A prospective examination of sex differences in posttraumatic autonomic functioning

Antonia V. Seligowski a,b,*, Elizabeth R. Steuber c, Rebecca Hinrichs d, Mariam H. Reda e, Charis N. Wiltshire 1, Cassandra P. Wanna f, Sterling J. Winters e, Karlye A. Phillips g,h, Stacey L. House i, Francesca L. Beaudoin i, Xinming An k, Jennifer S. Stevens d, Donglin Zeng l, Thomas C. Neylan m, Gari D. Clifford h,o, Sarah D. Linnstaedt k, Laura T. Germine p,q,a, Kenneth A. Bollen r, Guia Guffanti a,b, Scott L. Rauch p,s,a, John P. Haran t, Alan B. Storrow u, Christopher Lewandowski v, Paul I. Msey Jr. w, Phyllis L. Hendry x, Sophia Sheikh x, Christopher W. Jones y, Brittany E. Punches z,aa, Michael C. Kurz ab,ac,ad, Vishnu P. Murty ae, Meghan E. McGrath af, Lauren A. Hudak ag, Jose L. Pascual ah,ai, Mark J. Seamon aj,ai, Elizabeth M. Datner ak,al, Anna M. Chang am, Claire Pearson an, David A. Peak ao, Roland C. Merchant ap, Robert M. Domeier sq, Niels K. Rathlev ar, Brian J. O’Neil an, Leon D. Sanchez ap,av, Steven E. Bruce at, Mark W. Miller au,av, Robert H. Pietrzak aw,ax, Jutta Joermann ay, Deanna M. Barch az, Diego A. Pizzagalli b,a, John F. Sheridan ba,bb, Beatriz Luna bc, Steven E. Harte bd,be, James M. Elliott bf, bg,bh, Karestan C. Koenen bi, Ronald C. Kessler bj, Samuel A. McLean bk,k, Kerry J. Ressler ba, Tanja Jovanovic e

a Department of Psychiatry, Harvard Medical School, Boston, MA, 02115, USA
b Division of Depression and Anxiety, McLean Hospital, Belmont, MA, 02478, USA
c Department of Psychiatry, Johns Hopkins Hospital, Baltimore, MD, 21287, USA
d Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, 30329, USA
e Department of Psychiatry and Behavioral Neurosciences, Wayne State University, Detroit, MI, 48202, USA
f Wayne State University, Detroit, MI, 48202, USA

* Corresponding author. 115 Mill St. Mail Stop 212 Belmont, MA, USA.
E-mail address: aseligowski@mclean.harvard.edu (A.V. Seligowski).
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1. Introduction

Trauma exposure is very common, with lifetime prevalence rates up to 89% (Kilpatrick et al., 2013). Symptoms of posttraumatic stress disorder (PTSD) affect a substantial proportion of those exposed to trauma and include unwanted re-experiencing of the event, avoidance of trauma reminders, negative changes in thinking and mood, and hyperarousal (APA, 2013). Individuals with PTSD symptoms experience significant functional impairment across multiple domains, and they are at greater risk of having cardiometabolic diseases compared to the general population (Edmondson et al., 2013; Norman et al., 2006; Pacella et al., 2013). One of the proposed mechanisms underlying increased cardiometabolic disease incidence in PTSD is altered functioning of the autonomic nervous system, such as increased heart rate (HR) and blood pressure (BP), and decreased high frequency heart rate variability (HF-HRV; for reviews see Buckley and Kaloupek, 2001 and Michopoulos et al., 2015). While numerous cross-sectional studies have demonstrated that those with PTSD exhibit altered autonomic functioning (reviewed below), there is a paucity of longitudinal studies following individuals in the immediate aftermath of trauma. Further, it is well-established that PTSD rates are twice as high in women compared to men (Kessler et al., 1995), yet sex differences in autonomic functioning are relatively unknown among trauma-exposed populations.

