Journal of Psychiatric Research 89 (2017) 14–21

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Elevated C-reactive protein and posttraumatic stress pathology among survivors of the 9/11 World Trade Center attacks

Rebecca L. Rosen [a, b, *], Nomi Levy-Carrick [a, b], Joan Reibman [b, c, d], Ning Xu [e], Yongzhao Shao [b, e], Mengling Liu [b, e], Lucia Ferri [a, b], Angeliki Kazeros [b, c], Caralee E. Caplan-Shaw [b, c], Deepak R. Pradhan [b, c], Michael Marmor [b, e], Isaac R. Galatzer-Levy [a, f]

[a] NYU School of Medicine, Department of Psychiatry, 550 First Ave, New York, NY 10016, United States
[b] Health and Hospitals World Trade Center Environmental Health Center, Bellevue Hospital Center, Ambcare 2E, 462 First Ave, New York, NY 10016, United States
[c] NYU School of Medicine, Department of Medicine, 550 First Ave, New York, NY 10016, United States
[d] NYU School of Medicine, Department of Environmental Medicine, 550 First Ave, New York, NY 10016, United States
[e] NYU School of Medicine, Department of Population Health, 650 First Ave, Fifth Floor, New York, NY 10016, United States
[f] Steven and Alexandra Cohen Veteran's Center, NYU Langone Medical Center, 550 First Ave, New York, NY 10016, United States

ARTICLE INFO

Article history:
Received 18 August 2016
Received in revised form
15 December 2016
Accepted 12 January 2017

Keywords:
C-reactive protein
PTSD
Depression
Systemic inflammation
World Trade Center
Trauma

ABSTRACT

Background: Systemic inflammation has emerged as a promising marker and potential mechanism underlying post-traumatic stress disorder (PTSD). The relationship between posttraumatic stress pathology and systemic inflammation has not, however, been consistently replicated and is potentially confounded by comorbid illness or injury, common complications of trauma exposure.
Methods: We analyzed a large naturalistic cohort sharing a discrete physical and mental health trauma from the destruction of the World Trade Center (WTC) towers on September 11, 2001 (n = 641). We evaluated the relationship between multiple physical and mental health related indices collected through routine evaluations at the WTC Environmental Health Center (WTC EHC), a treatment program for community members exposed to the disaster. C-Reactive Protein (CRP), a marker of systemic inflammation, was examined in relation to scores for PTSD, PTSD symptom clusters (re-experiencing, avoidance, negative cognitions/mood, arousal), depression and anxiety, while controlling for WTC exposures, lower respiratory symptoms, age, sex, BMI and smoking as potential risks or confounders.
Results: CRP was positively associated with PTSD severity ($p < 0.001$), trending toward association with depression ($p = 0.06$), but not with anxiety ($p = 0.27$). CRP was positively associated with re-experiencing ($p < 0.001$) and avoidance ($p < 0.05$) symptom clusters, and trended toward associations with negative cognitions/mood ($p = 0.06$) and arousal ($p = 0.08$).
Conclusions: In this large study of the relationship between CRP and posttraumatic stress pathology, we demonstrated an association between systemic inflammation and stress pathology (PTSD; trending with depression), which remained after adjusting for potentially confounding variables. These results contribute to research findings suggesting a salient relationship between inflammation and post-traumatic stress pathology.

1. Introduction

Systemic inflammation has emerged as a potential biological mechanism in the pathogenesis of posttraumatic stress disorder (PTSD) (Baker et al., 2012; Passos et al., 2015) and depression (Haroon et al., 2012; Miller et al., 2009), the two most common and

* Corresponding author. New York University Medical Center, 550 First Avenue, Bellevue Hospital Room 7N24, New York, NY 10016, United States.
E-mail address: RebeccaLRosen@nyumc.org (R.L. Rosen).

http://dx.doi.org/10.1016/j.jpsychires.2017.01.007

highly comorbid posttraumatic stress responses (Flory and Yehuda, 2015; Galatzer-Levy et al., 2013; Kessler et al., 2005). Elevated levels of C-reactive protein (CRP), a pro-inflammatory acute phase protein that can be measured systemically, have been associated with both PTSD and depression (Gill et al., 2009; Howren et al., 2009; Valkanova et al., 2013), including in populations exposed to terrorism (Canetti et al., 2014). Variants of the CRP gene are also associated with PTSD (Michopoulos et al., 2015), and elevated CRP levels prior to trauma are associated with the development of PTSD prospectively (Eraly et al., 2014).

Post traumatic stress pathology is heterogeneous (Galatzer-Levy and Bryant, 2013) and symptoms of PTSD have been divided into four clusters reflecting these diverse components including symptoms of re-experiencing, avoidance, negative alterations in cognitions and mood (negative cognitions/mood), and alterations in arousal and reactivity (arousal). These components are supported by factor-analytic studies (Cox et al., 2002; Marshall et al., 2013) and have been adopted for the DSM-V criteria.

Elevated CRP levels have been reported in association with re-experiencing symptoms of PTSD (Canetti et al., 2014; Miller et al., 2001; von Känel et al., 2007), and recently, with arousal symptoms (Michopoulos et al., 2015). This growing body of research suggests that systemic inflammation may be a biological marker and participate in the development or persistence of posttraumatic stress responses. The mammalian response to danger and stress involves the rapid activation of the sympathetic nervous system and hypothalamic-pituitary-adrenal axis (HPA-axis). This axis interacts with inflammatory pathways and may be a link between inflammation and PTSD (Baker et al., 2012; Michopoulos et al., 2017). Despite this potential overlap, the data supporting a relationship between CRP and PTSD have not consistently been replicated; both high and low CRP levels or no association with PTSD have been reported (McCanlies et al., 2011; Söndergaard et al., 2004; von Känel et al., 2007). The inconsistency of findings may relate to small sample sizes, the use of cross sectional data, or variable trauma exposures. Further, key factors that are associated with both inflammation and trauma, including injury and illness, have not been accounted for in existing studies.

