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Cross-sectional association between high-sensitivity C-reactive protein and cognitive function in community-dwelling older adults: the SONIC study

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Abstract

Background A decline in cognitive function is associated with inflammatory processes. However, the association between high-sensitivity C-reactive protein (hs-CRP) levels and cognitive decline in the Japanese population remains inconclusive. Thus, this study aimed to determine whether hs-CRP is associated with low cognitive function in 70- and 80-year-old community-dwelling Japanese individuals.

Methods The participants in this cross-sectional study were 872 Japanese residents aged 70 and 80 years who voluntarily participated in the Septuagenarians, Octogenarians, Nonagenarians Investigation with Centenarians (SONIC) study between 2010 and 2011. Blood sample collection, cognitive assessment, and other measurements were performed at the venue. Low cognitive function was defined as a score of 25 points or lower on the Japanese version of the Montreal Cognitive Assessment. The odds ratio (OR) and 95% confidence interval (95% CI) for each hs-CRP quartile were calculated using logistic regression analysis.

Results A total of 288 (69.9%) parsons in the 70-year-old group and 372 (80.9%) in the 80-year-old group exhibited low cognitive function. The association between hs-CRP levels and low cognitive function was significant among 70- and 80-year-old Japanese community-dwelling adults. In particular, the fourth quartile of hs-CRP (0.727–7.420 mg/L) in the 70-year-old group and the second and fourth quartiles (0.214–0.404 and 0.911–9.890 mg/L) in the 80-year-old group were associated with low cognitive function. Furthermore, the third quartile (0.409–0.892 mg/L) in the 80-year-old group was closely associated with low cognitive function.

Conclusions High hs-CRP levels were associated with lower cognitive function in 70- and 80-year-old Japanese community-dwelling individuals, suggesting that high hs-CRP levels may influence cognitive function.

Keywords Cognitive impairment, MoCA-J, High-sensitivity C-reactive protein, Chronic inflammation, Epidemiologic study in general population

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Background

The incidence of dementia, one of the leading causes of care dependence and disability in older adults, is rapidly increasing worldwide [1]. The number of people living with dementia worldwide was estimated to be 55.2 million in 2019. This number is projected to increase to 78 million by 2030 and 139 million by 2050 [1]. In Japan, one of the most aged countries worldwide, the numbers of people living with dementia were estimated to be 4.6 million in 2012 and 7 million in 2025 [2]. Identifying individuals at high risk of developing dementia is crucial, as this condition has no cure [3]. Several risk factors for dementia were identified: aging [1], smoking [4], excessive alcohol consumption [5], obesity [6], diabetes [7], systolic hypertension [8], physical inactivity [9], and chronic inflammation. Determining the risk factors in persons aged 70 years and older is especially important as the prevalence of this disease increases with age.

The development of dementia appears to be associated with inflammatory processes. A meta-analysis demonstrated that several surrogates of systemic inflammation, such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor (TNF), were associated with Alzheimer's disease [10]. Previous research found a negative correlation between serum CRP levels and cognitive function in community-dwelling older Japanese people [11]. However, serum CRP is a clinical marker of high inflammation levels (>3.0 mg/L). Evidence suggests that low-grade chronic inflammation is associated with cognitive decline and disorders such as Alzheimer's disease [12, 13]. High-sensitivity CRP (hs-CRP) is useful for identifying low-grade chronic inflammation that cannot be detected using standard CRP testing. hs-CRP is associated with cognitive decline in the general population of England [12] and in Japanese Americans in Hawaii [13]. Therefore, we hypothesized that hs-CRP may serve as a biomarker of cognitive decline in older Japanese people.

However, the association between hs-CRP level and cognitive decline in the Japanese population remains inconclusive. Watanabe et al. showed an association between high hs-CRP levels (>1.0 mg/L) and cognitive decline but failed to show an association between low hs-CRP levels (<1.0 mg/L) and cognitive decline [14]. This study has three limitations. First, the study population comprised outpatients of a general hospital, not community residents. Second, the participants' age ranged from 29 to 91 years. Third, the criteria for selecting the cognitive test changed during the period of participant recruitment. Only those participants suspected of having cognitive problems during the first and second periods underwent the Mini-Mental State Examination. Therefore, the association between hs-CRP levels and cognitive decline in older Japanese community residents remains unclear.

This study aimed to determine whether hs-CRP is associated with low cognitive function among 70- and 80-year-old Japanese community-dwelling people. A cross-sectional analysis was performed using data from a survey of community-dwelling older adults.

