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Sex-dependent differences in vulnerability to early risk factors for posttraumatic stress disorder: results from the AURORA study

Stephanie Haering[1,2], Antonia V. Seligowski[3], Sarah D. Linnstaedt[4], Vasiliki Michopoulos[5], Stacey L. House[6], Francesca L. Beaudoin[7,8], Xinming An[4], Thomas C. Neylan[9], Gari D. Clifford[10,11], Laura T. Germine[12,13,14], Scott L. Rauch[12,3,14], John P. Haran[15], Alan B. Storrow[16], Christopher Lewandowski[17], Paul I. Musey Jr.[18], Phyllis L. Hendry[19], Sophia Sheikh[19], Christopher W. Jones[20], Brittany E. Punches[21,22], Robert A. Swor[23], Nina T. Gentile[24], Lauren A. Hudak[25], Jose L. Pascual[26,27], Mark J. Seamon[28,27], Claire Pearson[29], David A. Peak[30], Roland C. Merchant[31], Robert M. Domeier[32], Niels K. Rathlev[33], Brian J. O'Neil[34], Leon D. Sanchez[31,35], Steven E. Bruce[36], Steven E. Harte[37,38], Samuel A. McLean[39,40], Ronald C. Kessler[41], Karestan C. Koenen[42], Jennifer S. Stevens[5,*] and Abigail Powers[5,*]

Original Article

*Dr. Stevens and Dr. Powers contributed equally as co–senior authors.

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Corresponding author:
Abigail Powers;
Email: abigail.lott@emoryhealthcare.org

Abstract

Background. Knowledge of sex differences in risk factors for posttraumatic stress disorder (PTSD) can contribute to the development of refined preventive interventions. Therefore, the aim of this study was to examine if women and men differ in their vulnerability to risk factors for PTSD.

Methods. As part of the longitudinal AURORA study, 2924 patients seeking emergency department (ED) treatment in the acute aftermath of trauma provided self-report assessments of pre- peri- and post-traumatic risk factors, as well as 3-month PTSD severity. We systematically examined sex-dependent effects of 16 risk factors that have previously been hypothesized to show different associations with PTSD severity in women and men.

Results. Women reported higher PTSD severity at 3-months post-trauma. *Z*-score comparisons indicated that for five of the 16 examined risk factors the association with 3-month PTSD severity was stronger in men than in women. In multivariable models, interaction effects with sex were observed for pre-traumatic anxiety symptoms, and acute dissociative symptoms; both showed stronger associations with PTSD in men than in women. Subgroup analyses suggested trauma type-conditional effects.

Conclusions. Our findings indicate mechanisms to which men might be particularly vulnerable, demonstrating that known PTSD risk factors might behave differently in women and men. Analyses did not identify any risk factors to which women were more vulnerable than men, pointing toward further mechanisms to explain women's higher PTSD risk. Our study illustrates the need for a more systematic examination of sex differences in contributors to PTSD severity after trauma, which may inform refined preventive interventions.

Introduction

Sex differences in posttraumatic stress disorder (PTSD) have been documented widely. Across nations, time, study type, or diagnostic criteria, women have been reported to be at higher risk for PTSD than men (Ben-Ezra et al., 2018; Frans, Rimmo, Aberg, & Fredrikson, 2005; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995; Otten et al., 2021). Among the general population, women are approximately twice as likely to develop PTSD compared to men (Goldstein et al., 2016; McCall-Hosenfeld, Mukherjee, & Lehman, 2014; Seedat et al., 2009), with the highest reported risk differences ranging up to six-folds greater odds in women (Seedat et al., 2009). In addition, current research suggests women experience more chronic and severe PTSD symptoms than men (Carmassi et al., 2014; Carragher et al., 2016; Haering et al., 2024b; Kessler et al., 1995; Tolin & Foa, 2006). While female sex is sometimes considered a PTSD risk factor itself, settling at this point disregards the underlying mechanisms that drive these risk differences. Rather than oversimplifying this relationship to a maxim in

which women fundamentally are at higher vulnerability to adverse trauma-related outcomes, a better understanding of which risk factors affect whom, when, and how will allow researchers to design interventions that tackle modifiable constructs such as cognitive, behavioral, or structural processes that are associated with sex.

Several advances have been made in explaining the prominent sex differences in PTSD outcomes. Sexual trauma, for instance, more commonly experienced by women than men (Tolin & Foa, 2006), has been found to be associated with a higher risk for PTSD compared to other trauma types (Kessler et al., 1995; Perkonigg, Kessler, Storz, & Wittchen, 2000). Yet, even when controlling for sexual trauma exposure, sex differences in PTSD prevalence and severity remain (Tolin & Foa, 2006), and sex differences in PTSD have also been found in samples of non-sexual trauma survivors, such as victims of motor vehicle accidents (Fullerton et al., 2001). In addition to characteristics of the traumatic event, sex differences in neurobiological processes, such as fear mechanisms (Dark et al., 2022; Ramikie & Ressler, 2018), as well as physiological (Lalonde et al., 2021) and psychosocial risk factors, such as acute stress responses and appraisals (Olff, 2017; Olff, Langeland, Draijer, & Gersons, 2007) have been examined. More recently, researchers also have started to study the impact of gender-related factors such as gender norms or gender role stress (Christiansen & Berke, 2020), and now are slowly beginning to examine the interplay of sex- and gender-related factors (Christiansen, McCarthy, & Seeman, 2022). Tannenbaum, Ellis, Eyssel, Zou, and Schiebinger (2019) define sex as referring to biological attributes, and gender as referring to sociocultural factors, such as gender norms, gender identity, or gender relations. As the analyses included in this study are based on sex assigned at birth, we use the term sex in this text to refer to differences between women and men, while simultaneously acknowledging that both sex and gender are important predictors of health, mutually influence each other, and are often intertwined (Krieger, 2003).

