Published in final edited form as:
Acta Psychiatr Scand. 2012 December ; 126(6): 402–410. doi:10.1111/j.1600-0447.2012.01892.x.

C-reactive protein, early life stress, and wellbeing in healthy adults

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Abstract

Objective—To determine whether C-reactive protein (CRP) can serve as a marker for alterations in immune function prior to the manifestation of significant psychiatric and medical disorders.

Method—Ninety-two healthy adults were recruited from the community and determined to be free of psychiatric or medical disorders. The concentration of plasma CRP from a single resting sample was examined in relation to current mental and physical health as well as to self-reported history of early life adversity.

Results—C-reactive protein showed a significant positive correlation with body mass index (BMI; $r = 0.477$, $P < 0.001$). Non-specific pain, fatigue, and lower overall quality of physical health were all associated with higher CRP concentrations (all $P < 0.05$ or $P < 0.01$), after controlling for effect of BMI and other relevant covariates. Subthreshold depression symptoms and other indices of mental/emotional wellbeing were not associated with CRP, nor was CRP significantly linked to any measures of early life adversity.

Conclusion—Lower-quality physical health and wellbeing, but not the presence of mood/anxiety symptoms or early life stress (ELS), were significantly related to plasma CRP. Elevated CRP does not appear to be a fundamental consequence of ELS among healthy adults.

Keywords

C-reactive protein/analysis; mental health; health status; stress; psychological/immunity; health surveys

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Declaration of interest

In the last 3 years, Drs A. Tyrka, L. Carpenter, and L. Price have received research support from the National Institutes of Mental Health, NARSAD, UCB Pharma, Sepracor, Cyberonics, the Department of Defense, Medtronic, Neuronetics, and NeoSync. Dr Tyrka received honoraria for continuing medical education from Lundbeck and Takeda. Dr Price received speaker honoraria from MD Conferences/Psychiatry Review Course and served as a paid consultant to Gerson Lehrman, Wiley, Springer, Qatar National Research Fund, Alberta Heritage Foundation for Medical Research, Abbott, and AstraZeneca. Dr Carpenter served as a paid consultant to Abbott, Cyberonics, Lundbeck, Novartis, Wyeth, and Astra-Zeneca. Ms Gawuga has received grant support from the National Institute of General Medical Sciences (R25 GM083270) to Brown University.

Introduction

C-reactive protein (CRP), in the traditional immunological context, is an acute-phase protein produced by the Kupffer cells of the liver in response to acute infection or injury. Within the past 15 years, it has become clear that CRP is a marker of chronic, low-grade inflammation (1, 2). Clinical studies have demonstrated that a random sample of peripheral blood subjected to testing with the 'high-sensitivity' CRP assay (hs-CRP or simply 'CRP'; so named because it detects concentrations below 3.0 mg/l) can represent a meaningful indicator of low-grade systemic inflammation (3). Across medical disciplines, researchers have found elevated CRP to be associated with obesity (4–10). Although its utility in clinical practice is still debated (11, 12), CRP has been recognized as significant marker for pathological processes that result in cardiovascular disease (13). Longitudinal studies have demonstrated that among generally healthy adults, high baseline CRP independently predicted future onset of cardiovascular events and cardiac morbidity (14), raising the question of whether CRP plays a causative role in the pathogenesis of atherosclerotic diseases specifically, or simply reflects an epiphenomenon signaling the presence of an underlying inflammatory processes impacting disease trajectory (15–17). Data showing CRP as a powerful statistical predictor of future adverse outcomes outside the arena of cardiovascular health, such as those related to cancer (18, 19), cirrhosis (20), and pregnancy (21), have extended interest in CRP as an easily measurable universal prognostic biomarker that might offer potential for early detection of risk and new opportunities for interventions to prevent morbidity.

