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ADVANCING SCIENCE AND PROMOTING UNDERSTANDING OF TRAUMATIC STRESS

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Inflammation and PTSD

Veterans with posttraumatic stress disorder (PTSD) suffer from a high burden of diseases typically associated with aging including cardiovascular disease, autoimmune disorders, and dementia. A large literature demonstrates that PTSD is associated with a pro-inflammatory activation of the immune system, which may contribute to accelerated aging. The current state of the science suggests that there is a bidirectional causal relationship between PTSD and inflammation, which has implications for the development of clinically useful biomarkers and novel treatments.

Cross-Sectional Studies Demonstrating Association of PTSD with Elevated Markers of Inflammation

Many case control studies have found increases in immune mediators in Veterans and civilians with PTSD. Passos and colleagues (2015) published a meta-analysis of studies examining inflammatory markers in PTSD. Their study highlights several important points. In aggregate, the weight of the evidence supports the concept that PTSD is associated with elevations in pro-inflammatory cytokines such as interleukin 6 (IL-6), interleukin 1 β (IL1 β), tumor necrosis factor- α (TNF- α), and interferon γ (IFN γ). However, the meta-analysis identified several sources that account for the heterogeneity of findings in the literature including psychiatric medications, comorbid psychiatric disorders, especially major depressive disorder, sensitivity of assays, uncontrolled circadian effects, as well as severity and duration of illness. As an exemplar, there is considerable heterogeneity in the findings associating an increase in the acute phase reactant high sensitivity C-reactive protein (hsCRP) and PTSD, which in the meta-analysis appears to be attributable to these confounding factors. Another study highlights the critical importance of looking

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at the temporal course of PTSD. Increased inflammation was associated with current PTSD but not PTSD in remission in a large sample of Veterans ($N = 735$) who had participated in the Mind Your Heart Study (O'Donovan et al., 2017). Inflammatory markers in Veterans with PTSD in remission were no different than those in Veterans without PTSD. In the same study, elevated hsCRP and white blood cell (WBC) count were associated with increased threat sensitivity.

Several studies have examined a large battery of proteins in peripheral blood with various multiplex assays. Hoge and colleagues (2009) studied a large array of cytokines and chemokines with a multiplex platform and found a generalized pro-inflammatory pattern in a well-characterized case-control study. Their study illustrates several important features germane to this field. First, the field of immunology is quite complex and the number of immune mediators is large with large categories of markers including cytokines, cytokine receptors, acute phase reactants, chemokines, and soluble adhesion molecules. Further, the Hoge et al. study, like almost all studies in PTSD, focused on markers in the peripheral circulation. There are very few studies of immune factors in cerebrospinal fluid (CSF; e.g., Agorastos et al., 2019, which showed no group differences in either CSF or plasma IL-6 in PTSD and controls), and gene expression studies in the Department of Veterans Affairs' (VA) new National PTSD Brain Bank are only now underway (e.g., Morrison et al., 2019). The latter study showed decreased expression of interleukin 1A (IL1A) in dorsolateral prefrontal cortex in PTSD, which contrasts with the increase in peripheral IL1A found in PTSD in the Hoge et al. study. Much more work is needed to understand the signaling transduction of immune factors across the blood-brain barrier, as well as the dual role that cytokines have in both immunity and neurotransmission.

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A small number of studies have examined the role of transcription factors regulating inflammation in accounting for increased immune markers in PTSD. O'Donovan and colleagues (2011) examined gene expression in monocytes in a well-characterized case-control study. Target genes for the transcription factor nuclear factor- κ B (NF- κ B) were upregulated in PTSD in male and female subjects. Pace and colleagues (2012) similarly found evidence for increased NF- κ B activity in monocytes of PTSD subjects relative to controls that was correlated with symptom severity. These studies illustrate the importance of molecular signaling factors involved in the regulation of immune gene expression.

In summary, cross-sectional studies generally support the finding of increased activation of pro-inflammatory factors in PTSD. Some, but not all, of the reasons for heterogeneity of findings in the literature have been identified which include demographic factors, body mass index, burden of medical comorbidity, medications, and chronicity of illness. Much more work is needed to examine inflammatory factors in the central nervous system and how well peripheral markers serve as proxies for immune factors in the brain.

PTSD and Inflammation - Links to Comorbid Medical Disease Burden

Numerous studies have shown a link between elevated immune mediators and markers associated with comorbid medical disease burden in PTSD. The immune system has been implicated in neuronal health and multiple forms of neurodegenerative disorders. Increased soluble receptor II for TNF (sTNF-RII), and not IL-6 was associated with reduced hippocampal volume in a large sample of Veterans ($N = 246$) with neuroimaging measures (O'Donovan, Chao, et al., 2015). Though hippocampal volume was reduced in subjects with current PTSD, the relationship of sTNF-RII to hippocampal volume was independent of PTSD status. However, elevated sTNF-RII was associated with greater PTSD symptom severity.

Aside from studies demonstrating higher levels of pro-inflammatory markers in PTSD, there is evidence that subjects with PTSD have increased risk for major autoimmune disorders. In a large sample of Iraq and Afghanistan Veterans ($N = 666, 269$) receiving care at VA, PTSD diagnosis was associated with a two-fold increase in autoimmune thyroiditis, inflammatory bowel disease (Crohn's disease and ulcerative colitis), rheumatoid arthritis, multiple sclerosis, and lupus erythematosus (O'Donovan, Cohen, et al., 2015). Though there were no differences in PTSD-related risk in men versus women, female Veterans with PTSD showed much higher risk for autoimmune disorders overall (4.6% versus 1.7%) and women with PTSD had the highest prevalence of all (5.4%). Also noteworthy was the fact that exposure to military sexual trauma (MST) in both men and women was associated with increased risk for autoimmune disorder independent to having the PTSD diagnosis. This is consistent with several other studies that have found that trauma exposure, particularly but not exclusively early childhood adversity (e.g., Sumner et al., 2017), is associated with elevated inflammatory markers independent of PTSD

Sumner and colleagues (2017, 2018) in two papers presented data in the Nurses Health Study II, a large longitudinal study, showing that women with PTSD had elevated CRP, sTNF-RII and intercellular adhesion molecule-1 (ICAM-1), a marker of endothelial function implicated in risk for cardiovascular disease. Trauma exposure independent of PTSD diagnosis was also associated with elevated

sTNF-RII. PTSD was also associated with a greater increase in another measure of endothelial function, vascular cell adhesion molecule-1 (VCAM-1) over a time interval spanning 10-16 years (2017). Women with new onset PTSD between baseline and follow-up, showed elevated sTNF-RII and ICAM-1 prior to trauma exposure and development of PTSD and greater increases in VCAM-1 between baseline and follow-up (2018). This study is one of several that demonstrate elevated inflammation can be both a pre-existing risk factor (see below) for PTSD and a consequence of developing the disorder.

In summary, outside of the evidence demonstrating that both trauma exposure and the development of PTSD is associated with elevated pro-inflammatory immune factors, there is strong evidence that this pattern is consequential for the overall health of patients. PTSD is strongly associated with increased risk for autoimmune disorders and cardiovascular disease, and immune factors should be targeted in novel therapeutics to prevent the accrual of this comorbid burden in patients who remain chronically symptomatic.

