See commentary by Shale



# The Implication of Combat Stress and PTSD Trajectories in Metabolic Syndrome and Elevated C-Reactive Protein Levels: A Longitudinal Study

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## ABSTRACT

***Objective:*** This study sheds light on the importance of long-term follow-up of trauma survivors, posttraumatic stress disorder (PTSD) trajectories, and early detection of health risk factors in trauma survivors. The present study prospectively assessed the following over 23 years: (1) the association of psychological and physiologic stress during captivity with elevated C-reactive protein (CRP) levels and metabolic syndrome (MetS), which includes hypertension; elevated levels of insulin, triglycerides, and fasting glucose; decreased levels of high-density lipoprotein cholesterol; and obesity and (2) the implication of PTSD trajectories in elevated CRP levels and MetS.

***Methods:*** Measurements were taken in 1991, 2003, 2008, and 2015. Participants were 116 Israeli combat veterans of the 1973 Yom Kippur War (of these, 101 were former prisoners of war [ex-POWs] and 15 were comparable controls). The medical assessments relevant for this study were body mass index, fasting blood glucose levels, and diabetes, blood pressure or a diagnosis of hypertension, high-density lipoprotein cholesterol and triglyceride levels, and medication intake. In addition, the PTSD Inventory was used to assess PTSD symptoms and trajectories over time according to *DSM-IV-TR* PTSD criteria.

***Results:*** Captivity—in particular, the captivity stressors of weight loss, physical suffering, psychological suffering, and humiliation—was implicated in both elevated CRP levels and MetS, significantly so with elevated CRP levels ($P = .01$, $R^2 = 0.33$). Captivity-induced PTSD, in particular chronic and delayed PTSD trajectories, was associated with elevated CRP levels and MetS, significantly so for MetS ($P = .05$).

***Conclusions:*** Monitoring inflammation using markers like CRP level in trauma survivors can be beneficial, particularly if PTSD is chronic or delayed. Clinicians treating trauma survivors should raise awareness of the importance of such measures in light of long-term health vulnerabilities.

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Traumatic stress has consistently been associated with an increased risk for multiple somatic and psychological comorbidities, including posttraumatic stress disorder (PTSD),[1] inflammation-related autoimmune diseases,[2–4] cardiovascular morbidity,[5,6] and mortality.[7,8] One of the most severe intentional man-made traumas is war captivity, which often entails psychological and physical torture alongside deprivation of basic needs. Research has implicated captivity in both psychiatric disorder (ie, PTSD) and cardiovascular disease (CVD) as well as in premature mortality.[9–13]

PTSD is the most common and conspicuous psychiatric disorder arising after trauma, is highly comorbid,[14–16] and is highly associated with poor health[17–19] and physiologic manifestations. Prospective studies have documented an increased risk of CVD in persons with PTSD,[20–22] and several models have attempted to explain the underlying mechanisms linking traumatic stress and disease.[23–25] One potential biological mechanism is the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis leading to reduced levels of glucocorticoids and chronic inflammation (indexed by blood levels of proinflammatory cytokines and factors such as C-reactive protein [CRP]).[26–28] Another related mechanism leads from stress to the development of the metabolic syndrome (MetS), a combination of metabolic disorders including hypertension, insulin resistance, low levels of high-density lipoprotein cholesterol (HDL-C), elevated triglyceride levels, impaired fasting glucose, and obesity.[29] MetS significantly increases the risk for CVD, stroke, and diabetes.[30,31]

Regarding CRP, research has yielded inconsistent results. While some studies (eg, references [32–35]) found that PTSD was associated with elevated CRP levels, other studies found no such relation[36,37] or reduced levels.[38,39] The current study's primary aim is to cast further light on this unresolved issue and assess the implications of captivity and PTSD for CRP levels and MetS prevalence.

Moreover, previous studies were cross-sectional. Hence, it is unknown if PTSD is due to biological predispositions[40] or if PTSD leads to neuroendocrine changes that increase inflammation and CRP levels.[24] A recent prospective study[41] assessing the baseline levels of CRP in Marines suggested that a predeployment state of high inflammation may lead to heightened PTSD symptoms. This important study is based on a relatively short-term 7-month follow-up. Given that physiologic changes often develop over a longer period of time and that PTSD symptoms wax and wane, there is clearly a need to assess the interrelationships of PTSD and CRP levels over a longer time period, as proposed in the present study.