Despite recent progress, reviews on sex and/or gender differences in PTSD risk factors unanimously call for an improved consideration of sex and gender in trauma research, as the full picture of what accounts for the disparities in PTSD outcomes still remains unclear (Christiansen et al., 2022; Olff & Langeland, 2022; Ramikie & Ressler, 2018). This gap in knowledge is not surprising, however, given various methodological challenges in the examination of sex differences in PTSD risk factors: (1) First, risk factors should ideally be examined in a prospective manner. Yet, as it is difficult to foresee traumatic events, designing prospective PTSD studies is challenging. (2) Second, much of the prospective research on PTSD risk factors has been conducted in predominantly male samples, such as soldiers, police officers or firefighters (Eraly et al., 2014; Sopp, Michael, Lass-Hennemann, Haim-Nachum, & Lommen, 2021; Sørensen, Olesen, Midtgaard, & Willert, 2022). However, even in more naturalistic samples, such as prospective emergency department studies, men are studied twice as much as women (Haering et al., 2024b). The lack of female representation becomes even more apparent in psychobiological PTSD research, where only 2% of the research has been conducted in females (Olff, 2017), as it is feared that the 'messy' hormonal variability associated with the female menstrual cycle might confound study results (Bale & Epperson, 2017; Beery & Zucker, 2011). While recent research has shown that this dogma is inaccurate (Levy et al., 2023; Wiseman, 2023), the underrepresentation of females in prospective trauma research makes it hard to yield optimal conditions for the analysis of sex differences (Rechlin, Splinter, Hodges, Albert, & Galea, 2022). (3) Third, even when males and females are included in studies, sex is infrequently used as a discovery variable to examine potentially different mechanisms in women and men (Haering et al., 2024b; Rechlin et al., 2022). (4) Even if researchers are willing to conduct discovery analyses, they are faced with a lack of best practice examples on how to examine sex differences in risk factors of mental disorders. Other than in pre-clinical studies, studies on PTSD etiology usually have a limited sample size, experimental manipulation and control is not possible, and different statistical approaches come with variable advantages and disadvantages. This situation has, amongst others, led to a substantial proportion of reported sex differences not supported by sufficient statistical evidence (Garcia-Sifuentes & Maney, 2021). (5) Given ongoing controversies on publication bias (Ferguson & Heene, 2012) and hesitancy to publish null results, it is unclear if individual studies that published (statistically supported) sex differences in PTSD risk factors represent replicable insights in underlying mechanisms, or whether they are in fact just statistical artifacts. Given these shortcomings, it is still largely unclear which risk factors do or do not have sex-dependent effects in women and men.

We aimed to systematically explore sex differences in PTSD risk factors in a sample of 2924 participants (62% women) enrolled in the AURORA (Advancing Understanding of RecOvery afteR traumA) study, a prospective multisite longitudinal study of the onset and course of adverse posttraumatic neuropsychiatric sequalae. We pre-registered a sex-sensitive framework to systematically explore sex differences in PTSD risk factors with the AURORA consortium (Haering, Stevens, & Powers, 2022). The focus of the current study was to determine if a sex-dependent vulnerability to PTSD risk factors might contribute to women's higher PTSD severity 3-months post-acute trauma, i.e. to examine whether sex moderates the association between a risk factor and PTSD in a way that the strength, significance and/or direction of the association differs between women and men. We selected our predictors of interest based on a literature review of sex differences in PTSD predictors (Christiansen, 2016). Predictors that are assumed to be associated with PTSD differently for men and women, and were assessed in the AURORA study, were included in this analysis. Specifically, preexisting anxiety symptoms, prior trauma exposure, and peritraumatic distress as well as lower socioeconomic status, being member of a marginalized group, being unmarried or being unemployed have been summarized as risk factors more strongly associated with PTSD in men. On the other hand, preexisting depression symptoms, anxiety sensitivity, neuroticism, peritraumatic life threat and dissociation, as well as lack of social support and acute stress disorder have been summarized as risk factors more strongly associated with PTSD in women. Finally, mixed findings have been reported regarding the interaction of sex and age (Christiansen, 2016). In addition to these factors, we further included lifetime sexual assault exposure into our investigation of sex-dependent vulnerabilities. Although sex differences in sexual assault exposure are well-established, the impact of lifetime sexual assault exposure as a risk factor for posttraumatic dysfunction following a *new* trauma exposure has been less explored. Yet, recent evidence has highlighted the role of prior sexual assault exposure on subsequent trauma exposure (Rowland et al., 2023). Thus, we determined, whether the vulnerability to the aforementioned 16 pre-, peri-, and post-traumatic PTSD predictors differed between acutely traumatized women and men.

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Methods

Participants and procedure

Data from the $n = 2924$ AURORA participants ($n = 1124$ men and $n = 1818$ women) were collected from September 2017 through June 2021. Detailed information on participant characteristics is given in Table 1. An overview of risk factors by sex and by trauma type (mvc *v.* non-mvc trauma) is presented in eTable 1 and eTable 2 in the Supplement.

The AURORA study procedures are described in detail elsewhere (McLean et al., 2020). In brief, AURORA participants were adults who had experienced a traumatic event within the past 72 h and were evaluated in one of 29 emergency departments (ED) across the United States. Participants were 18–75 years old, able to speak and read English, able to comprehend the enrollment protocol, and possessed a smartphone and e-mail address. Participants were excluded from data collection if they were or became pregnant or incarcerated. In addition, we excluded one participant with missing information on sex assigned at birth. Participants completed assessments in the ED (baseline), and at scheduled follow-ups, during which information on psychological symptoms, physical health, and functioning was assessed. Data for the analyses in this report were collected via self-report at baseline, 2 weeks, 8 weeks, and 3 months post-trauma. All participants provided written informed consent and were compensated for their study participation at each follow-up. The project was approved by each participating institutional review board. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Measures

We assessed 16 PTSD risk factors spanning pre-, peri-, and acute posttraumatic predictors. Pre-traumatic predictors included age, race–ethnicity, marital status, education, income, employment status, pre-trauma depression symptoms, pre-trauma anxiety symptoms, neuroticism and trauma load and lifetime exposure to sexual assault. Peri-traumatic risk factors included peritraumatic distress and perceived life threat; and acute post-traumatic predictors included social support, acute stress disorder, and acute dissociative symptoms. Sex assigned at birth was used as stratification variable. Detailed information on all measures is presented in Supplement 1.

Outcome

The outcome evaluated was self-reported PTSD severity at the 3-month follow-up, as assessed by the PTSD Symptom Checklist for DSM-5 (PCL-5). The PCL-5 is a 20 item self-report questionnaire that assesses the presence and severity of various posttraumatic stress symptoms (Weathers et al., 2013). Participants rated the severity of each symptom on a scale of 0 (*not at all*) to 4 (*extremely*), and items were summed to create a total severity score.