There is a long-standing literature supporting an association between PTSD and autonomic deficits. Compared to healthy and trauma-exposed controls, individuals with PTSD demonstrate increased sympathetic
Sex differences in PTSD prevalence are well-established, however, little is known about sex differences in autonomic functioning among trauma-exposed samples (for a review, see Seligowski et al., 2020). In a study of assault survivors, women who experienced increased HR during script-driven imagery were more likely to be given a PTSD diagnosis six months later compared to men and compared to women who didn’t have such a response (Kleim et al., 2010). Among motor vehicle accident survivors seen in the emergency department, no sex differences were observed in HR, but women were more likely to have PTSD at follow-up (Irish et al., 2011). In contrast, another study found that men with PTSD exhibited higher HRV than trauma-exposed controls, and no effect in women, but it is possible that these differences were due in part to collecting HRV data during a dark-enhanced startle paradigm (Kamkwalala et al., 2012). In terms of skin conductance, women with PTSD appear to demonstrate higher responses during fear conditioning compared to men with PTSD (Inslicht et al., 2013), and high levels of progesterone have been implicated in extinction retention deficits among women with PTSD (Pineles et al., 2016, 2018). Given the apparent link between autonomic deficits and cardiometabolic disease risk in PTSD, as well as the elevated prevalence of PTSD in women, it is necessary to better understand sex differences in autonomic functioning that may confer differential risk following trauma.

The current study used a prospective design to examine several aspects of posttraumatic autonomic functioning as part of the AURORA study (McLean et al., 2020). Men and women were recruited from emergency departments immediately following trauma exposure and their skin conductance response to a trauma interview was gathered at this time. They completed a fear conditioning paradigm two weeks later where HR, HRV, and BP were assessed. We sought to identify potential sex differences in HR, HRV, and BP at this 2-week session, as well as to determine if skin conductance in the immediate post-trauma period was associated with autonomic functioning two weeks later. Given limited sex differences research in PTSD populations, we examined the effects of both sex and 8-week PTSD status on these autonomic indices.

2. Methods

2.1. Participants and procedure

As part of the multi-site AURORA study, participants were recruited from 22 emergency departments (EDs) across the U.S. immediately following a traumatic event (see McLean et al., 2020 for additional detail). Traumatic events included motor vehicle collisions, physical assault, sexual assault, and serious accidents. Exclusion criteria were intracranial injury, long bone fracture or significant extracranial hemorrhage, pregnancy, and admission due to intentional self-injury or suicide attempt. Given the study’s aim of examining acute trauma responses, participants were also excluded if they reported ongoing domestic violence. Fear conditioning was completed in a sub-sample of AURORA participants at one of four locations two weeks following the emergency department visit. All participants provided informed consent and the study was approved by each site’s Institutional Review Board. See Fig. 1 for a CONSORT diagram outlining participant flow through the study.

2.2. Measures

PTSD Checklist for DSM-5 (PCL-5; Weathers et al., 2013). The PCL-5 is a 20-item self-report measure of PTSD symptom severity and was administered eight weeks following the ED visit. Responses are on a scale from 0 (not at all) to 4 (extremely). A total score was used to assess overall PTSD severity. A score of 33 or higher was used to indicate probable PTSD diagnosis (Bovin et al., 2016).

2.3. ED skin conductance response measurement

deSense (Mindfield Biosystems, Inc., Berlin, Germany). Using previously validated procedures (Hinrichs et al., 2017), skin conductance levels were recorded with the deSense system during the initial ED visit. deSense software was downloaded to an iPad and two Velcro electrodes, which were connected to the iPad, were attached to the middle and index finger. Participants were asked to describe the traumatic event that brought them to the ED and deSense was used to continuously measure skin conductance levels during the interview. This method has been used previously in the ED among trauma-exposed adults (Hinrichs et al., 2019).

2.4. 2-Week psychophysiological assessment

Approximately two weeks following the ED visit, participants completed a follow-up session that included a seated BP assessment and a fear-potentiated startle (FPS) paradigm, during which HR and HRV...
were obtained. The FPS paradigm is a Pavlovian fear conditioning paradigm that has been validated in clinical and nonclinical samples (e.g., Glover et al., 2011; Jovanovic et al., 2012; Norrholm et al., 2006; Seligowski et al., 2018). It includes a habituation phase followed by fear acquisition and extinction phases. During habituation, 12 108 dB startle probes were delivered through headphones to assess baseline startle, and eight of these were delivered upon the termination of conditioned stimuli (CS), which were colored shapes presented on a computer screen. During acquisition, one of the shapes (CS+) was paired with an aversive unconditioned stimulus (US), while the other was not (CS-). The US was a 250 ms/140 p.s.i. air blast directed at the larynx. The CS+ and CS- were each presented for 6 s and the startle probe was presented at their termination. During acquisition, the CS+ and startle probe were followed by the US 0.5 s later. Habituation included four trials of each CS (not reinforced with air blasts) and four startle probes alone (noise alone [NA]). Acquisition included three conditioning blocks with four trials of each type (NA, CS+, CS-) in each block. Extinction included four blocks of four trials of each type (NA, CS+, [ unreinforced], and CS-) in each block. All trials were on a fixed schedule and the inter-trial interval was 9–22 s.

