



Serum Albumin and High-Sensitivity C-reactive Protein are Independent Risk Factors of Chronic Kidney Disease in Middle-Aged Japanese Individuals: the Circulatory Risk in Communities Study

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Aim: It is important to explore predictive markers other than conventional cardiovascular risk factors for early detection and treatment of chronic kidney disease (CKD), a major risk factor for end-stage renal failure. We hypothesized that serum albumin and high-sensitivity C-reactive protein (hs-CRP) to be independent markers, and examined their associations with the risk of CKD.

Methods: We examined the associations of serum albumin and hs-CRP levels with the risk of incident CKD, in 2535 Japanese adults aged 40–69 years without CKD at baseline during a median 9.0-year follow-up after adjustment for known cardiovascular risk factors.

Results: During the follow-up period, 367 cases of CKD developed. In multivariable analyses adjusted for known risk factors, the CKD hazard ratios (95% confidence intervals) for the highest versus lowest quartiles of serum albumin levels were 0.69 (0.40–1.17) for men and 0.42 (0.28–0.64) for women. Corresponding values for hs-CRP were 0.95 (0.54–1.67) for men and 1.85 (1.25–2.75) for women. The association of combined serum albumin and hs-CRP with the risk of CKD was examined for women. The hazard ratio was 1.72 (1.17–2.54) for low versus higher albumin levels at lower hs-CRP levels, but such an association was not observed at high hs-CRP level. The hazard ratio was 1.96 (1.44–2.66) for high versus lower hs-CRP levels at higher serum albumin levels, but such association was not observed at low serum albumin level.

Conclusion: Both low serum albumin and high hs-CRP levels were predictive of CKD for women.

Key words: Serum albumin, High-sensitivity C-reactive protein, Risk of chronic kidney disease, Prospective study

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Introduction

Japan's current elderly population has reached its highest number at 33 million, and the proportion of elderly in the overall population reached 26.0% in

2014¹. An estimated 13.3 million patients have chronic kidney disease (CKD), and more than 310000 are estimated to require chronic dialysis treatment. Accordingly, CKD has become a major public health issue².

CKD has been recognized as an independent risk factor for all-cause death and cardiovascular disease (CVD) onset as well as end-stage renal disease³⁻⁷, and thus early detection and treatment are important for the control of modifiable cardiovascular risk factors. Although cardiovascular risk factors, such as hypertension, diabetes mellitus, and dyslipidemia, have been

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addressed as predictive factors for CKD^{8,9}), other predictive factors have not been well elucidated.

The Atherosclerosis Risk in Communities Study and the Second National Health and Nutrition Examination Survey showed an inverse association between serum albumin levels and the risk of incident CKD in middle-aged adults^{10,11}. Furthermore, the Cardiovascular Health Study reported that lower serum albumin and higher CRP levels were associated with the progression of kidney dysfunction in elderly subjects aged ≥ 65 years¹².

Aim

We hypothesized serum albumin and high-sensitivity C-reactive protein (hs-CRP) to be independent markers of incident CKD. Thus, in this study, we examined their associations with the risk of incident CKD during an 11-year prospective cohort study.

Methods

Study Population

The Circulatory Risk in Communities Study (CIRCS) is an ongoing dynamic community cohort study involving five communities in Japan for which the study design and procedural details have been published elsewhere¹³. The subjects, who ranged in age from 40 to 69 years, resided in two communities from which the CIRCS populations were drawn: the town of Ikawa (a rural community in the Akita Prefecture, northwestern Japan) and the Minami-Takayasu district in Yao City (a suburb of the Osaka Prefecture, midwestern Japan). A total of 3126 subjects (1082 men and 2044 women) participated in the baseline cardiovascular risk surveys between 2002 and 2003, including 1217 (492 men and 725 women) in Ikawa and 1909 (590 men and 1319 women) in Yao. Of these, 2828 subjects (958 men and 1870 women) participated in at least one follow-up examination (and thus had available data) before the end of 2013. Additionally, we excluded eight subjects without serum data, 265 with a low eGFR (<60 mL/min per 1.73 m²) and/or urine protein level (1+ or more), 2 with prevalent kidney disorders, and 18 with prevalent liver disorders at the baseline survey. Therefore, a total of 2535 subjects (821 men and 1714 women) were finally enrolled in this study and followed up until the end of 2013 to determine incident CKD.

Informed consent was given verbally by community leaders and individual participants, according to the common practice in Japanese communities at that time. The CIRCS was approved by the ethics committees of the Osaka Center for Cancer and Cardiovascu-

lar Diseases Prevention and Osaka University Graduate School of Medicine.

