Abnormal Cytokines in Trauma Patients Explained by Obesity, Musculoskeletal Disease, Smoking, and Lung Disease

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Cytokines · Trauma · PTSD · Metabolic syndrome · Body mass index · Low-grade inflammation

Abstract
Introduction: Low-grade inflammation observed through abnormal plasma cytokine levels has been associated with post-traumatic stress disorder (PTSD). It is not clear whether PTSD independently causes the inflammation or if it is mainly through co-occurring somatic factors such as smoking and obesity. We wanted to explore the effects of biopsychosocial factors on cytokine levels in a clinical setting. Methods: The sample consisted of 51 patients with PTSD, 58 trauma patients without PTSD, and 40 matched controls. We selected cytokines and relevant risk factors for systemic inflammation through pairwise correlations. Then, we used linear regression to analyze the individual and combined effects of these on the (Log_{10}) cytokines, particularly estimating the effect of PTSD adjusted for other factors. Results: Higher age, female gender, cigarette smoking, presence of lung and musculoskeletal disease, use of antipsychotic medication, and higher BMI were correlated with higher levels of interleukins IL-1RA, IL-2RA, and IL-6. In the adjusted regression analysis, higher BMI was associated with increased IL-1RA ($B = 0.06, p < 0.01$), IL-2RA ($B = 0.01, p < 0.01$), and IL-6 ($B = 0.01, p = 0.03$). Presence of musculoskeletal disease was associated with increased IL-1RA ($B = 0.72, p < 0.01$) and IL-6 ($B = 0.16, p = 0.01$), and decreased IL-2RA ($B = -0.09, p < 0.01$). Cigarette smoking ($B = 0.16, p = 0.01$) and presence of lung disease ($B = 0.14, p = 0.02$) were associated with increased IL-6. PTSD diagnosis was associated with decreased IL-2RA ($B = -0.06, p = 0.04$). Discussion/Conclusion: Altered cytokine levels in distressed trauma-affected individuals are probably mostly through co-occurring risk factors and not PTSD diagnosis. Increased BMI and musculoskeletal (pain) disease may be particularly strong risk factors and should be addressed.

Introduction

An acute fear reaction in response to an imminent threat elicits many psychological and physiological responses. While the so-called fight-and-flight response could affect behavior to increase survival, acute changes in the immune system could also make the organism better prepared to overcome tissue damage and infections in
the short term. Distinct changes in pro- and anti-inflammatory systems have been associated with such reactions in humans [1, 2] and animals [3].

Post-traumatic stress disorder (PTSD), the only mental health disorder with an explicitly defined life-event trigger [4–6]. It is a chronic disorder that develops in a subset of people after one or several major traumatic events such as threatened death, serious injury, or sexual violence. In addition to the traumatic event(s), diagnostic criteria are psychological. The DSM-IV and ICD-11 require intrusive memories (flashbacks, nightmares etc.), avoidance (of memories/thoughts or situations/places), and hypervigilance (hyperarousal/ hyperreactivity) [4, 6]. In addition, the DSM-5 requires negative mood/cognition (negative affect, apathy, etc.) [5]. To fulfill the diagnostic criteria the symptoms cause significant distress and/or significant functional life impairment, and the condition should last at least several weeks/months.

There is strong empirical evidence indicating that people with PTSD have increased rates of somatic comorbidities. The most common are obesity and related metabolic disturbances [7–9]. This comes in addition to increased rates of smoking and alcohol/drug use/abuse [10]. Chronic PTSD may change behavior and lifestyle through its core symptoms. For instance, avoidance of places or people and spending more time and focus on the trauma may in turn lead to isolation, a poorer diet, and more sedentary lifestyle. Furthermore, smoking, alcohol, drugs, and “comfort eating” may be used as anxiety relievers in this population [11]. All these can increase the risk of a wide range of somatic and lifestyle conditions.

The observed somatic disturbances may be further mediated through dysfunction of the hypothalamic-pituitary-adrenal axis. For instance, the evidence is quite clear that cortisol levels are reduced [12] while the catecholamines are increased [13] in PTSD. This may be due to a chronic fear reaction and observed hypervigilance symptoms. The baseline levels of these hormones may in turn cause higher cortisol reactivity to stress, which may be more important for appetite and food intake than the baseline levels [14]. Together, all these may explain some of the links between the observed neuroendocrine changes, consumptive behaviors, and increased fat mass in PTSD [15].

Metabolic syndrome (MetS) has several different definitions, but it commonly refers to a combination of increased body mass index (BMI), waist circumference, blood pressure, cholesterol, lipids, and/or blood glucose [16, 17]. Epidemiological studies have shown a clear association between PTSD and MetS [9, 18–25]. MetS may explain part of the high association of PTSD with common coexisting health conditions such as cardiovascular diseases [26, 27], type 2 diabetes [28], decreased brain cortical thickness [29, 30], and accelerated aging [8, 31, 32]. All these together are probably the main cause of premature mortality seen in trauma and PTSD affected persons. It has been estimated that they live almost 20 years shorter on average [33, 34]. Furthermore, the combined mental and physical burdens of co-occurring PTSD and somatic conditions often have a large impact on health-related quality of life [35].

PTSD is not the only mental health disorder associated with MetS [36]. Most mental health disorders are associated with MetS and other somatic and lifestyle conditions [37–39]. There is increasing evidence, however, that PTSD is one of the disorders, which is most strongly linked to obesity and worsened metabolic profile. This may be true, even compared with the most severe disorders such as schizophrenia, bipolar disorder, and dementia [17, 40]. Furthermore, depression and anxiety very often co-occur with PTSD and both these disorders have been associated with MetS and inflammation [38].

Since the 1980s, there has been accumulating evidence that chronic inflammation is a major pathway between MetS and cardiovascular diseases [41]. Studies on each component of MetS have found strong associations with chronic low-grade inflammation, including increased levels of inflammatory biomarkers such as C-reactive protein (CRP) and cytokines [42–44]. It seems that adipose tissue plays a critical role in the immune homeostasis. Adipocytes may release the proinflammatory hormone leptin [45, 46] and inhibit the anti-inflammatory hormone adiponectin [47]. Furthermore, adipose macrophages are the main source of proinflammatory cytokines [48], which provide a potential specific link between inflammation and obesity/MetS [49]. An experimental study found that moderate weight reduction was accompanied by a reduction in leptin and proinflammatory cytokine levels, but no changes in adiponectin levels were observed [50]. Hypertension and hyperglycemia may also cause inflammation independently of adipose tissue, but the mechanisms here are less clear, and there may be bidirectional effects [51, 52].