**Clinical Points**

- Due to a lack of long-term longitudinal prospective data, outcomes of psychological trauma and the association with physiologic biomarkers are not well understood.
- Identification of physiologic biomarker precursors that result from prolonged psychological stress allows for possible prevention of negative outcomes.

MetS, like elevated CRP levels, is associated with increased risk for CVD and has also been suggested to play a role in the interaction between traumatic stress reactions and disease.[17,42] For example, a study[43] of US Army personnel found that PTSD severity was associated with MetS. To the best of our knowledge, no study has longitudinally assessed the implication of captivity-induced stress and, more importantly, PTSD trajectories over several decades.

PTSD trajectories have been shown to impact trauma survivors.[44] In general, 4 main trajectories have been identified: chronic, delayed, recovery, and resilient. However, the implications of CRP levels and MetS for PTSD over time are still not fully understood. The increase in CRP levels is evident years after the trauma, as reported in findings concerning adults who survived childhood trauma.[45,46] Hence, this leads to the question of the impact of PTSD trajectories on the presence of elevated CRP levels and MetS over time.

The present study prospectively assesses, during a 24-year span, (1) the association between psychological and physiologic stress in captivity with CRP levels and MetS and (2) the implication of PTSD trajectories for elevated CRP levels and MetS in former prisoners of war (ex-POWs) at 4 time points—18, 30, 35, and 42 years after the end of the war (ie, T1, T2, T3, and T4).

## METHODS

### Participants

This study is part of a larger prospective longitudinal study of Israeli veterans from the unique 1973 Yom Kippur War[47] (for details, see Dekel et al[48]). Comprehensive medical assessments and questionnaires were completed with 116 randomly selected combat veterans (101 were ex-POWs and 15 were comparable combat veterans) (for further details see Solomon et al[49]). Control veterans participated in the same war and were in combat in the same units as the ex-POWs, but were not taken captive and were matched on military background and sociodemographic status. None of the controls endorsed PTSD. Groups did not differ in regard to the number of negative life events since the war ($t_{66} = 1.76$ $P = .09$).

Participants attended the Tel Aviv Sourasky Medical Center for a comprehensive physical and filled out questionnaires, after receiving an explanation of the study and signing an informed consent form. This study was approved by the ethics committee of the Sourasky Medical Centre.

### Measures

***Captivity suffering.*** Captivity suffering was assessed in the initial study measurements (1991) via self-reports of weight loss, physical suffering, and psychological suffering in captivity, each on a scale of 1 (I did not suffer at all) to 5 (I suffered very much).

***Depression subscale of the Symptom Checklist-90.*** Based on the norms for psychiatric outpatients,[50] scores above 0.73 for each subscale of the Symptom Checklist-90 (SCL-90), including the depression subscale, were considered to be an indication for depression. A Cronbach α of 0.92 indicated considerable reliability.

***PTSD Inventory.*** The PTSD Inventory (PTSD-I)[51] was used to assess PTSD symptoms. Participants indicated the frequency of items, scored on a 4-point Likert scale, from 1 (least) to 4 (greatest). Responses of 3 or 4 were considered symptom endorsement. For each participant, the number of symptoms endorsed was calculated at each time point. In accordance to the *DSM-IV*[52] symptom clusters, we classified individuals as endorsing probable PTSD if they had at least 1 intrusion symptom and 3 avoidance and 2 hyperarousal symptoms and met functional criteria. The PTSD-I has strong reliability and convergent validity when compared to structured clinical interviews[51] and is a well-validated screening tool with high internal consistency. In the current study, the internal consistency was high at T1, T2, T3, and T4 ($\alpha = 0.95$, $\alpha = 0.92$, $\alpha = 0.93$, and $\alpha = 0.9$, respectively). Participants were considered to have PTSD if they met *DSM-IV-TR* criteria.[52]

Four PTSD trajectories were determined based on reports from the 3 waves of assessment: (1) chronic—symptoms reported at all 4 waves of measurement; (2) delayed—onset at any point after a period without PTSD symptoms; (3) recovery—remission of symptoms; and (4) resilient—no report of symptoms at any of the measurements.