Recently, elevated CRP concentrations have been associated with a growing number of mental conditions, including depressive syndromes (22–28), anxiety (29, 30), and psychological distress (31–34). Elevated concentrations of CRP have also been demonstrated in adults reporting a history of childhood maltreatment (35–37) and in those with exposure to stress associated with socioeconomic disadvantages (38–40), both considered risk factors for development of psychiatric conditions. Several research groups investigating CRP concentrations in patients meeting full diagnostic criteria for major depressive disorder have generated mixed results (41–44), but a more consistent link with CRP is apparent in the large body of literature describing associations of the biomarker with self-reported depressive symptoms across a continuum of severity.

While numerous studies have found associations between poor quality of overall health and peripheral markers of inflammation in large epidemiological samples or high-risk populations (45–48), relatively few have examined the cross-sectional relationship between CRP and subthreshold symptoms of mental and physical illness in a generally healthy adult population. Self-rated quality of health is an established independent predictor of morbidity and mortality (49). A recent study in generally healthy adults pointed to higher concentrations of peripheral inflammatory markers among those who perceived themselves as having low levels of overall health, even after accounting for relevant covariates and objective health conditions (45). Another preliminary report indicated poorer self-reported perceived health may be associated with diminished immune system capacity among individuals with no physical health disorders (50), underscoring the potential relevance of subthreshold symptoms.

Similar to low-level or early symptoms of many chronic medical diseases, self-reported subthreshold depressive symptoms can be associated with significant disability (51–53) and may represent early manifestations of underlying disease process that will eventually progress to threshold medical and mental health disorders (54, 55). As elevated CRP concentrations are increasingly linked with later development of various adverse health

outcomes, understanding the role of CRP in relation to quality of health *prior* to the onset of chronic and disabling disorders seems critically important.

Aims of the study

To better understand the breadth of utility of C-reactive protein (CRP) as a risk marker and its potential role in chronic inflammatory processes, the current study sought to examine the relationship between CRP and subthreshold symptoms in a medically and psychiatrically healthy adult population from the community. A second goal was to explore whether CRP reflects a trajectory of chronic inflammation that is intimately linked with exposure to stress during early development.

Material and methods

Subjects

Subjects were 92 adults (45 men, 47 women) ages 18–54 years, who were recruited from the community. Written informed consent was obtained from all subjects in this sample, representing a subset from a larger cohort in a longitudinal study of stress and biomarkers (56–58). The study was approved by the Butler Hospital Institutional Review Board. All subjects were free of pregnancy, significant medical illness, and recreational drug use, as established by complete physical examination and standard laboratory tests, including electrocardiogram, complete blood count, serum electrolytes, thyroid-stimulating hormone, urine toxicology, and urinalysis. Exclusion criteria included major physical or psychiatric illness, use of any psychotropic medication, or use of any other drugs thought to influence hypothalamic-pituitary-adrenal (HPA) axis function (including beta blockers, angiotensin-converting enzyme inhibitors, ketoconazole, metyrapone, and corticosteroids). Continuation of oral contraceptives and estrogen replacement therapy was permitted.

The Structured Clinical Interview for DSM-IV for Axis I Disorders (SCID-I) was used for psychiatric diagnostic assessments. Any subject diagnosed with a current or lifetime primary psychotic disorder, current substance dependence or abuse, or current major mood or anxiety disorder was excluded from participation. Subjects with prominent personality pathology (as detected though clinical interviews and interactions with research staff during the first two visits) were excluded. Subjects were compensated for their time and travel.

Measures

Assessment of mental and physical health—Participants completed a battery of questionnaires which assessed overall health and wellbeing in both mental/emotional and physical domains, including the following instruments: the Medical Outcomes Study 36-item Short Form Study (MOS SF-36) (59), the Fatigue Assessment Scale (FAS) (60), and the Quality of Life Enjoyment and Satisfaction Questionnaire (QLESQ) (61). Indices of mental/emotional health quality over the past month were determined by scores generated on the Inventory for Depressive Symptoms—Self-Report Version (IDS-SR) (62), the State-Trait Anxiety Inventory (STAI) (63), and the Perceived Stress Scale (PSS) (64). From these instruments, summary scores were selected for testing with CRP, with the goal of including both broad self-appraisals of health quality (e.g., overall physical health score, score for global emotional wellbeing) as well as specific symptoms experienced proximal to the time of CRP sampling (e.g., depression symptoms, anxiety, pain, fatigue) for each domain.

