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C-reactive protein, Interleukin-6, and posttraumatic stress disorder symptomology in urban police officers

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A B S T R A C T

Our aim was to examine the relationship between the level of the inflammatory markers, C-reactive protein (CRP) and interleukin-6 (IL-6), and posttraumatic stress disorder (PTSD) symptomology in a random sample of 115 police officers. CRP was measured in citrated plasma using a particle enhanced immunonephelometric assay and IL-6 was measured in serum with a solid-phase quantitative sandwich ELISA. The presence of high PTSD symptomology was defined as having an Impact of Event Scale score (IES) of $\geqslant$26 compared to <26 (low PTSD symptomology). 28% of the officers had high PTSD symptomology. Mean levels of CRP and IL-6 did not differ significantly between officers with high PTSD symptomology and those with low symptomology (CRP: 0.76 mg/l vs. 0.97 mg/l; IL-6: 2.03 pg/ml vs. 1.74 pg/ml).

We found no association of CRP and IL-6 levels with PTSD symptomology. This study was limited by sample size and its cross-sectional study design. A lack of association may occur if either CRP or IL-6 is elevated only at the onset of PTSD symptomology, or if inflammation is related to specific key components that define PTSD. Further research examining these relationships in a larger population may be worthwhile.

1. Introduction

Posttraumatic stress disorder (PTSD) is caused by exposure to traumatic events that include, but are not limited to serious injury, assault, war, or natural disasters [1–4]. While a diagnosis of PTSD requires clinical evaluation, PTSD consists of a set of core symptoms that include – numbing, re-experiencing the traumatic event, avoidance of event reminders, and hyperarousal due to the traumatic event [3].

Research indicates that individuals who suffer from PTSD and PTSD symptomology have higher rates of depression, sleep disorders, and more adverse cardiovascular disease (CVD) risk factors compared to those without [5–11]. For example, Violanti et al. found that police officers with severe PTSD symptoms had more metabolic syndrome (MS) components compared to police officers with few PTSD symptoms [6]. Similarly, Kubzansky found an association between PTSD symptomology and coronary heart disease in the Normative Aging Study [9].

The biological mechanism underlying the relationship between the stress response and CVD is still not fully understood. Research suggests that stress activates the inflammatory response system which upregulates the hypothalamic–pituitary–adrenal (HPA) axis [4,12,13]. If the stress response does not resolve, changes in the HPA system trigger a chronic low-grade inflammatory state as measured by the presence of pro-inflammatory cytokines such as C-reactive protein (CRP), IL-6, IL-1B, and IL-4 in individuals who report psychological stress [4,13–19]. The presence of pro-inflammatory cytokines in individuals experiencing stress has important biological implications since pro-inflammatory cytokines are associated with chronic illnesses such as CVD [12,20]. For this reason, a few studies have begun to measure pro-inflammatory cytokines in individuals who suffer from PTSD [4,15,21,22]. However, results have been inconsistent [4,15,21,22], and to our knowledge no studies have evaluated the level of inflammatory markers and PTSD symptomology.

The goal of this study was to examine the relationship between the level of inflammatory markers CRP and IL-6 and PTSD symptomology in a sample of police officers. We hypothesized that higher levels of CRP and IL-6 would occur more often in officers with PTSD symptomology as indicated by an Impact of Events Scale (IES) score of $\geqslant$26, compared to those with low PTSD symptomology.

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2. Material and methods

2.1. Study population

The Buffalo Police Health Study data was designed to identify the health consequences of stress using subclinical CVD biomarkers, body composition, and psychosocial factors. The City of Buffalo Police Department (Buffalo, NY) was the selected sample site, which consisted of 934 urban police officers [5]. The data were collected between June 1999 and May 2000 at the Center for Preventive Medicine, School of Public Health and Health Professions, State University of New York – University at Buffalo. A random sample ($n = 115$) of police officers in the department was generated and women were over-sampled to ensure adequate representation in the sample. Participants had to be sworn police officers and willing to participate voluntarily in the study. All participants completed an informed consent that was approved by the State University of New York at Buffalo Health Sciences Internal Review Board and the National Institute for Occupational Safety and Health Human Subjects Review Board.

