. Tumor necrosis factor induces glomerular damage in the rabbit. *Am J Pathol*. 1989 Feb;134(2):419–30.
- 6 Tomosugi NI, Cashman SJ, Hay H, Pusey CD, Evans DJ, Shaw A, et al. Modulation of antibody-mediated glomerular injury in vivo by bacterial lipopolysaccharide, tumor necrosis factor, and IL-1. *J Immunol*. 1989 May;142(9):3083–90.
- 7 Pai R, Ha H, Kirschenbaum MA, Kamanna VS. Role of tumor necrosis factor- α on mesangial cell MCP-1 expression and monocyte migration: mechanisms mediated by signal transduction. *J Am Soc Nephrol*. 1996 Jun;7(6):914–23.
- 8 Khan SB, Cook HT, Bhargal G, Smith J, Tam FW, Pusey CD. Antibody blockade of TNF- α reduces inflammation and scarring in experimental crescentic glomerulonephritis. *Kidney Int*. 2005 May;67(5):1812–20.
- 9 Tonelli M, Sacks F, Pfeffer M, Jhangri GS, Curhan G; Cholesterol and Recurrent Events (CARE) Trial Investigators. Biomarkers of inflammation and progression of chronic kidney disease. *Kidney Int*. 2005 Jul;68(1):237–45.
- 10 Fried L, Solomon C, Shlipak M, Seliger S, Stehman-Breen C, Bleyer AJ, et al. Inflammatory and prothrombotic markers and the progression of renal disease in elderly individuals. *J Am Soc Nephrol*. 2004 Dec;15(12):3184–91.
- 11 Keller C, Katz R, Sarnak MJ, Fried LF, Kestenbaum B, Cushman M, et al.; CHS study. Inflammatory biomarkers and decline in kidney function in the elderly: the Cardiovascular Health Study. *Nephrol Dial Transplant*. 2010 Jan;25(1):119–24.
- 12 Hiramoto JS, Katz R, Peralta CA, Ix JH, Fried L, Cushman M, et al. Inflammation and coagulation markers and kidney function decline: the Multi-Ethnic Study of Atherosclerosis (MESA). *Am J Kidney Dis*. 2012 Aug;60(2):225–32.
- 13 Kugler E, Cohen E, Goldberg E, Nardi Y, Levi A, Krause I, et al. C reactive protein and long-term risk for chronic kidney disease: a historical prospective study. *J Nephrol*. 2015 Jun;28(3):321–7.
- 14 Sarnak MJ, Poindexter A, Wang SR, Beck GJ, Kusek JW, Marcovina SM, et al. Serum C-reactive protein and leptin as predictors of kidney disease progression in the Modification of Diet in Renal Disease Study. *Kidney Int*. 2002 Dec;62(6):2208–15.

- 15 Shankar A, Sun L, Klein BE, Lee KE, Muntner P, Nieto FJ, et al. Markers of inflammation predict the long-term risk of developing chronic kidney disease: a population-based cohort study. *Kidney Int.* 2011 Dec;80(11):1231–8.
- 16 Wu S, Huang Z, Yang X, Zhou Y, Wang A, Chen L, et al. Prevalence of ideal cardiovascular health and its relationship with the 4-year cardiovascular events in a northern Chinese industrial city. *Circ Cardiovasc Qual Outcomes.* 2012 Jul;5(4):487–93.
- 17 Joint Committee for the Revision of the Guidelines for Prevention and Treatment of Dyslipidemia. Guidelines for the prevention and treatment of dyslipidemia in Chinese adults (revised edition 2016). *Chinese Journal of Cardiovascular Diseases.* 2016;44(10):833–53.
- 18 Rognant N, Lemoine S, Laville M, Hadj-Aïssa A, Dubourg L. Performance of the chronic kidney disease epidemiology collaboration equation to estimate glomerular filtration rate in diabetic patients. *Diabetes Care.* 2011 Jun;34(6):1320–2.
- 19 Hermans MM, Henry R, Dekker JM, Kooman JP, Kostense PJ, Nijpels G, et al. Estimated glomerular filtration rate and urinary albumin excretion are independently associated with greater arterial stiffness: the Hoorn Study. *J Am Soc Nephrol.* 2007 Jun;18(6):1942–52.
- 20 Lin L, Peng K, Du R, Huang X, Lu J, Xu Y, et al. Metabolically healthy obesity and incident chronic kidney disease: the role of systemic inflammation in a prospective study. *Obesity (Silver Spring).* 2017 Mar;25(3):634–41.
- 21 Hemmelgarn BR, Manns BJ, Lloyd A, James MT, Klarenbach S, Quinn RR, Wiebe N, Tonelli M; Alberta Kidney Disease Network. Relation Between Kidney Function, Proteinuria and Adverse Outcomes. *JAMA.* 2010 Feb 3;303(5):423–9.
- 22 Stuveling EM, Hillege HL, Bakker SJ, Gans RO, De Jong PE, De Zeeuw D. C-reactive protein is associated with renal function abnormalities in a non-diabetic population. *Kidney Int.* 2003 Feb;63(2):654–61.
- 23 Fakhrzadeh H, Ghaderpanahi M, Sharifi F, Badamchizade Z, Mirarefin M, Larijani B. Increased risk of chronic kidney disease in elderly with metabolic syndrome and high levels of C-reactive protein: Kahrizak Elderly Study. *Kidney Blood Press Res.* 2009;32(6):457–63.
- 24 National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis.* 2002 Feb;39(2 Suppl 1):S1–266.
- 25 Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, et al.; Centers for Disease Control and Prevention; American Heart Association. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation.* 2003 Jan;107(3):499–511.
- 26 Stuveling EM, Bakker SJ, Hillege HL, de Jong PE, Gans RO, de Zeeuw D. Biochemical risk markers: a novel area for better prediction of renal risk? *Nephrol Dial Transplant.* 2005 Mar;20(3):497–508.
- 27 Rodríguez-Iturbe B, Pons H, Herrera-Acosta J, Johnson RJ. Role of immunocompetent cells in nonimmune renal diseases. *Kidney Int.* 2001 May;59(5):1626–40.
- 28 Stengel B, Tarver-Carr ME, Powe NR, Eberhardt MS, Brancati FL. Lifestyle factors, obesity and the risk of chronic kidney disease. *Epidemiology.* 2003 Jul;14(4):479–87.
- 29 Kushner I, Rzewnicki D, Samols D. What does minor elevation of C-reactive protein signify? *Am J Med.* 2006 Feb;119(2):166.e17–28.
- 30 Lin CJ, Chen HH, Pan CF, Hsieh WS, Ho HT, Wu CJ. The characteristics of new semi-quantitative method for diagnosing proteinuria by using random urine samples. *J Clin Lab Anal.* 2011;25(1):14–9.