A recent systematic review selected 42 of 2,606 studies for meta-analysis on cytokines and PTSD [53]. It concluded that interleukin-1 beta (IL-1β), interleukin-2 (IL-2), interleukin-6 (IL-6), interferon-γ, tumor necrosis factor (TNF), CRP, and white blood cell count are elevated in PTSD patients compared to healthy controls. When they did a subgroup analysis comparing PTSD patients
with healthy controls with trauma exposure, they found much more conflicting findings between the studies. There was not enough evidence to conclude in one direction or the other in this case.

There are a few studies comparing cytokines in people with PTSD to people who also have experienced trauma and have mental health distress but do not have PTSD. It has been reported that trauma patients with PTSD have significantly elevated levels of CRP and a few proinflammatory cytokines such as IL-6 and TNF compared to trauma-affected controls without PTSD [44, 54–56]. The most robust findings are on peripherally produced IL-6. Two recent meta-analyses of PTSD and IL-1β [57] and TNF [58] found that while some studies reported increased levels in PTSD patients compared with trauma controls, others found equal or even lower levels of the same markers. Furthermore, they found that very few of these studies have adjusted for other known risk factors for inflammation. Other cytokines such as IL-1 receptor antagonist (IL-1RA), IL-2, IL-2 receptor antagonist (IL-2RA), and macrophage migration inhibitory factor (MIF) have been less studied in this setting. This represents a research gap.

Obesity, MetS, smoking, and other related factors can serve as moderators in the relationship between PTSD and low-grade inflammation. It is not clear if the inflammation markers found in PTSD affected individuals is primarily due to the PTSD diagnosis, to MetS, to other factors, or a combination [59–61]. Most systemic inflammation studies in PTSD patients have not adjusted for confounders or mediators such as age, gender, diet, exercise, BMI, lipids, smoking, medication, and comorbid physical and mental health diagnoses. The question remains if the psychological symptoms of the PTSD diagnosis can cause inflammation alone, for instance through hyperactivation symptoms and activation of the sympathetic nervous system, or if it is only through established mediators such as MetS and smoking.

Several datasets have recently been reanalyzed to find that previously significant results have become nonsignificant after adjusting for certain other risk factors. For instance, one study found that the PTSD-inflammation effect disappeared when adjusting for systolic blood pressure [62], another for smoking [63]. Similarly, a recent meta-analysis found that TNF in PTSD patients was no longer elevated when participants with comorbid depression on or on medication were excluded from the analyses [44, 64]. A recent thorough review has tried to untangle the relationship between PTSD and systemic inflammation, whether PTSD causes inflammation, if there are bi-directional effects, or if the effects are simply through other related factors [65]. They conclude that although there is a strong correlation between PTSD and cytokines, there is currently not enough evidence to support a causal relationship between PTSD and inflammation.

More research is needed to examine how different factors may influence cytokines in trauma patients, both individually and combined. We aimed to explore the association between low-grade inflammation markers, such as CRP and circulating cytokines, in patients with trauma history. We wanted to look at both well-studied and less researched cytokines. First, we aimed to compare both sets of trauma patients with healthy controls to confirm the differences in cytokine levels. Second, we aimed to compare trauma patients with PTSD to those without the diagnosis. In our sample, both groups experience distress at a degree where they have been referred to a second line mental health clinic, but some of them do not meet the criteria for a PTSD diagnosis. We wanted to examine the effect of key factors such as age, gender, MetS including body mass index (BMI), smoking, medication, and somatic and psychiatric comorbidity on certain inflammation markers.

We hypothesized that distressed traumatized patients referred to a mental health clinic both with and without PTSD will have higher levels of pro- and lower levels of anti-inflammatory cytokines compared to healthy controls. When comparing the two patient groups, cytokine levels and CRP may overall be higher in those with PTSD than in those without this diagnosis. We believed that many of the patients with and without PTSD would have somatic risk factors and altered cytokines, and that these would be associated with each other. For instance, higher BMI may be associated with antipsychotic medication and musculoskeletal diseases, and daily smoking may be associated with lung disease and male gender, and all of these with proinflammatory cytokines. We wanted to try to untangle the relationships between these. For instance, when adjusting for other risk factors, some risk factors for inflammation, including PTSD diagnosis, may no longer have independent effects on cytokine levels. Other risk factors may only show an effect after adjusting for other risk factors.

Materials and Methods

Participants
The Study of Health Outcome after Trauma (SHOT-study) is a cross-sectional study on mental health patients who are suffering after major psychological trauma. We recruited patients referred
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The main inclusion criteria were having experienced at least one serious trauma according to the DSM-IV-TR criteria, age between 18 and 60, proficiency in a Scandinavian language or English, and informed consent. The exclusion criteria were less than 1 month since trauma, serious brain- or other somatic disease (for instance, severe heart/lung/kidney failure), severe head injury, chronic psychotic disorder, serious alcohol abuse, or severe substance abuse, and/or serious dyslexia, or other serious difficulties with oral or written language.

Of the 119 patients who had originally signed the consent, 109 completed all the interviews and tests. Of these, 42 were men (38.5%, \( M_{\text{age}} = 43.6 \) years) and 67 were women (61.5%, \( M_{\text{age}} = 38.5 \) years). Assessments of the patients consisted of three parts: a self-report questionnaire, a clinical semi-structured interview, and clinical examination including several blood tests.

**Self-Reported Questions**

Initially, the patients received a set of self-administered questionnaires to be completed at home or in the waiting room. The general questionnaire assessed health status with self-evaluated current and past somatic and psychiatric illness. Furthermore, they were asked about past and current smoking habits, current somatic drug treatment, current psychiatric drug treatment, and any use in the last 2 years including dose, response, side effects, and reasons for change. Self-reported medication use was also cross-checked with the patient records and prescription registry. Use of alcohol and other addictive substances were assessed by using the validated World Health Organization Alcohol Use Disorders Identification Test (AUDIT) and Drug Use Disorder Identification Test (DUDIT).