Statistical analysis

All analyses were conducted in R version 4.2.1 (R Core Team, 2022). The code for all analyses can be found in the OSF repository: https://osf.io/tkncz/. Missing values for constructs that were assessed longitudinally in the AURORA study (depressive symptoms, anxiety symptoms, acute dissociative symptoms, and social support) were imputed using multiple imputation with predictive mean matching via the *aregImpute* function of the Hmisc package (Harrell, 2022), including the respective longitudinal assessments of each construct as auxiliary variables. In line with current recommendations for imputing data when moderation analyses are planned, missing values were imputed separately for males and females (Heymans & Eekhout, 2019). Student's *t* tests and χ^2 tests were performed to analyze sex differences in continuous and categorical variables, respectively.

To examine a sex-dependent vulnerability to the selected risk factors, we first calculated sex-disaggregated associations between each predictor and 3-month PTSD severity. As suggested by Christiansen, Olff, and Elklit (2014) the equality of coefficients was tested using Fisher's *z* tests and Zou's confidence intervals, applying the package *cocor* (Diedenhofen & Musch, 2015). Adapted from Jun et al. (2021) we then performed multivariable regression models controlling for participant demographics, baseline mental health, and life-time sexual assault exposure, and conducted subgroup analyses by including an interaction term between sex and the subgroup variable to the multivariable model. This procedure was done for each subgroup variable to identify significant effect differences between women and men. Finally, to assess the robustness of results across trauma types, we performed sensitivity analyses with the motor vehicle collision subgroup only ($n = 2194$, 74.6% of the full sample). Categorical variables were dummy coded, continuous variables were standardized for model estimations. Statistical significance was evaluated using 0.05-level two-sided tests. Most of the risk factors were positively associated with each other (see eTable 3). In spite of this inter-correlation, examination of the variance inflation factors (VIF) provided no indication of multicollinearity of the 16 predictors (all VIF < 3).

Results

Women and men differed significantly in PTSD severity at three months post trauma, with women scoring higher on the PCL-5 than men (M (S.D.)$_f = 26.7$ (18.9); M (S.D.)$_m = 22.3$ (19.3); $p < 0.001$). PTSD severity also differed by sex in the subgroup of participants with motor vehicle collisions (MVC; M (S.D.)$_{f\_mvc} = 26.6$ (18.8); M (S.D.)$_{m\_mvc} = 22.1$ (19.4); $p < 0.001$), which accounted for 74.6% of index trauma types in this sample. Sexual assault as index trauma was reported by less than 1% of all participants. As shown in Fig. 1, all 16 risk factors revealed statistically significant univariable associations with 3-month PTSD severity in men. In women, these associations were present for all predictors except for age and minority status. Statistical comparison of the male and female correlations demonstrated significant sex-dependent differences in the association of PTSD severity and five risk factors: acute dissociation (difference d, [95% CI] = −0.09 [−0.14 to −0.03], $p = 0.002$), peritraumatic distress ($d = -0.08$ [−0.15 to −0.01], $p = 0.018$), pre-traumatic anxiety symptoms ($d = -0.07$ [−0.13 to −0.01], $p = 0.027$), the participant-reported chance of dying during the index event ($d = -0.07$ [−0.14 to 0.00], $p = 0.044$), and acute stress disorder ($d = -0.05$ [−0.09 to −0.00], $p = 0.039$). As depicted in Fig. 1, the univariable correlations for all these six risk factors with PTSD severity were stronger in men than in women.

In a multi-variable regression model adjusting for participant demographics, baseline mental health, and lifetime sexual assault exposure, female sex remained an independent predictor of PTSD

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Table 1. Demographic and trauma characteristics

	Men ($N = 1124$)	Women ($N = 1818$)	p value	Overall ($N = 2942$)
Age mean (s.d.)	36.1 (13.1)	35.8 (13.4)	0.586	35.9 (13.3)
Race/Ethnicity[a]			0.213	
Hispanic	144 (12.8%)	197 (10.8%)		341 (11.6%)
Non-Hispanic Black	533 (47.4%)	925 (50.9%)		1458 (49.6%)
Non-Hispanic White	397 (35.3%)	623 (34.3%)		1020 (34.7%)
Race/Ethnicity not listed	45 (4.0%)	66 (3.6%)		111 (3.8%)
Marriage status			0.106	
Currently married	242 (21.5%)	365 (20.1%)		607 (20.6%)
Previously married	173 (15.4%)	334 (18.4%)		507 (17.2%)
Never married	701 (62.4%)	1110 (61.1%)		1811 (61.6%)
Highest degree[b]			<0.001	
Less than high school	153 (13.6%)	186 (10.2%)		339 (11.5%)
High school	764 (68.0%)	1207 (66.4%)		1971 (67.0%)
College	204 (18.1%)	419 (23.0%)		623 (21.2%)
Curently unemployed[c]	180 (16.0%)	293 (16.1%)	0.676	473 (16.1%)
Family income/year[d]			0.144	
Less than 19 k	304 (27.0%)	546 (30.0%)		850 (28.9%)
Between 19 k and 35 k	283 (25.2%)	511 (28.1%)		794 (27.0%)
More than 35 k	371 (33.0%)	566 (31.1%)		937 (31.8%)
Index trauma			<0.001	
mvc	756 (67.3%)	1438 (79.1%)		2194 (74.6%)
physical assault	143 (12.7%)	128 (7.0%)		271 (9.2%)
fall, <10 feet	52 (4.6%)	109 (6.0%)		161 (5.5%)
animal-related	25 (2.2%)	38 (2.1%)		63 (2.1%)
non-mvc collision	32 (2.8%)	21 (1.2%)		53 (1.8%)
fall, ≥10 feet	34 (3.0%)	17 (0.9%)		51 (1.7%)
sexual assault	0 (0%)	17 (0.9%)		17 (0.6%)
burns	6 (0.5%)	8 (0.4%)		14 (0.5%)
disaster[f]	7 (0.6%)	5 (0.3%)		12 (0.4%)
poisoning	1 (0.1%)	1 (0.1%)		2 (0.1%)
other	68 (6.0%)	36 (2.0%)		104 (3.5%)
Lifetime sexual assault exposure[e]	88 (7.8%)	547 (30.1%)	<0.001	635 (21.6%)

