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Posttraumatic stress disorder onset and inflammatory and endothelial function biomarkers in women

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ABSTRACT

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

1. Introduction

There is a growing appreciation that PTSD is associated with increased risk of cardiovascular disease (CVD) (Koenen et al., 2017). PTSD is characterized by dysregulation of the hypothalamic-pituitary-adrenal axis and sympathetic-adrenal-medullary system (Pitman et al., 2012), which may result in downstream physiological changes that promote CVD onset. This dysregulation may lead to increased systemic inflammation and impaired endothelial function (EF) (Wentworth et al., 2013), closely intertwined processes that contribute to CVD risk (Blake and Ridker, 2002). Few longitudinal studies have been conducted. Meta-analysis of cross-sectional evidence demonstrates significant associations of PTSD with inflammation (Passos et al., 2015). PTSD has also been associated with higher levels of EF biomarkers reflecting vascular inflammation (Blake and Ridker, 2002), including intercellular adhesion molecule-1 (ICAM-1) (Plantinga et al., 2013; von Känel et al., 2010; Farr et al., 2015) and vascular cell

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adhesion molecule-1 (VCAM-1) (von Känel et al., 2010), although results have been somewhat inconsistent (Plantinga et al., 2013; von Känel et al., 2008).

Investigators have generally hypothesized PTSD leads to physiological dysregulation rather than the reverse, but as most research on PTSD and inflammatory and EF biomarkers is cross-sectional, it leaves open questions about the directionality of effects. Findings may reflect processes whereby either PTSD leads to increases in inflammation or inflammation leads to increased susceptibility to PTSD. Indeed, in one study, elevated C-reactive protein (CRP) levels prospectively predicted likelihood of developing PTSD symptoms post-deployment in male Marines (Eraly et al., 2014). Additionally, in a small study of individuals hospitalized after orthopedic injuries, elevated inflammation at hospitalization was associated with having more PTSD symptoms one month later (Cohen et al., 2011). These findings are consistent with models postulating that peripheral inflammation increases likelihood of developing psychopathology after adversity like trauma (Nusslock and Miller, 2016). In fact, as with psychopathology such as depression, PTSD and inflammation-related processes may each influence one another (Koenen et al., 2017; Irwin and Miller, 2007).

To date, three longitudinal studies examined whether initial PTSD status predicted subsequent inflammatory and EF biomarker levels over and above baseline biomarker values (Farr et al., 2015; Jergović et al., 2015; Sumner et al., 2017). One study found that PTSD was associated with increased biomarkers levels over time (Farr et al., 2015), whereas the other did not (Jergović et al., 2015). In the third, we found that chronic PTSD (vs. no trauma) was associated with greater increases in VCAM-1 levels over 10–16 years in women in the Nurses' Health Study II (NHS II) (Sumner et al., 2017). A stronger test of whether PTSD leads to changes in inflammatory or EF biomarkers over time is to examine if levels of biomarkers representing these processes are lower before versus after PTSD onset; if so, this would be consistent with the notion that PTSD leads to increased inflammation and impaired EF. Although not proof of causality, such a study provides a methodologically rigorous way to address this issue given the unfeasibility of randomizing individuals to develop PTSD (Koenen et al., 2017). Alternatively, finding that biomarker levels assessed prior to PTSD onset are already elevated compared to those without trauma and/or predict greater severity of PTSD symptoms that subsequently onset would suggest that inflammation-related processes might contribute to increased PTSD risk.

We examined the nature of the relation of PTSD with inflammation-related processes in 525 middle-aged women in the NHS II with inflammatory and EF biomarkers measured twice, 10–16 years apart. We selected four biomarkers relevant to CVD risk that may be altered in response to activation of stress-related biological processes linked to PTSD (see (Black and Garbutt, 2002) for a review) and can be reliably assayed in plasma. We compared levels of CRP, tumor necrosis factor-alpha receptor-II (TNFRII), ICAM-1, and VCAM-1 among women who had their worst trauma exposure and PTSD onset in between blood draws to a) women with no trauma exposure and b) women with trauma exposure at the first blood draw but who had not developed PTSD. CRP, TNFRII, and ICAM-1 have predicted risk of incident CVD events in women (Pai et al., 2004). Furthermore, all the biomarkers selected for the current study have been linked to increased cardiometabolic disease risk in the NHS cohort (Pai et al., 2004; Meigs et al., 2004).