The current study tested the hypothesis that elevated CRP was associated with posttraumatic stress pathology, including PTSD symptom clusters, depression and anxiety, controlling for WTC exposures, lower respiratory symptoms, age, sex, BMI and tobacco use. We used a large civilian population exposed to the terrorist attack on the World Trade Center (WTC) towers and its ensuing environmental disaster. These patients were enrolled in the WTC Environmental Health Center (WTC EHC), a treatment and monitoring program for physical and psychological effects associated with the attacks (Reibman et al., 2009, 2016). Individuals had potential for acute environmental exposures to the initial dust clouds created as the WTC buildings collapsed (WTC dust cloud), as well as chronic inhalation and topical exposure from re-suspended dust and fumes from prolonged fires (Lioy and Georgopoulos, 2006; Lippmann et al., 2015; Maslow et al., 2012; Reibman et al., 2016). Adverse health effects in community members (residents, local workers, clean-up workers, and others) include upper and lower respiratory symptoms (Brackbill et al., 2009; Farfel et al., 2008; Friedman et al., 2013; Lin et al., 2007; Reibman et al., 2005). In addition, many individuals witnessed death and dismemberment and often experienced their own fear of death as they escaped collapsing buildings or engulfment by blinding dust clouds. Some individuals were exposed to extended rescue and recovery efforts or displacement from homes and workplaces due to clean up efforts.

2. Methods

2.1. Subjects

The Bellevue Hospital Center WTC EHC provides medical and mental health treatment for self-referred community members (Reibman et al., 2009, 2016). Well-described adverse health effects in this population include persistent lower respiratory symptoms (LRS) (Brackbill et al., 2009; Farfel et al., 2008; Friedman et al., 2013; Lin et al., 2005, 2007; Reibman et al., 2005). Mental health symptoms include those associated with PTSD, depression, and anxiety (Brackbill et al., 2009; DiGrande et al., 2008). The Institutional Review Board of New York University School of Medicine approved the research database (NCT00404898) and only data from patients who signed informed consent were used for analysis. CRP measurements were performed in patients undergoing initial evaluation or monitoring between August 2007 and December 2012. Patients were included in the analysis if they also had complete exposure information, and complete medical and mental health questionnaires.

2.2. Measures

Upon enrollment in the WTC EHC, patients completed a multidimensional, interviewer-administered questionnaire that included demographic information, characterizations of WTC-related exposure, and tobacco use (Reibman et al., 2009). Individuals were classified as positive for dust cloud exposure if they reported having been in a WTC dust cloud created by the collapsing buildings on 9/11/2001. Potential for WTC acute and chronic exposures were characterized by classification into four additional categories: local resident (resident), local worker, clean-up worker, other. Patients who reported more than 5 pack-year history of tobacco use were defined as smokers. The presence and severity of LRS of wheeze, cough, chest tightness and dyspnea were measured by standardized health questionnaires (Reibman et al., 2009) and patients with symptoms more than twice per week during the month preceding enrollment were considered positive for persistent LRS. In addition, body mass index (BMI) of patients were calculated using information gathered during the initial medical visit.

2.2.1. CRP

CRP was measured using a wide-range CRP assay (Siemen's Diagnostic Center, Tarrytown, NY). The wide range CRP (wr-CRP) assay is a clinically used measure that has a wide sensitivity range with a lower limit of detection of 0.12 mg/L. The wr-CRP correlates significantly with the high sensitivity CRP (hs-CRP) measurements and quantitation of microinflammatory activity in individuals (Rogowski et al., 2005). A value > 3 mg/L was considered “High” (Yeh and Willerson, 2003).

2.2.2. Psychiatric symptom assessments

2.2.2.1. Posttraumatic stress disorder symptoms. The Post-traumatic Check List-17 (PCL-17) (Weathers FW et al., 1993), was used to measure PTSD symptom presence and severity. A score ≥ 44 was used to suggest “probable PTSD” (PTSD) (Farfel et al., 2008). Questions from the PCL-17 were matched to the DSM-V diagnostic criteria for characterization into four clusters reflecting symptoms of re-experiencing, avoidance, negative alterations in cognitions and mood (negative cognitions/mood), and alterations in arousal and reactivity (arousal), and an average score was calculated for each cluster, ranging between 1 and 5.

2.2.2.2. Depression and anxiety. We used the Hopkins Symptom Checklist for depression and anxiety (HSCL-25) (Derogatis et al.,

1974). These scales provided scores of depression (HSCL-D) and anxiety (HSCL-A) severity with a score ≥ 1.75 considered to suggest "probable depression" (depression) or "probable anxiety" (anxiety).

2.3. Statistical methods

In addition to demographic variables, variables of interest included WTC exposure categories and WTC dust exposure, not only as proxies for trauma exposure, but also because they were found to be significantly associated with CRP levels in prior research by our group (Kazeros et al., 2015). In addition, BMI and smoking status were included in the analysis as they are consistently found in research to be associated with elevated CRP levels, along with age and sex; WTC-related lower respiratory illness was included, as respiratory illness can be related to adverse mental health and to inflammation (Kaptoge et al., 2010).

Descriptive statistics were calculated for CRP, demographic variables, exposures and lower respiratory symptoms, where categorical variables were summarized using counts and proportions, and continuous variables were summarized using means and standard deviations or median and inter-quartile range (IQR). CRP was summarized both as a categorical (high CRP when level>3, low CRP otherwise) and a continuous variable. To investigate univariate association of mental health symptoms with each of the predictor variables, the PTSD, depression and anxiety symptom scores were also summarized using median and IQR within each category of the categorical or dichotomized continuous predictors. Median and IQR were used because distributions of mental health symptoms were asymmetrical around their averages. Significance of such associations was assessed using the Kruskal-Wallis test. Subsequently, multivariate associations among mental health scores and predicting variables were studied using multiple linear regression. Each of the PTSD cluster scores was also modeled with linear regression. In all regression models, CRP score was log-transformed because its distribution is skewed. Log CRP is closer to being normally distributed, thus unit change is more easily interpreted. R, version 3.2.4, was used to perform the statistical analyses.

3. Results

3.1. Patient characteristics

The final study population consisted of 641 patients who enrolled in the WTC EHC between February 2005 and November 2011. The characteristics of the study population were similar to those previously described (Liu et al., 2012; Reibman et al., 2009), and are presented in Table 1. Half of the diverse population was female, 38% of the group identified as Hispanic, the overall mean age was 50, and the majority reported a low annual household income (≤$30K). Half of the population reported being caught in the WTC dust cloud and the majority were local workers. Patients reported high rates of persistent LRS as well as overall high rates of PTSD (41%), depression (59%) and anxiety (49%) symptoms. CRP levels were also high, with levels > 3 mg/L in 36%.