### Metabolic Syndrome and Components

Among other examinations, measurements relevant to this study were body mass index, fasting blood glucose and diabetes, blood pressure or a diagnosis of hypertension, and HDL-C and triglyceride levels. Medication intake was also recorded.

MetS and its components were defined as having at least 3 of the following characteristics: serum triglycerides ≥ 1.7 mmol/L (150 mg/dL); serum HDL-C < 1.036 mmol/L (40 mg/dL); blood pressure ≥ 130/85 mm Hg or taking antihypertensive medication; BMI > 30 kg/m$^2$; and fasting serum glucose ≥ 5.6 mmol/L (100 mg/dL) or a diagnosis of diabetes.[53,54]

### Blood Samples

Blood samples were obtained after a fast of at least 8 hours at 8:00 AM. Venous blood was obtained from all participants from the antecubital vein. White blood cell count and differential were performed using the Coulter STKS (Beckman Coulter, Nyon, Switzerland) electronic analyzer, and wide-range CRP level was determined by the Bayer wr-CRP assay (Bayer, Leverkusen, Germany).[55]

### Analytic Strategy

First, groups of ex-POWs and controls were compared on the MetS components, blood CRP level, and other inflammation measures. All of the measures were standardized to norms. We calculated the odds ratio for the ex-POWs versus controls. Next, we focused on the ex-POW group only and assessed whether PTSD over time is related to elevated CRP level and MetS, controlling for captivity stressors and depression at T1. As MetS comprises 5 factors, we conducted a final analysis with the same regression for the 5 components as outcomes.

**Table 1. Rates of MetS, Elevated C-Reactive Protein Concentrations, and Inflammation Indicators Above Reference Levels for Ex-POWs and Controls[a]**

| Outcome Variable | Ex-POWs (n = 101) | Controls (n = 15) | Risk Ratio | 95% CI |
|---|---|---|---|---|
| MetS | 38 (38) | 2 (13.3) | 2.85 | 0.54 to 11.9 |
| BMI, kg/m$^2$ | | | 1.12 (for ≥ 30) | 0.37 to 3.7 |
| 0–24.9 | 15 (15) | 1 (6.7) | | |
| 25–29.9 | 48 (48) | 9 (60) | | |
| ≥ 30 | 37 (37) | 5 (33.3) | | |
| Concentration outside of reference levels[b] | | | | |
| Blood pressure[c] | 39 (40.2) | 1 (6.7) | 6.66 | 3.1 to 9.51 |
| Triglycerides[d] | 34 (34) | 5 (33.3) | 1.02 | 0.35 to 3.99 |
| HDL cholesterol[e] | 21 (21) | 2 (13.3) | 1.61 | 0.26 to 2.29 |
| Fasting blood glucose[f] | 26 (26) | 2 (14) | 3.9 | 0.85 to 18.6 |
| Blood CRP (> 3 mg/L) | 28 (28) | 2 (13.3) | 2.00 | 0.54 to 11.9 |
| Hemoglobin (> 17 g/dL) | 10 (10) | 0 (0) | … | |
| Hematocrit (> 49%) | 13 (13) | 1 (7) | 1.85 | 0.8 to 2.9 |
| Thrombocytes[g] | 11 (11) | 1 (7) | 1.57 | 0.9 to 2.1 |
| Neutrophils[h] | 13 (13) | 1 (7) | 1.85 | 0.7 to 3.1 |
| Lymphocytes[i] | 16 (16) | 2 (15) | 1.06 | 0.4 to 1.66 |
| Monocytes[j] | 2 (2) | 1 (7) | 0.28 | –0.5 to 1.2 |

[a]Values shown as n (%) unless otherwise noted.
[b]Levels are serum concentrations unless otherwise noted.
*Reference levels:*
[c]≥ 130/85 mm Hg.
[d]≥ 1.7 mmol/L (150 mg/dL).
[e]< 1.036 mmol/L (40 mg/dL).
[f]≥ 5.6 mmol/L (100 mg/dL).
[g]> $450 \times 10^9$ cells/L.
[h]> $6 \times 10^9$ cells/L.
[i]> $3 \times 10^9$ cells/L.
[j]> $1.3 \times 10^9$ cells/L.
Abbreviations: BMI = body mass index, CRP = C-reactive protein, ex-POWs = former prisoners of war, HDL = high-density lipoprotein, MetS = metabolic syndrome.
Symbol: … = not applicable.

