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Trauma, psychological distress and markers of systemic inflammation among US women: A longitudinal study

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Abstract

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Background: Prior evidence links posttraumatic stress disorder (PTSD) and depression, separately, with chronic inflammation. However, whether effects are similar across each independently or potentiated when both are present is understudied. We evaluated combined measures of PTSD and depression in relation to inflammatory biomarker concentrations.

Methods: Data are from women (n's ranging 628–2,797) in the Nurses' Health Study II. Trauma exposure, PTSD, and depression symptoms were ascertained using validated questionnaires. We examined (a) a continuous combined psychological distress score summing symptoms for PTSD and depression, and (b) a categorical cross-classified measure of trauma/PTSD symptoms/ depressed mood status (reference group: no trauma or depressed mood). Three inflammatory biomarkers (C-reactive protein [CRP], interleukin-6 [IL-6], tumor necrosis factor alpha receptor 2 [TNFR2]) were assayed from at least one of two blood samples collected 10–16 years apart. We examined associations of our exposures with levels of each biomarker concentration (log-transformed and batch-corrected) as available across the two time points (cross-sectional analyses; CRP, IL-6 and TNFR2) and with rate of change in biomarkers across time (longitudinal analyses; CRP and IL-6) using separate linear mixed effects models.

Results: In sociodemographic-adjusted models accounting for trauma exposure, a one standard deviation increase in the continuous combined psychological distress score was associated with 10.2% (95% confidence interval (CI): 5.2–15.4%) higher CRP and 1.5% (95% CI: 0.5–2.5%) higher TNFR2 concentrations cross-sectionally. For the categorical exposure, women with trauma/ PTSD symptoms/ depressed mood versus those with no trauma or depressed mood had 29.5% (95% CI: 13.3–47.9%) higher CRP and 13.1% (95% CI: 5.1–21.7%) higher IL-6 cross-sectionally. In longitudinal analysis, trauma/PTSD symptoms/depressed mood was associated with increasing CRP levels over time.

Conclusions: High psychological distress levels with trauma exposure is associated with elevated inflammation and is a potential biologic pathway by which distress can impact development of inflammatory-related chronic diseases, such as cardiovascular disease. Considering multiple forms of distress in relation to these pathways may provide greater insight into who is at risk for biologic dysregulation and later susceptibility to chronic diseases.

Keywords

Trauma; PTSD; depression; inflammation; Nurses' Health Study; psychological distress

Introduction

Traumatic life experiences are highly prevalent and often followed by psychological distress, such as posttraumatic stress disorder (PTSD) and depression (Breslau et al., 2000; O'Donnell et al., 2004). Although PTSD and depression are highly comorbid, research considering the effects of trauma and psychological distress on physical health has typically treated them as separate exposures, often pitting one against the other to see which has a larger effect. Recent evidence has shown similar physical health sequelae between PTSD and depression, such as increased risk of chronic illness including cardiovascular disease (CVD) (Cohen et al., 2015; Edmondson et al., 2013; Edmondson and von Känel, 2017; Levine et al., 2021; Li et al., 2020; Roberts et al., 2015; Sumner et al., 2015; Trudel-

Fitzgerald et al., 2016; von Känel, 2012). Greater insight might therefore be gained by conceptualizing psychological distress more broadly to examine the joint role of these two distress manifestations on health-relevant biological sequalae in the context of trauma exposure (Breslau et al., 2000; Morris et al., 2012; O'Donnell et al., 2004).

PTSD and depression have previously been linked with greater inflammation, which may be one potential mechanism linking these disorders and elevated cardiometabolic risk (Bucciarelli et al., 2020; Osimo et al., 2020; Passos et al., 2015; Yang and Jiang, 2020). For example, in one of our prior studies in a select subset of women from the Nurses' Health Study II (NHS II; n = 524), we found that those with chronic PTSD had higher levels of C-reactive protein (CRP) and tumor necrosis factor alpha receptor 2 (TNFR2) (both of which are inflammatory biomarkers), although evidence was less consistent regarding associations with rate of change over the 10–16 year study period (Sumner et al., 2017). In sensitivity analysis, we adjusted for depression, finding some attenuation of results, but did not examine the combined effects of PTSD and depression together. Other prior studies on PTSD and depression have not evaluated their combined effects on inflammation and considered effects of depression occurring with trauma (Baker et al., 2012; Bob et al., 2010; Gill et al., 2010; Osimo et al., 2020; von Känel, 2012; von Känel et al., 2010; Yang and Jiang, 2020). Whether effects of PTSD and depression on inflammation are synergistic therefore remains unclear.

Research on potential health effects of trauma suggests exposure to trauma can lead to impaired biological function and greater risk of CVD (Levine et al., 2021); however, our work on PTSD has suggested there are some effects of trauma alone, but effects are substantially more pronounced when recurring psychological distress occurs in response to trauma (Sumner et al., 2017). While PTSD is a form of distress that specifically occurs as a result of trauma (and is diagnosed only in the presence of trauma exposure), depression can also commonly occur in response to traumatic experiences, and both frequently co-occur (Breslau et al., 2000; O'Donnell et al., 2004). However, whether sequelae of depression occurring in women that also experience lifetime trauma may be similar to those of PTSD or to depression that does not occur in the context of lifetime trauma is relatively under-explored. Thus, considering multiple forms of distress in the context of trauma may provide added insight when evaluating potential effects on health-related outcomes.