**The Clinical Semi-Structured Interview**

The patients were then evaluated by one of two experienced psychiatrists for the clinical semi-structured interview. Current PTSD diagnosis was determined by the Structured Clinical Interview for DSM-IV-TR PTSD Module (SCID-I-PTSD). Major depressive disorder and anxiety disorders (agoraphobia, panic disorder, social phobia, specific phobia, and generalized anxiety disorder) according to DSM-IV-TR were evaluated using the MINI Plus 4.0 neuropsychiatric interview.

**Clinical Examination and Blood Tests**

The patients were then examined by a medical doctor. The anthropometric measures were weight, height, waist and hip circumferences, blood pressure, and heart rate. BMI was calculated with the formula: body weight (kg)/height (m) squared.

Fasting blood samples were taken between 8 and 10:00 a.m. The general blood tests were plasma triglycerides and cholesterol (total, LDL, HDL, and ratio), glucose, HbA1C, C-peptide, leptin, CRP, leucocytes, and concentration of any active psychopharmacological agent in the blood.

**Control Group**

The control group consisted of 40 healthy blood donors matched for age and gender. Of these, 15 were men (37.5%, \( M_{\text{age}} = 38.2 \) years) and 25 were women (62.5%, \( M_{\text{age}} = 39.5 \) years). They completed a self-report form to exclude any known physical or mental illnesses, alcohol and substance use disorders, medications, and smoking. They got a basic physical examination, including blood pressure, and their blood was also screened negative for a wide range of diseases.

**Quantification of Plasma Cytokine Levels**

We used a custom 7-plex analysis from Bio-Rad Laboratories (cat. no.: 17007417) on plasma from all 149 participants to determine circulating levels of IL-1β, IL-1RA, IL-2, IL-2RA, IL-6, MIF, and TNF. All plasma samples were thawed, centrifuged at 10.000×G for 10 min at 4°C, and the supernatant was further diluted (1 + 3) with sample diluent reagent. Fifty microliters of samples were loaded on to the assay plate and cytokine levels were determined using a Luminex IS 200. All samples were run in duplicate. A spiked-in plasma control was used to determine the coefficient of variation (%CV). Intra-plate %CV ranged from 0.5 to 10 and interplate %CV ranged from 5 to 19.

**Statistical Analysis**

We used IBM SPSS version 25 for statistical analyses [66]. Descriptive statistics with skewness and kurtosis values, Kolmogorov-Smirnov test of normality, and histograms were used for assessing the normality of the distribution, linearity, and homoscedasticity for continuous variables. To compare significant differences between the two groups, either the nonparametric Mann-Whitney U test or independent-sample t-test was used dependent of the variety of distributions of continuous scores. The Kruskal-Wallis test was conducted for comparing more than two groups. Pearson’s \( \chi^2 \) test was used to explore the relationship between categorical variables. In the \( \chi^2 \) tests, we used adjusted residuals to identify between groups’ differences. Effect size (ES) was calculated using Cramer’s V, except when Mann-Whitney test was used where ES is calculated by dividing static z by the square of pairs. We used Cohen d classification of effect, ES = 0.3 as a small, ES = 0.5 as moderate, and ES ≥0.8 as large effect [67].

We used base-10 logarithmic transformation (Log10) of the cytokine values because they were positively skewed. A standard simple linear regression analysis was run with cytokines as the dependent variable and each of the selected risk factors as independent variables. Multiple linear regressions were used on the selected variables as covariates to examine whether PTSD diagnosis was independently associated with cytokines levels in the whole set of 109 trauma patients. Mediation effects were evaluated with Baron and Kenny regression techniques [68].

Significance values have been adjusted by the Bonferroni correction for multiple tests. The Bonferroni adjusted alpha level was set at 0.05.

**Results**

**Baseline Patient Characteristics**

Table 1 presents the demographic and health risk factors, medication, and psychiatric and somatic comorbidity in the 109 patients with and without PTSD. Slightly less than half of them (46.8%) had PTSD.

There were significant differences between the two groups in psychiatric comorbidity. Patients with PTSD...
had higher rates of major depression (63% vs. 37%, ES = 0.49, p < 0.01) and anxiety disorders (84% vs. 14%, ES = 0.36, p < 0.01). They also had significantly higher BMI (28.3 kg/m² vs. 26.3 kg/m², ES = 0.21, p = 0.03). Conversely, self-reported alcohol use (ES = 0.21, p = 0.03) and musculoskeletal diseases (ES = 0.26, p < 0.01) were significantly higher in patients without PTSD. The gender distribution; smoking habits; presence of metabolic syndrome; use of antipsychotic, antidepressant, and antihistamine medication; and lung disease were comparable between the groups.

In the healthy control group, we did not have all the same details, but we knew their age and gender and that they had crossed off “no” on all that of questions about a wide range of health conditions (including over- and underweight) and medication use. Furthermore, their blood was screened negative for a wide range of diseases and found to be normal.