Note: Data available for [a]99.6%, [b]99.7%, [c]88.2%, [d]87.7%, [e]83.3% of the sample, respectively; [f]Event exposing participant and at least several other individuals to traumatic stress, not covered by other categories (e.g. plane crash, natural disaster).

severity at 3-months (β [s.e.] = 0.13 [0.04], $p < 0.001$, see eTable 4 in the Supplement). Using this model as baseline model, we next performed subgroup analyses to identify significant interactions between sex and each of our predictors of interest (Fig. 2): Analyses identified a statistically significant interaction effect for pre-traumatic anxiety symptoms ($\beta = -0.11$ [0.04], $p = 0.005$) and acute dissociative symptoms ($\beta = -0.10$ [0.04], $p = 0.003$). Figure 3 depicts the sex-by-risk factor interaction effects under the specified model: the graphs show that women and men diverge at the lower end of the risk factor spectrum, with women showing more PTSD symptoms even at lower levels of anxiety and dissociation. Due to men's higher vulnerability to pre-traumatic anxiety and acute dissociative symptoms, PTSD levels of women and men converge at the upper end of the risk factor spectrum. For the remaining predictors, no significant sex differences in the association with PTSD were detected. Our subgroup analyses identified main effects (but no interaction effects) for acute stress disorder ($\beta = 0.56$ [0.03], $p < 0.001$), anxiety sensitivity ($\beta = 0.44$ [0.03], $p < 0.001$), neuroticism ($\beta = 0.38$, [0.03], $p < 0.001$), lifetime sexual assault ($\beta = 0.29$ [0.10], $p = 0.005$), pre-traumatic depressive symptoms ($\beta = 0.26$ [0.04], $p < 0.001$), peri-traumatic distress ($\beta = 0.24$ [0.03], $p < 0.001$), chance of dying ($\beta = 0.20$ [0.04], $p < 0.001$), minority status ($\beta = 0.17$ [0.07], $p = 0.008$), family income < 19 k ($\beta = 0.14$ [0.07], $p = 0.040$), social

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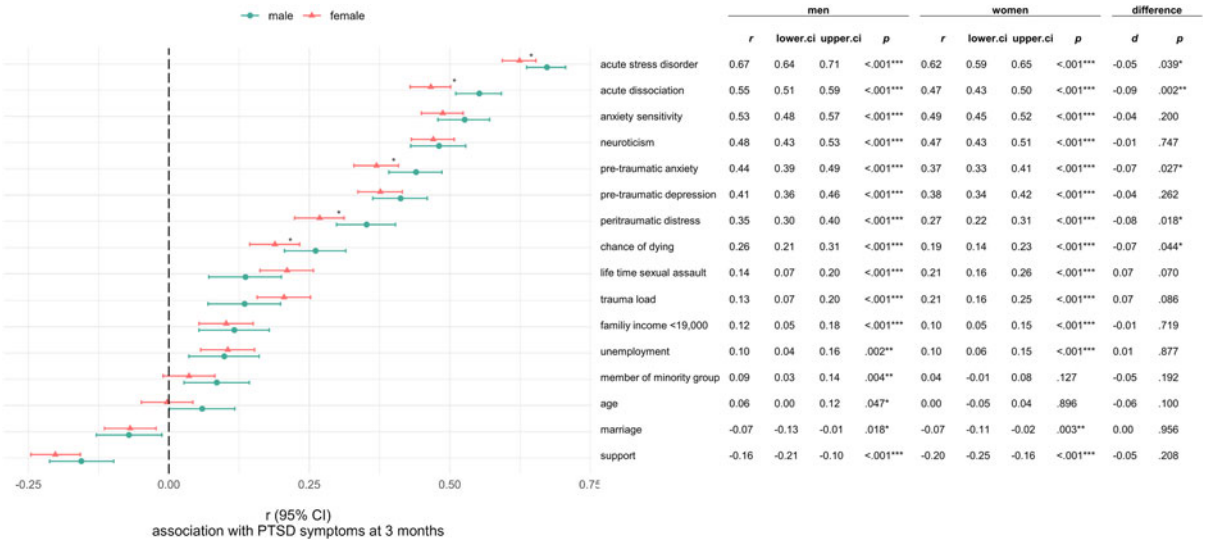
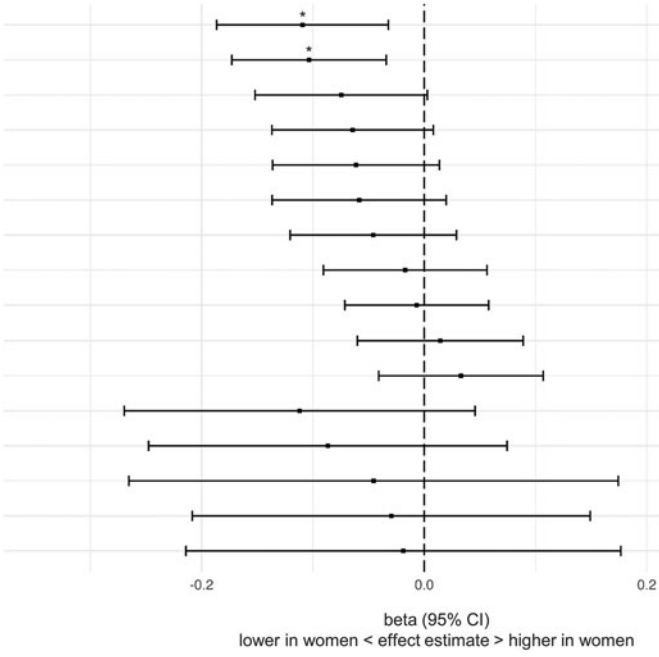


