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C-reactive protein is associated with disability independently of vascular events: the Northern Manhattan Study

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Abstract

Background: high-sensitivity C-reactive protein (CRP) has been associated with cardiovascular events and mortality, but the association of CRP with functional status is not well defined. We hypothesised that serum levels of high-sensitivity CRP are associated with long-term trajectories of functional status independently of vascular risk factors and stroke and myocardial infarction (MI) occurring during follow-up.
Design: prospective, population-based.
Setting: northern Manhattan Study.
Participants: stroke-free participants aged ≥40 years.
Measurements: annual assessments of disability with the Barthel index (BI) for a median of 13 years. BI was analysed as a continuous variable (range 0–100). Baseline demographics, risk factors and laboratory studies were collected, including CRP (n = 2,240). Separate generalised estimating equation models estimated standardised associations between CRP and (i) baseline functional status and (ii) change in function over time, adjusting for demographics, vascular risk factors, social variables, cognition, and depression measured at baseline, and stroke and MI occurring during follow-up.
Results: mean age was 69 (SD 10) years, 36% were male, 55% Hispanic, 75% hypertensive and 21% diabetic; 337 MIs and 369 first strokes occurred during follow-up. Mean CRP level was 5.24 mg/l (SD 8.86). logCRP was associated with baseline BI (−0.34 BI points per unit logCRP, 95% confidence interval −0.62, −0.06) but not with change over time.
Conclusions: in this large population-based study, higher serum CRP levels were associated with higher baseline disability, even when adjusting for baseline covariates and stroke and MI occurring during follow-up. Systemic inflammation may contribute to disability independently of clinical vascular events.

Keywords: *older people, C-reactive protein, disability, epidemiology*

Introduction

C-reactive protein (CRP) is an acute phase reactant that reflects acute inflammatory states and tissue injury [1]. CRP may also be directly implicated in pro-atherogenic processes, and several studies have shown associations between higher CRP levels and vascular events and mortality [2–4]. In the Cardiovascular Health Study (CHS), CRP was associated with white-matter lesions [5], and other studies have found associations between CRP and stroke severity and mortality. [6]. Beyond the association with vascular outcomes, inflammation has been associated with quality of life (QOL) in a limited number of studies [7, 8], but the association of inflammatory markers with disability has not been well studied, particularly among minority populations.

We hypothesised that elevated serum CRP levels independently predict worse functional status in those free of stroke at baseline. We estimated two components of functional trajectories: baseline functional status (which can be considered as a change in overall or mean function) and change over time. To our knowledge, this is the first analysis in which the association of CRP was assessed with both of these components of functional trajectories.

Methods

In the Northern Manhattan Study (NOMAS) population-based prospective cohort, 3,298 participants were recruited in a race/ethnically diverse community by random digit dialing of published and unpublished telephone numbers between 1993 and 2001. Participants were enrolled if they: (i) were ≥40 years of age; (ii) lived in northern Manhattan for ≥3 months in a household with a telephone and (iii) had no history of stroke. The study was approved by the institutional review boards of Columbia University and the University of Miami, and informed consent was obtained from all participants. Further characteristics of the cohort have previously described [9–11].

Baseline evaluation

Bilingual research assistants interviewed participants and collected data using standardised questions [12]. Baseline examination included comprehensive medical history, physical examination, medical record reviews, functional status assessed by the Barthel Index (BI), QOL assessed by the Spitzer QOL index and fasting blood samples.

Follow-up

All participants were followed annually via phone screening to detect change in vital status, new neurological or cardiac symptoms and events, interval hospitalisations, cognitive function and functional status via the BI. Only two participants were lost to follow-up after their baseline examination, and the average annual contact rate was 99%.

A positive screen for any potential cardiac or neurological event was followed by an in-person assessment. Also, all admissions and discharges were screened for outcomes that may not have been captured by telephone interview. Nearly 70% of vascular events led to hospitalisations at Columbia University Medical Center. Hospital records were reviewed to classify outcomes as previously reported [11]. Stroke included ischaemic stroke, intracerebral haemorrhage (ICH) and subarachnoid haemorrhage (SAH). At least two stroke neurologists verified and classified all stroke cases. Cardiologist-adjudicated myocardial infarction (MI) required at least two of the following criteria [13, 14]: (i) ischaemic cardiac pain determined to be typical angina; (ii) cardiac marker abnormalities (abnormal CK-MB fraction or troponin I values) and (iii) ischaemic EKG abnormalities.