Here, we considered associations of composite measures of psychological distress with three biomarkers of chronic inflammation linked with increased CVD risk: interleukin-6 (IL-6), TNFR2, and CRP (Pai et al., 2004; Ridker et al., 2000; Wirtz and von Känel, 2017). Using information on trauma exposure, PTSD, and depression, we characterized psychological distress in two ways and considered each in relation to biomarker concentrations. We first evaluated the joint impact of trauma and psychological distress - captured by deriving a score summing across both PTSD and depression symptoms (combined psychological distress score) – on each inflammatory biomarker. Building on prior work suggesting higher distress symptom scores indicate greater severity and thereby more potent effects on biological dysfunction (Almas et al., 2015; Jackson et al., 2018), we hypothesized that individuals with higher versus lower combined psychological distress scores would have elevated concentrations of each inflammatory biomarker and a faster rate of increase

in these concentrations over time, over and above potential effects of trauma. We also evaluated psychological distress using a categorical cross-classified measure of trauma/PTSD symptoms/depressed mood status by considering the combined presence/absence of these factors. We similarly hypothesized higher levels of inflammation for individuals with combined trauma exposure, PTSD symptoms and depressed mood, compared to individuals without trauma or depressed mood. Overall, we therefore examine the association of trauma and psychological distress broadly conceptualized with inflammation and separately evaluate the effects of depression occurring in the context of lifetime trauma.

Methods and Materials

Sample

Data are from the NHS II, a cohort of US female nurses (n = 116,429), aged 24–42 years at entry into the study in 1989. The study protocol was approved by the institutional review board of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, and participants' completion of questionnaires was considered implied consent. Participants reported information on sociodemographic factors, psychosocial factors, and health-related behaviors and conditions on questionnaires sent biennially. In 2008, as part of a sub-study, a subset of women were invited to complete a supplemental PTSD questionnaire including trauma and PTSD screening assessments (n = 54,703 returned). Additional protocol details for this sub-study are published elsewhere (Koenen et al., 2009).

NHS II conducted blood draws among a subset of all study participants at two time points. Briefly, women who did not report history of cancer were invited to provide a blood draw during 1996–1999 (blood draw 1); those who participated were then invited to provide another draw in 2008–2012 (blood draw 2). Using these banked blood samples, 12 sub-studies that focused on specific disease outcomes (e.g., myocardial infarction) or behaviors (e.g., diet quality) assayed inflammatory biomarkers including CRP, IL-6, and TNFR2 in select subsets of women (Bertone-Johnson et al., 2019; Huang et al., 2016). *One* of these 12 sub-studies was used for the prior investigations of PTSD and inflammation among a maximum of 525 women in this cohort (Sumner et al., 2017, 2018); the present study leverages data from *all* sub-studies and therefore includes a substantially larger sample of women with data on CRP. As only limited new data was available for TNFR2 at blood draw 2 relative to the earlier investigation of PTSD and inflammation, we did not conduct rate of change (longitudinal) analyses with this biomarker. For the present study, women were eligible if they responded to the trauma and PTSD questionnaire, provided at least one blood sample, and were selected into at least one of the sub-studies in which CRP, IL-6, and/or TNFR2 were assayed, and had valid biomarker values (see Supplementary Material). Samples in analyses vary by biomarker for the cross-sectional (n = 1,843 – 2,797) and longitudinal analyses (n = 628 – 1,092). Sample sizes were larger for the first blood draw compared to the second (e.g., n = 2,614 for blood draw 1 and n = 1,275 for blood draw 2 for CRP cross-sectional analysis) (see Supplementary Figure 1).

Measures: Psychological distress

Lifetime trauma exposure and PTSD symptoms were measured with a 16-item modified version of the Brief Trauma Questionnaire and Breslau's Short Screening Scale administered in NHS II in 2008 (Breslau et al., 1999; Morgan et al., 2001). Women reported their age at first trauma; we considered women as trauma unexposed until the reported year of their first event, if they reported trauma. Women also identified their worst trauma and their age at this event. PTSD symptoms were measured pertaining to the worst trauma exposure, yielding a symptom score (possible range from 0–7), with onset of PTSD symptoms considered as the year this worst event occurred (Koenen et al., 2009). Reported age of onset for symptoms has been validated in this cohort and previous research has reported the validity of this PTSD symptom score (Breslau et al., 1999). Depression symptoms were assessed by mental health screening scales administered via questionnaires. We used the validated Mental Health Inventory-5 (MHI-5; past-month symptoms; possible scores range from 0 (high depression)-100 (no depression)), administered in 1993, 1997, and 2001, and the validated 10-item Centers for Epidemiologic Study of Depression screener (CESD-10; past-week symptoms; possible scores ranging from 0–30) administered in 2008 (Andresen et al., 1994; Berwick et al., 1991; Chang et al., 2016; Gillis et al., 2019; Howren et al., 2009; McManus et al., 2005; Yamazaki et al., 2005). Across analyses, we used depression symptom scores closest to each blood draw, the MHI-5 for blood draw 1 and CESD-10 for blood draw 2.