Immune Markers as Pre-exposure Risk for PTSD

There are a growing number of studies demonstrating that immune factors measured pre-trauma exposure confer risk for developing PTSD following trauma. Erly and colleagues (2014) measured plasma levels of the inflammatory marker CRP in participants in the Marine Resiliency Study prior to deployment into combat in either Iraq or Afghanistan. After adjusting for baseline PTSD symptom severity (assessed by the Clinician-Administered PTSD Scale; CAPS) pre-deployment, higher levels of CRP were associated with higher post-deployment CAPS scores.

One other approach to examining the importance of pre-military trauma immune system functioning involved studies of Vietnam twin pairs which allows for the disentanglement of heritable and shared familial factors predisposing risk. Rooks, Veledar, Goldberg, Bremner, and Vaccarino (2012) examined CRP and IL-6 in 241 twin pairs (mixed monozygotic and dizygotic) recruited from the Vietnam Twin Registry. They found a strong association between early trauma exposure and elevated CRP but not IL-6. They did not find a significant within-pair association in early trauma and CRP or IL-6 in either monozygotic or dizygotic twins. They concluded that the association of early trauma and elevated inflammation is driven by shared exposure to the familial environment and less to heritable factors. This same group in a separate study from the Vietnam twin pairs reported that elevated hsCRP and ICAM-1 were associated with the PTSD diagnosis. Monozygotic twin pairs did not show a greater similarity of inflammatory markers relative to dizygotic twins. They similarly concluded that inflammatory markers were linked to familial environmental exposures and less to genetic factors (Plantinga et al., 2013).

Another set of studies examined if variation in genes coding for immune mediators were associated with PTSD. Michopoulos and colleagues (2015) tested if genetic variants encoding CRP were associated with PTSD risk. They reported on a large sample size ($N = 2,698$) from an urban inner-city population receiving care at Grady Memorial Hospital in Atlanta. One single-nucleotide polymorphism (SNP), rs1130864, was associated with greater PTSD symptoms and higher CRP levels. Further, elevated CRP was associated with greater hyperarousal symptoms and psychophysiological reactivity to fear-potentiated startle.

Miller and colleagues (2018) examined CRP genetic variants and epigenetic factors (e.g., DNA methylation) in a sample of military Veterans ($N = 286$) as moderators of the strength of the relationship between trauma exposure (number of categories from a list of 22 trauma exposures) and PTSD as well as CRP levels and symptom severity. PTSD was associated with higher CRP levels and a greater proportion of subjects with levels associated with higher risk for cardiovascular disease (>3 mg/L). The relationship between PTSD symptom severity and CRP was mediated by methylation of the SNP rs3091244 (which is in high linkage disequilibrium with rs1130864) at the AIM2 promoter locus for the CRP gene. Several other CRP SNPs were found to moderate the association between CRP levels and symptom severity. Collectively, these studies illustrate the complex relationship between trauma exposure, PTSD, and inflammation and suggest that elevated CRP may have a role in mediating hyperarousal, fear, and threat related symptoms.

Finally, Smid and colleagues (2015) conducted a study of immune mediators in a prospective sample of Dutch combat-deployed military personnel examining if post-deployment stressful life events further accounted for the relationship between trauma exposure, PTSD symptoms and inflammation. They conducted an in vitro assay of cytokine release in monocytes incubated with the mitogen lipopolysaccharide (LPS) in blood collected 1-month post-deployment. They found three-way interactions between high combat exposure, elevated cytokine response to LPS, and post-deployment stressful life events and elevated PTSD symptoms. Further high combat exposure was not associated with greater symptomatic distress to post-deployment life stressors except in those who demonstrated an elevated cytokine response to LPS. They concluded that inflammatory activity may contribute to elevated sensitivity to stress post-deployment.

Implications and Future Directions

Overall, there is strong evidence that PTSD is associated with a pro-inflammatory state that may account for the high comorbid disease burden associated with this disorder. There is some evidence that inflammatory proteins may be causal agents for producing some symptoms of PTSD. This has been studied more extensively in depression where there is compelling evidence that elevated cytokine levels are associated with sickness behavior, fatigue, anhedonia, and impaired concentration. The PTSD field is at the beginning stages of understanding how immune factors can contribute to trauma-related symptoms. The evidence to date suggests that immune factors can influence threat reactivity and hyperarousal in addition to sickness behavior. Future studies will need to test this with controlled experimental manipulations to better understand what specific symptoms are provoked by cytokines and what circuits in the brain are affected by trafficking of peripheral cytokines across the blood brain barrier.

Further, much more information is needed to understand the time sequence of gene by environmental events in subjects with genetic risk variants for both PTSD and elevated immune reactivity. Do genetic variants affect neurodevelopment, epigenetic modification of DNA in response to environmental stressors, risk for PTSD following trauma, immune events associated with PTSD remission, and accrual of pro-inflammatory states with symptom chronicity? We will need to better understand this biology to formulate strategies for early primary or secondary prevention. Further, mental health researchers will need to work closely with immunologists to move

beyond candidate cytokine studies to studies that tackle the complex systems biology underpinning acute and chronic inflammation and autoimmune diseases. Finally, new technologies have increased the sensitivity and precision of measuring a large array of immune proteins, which will enable the inclusion of markers that are biologically relevant even at levels below the sensitivity of older multiplex assays.

Regarding the potential of inflammation-targeted treatment for PTSD, a study by Raison and colleagues (2013) in a sample of treatment-resistant depression illustrates an important consideration for the design of future PTSD clinical trials. They recruited a sample of 60 outpatients with treatment-resistant depression for a placebo-controlled trial of the TNF antagonist infliximab. Results showed that the infliximab group showed no overall differences in therapeutic response relative to placebo. However, post-hoc analyses showed that patients with elevated CRP (>5 mg/L) showed a favorable therapeutic response and that patients with low levels of CRP at baseline did worse on infliximab relative to placebo. Their results illustrate an important point for future trials. Immune targeted treatments should select patients who demonstrate elevated inflammation at enrollment and immune targeted therapy should be restricted to the sub-population of PTSD where this mechanism is relevant to their clinical picture.

FEATURED ARTICLES

Eraly, S. A., Nievergelt, C. M., Maihofer, A. X., Barkauskas, D. A., Biswas, N., Agorastos, A., . . . Baker, D. G. (2014). **Assessment of plasma C-reactive protein as a biomarker of posttraumatic stress disorder risk.** *JAMA Psychiatry, 71*, 423-431. doi:10.1001/jamapsychiatry.2013.4374 *Importance:* Posttraumatic stress disorder (PTSD) has been associated in cross-sectional studies with peripheral inflammation. It is not known whether this observed association is the result of PTSD predisposing to inflammation (as sometimes postulated) or to inflammation predisposing to PTSD. *Objective:* To determine whether plasma concentration of the inflammatory marker C-reactive protein (CRP) helps predict PTSD symptoms. *Design, Setting, and Participants:* The Marine Resiliency Study, a prospective study of approximately 2600 war zone-deployed Marines, evaluated PTSD symptoms and various physiological and psychological parameters before deployment and at approximately 3 and 6 months following a 7-month deployment. Participants were recruited from 4 all-male infantry battalions imminently deploying to a war zone. Participation was requested of 2978 individuals; 2610 people (87.6%) consented and 2555 (85.8%) were included in the present analysis. Postdeployment data on combat-related trauma were included for 2208 participants (86.4% of the 2555 included) and on PTSD symptoms at 3 and 6 months after deployment for 1861 (72.8%) and 1617 (63.3%) participants, respectively. *Main Outcomes and Measures:* Severity of PTSD symptoms 3 months after deployment assessed by the Clinician-Administered PTSD Scale (CAPS). *Results:* We determined the effects of baseline plasma CRP concentration on postdeployment CAPS using zero-inflated negative binomial regression (ZINBR), a procedure designed for distributions, such as CAPS in this study, that have an excess of zeroes in addition to being positively skewed. Adjusting for the baseline CAPS score, trauma exposure, and other relevant covariates, we found baseline plasma CRP concentration to be a highly significant overall predictor of postdeployment CAPS