Baseline Examination

Serum creatinine levels were assayed using an enzymatic method, and the GFR was estimated using an established method proposed by a working group of the Japanese Chronic Kidney Disease initiative¹⁴ as follows:

$$\text{eGFR (ml/min per } 1.73 \text{ m}^2) = 194 \times [\text{serum creatinine (enzyme method)}]^{-1.094} \times (\text{age})^{-0.287} \times (0.739 \text{ for women}).$$

CKD was defined as a GFR <60 mL/min per 1.73 m², in accordance with the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines¹⁵. Serum albumin levels were analyzed using Bartholomew and Delaney's bromocresol green method and an AU2 700 automatic biochemical analyzer (Olympus, Tokyo, Japan). hs-CRP levels were determined using an automated immunonephelometric assay (Behring Nephelometer Protein Specific with N Latex CRP II; Dade Behring Inc., Tokyo, Japan).

BMI was calculated as the body weight (kg) divided by the height squared (m²). Height was measured while the subjects were in stocking feet, and weight was determined while the subjects wore light clothing. An interview was conducted to ascertain the smoking status, usual weekly alcohol intake, and diabetes mellitus, hypertension, or hyperlipidemia medication use.

Blood pressure levels were measured by trained physicians using standard mercury sphygmomanometers and standardized epidemiological methods¹⁶. Diabetes mellitus was defined as a fasting glucose level of ≥ 7.0 mmol/L (≥ 126 mg/dL), a non-fasting glucose level of ≥ 11.1 mmol/L (≥ 200 mg/dL), and/or diabetes medication use.

Follow-up Surveillance (Endpoint Determination)

The follow-up was conducted through annual cardiovascular risk surveys. For each participant, the number of person-years of follow-up was calculated as the sum of the individual follow-up time from the date of the baseline survey to the date of incident CKD or the latest exam without incident CKD, whichever occurred first.

Statistical Analysis

Differences in participant characteristics, defined as the age-adjusted mean values of baseline CKD risk factors, were compared through an analysis of variance; the F test was used for continuous variables and the chi-square test was used to compare percentages among the serum albumin and hs-CRP quartiles. We

Table 1. Sex-specific, age-adjusted mean values and prevalence rates of baseline risk characteristics according to quartiles of serum albumin levels

	Quartiles of serum albumin levels									
	Men					Women				
	Q1	Q2	Q3	Q4	<i>P</i> for trend	Q1	Q2	Q3	Q4	<i>P</i> for trend
Serum albumin range (g/dL)	≤4.3	4.4–4.5	4.6	≥4.7		≤4.3	4.4–4.5	4.6	≥4.7	
Serum albumin (g/dL) [#]	4.3	4.5	4.6	4.8		4.3	4.5	4.6	4.8	
Number of participants	174	262	152	233		349	634	301	430	
Age (y)	61.0	59.2	58.6	56.3	<0.001	56.6	57.1	57.3	57.3	0.206
Serum creatinine (mg/dL)	0.75	0.76	0.76	0.75	0.829	0.58	0.57	0.58	0.58	0.726
eGFR (mL/min per 1.73 m ²)	85.1	83.4	83.9	84.4	0.778	84.4	85.1	84.1	84.4	0.765
Body mass index (kg/m ²)	23.7	23.8	24.1	24.1	0.201	23.2	23.2	23.3	22.8	0.044
Current smokers (%)	51	44	42	37	0.004	6	5	4	5	0.456
Alcohol intake (ethanol g/day)	28.4	27.0	26.3	26.4	0.450	2.3	2.1	1.6	2.1	0.740
hs-CRP (mg/L)	1.86	1.18	1.10	0.84	0.003	2.02	0.96	0.73	0.62	<0.001
Systolic blood pressure (mmHg)	125	129	130	131	<0.001	122	124	125	128	<0.001
Diastolic blood pressure (mmHg)	78	81	82	83	<0.001	74	76	76	77	<0.001
Use of antihypertensive medication (%)	15	16	15	25	0.010	12	14	14	22	<0.001
Serum total cholesterol (mg/dL)	195	202	213	216	<0.001	211	220	224	231	<0.001
High-density lipoprotein cholesterol (mg/dL)	58	58	59	61	0.009	65	65	66	68	<0.001
Cholesterol-lowering medication (%)	3	3	2	6	0.180	8	9	9	15	<0.001
Diabetes mellitus (%)	9	4	11	12	0.115	4	3	4	5	0.135

[#]Median values are shown.

Abbreviations: hs-CRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate.

conducted tests for linear trends of covariates using the median values of serum albumin and hs-CRP quartiles. Cox proportional hazards regression models were used to calculate sex-specific hazard ratios and 95% CIs for incident CKD using the risks for subjects with the lowest quartiles of serum albumin, hs-CRP levels, and their combinations as reference.

The initial model was adjusted only for age and community, whereas the variables adjusted in the multivariable analysis included age, community, BMI (kg/m²), smoking status (never and former versus current), systolic blood pressure (mmHg), antihypertensive medication use (yes versus no), serum total cholesterol level (mg/dL), hyperlipidemia medication use (yes versus no), diabetes mellitus (yes versus no), eGFR (mL/min per 1.73 m²), and either hs-CRP (mg/L) or serum albumin (g/dL), depending on the exposure variable.

