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High Levels of Serum C-Reactive Protein (CRP) are Associated with Increased Risk of All-Cause Mortality, but not Dementia, in the Oldest-Old: Results from The 90+ Study

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Abstract

OBJECTIVES—To evaluate whether high levels of C-reactive protein (CRP) in serum are associated with increased risk of all-cause dementia or mortality in the oldest-old.

DESIGN—Prospective.

SETTING—Research clinic and in-home visits.

PARTICIPANTS—Population-based sample of adults (n = 227; age, 93.9 ± 2.8 years) from ***The 90+ Study***, a longitudinal cohort study of people aged 90 and older.

MEASUREMENTS—CRP levels were divided into three groups according to the assay detection limit: Undetectable (< 0.5 mg/dL), detectable (0.5-0.7 mg/dL) and elevated (≥ 0.8 mg/dL). Neurological examination was used to determine dementia diagnosis (DSM-IV criteria). Adjusted hazards ratios (HR) and 95% confidence intervals (CI) were computed using Cox regression and results were stratified by gender and apolipoprotein E4 (APOE4) genotype.

RESULTS—Subjects with detectable CRP levels had significantly increased risk of mortality (HR 1.7, 95% CI 1.0-2.9), but not dementia (HR 1.2, 95% CI 0.6-2.1), 0.4-4.5 years later relative to subjects with undetectable CRP. The highest relative risk for both dementia and mortality was in APOE4 carriers with detectable CRP (dementia HR: 4.5, 95% CI 0.9-23.3; mortality HR: 5.6, 95% CI 1.0-30.7).

CONCLUSION—High levels of CRP are associated with increased risk of mortality in those aged 90 and older, particularly in APOE4 carriers. There was a trend towards an increased risk of dementia in APOE4 carriers with high CRP levels, although this relationship did not reach significance. High levels of CRP in the oldest-old represent a risk factor for negative outcomes.

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Keywords

c-reactive protein; dementia; mortality; nonagenarian; serum

INTRODUCTION

C-reactive protein (CRP) is an acute-phase protein that is upregulated in response to infection or tissue injury1. CRP levels increase with age2 which may partly reflect increased prevalence of clinical and subclinical disease in the elderly3. High levels of CRP are a risk factor for both dementia and mortality.

Several large, prospective studies have found an association between high CRP levels and increased risk of dementia and cognitive decline. High levels of CRP were associated with increased risk of all-cause dementia 1.5, 4, and 25 years later in the Rotterdam Study, the Conselice Study of Brain Aging, and the Honolulu-Asia Aging Study, respectively4-6. High levels of CRP were associated with increased risk of 2-year cognitive decline in the Health ABC Study7, 5-year cognitive decline in the Helsinki Aging Study8, and cognitive decline 25-31 years later in the Honolulu-Asia Aging Study9. However, other studies have not found an association between high CRP levels and increased risk of cognitive decline10, 11, including a study of those aged 85-90 years12. Whether high levels of CRP are a risk factor for dementia in the oldest-old, those aged 90 and older, is not known.

High levels of CRP are also associated with increased risk of all-cause mortality in the elderly. The Helsinki Aging Study showed increased risk of both 5-year8 and 10-year13 all-cause mortality in those with high CRP levels. That study included subjects aged 75, 80, and 85 years and observed that the association between CRP and 10-year mortality weakened with age and was significant only in the 75-year old cohort13. The Vitality 90+ Study, a study of Finnish nonagenarians, found a trend towards increased risk of all-cause mortality in subjects with high CRP levels14, although this risk reached significance only in those lacking an apolipoprotein E4 (APOE4) allele15. Thus, high levels of CRP are associated with increased risk of mortality, although it is unclear if this association weakens with age and is modified by APOE genotype.

Those aged 90 and older are the fastest-growing age group in the United States16, but little is known about CRP levels and risk of dementia or mortality in this group. The purpose of this study was to determine if high levels of serum CRP are associated with increased risk of all-cause dementia or all-cause mortality in subjects aged 90 and older.