## RESULTS

### Ex-POWs and Controls MetS and CRP

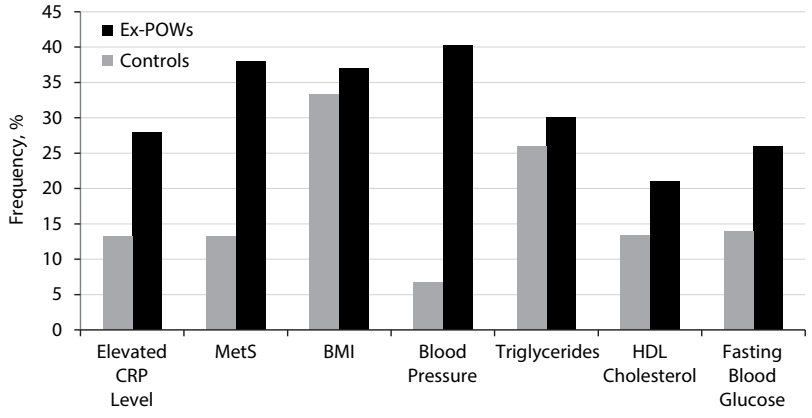
Rates of MetS and elevated CRP in ex-POWs and control veterans are presented in Table 1 and Figure 1. Thirty-eight ex-POWs (38%) were identified as having MetS compared to only 2 (13%) of the control veterans. Ex-POWs had a 2.85-fold higher risk to meet criteria for MetS compared to controls. Examining each MetS component revealed that 39 (40.2%) of ex-POWs met criteria for abnormally high blood pressure (> 130/85 mm Hg) compared to only 1 (6.7%) control. Ex-POWs had a greater risk for abnormally high blood pressure (6.66 times more) and glucose levels (> 99 mg/dL) (3.9 times more). However, ex-POWs had a greater protective factor of HDL-C compared to controls (1.61 times more). For BMI and triglycerides, the risk ratios were close to 1, suggesting that the groups did not differ in these parameters. (The mean of the continuous variable of BMI was 29.2 kg/m$^2$ with standard deviation of 6.09.)

Regarding inflammation indicators, ex-POWs had a higher risk (1.87 times more) for abnormally high levels of CRP (> 3.0 mg/L) compared to controls. Ex-POWs were more prone to have levels of hematocrit (45%–52%) (1.85 times), neutrophils (> $6 \times 10^9$ cells/L) (1.85 times), and thrombocytes (> $450 \times 10^9$ cells/L) (1.57 times) outside of the reference ranges compared to veterans, controlling for smoking status (see Table 1).

### PTSD

Due to the small number of controls, the following analyses assessing the correlation between PTSD and biomarkers focused solely on the ex-POW sample. Current PTSD total symptom scores indicated that 54 ex-POWs (54%) met *DSM-IV* criteria for probable PTSD.

**Figure 1. Frequency of Elevated CRP Level and MetS Components for Ex-POWs and Controls**




Abbreviations: BMI = body mass index, CRP = C-reactive protein, ex-POWs = former prisoners of war, HDL = high-density lipoprotein, MetS = metabolic syndrome.

### PTSD Trajectories

In order to examine whether ex-POWs had resilient, delayed, or chronic PTSD (only 1 veteran was defined as recovered, and hence this category was omitted from the analysis), two 1-way analyses of variance were conducted. Results indicated high CRP levels in ex-POWs with delayed and chronic PTSD compared to resilient ex-POWs. Higher rates of MetS were found in ex-POWs with chronic PTSD compared to resilient ex-POWs. No difference was found for MetS rates between those with delayed and resilient PTSD. Although not significant, it is substantial that ex-POWs with chronic PTSD had higher rates of elevated CRP and MetS compared to ex-POWs with resilient PTSD (see Table 2).