scores ($P = .002$): each 10-fold increment in CRP concentration was associated with an odds ratio of nonzero outcome (presence vs absence of any PTSD symptoms) of 1.51 (95% CI, 1.15-1.97; $P = .003$) and a fold increase in outcome with a nonzero value (extent of symptoms when present) of 1.06 (95% CI, 0.99-1.14; $P = .09$). **Conclusions and Relevance:** A marker of peripheral inflammation, plasma CRP may be prospectively associated with PTSD symptom emergence, suggesting that inflammation may predispose to PTSD.

Hoge, E. A., Brandstetter, K., Moshier, S., Pollack, M. H., Wong, K. K., & Simon, N. M. (2009). **Broad spectrum of cytokine abnormalities in panic disorder and posttraumatic stress disorder.** *Depression and Anxiety, 26*, 447-455. doi:10.1002/da.20564 **Background:** Proinflammatory cytokines have been reported to be elevated in individuals experiencing chronic stress as well as in those with major depressive disorder. Much less is known about cytokines in anxiety disorders such as posttraumatic stress disorder (PTSD) and panic disorder (PD). We hypothesized that PD and PTSD would be associated with a generalized proinflammatory cytokine signature. **Method:** We utilized Luminex technology to examine 20 cytokines and chemokines in serum from 48 well-characterized individuals with a primary DSM-IV PD or PTSD diagnosis, and 48 age- and gender-matched healthy controls. We conservatively employed a Bonferroni correction for multiple testing ($\alpha = .05/20 = .0025$). **Results:** Individuals with primary PTSD or PD had significantly elevated median peripheral cytokine levels for 18 of 20 different cytokines compared to age- and gender-matched healthy controls (all $P < .0025$). To assess for the presence of a generalized proinflammatory state, we also examined the proportion of subjects with detectable levels of at least six of nine common proinflammatory cytokines and chemokines (IL-6, IL-1 α , IL-1 β , IL-8, MCP-1, MIP-1 α , Eotaxin, GM-CSF, and IFN- α). For men and women, 87% of anxiety patients had six or more detectable levels of these proinflammatory cytokines, compared with only 25% of controls (Fisher's Exact Test (FET) $P = .000$). Confirmatory analysis of the subset of individuals without current psychiatric medication use or comorbid depression was of comparable significance. **Conclusions:** These findings suggest that a generalized inflammatory state may be present in individuals with PD or PTSD.

Michopoulos, V., Rothbaum, A. O., Jovanovic, T., Almlí, L. M., Bradley, B., Rothbaum, B. O., . . . 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.** *American Journal of Psychiatry, 172*, 353-362. doi:10.1176/appi.ajp.2014.14020263 **Objective:** Increased systemic inflammation is associated with stress-related psychopathology. Specifically, levels of the proinflammatory marker C-reactive protein (CRP) are elevated in individuals with posttraumatic stress disorder (PTSD). Furthermore, single-nucleotide polymorphisms (SNPs) in the *CRP* gene are associated with CRP level, risk for cardiovascular disease, and obesity. The authors examined whether polymorphisms within the *CRP* gene and increased CRP levels are associated with PTSD symptoms and fear physiology in a civilian population with high levels of trauma. **Method:** Cross-sectional data and DNA samples were collected from 2,698 individuals recruited from an inner-city public hospital that serves a primarily African American, low-socioeconomic-status population. A subgroup of 187 participants participated in further

interviews, testing, and physiological measures; of these, 135 were assessed using the fear-potentiated startle paradigm to assess fear-related phenotypes of PTSD. **Results:** One SNP within the *CRP* gene, rs1130864, was significantly associated with increased PTSD symptoms ($N = 2,692$), including "being overly alert" as the most significant individual symptom ($N = 2,698$). Additionally, *CRP* genotype was associated with the odds of PTSD diagnosis ($N = 2,692$). This SNP was also associated with increased CRP level ($N = 137$), and high CRP levels (> 3 mg/L) were positively associated with PTSD symptoms ($N = 187$) and fear-potentiated startle to a safety signal ($N = 135$). **Conclusions:** Together, these data indicate that genetic variability in the *CRP* gene is associated with serum CRP level and PTSD symptom severity, including that of hyperarousal symptoms. Elevated CRP levels were also associated with exacerbated fear-related psychophysiology and PTSD symptom ratings and diagnosis. These findings suggest a potential mechanism by which an increased proinflammatory state may lead to heightened PTSD symptoms.

Miller, M. W., Maniates, H., Wolf, E. J., Logue, M. W., Schichman, S. A., Stone, A., . . . McGlinchey, R. (2018). **CRP polymorphisms and DNA methylation of the *AIM2* gene influence associations between trauma exposure, PTSD, and C-reactive protein.** *Brain, Behavior, and Immunity, 67*, 194-202. doi:10.1016/j.bbi.2017.08.022 **Background:** Recent studies have implicated inflammatory processes in the pathophysiology of posttraumatic stress disorder (PTSD). C-reactive protein (CRP) is a widely-used measure of peripheral inflammation, but little is known about the genetic and epigenetic factors that influence blood levels of C-reactive protein (CRP) in individuals with PTSD. **Methods:** Participants were 286 U.S. military veterans of post-9/11 conflicts (57% with current PTSD). Analyses focused on single nucleotide polymorphisms (SNPs) in the *CRP* gene and DNA methylation at *cg10636246* in *AIM2*-a locus recently linked to CRP levels through results from a large-scale epigenome-wide association study. **Results:** PTSD was positively correlated with serum CRP levels with PTSD cases more likely to have CRP levels in the clinically-elevated range compared to those without a PTSD diagnosis. Multivariate analyses that controlled for white blood cell proportions, genetic principal components, age and sex, showed this association to be mediated by methylation at the *AIM2* locus. *rs3091244*, a functional SNP in the *CRP* promoter region, moderated the association between lifetime trauma exposure and current PTSD severity. Analyses also revealed that the top SNPs from the largest genome-wide association study of CRP conducted to date (*rs1205* and *rs2794520*) significantly interacted with PTSD to influence CRP levels. **Conclusions:** These findings provide new insights into genetic and epigenetic mechanisms of inflammatory processes in the pathophysiology of PTSD and point to new directions for biomarker identification and treatment development for patients with PTSD.