Table 1
Patient characteristics, n = 641.

Demographic characteristics	
Female gender, n (%)	325 (51)
Age, mean (SD)[a]	50.1 (11.6)
Race/ethnicity, n (%)	
Hispanic	241 (38)
Non-Hispanic white	204 (32)
Non-Hispanic black	131 (20)
Other	65 (10)
Education, n (%)	
>High school	431 (67)
≤High school	210 (33)
Income, n (%)	
>$30,000/year	239 (37)
≤$30,000/year	402 (63)
BMI, mean (SD)	28.6 (6.2)
Ever smoker, n (%)	146 (23)
Exposures	
WTC dust cloud exposure, n (%)	325 (51)
Exposure classification, n (%)	
Local worker	331 (52)
Resident	121 (19)
Clean-up worker	108 (17)
Other	81 (13)
Lower respiratory symptoms	
Cough, n (%)	433 (68)
Wheeze, n (%)	328 (51)
Chest tightness, n (%)	408 (64)
Dyspnea at rest, n (%)	262 (41)
Positive mental health score	
PTSD, n (%)	260 (41)
Depression, n (%)	374 (59)
Anxiety, n (%)	316 (49)
CRP	
CRP, median (IQR)[b]	1.54 (0.34,5.07)
CRP>3, n (%)	233 (36)

[a] SD, standard deviation.
[b] IQR, inter-quartile range.

3.2. Association of CRP and patient characteristics with mental health symptoms

We found significant elevations in PTSD ($p = 0.007$) and depression ($p = 0.05$) symptoms in relation to elevated CRP (>3) (Table 2). This association was not found for anxiety symptoms. PTSD, anxiety and depression were also associated with three demographic characteristics: race ($p < 0.001$ for all), income ($p < 0.001$ for all) and education ($p = 0.006$; $p < 0.001$; $p = 0.01$ respectively). WTC dust cloud exposure was significantly associated with elevated scores for PTSD ($p < 0.001$), whereas exposure classification (local worker, resident, etc.) was associated with all psychiatric symptom scores (PTSD $p = 0.007$; anxiety $p < 0.001$; depression $p = 0.003$). The presence of each LRS (cough, wheeze, dyspnea, chest tightness) was associated with positive scores for each psychiatric symptom, with p values ranging from <0.001 to 0.05. In contrast, general health indicators (BMI, tobacco use) were not significantly associated with psychiatric scores. Anxiety was significantly associated with younger age ($p = 0.04$).

Since both physical and mental health symptoms were frequent in community members after the disaster, we analyzed the relationship of CRP with psychiatric symptoms while controlling for demographic variables, WTC exposures, subsequent lower respiratory health symptoms, and other variables that might account for the shared variance between psychiatric symptoms and CRP (Table 3). CRP levels remained associated with PTSD ($\beta = 1.12$, standard error [SE] = 0.43 $p = 0.01$) and trended toward an association with depression symptoms ($\beta = 0.55$, $SE = 0.29$, $p = 0.06$). Many demographic characteristics remained associated with each psychiatric score. Importantly, exposure to the WTC dust cloud remained associated with PTSD ($\beta = 5.01$, $SE = 1.30$, $p < 0.01$).

3.3. Association of CRP and patient characteristics with PTSD clusters

To understand the relationship between CRP and components of PTSD, we examined the relationship of CRP levels to specific PTSD symptom clusters while controlling for other variables (Table 4). Re-experiencing and avoidance symptoms were associated with CRP levels ($\beta = 0.08$, $SE = 0.03$, $p = 0.002$; $\beta = 0.08$, $SE = 0.04$,

Table 2
Univariate tests for association of PTSD, anxiety and depression scores with each of the predictors; (n = 641).

	PTSD		Anxiety		Depression[a]	
	Median (IQR)[b]	P value	Median (IQR)	P value	Median (IQR)	P value
CRP > 3		**0.007**		0.73		**0.05**
Yes	42 (28,54)		17 (13,24)		30 (23,39)	
No	37 (25,51)		17 (13,24)		28 (21,37)	
Demographics						
Gender		0.09		0.27		0.08
Female	40 (27,53)		18 (14,24)		31 (22,39)	
Male	37 (25,52)		17 (13,23)		28 (21,37)	
Age at first visit>50		0.12		**0.04**		0.07
Yes	39 (25,51)		17 (13,23)		28 (21,37)	
No	39 (27,55)		18 (14,24)		30 (22,39)	
Race/ethnicity		**<0.001**		**<0.001**		**<0.001**
Hispanic	42 (31,56)		21 (15,26)		32 (25,40)	
Non-Hispanic white	35 (24,50)		17 (13,23)		28 (21,37)	
Non-Hispanic black	36 (24,50)		16 (13,22)		25 (20,34)	
Other	33 (23,52)		16 (12,22)		27 (20,35)	
Education		**0.006**		**<0.001**		**0.01**
>High school	37 (24,52)		17 (13,23)		28 (21,37)	
≤High school	41 (28,55)		20 (14,26)		32 (24,39)	
Income		**<0.001**		**<0.001**		**<0.001**
> $30,000/year	36 (24,50)		16 (12,22)		26 (20,35)	
≤ $30,000/year	41 (28,55)		19 (14,25)		31 (23,39)	
BMI>30		0.14		0.62		0.47
Yes	41 (28,53)		17 (13,25)		29 (22,39)	
No	38 (25,52)		17 (14,23)		29 (22,38)	
Ever smoker		0.90		0.18		0.77
Yes	40 (26,53)		17 (13,23)		28 (21,39)	
No	39 (26,53)		18 (13,24)		29 (22,38)	
Exposures						
WTC dust cloud		**<0.001**		0.11		0.08
Yes	42 (28,54)		18 (14,24)		30 (23,38)	
No	36 (24,51)		17 (13,24)		28 (21,38)	
Exposure classification		**0.007**		**<0.001**		**0.003**
Local worker	40 (26,53)		17 (13,23)		28 (21,38)	
Resident	35 (25,47)		17 (13,23)		28 (22,37)	
Clean-up worker	43 (30,58)		22 (17,28)		34 (27,41)	
Other	38 (24,47)		16 (13,23)		26 (22,36)	
Lower respiratory symptoms						
Cough		**0.05**		**0.009**		**0.03**
Yes	40 (27,53)		18 (14,25)		30 (22,39)	
No	36 (25,51)		16 (13,22)		28 (20,36)	
Wheeze		**0.002**		**<0.001**		**0.01**
Yes	42 (27,55)		19 (14,25)		30 (23,39)	
No	37 (24,50)		17 (13,23)		28 (21,37)	
Dyspnea at rest		**<0.001**		**<0.001**		**<0.001**
Yes	42 (28,56)		20 (15,26)		32 (23,41)	
No	37 (24,50)		16 (13,22)		28 (20,37)	
Chest tightness		**<0.001**		**<0.001**		**<0.001**
Yes	42 (27,56)		20 (14,25)		31 (23,40)	
No	35 (24,46)		16 (12,21)		26 (20,35)	

