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-Dr. Neylan has received research support from NIH, VA, and Rainwater Charitable Foundation, and consulting income from Jazz Pharmaceuticals.

- In the last three years Dr. Clifford has received research funding from the NSF, NIH and LifeBell AI, and unrestricted donations from AliveCor Inc, Amazon Research, the Center for Discovery, the Gates Foundation, Google, the Gordon and Betty Moore Foundation, MathWorks, Microsoft Research, Nextsense Inc, One Mind Foundation, the Rett Research Foundation, and Samsung Research. Dr Clifford has financial interest in AliveCor Inc and Nextsense Inc. He also is the CTO of MindChild Medical and CSO of LifeBell AI and has ownership in both companies. These relationships are unconnected to the current work.

- Dr. Germine receives funding from the National Institute of Mental Health (R01 MH121617) and is on the board of the Many Brains Project. Dr. Germine's family also has equity in Intelerad Medical Systems, Inc.

-Dr. Rauch reports grants from NIH during the conduct of the study; personal fees from SOBP (Society of Biological Psychiatry) paid role as secretary, other from Oxford University Press royalties, other from APP (American Psychiatric Publishing Inc.) royalties, other from VA (Veterans Administration) per diem for oversight committee, and other from Community Psychiatry/Mindpath Health paid board service, including equity outside the submitted work; other from National Association of Behavioral Healthcare for paid Board service; other from Springer Publishing royalties; and Leadership roles on Board or Council for SOBP, ADAA (Anxiety and Depression Association of America), and NNDC (National Network of Depression Centers).

- Dr. Jones has no competing interests related to this work, though he has been an investigator on studies funded by AstraZeneca, Vapotherm, Abbott, and Ophirex.

- Dr. Harte has no competing interest related to this work, though in the last three years he has received research funding from Aptinyx and Arbor Medical Innovations, and consulting payments from Indiana University and Memorial Sloan Kettering Cancer Center.

- Dr. McLean served as a consultant for Walter Reed Army Institute for Research and for Arbor Medical Innovations.

- 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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Code Availability
An R-based html markup document which reproduces our analyses and results is publicly available in a public OSF repository at https://osf.io/v3euk/.

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Abstract

Despite extensive research on sex/gender differences in posttraumatic stress disorder (PTSD), underlying mechanisms are still not fully understood. Here we present a systematic overview of three sex/gender-related risk pathways. We assessed 16 risk factors as well as 3-month PTSD severity in a prospective cohort study (n=2924) of acutely traumatized individuals and investigated potential mediators in the pathway between sex assigned at birth and PTSD severity using multiple mediation analysis with regularization. Six risk factors were more prevalent/severe in women, and none were more pronounced in men. Analyses showed that acute stress disorder, neuroticism, lifetime sexual assault exposure, anxiety sensitivity, and pre-trauma anxiety symptoms fully mediated and uniquely contributed to the relationship between sex assigned at birth and PTSD severity. Our results demonstrate different risk mechanisms for women and men. Such knowledge can inform targeted interventions. Our systematic approach to differential risk pathways can be transferred to other mental disorders to guide sex- and gender-sensitive mental health research.

Introduction

Women are at two to three times higher risk for being diagnosed with posttraumatic stress disorder (PTSD) than men.[1,2] In addition, women are more likely to suffer from more chronic and severe PTSD symptoms, as compared to men.[3–5] Sex as a biological variable and gender as a psychosocial construct, as well as the interplay between the two, have been shown to play a role in PTSD etiology.[6] We will use the term sex/gender to capture their intertwining and mutual relevance, and will use sex and gender individually when specifically referring to the respective construct. Including a sex- and gender-sensitive perspective to clinical psychological research has the potential to identify the underlying mechanisms that drive these differences. Yet, despite increasing attention to sex- and gender-sensitive research,[7–9] a systematic approach is lacking, and various challenges exist.[10–13]

Based on the possible pathways of how predictors might contribute to differential PTSD risk for women and men,[14–16] we created an overview to systematically describe possible sex/gender-related associations between risk factors and PTSD. As depicted in Fig. 1, risk factors may either be sex/gender-dependent or sex/gender-specific:[16] Sex/gender-dependent risk factors refer to quantitative differences by sex/gender, whereas sex/gender-specific

risk factors refer to qualitative differences. The latter are associated with risk only in one sex/gender, and are often related to reproductive functions.[14,16] Traumatic childbirth, for instance, is a risk factor for PTSD specifically related to the female sex.[17] Pregnancy, menopause, or menstrual-cycle related issues are further examples of female-specific matters that are currently explored with regards to their impact on PTSD development and manifestation.[18–21] Sex/gender-dependent risk factors, on the other hand, can be further classified into risk factors with prevalence or severity differences, and risk factors with vulnerability differences between women and men. Risk factors with prevalence or severity differences refer to predictors with sex/gender differences in the distribution within the (study) population.[14] In this regard, sexual trauma has gained the largest attention so far: certain trauma types such as rape or sexual abuse have been found to be associated with a relatively high risk for PTSD development in both women and men.[4] Since women and girls experience more sexual trauma than men and boys,[5] they are at an increased risk due to the higher exposure to sexual assault.[22] Risk factors associated with vulnerability differences, on the other hand, describe predictors with sex/gender-differential effects i.e., sex/gender moderates the association between a certain risk factor and PTSD in a manner that the strength, significance, and/or direction of the association differs by sex/gender.[15] For this group of risk factors, evidence is less clear. The most prominent risk factor from this category is social support. Research suggests that women are more susceptible to both the protective effects of social support as well as the detrimental effects of lacking social support.[15,23–25] The two sex/gender-dependent sub-groups are not mutually exclusive; risk factors might theoretically be associated with both sex/gender-differential prevalence/severity and vulnerability.