Methods

Study participants

This was a cross-sectional analysis of an epidemiological study on older Japanese adults called the Septuagenarians, Octogenarians, Nonagenarians Investigation with Centenarians (SONIC) study [15]. It is a joint research project involving researchers from various fields of expertise at the Osaka University Graduate School of Medicine, Human Sciences, and Dentistry; the National Center of Gerontology and Geriatrics; and Keio University. The participants were randomly selected from the basic resident registry by stratified sampling based on age, and invitations were sent to those who voluntarily participated in the survey. The 70-year-old group (aged 69–71 years) was invited to the venue for the survey in 2010 and the 80-year-old group (aged 79–81 years) in 2011. A narrow age-range cohort design was employed, with each cohort comprising individuals within the 3-year age range. The study focused on assessing the individual differences in the aging process and health outcomes in each age group without age adjustment [15].

A total of 1,005 70- or 80-year-old adults who participated in the Kansai region (Hyogo Prefecture) SONIC study between 2010 and 2011 were included in the present study. We excluded 59 participants with a history of dementia and/or stroke; 2 participants who did not undergo a cognitive function test; 58 participants who did not undergo a serum hs-CRP test; 11 participants with a serum hs-CRP level of ≥10 mg/L; which is indicative of acute inflammation [16]; and 3 participants with missing covariate data. The final number of participants in the analysis was 872, with 412 comprising the 70-year-old group and 460 comprising the 80-year-old group (Fig. 1).

The institutional review boards approved the SONIC study of the Osaka University Graduate School of Medicine, Dentistry, and Human Sciences and the Tokyo Metropolitan Institute of Gerontology (approval numbers 266, H22-E9, 22018, and 38). All participants provided written informed consent.

Data collection

High-sensitivity C-reactive protein

CRP is often used in clinical practice as an inflammatory marker for understanding inflammatory responses. hs-CRP measures low levels of CRP that cannot be detected by conventional measurements. In other words, hs-CRP is useful for identifying a low-grade chronic

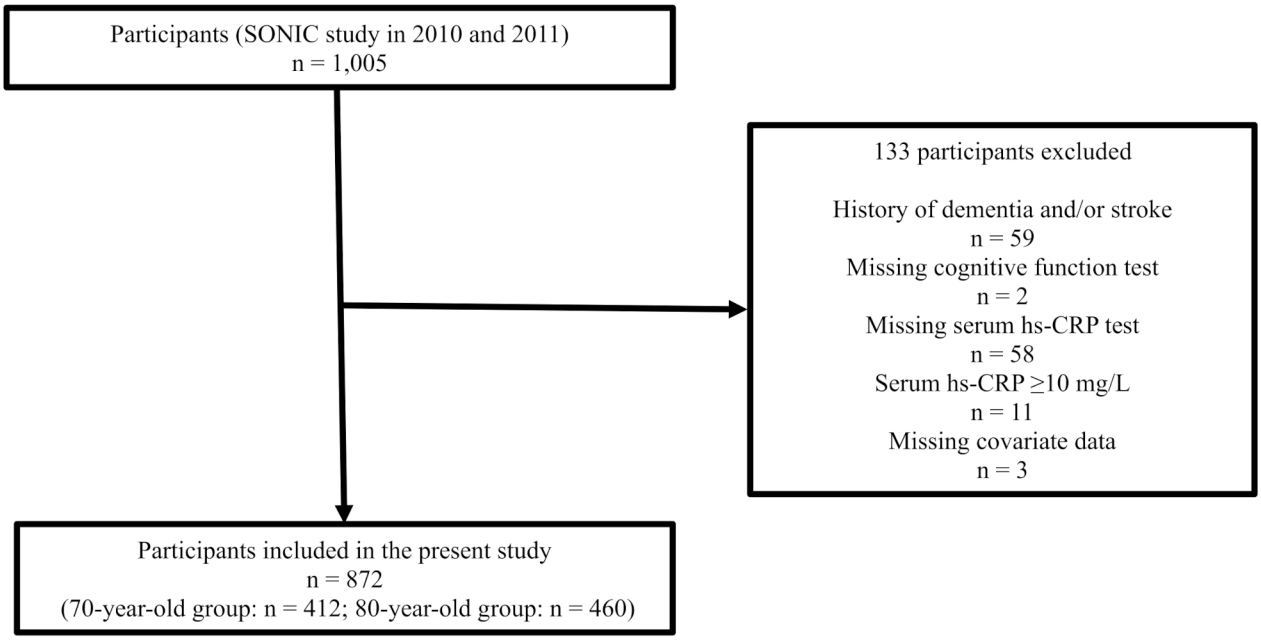

Fig. 1 Flowchart of the participant selection process

inflammation than that detectable using a standard CRP testing. The hs-CRP level can be used to assess inflammation due to atherosclerosis and predict cardiovascular disease independent of the traditional risk assessments such as the Framingham risk score [17, 18].