Significant P-values are bolded.
[a] 5 participants missing depression data: n = 636 for depression analysis.
[b] IRQ, inter-quartile range.

p = 0.02), whereas negative cognitions/mood and arousal trended toward an association (β = 0.06, SE = 0.03, p = 0.06; β = 0.05, SE = 0.03, p = 0.08).

4. Discussion

We examined the relationship between systemic CRP and multiple dimensions of posttraumatic stress pathology including specific PTSD symptom clusters, as well as depression and anxiety. Notably, we studied a civilian population with a shared discrete and well-documented physical and psychological trauma, allowing us to investigate the relationship between CRP and posttraumatic stress pathology while addressing alternative explanations for the relationship between inflammation and PTSD. Physical illness, health behaviors and ageing are some factors that can impact inflammation. Our study used a population undergoing treatment for symptoms related to this discrete disaster, allowing us to control for lower respiratory symptoms, BMI, smoking, age and sex, as well as type of exposure to the toxic aftermath. Our findings support and expand upon previous findings suggesting an important association between systemic inflammation and posttraumatic stress pathology and offers evidence of the relationship between systemic inflammation and PTSD, independent of illness.

C-reactive protein is an acute phase protein usually produced in the liver during acute inflammation in response to interleukin-6 (IL-6). As such, serum CRP is a non-specific biomarker of the innate immune response; its short half-life suggests that it is a measure of an ongoing process. Importantly, IL-6, upstream of CRP, is a product of macrophages, but in the brain, neurons, astrocytes, microglia and endothelial cells are all potential sources. The close

Table 3
Multiple linear regressions of PTSD, anxiety and depression scores; n = 641.

	PTSD		Anxiety		Depression[a]	
	β (SE)[b]	P value	β (SE)	P value	β (SE)	P value
log(CRP)	**1.12 (0.43)**	**0.01**	0.19 (0.18)	0.27	0.55 (0.29)	0.06
Demographics						
Gender - male	**−2.49 (1.25)**	**0.05**	−0.95 (0.51)	0.06	**−1.87 (0.84)**	**0.03**
Age at first visit	−0.07 (0.06)	0.26	−0.02 (0.02)	0.40	−0.07 (0.04)	0.06
Race/ethnicity Hispanic	**4.73 (1.53)**	**0.00**	**1.73 (0.62)**	**0.01**	**2.31 (1.03)**	**0.03**
Education ≤ High School	0.23 (1.5)	0.88	0.35 (0.61)	0.57	−0.08 (1.0)	0.93
Income ≤ $30k/year	**3.72 (1.36)**	**0.01**	**1.82 (0.55)**	**0.00**	**2.62 (0.91)**	**0.00**
log(BMI)	−3.57 (3.4)	0.29	−1.56 (1.38)	0.26	−2.28 (2.28)	0.32
Ever smoker	0.37 (1.54)	0.81	−0.62 (0.63)	0.33	0.06 (1.03)	0.95
Exposures						
WTC dust cloud exposure	**5.01 (1.3)**	**0.00**	**1.39 (0.53)**	**0.01**	**1.98 (0.87)**	**0.02**
Exposure classification						
Resident	−2.19 (1.72)	0.20	0.12 (0.70)	0.87	0.60 (1.15)	0.60
Clean-up worker	1.48 (2.16)	0.49	**2.41 (0.88)**	**0.01**	2.06 (1.44)	0.15
Other	−2.92 (2.0)	0.14	−0.49 (0.81)	0.55	−0.94 (1.34)	0.48
Lower respiratory symptoms						
Cough	0.47 (1.4)	0.74	0.52 (0.57)	0.37	0.87 (0.94)	0.35
Wheeze	0.71 (1.38)	0.61	0.38 (0.56)	0.50	0.41 (0.92)	0.66
Dyspnea at rest	**3.05 (1.37)**	**0.03**	**1.73 (0.56)**	**0.00**	**1.87 (0.92)**	**0.04**
Chest tightness	**4.70 (1.37)**	**0.00**	**2.61 (0.56)**	**0.00**	**2.79 (0.92)**	**0.00**

Significant P-values are bolded.
[a] 5 participants missing depression data: n = 636 for depression analysis.
[b] β, regression coefficient; (SE), standard error.

Table 4
Multiple linear regressions of PTSD symptom cluster scores; n = 641.