### Associations for CRP and MetS

To test the hypothesis that captivity stressors (ie, weight loss, physical suffering, and psychological suffering) would be significantly associated with elevated CRP levels, hierarchical linear regression was used to assess elevated CRP level, with captivity stressors entered as explanatory variables (step 1). To examine whether depression contributed to elevated CRP levels above and beyond captivity stressors, T1 clinical depression was inserted into the regression in step 2 as a dummy variable (1 for clinical depression and 0 for no clinical depression). More importantly, we aimed to assess whether PTSD trajectories would contribute to elevated CRP levels above and beyond the effects of captivity stressors and T1 depression on CRP. For this purpose, the PTSD trajectory variable was entered in step 3 as a dummy variable (1 for chronic and delayed and 0 for resilient). The model was significant with 33% variance explained ($F_{5,38} = 3.58$, $P = .01$, $R^2 = 0.33$), with a significant $R^2$ change of 8% ($P = .04$).

In the final step, physical suffering contributed to elevated levels of CRP, and higher CRP levels were found in ex-POWs with clinical depression. Importantly, PTSD trajectories were associated with elevated CRP levels above and beyond the effects of captivity stressors and depression on CRP (Table 3). The chronic and delayed groups had higher CRP levels than resilient ex-POWs.

Applying this analysis to infer MetS (see Table 4) yielded a nonsignificant model ($F_{5,38} = 1.09$, $P = .38$, $R^2 = 0.13$), explaining only 13% of variance. The $R^2$ change was 1% and not significant ($P = .72$). We then recalculated the regression based on the MetS components. According to the results, no significant models were found for glucose levels ($F_{5,37} = 1.75$, $P = .15$, $R^2 = 0.19$), blood pressure ($F_{5,37} = 0.61$, $P = .7$, $R^2 = 0.07$), HDL-C levels ($F_{5,37} = 0.52$, $P = .86$, $R^2 = 0.08$), and BMI ($F_{5,37} = 0.77$, $P = .6$, $R^2 = 0.06$). The only significant model was observed for triglycerides ($F_{5,37} = 3.43$, $P = .01$, $R^2 = 0.32$). In this model, the final step showed the one significant component to be psychological suffering (B = 22.9, SE = 8.5, $P = .01$). Neither the added variance of depression in the second step ($R^2$ change of 0.02, $P = .27$) nor the added variance of PTSD trajectories in step 3 ($R^2$ change of 0.02, $P = .35$) was significant.

**Table 2. Descriptive Statistics and Zero-Order Correlations Between All Study Variables[a]**

| Outcome Variable | Resilient (n = 31) | Delayed (n = 23) | Chronic (n = 3) | $F_{2,54}$ | *P* Value |
|---|---|---|---|---|---|
| Blood CRP level, mg/L | 2.7 (3.1) | 4.8 (5.4) | 6.9 (2.8) | 2.55 | .06 |
| MetS, no. of criteria met | 1.9 (1.25) | 2.3 (1.2) | 3.67 (0.5) | 2.88 | .05 |

[a]Values shown as mean (SD) unless otherwise noted.
Abbreviations: CRP = C-reactive protein, MetS = metabolic syndrome.

**Table 3. Regression Models of the Association of Elevated C-Reactive Protein Levels With PTSD Trajectories and Captivity Stressors**

| Model Predicting Elevated CRP Level | Variable[a] | B | SE | $R^2$ | $R^2\Lambda$ |
|---|---|---|---|---|---|
| Model 1 | Loss of weight (in pounds) | 0.00 | 0.02 | 0.09 | 0.09 |
| | Physical suffering | 1.28 | 0.73 | | |
| | Psychological suffering | 0.06 | 0.68 | | |
| Model 2 | Loss of weight (in pounds) | 0.00 | 0.02 | | |
| | Physical suffering | 1.76 | 0.69 | 0.25 | 0.16 |
| | Psychological suffering | –0.28 | 0.63 | | |
| | Depression at T1 (1 = clinical depression) | 4.52 | 1.58 | | |
| Model 3 | Loss of weight (in pounds) | –0.01 | 0.02 | 0.33 | 0.08 |
| | Physical suffering | 1.74 | 0.67 | | |
| | Psychological suffering | –0.16 | 0.62 | | |
| | Depression at T1 (1 = clinical depression) | 3.85 | 1.55 | | |
| | Trajectories (chronic and delayed vs resilient) | 2.71 | 1.3 | | |

[a]The clinical depression variable was inserted also as a dummy variable (1 for clinical depression and 0 for no depression). The PTSD trajectories variable was inserted into the regression as a dummy variable (1 for chronic and delayed PTSD and 0 for resilient PTSD).
Abbreviations: CRP = C-reactive protein, PTSD = posttraumatic stress disorder, T1 = time point 1.
Symbol: $R^2\Lambda = R^2$ change.