### Table 1. Sociodemographic and clinical characteristics of 109 patients with trauma history

|                  | 1. PTSD (−), n = 58 | 2. PTSD (+), n = 51 | Total, n = 109 | p value | ES |
|------------------|---------------------|---------------------|----------------|---------|----|
| Age, years, mean (SD) | 40.57 (11.39)       | 40.37 (10.99)       | 40.44 (11.11)  | 0.966   | *  |
| Gender, women, n (%) | 38 (65.5)           | 29 (56.9)           | 67 (61.5)      | 0.354   | *  |
| Smoking daily, n (%) | 19 (32.8)           | 16 (31.4)           | 35 (32.1)      | 0.877   | *  |
| AUDIT, mean (SD)   | 4.81 (5.95)         | 3.75 (6.18)         | 4.44 (6.17)    | 0.030   | 0.207 |
| DUDIT, mean (SD)   | 1.40 (3.75)         | 1.94 (4.81)         | 1.64 (4.25)    | 0.672   | *  |
| BMI, mean (SD)     | 26.31 (5.99)        | 28.27 (5.44)        | 27.22 (5.8)    | 0.031   | 0.207 |
| BMI categories, n (%) | –                  | –                   | –              | 0.264   | *  |
| ≤18.4             | 2 (3.4)             | 1 (2)               | 3 (2.8)        | –       | –   |
| 18.5–24.9         | 27 (46.6)           | 15 (29.4)           | 42 (38.5)      | –       | –   |
| 25–29.9           | 16 (27.6)           | 18 (35.3)           | 33 (31.2)      | –       | –   |
| ≥30               | 13 (22.4)           | 17 (33.3)           | 30 (27.5)      | –       | –   |
| Metabolic syndrome, n (%) | 24 (41.4)         | 24 (47.1)           | 48 (44.0)      | 0.551   | *  |
| Major depression, n (%) | 19 (32.8)         | 32 (62.7)           | 51 (46.8)      | <0.001  | 0.486 |
| Any anxiety disorder, n (%) | 8 (13.8)          | 43 (84.3)           | 51 (46.8)      | <0.001  | 0.362 |
| Lung disease, n (%) | 16 (28.1)           | 14 (28.0)           | 30 (28.0)      | 0.994   | *  |
| Musculoskeletal disorder, n (%) | 38 (65.5)       | 20 (40.0)           | 58 (53.7)      | 0.008   | 0.255 |
| Allergy/hay fever, n (%) | 29 (50.0)         | 25 (50.0)           | 54 (50.0)      | 1.000   | *  |
| Use of antipsychotics, n (%) | 10 (17.2)         | 10 (19.6)           | 20 (18.3)      | 0.750   | *  |
| Use of antidepressants n (%) | 24 (41.4)        | 28 (54.9)           | 52 (47.7)      | 0.158   | *  |
| Use of antihistamines, n (%) | 9 (15.8)          | 7 (13.7)            | 16 (14.8)      | 0.763   | *  |

Missing values: lung disease 2, musculoskeletal disease 1, allergy/hay fever 1, and use of antihistamines 1. PTSD, post-traumatic stress disorder diagnosis; ES, effect size; SD, standard deviation; AUDIT, alcohol use disorder identification test; DUDIT, drug use disorder identification test; BMI, body mass index; * Not applicable.

Inflammatory Markers in Patients with and without PTSD and Controls

The cytokines levels and CRP were analyzed pairwise between the 58 patients without PTSD, 51 patients with PTSD, and the 40 healthy controls. When we compared each of the groups of patients with healthy controls, they had significantly (p < 0.01) higher levels of IL-1RA (ES = 0.97), IL-2RA (ES = 1.54 and ES = 1.55), IL-6 (ES = 1.05), and TNF (ES = 1.17 and ES = 1.36). IL-2 had many undetectable levels in all groups, MIF did not show any significant differences between the groups and we did not have CRP levels in the control group. The finding from each pairwise analysis for each marker is summarized in Table 2.

**Variable Selection for Further Analysis**

Cytokines

More than half of the participants had concentrations of circulating IL-2 levels below the detection level in our examination (zero). This cytokine was therefore excluded for further analysis. MIF and IL-1β had mostly measurable values, but they did not show any correlation with any of our explanatory variables, including PTSD, and were excluded for this reason. IL-1β was however correlated with IL-1RA, so IL-1RA may be used to represent IL-1 system activation. TNF showed differences between the trauma and control group, and a weak correlation with BMI but not with any other of the factors. Furthermore, the combined regression model of Log₁₀ TNF
showed low fit ($R^2 = 0.14$). TNF was excluded for this reason. IL-1RA, IL-2RA, and IL-6 were considered fully analyzable and, therefore, chosen for further analysis.

### Metabolic Syndrome

Each factor of MetS (BMI, waist/hip circumference, blood pressure, cholesterol, lipids, and/or fasting blood glucose/HbA1c), leptin, and the combined MetS factor were all correlated with the selected three cytokines in our study patients. The effect size and significance values were strongest when BMI was analyzed alone. We therefore chose BMI as the only MetS variable for the following analyses.

### Inclusion of Other Variables

Age and gender are well established factors that influence inflammation and cytokine levels in population wide studies. Female gender and older age are generally correlated with higher levels of proinflammatory cytokines [69, 70]. Alcohol and drug use measured by AUDIT and DUDIT scores did not show significant correlation with any of the cytokines in our study and were therefore excluded from the multivariate analysis.

Both major depressive disorder and the anxiety disorder were highly correlated with each other and with PTSD but not with any of the cytokines that we had measured, neither alone nor in an adjusted analysis. We therefore excluded them from the adjusted analysis.

Of the self-reported somatic diseases, both lung and musculoskeletal diseases were correlated with several cytokines, while allergies/hay-fever was not. Endocrine, neurological, cardiovascular, and cancer diseases were reported by a very low number of participants (<3%) and were therefore excluded in the following analyses. Daily use of oral corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and use of mood stabilizers (for instance Lithium or Lamotrigine) were also infrequent (<6%) and had comparable rates between the 2 patient groups. These were therefore not included in the further analysis either.

### Correlations between Risk Factors that May Influence Inflammation

When we did a pairwise Pearson correlation between the selected risk factors, we found that BMI was positively correlated with age ($0.27, p < 0.01$), musculoskeletal diseases ($0.29, p < 0.01$), and current PTSD diagnosis ($0.17, p = 0.04$). The women were slightly younger and fewer smoked, indicated by negative correlations with age ($−0.23, p < 0.01$) and smoking ($−0.29, p < 0.01$). Daily smoking was slightly more common among those using antipsychotic medication ($0.17, p = 0.04$) and the smokers trended towards being older ($0.15, p = 0.06$).

Having a lung disease was not significantly correlated with any of the other factors, but there was a slight trend towards more lung disease among men, use of antipsychotic medication, and higher BMI, with Pearson correlation between 0.12 and 0.14 ($p < 0.10$). All the Pearson correlations and their respective significance values are summarized in Table 3 below.