The significance of the interactions for sex was tested using cross-product terms of sex with serum albumin and hs-CRP levels, and we also checked the cross-product terms of serum albumin with hs-CRP levels.

All statistical analyses were conducted using SAS statistical software package, version 9.3 (SAS Institute,

Inc., Cary, NC, USA). All statistical analyses were two-tailed, and a *p*-value < 0.05 was considered statistically significant.

Results

A total of 367 cases (123 men and 244 women) of incident CKD were identified during a median 9.0-year follow-up, yielding a total of 19413 person-years. **Table 1** shows the sex-specific, age-adjusted mean values and prevalence rates of selected CKD risk factors at the baseline, according to quartiles of serum albumin levels. The average age was 58.6 years for men and 57.1 years for women.

For men, the mean systolic blood pressure, diastolic blood pressure, serum total cholesterol, and high-density lipoprotein (HDL)-cholesterol values and the prevalence rates of antihypertensive medication use were higher and the mean hs-CRP value and prevalence of current smokers were lower among those with higher serum albumin levels. For women, the mean systolic blood pressure, diastolic blood pressure, serum total cholesterol, and HDL-cholesterol values and the prevalence rates of antihypertensive and cho-

Table 2. Sex-specific, age-adjusted mean values and prevalence rates of baseline risk characteristics according to quartiles of hs-CRP levels

	Quartiles of hs-CRP levels									
	Men					Women				
	Q1	Q2	Q3	Q4	<i>P</i> for trend	Q1	Q2	Q3	Q4	<i>P</i> for trend
hs-CRP range (mg/L)	<0.24	0.24–0.47	0.48–0.96	≥0.97		<0.17	0.17–0.35	0.36–0.77	≥0.78	
hs-CRP (mg/L) [#]	0.16	0.35	0.65	1.76		0.16	0.26	0.50	1.47	
Number of participants	205	206	205	205		427	430	429	428	
Age (y)	58.2	58.1	59.3	58.9	0.283	54.2	57.3	58.0	58.8	<0.001
Serum creatinine (mg/dL)	0.76	0.75	0.76	0.75	0.233	0.58	0.57	0.57	0.57	0.604
eGFR (mL/min per 1.73m ²)	83.5	84.8	83.2	85.0	0.382	84.2	84.8	84.4	85.0	0.460
Body mass index (kg/m ²)	22.8	23.7	24.5	24.7	<0.001	21.3	22.8	24.0	24.4	<0.001
Current smokers (%)	31	45	48	50	0.003	5	5	5	6	0.321
Alcohol intake (ethanol g/day)	23.7	28.0	28.9	27.3	0.463	1.7	2.3	1.7	2.4	0.212
Serum albumin (g/dL)	4.53	4.54	4.56	4.50	0.092	4.53	4.53	4.53	4.48	<0.001
Systolic blood pressure (mmHg)	126	128	130	131	0.002	121	124	126	127	<0.001
Diastolic blood pressure (mmHg)	80	81	81	82	0.145	74	76	77	77	<0.001
Use of antihypertensive medication (%)	14	16	19	23	0.012	9	13	21	20	<0.001
Serum total cholesterol (mg/dL)	202	208	209	207	0.339	220	223	224	220	0.521
High-density lipoprotein cholesterol (mg/dL)	64	61	57	55	<0.001	72	68	64	61	<0.001
Cholesterol-lowering medication (%)	2	3	4	6	0.008	8	9	13	10	0.669
Diabetes mellitus (%)	7	8	9	10	0.250	4	3	4	5	0.040

[#]Median values are shown.

Abbreviations: hs-CRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate.

lesterol-lowering medication use were higher, whereas the mean body mass index (BMI) and hs-CRP values were lower among those with higher serum albumin levels.

Table 2 shows the sex-specific, age-adjusted mean values and prevalence rates of selected CKD risk factors at the baseline, according to quartiles of hs-CRP levels. For men, the mean BMI and systolic blood pressure values and the prevalence rates of antihypertensive and cholesterol-lowering medication use, and current smokers were higher and the mean HDL-cholesterol level was lower in those with higher hs-CRP levels. For women, the mean BMI, systolic blood pressure, and diastolic blood pressure values and the prevalence rates of antihypertensive medication use, diabetes mellitus were higher, whereas the mean serum albumin and HDL-cholesterol values were lower in those with higher hs-CRP levels.