	men				women				difference	
	r	lower.ci	upper.ci	p	r	lower.ci	upper.ci	p	d	p
acute stress disorder	0.67	0.64	0.71	<.001***	0.62	0.59	0.65	<.001***	-0.05	.039*
acute dissociation	0.55	0.51	0.59	<.001***	0.47	0.43	0.50	<.001***	-0.09	.002**
anxiety sensitivity	0.53	0.48	0.57	<.001***	0.49	0.45	0.52	<.001***	-0.04	.200
neuroticism	0.48	0.43	0.53	<.001***	0.47	0.43	0.51	<.001***	-0.01	.747
pre-traumatic anxiety	0.44	0.39	0.49	<.001***	0.37	0.33	0.41	<.001***	-0.07	.027*
pre-traumatic depression	0.41	0.36	0.46	<.001***	0.38	0.34	0.42	<.001***	-0.04	.262
peritraumatic distress	0.35	0.30	0.40	<.001***	0.27	0.22	0.31	<.001***	-0.08	.018*
chance of dying	0.26	0.21	0.31	<.001***	0.19	0.14	0.23	<.001***	-0.07	.044*
life time sexual assault	0.14	0.07	0.20	<.001***	0.21	0.16	0.26	<.001***	0.07	.070
trauma load	0.13	0.07	0.20	<.001***	0.21	0.16	0.25	<.001***	0.07	.086
familiy income <19,000	0.12	0.05	0.18	<.001***	0.10	0.05	0.15	<.001***	-0.01	.719
unemployment	0.10	0.04	0.16	.002**	0.10	0.06	0.15	<.001***	0.01	.877
member of minority group	0.09	0.03	0.14	.004**	0.04	-0.01	0.08	.127	-0.05	.192
age	0.06	0.00	0.12	.047*	0.00	-0.05	0.04	.896	-0.06	.100
marriage	-0.07	-0.13	-0.01	.018*	-0.07	-0.11	-0.02	.003**	0.00	.956
support	-0.16	-0.21	-0.10	<.001***	-0.20	-0.25	-0.16	<.001***	-0.05	.208

Figure 1. Sex-disaggregated associations with 3-month PTSD severity. The forest plot depicts the univariable associations of each predictor with PTSD severity at 3-months post-trauma disaggregated by sex. The correlations are depicted in blue for men and in red for women. The equality of coefficients was tested using Fisher's *z* tests.

support ($\beta = -0.13$, [0.03], $p < 0.001$), age ($\beta = 0.09$ [0.04], $p = 0.006$), and trauma load ($\beta = 0.07$ [0.04], $p = 0.014$).

Sensitivity analyses for the motor vehicle collision (MVC) subgroup showed that sex differences in univariable comparisons remained robust for twelve of the 16 risk factors assessed. Compared to the main analyses, sex differences were no longer found for pre-traumatic anxiety symptoms and participant-reported chance of dying during the index event (see eTable 5). However, among the MVC subgroup significant sex differences were observed for the associations of 3-month PTSD severity with trauma load ($d = 0.11$ [0.01–0.20], $p = 0.027$) and lifetime sexual assault exposure ($d = 0.14$ [0.04–0.24], $p = 0.005$). In contrast to previous results among the full sample, analyses in the MVC subgroup thus revealed two risk factors for which associations with 3-month PTSD severity were stronger in female than male MVC-exposed individuals, and both reflected exposure to prior stressors, whereas the major risk factors favoring men reflected internal trait-like factors.



	beta	ci.lower	ci.upper	p
pre-traumatic anxiety	-0.11	-0.19	-0.03	.005**
dissociation	-0.10	-0.17	-0.03	.003**
pre-traumatic depression	-0.07	-0.15	0.00	.059
age	-0.06	-0.14	0.01	.109
anxiety sensitivity	-0.06	-0.14	0.01	.082
peritraumatic distress	-0.06	-0.14	0.02	.143
chance of dying	-0.05	-0.12	0.03	.230
neuroticism	-0.02	-0.09	0.06	.648
acute stress disorder	-0.01	-0.07	0.06	.838
support	0.01	-0.06	0.09	.705
trauma load	0.03	-0.04	0.11	.382
member of minority group	-0.11	-0.27	0.05	.164
familiy income <19,000	-0.09	-0.25	0.07	.292
life time sexual assault	-0.05	-0.27	0.17	.685
marriage	-0.03	-0.21	0.15	.745
unemployment	-0.02	-0.21	0.18	.851

Figure 2. Subgroup analysis for female sex as a predictor of PTSD severity at 3 months. The forest plot depicts the parameter estimate and 95% confidence interval associated with female sex (*v.* male sex as the reference group) within the subgroup specified in a multivariable regression model, including an interaction term between the subgroup variable and sex, adjusting for demographics, baseline mental health and lifetime sexual assault. Continuous variables were standardized, categorical variables were dummy coded.

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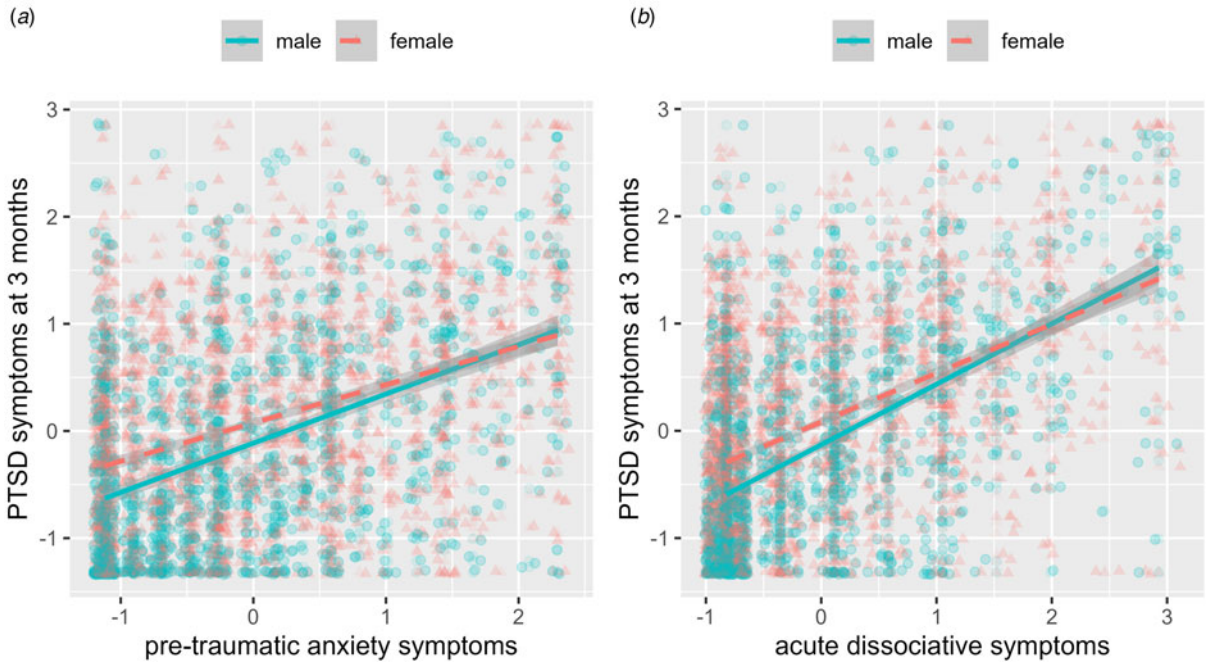

Figure 3. Interaction effects of sex and (a) pre-traumatic anxiety and (b) dissociation at week two post-trauma. The scatter plots depict the interaction effect of sex and (a) pre-traumatic anxiety symptoms as well as (b) dissociative symptoms at two weeks post-trauma, controlling for demographics, baseline mental health, and lifetime sexual assault. All variables were standardized to an overall sample mean of 0 and a standard deviation of 1.