### IL-1RA and Risk Factors

The effect of the selected risk factors on the anti-inflammatory cytokine (Log$_{10}$) IL-1RA was analyzed using linear regression. In the pairwise unadjusted models, we found that lung diseases ($B = 0.53, R^2 = 0.05, p = 0.02$),
### Table 3. Pearson correlation coefficients between selected individual risk factors for systemic inflammation in a group of 109 trauma patients

|                        | Age          | Gender (women) | Daily smoking | Lung diseases (asthma/COPD) | Musculoskeletal diseases | Antipsychotic medicines | BMI          | PTSD current |
|------------------------|--------------|----------------|---------------|-----------------------------|--------------------------|-------------------------|--------------|--------------|
| Age                    | 1            | −0.228* (p < 0.01) | 0.153** (p = 0.06) | 0.022 (p = 0.41) | 0.146** (p = 0.07) | 0.050 (p = 0.30) | 0.273* (p < 0.01) | −0.005 (p = 0.48) |
| Gender (women)         | −0.228* (p < 0.01) | 1              | −0.289* (p < 0.01) | 0.144** (p = 0.07) | −0.083 (p = 0.20) | −0.066 (p = 0.25) | −0.015 (p = 0.44) | −0.095 (p = 0.16) |
| Daily smoking          | 0.153** (p = 0.06) | −0.289* (p < 0.01) | 1              | 0.012 (p = 0.45) | 0.015 (p = 0.44) | 0.174* (p = 0.04) | −0.011 (p = 0.46) | −0.027 (p = 0.39) |
| Lung diseases (asthma/COPD) | 0.022 (p = 0.41) | 0.144** (p = 0.07) | 0.012 (p = 0.45) | 1              | 0.048 (p = 0.31) | 0.130** (p = 0.09) | 0.125** (p = 0.10) | 0.005 (p = 0.48) |
| Musculoskeletal diseases | 0.146** (p = 0.07) | −0.083 (p = 0.20) | 0.015 (p = 0.44) | 0.048 (p = 0.31) | 1              | −0.031 (p = 0.38) | 0.289* (p < 0.01) | −0.244* (p < 0.01) |
| Antipsychotic medicines | 0.050 (p = 0.30) | −0.066 (p = 0.25) | 0.174* (p = 0.04) | 0.130** (p = 0.09) | −0.031 (p = 0.38) | 1              | 0.058 (p = 0.28) | 0.34 (p = 0.36) |
| BMI                    | 0.273* (p < 0.01) | −0.015 (p = 0.44) | −0.011 (p = 0.46) | 0.125** (p = 0.10) | 0.289* (p < 0.01) | 0.058 (p = 0.28) | 1              | 0.169* (p = 0.04) |
| PTSD current           | −0.005 (p = 0.48) | −0.095 (p = 0.16) | −0.027 (p = 0.39) | 0.005 (p = 0.48) | −0.244* (p < 0.01) | 0.034 (p = 0.36) | 0.169* (p = 0.04) | 1              |

PTSD: post-traumatic stress disorder diagnosis; BMI, body mass index. * 1-tailed p values p ≤ 0.05. ** 1-tailed p values 0.05 < p ≤ 0.10.

### Table 4. Simple and multiple linear regression model with Log_{10} of interleukin-1 receptor antagonist as the dependent variable and selected risk factors for inflammation as independent variables in a group of 109 trauma patients

|                        | Log_{10} IL-1RA |
|------------------------|----------------|
|                        | unadjusted B (95% CI) | p value | adjusted B (95% CI) | p value |
| Age                    | 0.008 (−0.009 to 0.024) | 0.372 | −0.012 (−0.030 to 0.006) | 0.173 |
| Gender (women)         | 0.248 (−0.0116 to 0.612) | 0.180 | 0.264 (−0.149 to 0.678) | 0.208 |
| Smoking                | −0.042 (−0.0488 to 0.405) | 0.853 | 0.042 (−0.375 to 0.460) | 0.842 |
| Lung disease (asthma/COPD) | 0.532 (0.071–0.992) | 0.024* | 0.340 (−0.082 to 0.763) | 0.113 |
| Musculoskeletal diseases | 0.840 (0.450–1.229) | <0.001* | 0.718 (0.310–1.127) | 0.001* |
| Antipsychotic medicines | 0.365 (−0.150 to 0.880) | 0.163 | 0.238 (−0.251 to 0.727) | 0.337 |
| BMI                    | 0.071 (0.038–0.105) | <0.001* | 0.055 (0.019–0.091) | 0.003* |
| PTSD current           | −0.022 (−0.440 to 0.396) | 0.918 | 0.062 (−0.336 to 0.460) | 0.757 |

PTSD: post-traumatic stress disorder diagnosis. CI: confidence interval; BMI, body mass index. Model $R^2 = 0.291$. Constant: $B = 0.168$, (−1.121 to 1.457, $p = 0.797$). * p ≤ 0.05.
musculoskeletal diseases ($B = 0.84$, $R^2 = 0.15$, $p < 0.01$), and BMI ($B = 0.07$, $R^2 = 0.14$, $p < 0.01$) were significantly correlated with IL-1RA. In the adjusted model, lung diseases had no longer had a significant correlation with IL-1RA. Musculoskeletal diseases ($B = 0.72$, $p < 0.01$) and BMI ($B = 0.05$, $p < 0.01$) had significant independent effects on IL-1RA.

The model fit was $R^2 = 0.29$. The B coefficients and confidence intervals are summarized in Table 4 below.

### IL-2RA and Risk Factors

When analyzing the unadjusted effects of the selected factors on (Log$_{10}$) IL-2RA, we only found that BMI ($B = 0.01$, $R^2 = 0.08$, $p < 0.01$) had a statistically significant effect. In the adjusted model, however, both musculoskeletal diseases ($B = -0.09$, $p < 0.01$) and current PTSD ($B = -0.06$, $p = 0.04$) showed independent effects in addition to BMI ($B = 0.01$, $p < 0.01$). Note that a PTSD diagnosis had a negative effect on IL-2RA.

The model fit was $R^2 = 0.20$. The B coefficients and confidence intervals are summarized in Table 5 below.