Psychophysiological data were acquired using Biopac MP150 for Windows (Biopac Systems, Inc., Aero Camino, CA). HR and HF-HRV were continuously measured with Ag/AgCl electrodes in the Lead II placement of electrodes using the electrocardiogram (ECG) module, while eyelink startle was indexed using the electromyogram (EMG) module, which was measured with two Ag/AgCl electrodes placed below the participant’s pupil.

3. Data processing and analysis

3.1. Psychophysiology data processing

Skin conductance data were acquired using eSense on the iPad at a sampling rate of 10 Hz and the data were exported using .csv files. Baseline skin conductance was measured for 2 min and followed by the participant’s narrative of their traumatic event. Skin conductance measurements were obtained throughout the narrative.

HR and HF-HRV data were processed using MindWare software, which identifies R-waves and R-R intervals (i.e., the time between heartbeats), and detects artifacts, which were visually inspected and corrected (MindWare, Inc.). HR and HF-HRV were derived by spectral analysis of 1-min epochs with a Hamming windowing function and log transformed. Settings for the high frequency band were based on standard recommendations for HF-HRV data (0.12–0.40 Hz; Task Force, 1996). HR and HF-HRV values were averaged over the three acquisition blocks and four extinction blocks. The EMG sampling rate was 1 kHz, which was amplified by a gain of 2000, and filtered using 28 Hz and 500 Hz low and high pass filters; visual inspection was performed using MindWare. Following processing in MindWare, psychophysiological data were exported to SPSS. Consistent with American Heart Association guidelines, hypertension was defined as systolic BP ≥ 130 or diastolic BP ≥ 80 (heart.org).

3.2. Data analysis

Eight-week PCL-5 data were available for 192 participants. Using a cutoff score of 33 (Bovin et al., 2016), a dichotomous PTSD variable was created to indicate probable versus no PTSD. Of those with 8-week PCL-5 data, 158 participants had useable BP from the 2-week session, 151 participants had useable HR and HF-HRV data from 2-week fear conditioning, and 141 had useable eSense data from the ED. Reasons for missingness included data quality (e.g., noisy ECG signals) and incomplete data acquisition (e.g., participant did not complete fear conditioning). A chi-square analysis was used to compare the prevalence of hypertension among men versus women. Six univariate analyses of variance (ANOVs) were used to test the effects of sex and PTSD on systolic and diastolic BP, average HR during acquisition and extinction, and average HF-HRV during acquisition and extinction. These models controlled for age, race, and body mass index (BMI). Bivariate correlations were used to test associations among eSense and BP, HR, and HF-HRV. All analyses were conducted with SPSS v.24 and significance set to p < .05.

4. Results

Table 1 displays descriptive data among the total sample and by sex, and Table 2 displays bivariate correlations among the total sample. Of the 192 participants with 8-week PCL-5 data (Mage = 35.88, SD = 13.56), 78 (40.6%) met criteria for probable PTSD per the cutoff score of 33. There were no sex differences in putative PTSD diagnosis ($\chi^2(1, N=192) = 0.26$, p = .61) or PCL-5 score ($F(1,1190) = 0.74$, p = .39). In terms of race, 44.3% (n = 85) identified as Non-Hispanic Black, 33.3% (n = 64) identified as Non-Hispanic White, 17.7% (n = 34) identified as Hispanic, and 4.7% (n = 9) identified as Non-Hispanic “other” racial category.

Men were significantly more likely to meet criteria for hypertension than women, $\chi^2(1, N=192) = 0.01$, results of the first univariate ANOVA indicated a significant main effect of sex on systolic BP, $F(1,140) = 20.51$, p < .001, such that it was higher in men compared to women (Fig. 2). The PTSD by sex interaction was not significant, $F(1,140) = 0.34$, p = .56. There were no significant findings for diastolic BP. There was not a significant sex difference in baseline HF-HRV, $F(1,173) = 0.41$, p = .52. Further, there were no significant sex differences in eyelink startle to the CS+ or CS- during acquisition or extinction (see Fig. 3), nor any significant PTSD by sex interactions when controlling for age, race, and BMI ($p > 0.05$).