Morrison, F. G., Miller, M. W., Wolf, E. J., Logue, M. W., Maniates, H., Kwasiak, D., . . . Huber, B. R. (2019). **Reduced interleukin 1A gene expression in the dorsolateral prefrontal cortex of individuals with PTSD and depression.** *Neuroscience Letters, 692*, 204-209. doi:10.1016/j.neulet.2018.10.027 The inflammatory system has been implicated in the pathophysiology of a variety of psychiatric conditions. Individuals with PTSD, depression, and other fear- and anxiety-related disorders exhibit alterations in peripheral circulating inflammatory markers, suggesting dysregulation of the inflammatory system.

The relationship between inflammation and PTSD has been investigated almost exclusively in the periphery, and has not been extensively explored in human postmortem brain tissue. Interleukins (ILs) represent a subtype of cytokines and are key signaling proteins in the immune and inflammatory systems. Based on prior research implicating IL signaling in PTSD and depression, we performed a preliminary investigation of IL gene expression in a region of the cortex involved in emotion regulation and PTSD, the dorsolateral prefrontal cortex (dlPFC), using tissue from the newly established VA National PTSD Brain Bank. Gene expression analyses were conducted on post-mortem tissue from the dlPFC from 50 donors: 13 controls, 12 PTSD cases, and 25 depressed cases. RNA was extracted from frozen dlPFC tissue, reverse transcribed to cDNA, and quantitative polymerase chain reaction (qPCR) was performed to assess gene expression of *IL1A*, *IL1B*, *IL6*, *IL8*, *IL10*, *IL13*, and *IL15*. We found a multiple-testing corrected significant decrease in *IL1A* expression in the dlPFC for PTSD and depression cases compared to controls ($p < 0.005$) with age at death, sex, race and RNA integrity number (RIN) included as covariates. To our knowledge this finding is the first demonstration of altered IL expression in brain tissue from deceased individuals with histories of PTSD and/or depression.

O'Donovan, A., Ahmadian, A. J., Neylan, T. C., Pacult, M. A., Edmondson, D., & Cohen, B. E. (2017). **Current posttraumatic stress disorder and exaggerated threat sensitivity associated with elevated inflammation in the Mind Your Heart Study.** *Brain, Behavior, and Immunity, 60*, 198-205. doi:10.1016/j.bbi.2016.10.014

Objective: Elevated inflammation has been repeatedly observed in posttraumatic stress disorder (PTSD), and it may drive the development of both psychiatric symptoms and physical comorbidities. However, it is not clear if elevated inflammation is a feature of both remitted and current PTSD, and little is known about relationships between specific clusters of PTSD symptoms and inflammation. Exaggerated threat sensitivity, as indexed by threat reactivity and avoidance of perceived threats, may be particularly closely associated with inflammation. **Methods:** We assessed PTSD symptoms and threat sensitivity using the Clinician Administered PTSD Scale in 735 Veterans Affairs patients (35% current PTSD; 16% remitted PTSD) who participated in the Mind Your Heart Study (mean age=59±11; 94% male). High sensitivity C-reactive protein (hsCRP), white blood cell count (WBC), and fibrinogen were used as indices of inflammation. Analysis of covariance models with planned contrasts were used to examine differences in inflammation by PTSD status, adjusting for age, sex, race, kidney function and socioeconomic status. **Results:** Individuals with current PTSD had significantly higher hsCRP and WBC than patients with no history of PTSD, but there were no significant differences in inflammatory markers between those with remitted versus no history of PTSD. Within patients with current PTSD, higher threat reactivity was independently associated with higher hsCRP ($\beta=0.16$, $p=0.01$) and WBC count ($\beta=0.24$, $p<0.001$), and higher effortful avoidance was associated with higher fibrinogen ($\beta=0.13$, $p=0.04$). **Conclusion:** Our data indicate that elevated inflammation may be a feature of current, but not remitted, PTSD. Within patients with PTSD, higher threat reactivity was also associated with elevated inflammation. A better understanding of the relationship between threat sensitivity and inflammation may inform interventions for patients with PTSD.

O'Donovan, A., Chao, L. L., Paulson, J., Samuelson, K. W., Shigenaga, J. K., Grunfeld, C., . . . Neylan, T. C. (2015). **Altered inflammatory activity associated with reduced hippocampal volume and more severe posttraumatic stress symptoms in Gulf War veterans.** *Psychoneuroendocrinology, 51*, 557-566. doi:10.1016/j.psyneuen.2014.11.010 **Background:** Inflammation may reduce hippocampal volume by blocking neurogenesis and promoting neurodegeneration. Posttraumatic stress disorder (PTSD) has been linked with both elevated inflammation and reduced hippocampal volume. However, few studies have examined associations between inflammatory markers and hippocampal volume, and none have examined these associations in the context of PTSD. **Methods:** We measured levels of the inflammatory markers interleukin-6 (IL-6) and soluble receptor II for tumor necrosis factor (sTNF-RII) as well as hippocampal volume in 246 Gulf War veterans with and without current and past PTSD as assessed with the Clinician Administered PTSD Scale (CAPS). Enzyme-linked immunosorbent assays were used to measure inflammatory markers, and 1.5Tesla magnetic resonance imaging (MRI) and Freesurfer version 4.5 were used to quantify hippocampal volume. Hierarchical linear regression and analysis of covariance models were used to examine if hippocampal volume and PTSD status would be associated with elevated levels of IL-6 and sTNF-RII. **Results:** Increased sTNF-RII, but not IL-6, was significantly associated with reduced hippocampal volume ($\beta=-0.14$, $p=0.01$). The relationship between sTNF-RII and hippocampal volume was independent of potential confounds and covariates, including PTSD status. Although we observed no PTSD diagnosis-related differences in either IL-6 or sTNF-RII, higher PTSD severity was associated with significantly increased sTNF-RII ($\beta=0.24$, $p=0.04$) and reduced IL-6 levels ($\beta=-0.24$, $p=0.04$). **Conclusions:** Our results indicate that specific inflammatory proteins may be associated with brain structure and function as indexed by hippocampal volume and PTSD symptoms.

O'Donovan, A., Cohen, B. E., Seal, K. H., Bertenthal, D., Margaretten, M., Nishimi, K., & Neylan, T. C. (2015). **Elevated risk for autoimmune disorders in Iraq and Afghanistan veterans with posttraumatic stress disorder.** *Biological Psychiatry, 77*, 365-374. doi:10.1016/j.biopsych.2014.06.015

Background: Posttraumatic stress disorder (PTSD) is associated with endocrine and immune abnormalities that could increase risk for autoimmune disorders. However, little is known about the risk for autoimmune disorders among individuals with PTSD. **Methods:** We conducted a retrospective cohort study of 666,269 Iraq and Afghanistan veterans under age 55 who were enrolled in the Department of Veterans Affairs health care system between October 7, 2001, and March 31, 2011. Generalized linear models were used to examine if PTSD, other psychiatric disorders, and military sexual trauma exposure increased risk for autoimmune disorders, including thyroiditis, inflammatory bowel disease, rheumatoid arthritis, multiple sclerosis, and lupus erythematosus, adjusting for age, gender, race, and primary care visits. **Results:** PTSD was diagnosed in 203,766 veterans (30.6%), and psychiatric disorders other than PTSD were diagnosed in an additional 129,704 veterans (19.5%). Veterans diagnosed with PTSD had significantly higher adjusted relative risk (ARR) for diagnosis with any of the autoimmune disorders alone or in combination compared with veterans with no psychiatric diagnoses (ARR = 2.00; 95% confidence interval, 1.91-2.09) and compared with veterans diagnosed with psychiatric disorders other than PTSD (ARR = 1.51; 95% confidence interval, 1.43-1.59; $p < .001$).