METHODS

Subjects

Participants were members of *The 90+ Study*, a population-based, longitudinal cohort study of people aged 90 years and older. The cognitive and functional status of the subjects included in this study were evaluated in-person approximately every six months. In-person evaluation included a neurological examination, neuropsychological testing, medical history questionnaire, blood draw, and other procedures17. Functional status was determined by the Functional Activities Questionnaire (FAQ)18. As part of the neurological examination, a neurologist or nurse practitioner assigned a cognitive diagnosis of Dementia if the participant met Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria for dementia19. Participants with no cognitive or functional loss were assigned a diagnosis of Normal and participants with some cognitive loss or functional loss due to cognitive

impairment who did not meet criteria for dementia were assigned a diagnosis of Cognitive Impairment, No Dementia (CIND)20.

The inclusion criteria for this study were: 1) cognitive diagnosis of nondemented (Normal or CIND) from an in-person examination; 2) serum CRP measurement from that examination (baseline examination); and 3) cognitive diagnosis obtained at a follow-up in-person examination. Figure 1 shows a flow chart for participant inclusion in this study. Two hundred twenty seven subjects met the inclusion criteria. The 163 nondemented subjects who did not have a CRP measurement (which requires a blood draw) were significantly older, more likely to be female and more likely to have a diagnosis of CIND than those who did (all P-values < .02).

CRP measurement

Non-fasting serum CRP was measured using an immunoturbidimetric assay (Beckman Synchron LX System, Kit number 465131). Reference material was traceable to BCR CRM 470 and the coefficient of variation was < 5% for the range of CRP values reported in this study. This assay is not high-sensitivity. The lower detection limit of the assay is 0.5 mg/dL and values of 0.8 mg/dL or higher are considered elevated.

Covariates

The following variables were analyzed for an association with CRP: age, gender, education (≤ high school graduate, some college/vocational school/college grad, or any post-graduate education), presence of one or more APOE4 alleles, smoking, alcohol use, and estrogen use (in women)(current use versus not currently using), medical history of hypertension, coronary artery disease (CAD), myocardial infarction, atrial fibrillation/arrythmias, heart valve disease, congestive heart failure (CHF), stroke, transient ischemic attack (TIA), high cholesterol, diabetes, rheumatoid arthritis, or osteoarthritis (any history versus no history). All variables except APOE were self-reported as part of an in-person interview.

Outcomes

Two outcomes were selected as endpoints. The first outcome was a cognitive diagnosis of dementia determined by neurological examination. The second outcome was mortality (in the same group of subjects) to determine if subjects with high CRP may be dying before reaching the outcome dementia. Mortality was ascertained by informant report, generally during an attempt to schedule a follow-up visit, and by vital status search of national death indexes.

Statistical analysis

Differences were analyzed using chi-square for categorical variables, analysis of variance (ANOVA) for tests of means, Mann-Whitney or Kruskal-Wallis for tests of medians, and Spearman rho for correlations. CRP was categorized into three groups for the primary analysis: 1) undetectable levels (< 0.5 mg/dL); 2) detectable levels below the value considered elevated in this assay (0.5-0.7 mg/dL); and 3) elevated levels (≥ 0.8 mg/dL).

Cox regression with delayed entry was used to compute hazard ratios (HR) and 95% confidence intervals (CI) for the outcomes all-cause dementia and all-cause mortality. Chronological age was used as the time scale in the Cox model. Age at baseline examination was considered the age at entry, and age at first follow-up examination with a dementia diagnosis or age at death were considered the age at outcome. For both analyses, subjects not reaching the outcome of interest were censored at the age of their last follow-up examination. In addition to baseline age, gender, education, and APOE4 status, covariates were included in the model if that covariate was associated with CRP levels (P < .10) or

differed among the three CRP groups in frequency (P < .10). Two models were used: Model 1 adjusted for age and Model 2 adjusted for age, gender, education, APOE4 status, and medical history of hypertension, CAD, CHF, and TIA. Results were then stratified by gender and APOE genotype, and considered significant at P < .05. Analyses were performed using SAS 9.1.

Since subjects with high CRP levels may be in the early stages of dementia or ill and thus more likely to meet the outcomes of interest, lagged analyses were performed. Results were lagged one year, meaning that those subjects with less than one year of follow-up time were excluded.