There were 333 first MIs that occurred during follow-up, 184 (55.3%) definite, 81 (24.3%) probable and 68 (20.4%) possible. Only definite and probable MI were included. There were 369 first strokes that occurred during follow-up, 322 (87.3%) infarcts, 35 (9.5%) ICHs, 8 (2.2%) SAHs and 4 (1.1%) unknown, and all were included.

Study outcome

The BI [15] (Granger version) measures an individual's performance in 10 activities of daily living (ADLs) and ranges from 0 to 100 in 5-point increments, with 100 indicating normal physical functioning. Previous research has demonstrated the reliability of phone BI assessments [16]. Although it is an ordinal scale, several publications have advocated analysing the scale as a continuous variable due to increased power to detect associations, ability to describe the course of change over time in linear form, and avoidance of potential misclassification due to crude categorisation [17–19].

Explanatory variable: CRP

Blood samples were collected from 2,240 participants at baseline, and CRP levels were determined using a BNII nephelometer (Dade Behring, Deerfield, IL) by technicians blinded to clinical status. Serum CRP samples were drawn into EDTA tubes, spun immediately at 3,000 *g* at 4 °C for 20 min, and frozen at –70 °C for later analysis.

Since CRP levels were skewed, log transformation was performed. Additionally, CRP values were analysed per standard deviation, and categorised according to the three Centers of Disease Control (CDC)/American Heart Association (AHA) risk stratification levels: <1 mg/l; 1–3 mg/l and >3 mg/l [20].

Covariates

We adjusted for the following variables, measured at baseline: (i) demographics: age, sex, race/ethnicity, (ii) medical risk factors: body mass index (weight in kilograms divided by the square of height in metres), self-reported hypercholesterolaemia, diabetes mellitus (defined by self-report,

fasting blood glucose level ≥126 mg/dl, or insulin/oral hypoglycaemia use), hypertension (defined as a systolic blood pressure recording ≥140 mmHg or a diastolic blood pressure recording ≥90 mmHg based on the average of two blood pressure measurements or the patient's self-report of a history of hypertension or antihypertensive use), smoking (defined as either non-smoker or smoker within the last year), alcohol use (with moderate alcohol use classified as 1 drink/month to 2 drinks/day), physical activity (defined as any versus none), (iii) social variables: marital status, insurance status (classified as uninsured, Medicaid, Medicare or private insurance), number of friends (individuals whom the participant knows well enough to visit in their homes), years living in the community and (iv) cognitive and mood factors: depression (defined as a Hamilton Depression scale score of ≥12), performance on mini-mental state examination (analysed as a continuous variable) and Spitzer quality of life scale score [21].

Statistical analysis

The goal of this analysis was to determine whether serum CRP levels were associated with baseline BI and a steeper slope of decline over time. We first calculated distributions of explanatory variables, baseline covariates and BI, and we compared distributions of variables based on the availability of CRP data to detect differences in the inflammatory lab cohort compared with the full NOMAS prospective cohort. In order to assess for selection bias in functional status related to availability of CRP measurements, we compared the time trend of BI in the cohort with CRP measurements to the time trend in the cohort without CRP measurements, in unadjusted and fully adjusted models, fitting a model with a cohort by time interaction.

Due to correlations among repeated measures of outcomes in the same individual, regression models based upon generalised estimating equations (GEE) with an identity link function were used to assess the association between CRP levels and repeated measurements of BI, adjusting successively for baseline demographic variables, medical risk factors, social variables and cognitive/mood factors.

In order to assess whether CRP levels were associated with change in outcomes over time, we included interaction terms between time of follow-up assessment and CRP. We also pursued an alternative modelling strategy using mixed models. We used QIC for GEE models and AIC for mixed models as model selection criteria. Various model diagnostics including tests of linearity, residual plots and goodness of fit measures were used to evaluate the final model. As a working correlation structure for the GEE models, we chose the exchangeable (intraclass) structure and compared the QIC obtained with this model with one using the unstructured working correlation structure. In order to assess whether interval vascular events such as clinical stroke and MI were implicated in the trajectory of functional status, we ran a second set of models in which stroke and MI were included as time-varying covariates.