In this study, non-fasting blood sampling was performed by a physician or nurse at the survey venue. The total blood sample required for serum blood laboratory tests was approximately 6 mL. The hs-CRP level was determined using a latex nephelometry assay with an automatic analyzer (Behring Nephelometer II (BNII); Siemens Healthcare Diagnostics, Inc.). The intra- and inter-assay coefficients of variation values were 1.1–4.0% and 2.1–4.6%, respectively.

Other measurements and diagnostic criteria

Blood pressure measurements, blood sampling, and carotid ultrasonography examinations were performed at the venue. Carotid ultrasonography (GE Logiq Book X-P; GE Healthcare, Tokyo, Japan) was performed by an experienced physician to measure the intima-media thickness (IMT) of the left and right common carotid arteries as a surrogate marker of atherosclerosis [19]. Two measurements were taken on the left and right sides, and the mean IMT was calculated [20]. The body mass index (BMI) was calculated as weight/height^2 (kg/m^2). A physician or nurse conducted individual interviews with the participants regarding their smoking habits (never, past, or current), alcohol intake (never, moderate, or excessive), medical history, medications, and years of education. Diabetes mellitus was defined as a casual plasma glucose level of ≥200 mg/dL, a hemoglobin A1c level of ≥6.5%, a self-reported diagnosis of diabetes, or the use of antidiabetic agents based on the Japan Diabetes Society criteria [21]. Dyslipidemia was defined as a low-density lipoprotein cholesterol level of ≥140 mg dL, a high-density lipoprotein cholesterol level of <40 mg dL, a triglyceride level of ≥150 mg dL, or the use of antidyslipidemic medications according to the Japan Atherosclerosis Society Guidelines [22]. The blood pressure was measured twice in each arm by a physician or nurse, and the mean value from the two measurements was calculated. Hypertension was defined as a systolic blood pressure of ≥140 mmHg, a diastolic blood pressure of ≥90 mmHg, or the use of antihypertensive medications according to the hypertension management guidelines of the Japanese Society of Hypertension [23].

Assessment of cognitive function

The Japanese version of the Montreal Cognitive Assessment (MoCA-J) was used to assess cognitive function. MoCA-J is a simple cognitive screening tool for detecting mild cognitive impairment (MCI) [24, 25]. The cognitive tasks included visuospatial ability, naming, attention, language, abstraction, delayed recall, and orientation. A self-administered questionnaire was used to ascertain the number of years of education, with a maximum of 30 years. One point was added to the MoCA-J score if the number of years of education was less than 12 years. The MoCA-J score ranged from 0 to 30, with a sensitivity of 80–100% and a specificity of 50–87%. A score of ≤25 points is considered indicative of MCI [24, 25]. In this

study, low cognitive function was defined as a score of ≤25 points.

Statistical analysis

The participants were classified into four groups according to hs-CRP quartiles. The characteristics by hs-CRP quartiles in the 70- and 80-year-old groups were expressed as percentages for categorical variables or mean±standard deviation for continuous variables. The Spearman's rank correlation test was used to determine the trend of each item in the hs-CRP quartiles. The associations between the prevalence of low cognitive function (MoCA-J score≤25) and quartiles of hs-CRP concentrations were assessed by calculating the odds ratio (OR) and 95% confidence intervals (95% CIs) using logistic regression analysis. Subsequent analyses involved three models: Model 1 adjusted for sex; Model 2 adjusted for sex, education, and smoking; and Model 3 adjusted for sex, education, smoking, hypertension, diabetes mellitus, dyslipidemia, and mean IMT. These adjustments were made as these variables were associated with the progression of dementia and hs-CRP level in previous studies [4, 6–8]. All statistical analyses were performed using SPSS Statistics software (version 25.0; IBM Japan, Tokyo, Japan). A p-value of <0.05 was considered significant.

Results

A total of 288 (69.9%) patients in the 70-year-old group and 372 (80.9%) in the 80-year-old group exhibited low cognitive function. The first, second, third, and fourth quartiles were abbreviated as Q1, Q2, Q3, and Q4, respectively, in ascending order of the hs-CRP level. The hs-CRP distribution in this study was skewed (Additional file 1).