Table 3 shows the sex-specific, age-adjusted multivariable hazard ratios of CKD according to quartiles of serum albumin levels. For both men and women, a lower risk of CKD was observed for the second to fourth quartiles of serum albumin level than for the lowest quartile of serum albumin level. This associa-

tion became even stronger after adjusting for known CKD risk factors. The multivariable hazard ratios [95% confidence intervals (CI)] of CKD for the highest versus the lowest quartile of serum albumin levels were 0.69 (0.40–1.17) for men and 0.42 (0.28–0.64) for women, and the sex interaction was of borderline statistical significance (*P* for interaction=0.062). Furthermore, the multivariable hazard ratios (95% CI) of CKD for the combined category of the second to fourth quartiles versus the lowest quartile of serum albumin levels were 0.65 (0.42–1.00) for men and 0.74 (0.54–1.01) for women (data not shown).

Table 4 shows the sex-specific, age-adjusted multivariable hazard ratios of CKD according to quartiles of hs-CRP levels. Although risk of incident CKD tended to be higher for the second to fourth highest quartiles of hs-CRP levels, this association became null for men after adjusting for the known CKD risk factors. For women, compared with the lowest quartile, an excess risk of incident CKD was observed for the highest quartile of hs-CRP levels, and this association became stronger after adjusting for known CKD risk factors. The multivariable hazard ratio (95% CI) of CKD for the highest versus the lowest quartiles of

Table 3. Hazard ratios (HRs) of incident chronic kidney disease according to quartiles of serum albumin levels

	Quartiles of serum albumin			
	Q1	Q2	Q3	Q4
Men				
Number at risk	174	262	152	233
Person years	1247	1984	1183	1787
Number of cases (%)	32 (18.4)	41 (15.7)	19 (12.5)	31 (13.3)
Incidence, per 1000 person-years	25.7	20.7	16.1	17.3
Age and community-adjusted HR	1.00	0.83 (0.52–1.32)	0.69 (0.39–1.21)	0.88 (0.53–1.46)
Multivariable HR [#]	1.00	0.63 (0.38–1.04)	0.64 (0.36–1.16)	0.69 (0.40–1.17)
Women				
Number at risk	349	634	301	430
Person years	2596	4831	2319	3464
Number of cases (%)	57 (16.3)	96 (15.1)	43 (14.3)	48 (11.2)
Incidence, per 1000 person-years	22.0	19.9	18.5	13.9
Age and community-adjusted HR	1.00	0.86 (0.62–1.19)	0.82 (0.55–1.22)	0.60 (0.41–0.88)
Multivariable HR [#]	1.00	0.95 (0.68–1.34)	0.82 (0.55–1.23)	0.42 (0.28–0.64)
Total subjects				
Number at risk	523	896	453	663
Person years	3844	6816	3502	5251
Number of cases (%)	89 (17.0)	137 (15.3)	62 (13.7)	79 (11.9)
Incidence, per 1000 person-years	23.2	20.1	17.7	15.0
Sex, age and community-adjusted HR	1.00	0.87 (0.66–1.13)	0.78 (0.57–1.09)	0.68 (0.51–0.93)
Multivariable HR [#]	1.00	0.88 (0.67–1.15)	0.78 (0.56–1.08)	0.52 (0.38–0.72)

[#]The multivariable adjusted HR was further adjusted for body mass index, smoking status, systolic blood pressure, antihypertensive medication use, diabetes mellitus, serum total cholesterol, cholesterol-lowering medication use, estimated glomerular filtration rate, and high-sensitivity C-reactive protein levels.

Abbreviations: Q, quartile.

hs-CRP levels was 1.85 (1.25–2.75) for women, with the sex interaction of statistical significance (P for interaction=0.078). Furthermore, the multivariable hazard ratio (95% CI) of CKD for the highest quartile versus the combined category of the first to third quartiles of hs-CRP levels was 1.67 (1.27–2.19) for women (data not shown).

Table 5 shows the associations between the combination of serum albumin (the lowest versus higher quartiles) and hs-CRP (the highest versus lower quartiles) and the risk of CKD for women. The positive association between low serum albumin level and the risk of CKD was observed in the subgroup of lower hs-CRP levels, but not of high hs-CRP level. The multivariable hazard ratio (95% CI) of CKD for the lowest versus higher quartiles of serum albumin levels was 1.72 (1.17–2.54) in the subgroup of lower hs-CRP levels. The positive association between high hs-CRP level and the risk of CKD was observed in the

subgroup of higher albumin levels, but not of low albumin level. The multivariable hazard ratio (95% CI) of CKD for the highest versus lower hs-CRP levels was 1.96 (1.44–2.66) in the subgroup of higher albumin levels, with hs-CRP and serum albumin interaction of statistical significance (P for interaction=0.035).