Anthropomorphic measurements—Weight, height, and waist and hip circumference measurements were acquired by direct physical examination. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). The ratio of the waist and hip circumferences (WHR) was calculated as a proxy for central adiposity. While WHR was our

preferred physical health domain variable for testing associations between CRP and obesity, a growing published literature has already established BMI as a standard covariate for CRP analyses. Both BMI and WHR were therefore included to achieve methodological comparability with the literature and to facilitate interpretability of our results.

Assessment of early life stress (ELS)—The Childhood Trauma Questionnaire (CTQ) (65), a 28-item self-report instrument consisting of five subscales (emotional abuse, emotional neglect, physical abuse, physical neglect, and sexual abuse), was used to assess subjects' history of childhood maltreatment. Established cutoff scores for 'moderate to severe' level of maltreatment on any one or more of the CTQ subscales (66) were used to describe the sample in Table 1, but continuous data (the total CTQ score and the five subscale scores) were used for testing with CRP. A second measure of adverse early environment, quality of parental care during childhood, was assessed with the Parental Bonding Instrument [PBI; (67)]; care dimension ratings for each subject's mother and father were averaged to create a summary score for quality of parental care score. Additional exploratory measures of ELS stress included childhood socioeconomic adversity and stress related to neonatal health, each represented by a dichotomized variable (present or absent). Socioeconomic adversity during childhood was approximated by participants' responses to queries about degree of crime in the community where they were raised, perceived financial stability of their family during childhood, and whether all of their basic needs (food, shelter, and clothing) were met during childhood, on a semistructured interview and questionnaire developed by our research group. Similarly, exposure to significant stress during the neonatal period was categorically estimated by participants' responses to queries about complications surrounding their own births, gestational age, and prolonged hospital care after birth. The exploratory nature of analyses with these ELS items reflects inherent limitations of data not generated by psychometrically validated instruments.

High-sensitivity CRP—Plasma was extracted by centrifugation. High-sensitivity CRP (hs-CRP) was assayed using quantitative rate nephelometry (IMMAGE; Beckman Coulter (Brea, CA, USA)). The analytical sensitivity was 0.1 mg/dl and the intra-assay coefficient of variation was 3.6%.

Statistical analyses

Analyses were conducted using SPSS 19.0 for Macintosh (IBM Corporation, Somers, NY, United States). hs-CRP values were assessed as a continuous variable. CRP and BMI values were $\log_{10}$-transformed to fulfill the requirements for normal distribution in statistical analyses other than tests of correlation. Current annual income was used to characterize socioeconomic status (SES). Descriptive statistics were used to determine the clinical and demographic characteristics of the sample. *T*-tests were used to examine CRP in relation to gender. Bivariate Pearson's correlation coefficients were calculated to examine the relationships between CRP and continuous data (demographic variables, indices of ELS, and summary scores for mental and physical health domains). The SPSS general linear models (GLM) univariate test was used to perform regression analyses for *post hoc* examination of relationships between CRP and significant health outcome variables, controlling for the effects of BMI, SES, age, and gender. For these analyses, gender was entered as a fixed factor while the others in the model were entered as continuous variables. To reduce the possibility of type I error, a Bonferroni correction factor was applied within each hypothesis domain. All tests were two-tailed, with significance defined as $P < 0.05$.