The magnitude of the PTSD-related increase in risk for autoimmune disorders was similar in women and men, and military sexual trauma exposure was independently associated with increased risk in both women and men. **Conclusions:** Trauma exposure and PTSD may increase risk for autoimmune disorders. Altered immune function, lifestyle factors, or shared etiology may underlie this association.

O'Donovan, A., Sun, B., Cole, S., Rempel, H., Lenoci, M., Pulliam, L., & Neylan, T. (2011). **Transcriptional control of monocyte gene expression in post-traumatic stress disorder.** *Disease Markers*, *30*, 123-132. doi:10.3233/DMA-2011-0768 Post-traumatic stress disorder (PTSD) confers an increased risk for disorders with an inflammatory etiology. PTSD-related dysregulation of the sympathetic nervous system (SNS) and hypothalamic-pituitary adrenal (HPA) axis and associated alterations in inflammatory activity may contribute to this increased risk. However, little is known about convergent SNS, HPA and inflammatory signaling at the level of the immune cell transcriptome in PTSD. To explore such signaling, we examined the prevalence of specific transcription factor binding motifs in the promoter regions of differentially expressed genes in monocytes from individuals with PTSD and matched controls. Participants included 49 men (24 PTSD+ and 25 trauma-exposed controls) and 18 women (10 PTSD+ and 8 controls). Men with PTSD showed up-regulation of target genes for the NF- κ B/Rel family of transcription factors, which convey inflammatory signals, up-regulation of target genes for CREB/ATF transcription factors, which convey adrenergic signals from the SNS, and down-regulation of target genes for the glucocorticoid receptor, which conveys glucocorticoid signals from the HPA axis. Women with PTSD also showed significant up-regulation of target genes for NF- κ B and non-significant down-regulation of target genes for GR, but significant down-regulation of target genes for CREB/ATF. Altered transcriptional control of monocyte gene expression could contribute to exaggerated inflammatory activity in PTSD.

Pace, T. W. W., Wingenfeld, K., Schmidt, I., Meinschmidt, G., Hellhammer, D. H., & Heim, C. M. (2012). **Increased peripheral NF- κ B pathway activity in women with childhood abuse-related posttraumatic stress disorder.** *Brain, Behavior, and Immunity*, *26*, 13-17. doi:10.1016/j.bbi.2011.07.232 In addition to neuroendocrine changes PTSD pathophysiology may also involve dysfunction of the innate immune inflammatory system. PTSD patients have been found to exhibit increased concentrations of circulating inflammatory markers such as C-reactive protein and interleukin-6, suggesting dysfunction of the innate immune inflammatory system. However, few studies have investigated molecular signaling pathways known to critically regulate inflammation. Additionally, the relationship between inflammatory function and immune cell glucocorticoid sensitivity has not been extensively explored in PTSD. Nuclear factor- κ B (NF- κ B) pathway activity was examined in peripheral blood mononuclear cells obtained from 12 women with childhood abuse-related PTSD and 24 healthy controls (ages 19-48) using DNA-binding ELISA. Glucocorticoid sensitivity of monocytes in whole blood was measured as the concentration of dexamethasone needed to suppress in vitro lipopolysaccharide-induced tumor necrosis factor- α production by 50% (DEX IC₅₀). Women with PTSD displayed increased NF- κ B pathway activity compared to controls (t [34]=2.45, $p=0.02$) that was positively correlated with PTSD severity (determined by PTSD symptom severity scale)

($r_s=0.39$, $p=0.02$). Increased NF- κ B pathway activity was associated with increased whole blood monocyte DEX IC₅₀ (i.e. decreased sensitivity of monocytes to glucocorticoids) across all participants ($r=0.66$, $p<0.001$). These findings suggest that enhanced inflammatory system activity in participants with childhood abuse-related PTSD is observable at the level of NF- κ B, and that in general decreased immune cell glucocorticoid sensitivity may contribute to increased NF- κ B pathway activity. Enhanced inflammation may contribute to co-morbid somatic disease risk in persons with childhood abuse-related PTSD.

Passos, I. C., Vasconcelos-Moreno, M. P., Costa, L. G., Kunz, M., Brietzke, E., Quevedo, J., . . . Kauer-Sant'Anna, M. (2015).

Inflammatory markers in post-traumatic stress disorder: A systematic review, meta-analysis, and meta-regression. *Lancet Psychiatry*, *2*, 1002-1012. doi:10.1016/S2215-0366(15)00309-0

Background: Studies investigating inflammatory markers in post-traumatic stress disorder (PTSD) have yielded mixed results. The aim of our study was to compare concentrations of inflammatory markers in patients with PTSD compared with healthy controls. **Methods:** We did a meta-analysis and meta-regression of studies comparing inflammatory markers between patients with PTSD and healthy controls by searching PubMed, Embase, Scopus, Web of Science, and PsycINFO for articles published between Jan 1, 1960, and April 7, 2015. From eligible studies (ie, cross-sectional studies or baseline data from longitudinal studies of peripheral blood cytokine concentrations that compared adults with PTSD with healthy controls), we extracted outcomes of interest, such as mean and SD of peripheral blood cytokines, the time of day blood was collected, whether the study allowed patients with comorbid major depressive disorder in the PTSD group, whether patients were medication free, and severity of PTSD symptoms. We undertook meta-analyses whenever values of inflammatory markers were available in two or more studies. A random-effects model with restricted maximum-likelihood estimator was used to synthesise the effect size (assessed by standardised mean difference [SMD]) across studies. **Findings:** 8057 abstracts were identified and 20 studies were included. Interleukin 6 (SMD 0.88; $p=0.0003$), interleukin 1 β (SMD 1.42; $p=0.045$), and interferon γ (SMD 0.49; $p=0.002$) levels were higher in the PTSD group than in healthy controls. Subgroup meta-analysis of patients who were not given medication showed higher tumor necrosis factor α (TNF α ; SMD 0.69, 95% CI 0.35-1.02; $p<0.0001$) in the PTSD group than the control group in addition to the aforementioned cytokines. TNF α (SMD 1.32, 0.13-2.50; $p=0.003$), interleukin 1 β (SMD 2.35, 0.01-4.68; $p=0.048$), and interleukin 6 (SMD 1.75, 0.97-2.53; $p<0.0001$) levels remained increased in the PTSD group in a subgroup meta-analysis of studies that excluded comorbid major depressive disorder. Illness duration was positively associated with interleukin 1 β levels ($b=0.33$, $p<0.0001$) and severity with interleukin 6 ($b=0.02$, $p=0.042$). A model composed of several variables-presence of comorbid major depressive disorder, use of psychotropic medications, assay used, and time of day blood was collected-explained the large amount of heterogeneity between interleukin 1 β , interleukin 6, and C-reactive protein studies. Egger's linear regression test revealed a potential publication bias for interleukin 1 β . Additionally, for most inflammatory markers, study heterogeneity was reported to be high ($I^2>75\%$). **Interpretation:** PTSD is associated with increased interleukin 6, interleukin 1 β , TNF α , and interferon γ levels.