Table 1 shows the participants' characteristics according to the hs-CRP quartile in the 70-year-old group. The hs-CRP (mg/L) ranges were 0.050–0.160 for Q1, 0.161–0.364 for Q2, 0.365–0.720 for Q3, and 0.727–7.420 for Q4. Univariate analysis showed significant trends in the MoCA-J score, BMI, and dyslipidemia incidence toward the quartiles of hs-CRP. Table 2 shows the characteristics of the 80-year-old group across the hs-CRP quartiles. The hs-CRP (mg/L) ranges were 0.050–0.212 for Q1, 0.214–0.404 for Q2, 0.409–0.892 for Q3, and 0.911–9.890 for Q4. Univariate analysis showed significant trends in BMI, years of education, and dyslipidemia incidence across the hs-CRP quartiles.

Table 3 presents the OR and 95% CI for low cognitive function across the hs-CRP quartiles in the 70-year-old group. The OR for Q4 was significantly higher than that for Q1, and the trend across hs-CRP quartiles toward low cognitive function was significant (p for trend=0.023) after adjusting for sex, education, smoking, hypertension, diabetes mellitus, dyslipidemia, and mean IMT. Table 4 shows the OR and 95% CI for low cognitive function across the hs-CRP quartiles in the 80-year-old group. The ORs for Q2 and Q4 were significantly higher than those for Q1, while the OR for Q3 was marginally higher than that for Q1. The trend across the hs-CRP quartile toward low cognitive function was significant (p for trend=0.038) after adjusting for sex, education, smoking, hypertension, diabetes mellitus, dyslipidemia, and mean IMT.

Discussion

This study examined the association between hs-CRP levels and low cognitive function among 70- and 80-year-old Japanese community-dwelling people. The results

Table 1 Participant characteristics by quartile of serum high-sensitivity CRP (70-year-old group)

	Q1	Q2	Q3	Q4	
	(0.050–0.160 mg/L)	(0.161–0.364 mg/L)	(0.365–0.720 mg/L)	(0.727–7.420 mg/L)	*p* for trend
Number	103	103	103	103	
MoCA-J score, mean (SD)	24.2 (2.7)	24.0 (3.4)	24.2 (3.1)	22.8 (3.1)	0.003
Sex: male, n (%)	49 (47.6)	53 (51.5)	40 (38.8)	53 (51.5)	0.965
BMI (kg/m^2), mean (SD)	22.0 (3.1)	22.7 (2.8)	22.6 (2.6)	23.8 (3.7)	<0.001
Education (years), mean (SD)	12.4 (2.1)	12.2 (2.5)	11.6 (2.1)	12.0 (2.5)	0.084
Smoking					
Past, n (%)	30 (29.1)	27 (26.2)	24 (23.3)	36 (35.0)	0.461
Current, n (%)	7 (6.8)	8 (7.8)	7 (6.8)	11 (10.7)	
Alcohol intake					
Moderate, n (%)	33 (32.0)	36 (35.0)	23 (22.3)	30 (29.1)	0.866
Excessive, n (%)	7 (6.8)	3 (2.9)	6 (5.8)	6 (5.8)	
Hypertension, n (%)	61 (59.2)	67 (65.0)	62 (60.2)	68 (66.0)	0.618
Diabetes mellitus, n (%)	12 (11.7)	15 (14.6)	8 (7.8)	16 (15.5)	0.807
Dyslipidemia, n (%)	48 (46.6)	57 (55.3)	73 (70.9)	63 (61.2)	0.006
mean IMT (mm), mean (SD)	0.8 (0.1)	0.8 (0.3)	0.8 (0.2)	0.8 (0.2)	0.477

BMI=Body mass index, CRP=C-reactive protein, IMT=Intima-media thickness, MoCA-J=Japanese version of the Montreal Cognitive Assessment, Q=Quartile, SD=Standard deviation

Table 2 Participant characteristics by quartile of serum high-sensitivity CRP (80-year-old group)

	Q1	Q2	Q3	Q4	
	(0.050–0.212 mg/L)	**(0.214–0.404 mg/L)**	**(0.409–0.892 mg/L)**	**(0.911–9.890 mg/L)**	***p* for trend**
Number	115	115	115	115	
MoCA-J score, mean (SD)	22.3 (3.9)	22.2 (3.6)	21.9 (3.5)	21.6 (3.9)	0.120
Sex: male, n (%)	47 (40.9)	58 (50.4)	55 (47.8)	57 (49.6)	0.260
BMI (kg/m^2), mean (SD)	21.4 (3.0)	22.3 (2.8)	23.0 (2.9)	22.9 (3.0)	< 0.001
Education (years), mean (SD)	10.9 (2.9)	11.3 (3.1)	11.4 (3.0)	11.8 (2.8)	0.006
Smoking					
Past, n (%)	34 (29.6)	32 (27.8)	42 (36.5)	40 (34.8)	0.352
Current, n (%)	4 (3.5)	5 (4.3)	3 (2.6)	9 (7.8)	
Alcohol intake					
Moderate, n (%)	35 (30.4)	46 (40.0)	38 (33.0)	41 (35.7)	0.995
Excessive, n (%)	2 (1.7)	4 (3.5)	2 (1.7)	1 (0.9)	
Hypertension, n (%)	87 (75.7)	99 (86.1)	101 (87.8)	93 (80.9)	0.430
Diabetes mellitus, n (%)	16 (13.9)	11 (9.6)	12 (10.4)	21 (18.3)	0.416
Dyslipidemia, n (%)	57 (49.6)	67 (58.3)	81 (70.4)	74 (64.3)	0.005
mean IMT (mm), mean (SD)	0.9 (0.2)	0.9 (0.2)	0.9 (0.2)	0.9 (0.2)	0.175