In MVC subgroup analyses of the multivariable models, sex remained a robust moderator of acute dissociative symptoms ($\beta = -0.11$ [0.04], $p = 0.007$). Moreover, an interaction of sex with anxiety sensitivity was observed ($\beta = -0.09$ [0.05], $p = 0.044$), albeit with the 95% confidence interval nearly including zero. Detailed results of the multivariable MVC subgroup analyses are presented in eTable 6.

Discussion

The current study systematically examined sex differences in the vulnerability to PTSD risk factors to better understand which processes drive the prominent sex disparities in PTSD outcomes. In univariable analyses we found sex-dependent associations with 3-month PTSD severity in five of 16 risk factors, which previously had been hypothesized to show different associations with PTSD for women and men: pre-traumatic anxiety symptoms, peritraumatic distress, perceived chance of dying during the trauma, acute dissociative symptoms, and acute stress disorder symptoms showed stronger associations with PTSD severity at 3 months in men than in women. Two of these predictors, pre-traumatic anxiety and acute dissociative symptoms, also showed sex-dependent effects in multivariable models with interaction terms, indicating men might be more vulnerable to these risk factors than women, even when controlling for demographics and baseline mental health. Our main analyses did not indicate any risk factor to which women were more vulnerable, which was surprising given the selection of predictors based on prior research (Christiansen, 2016). Subgroup analyses of an MVC-only sample suggested trauma type-conditional sex vulnerabilities for trauma load and lifetime sexual assault exposure. Finally, a number of known PTSD risk factors showed similar predictive value for females and males, both in the main and subgroup analysis, including age, income below poverty line, racial/ethnic minority status, social support, trauma severity, and a variety of symptoms and personality factors.

Our study suggests how underlying processes may contribute differentially toward PTSD severity in men and in women. The results of our main analyses highlight two risk factors that consistently showed a stronger impact on men compared to women. First, pre-existing anxiety symptoms were more strongly related to PTSD severity in men than in women. This finding is in line with previous research, suggesting traumatized men are more vulnerable to pre-existing anxiety than women (Bromet, Sonnega, & Kessler, 1998; Christiansen & Elklit, 2008, 2012). Second, acute dissociation also showed stronger associations with PTSD severity in men than in women. Given previous evidence on sex-dependent effects of dissociation (Bryant & Harvey, 2003; Christiansen & Elklit, 2008; Fullerton et al., 2001), which suggested a stronger negative impact in women, this finding is unexpected. However, among prior studies, peritraumatic dissociative experiences rather than acute dissociative responses were examined (Fullerton et al., 2001), and reporting of sex differences was not always supported by sufficient statistical evidence (Bryant & Harvey, 2003; Christiansen & Elklit, 2008; Garcia-Sifuentes & Maney, 2021). Interpreting our results, it might be that men with high levels of dissociative experience are at greater risk for PTSD symptoms than women, as greater mental health stigma among men amplifies the negative impact of maladaptive cognitive beliefs. Previous evidence has shown a link between negative appraisals of initial PTSD symptoms (such as dissociative experiences) with later PTSD outcomes (Brown, Wood, Carter, & Kannis-Dymand, 2022; Kannis-Dymand, Carter, Lane, & Innes, 2019). Such negative appraisals include for instance interpretations of PTSD symptoms as meaning 'I am going crazy' (Steil & Ehlers, 2000). Given that men seem to hold greater stigmatizing beliefs about mental health symptoms (Bradbury, 2020; Chandra & Minkovitz, 2006), it might be that

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seemingly 'abnormal' experiences like dissociative experiences are more strongly linked to PTSD severity in men than in women, as men might have greater negative interpretations about them, which in turn affects PTSD development and maintenance.

Of note, within our study the majority of risk factors showed tendencies toward stronger negative impacts in men, i.e. a male vulnerability. Despite women's higher PTSD risk, these findings warrant the need for a closer examination of PTSD risk factors from a men-centered perspective. For men, our results suggest possible mechanisms that might be targeted when designing sex-sensitive preventive interventions, especially since men benefit less from trauma-focused treatment interventions for manifested PTSD. Exploring effective prevention options that integrate our full knowledge on sex-dependent mechanisms is needed.

Although our main analyses did not identify any risk factors to which women were more vulnerable than men, sensitivity analyses point toward trauma type-conditional effects: In sub-group analyses of the MVC sample, trauma load and lifetime sexual assault exposure entered in as sex-dependent risk factors, showing greater univariable associations with 3-month PTSD severity in women than in men. Interestingly, only MVC-specific analyses revealed risk factors to which women were more vulnerable to than men. Our subgroup analyses of the MVC sample thus suggest that for MVC-exposed individuals, men might be more vulnerable to internal factors, whereas women might be more vulnerable to external, exposure-based factors. One reason for the differences in the main *v.* subgroup analyses might be the fact that after an MVC, individuals are generally less likely to develop PTSD symptoms compared to other trauma types (e.g. interpersonal trauma; Kessler et al. (2017)). Thus, predisposing factors such as exposure-based predictors for women (i.e. lifetime sexual assault exposure, trauma load), might carry more weight in accidental traumas than in assault-based traumas, where individuals are at a higher risk for PTSD symptom development and variables such as perpetration characteristics may become more salient. Clearly, our findings once more are a testament to the intricate interplay of sex and trauma type which needs to be better understood in order to realize the full potential of targeted interventions.

