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Associations of Trauma and Posttraumatic Stress Disorder With Inflammation and Endothelial Function: On Timing, Specificity, and Mechanisms

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Exposure to traumatic psychological stress can increase risk for numerous physical and mental health problems. Exciting discoveries from trauma research have identified alterations in peripheral biological systems, including the immune and cardiovascular systems, as potential contributors to trauma-related ill health. Importantly, such discoveries are pointing us in new directions in the search for interventions to reduce the negative physical and mental health effects of trauma. However, there are still fundamental gaps in our understanding of when, how, and in whom trauma leads to long-term altered functioning of key peripheral biological systems.

Trauma and its associated psychiatric disorder, post-traumatic stress disorder (PTSD), have now been linked with elevated inflammation in many studies. Systemic inflammation, in turn, has been implicated in the pathophysiology of the most common chronic physical diseases that are more prevalent following trauma. Moreover, inflammation may elicit symptoms of PTSD, depression, and anxiety. In addition to directly impacting health, inflammatory proteins influence health by interacting with other bodily systems, including the vascular endothelium, and PTSD has now been associated with impaired endothelial function in a few studies.

In this issue of *Biological Psychiatry*, Sumner *et al.* (1) move trauma research forward by examining associations of trauma and PTSD with inflammatory and endothelial function markers in a single study, something rarely done in previous work. Additionally, they examined if trauma and PTSD predicted change over time in these markers, extending our understanding of the time course of associations of trauma and PTSD with inflammation and endothelial function. Sumner *et al.* used data from a supplemental study of the Nurses' Health Study II that involved administering self-report measures of trauma and PTSD symptoms. Based on these measures, participants were divided into three groups: 1) no trauma, 2) trauma but no or very few PTSD symptoms, and 3) chronic PTSD. The authors then examined differences among these groups in the inflammatory markers C-reactive

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protein and tumor necrosis factor alpha receptor II, and the endothelial cell adhesion markers intercellular adhesion molecule-1 and vascular cell adhesion molecule-1.

Sumner *et al.* report that women with chronic PTSD had higher levels of C-reactive protein, tumor necrosis factor alpha receptor II, and intercellular adhesion molecule-1. In addition, trauma alone in the absence of PTSD was associated with higher levels of tumor necrosis factor alpha receptor II. Prior work indicates that trauma alone may be associated with elevated inflammation, but prior studies have rarely been able to account for the presence of PTSD. The current study indicates that trauma alone may be associated with elevated inflammation, even in women who do not have PTSD, but that PTSD may be associated with more biomarkers.

The development of effective interventions to reduce the negative impact of trauma on health will require that we understand the time course of trauma-related changes in biological systems. However, little is known about the effects of trauma and PTSD on change over time in peripheral biomarkers. Sumner *et al.* examined levels of inflammatory and endothelial function markers at two time points, 10 to 16 years apart. Results indicate that neither trauma nor PTSD strongly predicted change over time in inflammation and endothelial function markers. Chronic PTSD was only associated with a greater increase in one of their tested makers over time, specifically the endothelial function marker vascular cell adhesion molecule-1, and trauma was not associated with change over time in any of the markers.

We know little about why trauma and PTSD were associated with some inflammatory and endothelial function markers and not others in Sumner *et al.* or in other studies. A recent meta-analysis revealed that levels of three inflammatory markers were significantly higher in individuals with versus without PTSD with moderate to large effect sizes, whereas eight other markers were not significantly different between groups (2). Importantly, C-reactive protein, which was one of the inflammatory markers not associated with PTSD in this meta-analysis, was significantly higher in women with chronic PTSD in Sumner *et al.* There are many possible reasons for this divergence in findings, including that different studies have had different proportions of men and women and different exclusion criteria. However, it is also possible that the proteins we typically examine as markers of systemic inflammation are not at the right level of analysis. Although it is possible that we will gain important insights by looking at which specific proteins are increased and which are not in PTSD, this approach has not proved fruitful to date. Studies that look at gene expression and transcriptional control pathways may yield more consistent findings (3).

What does it mean that Sumner *et al.* and others observe reasonably robust cross-sectional associations of trauma exposure and PTSD with markers of inflammation and endothelial function, but few effects on change over time? It could mean that the effects of trauma and PTSD were already present at baseline with no further impact on the systems over time. It could also mean that the timeline along which changes were investigated was insufficient to see change, the effects were too small to be seen in a sample of this size, or elevated inflammation is a risk factor for, rather than a consequence of, PTSD (4). It may also be that investigators are not adequately exploring dynamic associations of the psychological and biological sequelae of trauma. A better understanding of how alterations in peripheral

biological systems unfold dynamically over time following trauma is critical to moving the field forward.

Sumner *et al.* focus on the relevance of their findings for cardiovascular disease risk. However, their findings also have implications beyond cardiovascular disease. First, trauma exposure alone as well as PTSD is associated with increased risk for autoimmune and neurodegenerative diseases as well as cardiovascular disease (5–7). Second, trauma is one of the strongest risk factors for some of the most common psychiatric disorders, including depression and anxiety, and it is a prerequisite for the diagnosis of PTSD. Inflammation has the potential to drive the development of all of these conditions, both physical and mental. In fact, inflammation is emerging as a potential treatment target for PTSD symptoms. New treatments for PTSD are desperately needed, and targeted anti-inflammatories could reduce both the mental and physical health burdens of the disorder.