BMI = Body mass index, CRP = C-reactive protein, IMT = Intima-media thickness, MoCA-J = Japanese version of the Montreal Cognitive Assessment, Q = Quartile, SD = Standard deviation

Table 3 Association between high-sensitivity CRP and low cognitive function (70-year-old group)

	Q1	Q2	Q3	Q4	
	(0.050–0.160 mg/L)	**(0.161–0.364 mg/L)**	**(0.365–0.720 mg/L)**	**(0.727–7.420 mg/L)**	***p* for trend**
Number	103	103	103	103	
MoCA-J score, mean (SD)	24.2 (2.7)	24.0 (3.4)	24.2 (3.1)	22.8 (3.1)	
Low cognitive function, n (%)	66 (64.1)	71 (68.9)	66 (64.1)	85 (82.5)	
Model 1[a]					
OR (95% CI)	1 (ref.)	1.24 (0.69–2.21)	1.02 (0.57–1.80)	2.63 (1.38–5.04)	0.013
p-value		0.475	0.957	0.003	
Model 2[b]					
OR (95% CI)	1 (ref.)	1.16 (0.64–2.10)	0.88 (0.49–1.58)	2.47 (1.28–4.78)	0.031
p-value		0.626	0.671	0.007	
Model 3[c]					
OR (95% CI)	1 (ref.)	1.20 (0.65–2.19)	0.96 (0.53–1.76)	2.56 (1.30–5.02)	0.023
p-value		0.561	0.894	0.006	

Notes: CRP = C-reactive protein, MoCA-J = Japanese version of the Montreal Cognitive Assessment, IMT = Intima-media thickness, OR = Odds ratio, CI = Confidence interval, Q = Quartile, SD = Standard deviation

[a]Adjusted for sex; [b]Model 1 + education and smoking; [c]Model 2 + hypertension, diabetes mellitus, dyslipidemia, and mean IMT

showed that this association was significant in both groups. In particular, the fourth quartile of hs-CRP (0.727–7.420 mg/L) in the 70-year-old group and the second and fourth quartiles (0.214–0.404 and 0.911–9.890 mg/L) in the 80-year-old group were associated with low cognitive function. Furthermore, the third quartile (0.409–0.892 mg/L) in the 80-year-old group was closely associated with low cognitive function.

Watanabe et al. identified an association between the fourth quartile of hs-CRP (≥1.09 mg/L) and cognitive decline but did not find an association between the second and third quartiles (0.223–0.471 and 0.471–1.09 mg/L) and cognitive decline in Japanese outpatients aged 29–91 years [14]. Another Japanese study showed an association between hs-CRP and the risk of disabling dementia in patients with a history of stroke, but failed to show an association between hs-CRP and the risk of total disabling dementia in community residents aged 40–69 years [26]. This study assessed dementia using information from a national long-term care insurance program. In age-, sex, and community-matched model, the second to fourth quartiles of hs-CRP (0.17–0.41, 0.42–0.88, and 0.90–3.11 mg/L) was associated with risk of disabling dementia among individuals with a history of stroke. These findings suggest that both high hs-CRP levels (>1.0 mg/L) and low hs-CRP levels (<1.0 mg/L) are significant in assessing cognitive function in older Japanese community residents, particularly those with subclinical cerebrovascular changes.