2.2. PTSD symptoms

The psychological symptoms of PTSD were measured using the IES. The IES cannot be used as an alternative to a clinical diagnosis of PTSD. However, it is one of the most widely used measures of PTSD symptoms, capturing both the intrusive and avoidance symptomology [23,24]. It consists of 15 items that measure the intensity of the avoidance and intrusion experience due to posttraumatic stress. The items are constructed to measure PTSD symptoms in general, and are not related to specific incidents. Each participant is asked to rate, on a four point scale, a list of comments often made by people who have experienced a stressful event. The rating depends on how often each statement occurred in the past 7 days: 0 (not at all), 1 (rarely), 3 (sometimes), and 5 (often). Seven of the fifteen questions measure intrusive symptoms, while the other eight questions measure avoidance symptoms. The combined score provides the total subjective score for traumatic stress. A total score of $\geqslant 26$ is indicative of moderate to severe impact [23,25,26]. For the current investigation, a total score of $\geqslant 26$ was used to indicate high PTSD symptomology and a total score <26, low PTSD symptomology.

2.3. CRP and IL-6 analyses

A fasting blood sample (20 ml) was obtained from all participants by a trained phlebotomist. The plasma used to analyze CRP was collected in citrate tubes and the serum used to analyze IL-6 was collected in a serum tube. The blood samples were sent to Millard Fillmore Laboratory, Buffalo, NY. Additional blood samples (5% of all specimens) were also sent to the laboratory for quality control assurance. The analyses conducted included comprehensive blood chemistry with full lipid panel. IL-6 and C-reactive protein were measured by the University of Vermont in 2007 from frozen specimens stored at −80 °C. CRP was measured in citrated plasma and IL-6 was measured in a serum sample.

C-reactive protein (CRP) was measured using the BNII nephelometer from Dade Behring utilizing a particle enhanced immunonephelometric assay. Polystyrene particles are coated with monoclonal antibodies to CRP, which, in the presence of antigen (CRP) agglutinate to cause an increase in the intensity of scattered light. The increase in scattered light is proportional to the amount of CRP in the sample. Suitable specimens for this assay are serum, heparin, citrate plasma, or EDTA plasma. The assay range is 0.16–1100 μg/mL.(or mg/L). Expected values for CRP in normal, healthy individuals are $\leqslant$3 μg/mL. Inter-assay CVs range from 2.1% to 5.7%.

Human interleukin-6 (IL-6) was measured with a solid-phase quantitative sandwich ELISA provided by R&D Systems, Inc., Minneapolis, MN (Catalog #: HS600B). The assay has a low detection range of 0.16 with a high detection range between 10.0 and 12.0 pg/mL. Preferred samples for this assay are serum or EDTA plasma with a minimum volume of 180 μL. The expected normal range per the manufacturer is 0.24–12.5 pg/mL. Using this method, we have determined a routine inter-assay CV ranging from 8% to 12%.

2.4. Statistical analysis

We compared the characteristics of participants with high and low PTSD symptomology using Chi-square test analyses for categorical variables and Student *t*-test for continuous variables. We also examined if there were differences between high and low PTSD symptomology status by sociodemographic variables or lifestyle factors (age, sex, marital status, education, rank, years in service, medication use, physical activity, smoking history, alcohol consumption). Pearson's correlation was used to assess if the level of either CRP or IL-6 were correlated with age, alcohol consumption, systolic blood pressure (SBP), diastolic blood pressure (DBP), physical activity, glucose, total cholesterol, BMI, and waist circumference.