Discussion

In this large prospective cohort study of middle-aged Japanese residents, we identified an association between low serum albumin levels (≤ 4.3 g/dL) and a two-fold higher risk of incident CKD; notably, this association was more evident for women than for men. We also found that higher hs-CRP levels (≥ 0.78 mg/L) were associated with a two-fold higher risk of incident CKD for women but not for men. When the serum albumin and hs-CRP categories were com-

Table 4. Hazard ratios (HRs) of incident chronic kidney disease according to quartiles of hs-CRP levels

	Quartiles of hs-CRP			
	Q1	Q2	Q3	Q4
Men				
Number at risk	205	206	205	205
Person years	1589	1518	1489	1607
Number of cases (%)	27 (13.2)	31 (15.0)	33 (16.1)	32 (15.6)
Incidence, per 1000 person-years	17.0	20.4	21.9	19.9
Age and community-adjusted HR	1.00	1.20 (0.72–2.02)	1.18 (0.71–1.97)	1.12 (0.67–1.88)
Multivariable HR [#]	1.00	1.01 (0.59–1.74)	0.90 (0.53–1.54)	0.95 (0.54–1.67)
Women				
Number at risk	427	430	429	428
Person years	3304	3340	3423	3143
Number of cases (%)	41 (9.6)	55 (12.8)	58 (13.5)	90 (21.0)
Incidence, per 1000 person-years	12.4	16.5	16.9	28.6
Age and community-adjusted HR	1.00	1.08 (0.72–1.62)	1.07 (0.72–1.60)	1.72 (1.18–2.50)
Multivariable HR [#]	1.00	1.30 (0.86–1.97)	1.05 (0.68–1.60)	1.85 (1.25–2.75)
Total subjects				
Number at risk	632	636	634	633
Person years	4893	4858	4912	4750
Number of cases (%)	68 (10.8)	86 (13.5)	91 (14.4)	122 (19.3)
Incidence, per 1000 person-years	13.9	17.7	18.5	25.7
Sex, age and community-adjusted HR	1.00	1.12 (0.81–1.54)	1.11 (0.81–1.53)	1.51 (1.12–2.04)
Multivariable HR [#]	1.00	1.16 (0.84–1.61)	0.97 (0.70–1.35)	1.52 (1.10–2.08)

[#]The multivariable-adjusted HR was further adjusted for body mass index, smoking status, systolic blood pressure, antihypertensive medication use, diabetes mellitus, serum total cholesterol, cholesterol-lowering medication use, estimated glomerular filtration rate, and serum albumin levels. Abbreviations: hs-CRP, high-sensitivity C-reactive protein; Q, quartile.

bined, the risk of CKD was 2.0-fold higher for women with higher serum albumin and high hs-CRP than for those with higher serum albumin and lower hs-CRP.

To the best of our knowledge, this is the first population-based prospective cohort study to examine the associations of serum albumin and hs-CRP levels with the risk of CKD. A 14-year follow-up study of American men and women aged 45–64 years, who were free from CKD at the baseline, identified a strong inverse association between serum albumin levels and the risk of CKD. In that study, the multivariable hazard ratio (95% CI) of CKD after adjusting for age, race, sex, smoking, blood pressure, diabetes, log triglycerides, HDL, low-density lipoprotein (LDL), prior myocardial infarction, antihypertensive use, alcohol use, year of marker measurement, and baseline estimated glomerular filtration rate (eGFR) was 0.63 (0.55–0.72) for the highest versus the lowest quartile of serum albumin levels (≥ 4.1 g/dL versus < 3.7 g/dL)¹⁰, which was consistent with our finding.

A 15-year follow-up of 2877 subjects aged 43–84 years in the Beaver Dam Chronic Kidney Disease Study found that hs-CRP levels were not associated with the risk of incident CKD. The multivariable hazard ratio (95% CI) of CKD after adjusting for age, sex, education, smoking, alcohol intake, BMI, glycosylated hemoglobin, mean arterial blood pressure, and serum total cholesterol was 1.14 (0.95–1.37) for the highest (men: > 2.60 mg/dL and women: > 2.99 mg/dL) versus the lowest CRP tertile (men: < 1.13 mg/dL and women: < 1.19 mg/dL). However, this study did not report sex-specific results¹⁷. During a median 9.0-year follow-up in our study, the risk of CKD for women was two-fold higher at the highest hs-CRP level (≥ 0.78 mg/L) than at the lowest hs-CRP level (< 0.17 mg/L); notably, these hs-CRP levels were much lower than those reported for Caucasians^{18, 19}.