Results

Baseline characteristics of the sample are displayed in Table 1. CRP values ranged from 0.20 to 18.10 (mean ± SD, 3.88 ± 3.58). As anticipated, there was a significant association between CRP and BMI ($r = 0.44$, $P < 0.001$), but there was no significant difference in CRP between male and female subjects ($t = -8.8$, $P = 0.70$), and no significant association with subject age. Current SES was not significantly correlated with CRP in our sample. Only four subjects reported cigarette smoking, so this variable was not used as a covariate in subsequent analyses.

CRP and physical/somatic health

As summarized in Table 2, both BMI and WHR measures of adiposity were significantly correlated with CRP. Higher levels of fatigue, pain, and decreased overall quality of physical health were linked to elevated CRP in bivariate correlations. The individual associations between CRP and pain ($F = 7.98$, $P = 0.006$), and CRP and overall physical health ($F = 16.82$, $P = <0.001$) remained significant after controlling for age, sex, BMI, and SES in regression models; pain and physical health retained significance after Bonferroni correction.

CRP and mental/emotional health

We did not find an association between CRP and depressive symptoms or perceived stress levels (Table 2). Further, no significant bivariate correlation was found with state anxiety, overall emotional health and wellbeing, or overall level of life satisfaction and contentment.

CRP and ELS

Twenty-one subjects (23%) endorsed criteria for ‘moderate or severe’ maltreatment on at least one of the CTQ subscales. Emotional neglect was the most common subtype (16.3%), followed by emotional abuse (8.7%), physical abuse (6.5%), sexual abuse (4.4%), and physical abuse (6.5%). Twenty-two subjects (24%) reported a history of neonatal stress, and eight subjects (9%) reported socioeconomic adversity during childhood. No significant findings emerged between CRP and scores on any of the CTQ subscales. The CTQ 28-item scale total, the PBI index of quality of parental care, and our neonatal stress and childhood socioeconomic stress variables also did not show any significant relationships with CRP at $P < 0.05$ or trends at $P < 0.10$ (45), even before correction for multiple comparisons.

Discussion

Extensive research has demonstrated that chronic low-grade inflammation, as measured by CRP, is present in subjects with a wide variety of mental and physical disorders and that exposure to stress during early development may predispose to the development of a common biological trajectory toward numerous adult health conditions characterized by elevated concentrations of CRP. In a population of 92 adults selected for participation on the basis of their *absence* of major medical and psychiatric disorders, we found CRP concentrations to be significantly linked to BMI and subthreshold pain, and overall somatic health, but not to indices of mental health or self-reported history of ELS.

Our findings regarding CRP and physical health outcomes mirror and extend those previously demonstrated in medically ill patients (68–72) and in population-based samples (7, 45, 73–75). It is noteworthy that only 20% of the subjects in our sample met BMI criteria for obesity, yet a marked effect of BMI was still seen on CRP, and the correlations we found for CRP with pain and overall physical health were independent of the effects of BMI. Although the underlying mechanisms have yet to be elucidated, our findings suggest CRP

may potentially serve as a biomarker for future physical morbidity, even in the absence of significant risk factors. A longitudinal study would be needed to definitively determine whether elevated CRP values such as those we measured predict relevant threshold health outcomes.