### IL-6 and Risk Factors

In the simple linear regression analyses on (Log$_{10}$) IL-6, the unadjusted models of all factors showed effects on IL-6, except gender and PTSD diagnosis. The IL-6 level was affected by age ($B = 0.01$, $R^2 = 0.06$, $p < 0.01$), daily smoking ($B = 0.17$, $R^2 = 0.06$, $p < 0.01$), lung diseases ($B = 0.20$, $R^2 = 0.08$, $p < 0.01$), musculoskeletal diseases ($B = 0.20$, $R^2 = 0.09$, $p < 0.01$), using antipsychotic medication

| Table 5. Simple and multiple linear regression model with Log$_{10}$ of interleukin-2 receptor antagonist as the dependent variable and selected risk factors for inflammation as independent variables in a group of 109 trauma patients |
|-----------------------------------------------|
| **Log$_{10}$ IL-2RA**                       |
| **unadjusted $B$ (95% CI)**                  | **p value** | **adjusted $B$ (95% CI)** | **p value** |
| Age                                          | 0.000 (−0.002 to 0.003) | 0.774 | −0.002 (−0.004 to 0.001) | 0.264 |
| Gender (women)                               | −0.016 (−0.077 to 0.046) | 0.617 | −0.013 (−0.076 to 0.050) | 0.683 |
| Smoking                                      | 0.054 (−0.009 to 0.118) | 0.090 | 0.054 (−0.009 to 0.118) | 0.092 |
| Lung diseases (asthma/COPD)                  | −0.005 (−0.071 to 0.081) | 0.877 | −0.019 (−0.084 to 0.045) | 0.550 |
| Musculoskeletal diseases                     | −0.037 (−0.117 to 0.043) | 0.221 | −0.087 (−0.149 to −0.025) | 0.006* |
| Antipsychotic medicines                      | 0.050 (−0.024 to 0.124) | 0.182 | 0.021 (−0.054 to 0.095) | 0.586 |
| Body mass index                              | 0.008 (0.003–0.031) | 0.002* | 0.012 (0.006–0.017) | <0.001* |
| PTSD current                                 | −0.018 (−0.077 to 0.042) | 0.563 | −0.062 (−0.062 to −0.123) | 0.043* |

PTSD, post-traumatic stress disorder diagnosis; CI, confidence interval. Model $R^2 = 0.203$; Constant $B = 2.082$, (1.886–2.278, $p < 0.001$).

| Table 6. Simple and multiple linear regression model with Log$_{10}$ of interleukin 6 as the dependent variable and selected risk factors for inflammation as independent variables in a group of 109 trauma patients |
|-----------------------------------------------|
| **Log$_{10}$ IL-6**                           |
| **unadjusted $B$ (95% CI)**                  | **p value** | **adjusted $B$ (95% CI)** | **p value** |
| Age                                          | 0.008 (0.003–0.130) | 0.002* | 0.002 (−0.003 to 0.007) | 0.475 |
| Gender (women)                               | 0.021 (−0.088 to 0.131) | 0.701 | 0.051 (−0.069 to 0.172) | 0.399 |
| Daily smoking                                | 0.170 (0.043–0.297) | 0.009* | 0.158 (0.036 to 0.279) | 0.011* |
| Lung diseases (asthma/COPD)                  | 0.197 (0.064–0.330) | 0.004* | 0.144 (0.021 to 0.267) | 0.022* |
| Musculoskeletal diseases                     | 0.195 (0.077–0.313) | 0.001* | 0.158 (0.039 to 0.277) | 0.010* |
| Antipsychotic medicines                      | 0.187 (0.032–0.342) | 0.018* | 0.128 (−0.014 to 0.271) | 0.077 |
| Body mass index                              | 0.019 (0.009–0.029) | <0.001* | 0.012 (0.001 to 0.022) | 0.030* |
| PTSD current                                 | 0.019 (−0.103 to 0.142) | 0.754 | 0.040 (−0.076 to 0.156) | 0.493 |

PTSD, post-traumatic stress disorder diagnosis; CI, confidence interval. Model $R^2 = 0.306$; Constant $B = −0.213$, (−0.588 to 0.162, $p = 0.263$). * $p ≤ 0.05$. 

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Cytokines in Trauma Patients: Somatic Factors or PTSD Diagnosis?

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In the adjusted model, age and use of antipsychotic medication no longer had a significant independent effect on IL-6. The independent effects of smoking ($B = 0.16, p = 0.01$), lung diseases ($B = 0.14, p = 0.02$), musculoskeletal diseases ($B = 0.16, p = 0.01$), and BMI ($B = 0.01, p = 0.03$) were relatively constant. The model fit increased to $R^2 = 0.31$. The B coefficients and confidence intervals are summarized in Table 6 below.

**Discussion**

**Variable Selection**

In our sample, we found that IL-6 correlated with the highest number of risk factors from the preliminary analyses. This is also the cytokine with the most robust findings in PTSD research [71]. TNF, IL-1β and IL-2, and PTSD have been frequently researched, but findings have been somewhat mixed, particularly in subgroup analysis and where other risk factors are adjusted for [44]. There are quite a few studies on IL-2 and PTSD, and some have reported higher levels [53]. Meanwhile, others have reported lower levels [72].

IL-1RA and IL-2RA have been much less researched. One study found that elevated IL-1RA levels in PTSD patients persisted even after PTSD symptoms had subsided, and that it took a whole year before IL-1RA was normalized [73]. We have not found any published studies on IL-2RA in PTSD patients, so these new findings warrant further study.

We had many different and detailed measures of MetS and related factors, which normally is an advantage. This can also be a challenge in the selection of which variables to include in the analysis. Many of the MetS variables are strongly related and correlated with each other, and there is a high risk of collinearity in a regression analysis. In our study, we had information about BMI (height and weight), waist and hip circumferences (and the ratio), and blood pressure; triglycerides and cholesterol (total, LDL, HDL and ratio), fasting glucose, HbA1C, C-peptide, and leptin. Out of all of these, BMI clearly correlated with most of the cytokines and the other factors. We therefore used BMI as a substrate for MetS and related factors. This is in line with existing literature, where BMI has been shown to have a particularly strong correlation with elevated levels of inflammatory cytokines [74]. Choosing only BMI also reduces the risk of collinearity in the adjusted model.