As our primary exposure, we created a combined psychological distress score (Chang et al., 2016; Gillis et al., 2019). First, we z-scored the PTSD and depression symptom scores separately (after reverse coding the MHI-5 score). Of note, while PTSD symptoms were scored only among individuals exposed to trauma, depression symptoms were scored regardless of trauma exposure. Next, we summed the z-scores of PTSD with depression symptom z-scores (MHI-5 or CESD-10 depending on blood draw) to create a combined psychological distress score, whereby higher scores indicate higher distress. Lastly, we z-scored the combined psychological distress score among our analytic sample.

As a secondary approach, we created a categorical cross-classified variable for trauma/PTSD symptoms/depressed mood status to capture presence/absence of these measures. We coded this categorical variable as: (a) no trauma with no depressed mood, (b) no trauma with depressed mood, (c) trauma, no PTSD symptoms, with no depressed mood, (d) trauma, no PTSD symptoms, with depressed mood, (e) trauma, any PTSD symptoms (≥1 PTSD symptom), with no depressed mood, and (f) trauma, any PTSD symptoms (≥1 PTSD symptom), with depressed mood. For this, we derived an indicator for lifetime depressed mood which, in addition to depression symptoms, also considered relevant measures routinely collected on cohort questionnaires including antidepressant medication use (biennially reported from 1993, except for in 1995), and self-reported physician-diagnosed depression (biennially reported since 2003) (Pan et al., 2010; Pan et al., 2012). Antidepressant medications included selective serotonin reuptake inhibitors (e.g., Prozac, Zoloft, Paxil, Celexa) and other antidepressants (e.g., Elavil, Tofranil, Pamelor) (Huang et al., 2015; Pan et al., 2010; Pan et al., 2011). We characterized lifetime depressed mood according to whether women reported ever being diagnosed with depression, ever

using antidepressants, or had a score of ≤60 on the MHI-5 and/or ≥10 on the CESD-10 (Andresen et al., 1994; McManus et al., 2005; Rumpf et al., 2001; Yamazaki et al., 2005) prior to blood draw (i.e., this measure was time-updated to the date of blood draw used in analysis). We considered PTSD present if only 1 symptom was reported. We used this conservative approach for assessing PTSD because we did not have sufficient sample size to categorize different levels of symptoms more finely. In sensitivity analysis, we included a definition for depression that included antidepressant medication use and self-reported physician-diagnosed depression but not depression symptoms on the MHI-5 or CESD-10.

Measures: Inflammatory biomarkers

A total of 10 sub-studies used the 1996–1999 blood sample only and 2 sub-studies measured samples from both blood collections. Laboratory details for assays are provided in Supplementary Material. Coefficients of variation ranged 0.3–11.8% for CRP, 1.9–20.4% for IL6, 2.0–8.7% for TNFR2 across sub-studies. To address potential batch effects, we log-transformed biomarker values and conducted an average batch correction method as described previously (Huang et al., 2016; Poole et al., 2011; Rosner et al., 2008).

Covariates

We considered an extensive range of covariates which could be considered confounders and/or mediators of the association between psychological distress and inflammation. Covariates included sociodemographic factors, health conditions, and medication use (which could be confounders or mediators) and biobehavioral factors (likely to be mediators). For sociodemographics, we modeled age at blood draw (years; continuous, centered at 40 years old), age at blood draw squared (continuous, centered at 40 years old; to account for non-linearity in age), race/ethnicity (Non-Hispanic White, all other race/ethnicities, missing), parental education (high school or less, some college, college or more, missing). We also included relevant blood collection factors such as blood draw (1 vs. 2) as well as fasting status (≥8 hours since last meal vs. <8 hours since last meal/missing), blood draw time of day (2am-<8am, 8am-<2pm, and 2pm-<2am), season of blood draw for the relevant draw (winter (December-February), spring (March-May), summer (June-August), and fall (September-November)), time from PTSD onset to blood draw (in years; time updated), and time from depression assessment to blood draw (in years; time updated). For health conditions we included measures of menopausal status (premenopausal, postmenopausal, unknown/missing), postmenopausal hormone therapy use (past/never, current, unknown/missing), use of anti-inflammatory medication (yes vs. no/missing), use of anti-hypertensive medication (yes vs. no/missing), use of lipid-lowering medication (yes vs. no/missing), and case/control status based on the disease specific sub-study (i.e., the participants who developed disease after either blood draw were cases; participants in behavior-related sub-studies were coded as controls). Lastly, biobehavioral factors such as smoking status (past, current, never/missing), alcohol intake (none, 0-<5g/day, 5+g/day, missing), physical activity (metabolic equivalent task hours per week: 0-<9 MET-hrs/wk, 9+ MET-hrs/wk), and diet quality (continuous; measured using the Alternative Healthy Eating Index (Chiuve et al., 2012)), as well as body mass index (BMI) (<18.5/missing, 18.5-<25.0, 25.0-<30, 30+) were also considered. For antidepressants, used in sensitivity analysis, history of antidepressant use was operationalized as ever versus never/missing. Missing data was mainly handled

using missing indicators (see Supplementary Material). Further detail on covariates is provided in Supplementary Material.