Contrary to our expectations, quality of mental health and current subjective stress levels did not emerge as significantly associated with CRP. Previously published findings include elevated concentrations of CRP in patients with depression, as well as independent or mediating effects of distress, depression, and anxiety symptoms from statistical models predicting CRP (25, 30, 76, 77), so additional interpretation of our notable negative finding in this domain is warranted. The previously reported relationship between depressive syndromes and CRP may be owing to the concurrent presence of physical symptoms of the depressive syndrome itself (such as anergia, fatigue, and pain), or of common comorbid medical conditions (such as fibromyalgia, chronic fatigue, migraine, irritable bowel syndrome, and other chronic pain disorders). Elevated mean CRP concentrations seen among depressed patient samples may not actually reflect a biologically relevant association of the inflammatory marker with the more cognitive symptoms of depression, such as guilt, impaired concentration, pessimism/hopelessness, and negative self-appraisal that are captured with the measures we used. The direction of the relationship between CRP and depression may be such that mood symptoms preceded the rise in CRP. A recent, large-scale longitudinal study in patients with established coronary heart disease demonstrated that normal baseline CRP concentrations were not associated with future onset of depressive symptoms, while baseline or chronic subthreshold depressive symptoms did predict subsequent CRP elevations (78). However, once physical health factors such as BMI and exercise habits were accounted for, the relationship between CRP concentrations and depressive symptoms was no longer significant. A study of circulating inflammatory markers in healthy young adults also did not find CRP to be statistically related to measures of psychological distress, although CRP was correlated with fibrinogen (31). Even in a large birth cohort study that found CRP predicted anxiety and anxious depressive syndromes in men, an independent effect was not seen for depressive symptoms in the absence of anxiety, and none of the mental health measures was statistically related to CRP in women (30). Another group reported that the significant association between depressive symptoms and CRP was lost when pain and disability were included as covariates in the statistical model (79). Our results, in combination with these other recent findings, suggest that CRP is not a likely biomarker signaling risk for future development of psychiatric symptoms or disorders that occur outside the context of comorbid medical disorders or broader physical health syndromes.

None of our measures of adverse early environment, including retrospective ratings of early life trauma, quality of childhood parental care, and approximations of neonatal stress and childhood socioeconomic adversity, showed a statistically significant relationship with CRP concentrations in the healthy adults we studied. We relied on self-report data to summarize quality of early environment, but used widely accepted scales and also conducted individual interviews with each subject to enhance reliability. The prevalence of threshold ELS cases (based on score corresponding with moderate–severe level on any CTQ subtype of childhood stressor) was low (23%) in this study population, which may have contributed to the null result. However, the inclusion of several different ELS measures, all of which failed to show associations with CRP, lends additional confidence to our negative findings. With 92 subjects, our analyses had 83.5% power to detect effects at least medium in size ($r = 0.3$). However, we had low power to detect small effects, particularly given that a relatively small proportion of our participants had ELS. Furthermore, studies reporting an association between ELS and adult inflammation have typically included subjects with more risk factors for diseases associated with inflammation and higher rates of morbidity (35–37) than ours.

Psychological resilience has been found to reduce psychiatric morbidity in adults with a history of childhood maltreatment (80), and it is possible we recruited a sample with an atypically high degree of resilience. It is also possible that our targeted inclusion of physically and mentally healthy subjects resulted in the selection of a sample whose experiences with early life adversity were buffered by the protective effect of maternal warmth (81) or other positive influences. Although considerable evidence indicates childhood adversity may heighten risk for poorer health in adulthood, the data from this study do not support a critical role for CRP in the immune mechanisms hypothesized to underlie that trajectory, at least in its earliest stages where symptoms remain at the subthreshold level.

The immune system is activated by both acute and chronic stressors (82). During an acute-phase immune response, interleukin-6 is the primary inducer of the CRP gene, rapidly inducing synthesis of CRP by liver macrophages to produce 1000-fold increases in blood concentrations within 48 h (83). Under normal physiologic conditions, CRP is synthesized at much lower rates, with a half-life of 18 h (as compared with 75 min in the acute phase). Elevated CRP concentrations in the absence of acute medical conditions such as infection, trauma, tissue necrosis, or malignancies are thus thought to reflect a heightened rate of production of CRP triggered by low-grade inflammatory processes during periods of chronic stress. Our findings are consistent with the notion that chronic inflammatory processes may be active and detectable well before the frank onset of threshold clinical syndromes. More research assessing broad arenas of health and with longitudinal observation will be needed to elucidate the complex and likely multifaceted determinants of disease onset and to evaluate whether changes in circulating concentrations of CRP over time predict future quality of physical and mental health.