CRP and IL-6 were not normally distributed, so the mean values of CRP and IL-6 were log transformed for analyses. However, back transformation was used when reporting the mean and standard error. The log of CRP and IL-6 were plotted against the IES score and the correlation coefficients calculated. Generalized linear models were used to assess the association between the mean levels of CRP and IL-6 with PTSD symptomology. The level of the inflammatory markers was the dependent variable and the presence of PTSD symptomology was the independent variable. We adjusted for age, sex, smoking, abdominal height, marital status, school education, race, and medication use (anti-inflammatory, high cholesterol and blood pressure medication) in the final model. Variables with p-value $\geqslant 0.3$ in univariate analysis were not included in the multivariate analysis (rank, years in service, physical activity, alcohol consumption). All analyses were two tailed at a $p \leqslant 0.05$. All data were analyzed using SPSS statistical software package (version 17.0; SPSS Inc., Chicago, IL).

3. Results

Of the 115 officers, complete demographic, life style and physiological measurement data were available for 111 (Table 1). There were 43 women (38.7%) and 68 men (61.2%) with a mean age of 40.20 ± 7.50 years. Thirty-two participants (28.8%) had high PTSD symptomology (IES score $\geqslant 26$). There were no significant differences in demographic factors or other covariates between officers with high compared to those with low PTSD symptomology (Table 1). The mean level of CRP was lower in officers with high PTSD symptomology compared to those low PTSD symptomology, but this difference was not significant (0.85 mg/l, SD = 0.90 vs. 0.92 mg/l, SD = 1.0; $p = 0.73$). In contrast, the mean level of IL-6 was higher in officers with high PTSD symptomology compared to those with low PTSD symptomology. This difference was also not significant (2.02 pg/ml, SD = 0.63 vs. 1.78 pg/ml, SD = 0.73; $p = 0.40$).

There was no correlation between the IES score and either logCRP ($r = -0.01$; $p = 0.90$; Fig. 1) or logIL-6 ($r = 0.53$; $p = 0.58$; Fig. 2). Univariate correlation between the continuous variables and the inflammatory markers CRP and IL-6 indicated that CRP was

Table 1
Demographic, life style, and physiological characteristics in officers stratified by IES score.

Chararcteristics[a,b]	IES ⩾ 26 (N = 32)		IES < 26 (N = 79)		p-Value
Sex					
Female	12	37.5	31	39.2	0.865
Male	20	62.5	48	60.8	
Marital status					
Single	3	9.4	19	24.1	0.213
Married	24	70.0	50	63.3	
Divorced	5	15.6	10	12.7	
Education					
High school/GED	6	18.8	15	18.8	0.953
College <4yrs	17	53.1	44	55.0	
College 4 +yrs	9	28.1	20	26.3	
Smoking status					
Never	15	46.9	37	46.8	0.552
Current	4	12.5	17	21.5	
Former	13	40.6	24	30.4	
Years in service					
1–5 yrs	8	25.0	19	24.1	0.447
6–10 yrs	2	6.3	14	17.7	
11–15 yrs	8	25.0	19	24.1	
15 + yrs	14	43.8	27	34.2	
Rank					
Police officer	15	46.9	56	70.9	0.052
Sergeant/lieutenant	7	21.9	11	13.9	
Captain/detective	10	31.3	12	15.2	
Race					
Caucasian	25	78.1	55	69.6	0.465
African American	4	12.5	18	22.8	
Hispanic	3	9.4	6	7.6	
Blood pressure medication	2	6.5	3	3.8	0.548
Anti-inflammatory medication	15	46.9	34	43.0	0.712
High cholesterol medication	2	6.3	6	7.8	0.779
Age (yrs)[b]	41.4	7.8	39	7.4	0.120
Alcohol (drinks/week)	2.8	3.2	3.2	4.1	0.616
BMI (kg/m^2)	28.6	5.3	27.8	4.0	0.305
SBP (mmHg)	115.3	12.8	112.2	12.4	0.24
DBP (mmHg)	72.1	10.1	71.5	9.5	0.721
Physical activity/week (METS)	278.8	56.1	286.7	84.2	0.628
Abdominal height (cm)	21.1	3.9	21.0	2.8	0.346
Waist circumference (cm)	92.0	14.2	90.1	12.6	0.546
Glucose level (mg/dl)	93.7	11.5	92.1	13.0	0.543
Cholesterol (mg/dl)	203.1	33.9	190.8	34.7	0.089
CRP (mg/l)	1.0	0.9	0.9	1.0	0.737
IL-6 (pg/ml)	2.0	0.6	1.8	0.7	0.406