In our analyses, we found no correlations between depression and anxiety diagnosis or alcohol and drug (ab) use and any of the cytokine levels. Depression has previously been found to have a particularly strong correlation with increased IL-1β and IL-6 [75, 76], so this is surprising. It could be that our study population was relatively smaller and had many other risk factors that overshadowed a possible effect of depression on cytokines.

When evaluating anxiety disorders and inflammation, the current knowledge on cytokines is not as clear. A large study from the Netherlands compared people with anxiety disorder with controls and adjusted for certain risk factors found, for instance, increased cytokine levels only among men [77].

Cytokines and alcohol use is less studied, but a recent meta-analysis that included 17 studies found increased inflammatory cytokines in patients with alcohol use disorder [78]. The most pronounced difference was in the withdrawal state or in daily heavy drinking. Patients with AUDIT scores over 20 were excluded from this study. This may explain why we did not find any effect of AUDIT scores and cytokine levels. Furthermore, our participants had overall low scores on AUDIT (mean score 5).

The effect of drug abuse on cytokine levels is less studied and mostly based on animal and smaller human studies [79]. Current findings are somewhat similar to those in alcohol use, but some types of drugs such as opioids and cannabinoids may have more pronounced anti-inflammatory than proinflammatory effects. In human studies, these effects are mainly seen in one-time high doses, but daily heavy use over time may also elicit these changes. In our study, the use of illicit drugs was uncommon with an average DUDIT score of less than 2. Furthermore, those with DUDIT scores over 25 were excluded. This may explain why we did not find any effect on the cytokines we measured.

Both the use of antidepressants and antihistamines has been shown to have anti-inflammatory effects [80, 81]. Whether this is mediated through normalization of cytokines or through cellular or other mechanisms is not known. In the case of antidepressants, there are some, mostly pre-clinical, studies showing normalization of cytokine levels [82]. There are much fewer studies on the effect of antihistamines on cytokine levels, but the COVID-19 pandemic has caused a renewed interest in the anti-inflammatory effects of antihistamines with some small human studies indicating normalization of some cytokines [83, 84]. In our sample, we did not find significant effects on these medication classes on cytokine levels. It could be that if there is an effect, it is relatively smaller than those of other factors, such as BMI, and therefore, not visible in our analyses.
Correlation between Risk Factors

Many studies have shown strong correlations between pain syndromes and PTSD. One large study found, however, that only 4% of those with comorbid fibromyalgia and PTSD got both within a year after the major traumatic event [85]. In our study, PTSD was negatively correlated with self-reported musculoskeletal diseases. Within a population of mental health patients, pain syndromes, and PTSD may be distinctly different distress reactions to trauma. A review paper from 2015 also supports this theory [86].

The other significant correlations between risk factors were mostly in line with established consensus. For instance, increased BMI was associated PTSD and musculoskeletal disease [87], and smoking was associated with antipsychotic use [88]. We had expected to find that current smoking was associated with lung disease but we did not. It could be that some of those with lung diseases have stopped smoking or do not smoke since they have asthma, as we had grouped all lung diseases together.

The probable causal direction between these risk factors is in many cases established as given, such as those smoking and lung disease among men. Others, such as how obesity and antipsychotic medication use both may cause more smoking and lung disease are based on theories from recent research [87, 88]. Furthermore, we believe that there may be a bidirectional relationship between obesity and musculoskeletal disorders. Being overweight may lead to more inactivity and in turn more pain. Musculoskeletal pain may also lead to more inactivity and weight gain. In the current literature, both a PTSD diagnosis and musculoskeletal pain syndromes are often considered to cause weight gain on the group level. More recently, it has been suggested that there could be bidirectional effects here as well [89]. We have summarized our suggestions about possible directional effects between the associated risk factors in Figure 1 below.

The directional relationship between these risk factors and inflammation measured by cytokine levels has historically been considered unidirectional; metabolic changes can cause inflammation. Recently, there have been some studies suggesting that there also may be bidirectional potentiating effects of chronic systemic low-grade inflammation on some of the risk factors [90]. Except for musculoskeletal disease and BMI, we did not consider this in our analysis.

Interleukin-1 Receptor Antagonist

Endogenous IL-1RA is an anti-inflammatory cytokine often co-released with IL-1α, IL-1β, and interleukin 33 (IL-33) to modulate their inflammatory effects [91]. All these are often released concordant with activation of the sympathetic central nervous system [92]. IL-1 is a potent proinflammatory cytokine that is often considered as an "orchestrator of leukocyte inter-communication," and the antagonist receptor has been a target for rheumatological treatment [93]. We did not find elevated levels of IL-1β in any of the comparison groups. IL-1β is a potent inflammatory cytokine and may have a significant inflammatory effect at low levels and small increases. Since it was correlated with IL-1RA, this could represent activation of the IL-1 system.

Another Norwegian study found that IL-1RA was still elevated after successful treatment of PTSD, where the participants still had sub-diagnostic distress levels [94]. We found that Log_{10} IL-1RA was affected by BMI and musculoskeletal diseases in the combined model. Increased IL-1RA has been strongly associated with obesity in other studies [95]. Together this supports the hypothesis that distress after trauma causes elevated cytokines through cardiometabolic factors (mainly overweight) and not the PTSD diagnosis alone.

Interleukin-2 Receptor Antagonist

IL-2 has both pro- and anti-inflammatory effects depending on the cell type and setting it interacts in [96]. Furthermore, the IL-2 receptor can both activate and inhibit IL-2 function. The IL-2 system seems to be important in maintenance and tolerance in long-term immune activation. It might therefore not be surprising that many studies collectively point to IL-2 elevation in PTSD patients compared with healthy controls [53]. This meta-analysis did find that in the subgroup using psychotropic medication (all types combined in one factor), there no longer was an elevation of IL-2.

We have not found any previous publications of IL-2RA in PTSD/trauma patients, but it has recently been named an important molecule in precision medicine for the future [96]. We found negative correlations with musculoskeletal disease and PTSD diagnosis, while the BMI had a positive effect on IL-2RA in the adjusted analysis. The conflicting directions of these findings might be due to the complicated nature of the IL-2 system, where the same molecule can be both pro- and anti-inflammatory depending on the cell type and setting.