Acknowledgments

We thank Kelly Colombo, B.A., for her assistance with data management. This study was supported by NIH grant 5R01MH068767-08 (LLC).

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Significant outcomes

- High plasma C-reactive protein (CRP) concentrations were significantly linked to body mass index (BMI), lower-quality physical health, pain, and fatigue.
- Subjective stress level, emotional wellbeing, and subthreshold symptoms of depression and anxiety were not associated with plasma CRP concentrations.
- There was no significant association between plasma CRP and history of early life adversity.

Limitations

- Only 23% of the sample met categorical criteria for any of the subtypes of early life adversity we examined.
- The use of oral contraceptives and estrogen replacement therapies was permitted, which may have masked relationships between depressive symptoms and CRP in postmenopausal female subjects.
- Results from this sample of generally healthy adults without major medical disorders or threshold psychiatric disorders may not be generalizable to populations with greater morbidity and less resilience.

Table 1

Characteristics for $n = 92$ healthy adult subjects

Age, mean (SD) years; range	30.5 (9.2); 18–54
Gender, *n* (%) Female / *n* (%) Male	47 (51.1) / 45 (48.9)
Education level, *n* (%)	
High school graduate	3 (3.3)
Technical school	2 (2.2)
Partial college	21 (22.8)
College graduate	47 (51.1)
Graduate school / Professional degree	19 (20.7)
Total family annual income (adult subject) (%)	
Less than $25 000	31 (33.7)
$25 000–49 999	21 (22.8)
$50 000–74 999	15 (16.3)
$75 000–99 999	12 (13.0)
More than $100 000	13 (14.1)
Body mass index, mean (SD); range	26.1 (5.0); 19.0–43.3
Normal weight; *n* (%)	47 (51.1)
Overweight; *n* (%)	27 (29.3)
Obese; *n* (%)	18 (19.6)
Cigarette smoker *n* (%)	4 (4.3)

Table 2

Health outcomes (Mean ± SD) and their correlations with plasma

	Mean ± SD	*r*	*P*
Mental / Emotional health domain			
Depression symptoms †	6.97± 5.88	0.199	0.207
Perceived stress ‡	16.58± 5.83	−0.069	0.515
State anxiety §	27.91± 7.53	0.58	0.585
Emotional wellbeing ¶	83.83± 11.33	−0.170	0.106
Satisfaction and contentment **	4.30± 0.68	−0.154	0.147
Physical / Somatic health domain			
Body mass index	26.12± 5.01	0.465	<0.001 *
Central adiposity (waist / hip ratio)	0.84± 0.08	0.344	0.001 *
Fatigue ††	19.08± 3.57	0.221	0.034
Pain ¶	91.30± 9.96	0.365	<0.001 *
Overall physical health ¶	92.69± 5.77	−0.511	<0.001 *
Early life stress domain			
CTQ total score	6.94± 2.96	0.038	0.720
Physical abuse (CTQ)	6.15± 2.62	0.202	0.054
Physical neglect (CTQ)	6.72± 10.25	−0.069	0.516
Sexual abuse (CTQ)	5.51± 2.24	0.055	0.599
Emotional abuse (CTQ)	7.23± 3.44	0.110	0.297
Emotional neglect (CTQ)	9.11± 4.17	0.056	0.618
Quality of parental care (PBI)	27.41± 6.12	0.060	0.573

* Retains significance after correction for multiple tests within each domain.

† Inventory of Depressive Symptomatology-Self-Report Version (IDS-SR).

‡ Perceived Stress Scale.

§ Subscale, State-Trait Anxiety Inventory (STAI).

¶ Subscale, Medical Outcomes Survey – 36 item (MOS-36).

** Subscale Score, Quality of Life Enjoyment and Satisfaction Questionnaire (QLESQ).

†† Fatigue Assessment Scale (FAS).

CTQ, Childhood Trauma Questionnaire (65); PBI, Parental Bonding Instrument.