The functions of serum albumin are to maintain normal microvessel wall permeability, inhibit platelet aggregation, and reduce blood viscosity^{20–22}. In addi-

Table 5. Hazard ratios (HRs) of incident chronic kidney disease according to two categories of serum albumin or hs-CRP levels, stratified by hs-CRP or serum albumin levels for women

	Lower hs-CRP (Q1–Q3)		High hs-CRP (Q4)	
	Higher albumin Q2–Q4	Low albumin Q1	Higher albumin Q2–Q4	Low albumin Q1
Number at risk	1050	236	315	113
Person years	8301	1767	2314	830
Number of cases (%)	119 (11.3)	35 (14.8)	68 (21.6)	22 (19.5)
Incidence, per 1000 person-years	14.3	19.8	29.4	26.5
Age- and community-adjusted HR	1.00	1.59 (1.09–2.32)	1.00	0.82 (0.51–1.33)
Multivariable HR [#]	1.00	1.72 (1.17–2.54)	1.00	0.89 (0.54–1.44)

	Higher albumin (Q2–Q4)		Low albumin (Q1)	
	Lower hs-CRP Q1–Q3	High hs-CRP Q4	Lower hs-CRP Q1–Q3	High hs-CRP Q4
Number at risk	1050	315	236	113
Person years	8301	2314	1767	830
Number of cases (%)	119 (11.3)	68 (21.6)	35 (14.8)	22 (19.5)
Incidence, per 1000 person-years	14.3	29.4	19.8	26.5
Age- and community-adjusted HR	1.00	1.87 (1.39–2.52)	1.00	0.96 (0.56–1.65)
Multivariable HR [#]	1.00	1.96 (1.44–2.66)	1.00	1.01 (0.58–1.73)

[#]The multivariable-adjusted HR was further adjusted for body mass index, smoking status, systolic blood pressure, antihypertensive medication use, diabetes mellitus, serum total cholesterol, cholesterol-lowering medication use, and estimated glomerular filtration rate. Abbreviations: hs-CRP, high-sensitivity C-reactive protein; Q, quartile.

tion, serum albumin acts as an extracellular antioxidant by inhibiting the formation of oxidized LDL-cholesterol²³⁾ and by binding and thus preventing the toxic effects of free fatty acids in the serum²⁴⁾. Accordingly, low serum albumin levels have been associated with the risks of myocardial infarction, atrial fibrillation, cardiovascular disease, and death^{25–28)}.

During the process of atherogenesis, CRP accelerates LDL uptake by macrophages, leading to the formation of foam cells²⁹⁾. CRP also impairs endothelial function by attenuating the nitric oxide production through the downregulation of endothelial nitric oxide synthase mRNA and facilitates the apoptosis of endothelial cells³⁰⁾. Furthermore, CRP stimulates the proliferation and migration of vascular smooth muscle cells^{31, 32)}.

The reported median hs-CRP levels in Japanese populations have been relatively lower than those in Western populations^{33–36)}. In this study, the median hs-CRP values of 0.48 mg/L for men and 0.36 mg/L for women were approximately one third of the median value reported for Caucasian men (1.7 mg/L) and one seventh of the median values reported for Caucasians women (2.0–3.2 mg/L)^{18, 19)}. A previous Japanese study reported significant correlations of hs-

CRP levels with BMI, systolic blood pressure, diastolic blood pressure, total cholesterol (women only), LDL-cholesterol (women only), HDL-cholesterol, triglycerides, fasting glucose, overweight, hypertension, dyslipidemia, diabetes, cardiovascular history (men only), and smoking (men only)³⁶⁾. In our study, a positive correlation with diastolic blood pressure was only found for women.

In our study, we measured two markers of inflammation, i.e., serum albumin and hs-CRP levels and examined their combined associations with the risk of incident CKD. We identified the associations between low serum albumin or high hs-CRP and the risk of CKD in the subgroup of lower hs-CRP or higher serum albumin levels, respectively, but these association were not observed in the other subgroups. We could not elucidate the mechanism of this result from our study, but we considered that serum albumin and hs-CRP levels are independent risk factors of developing CKD.

Furthermore, we found that low serum albumin and high hs-CRP levels were predictive for CKD for women but not for men. However, previous studies did not report sex-specific results; hence, we did not examine the consistency of the findings.

The strengths of our study include its large sample size, prospective design, and long-term follow-up, during which surveys were annually conducted to verify the participants' vital statuses. Also, as our findings were determined from a community-based population without CKD at the baseline, it is likely that they can be extrapolated to general Japanese populations. Furthermore, we examined the association of serum hs-CRP levels with the risk of incident CKD in subpopulations stratified by serum albumin levels, which allowed us to examine the joint impact of these two biomarkers on the risk of incident CKD.

Regarding study limitations, CKD in this study was defined using a single creatinine measurement. However, a previous study reported fairly good repeatability for CKD diagnosis; as the coefficients of variation for serum creatinine in the present study were 0.6%–0.7%, the potential for misclassification may be low.

Conclusion

This prospective cohort study found that both low serum albumin and high hs-CRP levels were independent predictors of incident CKD in middle-aged Japanese women.

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There are no conflicts of interest to declare.