[a] For categorical variables, the values are numbers and percentages.
[b] For continuous variables the values are means and standard deviations.

significantly correlated with BMI ($r = 0.35$, $p < 0.01$), abdominal height ($r = 0.30$, $p < 0.01$) and waist circumference ($r = 0.32$, $p < 0.01$), while IL-6 was significantly correlated with abdominal height ($r = 0.22$, $p = 0.02$) (Table 2).

After adjusting for age, sex, smoking, abdominal height, marital status, education, race, and anti-inflammatory medication, the mean level of CRP was 0.76 mg/l in participants with high PTSD symptomology, and 0.97 mg/l in participants low PTSD symptomology ($p = 0.55$). The adjusted mean level of IL-6 was 2.03 pg/ml for participants with high PTSD symptomology and 1.74 pg/ml for those with low PTSD symptomology ($p = 0.32$) (Table 3). Using IES score as a continuous variable in the models as a predictor for the CRP and IL-6 biomarkers did not reveal any significant results ($\beta \pm SE = -0.001 \pm 0.006$ with p-value = 0.904 and $\beta \pm SE = 0.002 \pm 0.004$ with p-value = 0.583, respectively). Adjusting for age, sex, smoking, abdominal height, marital status, race, education and anti-inflammatory medication did not appreciably alter the results ($\beta \pm SE = -0.005 \pm 0.006$ with p-value = 0.385 and $\beta \pm SE = 0.004 \pm 0.004$ with p-value = 0.388, respectively).

4. Discussion

Previous research suggests that exposure to traumatic stress may alter the HPA axis response resulting in an increase in the production of the inflammatory markers CRP and IL-6 [4,14,15]. Therefore, we hypothesized that police officers with PTSD symptomology might have higher levels of CRP and IL-6. However, we found no significant associations between PTSD symptomology and either CRP or IL-6. To our knowledge there are not any studies that have evaluated the level of inflammatory markers CRP and

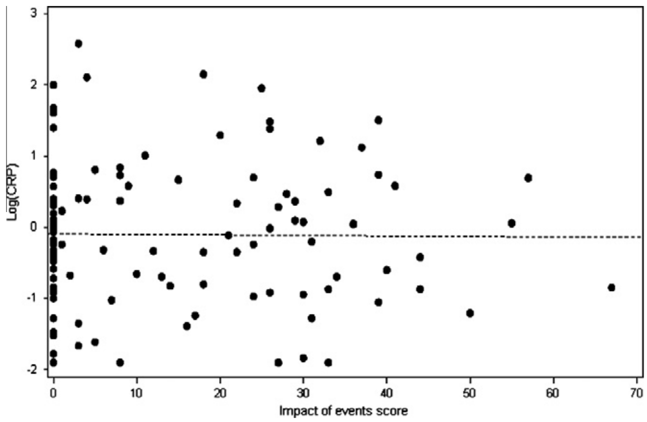

Fig. 1. A scattergram plotting the logCRP against the Impact of Events Score in officers. The regression line indicates that there is no correlation between CRP and Impact of Events Score in this population ($r = -0.01$, $p = 0.90$).