There was a significant main effect of sex on HR during fear acquisition, $F(1,138) = 14.80$, p < .001. The PTSD by sex interaction was not significant. During fear extinction, there was a significant main effect of sex on HR, $F(1,130) = 9.90$, p = .002, as well as a significant PTSD by sex interaction, $F(1,130) = 4.10$, p = .045. Post-hoc tests for this interaction indicated that HR was significantly different for men versus women only in the PTSD group, $F(1,123) = 10.94$, p = .001, whereas there was no significant effect of PTSD within either sex. As depicted in Fig. 4, women demonstrated higher HR compared to men during both fear acquisition and extinction, and this effect was stronger in the PTSD group during extinction, where HR was significantly higher in women ($M = 78.53$) compared to men ($M = 67.70$).

There was a significant main effect of sex on HF-HRV during fear acquisition, $F(1,138) = 4.60$, p = .034. The PTSD by sex interaction was not significant, $F(1,138) = 3.41$, p = .067. During fear extinction, there was a significant PTSD by sex interaction, $F(1,129) = 5.18$, p = .025. Post-hoc tests for this interaction indicated that HF-HRV was significantly different for men versus women only in the PTSD group, $F(1,122) = 7.20$, p = .008, whereas there was no significant effect of PTSD within either sex. As depicted in Fig. 5, women demonstrated lower HF-HRV compared to men during fear acquisition, and this effect was stronger in the PTSD group during extinction, where HF-HRV was significantly lower in women ($M = 5.41$) compared to men ($M = 6.49$).

Next, we examined associations among eSense skin conductance in the ED and 2-week BP, HR, and HF-HRV. Skin conductance values were significantly and positively associated with HR and negatively associated with HF-HRV only among women who developed PTSD ($p < .05$; see Table 3), indicative of increased sympathetic arousal and decreased parasympathetic control during fear conditioning. When controlling for age, race, and BMI using linear regression models, only the association between baseline eSense and extinction HF-HRV in women with PTSD remained significant ($\beta = -0.36$, p = .006). This suggests that increased sympathetic arousal in the immediate aftermath of trauma was associated with worse parasympathetic responses to fear extinction in women but not men with PTSD. No significant findings were observed in men or in women without PTSD.
most women were pre-menopausal. While prior studies have found that is important to note that the average age in our sample was 35 and thus may explain lower rates of hypertension in pre-menopausal women; for ciation,
women demonstrated significantly higher HR and lower HF-HRV, and
men demonstrated significantly higher BP and rates of hypertension, women. Sex differences were observed and varied by biomarker. While
autonomic functioning among a sample of recently traumatized men and

5. Discussion
This study used a prospective design to examine sex differences in
autonomic functioning among a sample of recently traumatized men and
women. Sex differences were observed and varied by biomarker. While
men demonstrated significantly higher BP and rates of hypertension, women demonstrated significantly higher HR and lower HF-HRV, and these effects were strongest among women who subsequently developed PTSD. Further, acute sympathetic arousal (indexed via skin conductance
response) associated with HR and HF-HRV during fear conditioning but only among women who subsequently developed PTSD.

Our findings regarding BP and hypertension are consistent with what is commonly observed in the general population, such that men are more likely to experience hypertension (American Heart Association, heart.org). This sex difference is known to decrease among older age groups and it is thought that decreasing estradiol levels as a result of menopause in women play a role (i.e., estradiol is cardioprotective and may explain lower rates of hypertension in pre-menopausal women; for reviews, see Colafella and Denton, 2018; Regitz-Zagrosek et al., 2016). It is important to note that the average age in our sample was 35 and thus most women were pre-menopausal. While prior studies have found that individuals with PTSD demonstrate higher BP than those without PTSD (for a review, see Buckley and Kaloupek, 2001), we did not observe an effect of PTSD status. One potential explanation is that our sample is not as highly traumatized as comparisons in prior work (e.g., most participants were in motor vehicle collisions). Similarly, BP was assessed with only one measurement and this occurred two weeks following trauma exposure. It is therefore possible that the higher levels of BP observed in prior PTSD studies were a result of more chronic PTSD symptoms and sympathetic hyperarousal, which our study did not capture.