RESULTS

Baseline CRP by covariates

CRP levels increased with age (Spearman's rho = 0.18; P < .01) and were significantly higher in those with a history of hypertension (P = .03). There was a trend towards higher CRP in those with a history of CHF (P = .08) and TIA (P = .06). CRP did not differ by other variables (P > .10), including gender (P = .92) and APOE4 status (P = .22).

Baseline characteristics by CRP group

At baseline, subjects ranged in age from 90-102 years (mean ± standard deviation; 93.9 ± 2.8 years). Subjects with elevated CRP levels were significantly older (94.7 ± 3.2 years) than subjects with undetectable (93.5 ± 2.7 years) or detectable (93.5 ± 2.5 years) CRP levels (P = .01).

Table 1 shows the baseline variables for all subjects and subjects by CRP group. The P-values are for comparisons of variable frequency between the three CRP groups. The three groups differed significantly by history of hypertension (P = .04) and history of CAD (P < .01). There was a trend towards a difference in education (P = .06).

All-cause dementia

Follow-up times ranged from 0.4-4.3 years (2.1 ± 1.2; total person-years = 472.3). The average time to dementia was 1.7 ± 1.1 years. Table 2 shows the hazard ratios for all-cause dementia in subjects with detectable or elevated CRP levels relative to subjects with undetectable CRP. In both age-adjusted and fully-adjusted models, detectable and elevated CRP were not associated with risk of dementia in all subjects or in men or women alone. While APOE4 was not a significant risk factor for dementia (HR 1.3, 95% CI 0.7-2.1), the highest relative risk of dementia was in subjects with an APOE4 allele and detectable CRP (HR 4.5, 95% CI 0.9-23.3). In all subjects, hazard ratios were similar when results were lagged one year (N = 192; fully-adjusted HR 1.4, 95% CI 0.7-2.7 for detectable CRP; fully-adjusted HR 1.0, 95% CI 0.5-2.1 for elevated CRP).

All-cause mortality

Follow-up times ranged from 0.5-4.5 years (2.4 ± 1.1; total person-years = 552.0). One hundred and eight subjects died during the follow-up period, of which 78 (72%) had a death certificate on file. The immediate cause of death was reported as cardiovascular disease (33%), cardiopulmonary arrest (32%), respiratory problems including pneumonia (16%), cancer (4%), dementia (4%), septic shock (3%), or other cause of death (8%). Table 2 shows the hazard ratios for all-cause mortality in subjects with detectable or elevated CRP relative to subjects with undetectable CRP. In both age-adjusted and fully-adjusted models, detectable but not elevated CRP was associated with increased risk of mortality in all subjects and in women alone. While APOE4 was not a significant risk factor for mortality

(HR 0.9, 95% CI 0.5-1.4), the highest relative risk of mortality was in subjects with an APOE4 allele and detectable CRP (HR 5.6, 95% CI 1.0-30.7). In all subjects, hazard ratios were similar when results were lagged one year (N = 208; fully-adjusted HR 1.8, 95% CI 1.0-3.1 for detectable CRP; fully-adjusted HR 1.2, 95% CI 0.7-2.2 for elevated CRP). Among subjects who died, there was no difference in CRP levels between those subjects who died < 1 year after baseline (N = 6), 1 to < 2 years after baseline (N = 37), 2 to < 3 years after baseline (N = 33), and 3 or more years after baseline (N = 32)(P = .25).