This information might be useful for consideration of chronic low-grade inflammation as a potential target or biomarker in PTSD treatment. Use of psychotropic medication and presence of comorbid major depressive disorder were important moderators that might explain the inconsistency between results of previous studies. Our search strategy used a range of databases and we made exhaustive effort to acquire data by contacting the authors. Notably, high levels of between-study heterogeneity were recorded for most cytokine variables measured in our analysis. However, meta-regression analysis could explain a large amount of this heterogeneity.

Plantinga, L., Bremner, J. D., Miller, A. H., Jones, D. P., Veledar, E., Goldberg, J., & Vaccarino, V. (2013). **Association between posttraumatic stress disorder and inflammation: A twin study.** *Brain, Behavior, and Immunity, 30*, 125-132. doi:10.1016/j.bbi.2013.01.081 The association of posttraumatic stress disorder (PTSD) with cardiovascular disease risk may be mediated by inflammation. Our objective was to examine the association between PTSD and measures of inflammation and to determine whether these associations are due to shared familial or genetic factors. We measured lifetime history of PTSD using the Structured Clinical Interview for DSM-IV in 238 male middle-aged military veteran twin pairs (476 individuals), selected from the Vietnam Era Twins Registry, who were free of cardiovascular disease at baseline. We assessed inflammation using levels of high-sensitivity C-reactive protein (hsCRP), interleukin 6 (IL-6), fibrinogen, white blood cells, vascular cell adhesion molecule-1, and intercellular adhesion molecule-1 (ICAM-1). Geometric mean levels and percent differences by PTSD were obtained from mixed-model linear regression analyses with adjustment for potential confounders. Within-pair analysis was conducted to adjust for shared family environment and genetics (monozygotic pairs). Overall, 12.4% of participants had a lifetime history of PTSD. Adjusted mean levels of hsCRP and ICAM-1 were significantly higher among those with vs. without PTSD [hsCRP: 1.75 vs. 1.31mg/l (33% difference); ICAM-1: 319 vs. 293ng/ml (9% difference)]. Adjustment for depression rendered the association of PTSD with hsCRP non-statistically significant. For IL-6, no consistent association was seen. Within-pair analysis produced associations that were similar in direction for all three markers but lesser in magnitude for hsCRP and IL-6. There was no evidence of interaction by zygosity. Elevated hsCRP and ICAM-1 are associated with PTSD, and these associations may be confounded by shared non-genetic, antecedent familial and environmental factors.

Raison, C. L., Rutherford, R. E., Woolwine, B. J., Shuo, C., Schettler, P., Drake, D. F., . . . Miller, A. H. (2013). **A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: The role of baseline inflammatory biomarkers.** *JAMA Psychiatry, 70*, 31-41. doi:10.1001/2013.jamapsychiatry.4 Context: Increased concentrations of inflammatory biomarkers predict antidepressant nonresponse, and inflammatory cytokines can sabotage and circumvent the mechanisms of action of conventional antidepressants. Objectives: To determine whether inhibition of the inflammatory cytokine tumor necrosis factor (TNF) reduces depressive symptoms in patients with treatment-resistant depression and whether an increase in baseline plasma inflammatory biomarkers, including high-sensitivity C-reactive protein (hs-CRP),

TNF, and its soluble receptors, predicts treatment response. Design: Double-blind, placebo-controlled, randomized clinical trial. Setting: Outpatient infusion center at Emory University in Atlanta, Georgia. Participants: A total of 60 medically stable outpatients with major depression who were either on a consistent antidepressant regimen (n = 37) or medication-free (n = 23) for 4 weeks or more and who were moderately resistant to treatment as determined by the Massachusetts General Hospital Staging method. Interventions: Three infusions of the TNF antagonist infliximab (5 mg/kg) (n = 30) or placebo (n = 30) at baseline and weeks 2 and 6 of a 12-week trial. Main Outcome Measures: The 17-item Hamilton Scale for Depression (HAM-D) scores. Results: No overall difference in change of HAM-D scores between treatment groups across time was found. However, there was a significant interaction between treatment, time, and log baseline hs-CRP concentration (P = .01), with change in HAM-D scores (baseline to week 12) favoring infliximab-treated patients at a baseline hs-CRP concentration greater than 5 mg/L and favoring placebo-treated patients at a baseline hs-CRP concentration of 5 mg/L or less. Exploratory analyses focusing on patients with a baseline hs-CRP concentration greater than 5 mg/L revealed a treatment response (≥50% reduction in HAM-D score at any point during treatment) of 62% (8 of 13 patients) in infliximab-treated patients vs 33% (3 of 9 patients) in placebo-treated patients (P = .19). Baseline concentrations of TNF and its soluble receptors were significantly higher in infliximab-treated responders vs nonresponders (P < .05), and infliximab-treated responders exhibited significantly greater decreases in hs-CRP from baseline to week 12 compared with placebo-treated responders (P < .01). Dropouts and adverse events were limited and did not differ between groups. Conclusions: This proof-of-concept study suggests that TNF antagonism does not have generalized efficacy in treatment-resistant depression but may improve depressive symptoms in patients with high baseline inflammatory biomarkers.

Rooks, C., Veledar, E., Goldberg, J., Bremner, J. D., & Vaccarino, V. (2012). **Early trauma and inflammation: Role of familial factors in a study of twins.** *Psychosomatic Medicine, 74*, 146-152. doi:10.1097/PSY.0b013e318240a7d8 Objective: Although early trauma (trauma in childhood) has been linked to adult inflammation and adult disease of inflammatory origin, it remains unknown whether this relationship is due to long-term consequences of early life stress or other familial factors. Methods: We examined 482 male middle-aged twins (241 pairs) born between 1946 and 1956 from the Vietnam Era Twin Registry. Childhood traumatic experiences, before the age of 18 years, were measured retrospectively with the Early Trauma Inventory and included physical, sexual, emotional abuse and general trauma. Lifetime major depressive disorder and posttraumatic stress disorder were assessed with the Structured Clinical Interview for DSM-IV. Traditional risk factors for cardiovascular disease were also assessed. Plasma C-reactive protein and interleukin 6 were measured to determine levels of inflammation. Mixed-effects regression models with a random intercept for pair were used to separate between- and within-twin pair effects. Results: When twins were analyzed as individuals, increasing levels of early trauma were positively related to C-reactive protein (p = .03) but not to interleukin 6 (p = .12). When estimating within- and between-pair effects, only the between-pair association of early trauma with the inflammatory markers remained significant.

Conclusions: The link between early trauma and inflammation is largely explained by familial factors shared by the twins because levels of inflammation were highest when both twins were exposed to trauma. Exposure to early trauma may be a marker for an unhealthy familial environment. Clarification of familial factors associated with early stress and adult inflammation will be important to uncover correlates of stress and disease.