In terms of HR and HF-HRV, our findings indicate that women experienced worse autonomic functioning during fear conditioning compared to men, and this was particularly seen in those women who subsequently developed PTSD. Specifically, trauma-exposed women demonstrated stronger sympathetic arousal and worse parasympathetic control than men during fear learning, where main effects of sex were observed, and those with PTSD demonstrated particularly worse functioning during extinction. This is consistent with prior literature implicating extinction deficits as a biomarker specific to PTSD (Jovanovic et al., 2012) and further suggests that women may be more likely than men to experience these deficits. Given that HF-HRV has been shown to be higher in healthy women compared to men (for a review, see Koenig and Thayer, 2016), our findings also highlight the importance of trauma and PTSD status in sex differences in autonomic function. The lack of sex

### Table 1
Descriptive statistics for total sample and by sex.

<table>
<thead>
<tr>
<th></th>
<th>Male (n = 61)</th>
<th>Female (n = 131)</th>
<th>Total (N = 192)</th>
<th>Missing values</th>
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<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
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<tr>
<td>Race</td>
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<td>Non-Hispanic Black</td>
<td>20</td>
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<td>Non-Hispanic White</td>
<td>26</td>
<td>42.6</td>
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<tr>
<td>Hispanic</td>
<td>13</td>
<td>21.3</td>
<td>21</td>
<td>16.0</td>
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<td>3.3</td>
<td>7</td>
<td>5.3</td>
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<td>Hypertension (2-weeks)</td>
<td>26</td>
<td>42.6</td>
<td>21</td>
<td>16.0</td>
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<tr>
<td>PTSD (8-weeks)</td>
<td>22</td>
<td>36.1</td>
<td>56</td>
<td>42.7</td>
</tr>
<tr>
<td>M SD</td>
<td>M SD</td>
<td>M SD</td>
<td>M SD</td>
<td>n %</td>
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<tr>
<td>BMI</td>
<td>27.13</td>
<td>5.16</td>
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<td>4.21</td>
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<td>6.18</td>
<td>6.08</td>
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<td>eSense End (ED)</td>
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<td>5.22</td>
<td>3.29</td>
<td>2.14</td>
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<td>BP – Diastolic (2-weeks)</td>
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<td>27.10</td>
<td>17.67</td>
<td>29.58</td>
<td>18.96</td>
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</table>

Note. BMI = body mass index; BP = blood pressure; HR = heart rate; HRV = heart rate variability.

### Table 2
Descriptives and bivariate correlations among study variables.

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<td>–</td>
<td>.830**</td>
<td>–</td>
<td>.947**</td>
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<td>–</td>
<td>.891**</td>
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<td>.947**</td>
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<td>4. eSense End (ED)</td>
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<td>5. BP – Systolic (2-weeks)</td>
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<td>7. HR – Acquisition (2-weeks)</td>
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<td>8. HRV – Acquisition (2-weeks)</td>
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<td>9. HR – Extinction (2-weeks)</td>
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<td>.099</td>
<td>.137</td>
<td>.088</td>
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<td>.503**</td>
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<td>11. PTSD symptoms (8-weeks)</td>
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<td>Mean</td>
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<td>Maximum</td>
<td>9.02</td>
<td>9.26</td>
<td>14.90</td>
<td>10.12</td>
<td>207.00</td>
<td>120.00</td>
<td>94.96</td>
<td>10.17</td>
<td>92.81</td>
<td>10.36</td>
<td>75</td>
</tr>
</tbody>
</table>

Note. *p < .05; **p < .01; BP = blood pressure; HR = heart rate; HRV = heart rate variability.
differences in eyeblink startle (a brainstem-mediated reflex and not an autonomic indicator) suggests that there may be specificity of our sex-based findings to peripheral autonomic and cardiovascular physiology (i.e., HR and HF-HRV). Additionally, low levels of estradiol have been implicated as a contributing factor to fear inhibition and extinction deficits in women with PTSD (indexed via eyeblink startle; Glover et al., 2012, 2013) as well as healthy controls (indexed via skin conductance; Milad et al., 2010). Thus, future research is needed to determine if an interaction between PTSD status and high versus low estradiol confers greater risk for autonomic and inhibition/extinction deficits (indexed via startle) in trauma-exposed women.

eSense has previously demonstrated utility in predicting PTSD status and symptom trajectory when used to measure skin conductance in recently traumatized individuals in emergency departments (Hinrichs et al., 2019). Our findings suggest it may have additional, and perhaps more specific utility among women, such that eSense skin conductance levels were significantly associated with future HR and HF-HRV only in women who developed PTSD. Given that autonomic deficits have been implicated in the increased risk of cardiovascular disease in PTSD, future research testing eSense as a predictor of autonomic functioning and subsequent cardiac events could be extremely useful in determining which trauma-exposed individuals are at highest risk for developing cardiovascular disease. Findings from the current study indicate that this may be a particularly useful tool among women, though replication is needed.