**Table 4. Regression Models of the Association of Metabolic Syndrome With PTSD Trajectories and Captivity Stressors**

| Predicting CRP | Variable[a] | B | SE | $R^2$ | $R^2\Lambda$ |
|---|---|---|---|---|---|
| Model 1 | Loss of weight (in pounds) | 0.00 | 0.01 | 0.04 | 0.04 |
| | Physical suffering | –0.2 | 0.22 | | |
| | Psychological suffering | 0.1 | 0.2 | | |
| Model 2 | Loss of weight (in pounds) | 0.00 | 0.01 | | |
| | Physical suffering | –0.1 | 0.21 | 0.12 | 0.08 |
| | Psychological suffering | 0.12 | 0.2 | | |
| | Depression at T1 (1 = clinical depression) | 0.94 | 0.5 | | |
| Model 3 | Loss of weight (in pounds) | 0.00 | 0.01 | 0.13 | 0.00 |
| | Physical suffering | –0.1 | 0.22 | | |
| | Psychological suffering | 0.13 | 0.2 | | |
| | Depression at T1 (1 = clinical depression) | 0.91 | 0.51 | | |
| | Trajectories (chronic and delayed vs resilient) | 0.15 | 0.42 | | |

[a]The clinical depression variable was inserted also as a dummy variable (1 for clinical depression and 0 for no depression). The PTSD trajectories variable was inserted into the regression as a dummy variable (1 for chronic and delayed PTSD and 0 for resilient PTSD).
Abbreviations: CRP = C-reactive protein, PTSD = posttraumatic stress disorder, T1 = time point 1.
Symbol: $R^2\Lambda = R^2$ change.

## DISCUSSION

Results indicated that ex-POWs, held captive more than 40 years ago, were almost 3 times more likely to develop MetS than controls who underwent combat but were not taken captive. Furthermore, inflammation levels, quantified as blood levels of CRP, were abnormally high in a large percentage of ex-POWs and were related to the level of physical and psychological stressors experienced during captivity. The unique cohort in this study allowed examination of the impact of longitudinal PTSD trajectories on inflammation levels, with findings of higher levels of CRP in ex-POWs with chronic and delayed PTSD, compared to controls.

Biological effects of severe trauma reveal short- and long-term changes in 2 hormonal systems: the HPA axis and sympatho-adrenomedullary (SAM) system.

Both are important in regulating the body's stress response, employing glucocorticoids and catecholamines as "stress hormones."[19,56] The short-term effects of the stress response represent efficient survival-promoting reactions, recruiting multiple systems, including metabolic, cardiovascular, and immune systems, to mobilize fight-or-flight responses. Coordination of these responses requires the brain's evaluation of threat and execution of physiologic responses.

While efficient in the short term, the long-term effects of repeated or chronic stress response activation, or a failure to stop the stress response once the challenge has been surpassed, depletes the body's resources, a phenomenon termed *allostatic load*.[57] Allostatic load represents a shift from normal homeostatic ranges toward abnormal ranges, as a result of prolonged secretion of stress hormones. This physiologic burden damages coping capacity and leads to an increased risk of pathophysiology such as hypertension, CVD, and inflammatory disorders, as well as accelerated aging.[58,59] Dealing with severe prolonged trauma, such as captivity under conditions of harsh treatment and uncertainty, creates conditions of severe allostatic load, manifested years later as increased MetS and obesity (BMI > 30) in ex-POWs relative to controls. Both obesity and MetS increase inflammation and risk for disease,[60] providing evidence for increased allostatic load and a vicious cycle of stress and disease in ex-POWs.