Table 4 Association between high-sensitivity CRP and low cognitive function (80-year-old group)

	Q1	Q2	Q3	Q4	
	(0.050–0.212 mg/L)	**(0.214–0.404 mg/L)**	**(0.409–0.892 mg/L)**	**(0.911–9.890 mg/L)**	***p* for trend**
Number	115	115	115	115	
MoCA-J score, mean (SD)	22.3 (3.9)	22.2 (3.6)	21.9 (3.5)	21.6 (3.9)	
Low cognitive function, n (%)	83 (72.2)	97 (84.3)	95 (82.6)	97 (84.3)	
Model 1[a]					
OR (95%CI)	1 (ref.)	2.09 (1.09–4.01)	1.84 (0.98–3.47)	2.09 (1.09–4.00)	0.034
p-value		0.026	0.058	0.026	
Model 2[b]					
OR (95%CI)	1 (ref.)	2.33 (1.20–4.52)	1.96 (1.03–3.74)	2.54 (1.29–5.00)	0.011
p-value		0.013	0.040	0.007	
Model 3[c]					
OR (95%CI)	1 (ref.)	2.40 (1.19–4.82)	1.83 (0.93–3.60)	2.27 (1.14–4.55)	0.038
p-value		0.014	0.080	0.020	

Notes: CRP = C-reactive protein, MoCA-J = Japanese version of the Montreal Cognitive Assessment, IMT = Intima-media thickness, OR = Odds ratio, CI = Confidence interval, Q = Quartile, SD = Standard deviation

[a]Adjusted for sex, [b]Model 1 + education and smoking, [c]Model 2 + hypertension, diabetes mellitus, dyslipidemia, and mean IMT

The CRP levels in Japanese individuals are lower than those in individuals of other ethnicities. The median CRP levels in Japanese individuals (0.5 mg/L) were lower than those in African-American (3.2 mg/L), Hispanic (2.3 mg/L), white (1.5 mg/L), and Chinese individuals (0.7 mg/L) [27]. The Japanese study participants appeared to be well-suited for assessing an hs-CRP level below 1.0 mg/L.

A 25-year follow-up study showed that the second to fourth quartiles of hs-CRP (0.34–0.56, 0.57–1.00, and >1.00 mg/L) were associated with dementia risk in Japanese-American male residents [13]. Long-term systemic inflammation appears to be associated with the development of dementia.

The association between CRP level and dementia varies across dementia subtypes. Previous studies have shown that CRP concentration is associated with vascular dementia risk but not with Alzheimer's disease risk [28, 29]. Data on the dementia subtypes were not collected in this study. Dyslipidemia and BMI correlated with hs-CRP levels (Tables 1 and 2). Vascular dementia related to atherosclerosis was associated with both dyslipidemia and a higher BMI [30, 31], which were considered important risk factors for low cognitive function in the present study.

Years of education were correlated with hs-CRP levels in the 80-year-old group (Table 2). Lower years of education were associated with lower cognitive function [32]. In the present study, longer years of education were associated with the highest hs-CRP levels. Although the exact reason remains unclear, survivor bias may explain why thr participants with the highest hs-CRP levels had more years of education. To account for this confounding variable, Models 2 and 3 were adjusted for years of education.

Inflammation is a biological "response to injury." It is the response of cells and related substances in the body to external invasion, such as infection or traumatic stress, to protect the body from attack [33]. Although this study did not elucidate the specific pathophysiology of chronic inflammation, elevated blood cytokine levels due to chronic systemic inflammation caused by various factors can stimulate receptors in cerebral vascular cells, promote the opening of the tight junctions of the blood-brain barrier, and stimulate medullary reticular formation and the hypothalamus via the vagus nerve [34, 35]. This mechanism promotes excessive activation of microglia and astrocytes in the brain and causes neuronal degeneration and dementia [34].

The strength of the SONIC study was its narrow age range. Although aging is a major risk factor for cognitive decline, the present study examined the association between hs-CRP levels and MoCA-J scores in different age groups. This study involved a multidisciplinary team (physicians, nurses, nutritionists, dentists, and psychologists) and collected reliable data that included a wide range of confounding factors.

This study has several limitations. Owing to the cross-sectional and observational nature of this study, a causal relationship between hs-CRP levels and low cognitive function could not be established. Therefore, the relationship between hs-CRP levels and low cognitive function must be investigated in a prospective study. Further studies are needed to determine whether inflammatory markers are associated with the onset and progression of dementia in the Japanese population. Older adults who voluntarily participated in this study appeared to be healthier than those who did not. A previous study showed that the apolipoprotein E4 allele alters the association between CRP and dementia [36]; however, these data were not obtained.

Conclusions

This study found that high hs-CRP levels were associated with low cognitive function in both 70- and 80-year-old community-dwelling Japanese individuals.

Abbreviations

Hs-CRP	High-sensitivity C-reactive protein
OR	Odds ratio
CI	Confidence interval
CRP	C-reactive protein
SONIC study	Septuagenarians, Octogenarians, Nonagenarians Investigation with Centenarians study
IMT	Intima-media thickness
BMI	Body mass index
MCI	Mild cognitive impairment
MoCA-J	Japanese version of the Montreal Cognitive Assessment
Q	Quartile
SD	Standard deviation

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12877-024-05354-x.