Importantly, even though women in our main sample were less affected by the negative impacts of pre-existing anxiety or acute dissociation symptoms, they largely still experienced greater PTSD symptoms than men. Our results highlight the need to explore further aspects that contribute to women's higher PTSD severity, including different constructs, pathways, and mechanisms. For instance, understanding how sex interacts with cognitive factors might provide modifiable targets for early interventions. Furthermore, greater knowledge about hormonal (Ney, Gogos, Ken Hsu, & Felmingham, 2019) or genetic (Yu et al., 2018) factors can increase our knowledge of sex-based contributors to PTSD. Finally, independent of vulnerability differences, i.e. differences in the strength of an association between a risk factor and PTSD severity, differences in risk factor prevalence/severity among women and men can further contribute to sex differences in PTSD severity. Thus, greater exposure to certain risk factors (Christiansen & Hansen, 2015) might help to explain women's higher PTSD severity in the present sample. A systematic overview of risk pathways between sex and PTSD as well as a complementary analysis is presented in Haering et al. (2024c). A clear distinction between various forms of sex-related effects will not only help to better understand sex differences in mental health outcomes, it will also help to create a more rigorous and replicable mental health science.

Several limitations need to be taken into consideration when looking at our findings. Possible selection bias in who gets treated in the ED after trauma may impact generalizability of results. While EDs visits present a unique opportunity for providing traumatized individuals with secondary interventions, it is unclear, to what extent our findings may be transferable to other study contexts. It is furthermore not clear, whether results are generalizable across cultures, as data for this study was collected in the US only. Future research with international (Haering et al., 2024a; Young & Chan, 2015) as well as intersectional (Bryant-Davis, 2019; Crenshaw, 2013; Seng, Lopez, Sperlich, Hamama, & Reed Meldrum, 2012) perspectives can help to further improve our understanding of health disparities in trauma-related health outcomes and beyond. Furthermore, the majority of participants included in this study were individuals who experienced an MVC. Future research should aim to specifically target large and diverse samples beyond MVC-exposed individuals to disentangle how sex and trauma characteristics interact in the case of physical and sexual assault as well as other trauma types. Another limitation includes the assessment of PTSD symptoms via self-report. Clinician-based interviews have been shown to increase diagnostic accuracy through better comprehension of symptoms or increased awareness (Kramer, Whiteman, Petri, Spitzer, & Weathers, 2023). Finally, this study is limited to the analysis of sex differences. To fully disentangle why women are more vulnerable to PTSD development, future studies should take gender-related aspects as well as the interplay of sex and gender into account. These limitations notwithstanding, to the best of our knowledge, this study was the first to examine how the effects of a comprehensive set of risk factors, that have previously been suggested to show sex-differential associations with PTSD development, differs between men and women. The strengths of our study include its prospective design, controlled timing of assessments following trauma, as well as size and diversity of the study sample. Moreover, all statistical code for the analyses is shared open-access, and we encourage researchers to perform replication analyses to examine the generalizability of our findings in further study cohorts.

In summary, our study highlights the need for more sex- and gender-sensitive examinations of PTSD risk factors. Our results point toward the need to consider other pathways and mechanisms to explain women's higher PTSD risk. Our study also indicates mechanisms to which men might be particularly vulnerable. Continuing our efforts to disentangle sex differences in PTSD risk factors can help to more accurately understand how underlying mechanisms contribute toward an individual's PTSD risk and may lead to the development of refined targeted preventive interventions.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291724000941.

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Author contributions. **Conceptualization:** Samuel A. McLean, Ronald C. Kessler, Karestan C. Koenen, Stephanie Haering, Abigail Powers, Jennifer S. Stevens, Antonia Seligowski, Sarah Linnstaedt, Vasiliki Michopoulos; **Methodology:** Stacey L. House, Francesca L. Beaudoin, Xinming An, Jennifer S. Stevens, Thomas C. Neylan, Gari D. Clifford, Sarah D. Linnstaedt, Laura T. Germine, Scott L. Rauch, Samuel A. McLean, Ronald C. Kessler, Karestan C. Koenen; **Formal analysis:** Stephanie Haering, Abigail Powers, Jennifer S. Stevens; **Investigation:** Stacey L. House, Francesca L. Beaudoin, Xinming An, Jennifer S. Stevens, Thomas C. Neylan, Gari D. Clifford, Sarah D. Linnstaedt, Laura T. Germine, Scott L. Rauch, John P. Haran, Alan B. Storrow, Paul I. Musey Jr., Phyllis L. Hendry, Sophia Sheikh, Christopher W. Jones, Brittany E. Punches, Robert A. Swor, Nina T. Gentile, Lauren A. Hudak, Jose L. Pascual, Mark J. Seamon, Claire Pearson, David A. Peak, Roland C. Merchant, Robert M. Domeier, Niels K. Rathlev, Brian J. O'Neil, Leon D. Sanchez, Steven E. Bruce, Samuel A. McLean, Ronald C. Kessler, Karestan C. Koenen; **Resources:** Stacey L. House, Francesca L. Beaudoin, Xinming An, Jennifer S. Stevens, Thomas C. Neylan, Gari D. Clifford, Sarah D. Linnstaedt, Laura T. Germine, Scott L. Rauch, John P. Haran, Alan B. Storrow, Paul I. Musey Jr., Phyllis L. Hendry, Sophia Sheikh, Christopher W. Jones, Brittany E. Punches, Robert A. Swor, Nina T. Gentile, Lauren A. Hudak, Jose L. Pascual, Mark J. Seamon, Claire Pearson, David A. Peak, Roland C. Merchant, Robert M. Domeier, Niels K. Rathlev, Brian J. O'Neil, Leon D. Sanchez, Steven E. Bruce, Samuel A. McLean, Ronald C. Kessler, Karestan C. Koenen; **Data Curation:** Stacey L. House, Francesca L. Beaudoin, Xinming An, Jennifer S. Stevens, Thomas C. Neylan, Gari D. Clifford, Sarah D. Linnstaedt, Laura T. Germine, Scott L. Rauch, Samuel A. McLean, Ronald C. Kessler, Karestan C. Koenen; **Writing – Original Draft:** Stephanie Haering, Abigail Powers, Jennifer S. Stevens; **Writing – Review & Editing:** Antonia Seligowski, Sarah Linnstaedt, Vasiliki Michopoulos, Stacey L. House, Francesca L. Beaudoin, Xinming An, Thomas C. Neylan; Gari D. Clifford; Laura T. Germine; Scott L. Rauch; John P. Haran, Alan B. Storrow, Christopher Lewandowski, Paul I. Musey Jr., Phyllis L. Hendry, Sophia Sheikh, Christopher W. Jones, Brittany E. Punches, Robert A. Swor, Nina T. Gentile, Lauren A. Hudak, Jose L. Pascual, Mark J. Seamon, Claire Pearson, David A. Peak, Roland C. Merchant, Robert M. Domeier, Niels K. Rathlev, Brian J. O'Neil, Leon D. Sanchez, Steven E. Bruce; Steven E. Harte Samuel A. McLean, Ronald C. Kessler; Karestan C. Koenen; Jennifer S. Stevens, Abigail Powers **Visualization:** Stephanie Haering, Abigail Powers, Jennifer S. Stevens; **Supervision:** Samuel A. McLean, Ronald C. Kessler, Karestan C. Koenen, Stephanie Haering, Jennifer S. Stevens, Abigail Powers; **Project Administration:** Stacey L. House, Francesca L. Beaudoin, Jennifer S. Stevens, John P. Haran, Alan B. Storrow, Paul I. Musey Jr., Phyllis L. Hendry, Sophia Sheikh, Christopher W. Jones, Brittany E. Punches, Robert A. Swor, Nina T. Gentile, Lauren A. Hudak, Jose L. Pascual, Mark J. Seamon, Claire Pearson, David A. Peak, Roland C. Merchant, Robert M. Domeier, Niels K. Rathlev, Brian J. O'Neil, Leon D. Sanchez, Steven E. Bruce, Samuel A. McLean, Ronald C. Kessler, Karestan C. Koenen; **Funding Acquisition:** Samuel A. McLean, Ronald C. Kessler, Karestan C. Koenen. All authors revised the paper critically for important intellectual context and approved the final manuscript.

