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Original Research Article

Elevated C-Reactive Protein Is Associated with Cognitive Decline in Outpatients of a General Hospital: The Project in Sado for Total Health (PROST)

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Key Words

C-reactive protein · Cognition in outpatients · Elderly Japanese population · Cross-sectional studies · Epidemiology

Abstract

Background/Aims: We aimed to determine whether the concentration of serum C-reactive protein (CRP) is associated with cognitive function in an adult Japanese population. ***Methods:*** Participants of this cross-sectional study were from a subgroup of the Project in Sado for Total Health (PROST; n = 454; mean age, 70.5 years). The cognitive state was evaluated using the Mini-Mental State Examination (MMSE), and those with an MMSE score <24 were considered 'cognitively declined'. Concentrations of serum high-sensitivity CRP were measured. Multiple logistic regression analysis was used to calculate odds ratios (ORs) for cognitive decline, adjusting for the covariates of age, sex, BMI, disease history, and *APOE* allele. ***Results:*** Of the 454 participants, 94 (20.7%) were cognitively declined. Relative to the lowest (first) quartile of CRP concentration, adjusted ORs were 1.29 (95% CI 0.61–2.75) for the second, 1.78 (95% CI 0.82–3.86) for the third, and 3.05 (95% CI 1.45–6.42) for the highest (fourth) quartiles (p for trend = 0.018). When data were stratified by sex, the association between CRP concentration and cognitive decline was observed only in women. ***Conclusion:*** Our findings suggest an association between higher CRP concentration and lower cognitive function. Chronic inflammation may affect cognitive function in adults, in particular women.

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Introduction

The aging of populations, and the resulting increase in the number of elderly with cognitive decline and dementia, is a global health issue [1, 2]. Alzheimer's disease is the most common form of dementia, accounting for 60–80% of dementia cases [3]. The disease is also an immediate issue in Japan, where the population aging rate is the highest in the world [4]. Recent studies have shown that pathological changes in patients with Alzheimer's disease occur while individuals are cognitively normal [5].

C-reactive protein (CRP) participates in the systemic response to inflammation [6], and is the most commonly used marker of acute inflammation. Recent studies have shown that chronic, low-grade inflammation, as reflected in a slight increase in CRP concentration within a normal range, underpins many diseases, such as cardiovascular disease (CVD), metabolic syndrome, and cancer [7–9]. Emerging evidence suggests the contribution of chronic activation of immune responses in neurodegeneration, which leads to cognitive dysfunction [10].

Despite the physiological relevance of chronic inflammation in neurodegenerative diseases [11, 12], evidence for an association between CRP concentration and cognitive decline is insufficient. Although some studies have reported an association between increased CRP concentration and a modest increase in the risk of dementia [13] or cognitive decline [14], this association is inconclusive. Moreover, among studies that have reported on this association, population-based epidemiological studies using East Asian populations are limited [15–18]. CRP concentration varies widely by ethnic background. Indeed, Japanese and Chinese populations exhibit markedly lower CRP concentrations compared to non-Asian populations [19, 20].

Against this backdrop, this study aimed to assess the relationship between serum CRP concentration and cognitive status in a Japanese population consisting of middle-aged and older individuals.

Materials and Methods

Population

The present cross-sectional study analyzed a subgroup of the Project in Sado for Total Health (PROST), a hospital-based cohort study in Sado City, Niigata Prefecture, Japan (http://square.umin.ac.jp/prost/). The PROST began in June 2008 and is an ongoing cohort study targeting outpatients (age ≥20 years) of Sado General Hospital [21]. In the current study, 1,272 individuals registered with the PROST before November 19, 2012 were analyzed. All participants underwent a general physical examination and provided their medical histories. From June 2008 to May 2011 (the first period), participants who were suspected of having a cognitive problem from a self-administered questionnaire [22] were asked to take the Mini-Mental State Examination (MMSE). From June 2011 to the present, all participants were asked to take the MMSE. The current study used data of participants registered between June 2008 and November 19, 2012. In the first period, 858 individuals were registered, and 210 took the MMSE (24.5%). From June 2011 to November 19, 2012 (the second period), 372 (89.9%) of 414 participants took the MMSE. The distribution of age, male percentage, and the MMSE score significantly differed by period of registration. The mean ± SD of age was 73.1 ± 9.3 years for the first period and 68.7 ± 10.6 years for the second period ($p < 0.001$ by Student's t test). The male percentage was 37.2% (n = 70) for the first period and 54.1% (n = 144) for the second period ($p < 0.001$ by χ^2 test). The mean ± SD of the MMSE score was 25.3 ± 3.2 points for the first period and 26.3 ± 3.4 points for the second period ($p < 0.001$ by Student's t test). There was no significant difference in the distribution of the serum CRP