Progress toward new treatments for trauma-related ill health cannot come before we uncover the psychological, behavioral, and biological mechanisms that account for increased inflammation and impaired endothelial function in PTSD. One hypothesis is that adverse health behaviors cause damage in bodily systems following trauma. In line with other studies, Sumner *et al.* report that associations of trauma and PTSD with inflammation and endothelial function were attenuated when adjusting for cigarette smoking, alcohol consumption, physical activity, diet quality, and body mass index. However, few studies have examined if interventions targeting health behaviors reduce inflammation and improve endothelial function in trauma-exposed individuals. Another potential mechanism of trauma's effects on inflammation and endothelial function is exaggerated threat sensitivity, which can drive activation of biological stress systems that promote inflammation, underlie symptoms of PTSD, and increase risk for poor health behaviors (8). One previous study indicated that individuals with PTSD and higher levels of threat sensitivity had the highest levels of inflammation (9). Future work should examine if cognitive behavioral interventions directly targeting threat sensitivity could reduce the negative impact of trauma on both biomarkers of ill health and disease risk.

On the biological side, understanding precisely which aspects of inflammation are impacted by trauma will be crucial for identifying targeted anti-inflammatory treatments for trauma-related ill health. A better understanding of the precise transcriptional control pathways underlying elevated inflammation following trauma may point us in the direction of targeted anti-inflammatory treatments to reduce trauma-related ill health (3). Although we do not yet know which targeted treatments are most appropriate, evidence from other areas of biological psychiatry indicates that we cannot assume that all patients with trauma-related ill health will benefit from anti-inflammatory treatments or that nonspecific anti-inflammatories will be beneficial at all (10).

Some of the most exciting new directions in this field of research will involve experimental approaches that tackle causal direction in associations of trauma and PTSD with inflammation and endothelial function. First, we will need experimental studies that manipulate key biological systems to clarify causal direction in associations of trauma and PTSD with inflammation and endothelial function. One key goal of these studies will be to

identify how and in whom inflammation can promote psychiatric symptoms and vice versa. Second, we need to conduct clinical trials focused on the presumed psychological and behavioral mechanisms of trauma- and PTSD-related ill health. Papers such as this one by Sumner *et al*. highlight inflammation and endothelial function as potential targets and intermediate endpoints that can be helpfully employed in such clinical trials.

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References

1. Sumner JA, Chen Q, Roberts AL, Winning A, Rimm EB, Gilsanz P, et al. Cross-sectional and longitudinal associations of chronic posttraumatic stress disorder with inflammatory and endothelial function markers in women. Biol Psychiatry. 2017; 82:875–884. [PubMed: 28778657]
2. Passos IC, Vasconcelos-Moreno MP, Costa LG, Kunz M, Brietzke E, Quevedo J, et al. Inflammatory markers in post-traumatic stress disorder: a systematic review, meta-analysis, and meta-regression. Lancet Psychiatry. 2015; 2:1002–1012. [PubMed: 26544749]
3. O'Donovan A, Sun B, Cole S, Rempel H, Lenoci M, Pulliam L, Neylan T. Transcriptional control of monocyte gene expression in post-traumatic stress disorder. Dis Markers. 2011; 30:123–132. [PubMed: 21508516]
4. Eraly SA, Nievergelt CM, Maihofer AX, Barkauskas DA, Biswas N, Agorastos A, et al. Assessment of plasma C-reactive protein as a biomarker of posttraumatic stress disorder risk. JAMA Psychiatry. 2014; 71:423–431. [PubMed: 24576974]
5. O'Donovan A, Cohen BE, Seal KH, Bertenthal D, Margaretten M, Nishimi K, Neylan TC. Elevated risk for autoimmune disorders in Iraq and Afghanistan veterans with posttraumatic stress disorder. Biol Psychiatry. 2015; 77:365–374. [PubMed: 25104173]
6. Yaffe K, Vittinghoff E, Lindquist K, Barnes D, Covinsky KE, Neylan T, et al. Posttraumatic stress disorder and risk of dementia among US veterans. Arch Gen Psychiatry. 2010; 67:608–613. [PubMed: 20530010]
7. Sumner JA, Kubzansky LD, Elkind MS, Roberts AL, Agnew-Blais J, Chen Q, et al. Trauma exposure and posttraumatic stress disorder symptoms predict onset of cardiovascular events in women. Circulation. 2015; 132:251–259. [PubMed: 26124186]
8. O'Donovan A, Slavich GM, Epel ES, Neylan TC. Exaggerated neurobiological sensitivity to threat as a mechanism linking anxiety with increased risk for diseases of aging. Neurosci Biobehav Rev. 2013; 37:96–108. [PubMed: 23127296]
9. O'Donovan A, Ahmadian AJ, Neylan TC, Pacult MA, Edmondson D, Cohen BE. Current posttraumatic stress disorder and exaggerated threat sensitivity associated with elevated inflammation in the Mind Your Heart Study. Brain Behav Immun. 2017; 60:198–205. [PubMed: 27765647]
10. Raison, CL. The promise and limitations of anti-inflammatory agents for the treatment of major depressive disorder. In: Dantzer, R., Capuron, L., editors. Inflammation-Associated Depression: Evidence, Mechanisms and Implications. Berlin, Germany: Springer; 2016. p. 287-302.