Analysis

We examined associations of our exposures with levels of each biomarker concentration (log-transformed and batch-corrected) across the two time points (cross-sectional analyses; CRP, IL-6 and TNFR2) and with rate of change in biomarkers across time (longitudinal analyses; CRP and IL-6). We excluded inflammatory biomarker values beyond 3 standard deviations of the mean across batches, prior to average batch correction, and batches with less than 5 samples. We also excluded women who reported illness as their worst trauma, if PTSD occurred after the relevant blood draw, or who developed the sub-study disease of interest ***within two years*** after blood either draw (to reduce concerns regarding subclinical inflammatory related diseases and account for potential reverse causation). Accordingly, we have multiple analytic samples; our sample included 2,797 (cross-sectional) and 1,092 (longitudinal) women for CRP, 2,186 (cross-sectional) and 628 (longitudinal) women for IL-6, and 1,843 (cross-sectional) women for TNFR2 analyses (see Supplementary Figure 1). Across analyses, in model 1, we adjusted for sociodemographic and blood collection factors (race/ethnicity, parental education, blood draw time of day, fasting status, and season of blood draw, age and age squared (age at baseline for longitudinal and time-updated age for cross-sectional analysis, time from PTSD onset to blood draw, and time from depression assessment to blood draw). Cross-sectional analyses also adjusted for blood draw in model 1. Model 2 further adjusted for health conditions and medication use including menopausal status, regular medication use (anti-inflammatory, anti-hypertensives, and anti-lipid lowering medication) and case/control status. Model 3 additionally adjusted for biobehavioral factors (smoking status, alcohol intake, physical activity, diet quality, and BMI). Given the complexity of the current analyses and the timing with which key variables were obtained and measured, we did not conduct formal mediation analyses to evaluate specifically the role of these biobehavioral factors in the relationships of interest. An alpha value of 0.05 was used to determine significance.

Descriptive statistics

We examined the relationship between the continuous combined distress score and covariates. We also calculated the intra-class correlation (ICC) of each biomarker (log-transformed and batch-corrected) within individuals over the two blood draws.

Cross-sectional analyses

For cross-sectional analyses, we used linear mixed effects models. Trauma and the combined psychological distress score were included in models simultaneously and assessed in relation to concentrations of each inflammatory biomarker. Covariates were time-updated (see Supplementary Material). We calculated the percent difference in inflammatory biomarker level by exposure (per 1 SD increase for our combined distress score; exposed vs. unexposed for trauma) using $\left(e^{\beta}-1\right)*100$. To account for within-person correlation across the two inflammatory biomarker measures, a random intercept for participant was included in each model. In a secondary approach, we performed the same sets of analyses with our

categorical trauma/PTSD symptoms/depressed mood variable as the exposure (reference group: no trauma/no depressed mood). Lastly, we repeated cross-sectional analyses with our distress score while also adjusting for anti-depressant use (in addition to model 2 covariates).

Longitudinal

For longitudinal analyses, we used linear mixed effects models evaluating the relationship of exposure status at first blood draw with concentrations of CRP and IL-6 using an interaction term of time with either trauma or distress score, including random intercept terms for participant. The interaction terms represent the change of log-transformed inflammatory biomarker from first to second blood collection. We used covariate status at baseline, except age terms and blood collection factors which were time-updated for each blood draw, as some other covariates could lie on the pathway between distress and inflammation. Secondarily, we repeated these analyses with our categorical trauma/PTSD symptoms/depressed mood variable as the exposure (reference group: no trauma/no depressed mood).

Results

Descriptive statistics

Table 1 describes the distribution of distress by covariates for the CRP analysis. Distress scores in this sample ranged from −1.93–3.79 (mean: −0.04; SD: 1.0). The distribution of biomarkers appeared normally distributed and are presented in Supplementary Figure S1. The ICC between blood draws (i.e., over 10–16 years) were 0.64, 0.40, and 0.53 for CRP, IL-6 and TNFR2, respectively (Supplementary Table S1). There was a modest correlation between CESD-10 (2008) and MHI-5 (2001) ($r = 0.42$, p-value <0.0001) in the cross-sectional CRP sample, which may be due to the extended time period between assessments. The distribution of distress by covariates for IL-6 and TNFR2 are presented in Supplementary Tables S2 and S3, respectively. There was a high degree of overlap between samples, with 67.2% of the analytic sample for examining IL-6 and 54.6% of the analytic sample for examining TNFR2 also included in the cross-sectional CRP sample. Among women who reported trauma, the average length of time between PTSD symptom onset (according to reported age at worst trauma) and blood draw ranged between 19.7–30.5 years (Supplementary Table S4).

Cross-sectional analyses

In minimally-adjusted models, a one standard deviation increase in distress scores was associated with 10.2% (95% confidence interval (CI): 5.2–15.4%) higher CRP levels (Table 2; Supplementary Table S5, S6 and S7). These patterns remained evident after further adjusting for health conditions and case-control status but were substantially attenuated after adjusting for biobehavioral factors (in model 3). Further exploration suggested that BMI was the main contributor to the attenuation (when adding each biobehavioral factor in separate models; Supplementary Table S8). An increased distress score was also associated with higher TNFR2 levels, although estimates were small (e.g., 1.5% higher, 95% CI: 0.5–2.5% in model 1). While associations of distress with IL-6 were not statistically significant after adjustment for biobehavioral factors, estimates were positive, with higher distress

scored predicting higher concentrations in models 1 and 2. We found no clear evidence for associations between trauma and concentrations of any inflammatory biomarker.