concentration between the first and second periods; medians and interquartile ranges were 0.482 mg/l (0.215–1.20) and 0.465 mg/l (0.233–1.060), respectively (p = 0.892 by Student's t test of the logarithm of CRP). Accordingly, a total of 582 participants who took the MMSE were considered the starting population. They visited departments of internal medicine (84.6%), ophthalmology (26.7%), orthopedics (22.9%), neurology (11.9%), dermatology (6.2%), otorhinology (5.3%), dentistry (5.1%), neurosurgery (2.9%), general surgery (2.6%), obstetrics and gynecology (2.4%), and cardiac surgery (0.4%) (multiple answers were allowed for this survey). None of the participants visited departments of radiation or anesthesiology. Of the 582 participants, 581 agreed to undergo blood examinations, and CRP measurements could be obtained from 567 samples. Eighty-nine participants undergoing hemodialysis and 24 with a CRP level ≥10 mg/l (i.e., a value indicative of acute inflammation) were excluded [23]. The final study population consisted of 454 participants for whom data on both serum CRP concentration (<10 mg/l) and MMSE were available. Informed consent was obtained from all participants. The Ethics Committee of Niigata University School of Medicine approved the study protocol.

Outcome and Predictor Variables

The primary outcome of this study was cognitive function, as assessed by the MMSE [24], a simple 30-point test of general cognitive function. An MMSE score <24 was defined as 'cognitively declined' [24]. The main predictor variable was the concentration of serum high-sensitivity CRP. Covariates included age, sex, BMI, self-reported history of stroke, ischemic heart disease, hypertension, diabetes, and *APOE* ε4 allele. For analysis, variables were categorized as follows: cognitively declined (absence = 0, presence = 1), CRP (1, 2, 3, and 4 from the lowest to highest quartile), sex (male = 1, female = 2), self-reported history of stroke (absence = 0, presence = 1), self-reported history of ischemic heart disease (absence = 0, presence = 1), self-reported history of hypertension (absence = 0, presence = 1), self-reported history of diabetes (absence = 0, presence = 1), and *APOE* ε4 allele (null = 0, heterozygous or homozygous = 1).

Laboratory Measurements

A nonfasting blood sample was drawn from each participant and immediately stored at 4°C. Serum was obtained the same day by centrifuging the sample at 3,000 rpm for 10 min and stored at −80°C until biochemical analysis. Serum high-sensitivity CRP concentration was determined with a latex nephelometry assay using an automatic analyzer (Behring Nephelometer II; Siemens Healthcare Diagnostics Inc.; Deerfield, Ill., USA). Intra- and interassay coefficient of variation values were 0.9–1.7 and 2.3–3.0%, respectively. The *APOE* allele was genotyped as previously described [25].

Statistical Analysis

Data for participant characteristics are presented as percentages or mean ± SD. The linear trend of these characteristics based on quartiles of CRP concentration was analyzed with the Cochran-Armitage trend test for categorical variables, and simple regression analysis for continuous variables. Correlation coefficients for all pairs of variables, as assessed by Spearman's correlation analyses, were less than 0.3; hence, multicolinearity was not considered. In association analyses, serum CRP concentration was divided into quartiles, from the lowest to the highest concentration. Associations between the prevalence of cognitive decline (MMSE score <24) and quartiles of CRP concentrations were assessed by calculating odds ratios (ORs) with simple and multiple logistic regression analyses. Interactions between quartiles of CRP concentration and covariates were assessed by addition of the interaction terms: 'CRP quartile' × 'covariates', with the backward elimination procedure. This was

Table 1. Participant characteristics by quartiles of serum CRP concentration

	Quartile of serum CRP concentration				p for trend
	1 <0.223 mg/l (n = 113)	2 0.223–0.471 mg/l (n = 114)	3 0.471–1.09 mg/l (n = 112)	4 ≥1.09 mg/l (n = 115)	
Male	49 (43.4)	52 (45.6)	59 (52.7)	54 (47.0)	0.399
Age, years	70.0±9.9	70.7±10.6	71.6±8.6	69.8±11.9	0.616
Body mass index	22.8±3.1[a]	23.7±3.4	24.2±4.2[b]	25.4±4.5[a]	<0.001
Stroke (self-reported history)	9 (8.0)	14 (12.4)[a]	11[a] (9.9)	9 (7.8)	0.809
Ischemic heart disease (self-reported history)	8 (7.0)	11 (9.7)[a]	7 (6.3)	9 (7.8)	0.913
Hypertension (self-reported history)	63 (55.8)	68 (59.7)	79 (70.5)	74 (64.9)[a]	0.060
Diabetes (self-reported history)	33 (29.5)[a]	29 (25.7)[a]	34 (30.4)	32 (27.8)	0.990
Presence of *APOE* ε4 allele	36 (31.9)	28 (24.6)	8 (7.3)[b]	22 (19.1)	0.001
MMSE score	26.2±3.7	26.4±3.1	25.8±3.2	25.2±3.3	0.009