In a sensitivity analysis, we examined whether the relationship between CRP levels and functional status differed for mobility (transfers, mobility and stair use) and non-mobility (feeding, bathing, grooming, dressing, bowels, bladder and toilet use) BI domains. We also performed three other sensitivity analyses, but models did not significantly differ from the primary analyses and are not presented here: (i) adding possible MI to the MI definition; (ii) excluding those with baseline coronary artery disease and (iii) excluding those with baseline BI <100 (n = 761).

Results

Table 1 shows distributions of variables stratified by availability of CRP. There were significant differences in the distributions of several variables based on the availability of CRP, but there were no differences in major vascular risk factors. There were a total of 25,924 BI assessments. There were no differences in the time trend of BI when the cohort with CRP measurements was compared with the cohort without CRP measurements, in unadjusted and fully adjusted models, suggesting no significant selection bias. The mean CRP level was 5.24 mg/l (median = 2.55, interquartile range = 4.82 and standard deviation = 8.86). Log-transformed CRP levels followed a normal distribution. In terms of AHA/CDC CRP categories, 524 (23.4%) had levels <1 mg/l, 710 (31.7%) 1–3 mg/l and 1,006 (44.9%) >3 mg/l. There was no evidence to suggest lack of linearity in the final models. We chose the exchangeable model, with the lower QIC, as the final model.

Table 2 shows associations between logCRP levels and trajectories of functional status, in unadjusted and adjusted models. In most models, there was a significant annual decline in functional status of ~1 BI point per year, and of 0.39 points per year in a model adjusted for stroke and MI occurring during follow-up. In addition, in most models, including the fully adjusted model, higher logCRP levels were associated with a lower baseline mean functional score (−0.34 BI points per unit logCRP, 95% confidence interval (CI) −0.6, −0.06). The largest drop in the magnitude of this estimate occurred when vascular risk factors were added to the model. Finally, logCRP levels were not significantly associated with change in functional status over time. Similarly to the GEE models, using adjusted mixed models, increasing logCRP levels were associated with lower overall functional status (−0.41, 95% CI −0.82, 0.002; P = 0.051) but no change in function over time (0.05 per year, 95% CI −0.06, 0.16; P = 0.4).

Patterns of association were similar when standardised CRP levels were tested as the main predictor—namely, a significant overall annual decline in function in the overall cohort (−0.39 BI points per year, 95% CI −0.52, −0.25), a lower baseline functional level with higher CRP levels (−0.41 BI points per SD increase in CRP levels, 95% CI −0.82, −0.002) and no significant association between CRP levels and change in functional status over time (0.04 BI points per SD increase in CRP levels, 95% CI −0.06,

Table 1. Baseline characteristics of the cohort, by availability of CRP

Variable	Cohort with CRP	Cohort without CRP	*P*-value
Number of participants, No. (%)	2,240 (67.9)	1,058 (32.1)	–
Biological characteristics			
Age, mean (SD), years	69.4 (10.1)	70.5 (10.6)	0.005
Body mass index, mean (SD), kg/m^2	27.9 (5.5)	27.7 (5.5)	0.2
Demographics			
Male, No. (%)	804 (35.9)	423 (40.0)	0.02
Race-ethnicity			<0.0001
Non-Hispanic white, No. (%)	420 (18.8)	270 (18.8)	
Non-Hispanic black, No. (%)	526 (23.5)	277 (26.2)	
Hispanic, No. (%)	1,237 (55.2)	491 (46.4)	
Other, No. (%)	57 (2.5)	20 (1.9)	
Received at least high school education, No. (%)	996 (44.5)	515 (48.7)	0.02
Marital status, No. (%) married	721 (32.2)	321 (30.3)	0.3
Health insurance, No. (%)			<0.0001
Medicaid or no insurance	1,028 (46.2)	407 (38.7)	
Medicare or private insurance	1,197 (53.8)	644 (61.3)	
Vascular risk factors, No. (%)			
Hypertension	1,671 (74.6)	758 (71.6)	0.07
Alcohol consumption			0.5
Never drank	538 (24.0)	283 (26.8)	
Past drinker	553 (24.7)	246 (23.3)	
Light drinker	293 (13.1)	128 (12.1)	
Moderate drinker	745 (33.3)	341 (32.2)	
Intermediate drinker	77 (3.4)	43 (4.1)	
Heavy drinker	34 (1.5)	17 (1.6)	
Physical activity, any	1,226 (54.7)	683 (64.6)	<0.0001
Diabetes mellitus	479 (21.4)	237 (22.4)	0.5
Smoking			0.3
Never	1,070 (47.8)	475 (44.9)	
Former	829 (37.0)	420 (39.7)	
Current	339 (15.2)	163 (15.4)	
Hypercholesterolaemia	1,414 (63.1)	636 (60.1)	0.1
History of atrial fibrillation	100 (4.5)	43 (4.1)	0.6
History of coronary heart disease	475 (21.2)	229 (21.6)	0.8
Spitzer quality of scale score, mean (SD)	9.1 (1.3)	9.1 (1.3)	0.8
Other medical conditions, No. (%)			
Hamilton depression scale score, mean (SD)	3.3 (3.8)	3.0 (3.9)	0.04
Hamilton depression score ≥12	90 (4.1)	49 (4.7)	0.4
Mini-mental state score, mean (SD)	25.9 (3.8)	26.2 (3.6)	0.02
Social variables, No. (%)			
Number of people known well enough to visit with in their homes			0.5
None	85 (3.8)	45 (4.3)	
1 or 2	238 (10.6)	129 (12.2)	
3 or 4	443 (19.8)	210 (19.9)	
5 or more	1,472 (65.8)	673 (63.7)	
Years lived in community	28.5 (16.3)	31.4 (17.2)	<0.0001