	Re-experiencing		Avoidance		Negative cognitions/mood		Arousal	
	β (SE)[a]	P value	β (SE)	P value	β (SE)	P value	β (SE)	P value
log(CRP)	**0.08 (0.03)**	**0.002**	**0.08 (0.04)**	**0.02**	0.06 (0.03)	0.06	0.05 (0.03)	0.08
Demographics								
Gender - male	−0.13 (0.08)	0.09	**−0.35 (0.10)**	**0.001**	−0.07 (0.08)	0.42	−0.16 (0.09)	0.07
Age at first visit	0.00 (0.00)	0.78	0.00 (0.00)	0.41	−0.01 (0.00)	0.16	0.00 (0.00)	0.24
Race/ethnicity Hispanic	**0.25 (0.10)**	**0.008**	**0.30 (0.13)**	**0.02**	**0.21 (0.10)**	**0.04**	**0.36 (0.11)**	**0.001**
Education ≤ High school	0.04 (0.09)	0.67	−0.03 (0.13)	0.80	−0.04 (0.10)	0.68	0.06 (0.11)	0.58
Income≤ $30k/year	**0.29 (0.08)**	**0.001**	**0.34 (0.11)**	**0.003**	**0.19 (0.09)**	**0.04**	0.13 (0.10)	0.17
log(BMI)	−0.11 (0.21)	0.62	−0.52 (0.28)	0.07	−0.19 (0.23)	0.41	−0.21 (0.24)	0.39
Ever smoker	−0.08 (0.10)	0.40	−0.04 (0.13)	0.76	0.08 (0.10)	0.47	0.09 (0.11)	0.39
Exposures								
WTC dust cloud	**0.30 (0.08)**	**0.00**	**0.34 (0.11)**	**0.002**	**0.25 (0.09)**	**0.005**	**0.32 (0.09)**	**0.001**
Exposure classification								
Resident	−0.16 (0.11)	0.13	**−0.28 (0.14)**	**0.05**	−0.06 (0.12)	0.60	−0.11 (0.12)	0.39
Clean-up worker	0.02 (0.13)	0.89	0.06 (0.18)	0.74	0.17 (0.15)	0.23	0.08 (0.15)	0.61
Other	−0.17 (0.12)	0.16	−0.25 (0.17)	0.14	−0.19 (0.13)	0.17	−0.12 (0.14)	0.38
Lower respiratory symptoms								
Cough	0.01 (0.09)	0.88	−0.03 (0.12)	0.80	0.05 (0.09)	0.57	0.04 (0.10)	0.70
Wheeze	−0.01 (0.09)	0.89	0.08 (0.12)	0.50	0.04 (0.09)	0.66	0.08 (0.10)	0.42
Dyspnea at rest	**0.20 (0.08)**	**0.02**	0.21 (0.11)	0.07	0.17 (0.09)	0.06	0.15 (0.10)	0.13
Chest tightness	**0.30 (0.08)**	**0.00**	0.19 (0.11)	0.09	**0.24 (0.09)**	**0.01**	**0.33 (0.10)**	**0.001**

Significant P-values are bolded.
[a] β, regression coefficient; (SE), standard error.

relationship between neuroinflammatory pathways such as IL-6, and dysregulation of the HPA axis are well described (Furtado and Katzman, 2015). Synaptic plasticity, learning, and memory, as well as motivation, sleep and arousal are impacted by inflammation (Khairova et al., 2009; McAfoose and Baune, 2009; Ransohoff, 2009; Yirmiya and Goshen, 2011) and are perturbed in both PTSD and depression (Olbert et al., 2014; Pitman et al., 2012; Yehuda and LeDoux, 2007), suggesting a potential shared etiology for post-traumatic stress pathology involving inflammatory pathways. Our findings reinforce the potential for an interplay between systemic inflammation and posttraumatic stress pathology. Interestingly, we do not observe a relationship between CRP and measures of anxiety in this population. We propose that we are identifying a relationship between a systemic measure of inflammation, which may be related to HPA-Axis regulation and a specific role in learned fear and threat responses, rather than a more general anxiety response. This interplay has been suggested by others (Norrholm et al., 2015).

The current study demonstrates an association between elevated CRP and particular PTSD clusters. Elevated CRP was most strongly associated with re-experiencing. This suggests that this component of posttraumatic stress pathology may be most related to the stress response, and thus associated with aberrant HPA-axis regulation and inflammation. This symptom cluster association is consistent with studies of individuals with PTSD symptomatology after terrorist attack or other traumatic events

(Canetti et al., 2014; Miller et al., 2001; von Känel et al., 2007). In our study, PTSD symptoms were assessed 6–11 years after 9/11/2001, suggesting a relationship between chronic re-experiencing and inflammation. The avoidance cluster of symptoms was also associated with inflammation consistent with the concept that re-experiencing and avoidance may be linked. We did not identify a significant relationship of CRP with the arousal symptom cluster in our study. In contrast, elevated CRP has been shown to be associated with an individual symptom of arousal, i.e. "overly alert" in another population with chronic trauma symptoms (Michopoulos et al., 2015). The difference in findings may be due to sample size, our analysis of symptom clusters rather than individual symptoms, or the use of different instruments in the assessment of symptoms.

The relationship between depression and inflammation is more established in the literature than that between PTSD and inflammation (Haroon et al., 2012; Howren et al., 2009; Valkanova et al., 2013). Both the PCL and the Hopkins symptoms checklist assess symptoms of depression using different questions. We identified a trend in the association between inflammation and depressive symptoms, even when measured by two separate questionnaires, rather than the strong association reported by others. The absence of a strong association may be due to sample size. Another explanation may be that posttraumatic depression is a distinct construct from major depression and, as such, may have a distinct etiology. This explanation is supported by prospective studies of major health events demonstrating that emergent depression following the event has a distinct trajectory from major depression (Burton et al., 2015; Flory and Yehuda, 2015; Galatzer-Levy and Bonanno, 2014; Zhu et al., 2014).

The association of inflammation with PTSD has important implications for health risks and management. Inflammation is associated with significant metabolic dysfunction, as is PTSD, suggesting that the inflammatory and stress response to trauma are important pathways to long-term health problems (Daskalakis et al., 2013; Farr et al., 2014). The heterogeneity in posttraumatic stress pathology and the relationship between specific PTSD symptom cluster and inflammatory pathways may also have important prevention and treatment implications. Selective serotonin reuptake inhibitors (SSRIs), the first line of medication treatment for PTSD, differ in their ability to suppress inflammatory signals such as IL-6 and tumor necrosis factor-α (TNF-α) (Eyre et al., 2016). These differences in anti-inflammatory potency, coupled with the association of inflammation with PTSD suggest potential targeting of specific SSRIs in PTSD treatment. Moreover, the differences in inflammatory markers within PTSD clusters, suggests potential targeting of SSRIs depending upon the PTSD pathology. PTSD with co-morbid depression is difficult to treat, and further elucidation of predominant symptom clusters may help in refining psychotherapy choices as well as adjunctive psychopharmacology (Flory and Yehuda, 2015).