Values are presented as mean ± standard deviation or n (%). [a] One missing value. [b] Two missing values.

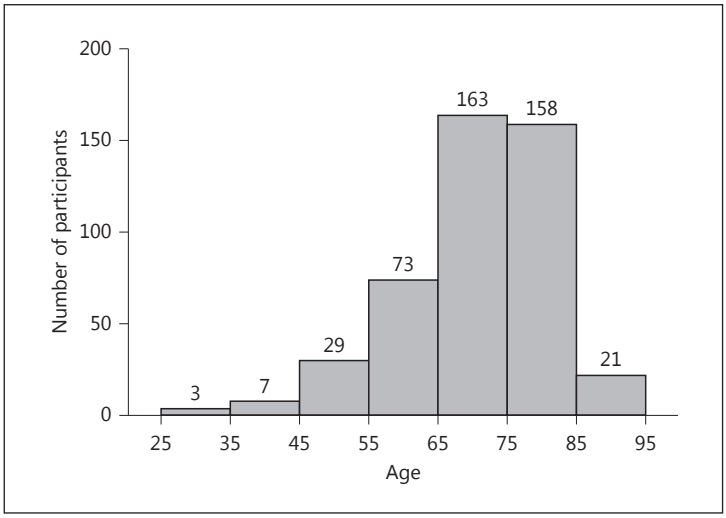

Fig. 1. The age distribution of study participants. The value above the bar shows the number of subjects in each bin.

followed by calculation of unadjusted ORs, ORs adjusted for age and sex, and ORs adjusted for all covariates. All analyses were conducted using SAS (ver. 9.4, SAS Institute Inc., Cary, N.C., USA). $p < 0.05$ was considered statistically significant.

Results

The study population consisted of 454 participants (mean age, 70.5 ± 10.3 years; range, 29–91 years; fig. 1), of whom 214 (47.4%) were male. The mean MMSE score was 25.9 ± 3.3, and 94 (20.7%) participants had an MMSE score <24 and were considered cognitively declined. The mean BMI was 24.0 ± 3.9 (n = 450), and the median serum CRP concentration was 0.471 mg/l (interquartile range, 0.223–1.09). For the 452 participants with successful genotyping results, 94 (20.8%) were found to have at least one allele of *APOE* ε4. Participant characteristics based on quartiles of serum CRP concentration are shown in table 1. Those

Table 2. ORs for cognitive decline (MMSE score <24) according to quartiles of serum CRP concentration

	Quartile of serum CRP concentration				p for trend
	1 <0.223 mg/l	2 0.223–0.471 mg/l	3 0.471–1.09 mg/l	4 ≥1.09 mg/l	
All (n = 454)					
Not adjusted	1 (ref.)	1.28 (0.63–2.57)	1.38 (0.69–2.77)	2.37 (1.23–4.55)	0.047
Adjusted for age and sex	1 (ref.)	1.19 (0.57–2.47)	1.31 (0.64–2.69)	2.47 (1.25–4.91)	0.036
Adjusted for all covariates[a]	1 (ref.)	1.29 (0.61–2.75)	1.78 (0.82–3.86)	3.05 (1.45–6.42)	0.018
Men (n = 214)					
Not adjusted	1 (ref.)	1.71 (0.64–4.60)	0.80 (0.28–2.33)	1.31 (0.64–4.57)	0.455
Adjusted for age	1 (ref.)	1.73 (0.62–4.77)	0.71 (0.24–2.12)	1.38 (0.49–3.90)	0.343
Adjusted for all covariates[b]	1 (ref.)	2.27 (0.76–6.81)	1.29 (0.39–4.30)	2.35 (0.74–7.44)	0.347
Women (n = 240)					
Not adjusted	1 (ref.)	0.90 (0.33–2.52)	2.19 (0.86–5.57)	3.70 (1.54–8.87)	0.004
Adjusted for age	1 (ref.)	0.77 (0.26–2.24)	2.21 (0.83–5.92)	3.84 (1.50–9.80)	0.003
Adjusted for all covariates[b]	1 (ref.)	0.85 (0.27–2.62)	3.29 (1.11–9.79)	3.66 (1.30–10.28)	0.008