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Competing interests

- Dr Neylan has received research support from NIH, VA, and Rainwater Charitable Foundation, and consulting income from Jazz Pharmaceuticals.
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- In the past 3 years, Dr Kessler was a consultant for Cambridge Health Alliance, Canandaigua VA Medical Center, Holmusk, Partners Healthcare, Inc., RallyPoint Networks, Inc., and Sage Therapeutics. He has stock options in Cerebral Inc., Mirah, PYM, and Roga Sciences.
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[1]Department of Education and Psychology, Clinical Psychological Intervention, Freie Universität Berlin, Berlin, Germany; [2]Charité Center for Health and Human Sciences, Gender in Medicine, Charité-Universitätsmedizin Berlin, Berlin, Germany; [3]Department of Psychiatry, McLean Hospital, Belmont, MA, USA; [4]Department of Anesthesiology, Institute for Trauma Recovery, University of

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North Carolina at Chapel Hill, Chapel Hill, NC, USA; [5]Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA; [6]Department of Emergency Medicine, Washington University School of Medicine, St. Louis, MO, USA; [7]Department of Epidemiology, Brown University, Providence, RI, USA; [8]Department of Emergency Medicine, Brown University, Providence, RI, USA; [9]Departments of Psychiatry and Neurology, University of California San Francisco, San Francisco, CA, USA; [10]Department of Biomedical Informatics, Emory University School of Medicine, Atlanta, GA, USA; [11]Department of Biomedical Engineering, Georgia Institute of Technology and Emory University, Atlanta, GA, USA; [12]Institute for Technology in Psychiatry, McLean Hospital, Belmont, MA, USA; [13]The Many Brains Project, Belmont, MA, USA; [14]Department of Psychiatry, Harvard Medical School, Boston, MA, USA; [15]Department of Emergency Medicine, University of Massachusetts Chan Medical School, Worcester, MA, USA; [16]Department of Emergency Medicine, Vanderbilt University Medical Center, Nashville, TN, USA; [17]Department of Emergency Medicine, Henry Ford Health System, Detroit, MI, USA; [18]Department of Emergency Medicine, Indiana University School of Medicine, Indianapolis, IN, USA; [19]Department of Emergency Medicine, University of Florida College of Medicine -Jacksonville, Jacksonville, FL, USA; [20]Department of Emergency Medicine, Cooper Medical School of Rowan University, Camden, NJ, USA; [21]Department of Emergency Medicine, Ohio State University College of Medicine, Columbus, OH, USA; [22]Ohio State University College of Nursing, Columbus, OH, USA; [23]Department of Emergency Medicine, Oakland University William Beaumont School of Medicine, Rochester, MI, USA; [24]Department of Emergency Medicine, Lewis Katz School of Medicine, Temple University, Philadelphia, PA, USA; [25]Department of Emergency Medicine, Emory University School of Medicine, Atlanta, GA, USA; [26]Department of Surgery, Department of Neurosurgery, University of Pennsylvania, Philadelphia, PA, USA; [27]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [28]Department of Surgery, Division of Traumatology, Surgical Critical Care and Emergency Surgery, University of Pennsylvania, Philadelphia, PA, USA; [29]Department of Emergency Medicine, Wayne State University, Ascension St. John Hospital, Detroit, MI, USA; [30]Department of Emergency Medicine, Massachusetts General Hospital, Boston, MA, USA; [31]Department of Emergency Medicine, Brigham and Women's Hospital, Boston, MA, USA; [32]Department of Emergency Medicine, Trinity Health-Ann Arbor, Ypsilanti, MI, USA; [33]Department of Emergency Medicine, University of Massachusetts Medical School-Baystate, Springfield, MA, USA; [34]Department of Emergency Medicine, Wayne State University, Detroit Receiving Hospital, Detroit, MI, USA; [35]Department of Emergency Medicine, Harvard Medical School, Boston, MA, USA; [36]Department of Psychological Sciences, University of Missouri – St. Louis, St. Louis, MO, USA; [37]Department of Anesthesiology, University of Michigan Medical School, Ann Arbor, MI, USA; [38]Department of Internal Medicine-Rheumatology, University of Michigan Medical School, Ann Arbor, MI, USA; [39]Department of Emergency Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [40]Department of Psychiatry, Institute for Trauma Recovery, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [41]Department of Health Care Policy, Harvard Medical School, Boston, MA, USA and [42]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Harvard University, Boston, MA, USA

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