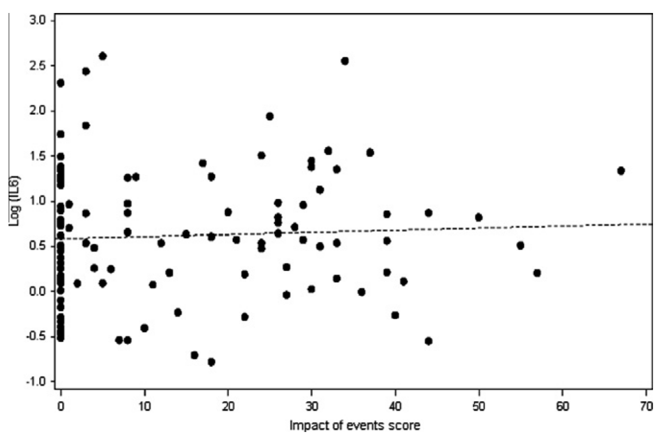

Fig. 2. A scattergram plotting the logIL-6 against the Impact of Events Score in officers. The regression line indicates that there is no correlation between IL-6 and Impact of Events Score in this population ($r = 0.53$; $p = 0.58$).

Table 2
Univariate correlations between CRP, IL-6 and cardiovascular disease risk factors.

Characteristics	Log CRP	*p*-Value	Log IL-6	*p*-Value
Age (yrs)	0.040	0.676	0.095	0.319
Alcohol (drinks/week)	−0.070	0.466	−0.093	0.330
BMI (kg/m^2)	0.351	0.001[a]	0.175	0.071
SBP (mmHg)	0.067	0.490	0.043	0.655
DBP (mmHg)	0.077	0.426	0.085	0.379
Physical activity/week (METS)	-0.048	0.620	-0.003	0.974
Abdominal height (cm)	0.301	0.002[a]	0.224	0.022[a]
Waist circumference (cm)	0.320	0.001[a]	0.155	0.110
Glucose level(mg/dl)	0.071	0.463	0.085	0.380
Cholesterol (mg/dl)	0.030	0.756	0.045	0.642

[a] Correlation is significant at the 0.05 level (2-tailed).

IL-6 with high or low PTSD symptomology. However, a number of studies have evaluated the level of inflammatory markers and clinically diagnosed PTSD and Miller et al. examined mean level of CRP with both the Davidson's trauma scale (DTS) intrusion subscale and the Impact of Events Scale – revised (RIES) intrusion subscale [15]. The RIES is the IES, revised to include a hyperarousal component. Our findings are consistent with those of Von Känel et al. and Sondergaard et al. who did not find an association between PTSD and CRP [21,22], but inconsistent with those of Spitzer et al., who reported a clear association between levels of CRP and PTSD [4].

Von Känel et al. measured the levels of CRP, IL-1β, IL-6, and tumor necrosis factor-alpha in the blood of 14 individuals with clinically diagnosed PTSD and 14 gender and age matched (±5 years) controls. The cases and controls were recruited from a psychiatric outpatient clinic and the department of trauma surgery, respectively. Neither CRP nor IL-6 was increased in PTSD patients compared to the controls [21]. Sondegaard et al. analyzed the level of CRP and serum amyloid A (SAA) in refugees from Iraq between the ages of 18–48 years in individuals with and without a clinical diagnosis of PTSD. The level of CRP was lower at baseline in participants with PTSD compared to participants without PTSD. However, during three subsequent follow-up visits the participants with PTSD had lower mean levels of CRP than at baseline [22]. The study by Spitzer et al. measured the levels of CRP in the blood of 55 participants with clinically diagnosed PTSD and 2994 participants without PTSD between the ages of 20–79 years. Individuals with PTSD were two times more likely than those without PTSD to have elevated levels of CRP ($\geqslant$3 mg/L) [4]. This study has a number of strengths including its large sample size; participants selected from the general population, and clinically diagnosed PTSD.