4.1. Limitations and future directions

There are specific limitations to this study. We studied a cross-sectional civilian population, limiting the ability to explore cause and effect. Our analyses included variables with potential to influence CRP including BMI, smoking, age and gender. The possibility exists that concurrent medication use (statins), as well as other physical conditions such as diabetes or cardiovascular disease had potential to modify CRP levels. Future analyses should account for these potential confounders. While the population has all been exposed to the same trauma, a noted strength of the study, this may limit the generalizability of these results. Participants were self-referred patients seeking treatment for physical or mental health symptoms and were not drawn from a general, WTC exposed population of survivors, raising the potential for selection bias for these symptoms. However, our analyses are between symptoms and CRP levels, and patients did not self-refer for CRP measurements. Our findings support and expand upon those described by others with general population reference groups (Michopoulos et al., 2017; Passos et al., 2015).

Importantly, alterations in CRP represent a non-specific inflammatory response. A recent meta-analysis of cytokine levels in relation to PTSD have pointed to more upstream effects that ultimately may influence the observed CRP levels in the current study. Specifically, Passos et al. (2015) demonstrate abnormal levels of IL-6, TNF-α, interleukin 1β (IL-1β), and interferon γ (IFN- γ) in PTSD. These analyses are consistent with our findings and may represent more specific pathways and targets for treatment. Future work in this population and others should explore cytokine pathways leading to elevations in CRP. In addition, we did not examine the activation of other inflammatory pathways, including those unrelated to CRP. CRP has a short half-life and we describe CRP levels and mental health findings years after the presumed inciting event. As such, we cannot characterize cause and effect, however, the short half-life suggests that the stimulus for CRP is ongoing, consistent with the persistence of PTSD pathology in our population. The possibility exists that the physiologic corollary to the re-experiencing cluster of symptoms is a mechanism that triggers acute inflammatory cytokines.

The current findings further our understanding of the important relationship between systemic inflammation and posttraumatic stress pathology. Heterogeneity of the posttraumatic stress diagnosis warrants refinement of symptom clusters to inform potential targets for therapeutic intervention. Identifying the biologic pathways associated with these underlying dimensions of posttraumatic stress responses has potential to lead to additional targeted approaches to treatment.

Role of funding source

Funding for this study was provided by Centers for Disease Control and Prevention (CDC) – National Institute for Occupational Services and Health (NIOSH) CDC 200-2011-39391-WTC Clinical Centers of Excellence, CDC-NIOSH 200-2011-39379, CDC-NIOSH 5U01OH010404. The funding body had no further role in study design; in the collection, analysis or interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Contributors

Rebecca L. Rosen, Ph.D contributed to the study design, interpretation of results, and writing of the manuscript.

Nomi Levy-Carrick, MD, MPhil contributed to the study design, interpretation of results, and writing of the manuscript.

Joan Reibman, MD, contributed to the study design, interpretation of results, and writing of the manuscript.

Ning Xu, MS contributed to the data analysis.

Yongzhao Shao, Ph.D contributed to the study design, data analysis, and writing of the manuscript.

Mengling Liu, Ph.D contributed to the study design and data analysis.

Lucia Ferri, Ph.D contributed to the study design and interpretation of results.

Angeliki Kazeros, MD, contributed to the study design and interpretation of results.

Caralee E. Caplan-Shaw, MD contributed to the interpretation of results.

Deepak R. Pradhan, MD contributed to the interpretation of results.

Michael Marmor, Ph.D contributed to interpretation of results.

Isaac R. Galatzer-Levy contributed to interpretation of results and writing of the manuscript.

All authors critically reviewed and approved the manuscript.

Acknowledgements

We thank Terry Miles for his ongoing support and advice. We graciously appreciate Edith Davis, Evelin Zumba, and Scott Penn for their tireless administration of the program. We thank Priyanka Uppadhyaya and the mental health and medical staff of the WTC Environmental Health Center for their dedication to the treatment and support of our patients. We also thank members of the WTC Health Program Survivor Steering Committee for their invaluable advice and efforts on behalf of the community.

References

Baker, D.G., Nievergelt, C.M., O'Connor, D.T., 2012. Biomarkers of PTSD: neuropeptides and immune signaling. Neuropharmacology 62 (2), 663–673.

Brackbill, R.M., Hadler, J.L., DiGrande, L., Ekenga, C.C., Farfel, M.R., Friedman, S., Perlman, S.E., Stellman, S.D., Walker, D.J., Wu, D., Yu, S., Thorpe, L.E., 2009. Asthma and posttraumatic stress symptoms 5 to 6 years following exposure to the World Trade Center terrorist attack. Jama 302 (5), 502–516.

Burton, C.L., Galatzer-Levy, I.R., Bonanno, G.A., 2015. Treatment type and demographic characteristics as predictors for cancer adjustment: prospective trajectories of depressive symptoms in a population sample. Health Psychol. 34 (6), 602.

Canetti, D., Russ, E., Luborsky, J., Gerhart, J.I., Hobfoll, S.E., 2014. Inflamed by the flames? The impact of terrorism and war on immunity. J. Trauma. stress 27 (3), 345–352.

Cox, B.J., Clara, I.P., Enns, M.W., 2002. Posttraumatic stress disorder and the structure of common mental disorders. Depress Anxiety 15 (4), 168–171.

Daskalakis, N.P., Lehrner, A., Yehuda, R., 2013. Endocrine aspects of post-traumatic stress disorder and implications for diagnosis and treatment. Endocrinol. Metab. Clin. North Am. 42 (3), 503–513.

Derogatis, L.R., Lipman, R.S., Rickels, K., Uhlenhuth, E.H., Covi, L., 1974. The Hopkins Symptom Checklist (HSCL): a self-report symptom inventory. Behav. Sci. 19 (1), 1–15.

DiGrande, L., Perrin, M.A., Thorpe, L.E., Thalji, L., Murphy, J., Wu, D., Farfel, M., Brackbill, R.M., 2008. Posttraumatic stress symptoms, PTSD, and risk factors among lower Manhattan residents 2-3 years after the September 11, 2001 terrorist attacks. J. Trauma. stress 21 (3), 264–273.