DISCUSSION

Subjects with CRP levels of 0.5-0.7 mg/dL had a significantly increased risk of all-cause mortality, but not all-cause dementia, when compared to those with CRP levels < 0.5 mg/dL. The magnitude of the increase in risk of all-cause mortality is in agreement with previous studies. Although age-specific risk was not specified, in a study of 75-, 80-, and 85-year-olds, the combined relative risk for 5-year mortality with CRP > 0.5 mg/dL was 1.68 (95% CI 1.02-2.74)8. The estimate for 4-year mortality in nonagenarians with CRP > 0.36 mg/dL from the Vitality 90+ Study was similar, although it did not reach statistical significance (HR 1.51, 95% CI 0.93-2.43)14. Taken together with the finding presented here, these results suggest that elderly subjects with high CRP are 50-70% more likely to die during the follow-up period than those with low CRP, even after adjustment for covariates. Hazard ratios did not change significantly when results were lagged to exclude subjects with less than one year of follow-up, indicating that deaths within the first year are not driving the association between CRP and mortality. People with CRP levels of 0.5 - 0.7 mg/dL may have chronic, low-grade inflammation which could slowly cause damage and account for the association between CRP and mortality in the long-term.

When results were stratified by gender, women with CRP levels of 0.5-0.7 mg/dL had a significantly increased risk of mortality, whereas men did not. The Vitality 90+ Study found a similar gender effect14. Both studies had fewer men than women, and it is possible that a larger study with more men would be able to detect an increased risk of mortality in nonagenarian men with high CRP levels. In general, women have higher CRP levels than men2, and a lower cut-point may be necessary to assess risk in men.

The highest relative risk of both dementia and mortality was in APOE4 carriers with CRP levels between 0.5-0.7 mg/dL. The dementia finding is consistent with results from the Leiden 85+ Study, which found that the association between high levels of CRP and cognitive decline was strongest in APOE4 carriers12. However, the association with mortality in APOE4 carriers is not consistent with previous findings. A previous study of CRP and mortality in nonagenarians reported that high levels of CRP did not confer an increase in risk in subjects with an APOE4 allele, although there were a small number of participants with an APOE4 allele and thus the power to detect a difference in risk was low15. Other studies have reported lower CRP levels in subjects with an APOE4 allele21, including nonagenarians22, and it has been hypothesized that lower CRP levels may partially account for the ability of APOE4 carriers to reach extreme old age despite high cholesterol levels22. The subjects in the current study were older than in previous studies and the APOE4 carriers did not have significantly lower CRP levels, raising the possibility that the relationship between the APOE4 allele and low CRP levels weakens with age. While the underlying cause and significance of lower CRP levels in APOE4 carriers needs to be explored further, the results shown here support the idea that high CRP levels in APOE4 carriers are detrimental.

Participants with CRP levels of ≥ 0.8 mg/dL had a non-significant increase in the risk of mortality. This result was somewhat surprising given that CRP levels of 0.5 - 0.7 mg/dL

were significantly associated with mortality. One explanation may be that this study did not include those subjects who died shortly after CRP assessment. Because the evaluation of the dementia outcome required at least one follow-up examination approximately six months later, subjects who died shortly after the baseline examination were not included. A significant relationship between CRP levels of ≥ 0.8 mg/dL and mortality may have been found if subjects with a shorter follow-up time were included. In addition, CRP levels were only measured once, and subjects with CRP levels of ≥ 0.8 mg/dL could have been acutely ill and had a transient increase in CRP levels. These subjects would have been misclassified as having CRP levels of ≥ 0.8 mg/dL when they usually would have been classified in a lower CRP group. In order to evaluate whether high CRP levels were due to acute infections we looked at the association between CRP levels and levels of several infection markers on a separate group of 62 nondemented subjects from ***The 90+ Study*** (26 with CRP < 0.5 mg/dL, 20 with CRP 0.5-0.7, and 16 with CRP ≥ 0.8 mg/dL). White blood cell count and levels of neutrophils, lymphocytes, monocytes, eosinophils, or basophils were not significantly higher in those with detectable or elevated CRP levels compared to those with undetectable CRP levels (all $p > 0.25$). Although we were unable to measure infection markers on the same subjects included in the main analyses, these results suggests that infection does not account for the majority of high CRP levels in this age group.

Our failure to detect an association between high CRP levels and dementia may be due to competing risks in this group. This is a cohort with high mortality, approximately 50% of the subjects died during the follow-up period, and subjects with high CRP levels may have died before they had a chance to develop dementia. The stronger association between CRP and mortality may have made it difficult to detect an association between CRP and dementia.