The inconsistencies observed between our study and those of others may be due to differences in the populations studied, accuracy of PTSD diagnosis, sample sizes, or clinical and biological differences between PTSD symptomology and clinically diagnosed PTSD. Boals and Hathaway suggest that two critical core symptoms in distinguishing a traumatic event that results in PTSD are the persistence of the symptoms, criterion E of the APA's Diagnostic and Statistical Manual of Mental Disorders, 4th-edition-text revision (DSM-IV, APA, 2000) and impairment level, criterion F of the DSM-IV [27]. In fact, Boals and Hathaway conducted two separate studies that demonstrated the importance of including all the DSM-IV criteria for diagnosing PTSD [27]. The IES assesses for the presence of re-experiencing and avoidance, but not duration or impairment level; therefore a high score on the IES is not necessarily equivalent to a clinical diagnosis of PTSD. However, in a pilot study by Miller et al., the levels of CRP and interleukin-6 receptor (sIL-6r) were measured in 15 participants with clinically diagnosed PTSD and 8 participants without PTSD. Although there was no difference between the levels of CRP or sIL-6r between individuals with PTSD and those without, a significantly positive relationship was found between the level of sIL-6r and the intrusion subscale of the RIES. CRP was reported to be significantly associated with the intrusion subscale of the Davidson's trauma scale and the intrusion subscale of the RIES. Neither the level of CRP nor sIL-6r were statistically significantly associated with the RIES total score [15]. So, while Boals and Hathaway [28] might argue that an accurate diagnosis of PTSD must include all the DSM-IV PTSD criteria, Miller's [15] results indicate that the levels of inflammatory markers may be associated with specific components of the PTSD criteria and not just PTSD in general. This is further supported by the fact that they did not find an association between the mean level of CRP and the total RIES score [15]. These results are consistent with ours and may indicate that the role of inflammatory markers in PTSD might be better gleaned by evaluating individual criteria that compose PTSD rather than the total number of symptoms or PTSD in general.

Our study had a number of strengths. Data were available for a randomly selected mid-sized urban police force including men and women. All data collection (blood and physical measures) was performed in a clinical setting by trained staff members and was processed at a laboratory using standardized methods. The study participants were selected from a population of active-duty police officers, and not from hospital sources. Therefore, it is expected that they are an otherwise healthy population, and not subject to other physical trauma which could have contributed to inflammation. Stressful occupations such as police work have a higher rate of

Table 3
Undjusted and adjusted mean levels of CRP and IL-6 by IES score.

	CRP (mg/l)		IL-6 (pg/ml)	
	IES Score		IES Score	
	⩾26	<26	⩾26	<26
Crude	0.858 (0.599–1.228)[a]	0.923 (0.734–1.158)	2.025 (1.580–2.598)	1.789 (1.528–2.098)
Age-adjusted	0.848 (0.590–1.221)	0.926 (0.736–1.166)	1.997 (1.555–2.567)	1.800 (1.535–2.110)
Age- and sex-adjusted	0.848 (0.589–1.222)	0.926 (0.735–1.166)	1.997 (1.555–2.567)	1.800 (1.535–2.112)
Multi-variable adjusted models [b]	0.757 (0.532–1.077)	0.966 (0.770–1.214)	2.031 (1.595–2.585)	1.738 (1.488–2.031)

[a] Values are means and 95% confidence intervals.
[b] Adjusted for age, sex, smoking, abdominal height, marital status, education, race, and anti-inflammatory medication.

exposure to traumatic events leading to the development of PTSD. This aspect of this population makes them a unique and valuable resource for studying the biological and psychological effects of trauma.

Overall, these results stress that further work remains to be done in order to understand the association between PTSD, PTSD symptoms and inflammation that may place individuals with PTSD or PTSD symptoms at a higher risk for CVD compared to individuals without PTSD or PTSD symptoms. A number of other inflammatory markers (e.g. TNF-α, IL-B, IL-4) are also important factors in the development of CVD and should be considered along with CRP and IL-6 [29].

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Conflict of interest

None.

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