0.15). When the AHA/CDC categorisation of CRP levels was used, similar trends were seen, with reduced power from the use of categorical instead of continuous variables.

In domain analysis, logCRP levels were significantly associated with baseline functional status in mobility (−0.15, 95% CI −0.30, −0.01, P = 0.037) and non-mobility domains (−0.18, 95% CI −0.35, −0.01, P = 0.04), in fully adjusted models. There were no associations with BI change over time.

Discussion

NOMAS is a large, population-based study with frequent, regular measurements of functional status, and it is well suited to estimate functional trajectories and identify the key influencing factors. Among NOMAS participants with inflammatory biomarker data at baseline, the prevalence of elevated CRP levels was high. There was an overall decline in functional status over time in the entire cohort. Higher CRP levels, examined using different cutoffs and variable definitions, were associated with lower baseline functional score but not with change in slope of function over time. For each unit increase in logCRP levels, there was a decrease in baseline functional score equivalent to the decline in function associated with a year of ageing. In addition to GEE models, we also used mixed models to estimate associations, which confirmed the significance and

Table 2. Associations between log of CRP levels and trajectories of functional status

Variable	Change in BI score	95% CI	*P*-value
Unadjusted model			
Annual change in BI score	−1.01	−1.09, −0.93	<0.0001
Change in BI score per unit increase in log of CRP levels	−0.72	−1.13, −0.31	0.0006
Additional annual change in BI score per unit increase in log of CRP levels	−0.03	−0.10, 0.05	0.5
Adjusted for demographics[a]			
Annual change in BI score	−1.02	−1.10, −0.94	<0.0001
Change in BI score per unit increase in log of CRP levels	−0.79	−1.22, −0.36	0.0003
Additional annual change in BI score per unit increase in log of CRP levels	−0.03	−0.10, 0.04	0.4
Adjusted for vascular risk factors[b]			
Annual change in BI score	−1.03	−1.11, −0.94	<0.0001
Change in BI score per unit increase in log of CRP levels	−0.40	−0.85, 0.05	0.08
Additional annual change in BI score per unit increase in log of CRP levels	−0.03	−0.11, 0.04	0.4
Adjusted for social variables[c]			
Annual change in BI score	−1.01	−1.09, −0.93	<0.0001
Change in BI score per unit increase in log of CRP levels	−0.33	−0.78, 0.11	0.14
Additional annual change in BI score per unit increase in log of CRP levels	−0.03	−0.11, 0.04	0.4
Adjusted for mood and cognitive variables[d]			
Annual change in BI score	−0.57	−0.72, −0.43	<0.0001
Change in BI score per unit increase in log of CRP levels	−0.30	−0.58, −0.02	0.04
Additional annual change in BI score per unit increase in log of CRP levels	0.00	−0.12, 0.13	0.96
Adjusted for stroke and MI[e]			
Annual change in BI score	−0.39	−0.53, −0.26	<0.0001
Change in BI score per unit increase in log of CRP levels	−0.34	−0.62, −0.06	0.02
Additional annual change in BI score per unit increase in log of CRP levels	0.02	−0.11, 0.14	0.8