Additional files 1: Description of data: (A) Histogram of the hs-CRP levels in the 70-year-old group; (B) Histogram of the hs-CRP levels in 80-year-old group

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Author contributions

KK, YG, KI, and HR designed the study. KK, HR, MK, KG, YA, YT, HA, YT, YT, KY, MK, TH, TI, YA, and MH collected the medical data. YG, SY, and YM collected the cognitive, psychological, and social data. MH conducted the statistical analyses. MH, MK, and KK wrote the manuscript. All authors have read and approved the final version of the manuscript.

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Data availability

The datasets analyzed during this study cannot be publicly shared due to ethical restrictions but are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The institutional review boards approved the SONIC study of the Osaka University Graduate School of Medicine, Dentistry, and Human Sciences and the Tokyo Metropolitan Institute of Gerontology (approval numbers 266, H22-E9, 22018, and 38, respectively). All participants provided written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. Global status report on the public health response to dementia. Geneva: World Health Organization. 2021. https://www.who.int/publications/i/item/9789240033245. Accessed 12 February 2024.
2. Ninomiya T. Research on future projection of the population of the elderly with dementia in Japan 2015. Ministry of Health, Labour and Welfare; 2015.
3. de la Torre JC. Alzheimer's disease is incurable but preventable. J Alzheimers Dis. 2010;20:861–70.
4. Zhong G, Wang Y, Zhang Y, Guo JJ, Zhao Y. Smoking is associated with an increased risk of dementia: a meta-analysis of prospective cohort studies with investigation of potential effect modifiers. PLoS ONE. 2015;10:e0118333.
5. Rehm J, Hasan OSM, Black SE, Shield KD, Schwarzinger M. Alcohol use and dementia: a systematic scoping review. Alzheimers Res Ther. 2019;11:1.
6. Kivipelto M, Ngandu T, Fratiglioni L, Viitanen M, Kåreholt I, Winblad B, et al. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. Arch Neurol. 2005;62:1556–60.
7. Ohara T, Doi Y, Ninomiya T, Hirakawa Y, Hata J, Iwaki T, et al. Glucose tolerance status and risk of dementia in the community: the Hisayama study. Neurology. 2011;77:1126–34.
8. McGrath ER, Beiser AS, DeCarli C, Plourde KL, Vasan RS, Greenberg SM, et al. Blood pressure from mid- to late life and risk of incident dementia. Neurology. 2017;89:2447–54.
9. Kivimäki M, Singh-Manoux A, Pentti J, Sabia S, Nyberg ST, Alfredsson L, et al. Physical inactivity, cardiometabolic disease, and risk of dementia: an individual-participant meta-analysis. BMJ. 2019;365:l1495.
10. Leonardo S, Fregni F. Association of inflammation and cognition in the elderly: a systematic review and meta-analysis. Front Aging Neurosci. 2023;15:1069439.
11. Maeda S, Takeya Y, Oguro R, Akasaka H, Ryuno H, Kabayama M, et al. Serum albumin/globulin ratio is associated with cognitive function in community-dwelling older people: the septuagenarians, octogenarians, nonagenarians Investigation with centenarians study. Geriatr Gerontol Int. 2019;19:967–71.
12. Zheng F, Xie W. High-sensitivity C-reactive protein and cognitive decline: the English Longitudinal Study of Ageing. Psychol Med. 2018;48:1381–9.
13. Schmidt R, Schmidt H, Curb JD, Masaki K, White LR, Launer LJ. Early inflammation and dementia: a 25-year follow-up of the Honolulu-Asia Aging Study. Ann Neurol. 2002;52:168–74.
14. Watanabe Y, Kitamura K, Nakamura K, Sanpei K, Wakasugi M, Yokoseki A, et al. Elevated C-reactive protein is associated with cognitive decline in outpatients of a general hospital: the Project in Sado for Total Health (PROST). Dement Geriatr Cogn Dis Extra. 2016;6:10–9.
15. Gondo Y, Masui Y, Kamide K, Ikebe K, Arai Y, Ishizaki T. SONIC study: a longitudinal cohort study of the older people as part of a centenarian study. In: Pachana NA, editor. Encyclopedia of Geropsychology. Singapore: Springer; 2017. pp. 2227–36.
16. Myers GL, Rifai N, Tracy RP, Roberts WL, Alexander RW, Biasucci LM, et al. CDC/AHA Workshop on Markers of Inflammation and cardiovascular disease: application to clinical and Public Health Practice: report from the laboratory science discussion group. Circulation. 2004;110:e545–9.