We examined if PTSD onset was associated with change in inflammatory and EF biomarkers. We hypothesized that, compared to no trauma, PTSD onset would be associated with an increase in biomarker levels. As trauma exposure alone has been associated with elevated inflammation (although not to as large a degree as PTSD) (Tursich et al., 2014), we hypothesized that the PTSD onset group would have lower inflammatory and EF biomarker levels at the first draw only compared to women with trauma/no PTSD. We accounted for various covariates identified by previous research on inflammation and PTSD (e.g., age, menopausal status, medication use) (Passos et al., 2015; Tursich et al., 2014). Additionally, we evaluated the hypothesis that inflammatory and EF biomarkers could indicate risk of PTSD. First, we examined if the PTSD onset group had elevated biomarker levels at draw 1 (prior to PTSD onset) compared to the no trauma and trauma/no PTSD groups. Second, we investigated whether draw 1 biomarker values predicted PTSD symptom severity in the PTSD onset group.

2. Materials and methods

2.1. Participants and procedure

Women were participants in the NHS II, a longitudinal study of women's health. The NHS II cohort comprises 116,429 female U.S. nurses enrolled in 1989 at ages 25–42 years and followed biennially. Blood samples were collected in 1996–1999 (draw 1) and in 2008–2012 (draw 2) (Huang et al., 2016). The current study examined a subset of NHS II women who completed a PTSD substudy, participated in both blood draws, and had no history of CVD (see Supplementary Materials for details) (Koenen et al., 2009). This study was approved by the Partners Healthcare Human Research Committee; return of questionnaires by mail represented implied consent.

2.2. Trauma and PTSD assessment

Women in the PTSD substudy completed a trauma and PTSD screening questionnaire in 2008. This questionnaire assessed lifetime trauma exposure with a modified version of the Brief Trauma Questionnaire (Morgan et al., 2001); additionally, women reported which event was the worst and if they ever experienced seven PTSD symptoms in relation to their worst trauma on the Short Screening Scale for *DSM-IV* PTSD (Breslau et al., 1999). A subset of women who reported trauma on this screening questionnaire completed diagnostic interviews to determine PTSD case status ($n = 3013$).

We randomly selected three groups of 175 women each from those eligible for the trauma/PTSD status groups: 1) a no trauma group comprising women who reported no lifetime trauma exposure on the 2008 screening questionnaire nor any childhood moderate or severe sexual abuse or serious physical-emotional abuse on a 2001 questionnaire querying violence exposure (Rich-Edwards et al., 2012) (175 women of 1174 eligible; women who were and were not selected for the no trauma group were highly similar on all covariates); 2) a trauma/no PTSD group who reported exposure to their worst trauma prior to the first blood draw but few (if any) PTSD symptoms in response to that trauma in the interview (175 of 187 eligible); and 3) a PTSD onset group comprising women whose worst trauma occurred between draws 1 and 2 and led to PTSD; to minimize the likelihood of PTSD prior to draw 1, women without any severe childhood sexual or physical-emotional abuse were selected (175 of 208 eligible). We selected 175 women for each group as this represented the largest sample in which we could assay our biomarkers of interest given our budgetary constraints. Mean time between PTSD onset and draw 2 was 6.6 years ($SD = 2.9$, range = 1–13 years). PTSD symptom severity was determined by summing responses to the 17 interview items corresponding to *DSM-IV* PTSD criteria (see Supplementary Materials). Items were rated on a 1 (Not at all) to 5 (Extremely) scale; symptom severity could range from 17 to 85. Women in the trauma/no PTSD and PTSD onset groups had symptom severity ranging from 17 to 19 and 23 to 81, respectively.

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