[a]Adjusted for: baseline age, sex and race-ethnicity.
[b]Additionally adjusted for: diabetes, hypertension, coronary artery disease, hypercholesterolaemia, physical activity, alcohol use, smoking and body mass index.
[c]Additionally adjusted for: marital status, insurance, number of friends and years lived in the neighbourhood.
[d]Additionally adjusted for: depression, mini-mental state score and Spitzer quality of life index.
[e]Additionally adjusted for: stroke or myocardial infarction occurring during follow-up.

magnitude of effects seen with GEE models. Also, we adjusted for the occurrence of stroke and MI during follow-up, and the relationship of CRP to functional status was independent of these events. When we examined mobility and non-mobility domains of the BI separately, we found associations for both domains. In addition, there was evidence for vascular functional impairment, with a significant reduction in the magnitude of associations when vascular risk factors were adjusted for. However, the associations between CRP levels and functional status remained even after this adjustment.

Prior studies have examined the association between CRP and vascular outcomes, mortality, disability and frailty. In a meta-analysis of 160,309 individuals without vascular disease from 54 prospective studies [2], higher logCRP levels were independently associated with coronary heart disease, ischaemic stroke and vascular and non-vascular death. Among 807 consecutively admitted ICH patients in Finland [22], elevated CRP levels at admission were associated with worse modified Rankin scores at 3 months. In contrast, we examined functional status over a longer time period. In a population-based sample of 1255 individuals [23], inflammation (including CRP) partially mediated the relationship between risk factors and disability. In a cross-sectional analysis using 10 years of data among 1,729 adults with diabetes [24], elevated CRP was independently associated with disability and lower extremity mobility. In CHS, higher CRP levels were associated with incident frailty up to 9 years of follow-up [25]. Other studies have shown variable associations between CRP and frailty but have not examined trajectories of functional status over time.[26, 27]

In the only study prior to ours that examined change of function over time, among 624 individuals ≥70 years of age [28], elevated CRP was associated with decreased mobility in the entire cohort, as well as incident disability and gait speed decline among those without vascular disease, over a median of 2 years of follow-up. In contrast, we adjusted for vascular events occurring during follow-up, had longer follow-up and examined a larger cohort both with and without vascular disease.

There are several possible mechanisms that could explain the association between CRP and disability seen in this study. CRP may be a measure of subclinical cerebrovascular disease that is responsible for the decreased functional status [29]. Or, CRP may be a marker of a diffuse vascular disease burden that contributes to decreased functional status, i.e. diffuse atherosclerosis with impaired perfusion of all vessels in the body. Alternatively, CRP may be measuring frailty and not necessarily a specific vascular process; indeed, CRP has been associated with non-vascular mortality and non-vascular conditions [2]. Finally, the findings may have been due to residual confounding; elevated CRP levels may be an epiphenomenon of other risk factors that are incompletely measured but are responsible for disability, such as diabetes, which has varying severities and has been previously associated with trajectories of disability [30].

Strengths of this analysis include a large, population-based cohort with repeated, regular measurements of functional status with a validated scale over long-term follow-up. There was also regular surveillance for vascular events and hospitalisation and expert adjudication of events. One limitation of the proposed study involves deficiencies in the primary outcome measure. The BI, as a measure of ADLs and not additionally instrumental ADLs, is subject to ceiling effects and is insensitive to small changes in disability [31]. Analysing the BI as a continuous variable can capture and quantify the variance and course of change over time [18, 19]. Multiple prior studies have demonstrated associations between CRP and vascular outcomes, mortality, and disability measured at single time points. However, the current analysis is the only one, among studies of inflammatory biomarkers, in which both baseline functional status and the trajectory of change over time were analysed. Most prior studies examining disability have focused on single measurements at discrete time points, which ignores ongoing decline in functional status that can be accelerated by various factors [30, 32].

Key points

- C-reactive protein is associated with disability.
- This effect is independent of vascular events.
- This effect is seen over a long follow-up.

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Conflicts of interest

None declared.

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Important factors in predicting mortality outcome from stroke: findings from the Anglia Stroke Clinical Network Evaluation Study

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Abstract

Background: although variation in stroke service provision and outcomes have been previously investigated, it is less well known what service characteristics are associated with reduced short- and medium-term mortality.