Smid, G. E., van Zuiden, M., Geuze, E., Kavelaars, A., Heijnen, C. J., & Vermetten, E. (2015). **Cytokine production as a putative biological mechanism underlying stress sensitization in high combat exposed soldiers.** *Psychoneuroendocrinology*, *51*, 534-546. doi:10.1016/j.psyneuen.2014.07.010 **Objective:** Combat stress exposed soldiers may respond to post-deployment stressful life events (SLE) with increases in symptoms of posttraumatic stress disorder (PTSD), consistent with a model of stress sensitization. Several lines of research point to sensitization as a model to describe the relations between exposure to traumatic events, subsequent SLE, and symptoms of PTSD. Based on previous findings we hypothesized that immune activation, measured as a high in vitro capacity of leukocytes to produce cytokines upon stimulation, underlies stress sensitization. **Methods:** We assessed mitogen-induced cytokine production at 1 month, SLE at 1 year, and PTSD symptoms from 1 month up to 2 years post-deployment in soldiers returned from deployment to Afghanistan ($N=693$). Exploratory structural equation modeling as well as latent growth models were applied. **Results:** The data demonstrated significant three-way interaction effects of combat stress exposure, cytokine production, and post-deployment SLE on linear change in PTSD symptoms over the first 2 years following return from deployment. In soldiers reporting high combat stress exposure, both high mitogen-stimulated T-cell cytokine production and high innate cytokine production were associated with increases in PTSD symptoms in response to post-deployment SLE. In low combat stress exposed soldiers as well as those with low cytokine production, post-deployment SLE were not associated with increases in PTSD symptoms. **Conclusion:** High stimulated T-cell and innate cytokine production may contribute to stress sensitization in recently deployed, high combat stress exposed soldiers. These findings suggest that detecting and eventually normalizing immune activation may potentially complement future strategies to prevent progression of PTSD symptoms following return from deployment.

Sumner, J. A., Chen, Q., Roberts, A. L., Winning, A., Rimm, E. B., Gilsanz, P., . . . Kubzansky, L. D. (2017). **Cross-sectional and longitudinal associations of chronic posttraumatic stress disorder with inflammatory and endothelial function markers in women.** *Biological Psychiatry*, *82*, 875-884. doi:10.1016/j.biopsych.2017.06.020 **Background:** Posttraumatic stress disorder (PTSD) may contribute to heightened cardiovascular disease risk by promoting a proinflammatory state and impaired endothelial function. Previous research has demonstrated associations of PTSD with inflammatory and endothelial function biomarkers, but most work has been cross-sectional and does not separate the effects of trauma exposure from those of PTSD. **Methods:** We investigated associations of trauma exposure and chronic PTSD with biomarkers of inflammation (C-reactive

protein and tumor necrosis factor alpha receptor II) and endothelial function (intercellular adhesion molecule-1 and vascular cell adhesion molecule-1) in 524 middle-aged women in the Nurses' Health Study II. Using linear mixed models, we examined associations of trauma/PTSD status with biomarkers measured twice, 10 to 16 years apart, in cardiovascular disease-free women, considering either average levels over time (cross-sectional) or change in levels over time (longitudinal). Biomarker levels were log-transformed. Trauma/PTSD status (based on structured diagnostic interviews) was defined as no trauma at either blood draw ($n = 175$), trauma at blood draw 1 but no PTSD at either draw ($n = 175$), and PTSD that persisted beyond blood draw 1 (chronic PTSD; $n = 174$). The reference group was women without trauma. **Results:** In models adjusted for known potential confounders, women with chronic PTSD had higher average C-reactive protein ($B = 0.27$, $p < .05$), tumor necrosis factor alpha receptor II ($B = 0.07$, $p < .01$), and intercellular adhesion molecule-1 ($B = 0.04$, $p < .05$) levels. Women with trauma but without PTSD had higher average tumor necrosis factor alpha receptor II levels ($B = 0.05$, $p < .05$). In addition, women with chronic PTSD had a greater increase in vascular cell adhesion molecule-1 over time ($B = 0.003$, $p < .05$). **Conclusions:** Increased inflammation and impaired endothelial function may be pathways by which chronic PTSD increases cardiovascular disease risk.

Sumner, J. A., Chen, Q., Roberts, A. L., Winning, A., Rimm, E. B., Gilsanz, P., . . . Kubzansky, L. D. (2018). **Posttraumatic stress disorder onset and inflammatory and endothelial function biomarkers in women.** *Brain, Behavior, and Immunity*, *69*, 203-209. doi:10.1016/j.bbi.2017.11.013 **Background:** Research has linked posttraumatic stress disorder (PTSD) with higher circulating levels of inflammatory and endothelial function (EF) biomarkers, and effects may be bidirectional. We conducted the first investigation of new-onset PTSD and changes in inflammatory and EF biomarkers. **Methods:** Data were from women in the Nurses' Health Study II. Biomarkers obtained at two blood draws, 10-16 years apart, included C-reactive protein (CRP), tumor necrosis factor-alpha receptor-II (TNFR2), intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1). PTSD was assessed via interview. Analyses compared biomarker levels in women with PTSD that onset between draws ($n = 175$) to women with no history of trauma ($n = 175$) and to women with history of trauma at draw 1 and no PTSD at either draw ($n = 175$). We examined if PTSD onset was associated with biomarker change over time and if pre-PTSD-onset biomarker levels indicated risk of subsequent PTSD using linear mixed models and linear regression, respectively. Biomarkers were log-transformed. **Results:** Compared to women without trauma, women in the PTSD onset group had larger increases in VCAM-1 over time ($b = 0.003$, $p = .068$). They also had higher TNFR2 ($b = 0.05$, $p = .049$) and ICAM-1 ($b = 0.04$, $p = .060$) levels at draw 1 (prior to trauma and PTSD onset). However, pre-PTSD-onset biomarker levels did not predict onset of more severe PTSD. **Conclusions:** PTSD onset (vs. no trauma) was associated with increases in one inflammation-related biomarker. Effects may be small and cumulative; longer follow-up periods with larger samples are needed. We did not observe strong support that pre-PTSD-onset biomarkers predicted risk of subsequent PTSD.

ADDITIONAL CITATIONS

Agorastos, A., Hauger, R. L., Barkauskas, D. A., Lerman, I. R., Moeller-Bertram, T., Snijders, C., . . . Baker, D. G. (2019). **Relations of combat stress and posttraumatic stress disorder to 24-h plasma and cerebrospinal fluid interleukin-6 levels and circadian rhythmicity.** *Psychoneuroendocrinology*, *100*, 237-245. doi:10.1016/j.psyneuen.2018.09.009 This study sampled plasma and CSF concurrently every 30 minutes over 24 hours in a small sample of combat Veterans, combat controls, and non-deployed controls. Results showed no group differences in either 24 hour CSF or plasma IL-6.

Baumert, J., Lukaschek, K., Kruse, J., Emeny, R. T., Koenig, W., von Känel, R., & Ladwig, K.-H. (2013). **No evidence for an association of posttraumatic stress disorder with circulating levels of CRP and IL-18 in a population-based study.** *Cytokine*, *63*, 201-208. doi:10.1016/j.cyto.2013.04.033 This study examined the association of CRP and IL-18 in a community-based sample of 3012 adults living in southern Germany in 2006-2008. They found no association with continuous PTSD symptoms with CRP and IL-18.

Bruenig, D., Mehta, D., Morris, C. P., Harvey, W., Lawford, B., Young, R. M., & Voisey, J. (2017). **Genetic and serum biomarker evidence for a relationship between TNF α and PTSD in Vietnam war combat veterans.** *Comprehensive Psychiatry*, *74*, 125-133. doi:10.1016/j.comppsy.2017.01.015 A polymorphism in the promoter for TNF- α , previously associated with elevated risk for psychiatric illness, was found to be associated with PTSD symptom severity. Elevated serum TNF- α was associated with PTSD symptom severity, though the strength of the association was reduced after controlling for covariates such as depression, age, smoking, and medications.