Eraly, S.A., Nievergelt, C.M., Maihofer, A.X., Barkauskas, D.A., Biswas, N., Agorastos, A., O'Connor, D.T., Baker, D.G., 2014. Assessment of plasma C-reactive protein as a biomarker of posttraumatic stress disorder risk. JAMA psychiatry 71 (4), 423–431.

Eyre, H.A., Lavretsky, H., Kartika, J., Qassim, A., Baune, B.T., 2016. Modulatory effects of antidepressant classes on the innate and adaptive immune system in depression. Pharmacopsychiatry 49 (3), 85–96.

Farfel, M., DiGrande, L., Brackbill, R., Prann, A., Cone, J., Friedman, S., Walker, D.J., Pezeshki, G., Thomas, P., Galea, S., Williamson, D., Frieden, T.R., Thorpe, L., 2008. An overview of 9/11 experiences and respiratory and mental health conditions among World Trade Center Health Registry enrollees. J. urban health Bull. N. Y. Acad. Med. 85 (6), 880–909.

Farr, O.M., Sloan, D.M., Keane, T.M., Mantzoros, C.S., 2014. Stress-and PTSD-associated obesity and metabolic dysfunction: a growing problem requiring further research and novel treatments. Metabolism Clin. Exp. 63 (12), 1463–1468.

Flory, J.D., Yehuda, R., 2015. Comorbidity between post-traumatic stress disorder and major depressive disorder: alternative explanations and treatment considerations. Dialogues Clin. Neurosci. 17 (2), 141–150.

Friedman, S.M., Farfel, M.R., Maslow, C.B., Cone, J.E., Brackbill, R.M., Stellman, S.D., 2013. Comorbid persistent lower respiratory symptoms and posttraumatic stress disorder 5-6 years post-9/11 in responders enrolled in the World Trade Center Health Registry. Am. J. industrial Med. 56 (11), 1251–1261.

Furtado, M., Katzman, M.A., 2015. Examining the role of neuroinflammation in major depression. Psychiatry Res. 229 (1–2), 27–36.

Galatzer-Levy, I.R., Bonanno, G.A., 2014. Optimism and Death Predicting the Course and Consequences of Depression Trajectories in Response to Heart Attack. Psychological science, 0956797614551750.

Galatzer-Levy, I.R., Bryant, R.A., 2013. 636,120 ways to have posttraumatic stress disorder. Perspect. Psychol. Sci. 8 (6), 651–662.

Galatzer-Levy, I.R., Nickerson, A., Litz, B.T., Marmar, C.R., 2013. Patterns of lifetime PTSD comorbidity: a latent class analysis. Depress Anxiety 30 (5), 489–496.

Gill, J.M., Saligan, L., Woods, S., Page, G., 2009. PTSD is associated with an excess of inflammatory immune activities. Perspect. psychiatric care 45 (4), 262–277.

Haroon, E., Raison, C.L., Miller, A.H., 2012. Psychoneuroimmunology meets neuropsychopharmacology: translational implications of the impact of inflammation on behavior. Neuropsychopharmacology 37 (1), 137–162.

Howren, M.B., Lamkin, D.M., Suls, J., 2009. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom. Med. 71 (2), 171–186.

Kaptoge, S., Di Angelantonio, E., Lowe, G., Pepys, M.B., Thompson, S.G., Collins, R., Danesh, J., 2010. The Emerging Risk Factors Collaboration. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-anlysis. Lancet 375 (9709), 132–140.

Kazeros, A., Zhang, E., Cheng, X., Shao, Y., Liu, M., Qian, M., Caplan-Shaw, C., Berger, K.I., Goldring, R.M., Ghumman, M., Chokshi, N.P., Levy-Carrick, N., Fernandez-Beros, M.E., Parsia, S., Marmor, M., Reibman, J., 2015. Systemic inflammation associated with world trade center dust exposures and airway abnormalities in the local community. J. Occup. Environ. Med./Am. Coll. Occup. Environ. Med. 57 (6), 610–616.

Kessler, R.C., Berglund, P., Demler, O., Jin, R., Merikangas, K.R., Walters, E.E., 2005. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey replication. Arch. Gen. Psychiatry 62 (6), 593–602.

Khairova, R.A., Machado-Vieira, R., Du, J., Manji, H.K., 2009. A potential role for pro-inflammatory cytokines in regulating synaptic plasticity in major depressive disorder. Int. J. Neuropsychopharmacol. 12 (4), 561–578.

Lin, S., Jones, R., Reibman, J., Bowers, J., Fitzgerald, E.F., Hwang, S.A., 2007. Reported respiratory symptoms and adverse home conditions after 9/11 among residents living near the World Trade Center. J. asthma official J. Assoc. Care Asthma 44 (4), 325–332.

Lin, S., Reibman, J., Bowers, J.A., Hwang, S.-A., Hoerning, A., Gomez, M.I., Fitzgerald, E.F., 2005. Upper respiratory symptoms and other health effects among residents living near the world trade center site after September 11, 2001. Am. J. Epidemiol. 162 (6), 499–507.

Lioy, P.J., Georgopoulos, P., 2006. The anatomy of the exposures that occurred around the World Trade Center site: 9/11 and beyond. Ann. N. Y. Acad. Sci. 1076, 54–79.

Lippmann, M., Cohen, M.D., Chen, L.C., 2015. Health effects of World Trade Center (WTC) Dust: an unprecedented disaster's inadequate risk management. Crit. Rev. Toxicol. 45 (6), 492–530.

Liu, M., Qian, M., Cheng, Q., Berger, K.I., Shao, Y., Turetz, M., Kazeros, A., Parsia, S., Goldring, R.M., Caplan-Shaw, C., Elena Fernandez-Beros, M., Marmor, M., Reibman, J., 2012. Longitudinal spirometry among patients in a treatment program for community members with World Trade Center-related illness. J. Occup. Environ. Med. 54 (10), 1208–1213.

Marshall, G.N., Schell, T.L., Miles, J.N., 2013. A multi-sample confirmatory factor analysis of PTSD symptoms: what exactly is wrong with the DSM-IV structure? Clin. Psychol. Rev. 33 (1), 54–66.

Maslow, C.B., Friedman, S.M., Pillai, P.S., Reibman, J., Berger, K.I., Goldring, R., Stellman, S.D., Farfel, M., 2012. Chronic and acute exposures to the world trade center disaster and lower respiratory symptoms: area residents and workers. Am. J. Public Health 102 (6), 1186–1194.