References

- 1) Cabinet Office, government of Japan: Annual Report on Aging Society 2015, 2015
- 2) Nakai S, Hanafusa N, Masakane I, Taniguchi M, Hamano T, Shoji T, Hasegawa T, Itami N, Yamagata K, Shinoda T, Kazama JJ, Watanabe Y, Shigematsu T, Marubayashi S, Morita O, Wada A, Hashimoto S, Suzuki K, Nakamoto H, Kimata N, Wakai K, Fujii N, Ogata S, Tsuchida K, Nishi H, Iseki K, and Tsubakihara Y: An overview of regular dialysis treatment in Japan (as of 31 December 2012). *Ther Apher Dial*, 2004; 18: 535-602
- 3) Manjunath G, Tighiouart H, Ibrahim H, MacLeod B, Salem DN, Griffith JL, Coresh J, Levey AS, and Sarnak MJ: Level of kidney function as a risk factor for atherosclerotic cardiovascular outcomes in the community. *J Am Coll Cardiol*, 2003; 41: 47-55
- 4) Go AS, Chertow GM, Fan D, McCulloch CE, and Hsu C: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*, 2004; 351: 1296-1305
- 5) Weiner DE, Tighiouart H, Amin MG, Stark PC, Macleod B, Griffith JL, Salem DN, Levey AS, and Sarnak MJ: Chronic Kidney Disease as a Risk Factor for Cardiovascular Disease and All-Cause Mortality: A Pooled Analysis of Community-Based Studies. *J Am Soc Nephrol*, 2004; 15: 1307-1315
- 6) Ninomiya T, Kiyohara Y, Kubo M, Tanizaki Y, Doi Y, Okubo K, Wakugawa Y, Hata J, Oishi Y, Shinkawa K, Yonemoto K, Hirakata H, and Iida M: Chronic kidney disease and cardiovascular disease in a general Japanese population: The Hisayama Study. *Kidney Int*, 2005; 68: 228-236
- 7) Irie F, Iso H, Sairenchi T, Fukasawa N, Yamagishi K, Ikehara S, Kanashiki M, Saito Y, Ota H, and Nose T: The