Using the categorical cross-classification measure for trauma/PTSD symptoms/depressed mood, women with trauma and both PTSD symptoms and depressed mood had higher levels of CRP and IL-6 than women with no trauma/no depressed mood, adjusting for blood collection and sociodemographic factors (Supplementary Table S9). For instance, compared to women with neither trauma nor depressed mood, those with trauma, PTSD symptoms, and depressed mood had 29.5% (95% CI: 13.3, 47.9) higher CRP levels and 13.1% (95% CI: 5.1, 21.7) higher IL-6 levels, adjusting for sociodemographic and blood collection factors. Results remained evident when additionally adjusting for health conditions in model 2 but were again substantially attenuated in model 3. We observed no clear evidence of associations for any combination of trauma/PTSD symptoms/depressed mood with TNFR2 concentrations. After further adjusting for anti-depressant use in model 2, findings were consistent with our main results for our distress score and CRP (i.e., 5.9% increase, 95% CI: 1.1–11.0) as well as TNFR2 (i.e., 1.1% increase, 95% CI: 0.1–2.1). In sensitivity analysis, using a measure of depression that did not include depression symptoms, results were overall similar, suggesting that the use of a one-time symptom score is not skewing our results. However, it should be noted that this sensitivity analysis resulted in a smaller sample size due to greater missingness when not including depression symptoms in our measure, and subsequently women were moved from depression(+) to depression(−) which could indicate that some women are misclassified across measures (Supplementary Table S10).

Longitudinal analyses

As women aged across the two time points of blood draw, there was an association with increased CRP and a trend toward decreased IL-6 concentrations (Table 3). No associations of trauma or the combined distress score at first blood draw with rate of change in CRP over 10–16 years were evident. However, trauma was associated with rate of change in IL-6, such that concentrations of IL-6 declined less rapidly over time for those with versus without trauma (Table 3). In contrast, compared to having no trauma or depressed mood, trauma alone and trauma/PTSD symptoms/depressed mood were associated with a more rapid increase in CRP over time (Supplementary Table S11 and S12).

Discussion

In this study, we examined associations of trauma and psychological distress in relation to inflammation among middle-aged women across a 10–16-years. We observed that trauma exposure alone was not associated with inflammatory biomarker concentrations cross-sectionally, when accounting for psychological distress. In our previous work in this cohort, trauma alone was associated with higher inflammation, however associations were stronger for PTSD following trauma (Sumner et al., 2017). We found evidence of associations between higher distress (using a combined distress continuous score) and levels of all inflammatory biomarkers, although this was attenuated when accounting for BMI, which may be a key mediator given that distress predicts higher BMI and more rapid weight gain over time (Kubzansky et al., 2014). Particularly striking, findings were

strongest among women experiencing multiple manifestations of distress rather than any single form of distress. Thus, women with higher distress scores or those with trauma exposure and both depressed mood and PTSD symptoms had higher concentrations of CRP. Results were significant for TNFR2 for the combined distress score only and for IL-6 levels only in relation to trauma/PTSD symptoms/depressed mood. We did not find clear evidence that our combined distress score was related to rate of change in the inflammatory biomarkers over 10–16 years however, when considering the categorical cross-classified variable, trauma alone and trauma with both depressed mood and PTSD symptoms were associated with a higher rate of increase in CRP over time compared to those with no trauma or depressed mood. This study differs substantially from our prior work considering PTSD and inflammation in this sample, as here we had a larger sample for CRP, included IL-6 as an outcome, conceptualized psychological distress more broadly than just according to PTSD status, and also evaluated the joint effects of PTSD and depression occurring in the context of trauma (Sumner et al., 2017, 2018). Overall, our findings demonstrate the importance of considering different manifestations of distress and trauma together in relation to health-relevant biological processes.

Previous evidence has shown that psychological distress is associated with increased concentrations of IL-6 and TNF-α, with less consistent findings for CRP (Marsland et al., 2017; Slavish et al., 2015). Our previous cross-sectional work in a smaller sample in this cohort, using an interview-based measure of PTSD ($n = 524$), also found that PTSD symptoms were associated with higher levels of CRP and TNFR2 (Sumner et al., 2017). In general, prior cross-sectional studies considering PTSD or depression separately have shown these are associated with elevated inflammation (Osimo et al., 2020; Passos et al., 2015; Yang and Jiang, 2020), while longitudinal studies often suggest PTSD has limited impact on change in inflammation over time (Jergović et al., 2015; Sumner et al., 2017, 2018). These findings can be interpreted variously. It is possible that distress leads to changes in inflammation relatively earlier in life (or relatively soon after the onset of distress) and this change is then carried through a stable trajectory across time. Thus, while distress may alter the level of inflammation at one time point, once these levels are set, distress may not lead to more rapid subsequent rise in inflammation. If inflammation levels are not assessed near in time to the onset of distress, it may be hard to capture effects on rate of change. Conversely, a high inflammatory milieu may precede the onset of various manifestations of psychological distress. That said, a previous study in this cohort found that pre-PTSD inflammation levels did not predict subsequent PTSD and some studies of depression have also demonstrated depression precedes increases in inflammation (Copeland et al., 2012). Bi-directional relationships between PTSD and inflammation are also plausible, and additional research will need to carefully consider the timing of effects in relation to the research question of interest (Sumner et al., 2018; Sumner et al., 2020b).