Bruenig, D., Mehta, D., Morris, C. P., Lawford, B., Harvey, W., Young, R. M., & Voisey, J. (2018). **Correlation between interferon γ and interleukin 6 with PTSD and resilience.** *Psychiatry Research*, *260*, 193-198. doi:10.1016/j.psychres.2017.11.069 In a sample of Vietnam combat Veterans, PTSD symptom severity was associated with small but significant decreases in IL-6 and IFN γ . This paper was selected as another example of a study that did not find evidence for increased inflammation in PTSD.

Gill, J., Luckenbaugh, D., Charney, D., & Vythilingam, M. (2010). **Sustained elevation of serum interleukin-6 and relative insensitivity to hydrocortisone differentiates posttraumatic stress disorder with and without depression.** *Biological Psychiatry*, *68*, 999-1006. doi:10.1016/j.biopsych.2010.07.033 Serum IL-6 was sampled every hour between 7:00PM and 7:00AM in a small sample of subjects with PTSD plus major depressive disorder (MDD), PTSD without MDD, and healthy trauma-unexposed controls. Overnight elevation in IL-6 was found in the PTSD plus MDD group relative to PTSD – MDD and controls. Peak overnight IL-6 was associated with severity of PTSD and depressive symptoms.

Glatt, S. J., Tylee, D. S., Chandler, S. D., Pazol, J., Nievergelt, C. M., Woelk, C. H., . . . Marine Resiliency Study Investigators. (2013). **Blood-based gene-expression predictors of PTSD risk and resilience among deployed marines: A pilot study.** *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *162B*, 313-326. doi:10.1002/ajmg.b.32167 Gene expression from peripheral blood cells obtained pre-deployment was compared in a sample of Marines who later did and did not develop PTSD post-deployment to

Iraq or Afghanistan. The Marines who developed PTSD showed increased pre-deployment expression of immune-related genes compared to the group who remained without PTSD suggesting that inflammatory factors comprise a pre-exposure risk factor.

Gola, H., Engler, H., Sommershof, A., Adenauer, H., Kolassa, S., Schedlowski, M., . . . Kolassa I.-T. (2013). **Posttraumatic stress disorder is associated with an enhanced spontaneous production of pro-inflammatory cytokines by peripheral blood mononuclear cells.** *BMC Psychiatry*, *13*, 40. doi:10.1186/1471-244X-13-40 In vitro spontaneous release of IL-6 and TNF α in isolated peripheral blood mononuclear cells was elevated in PTSD in a case-control study. In contrast, circulating plasma levels of cytokines were no different in the two groups. The study demonstrates the potential value of controlled in vitro studies in isolated blood mononuclear cells.

Groer, M. W., Kane, B., Williams, S. N., & Duffy, A. (2015). **Relationship of PTSD symptoms with combat exposure, stress, and inflammation in American soldiers.** *Biological Research for Nursing*, *17*, 303-310. doi:10.1177/1099800414544949 Elevated CRP was associated with both PTSD and depressive symptoms in a cross-sectional study of active duty enlisted and reservist Soldiers. The study is selected as an example that shows that PTSD and depression both predict elevated inflammatory factors.

Lindqvist, D., Dhabhar, F. S., Mellon, S. H., Yehuda, R., Grenon, S. M., Flory, J. D., . . . Wolkowitz, O. M. (2017). **Increased pro-inflammatory milieu in combat related PTSD - A new cohort replication study.** *Brain, Behavior, and Immunity*, *59*, 260-264. doi:10.1016/j.bbi.2016.09.012 This study replicated the finding of an increased pro-inflammation score in a new sample of PTSD versus controls obtained by the same investigative team as the study below.

Lindqvist, D., Wolkowitz, O. M., Mellon, S., Yehuda, R., Flory, J. D., Henn-Haase, C., . . . Dhabhar, F. S. (2014). **Proinflammatory milieu in combat-related PTSD is independent of depression and early life stress.** *Brain, Behavior, and Immunity*, *42*, 81-88. doi:10.1016/j.bbi.2014.06.003 This case control study utilized an aggregate pro-inflammation score from standardized scores of IL-1 β , IL-6, TNF α , IFN γ , and CRP. PTSD was associated with a higher pro-inflammation score even after accounting for depression and early life trauma.

Maes, M., Lin, A.-H., Delmeire, L., Van Gastel, A., Kenis, G., De Jongh, R., & Bosmans, E. (1999). **Elevated serum interleukin-6 (IL-6) and IL-6 receptor concentrations in posttraumatic stress disorder following accidental man-made traumatic events.** *Biological Psychiatry*, *45*, 833-839. doi:10.1016/S0006-3223(98)00131-0 This is an early and prototypical case control study demonstrating increased IL-6 and soluble IL-6 receptor in serum of PTSD patients versus controls. Patients with PTSD and MDD had higher IL-6R than PTSD patients without MDD.

Smith, A. K., Conneely, K. N., Kilaru, V., Mercer, K. B., Weiss, T. E., Bradley, B., . . . Ressler, K. J. (2011). **Differential immune system DNA methylation and cytokine regulation in post-traumatic stress disorder.** *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *156B*, 700-708. doi:10.1002/ajmg.b.31212 This study examined DNA methylation and plasma cytokines in 4 groups of subjects defined by presence or absence of PTSD crossed with history of child abuse.

The results showed increased DNA methylation in PTSD particularly in genes associated with inflammation. PTSD, child abuse, and total life stress were independently associated with IL4, IL2 and TNF α levels.

Spitzer, C., Barnow, S., Völzke, H., Wallaschowski, H., John, U., Freyberger, H. J., . . . Grabe, H. J. (2010). **Association of posttraumatic stress disorder with low-grade elevation of C-reactive protein: Evidence from the general population.** *Journal of Psychiatric Research, 44*, 15-21. doi:10.1016/j.jpsychires.2009.06.002

This is another population based study ($N = 3049$) which examined the association of PTSD with CRP. PTSD diagnosis was associated with a nearly twofold risk for elevated CRP even after controlling for sociodemographics, body mass index, blood pressure, lipids, physical disease burden, and history of trauma exposure.

Tucker, P., Ruwe, W. D., Masters, B., Parker, D. E., Hossain, A., Trautman, R. P., & Wyatt, D. B. (2004). **Neuroimmune and cortisol changes in selective serotonin reuptake inhibitor and placebo treatment of chronic posttraumatic stress disorder.** *Biological Psychiatry, 56*, 121-128. doi:10.1016/j.biopsych.2004.03.009 This is a case control study comparing IL1 β and soluble IL2 receptors in PTSD and controls; and a pre-post selective serotonin reuptake inhibitor (SSRI) treatment study within the PTSD group looking for the effect of treatment on cytokines. The results showed greater IL1 β and lower IL-2R levels in PTSD versus controls. SSRI treatment of PTSD significantly normalized these factors to control subject levels.

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.** *Journal of Psychiatric Research, 41*, 744-752. doi:10.1016/j.jpsychires.2006.06.009 This is a small case control study which showed elevated TNF α and IL1 β in PTSD versus controls. This demonstrated that controlling for time since trauma exposure attenuates the association between PTSD status and cytokines.