Figures in parentheses indicate 95% CIs. [a] Age, sex, body mass index, history of stroke, history of ischemic heart disease, history of hypertension, history of diabetes, and presence of *APOE* ε4 allele. [b] Age, body mass index, history of stroke, history of ischemic heart disease, history of hypertension, history of diabetes, and presence of *APOE* ε4 allele.

with a higher BMI had significantly higher concentrations of serum CRP (p for trend < 0.001). The percentage of *APOE* ε4 carriers was significantly lower in higher CRP quartiles (p for trend = 0.001). MMSE scores were also significantly lower in higher CRP quartiles (p for trend = 0.009).

ORs for cognitive decline in relation to CRP quartiles are shown in table 2. In all models analyzed, higher CRP quartiles were significantly associated with increased ORs for cognitive decline (MMSE score <24). The unadjusted OR for the highest quartile (Q4) compared with the lowest quartile (Q1, reference) was 2.37 (95% CI 1.23–4.55). When adjusted for age and sex, the OR for Q4 compared with Q1 was similar to the unadjusted model (OR 2.47, 95% CI 1.25–4.91). Adjusting for all covariates increased the OR for Q4 compared with Q1 (OR 3.05, 95% CI 1.45–6.42). When stratified by sex, the association of CRP concentration with cognitive decline was observed in women (adjusted p for trend = 0.008), but not in men (adjusted p for trend = 0.347) (table 2). The interaction of sex and CRP concentration with cognitive function was of marginal significance (p = 0.0603). The distribution of CRP concentrations did not significantly differ between women and men (median, 0.435 vs. 0.500 mg/l; p = 0.272, Wilcoxon rank sum test).

Discussion

The present study evaluated associations between serum concentrations of CRP and cognitive decline (MMSE <24 points) in a middle-aged and elderly Japanese population. The OR for cognitive decline was significantly higher in participants in the highest CRP quartile compared to those in the lowest quartile. The significance of this finding was even stronger after controlling for age, sex, BMI, history of stroke, history of ischemic heart disease, history of hypertension, history of diabetes, and presence of the *APOE* ε4 allele.

Previous epidemiological studies that assessed the association between CRP concentration and cognitive function in general populations were mainly from Western countries,

and only a few such studies have been conducted in East Asian populations. Regarding the latter, two studies targeted Chinese populations and one targeted a Japanese population [15–17]. The first study was a hospital-based case-control study which found higher CRP concentrations in the cognitive impairment (case) group [15]. The second study, a prospective study of patients with mild cognitive impairment, reported that a higher CRP concentration at baseline increased the risk of dementia at 2 years of follow-up [16]. The third study was a case-control study of residents from two rural communities of Japan that found an association between higher CRP concentrations and an increased risk of disabling dementia (case), however only in individuals with a history of stroke [17]. In that study [17], the participants with disabling dementia were selected based on information from the national long-term care insurance program, and so no information was available regarding cognitive function, making cross-study comparisons difficult. In the present study, we found a clear association between CRP concentration and cognitive decline using the MMSE, an objective measure of cognitive status.

Recent studies revealed that systemic inflammation is strongly associated with atherosclerosis and diabetes, and is a well-known risk factor for Alzheimer's disease [26, 27]. CRP, an acute-phase plasma protein, increases rapidly in response to inflammation and infection [6]. CRP is mainly produced in hepatocytes, but Yasojima et al. [28] observed the neuronal expression of CRP in postmortem AD brains. Neuroinflammation is involved in the pathogenesis, progression, and prognosis of various neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease [10]. Although it is unlikely that neuronal CRP affects the concentration of blood CRP, it would be of interest to know if inflammatory changes in the CNS affect the peripheral immune response.

Concentrations of CRP vary across ethnicities [19, 20], with the highest concentrations found in African-Americans, followed by Hispanics and Caucasians [19]. East Asians, such as Japanese and Chinese populations, have the lowest concentrations of CRP [19]. Studies of the general Japanese population living in Japan reported a median CRP concentration of <0.5 mg/l [29, 30], which is consistent with that found in the present study. In contrast, the average concentration of CRP in healthy American adults is reportedly about or more than 2 mg/l [31, 32]. The Honolulu Aging Study reported a median CRP concentration of 0.57 mg/l for Japanese Americans [33], which is lower than that of non-Asian populations, but higher than that of Japanese people living in Japan [29, 30] (including our study population). These findings suggest that differences in concentrations of CRP derive mainly from the genetic background, but are also affected by lifestyle factors [29].