This study has several strengths, including a large number of subjects over the age of 90 and a follow-up time of up to 4.5 years. Numerous chronic conditions were ascertained and included in the analysis, however, some chronic condition and covariates, such as body-mass index, diet, and physical activity, were not included due to data unavailability. The lack of these covariates, as well as possible underreporting of medical conditions in the oldest-old23, could contribute to underadjustment of the model. Subjects used in this study were predominantly Caucasian, well-educated, and moderately affluent, and these results may not generalize to other populations. Those subjects who did not have a CRP measurement were older, more likely to be female, and more likely to have a diagnosis of CIND. The exclusion of these subjects likely skewed the sample towards younger, healthier subjects. This may have weakened the results, as those subjects who were excluded presumably had higher CRP levels and were more likely to meet the outcomes of dementia or mortality. The low sensitivity of the CRP assay is also a limitation. The assay was chosen because of concern that the high levels of CRP seen in nonagenarians would exceed the upper detection limit of the high-sensitivity CRP assay available at the time. Levels of CRP as low as 0.1 mg/dL have been associated with increased risk of developing dementia6 and the assay used here did not permit differentiation of CRP levels below the 0.5 mg/dL detection limit. This limitation could have resulted in subjects with increased risk of dementia or mortality being placed into the reference group, which would reduce the relative risk between the reference group and the high CRP groups.

To date, this is the first study of CRP and risk of dementia in the oldest-old. We did not find an association between CRP and all-cause dementia, but did find an association between CRP and all-cause mortality. High levels of CRP are associated with increased risk of vascular dementia4,6 and cardiovascular disease mortality24, although there were insufficient numbers to evaluate these outcomes in this study. Future studies in this cohort

will have sufficient numbers to evaluate the association between CRP and dementia type and cause-specific mortality.

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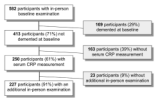

Figure 1.
Flow Chart for Participant Inclusion. Participants were included in the study of C-reactive protein (CRP) and incident dementia and mortality if they were not demented at baseline examination, had a serum CRP measurement from baseline examination, and an additional in-person examination.

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Table 1

Distribution of Variables at Baseline and Outcomes in All Subjects and Subjects Divided into Three CRP Groups

		C-reactive Protein (CRP) Levels			
	All subjects	Undetectable < 0.5 mg/dL	Detectable 0.5-0.7 mg/dL	Elevated ≥ 0.8 mg/dL	
	N = 227	N = 80	N = 81	N = 66	
Variable	**% (#)**	**%**	**%**	**%**	**p-value**
Demographics					
Female	62 (141)	61	65	59	0.719
Have APOE4 allele	20 (45)	21	23	14	0.307
Education level					
≤ High school graduate	26 (59)	20	27	32	0.060
Some college to college graduate	49 (111)	44	54	49	
Post-graduate education	25 (57)	36	19	19	
Lifestyle					
Smoke	1 (3)	3	1	0	0.411
Drink alcohol	67 (152)	69	69	62	0.739
Use estrogen (women only)	6 (14)	4	9	6	0.422
Medical history					
Hypertension	51 (116)	40	57	59	0.041 *
Coronary Artery Disease	14 (32)	12	25	5	0.001 *
Myocardial Infaction	14 (31)	14	11	17	0.639
Atrial fibrillation/arrythmias	29 (66)	24	31	35	0.378
Heart Valve Disease	6 (14)	5	9	5	0.517
Congestive Heart Failure	8 (18)	4	9	12	0.190
Stroke	7 (17)	10	7	5	0.447
Transient Ischemic Attack	15 (33)	13	12	22	0.203
High Cholesterol	29 (66)	26	34	30	0.534
Diabetes	4 (10)	4	6	3	0.618

		C-reactive Protein (CRP) Levels			
	All subjects	Undetectable < 0.5 mg/dL	Detectable 0.5-0.7 mg/dL	Elevated ≥ 0.8 mg/dL	
	N = 227	N = 80	N = 81	N = 66	
Variable	**% (#)**	**%**	**%**	**%**	**p-value**
Rheumatoid Arthritis	8 (18)	11	4	11	0.202
Osteoarthritis	41 (88)	41	42	40	0.982
Cognitive diagnosis					
Normal	56 (127)	54	57	58	0.882
CIND	44 (100)	46	43	42	
Outcomes					
All-cause Dementia	36 (82)	39	32	38	0.639
All-cause Mortality	48 (108)	38	53	53	0.081