17. Ridker PM. High-sensitivity C-reactive protein, inflammation, and cardiovascular risk: from concept to clinical practice to clinical benefit. Am Heart J. 2004;148(Suppl):S19–26.
18. Cushman M, Arnold AM, Psaty BM, Manolio TA, Kuller LH, Burke GL, et al. C-reactive protein and the 10-year incidence of coronary heart disease in older men and women: the cardiovascular health study. Circulation. 2005;112:25–31.
19. de Groot E, Hovingh GK, Wiegman A, Duriez P, Smit AJ, Fruchart JC, et al. Measurement of arterial wall thickness as a surrogate marker for atherosclerosis. Circulation. 2004;109(Suppl 1):III33–8.
20. Takiuchi S, Kamide K, Miwa Y, Tomiyama M, Yoshii M, Matayoshi T, et al. Diagnostic value of carotid intima-media thickness and plaque score for predicting target organ damage in patients with essential hypertension. J Hum Hypertens. 2004;18:17–23.
21. Araki E, Goto A, Kondo T, Noda M, Noto H, Origasa H, et al. Japanese clinical practice guideline for diabetes 2019. Diabetol Int. 2020;11:165–223.
22. Kinoshita M, Yokote K, Arai H, Iida M, Ishigaki Y, Ishibashi S, et al. Japan Atherosclerosis Society (JAS) guidelines for prevention of atherosclerotic cardiovascular diseases 2017. J Atheroscler Thromb. 2018;25:846–984.
23. Umemura S, Arima H, Arima S, Asayama K, Dohi Y, Hirooka Y, et al. The Japanese Society of Hypertension guidelines for the management of hypertension (JSH 2019). Hypertens Res. 2019;42:1235–481.
24. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53:695–9.
25. Fujiwara Y, Suzuki H, Yasunaga M, Sugiyama M, Ijuin M, Sakuma N, et al. Brief screening tool for mild cognitive impairment in older Japanese: validation of the Japanese version of the Montreal Cognitive Assessment. Geriatr Gerontol Int. 2010;10:225–32.
26. Chei CL, Yamagishi K, Ikeda A, Noda H, Maruyama M, Cui R, et al. C-reactive protein levels and risk of disabling dementia with and without stroke in Japanese: the circulatory risk in communities Study (CIRCS). Atherosclerosis. 2014;236:438–43.
27. Kelley-Hedgepeth A, Lloyd-Jones DM, Colvin A, Matthews KA, Johnston J, Sowers MR, et al. Ethnic differences in C-reactive protein concentrations. Clin Chem. 2008;54:1027–37.
28. Engelhart MJ, Geerlings MI, Meijer J, Kiliaan A, Ruitenberg A, van Swieten JC, et al. Inflammatory proteins in plasma and the risk of dementia: the Rotterdam study. Arch Neurol. 2004;61:668–72.
29. Ravaglia G, Forti P, Maioli F, Chiappelli M, Montesi F, Tumini E, et al. Blood inflammatory markers and risk of dementia: the Conselice Study of Brain Aging. Neurobiol Aging. 2007;28:1810–20.
30. Watanabe T, Koba S, Kawamura M, Itokawa M, Idei T, Nakagawa Y, et al. Small dense low-density lipoprotein and carotid atherosclerosis in relation to vascular dementia. Metabolism. 2004;53:476–82.
31. Solfrizzi V, Scafato E, Capurso C, D'Introno A, Colacicco AM, Frisardi V, et al. Metabolic syndrome and the risk of vascular dementia: the Italian longitudinal study on Ageing. J Neurol Neurosurg Psychiatr. 2010;81:433–40.
32. Takasugi T, Tsuji T, Nagamine Y, Miyaguni Y, Kondo K. Socio-economic status and dementia onset among older Japanese: a 6-year prospective cohort study from the Japan gerontological evaluation study. Int J Geriatr Psychiatr. 2019;34:1642–50.
33. Camps J, García-Heredia A. Introduction: oxidation and inflammation, a molecular link between non-communicable diseases. Adv Exp Med Biol. 2014;824:1–4.
34. Walker KA, Ficek BN, Westbrook R. Understanding the role of systemic inflammation in Alzheimer's disease. ACS Chem Neurosci. 2019;10:3340–2.
35. Huang X, Hussain B, Chang J. Peripheral inflammation and blood-brain barrier disruption: effects and mechanisms. CNS Neurosci Ther. 2021;27:36–47.
36. Haan MN, Aiello AE, West NA, Jagust WJ. C-reactive protein and rate of dementia in carriers and non carriers of apolipoprotein APOE4 genotype. Neurobiol Aging. 2008;29:1774–82.

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