Interleukin-6

IL-6 is considered both a proinflammatory cytokine and an anti-inflammatory myokine (cytokine in muscle tissue). It plays an important role in both the innate and
adaptive immune responses against a wide variety of infections and is important for a quick and effective immune response [97]. It stimulates the liver to produce acute phase proteins, and we found a correlation with CRP as expected. If the inflammatory changes seen in traumatic events and PTSD is an adaptive mechanism to protect against possible infections after tissue damage, this might be the reason why this cytokine has so robust findings in PTSD patients.

We found that smoking, lung and musculoskeletal disease, and BMI affected IL-6 but not a PTSD diagnosis in an adjusted model. A somewhat similar study on war veterans who had experienced severe traumatic events with and without PTSD did, however, find that IL-6 was elevated in PTSD patients after adjusting for age, BMI, smoking, somatic comorbidity, and medications [55]. In our study, the comparison group was with trauma patients with distress and mental health symptoms to a degree where they were referred to, and accepted at, a second-line mental health clinic. In the veteran study, the controls were recruited through advertisements and veterans’ organizations [98]. Furthermore, the veteran study did not find that.

The degree of PTSD symptoms affected cytokine levels. It could therefore be that it is the trauma-induced distress, regardless of PTSD diagnosis and severity of symptoms, that most strongly predicts inflammation and increased cytokine levels. Meanwhile, people who have experienced severe trauma without significant long-term distress might not have the same altered immune response.

**Conclusion**

In a study population of patients who had experienced severe trauma and were referred to a second line mental health center, they had elevated pro- and reduced anti-

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**Fig. 1.** Suggested directional causation between selected risk factors for inflammation in a group of 109 patients with and without PTSD from Pearson correlations. Solid arrow: 1-tailed \( p \leq 0.05 \). Dotted arrow: 1-tailed \( p \leq 0.10 \).
inflammatory cytokine levels compared to healthy controls. This supports previous findings of an inflammatory response in these patients. When comparing the patients with and without PTSD, PTSD diagnosis was only weakly, negatively associated with the anti-inflammatory marker IL-2RA in the adjusted model. Otherwise, there were no signals in any other correlation to indicate a significant effect of the trauma diagnosis on cytokine levels. The IL-2RA findings are novel and warrant further studies on this cytokine in trauma and PTSD patients.

When trauma patients experience distress to a degree that they require attention in a second line mental health clinic, they may have co-occurring systemic low-grade inflammation. This may mostly be due to cardiometabolic and other risk factors associated with chronic stress, while the PTSD diagnosis itself may be less important. Increased BMI and musculoskeletal disease seem to be the most important risk factors affecting many cytokines after adjusting for other risk factors.

This supports a hypothesis that chronic stress after trauma may be correlated with a wide range of metabolic changes with comorbid low-grade inflammation. Whether a threshold for PTSD diagnosis is met, or not, may be less important in this respect. All trauma-affected individuals with chronic distress, both with and without PTSD diagnosis, should be screened for cardiometabolic risk factors. Any somatic conditions that co-occur should be addressed appropriately if present. This may reduce chronic inflammation and in turn reduce the risk of cardiovascular events and improve life expectancy in the long term.

**Strengths and Limitations**

The main strengths of this study are the rigorous and detailed biopsychosocial examinations of the participants; we have a lot of data on them and few missing values. This can also be a limitation because of the problem of multiple comparisons and type 1 errors. The Bonferroni corrections for this can often be too conservative, particularly since so many of our variables are related to and affect each other. This can again risk issues with multicollinearity in regression analysis.

Furthermore, it may be a strength that we used a clinically distressed trauma-affected group without PTSD for comparison, while most other studies use healthy controls or controls who have experienced trauma but are not necessarily experiencing stress at the assessment point. This may give a clearer picture of the effect of the PTSD diagnosis alone.

Some of the variables, such as somatic disease, were mostly based on self-report, so this is a potential weakness. Some of these categories are wide and can represent many different entities. For instance, the self-reported musculoskeletal disorders can represent anything from arthritis, to diagnosed fibromyalgia, and to undiagnosed pain syndromes.

The healthy control group may pose additional limitations. We had much less data on this group, including whether they had suffered major trauma. They were only used for the initial, preliminary analysis, however, so it should not affect our main analysis.

Cytokine levels have high levels of uncertainty because these are affected by many things, and can fluctuate from day to day. One study found altered overnight levels of cytokines in men and women with PTSD [99]. They propose that cytokine levels may rapidly change due to sex, sleep, and time of day, among other things. As discussed earlier, directionality is a major issue affecting most of the risk factors, PTSD diagnosis, and cytokine levels. In the real world there may be alternating, multifactorial, and multidirectional effects between all of these. It is probably impossible to give definitive answers on causal relationships in these kinds of studies. For instance, there may be similar genetic dispositions for PTSD and atherosclerosis, as is seen in a few other mental health disorders [100]. Large longitudinal or randomized studies are difficult or impossible to address these research questions. Recent introductions of artificial intelligence show promising results in untangling the causes and effects of trauma and PTSD [101].

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**Statement of Ethics**

This study was approved by the Regional Ethical Committee in South-Eastern Norway (approval no. 2015/2081/REK-A) and Oslo University Hospital’s privacy officer. All participants were thoroughly informed before signing a written consent.
Conflict of Interest Statement

The authors reported no conflicts of interest. The authors alone are responsible for the content and writing.

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Author Contributions

Erik Ganesh Iyer Søegaard contributed to conceiving the study, collecting and analyzing the data, drafting the manuscript, and a major revision after review. Zhanna Kan contributed to analyzing the data and drafting the manuscript. Hans Christian Dalsbotten Aass contributed by running the cytokine analyses and providing critical feedback on the manuscript. Rishav Koirala provided critical feedback on the manuscript. Edvard Hauff contributed in conceiving the study, collecting the data, and drafting and reviewing the manuscript.

Data Availability Statement

The raw data of this study are openly available in Figshare at https://doi.org/10.6084/m9.figshare.19758661.v1.

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