Our findings regarding sex differences in autonomic functioning may have clinical implications. Specifically, men and women differed in their sympathetic arousal, with men demonstrating higher BP and women demonstrating higher HR. Further, women demonstrated lower parasympathetic function than men. As mentioned above, autonomic deficits have been implicated in the increased risk of cardiovascular disease in PTSD. Our findings suggest that the specific autonomic mechanisms through which cardiovascular disease develops could differ for men versus women with PTSD. For example, there is preliminary evidence that blockade of the renin-angiotensin system (responsible for BP regulation) via ace-inhibitors and angiotensin receptor blockers is associated with decreased likelihood of PTSD diagnosis (Khoury et al., 2012; Seligowski et al., 2021). We recently observed a sex effect such that the protective effects of these medications may be greater among men versus women (Seligowski et al., 2021). Thus, medications targeting BP may be more effective in men versus women with PTSD because men are more likely to experience hypertension and therefore see an effect of such medications. Prospective trials of antihypertensive medications for PTSD are needed to further explore sex differences in their effects. Another possible avenue for future trials is to determine if the autonomic deficits we observed during extinction in women with PTSD translate to clinical outcomes (e.g., do women with PTSD experience less symptom reduction from exposure treatments than men?). Thus far, sex differences in exposure-based treatments have not been reported, but we are not aware of any trials that examined sex differences in autonomic functioning during these treatments.

While capturing acute trauma reactions with a prospective design is a strength of this study, an important limitation is that our sample is not as highly symptomatic as comparisons from the literature. For example, we did not see main effects of PTSD status on BP, HR, of HF-HRV and this may be due to the recency of trauma exposure and the absence of severe PTSD symptoms in this cohort. Another limitation relates to trauma type, such that the index trauma for most participants was a motor vehicle collision and the incidence of PTSD in that population is lower than that of other trauma types, such as interpersonal violence and combat exposure (Kessler et al., 2017). Additionally, while we used a recommended cutoff for provisional PTSD diagnosis (Bovin et al., 2016) at 8-weeks, the current study relied on self-reported symptoms and did not include a structured clinical interview of PTSD. Future studies with more robust PTSD assessment among individuals with a broader range of trauma exposure will be needed to replicate and extend our findings. Despite these limitations, this study adds to a very scant literature regarding both 1) prospective assessments of posttraumatic autonomic functioning and 2) sex differences in posttraumatic autonomic functioning.

The current study identified sex differences in multiple domains of autonomic functioning among a recently traumatized sample. Our findings suggest that men and women demonstrate different patterns of sympathetic arousal, with men exhibiting higher BP and women exhibiting higher HR. Women also exhibited worse parasympathetic function as indicated by lower HF-HRV during fear conditioning, as was particularly seen in women who developed PTSD. Acute sympathetic arousal indexed by skin conductance in the emergency department was associated with HR and HF-HRV among women who developed PTSD, suggesting it may be a useful biomarker of subsequent autonomic functioning in this population. Additional studies examining subsequent sex differences in cardiovascular risk as a result of differential autonomic mechanisms are warranted.

**CRediT authorship contribution statement**

Antonia V. Seligowski: Data processing, Formal analysis, Data interpretation, Writing – original draft. Elizabeth R. Steuber: Data processing, Formal analysis, Data interpretation, Writing – original draft. Rebecca Hinrichs: Data processing, Formal analysis. Mariam H. Reda: Data processing, Formal analysis. Charis N. Wiltshire: Data processing, Formal analysis, Data interpretation.
a. FPS by sex during fear acquisition at 2-weeks

**Figure 3a.** FPS by sex during fear acquisition at 2-weeks.

**Fig. 3b.** FPS by sex during fear extinction at 2-weeks.


Declaration of competing interest

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Fig. 4a. Sex effect on HR during fear acquisition at 2-weeks
Figure 4b. Sex and interaction effects on HR during fear extinction at 2-weeks.
Fig. 5a. Sex effect on HF-HRV during fear acquisition at 2-weeks
Figure 5b. Interaction effect on HF-HRV during fear extinction at 2-weeks.
Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ynstr.2021.100384.
A.V. Seligowski et al.

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