CRP is the most extensively studied risk factor of CVD and recommended strongly as a prognostic marker of acute coronary syndrome [34]. However, a recent study reported a significant influence of ethnicity on biomarker risk association with the incidence of CVD in an ethnic cohort which included Caucasians, African Americans, Hispanics, and Chinese people. That study reported that CRP concentration was only associated with the incidence of CVD in Caucasians [35]. Given the systemic effects of high CRP concentrations, or differences in mechanisms that lead to high CRP concentrations in certain ethnicities, the effects of high CRP concentrations on cognitive function may also differ across ethnicities.

Previous cross-sectional studies targeting general community-dwelling populations [36–42] agree for the most part that higher CRP concentrations are associated with lower cognitive function. Yet, results from prospective studies targeting general populations have not always been consistent. For instance, some prospective studies have reported positive or marginal associations [33, 36, 43–45], whereas some report no association [46, 47] or even an inverse association [48, 49]. Most of these studies were conducted using a multiethnic background. Heterogeneity of the study population may have accounted for some of these inconsistencies.

In a cross-sectional study of 445 males and 422 females aged >60 years, Canon and Crimmins [38] found an association between higher CRP concentrations and cognitive decline in females, but not in males. In the present study, when stratifying participants by sex, cognitive decline was only associated with high CRP concentrations in women. The probability of interaction was not statistically significant, but marginal ($p = 0.0603$). However, with a larger sample size, the interaction of sex with CRP concentration may have been more pronounced. Age-related reductions in sex hormones affect the immune system and cause chronic, low-grade inflammation in the elderly [50]. This reduction in sex hormones, especially estrogen and progesterone, is far more pronounced in postmenopausal women than in men. Studies on autoimmune diseases suggest that immune responses present differently in men and women [51]. It will be interesting to clarify the effects of various sex-dependent hormonal environments on the maintenance of cognitive function in old age.

APOE ε4 allele is the most potent genetic risk factor of Alzheimer's disease [52–54]. In our study, *APOE* ε4 was an independent predictor of a lower MMSE score (data not shown). Interestingly, the percentage of *APOE* ε4 carriers was lower in participants with a higher serum CRP concentration (table 1). A lower CRP concentration is reportedly associated with *APOE* ε4 allele in a variety of populations [55–61], and a higher CRP has been suggested to be associated with a lower risk of dementia including Alzheimer's disease in older Mexican Americans carrying at least one ε4 allele [61]. In our study, however, no association was found between CRP and *APOE* ε4 allele ($p = 0.576$). Several lines of evidence suggest a pronounced link between *APOE* ε4 and Alzheimer's disease in women compared to men [62]. In addition to the association between CRP and sex discussed above, it would be interesting to analyze the effect of the *APOE* ε4 genotype with a larger sample size.

This study has some limitations worth noting. First, participants were outpatients of Sado General Hospital. Nonetheless, we believe that our participants form a major portion of the community-dwelling elderly of Sado City for the following reasons: Sado City is located on an island, and Sado General Hospital is the only core hospital on the island. One feature of the Japanese medical system is free access to medical institutions. Thus, most residents of Sado City receive care at Sado General Hospital. The second limitation of the study is that the subject selection criterion for those taking the MMSE was changed during the period of subject recruitment. During the first period (from June 2008 to May 2011), those who were asked to take the MMSE were suspected of having some cognitive problem; during the second period (from June 2011 to November 19, 2012), all participants were asked to take the MMSE. The average age, the MMSE score, and the percentage of male participants differed by period of registration, but not the median of serum CRP concentration. In the Hisayama study, a community-based prospective study in Japan, the median of CRP concentration among 2,589 residents aged over 40 years was 0.43 mg/ml [29], which was comparable with the result of the current study (median 0.47 mg/ml), despite the above two limitations. Thus, we believe the selection bias would be small. Finally, this was a cross-sectional study, and thus causal relationships could not be determined. Prospective studies that assess the causal relationship between CRP concentration and cognitive decline are warranted.

In conclusion, the present study revealed a clear association between serum CRP concentration and cognitive impairment in a community-dwelling elderly population in Japan. PROST is an ongoing prospective cohort study carried out in a suburban city in Japan. Further studies with a larger sample size would allow more detailed analysis of the contribution of gender and *APOE* ε4 genotype difference to the risk of cognitive decline. Furthermore, longitudinal analyses of this population may provide further insight into the possibility of predicting future cognitive decline using peripheral inflammatory markers.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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