Possible pathways

Prior work has pointed to biobehavioral mechanisms that may underlie the connection between psychological distress and inflammation (Howren et al., 2009; Pitharouli et al., 2021; Puustinen et al., 2011; Wirtz and von Känel, 2017). For example, BMI, and smoking have previously been associated with increased levels of CRP (McDade et al., 2006; Wong

et al., 2001), and have also been related to measures of psychological distress (Kubzansky et al., 2014; van den Berk-Clark et al., 2018). In fact, in the current cohort and in one of its sister cohorts, depression and PTSD have been linked with subsequent increases in BMI, although bidirectional associations with depression have also been noted (Kubzansky et al., 2014; Pan et al., 2012). In the present study, analysis suggested that BMI was a main contributor to attenuation across models. In line with this, our previous work in this cohort also showed attenuated results when adjusting for biobehavioral factors, including BMI, in the relation of PTSD and inflammatory biomarkers (Sumner et al., 2017). BMI has also been highlighted as a key factor between psychological distress and CVD (Levine et al., 2021). Multiple mechanisms for how obesity leads to increased inflammation have been proposed, such as oxidative stress and interreference with the insulin (Dandona et al., 2004; Deng et al., 2016). Our findings point to the value of further work specifically evaluating BMI as a potential mediator of the observed distress-inflammation associations.

Other explanations regarding linkages between psychological distress and inflammation include biological mechanisms. Stress, as well as specific manifestations of distress like PTSD and depression, may disrupt activity of the hypothalamic-pituitary-adrenal axis and balance between the sympathetic-parasympathetic nervous systems. This can dysregulate secretion of catecholamines (e.g., norepinephrine) and cortisol, which in turn can elevate the production of pro-inflammatory cytokines such as TNF-α and IL-6 and downstream acute-phase reactant proteins such as CRP (Dowlati et al., 2010; Pitman et al., 2012; Sumner et al., 2017; Sumner et al., 2020b; Wirtz and von Känel, 2017).

Limitations and Strengths

This study has several limitations. First, our cross-sectional analysis cannot rule out the possibility that inflammation is a precursor or underlying causal factor for increased susceptibility to distress. However, to reduce concerns that subclinical inflammatory related diseases (e.g., cancer or CVD) might be driving our findings, we excluded individuals who went on to develop such diseases within 2-years after blood draw. Second, depression symptoms were measured prospectively between the blood draws, but trauma and PTSD symptoms were measured retrospectively at one-time point and only in relation to worst trauma exposure, which might result in misclassification of PTSD, potentially biasing results towards the null (Moffitt et al., 2010). However, the PTSD measurement was concurrent with or before the date of second blood draw. Moreover, the time between depression or PTSD assessment and blood draw varied somewhat; however, it is unclear whether such variation would meaningfully affect findings and all analyses adjusted for this factor. Third, we did not have information on the timing of depression onset, and therefore could not confirm that depression followed trauma exposure. However, trauma often occurs in early life; among a subset of the NHS2 cohort specifically, a prior study indicated that 91% of trauma-exposed women reported their first trauma occurring before 1989 (Sumner et al., 2020a). As depression most typically onsets in adulthood (Kessler et al., 2005), it is likely trauma preceded depression for many women in our sample. Future studies should examine the relationship between trauma, psychological distress and inflammation using measures with information on timing. In addition, capturing data on catecholamines may provide important insight into potential biobehavioral mechanisms of these relationships,

although catecholamines can be difficult to measure in the context of cohort studies. Fourth, our sample only included women (majority white professional) and generalizability of our findings may therefore be limited. Future studies should aim to replicate these findings in other data in an effort for reproducibility as well as increasing generalizability. However, women are disproportionally affected by PTSD and depression, and CVD is the leading cause of death in women (Kessler, 2003; Kilpatrick et al., 2013; Peters et al., 2019; Tolin and Foa, 2006). Finally, as this was an observational study, the possibility of unmeasured confounding remains.

Our study has a number of strengths. We examined the role of trauma and multiple manifestations of psychological distress separately and combined. Prior work on PTSD has generally adjusted for depression but not considered it in combination with trauma and PTSD (Passos et al., 2015; Sumner et al., 2017; Yang and Jiang, 2020). By using a continuous score of psychological distress regardless of clinical manifestation, as well as considering the role of PTSD symptoms and depression in the presence or absence of trauma, we were able to demonstrate that considering the comorbidity of trauma and multiple manifestations of psychological distress may lead to new insights regarding potential effects on inflammation and health sequalae (Breslau et al., 2000; Morris et al., 2012; O'Donnell et al., 2004). This approach may also reduce misclassification of distress (Cohen et al., 2015; Levine et al., 2021). Lastly, data are from a richly characterized ongoing cohort of women, which made it possible to account for an extensive range of relevant covariates that could impact inflammation levels.

Conclusions

PTSD and depression are two highly comorbid forms of psychological distress commonly experienced following trauma. Prior research investigating the effects of trauma and psychological distress on physical health has typically treated PTSD and depression as separate exposures, often seeking to evaluate their independent effects (Barbano et al., 2019; Cohen et al., 2015; Dowlati et al., 2010; Passos et al., 2015; Sumner et al., 2017; von Känel, 2012; von Känel et al., 2010). However, together with accumulating evidence showing that PTSD and depression can have similar impacts on immune dysregulation and elevated risk of CVD and other health conditions (Cohen et al., 2015; Edmondson et al., 2013; Edmondson and von Känel, 2017; Levine et al., 2021) and given these manifestations of distress so often occur together, more complex consideration of associations may be warranted. It is possible, for example, that each form of distress is equally health-damaging but once one manifestation is present, there is no additional harm imposed by having another form of distress. Or, it may be that having multiple forms of distress are either additive or multiplicative in their effects on downstream biological processes and health. Addressing these questions is critical in order to provide a clearer sense of who is at risk for subsequent poor health outcomes and how much risk is likely. Such information can be helpful not only for a greater understanding of the epidemiology of cardiovascular disease but also for clinicians working with patients who have experienced trauma and varying forms of distress. Our findings suggest that considering multiple combined manifestations of psychological distress and trauma on subsequent outcomes, such as inflammation, may be particularly important for research in understanding both short- and longer-term health implications.