McAfoose, J., Baune, B., 2009. Evidence for a cytokine model of cognitive function. Neurosci. Biobehav. Rev. 33 (3), 355–366.

McCanlies, E.C., Araia, S.K., Joseph, P.N., Mnatsakanova, A., Andrew, M.E., Burchfiel, C.M., Violanti, J.M., 2011. C-reactive protein, interleukin-6, and post-traumatic stress disorder symptomology in urban police officers. Cytokine 55 (1), 74–78.

Michopoulos, V., Powers, A., Gillespie, C.F., Ressler, K.J., Jovanovic, T., 2017. Inflammation in fear- and anxiety-based disorders: PTSD, GAD, and beyond. Neuropsychopharmacology 42 (1), 254–270.

Michopoulos, V., Rothbaum, A.O., Jovanovic, T., Almli, L.M., Bradley, B., Rothbaum, B.O., Gillespie, C.F., Ressler, K.J., 2015. Association of CRP genetic variation and CRP level with elevated PTSD symptoms and physiological responses in a civilian population with high levels of trauma. Am. J. Psychiatry 172 (4), 353–362.

Miller, A.H., Maletic, V., Raison, C.L., 2009. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. Biol. psychiatry 65 (9), 732–741.

Miller, R.J., Sutherland, A.G., Hutchison, J.D., Alexander, D.A., 2001. C-reactive protein and interleukin 6 receptor in post-traumatic stress disorder: a pilot study. Cytokine 13 (4), 253–255.

Norrholm, S.D., Glover, E.M., Stevens, J.S., Fani, N., Galatzer-Levy, I.R., Bradley, B., Ressler, K.J., Jovanovic, T., 2015. Fear load: the psychophysiological over-expression of fear as an intermediate phenotype associated with trauma reactions. Int. J. Psychophysiol. 98 (2 Pt 2), 270–275.

Olbert, C.M., Gala, G.J., Tupler, L.A., 2014. Quantifying heterogeneity attributable to polythetic diagnostic criteria: theoretical framework and empirical application. J. Abnorm Psychol. 123 (2), 452–462.

Passos, I.C., Vasconcelos-Moreno, M.P., Costa, L.G., Kunz, M., Brietzke, E., Quevedo, J., Salum, G., Magalhães, P.V., Kapczinski, F., Kauer-Sant'Anna, M., 2015. Inflammatory markers in post-traumatic stress disorder: a systematic review, meta-analysis, and meta-regression. Lancet Psychiatry 2 (11), 1002–1012.

Pitman, R.K., Rasmusson, A.M., Koenen, K.C., Shin, L.M., Orr, S.P., Gilbertson, M.W., Milad, M.R., Liberzon, I., 2012. Biological studies of post-traumatic stress disorder. Nat. Rev. Neurosci. 13 (11), 769–787.

Ransohoff, R.M., 2009. Chemokines and chemokine receptors: standing at the crossroads of immunobiology and neurobiology. Immunity 31 (5), 711–721.

Reibman, J., Levy-Carrick, N., Miles, T., Flynn, K., Hughes, C., Crane, M., Lucchini, R.G., 2016. Destruction of the World Trade Towers: Lessons Learned from an Environmental Health Disaster. Annals of the American Thoracic Society.

Reibman, J., Lin, S., Hwang, S.-A.A., Gulati, M., Bowers, J.A., Rogers, L., Berger, K.I., Hoerning, A., Gomez, M., Fitzgerald, E.F., 2005. The World Trade Center residents' respiratory health study: new-onset respiratory symptoms and pulmonary function. Environ. health Perspect. 406–411.

Reibman, J., Liu, M., Cheng, Q., Liautaud, S., Rogers, L., Lau, S., Berger, K.I., Goldring, R.M., Marmor, M., Fernandez-Beros, M.E., Tonorezos, E.S., Caplan-Shaw, C.E., Gonzalez, J., Filner, J., Walter, D., Kyng, K., Rom, W.N., 2009. Characteristics of a residential and working community with diverse exposure to World Trade Center dust, gas, and fumes. J. Occup. Environ. Med./Am. Coll. Occup. Environ. Med. 51 (5), 534–541.

Rogowski, O., Vered, Y., Shapira, I., Hirsh, M., Zakut, V., Berliner, S., 2005. Introducing the wide range C-reactive protein (wr-CRP) into clinical use for the detection of microinflammation. Clin. Chim. Acta 358 (1–2), 151–158.

Söndergaard, H.P., Hansson, L.-O., Theorell, T., 2004. The inflammatory markers C-reactive protein and serum amyloid A in refugees with and without posttraumatic stress disorder. Clin. Chim. acta 342 (1), 93–98.

Valkanova, V., Ebmeier, K.P., Allan, C.L., 2013. CRP, IL-6 and depression: a systematic review and meta-analysis of longitudinal studies. J. Affect Disord. 150 (3), 736–744.

von Känel, R., Hepp, U., Kraemer, B., Traber, R., Keel, M., Mica, L., Schnyder, U., 2007. Evidence for low-grade systemic proinflammatory activity in patients with posttraumatic stress disorder. J. psychiatric Res. 41 (9), 744–752.

Weathers FW, L.B., Herman, D.S., Huska, J.A., Keane, T.M., 1993. The PTSD Checklist (PCL): Reliability, Validity, and Diagnostic Utility. International Society for Truamatic Stress Studies.

Yeh, E.T., Willerson, J.T., 2003. Coming of age of C-reactive protein: using inflammation markers in cardiology. Circulation 107 (3), 370–371.

Yehuda, R., LeDoux, J., 2007. Response variation following trauma: a translational neuroscience approach to understanding PTSD. Neuron 56 (1), 19–32.

Yirmiya, R., Goshen, I., 2011. Immune modulation of learning, memory, neural plasticity and neurogenesis. Brain, Behav. Immun. 25 (2), 181–213.

Zhu, Z., Galatzer-Levy, I.R., Bonanno, G.A., 2014. Heterogeneous depression responses to chronic pain onset among middle-aged adults: a prospective study. Psychiatry Res. 217 (1), 60–66.