- relationships of proteinuria, serum creatinine, glomerular filtration rate with cardiovascular disease mortality in Japanese general population. *Kidney Int*, 2006; 69: 1264-1271
- 8) Yamagata K, Ishida K, Sairenchi T, Takahashi H, Ohba S, Shiigai T, Narita M, and Koyama A: Risk factors for chronic kidney disease in a community-based population: a 10-year follow-up study. *Kidney Int*, 2007; 71: 159-166
 - 9) Fox CS, Larson MG, Leip EP, Culleton B, Wilson PWF, and Levy D: Predictors of new-onset kidney disease in a community-based population. *JAMA*, 2004; 291: 844-850
 - 10) Bash LD, Erlinger TP, Coresh J, Marsh-Manzi J, Folsom AR, and Astor BC: Inflammation, hemostasis, and the risk of kidney function decline in the Atherosclerosis Risk in Communities (ARIC) Study. *Am J kidney Dis*, 2009; 53: 596-605
 - 11) Erlinger TP, Tarver-Carr ME, Powe NR, Appel LJ, Coresh J, and Eberhardt MS: Leukocytosis, hypoalbuminemia, and the risk for chronic kidney disease in US adults. *Am J kidney Dis*, 2003; 42: 256-263
 - 12) Fried L, Solomon C, Shlipak M, Seliger S, Stehman-breen C, Bleyer AJ, Chaves P, Furberg C, Kuller L, and Newman A: Inflammatory and prothrombotic markers and the progression of renal disease in elderly individuals. *J Am Soc Nephrol*, 2004; 15: 3184-3191
 - 13) Imano H, Iso H, Kiyama M, Yamagishi K, Ohira T, Sato S, Noda H, Maeda K, Okada T, Tanigawa T, Kitamura A, and The CIRCUS Investigators: Non-fasting blood glucose and risk of incident coronary heart disease in middle-aged general population: The Circulatory Risk in Communities Study (CIRCUS). *Prev Med*, 2012; 55: 603-607
 - 14) Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, and Hishida A: Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis*, 2009; 53: 982-992
 - 15) Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA, Tamura MK, and Feldman HI: KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. *Am J Kidney Dis*, 2014; 63: 713-735
 - 16) Imano H, Kitamura A, Sato S, Kiyama M, Ohira T, Yamagishi K, Noda H, Tanigawa T, Iso H, and Shimamoto T: Trends for blood pressure and its contribution to stroke incidence in the middle-aged Japanese population: The Circulatory Risk in Communities Study (CIRCUS). *Stroke*, 2009; 40: 1571-1577
 - 17) Shankar A, Sun L, Klein BEK, Lee KE, Muntner P, Nieto FJ, Tsai MY, Cruickshanks KJ, Schubert CR, Brazy PC, Coresh J, and Klein R: Markers of inflammation predict the long-term risk of developing chronic kidney disease: a population-based cohort study. *Kidney Int*, 2011; 80: 1231-1238
 - 18) Albert MA, Glynn RJ, Buring J, and Ridker PM: C-reactive protein levels among women of various ethnic groups living in the United States (from the Women's Health Study). *Am J Cardiol*, 2004; 93: 1238-1242
 - 19) Khera A, McGuire DK, Murphy SA, Stanek HG, Das SR, Vongpatanasin W, Wians FH, Grundy SM, and Lemos JA: Race and gender differences in C-reactive protein levels. *J Am Coll Cardiol*, 2005; 46: 464-469
 - 20) He P, and Curry FE: Albumin modulation of capillary permeability: role of endothelial cell [Ca²⁺]_i. *Am J Physiol*, 1993; 265: 74-82
 - 21) Jørgensen KA, and Stoffersen E: On the inhibitory effect of albumin on platelet aggregation. *Thromb Res*, 1980; 17: 13-18
 - 22) Belayev L, Zhao W, Pattany PM, Weaver RG, Huh PW, Lin B, Busto R, and Ginsberg MD: Diffusion-weighted magnetic resonance imaging confirms marked neuroprotective efficacy of albumin therapy in focal cerebral ischemia. *Stroke*, 1998; 29
 - 23) Halliwell B: Albumin – an important extracellular antioxidant? *Biochem Pharmacol*, 1988; 37: 569-571
 - 24) Roche M, Rondeau P, Singh NR, Tarnus E, and Bourdon E: The antioxidant properties of serum albumin. *FEBS Lett*, 2008; 582: 1783-1787
 - 25) Djoussé L, Rothman KJ, Cupples LA, Levy D, and Ellison RC: Serum albumin and risk of myocardial infarction and all-cause mortality in the Framingham Offspring Study. *Circulation*, 2002; 106: 2919-2924
 - 26) Mukamal KJ, Tolstrup JS, Friberg J, Grønbaek M, and Jensen G: Fibrinogen and albumin levels and risk of atrial fibrillation in men and women (the Copenhagen City Heart Study). *Am J Cardiol*, 2006; 98: 75-81
 - 27) Phillips A, Shaper AG, and Whincup PH: Association between serum albumin and mortality from cardiovascular disease, cancer, and other causes. *Lancet*, 1989; 334: 1434-1436
 - 28) Babu MS, Kaul S, Dadheech S, Rajeshwar K, Jyothy A, and Munshi A: Serum albumin levels in ischemic stroke and its subtypes: Correlation with clinical outcome. *Nutrition*, 2013; 29: 872-875
 - 29) Zwaka TP, Hombach V, and Torzewski J: C-reactive protein-mediated low density lipoprotein uptake by macrophages: implications for atherosclerosis. *Circulation*, 2001; 103: 1194-1197
 - 30) Verma S, Wang CH, Li SH, Dumont AS, Fedak PWM, Badiwala MV, Dhillon B, Weisel RD, Li RK, Mickle DAG, and Stewart DJ: A self-fulfilling prophecy: C-reactive protein attenuates nitric oxide production and inhibits angiogenesis. *Circulation*, 2002; 106: 913-919
 - 31) Ross R: Atherosclerosis -- An Inflammatory Disease. *N Engl J Med*, 1999; 340: 115-126
 - 32) Hattori Y, Matsumura M, and Kasai K: Vascular smooth muscle cell activation by C-reactive protein. *Cardiovasc Res*, 2003; 58: 186-195
 - 33) Arima H, Kubo M, Yonemoto K, Doi Y, Ninomiya T, Tanizaki Y, Hata J, Matsumura K, Iida M, and Kiyohara Y: High-sensitivity C-reactive protein and coronary heart disease in a general population of Japanese: The Hisayama study. *Arterioscler Thromb Vasc Biol*, 2008; 28: 1385-1391
 - 34) Makita S, Nakamura M, Satoh K, Tanaka F, Onoda T, Kawamura K, Ohsawa M, Tanno K, Itai K, Sakata K, Okayama A, Terayama Y, Yoshida Y, and Ogawa A: Serum C-reactive protein levels can be used to predict future ischemic stroke and mortality in Japanese men from the general population. *Atherosclerosis*, 2009; 204: 234-238
 - 35) Yamada S, Gotoh T, Nakashima Y, Kayaba K, Ishikawa S, Nago N, Nakamura Y, Itoh Y, and Kajii E: Distribution of serum C-reactive protein and its association with ath-

- therosclerotic risk factors in a Japanese population. *Am J Epidemiol*, 2001; 153: 1183-1190
- 36) Saito I, Sato S, Nakamura M, Kokubo Y, Mannami T, Adachi H, Konishi M, Okada K, Iso H, Kario K, Ohsuzu F, Momiyama Y, and Tsushima M: A low level of C-reactive protein in Japanese adults and its association with cardiovascular risk factors: The Japan NCVS-Collaborative Inflammation Cohort (JNIC) Study. *Atherosclerosis*, 2007; 194: 238-224