Indeed, ex-POWs show more clinically high levels of CRP, relative to controls. CRP is a promising biomarker of inflammatory activation used regularly in clinical settings, and in prospective studies was found to be a risk factor for developing MetS, CVD, and even PTSD.[41,54,61,62] Markers of pro-inflammatory activity can be monitored by a simple blood test, enabling detection of the biological toll of chronic stress on health and well-being many years after trauma.[45]

The increased level of inflammation in ex-POWs can be explained by several nonexclusive accounts. First, levels of CRP and inflammation can be attributed to obesity[63]; as more ex-POWs suffer from increased BMI and higher fasting glucose than control veterans, this can be a correlational result. Second, inflammation is an outcome of allostatic lode; changes in the activity of the HPA and SAM systems lead to a change in the functioning of the immune system by increasing the levels of pro-inflammatory factors such as CRP.[64] Given that ex-POWs are under more strain than controls, this finding may be an indication of the bodily toll after years of chronic stress. Third, psychosocial stress has been shown to increase CRP levels, and dwelling on stressful events, as many PTSD survivors do repeatedly, has a physiologic effect on inflammation levels. For example, a recent experimental study[65] found that participants who were asked to dwell on an experimentally induced stressful event showed a rise in CRP levels in comparison to participants who were asked to think about neutral activities or pictures. Again, given that ex-POWs are under more strain and have painful memories that torment them for many years, psychological coping might partially explain the physiologic finding.

Surprisingly, our finding that ex-POWs showed higher levels of CRP is independent of a PTSD diagnosis. This is in line with some reports regarding military populations[66] but not others.[67,68] Longitudinal studies of military cohorts usually employed follow-up periods ranging from several months[69,70] to several years,[71,72] significantly less time than the 40-year period used in this study. Most often such studies have focused on pre-combat and peri-combat traumatic risk factors in an attempt to understand who will suffer from chronic PTSD. To the best of our knowledge, long-term health outcomes of combat stress have not yet been measured using a trajectory analysis. Studies that examined long-term health outcomes of ex-POWs[73,74] have found a connection between conditions during captivity and the prevalence of somatic and mental health disorders. However, these studies suffer from limitations; namely, conditions during captivity are rated many years after the fact and not, as in our cohort, within recent proximity to the trauma. Additionally, health status was diagnosis- and compensation-based and, unlike the current report, did not include blood-based clinical measurements.

In the current study, we used longitudinal data, accumulated over 40 years of follow-up, and 4 previously identified long-term PTSD trajectories of resilient, recovery, delayed, and chronic[75] to examine whether trajectories convey information about the long-term health costs of trauma. While we found that trauma characteristics are significantly associated with increased levels of CRP regardless of PTSD, adding the PTSD trajectory to the regression model increased the explained variance almost 2-fold, to 32%. We therefore conclude that the course of PTSD over time is very informative when considering the consequences of trauma on health and well-being. Specifically, we found that chronic and delayed PTSD trajectories increased the inflammation level and, as a consequence, increased the risk of developing inflammation-related diseases, such as autoimmune disease, diabetes, CVD, and Alzheimer's disease.

The current study suffers from several limitations. While this study is indeed a prospective longitudinal study, the assessment of trauma exposure was done retrospectively and may therefore be influenced by memory recall. Moreover, we did not have clinical data for a sufficient number of control participants, as the many years since the war made it difficult to maintain contact; this limits the possible interpretation of the findings. Furthermore, the study was done among an aging population, who are in a higher risk period for PTSD and biological markers. Additionally, there was a lack of data regarding specific medication use and family history of PTSD. Generally, caution should be taken in interpreting these results. This study also lacked the analysis of specific pro-inflammatory and anti-inflammatory cytokines, which may have allowed a wider interpretation of the results, especially when coupled with a dynamic measurement of cortisol levels. Additionally, as these tests were taken during a general health survey, we did not focus specifically on immune cells. Future, more detailed studies should elucidate the role of specific cytokines in the long-term consequences

of different trajectories of PTSD and the relationship to disease for further understanding of the current findings.

This study sheds light on the importance of long-term follow-up and early detection of health risk factors in trauma survivors. Since previous studies have indicated that increased levels of CRP can be present many years before the actual disease, such as CVD and diabetes,[54,62] sets in, monitoring inflammation levels using markers like CRP in trauma survivors can be beneficial, particularly if the PTSD diagnosis is chronic or delayed. Furthermore, health behaviors such as not smoking and engaging in moderate exercise have been found to decrease CRP level,[76] suggesting that clinicians treating ex-POWs and trauma survivors will find it beneficial to raise awareness of the importance of such measures in light of long-term health vulnerabilities in these populations.

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