APOE4 = apolipoprotein E4; CIND = Cognitively Impaired Not Demented

* $p < 0.05$ level

Table 2

Hazard Ratios* for All-Cause Dementia and All-Cause Mortality

	N	Undetectable (N = 80)	Detectable (N = 81)	p-value	Elevated (N = 66)	p-value
All-Cause Dementia						
All Subjects †						
Model 1	*227*	1.0	1.1 (0.6 - 1.8)	0.848	1.1 (0.6 - 1.9)	0.811
Model 2	*212*	1.0	1.2 (0.6 - 2.1)	0.629	1.0 (0.5 - 1.8)	0.916
Gender						
Men						
Model 1	*86*	1.0	0.9 (0.3 - 2.3)	0.777	0.9 (0.4 - 2.2)	0.812
Model 2	*78*	1.0	0.7 (0.2 - 2.3)	0.581	0.7 (0.2 - 2.0)	0.523
Women						
Model 1	*141*	1.0	1.1 (0.6 - 2.2)	0.734	1.2 (0.6 - 2.4)	0.654
Model 2	*134*	1.0	1.4 (0.7 - 3.0)	0.360	1.2 (0.5 - 2.8)	0.652
APOE genotype						
APOE4-						
Model 1	*182*	1.0	0.9 (0.5 - 1.6)	0.656	0.9 (0.5 - 1.8)	0.864
Model 2	167	1.0	1.0 (0.5 - 2.1)	0.903	0.9 (0.4 - 1.8)	0.711
APOE4+						
Model 1	*45*	1.0	1.6 (0.5 - 4.9)	0.415	1.9 (0.5 - 6.5)	0.319
Model 2	*45*	1.0	4.5 (0.9 - 23.3)	0.074	2.7 (0.6 - 12.2)	0.209
All-Cause Mortality						
All Subjects †						
Model 1	*227*	1.0	1.7 (1.1 - 2.8)	0.025	1.4 (0.9 - 2.4)	0.187
Model 2	*212*	1.0	1.7 (1.0 - 2.9)	0.042	1.3 (0.7 - 2.2)	0.384
Gender						
Men						
Model 1	*86*	1.0	1.4 (0.7 - 2.9)	0.311	1.0 (0.5 - 2.2)	0.952
Model 2	*78*	1.0	1.5 (0.7 - 3.6)	0.331	0.9 (0.4 - 2.1)	0.720

	N	Undetectable (N = 80)	Detectable (N = 81)	p-value	Elevated (N = 66)	p-value
Women						
Model 1	*141*	1.0	2.1 (1.1 - 4.2)	0.034	2.1 (1.0 - 4.3)	0.050
Model 2	*134*	1.0	2.1 (1.0 - 4.5)	0.057	1.7 (0.8 - 4.0)	0.192
APOE genotype						
APOE4-						
Model 1	*182*	1.0	1.7 (1.0 - 2.9)	0.055	1.3 (0.7 - 2.2)	0.419
Model 2	*167*	1.0	1.6 (0.9 - 2.9)	0.106	1.1 (0.6 - 2.1)	0.700
APOE4+						
Model 1	*45*	1.0	2.1 (0.7 - 6.5)	0.212	1.9 (0.5 - 7.2)	0.339
Model 2	*45*	1.0	5.6 (1.0 - 30.7)	0.046	2.6 (0.4 - 18.7)	0.345

*Hazard ratios (HR), 95% confidence intervals (CI), and p-values were computed using Cox regression. Model 1 was adjusted for age. Model 2 was adjusted for age, gender, education, apolipoprotein E4 (APOE4) status, and medical history of hypertension, coronary artery disease, congestive heart failure, and transient ischemic attack. The number of subjects (N) shown is the total number included in that analysis.

†In all subjects, age was significant in both models, and history of CHF was significant in Model 2.