This work clearly points to important shared pathways by which different manifestations of distress can alter biological function. However, our findings also suggest that considering specific forms of distress that occur with trauma may be important. Overall, a broader approach to how we conceptualize psychological factors, such as that characterized by the Research Domain Criteria, may prove fruitful when considering the role of psychological distress in relation to physical health. This perspective may encourage researchers to conceptualize psychological distress more broadly, as well as to consider multiple forms of distress singly and in combination, rather than focusing solely on specific disorders one at a time. Triangulating across approaches will facilitate a stronger understanding of how and why psychological distress influences inflammation and other health-relevant outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Distribution of a combined psychological distress score by covariates at blood draw among 2,797 women in NHS II with measured circulating CRP levels.

	N (%) or mean (SD)	Distress score, mean (SD) or correlation
Sociodemographic factors		
Age at blood draw, mean (SD); correlation	43.4 (4.6)	−0.02
Race/ethnicity, n(%)		
Non-Hispanic White	2691 (96.2)	−0.04 (1.0)
All other race/ethnicities	72 (2.6)	−0.03 (1.1)
Missing	34 (1.2)	−0.2 (0.8)
Parental education, n(%)		
High school or less	1,390 (49.7)	−0.02 (1.0)
Some college	690 (24.7)	−0.1 (1.0)
College or more	664 (23.7)	−0.1 (1.0)
Missing	53 (1.9)	0.2 (1.0)
Blood collection factors		
Fasting status, n(%)		
≥8 hours since last meal	2304 (82.4)	−0.1 (1.0)
<8 hours since last meal/missing	493 (17.6)	0.04 (1.1)
Blood draw time of day, n(%)		
2am-<8am	675 (24.1)	−0.1 (1.0)
8am-<2pm	2053 (73.4)	−0.04 (1.0)
2pm-<2am	69 (2.5)	0.1 (1.1)
Season of blood draw		
Winter (Dec-Feb)	658 (23.5)	−0.01 (1.0)
Spring (March -May)	769 (27.5)	−0.1 (1.0)
Summer (June-Aug)	564 (20.2)	−0.04 (1.0)
Fall (Sept-Nov)	806 (28.8)	−0.04 (1.0)
Health conditions		
Menopausal status, n(%)		
Premenopausal	2,168 (77.5)	−0.1 (1.0)
Postmenopausal	462 (16.5)	0.1 (1.1)
Unknown/missing	167 (6.0)	0.01 (1.0)
Post menopausal Hormone therapy use, n(%)		
Past/never	2,501 (89.4)	−0.04 (1.0)
Current	296 (10.6)	−0.1 (1.1)
Other medication use *, n (%)		
No/missing	2,594 (92.7)	−0.1 (1.0)
Yes	203 (7.3)	0.3 (1.0)

	N (%) or mean (SD)	Distress score, mean (SD) or correlation
Anti-depressant medication use, n(%)		
Never	2293 (82.0)	−0.2 (0.9)
Ever	504 (18.0)	0.7 (1.1)
Case/control status **, n(%)		
Cases	250 (8.9)	0.1 (1.1)
Controls	2,547 (91.1)	−0.1 (1.0)
Biobehavioral factors		
Physical activity, n(%)		
0-<9 MET-hrs/wk	1126 (40.2)	0.04 (1.0)
9+ MET-hrs/wk	1671 (59.7)	−0.1 (1.0)
Smoking status, n(%)		
Never/Missing	1,933 (69.1)	−0.1 (1.0)
Past	650 (23.2)	0.1 (1.1)
Current	214 (7.7)	0.1 (1.1)
Alcohol intake, n(%)		
None	1040 (37.2)	−0.02 (1.0)
>0 to <5 g/day	930 (33.3)	−0.1 (1.0)
≥5 g/day	739 (26.4)	−0.1 (0.9)
Missing	88 (3.2)	0.4 (1.1)
Diet quality ***, mean (SD); correlation	46.0 (10.9)	0.08
BMI, n(%)		
<18.5 kg/m^2	49 (1.8)	−0.3 (1.0)
18.5-<25.0 kg/m^2	1605 (57.4)	−0.1 (1.0)
25.0-<30 kg/m^2	693 (24.8)	−0.01 (1.0)
30+ kg/m^2	450 (16.1)	0.1 (1.1)

Note: A higher combined psychological distress score indicates higher levels of PTSD and depression symptoms. Sample was women at first available measure for CRP from either blood draw (our largest sample and used in cross-sectional CRP analysis). Values of polytomous variables may not sum to 100% due to rounding and/or missing. Abbreviations: CRP: C-reactive protein; SD: standard deviation; MET-hrs/wk: metabolic-equivalent hours per week; BMI: body mass index; g/day: grams per day.

* Other medication use is collapsed for presentation; each drug type was included as separate binary variables in models. Drug types included: anti-inflammatory medications, lipid-lowering medications, and anti-hypertensive medications.

** Cases were defined as women classified as having the disease of interest in a disease-related sub-study (i.e., the participant developed disease after the blood draw). Controls were defined as women who did not develop sub-study-relevant diseases or who were in the behavior-related sub-studies.

*** Diet quality was measured using the Alternative Healthy Eating Index

Table 2.

Cross-sectional association of trauma and a combined psychological distress score with inflammatory biomarkers among women in NHS II, 1996–2012, using linear mixed effects models with a random intercept for participant.

Biomarkers[a] (n at blood draw 1; n at blood draw 2)	% Difference (95% CI)[b]		
	Model 1	Model 2	Model 3
CRP (n=2,614; n=1,275)			
Distress (per SD)	**9.8 (4.9, 15.0)**	**8.2 (3.4, 13.2)**	2.6 (−1.5, 6.8)
Trauma (exposed vs. unexposed)	−12.3 (−35.7, 19.5)	−10.5 (−34, 21.4)	−10.6 (−31.3, 16.4)
IL-6 (n=2,094; n=720)			
Distress (per SD)	**3.1 (0.4, 6.0)**	2.4 (−0.3, 5.2)	0.5 (−2.0, 3.0)
Trauma (exposed vs. unexposed)	−2.8 (−40.9, 59.8)	−2.0 (−40.3, 60.8)	−2.2 (−38.0, 54.3)
TNFR2 (n=1,748; n=540)			
Distress (per SD)	**1.4 (0.4, 2.5)**	**1.2 (0.2, 2.2)**	0.8 (−0.2, 1.8)
Trauma (exposed vs. unexposed)	**−4.4 (−7.3, −1.5)**	**−4.2 (−7.0, −1.2)**	**−4.2 (−7.0, −1.4)**

Note: Trauma and psychological distress are included in the models simultaneously. Bold values indicate those reaching statistical significance using $p<0.05$.

Model 1: sociodemographic, blood collection factors, blood draw indicator, time from PTSD onset to blood draw (in years), and time from depression assessment to blood draw (in years); Model 2: Model 1 + health conditions; Model 3: Model 2 + biobehavioral factors.

Abbreviations: SD: standard deviation; CRP: C-reactive protein; IL-6: interleukin-6; TNFR2: tumor necrosis factor alpha receptor 2.

[a] Raw biomarker values were log-transformed and batch-corrected.

[b] Percentage difference in levels of inflammatory biomarkers was calculated by $(e^{\beta}-1)*100$, whereby β was obtained from models. Untransformed model estimates and p-values are presented in Supplementary Table S6.

Table 3.

Longitudinal association of baseline trauma and a combined psychological distress score with rate of change of inflammatory biomarkers (log-transformed, batch-corrected) over time among women in NHS II, 1996–2012, using linear mixed effects models with a random intercept for participant.

	β (95% CI)		
	Model 1	**Model 2**	**Model 3**
CRP (n=1,092)			
Distress[a]	**0.08 (0.02, 0.13)**	**0.06 (0.01, 0.11)**	0.01 (−0.04, 0.06)
Time[b]	0.08 (−0.04, 0.19)	−0.05 (−0.21, 0.10)	−0.03 (−0.18, 0.12)
Distress*Time[b] interaction	−0.01 (−0.08, 0.05)	0.001 (−0.06, 0.06)	−0.012 (−0.07, 0.05)
Trauma[c]	−0.10 (−0.26, 0.05)	−0.07 (−0.22, 0.08)	−0.05 (−0.18, 0.08)
Trauma*Time[b] interaction	0.07 (−0.08, 0.23)	0.07 (−0.08, 0.22)	0.11 (−0.04, 0.25)
IL-6 (n=628)			
Distress[a]	**0.03 (0.0003, 0.06)**	0.02 (−0.01, 0.05)	0.01 (−0.02, 0.03)
Time[b]	**−0.13 (−0.22, −0.04)**	**−0.16 (−0.27, −0.05)**	**−0.12 (−0.23, −0.02)**
Distress*Time[b] interaction	−0.02 (−0.07, 0.03)	−0.02 (−0.07, 0.04)	−0.02 (−0.07, 0.03)
Trauma[c]	−0.05 (−0.14, 0.03)	−0.05 (−0.13, 0.03)	−0.04 (−0.11, 0.04)
Trauma*Time[b] interaction	**0.09 (−0.02, 0.20)**	0.10 (−0.01, 0.21)	**0.11 (0.01, 0.22)**

Note: Trauma and psychological distress are included in the models simultaneously. Bold values represent those reaching statistical significance using p<0.05.

Model 1: age at blood draw 1 (centered), sociodemographic, blood collection factors, time from PTSD onset to blood draw (in years), and time from depression assessment to blood draw (in years); Model 2: Model 1 + health conditions; Model 3: Model 2 + biobehavioral factors.

[a]Estimates represent the mean difference in the level of each inflammatory biomarker by 1 SD difference in a combined psychological distress score.

[b]Time was coded as continuous time in years since the first blood draw.

[c]Trauma estimates represent the mean difference in level of each biomarker comparing trauma exposed vs. unexposed.