Using this framework as theoretical rationale, we pre-registered a sex-sensitive analysis of PTSD risk factors in a sample of acutely traumatized individuals with the AURORA (Advancing Understanding of RecOvery afteR traumA) study consortium.[26] The AURORA study was a prospective multisite longitudinal study of the onset and course of adverse posttraumatic neuropsychiatric sequalae. Note that we will refer to sex (rather than gender) when explaining the study aim, methods and results in the remaining manuscript, as analyses were conducted based on sex assigned at birth as the stratification variable. Sex-specific investigations were not possible, as no sex-specific risk factors were assessed in this study sample (furthermore, no gender-specific risk factors were assessed). Sex-differential vulnerabilities to PTSD risk factors have been studied in detail in a previous investigation,[12] in which we systematically examined sex-dependent effects of 16 risk factors that had previously been summarized as candidates for different associations with PTSD in women and men,[15] and that were also assessed as part of the AURORA study. Despite women's higher PTSD risk, the analyses did not identify any risk factors to which women were more vulnerable than men.[12] Results hence pointed towards the consideration of further pathways to explain women's higher PTSD symptom load. Therefore, the objective of the current study was to further disentangle sex differences in PTSD risk factors in the AURORA study. Focusing on the same set of candidates previously examined for sex-differential risk factor vulnerability,[12] we now aimed to analyze whether women's higher PTSD severity at 3-months post-trauma could be partially explained by differences in the prevalence and severity of these 16 predictors, including age, marital status, employment status, family

income/year, being member of a marginalized group, lifetime sexual assault exposure, trauma load, chance of dying during index event, peritraumatic distress, pre-trauma depression symptoms, pre-trauma anxiety symptoms, acute stress disorder symptoms, acute dissociative symptoms, social support, anxiety sensitivity, and neuroticism. Our goal was to identify potential mediators in the pathway between sex and PTSD severity using multiple mediation analysis with regularization (Xmed).

Results

Information about participant characteristics is presented in Table 1. As stated previously,[12] women and men differed significantly in PTSD severity at 3-months post trauma, with women experiencing higher symptom load than men (Cohen's $d = .24$, $p < .001$; Extended Data Fig. 1). Sex-differences in PTSD severity remained robust when examined for the subgroup of participants had experienced motor vehicle accidents (74.6%) as index trauma. Sexual assault was reported as index trauma by less than 1% of participants. Despite an intercorrelation of risk factors (Supplementary Table S1), examination of the variance inflation factors (VIF) provided no indication of multicollinearity (all VIF < 3).

Sex differences in prevalence/severity of risk factors

Analyses identified prevalence/severity differences between women and men in six of the 16 risk factors examined (see Table 2). A prevalence difference was observed for lifetime exposure to sexual assault ($X^2(1, N = 2450) = 185.18$, $p < .001$), and severity differences were observed for pre-traumatic anxiety symptoms ($t(2458) = -3.26$, $p = .001$), anxiety sensitivity ($t(2077) = -3.77$, $p < .001$), levels of neuroticism ($t(2005) = -10.28$, $p < .001$), peritraumatic distress ($t(2258) = -12{,}37$, $p < .001$), and acute stress disorder symptoms ($t(1923) = -9.06$, $p < .001$), with women showing greater endorsement of all of these risk factors.

Multiple mediation analysis

Only risk factors with sex differences were considered potential mediators. In the first stage of the exploratory mediation analysis with regularization, no indirect effect was specified as nonzero by the model. Accordingly, all six risk factors were carried on to stage two of the analysis. As shown in Fig. 2, the combined risk factors fully mediated the relationship between sex and PTSD severity; whereas the total effect of sex (c) was 0.26 (95% CI: 0.18, 0.34; $p < .001$), the direct effect of sex (c') after accounting for the mediating factors, was −0.05 (95% CI: −0.12, 0.02; $p = .169$). Five of the six risk factors were identified as uniquely significant mediators, albeit with different mediation weights. Table 3 shows the specific indirect effects: Acute stress disorder was the most influential mediator, the remaining predictors showed much lower indirect effects. Notably, the bootstrap confidence intervals for pre-trauma anxiety symptoms was very close to zero. Peritraumatic distress did not emerge as uniquely significant mediator under the specified model. Results remained robust when conducting a sensitivity analysis where we repeatedly re-sampled the cohort of women to match the number of men, to avoid a sex imbalance (see Supplementary Table S2)

Using the formula 1- (c'/c), the mediating factors accounted for 119% of the total effect of sex on PTSD severity. This means, that after accounting for the combined multiple mediation effect, the direct effect of sex changed directions, as indicated by the negative value of c'. Supplementary analyses suggested that when excluding acute stress disorder from the main model, peritraumatic distress became a statistically relevant mediator. Together the five predictors fully mediated the effect of sex, still accounting for 113% of the total effect of sex on PTSD symptoms at 3-months post-trauma (see Supplementary Table S3). Further supplemental analyses showed, that peritraumatic distress alone could explain 62% of the total effect of sex (see Supplementary Table S4). Finally, in our supplementary multiple mediation analysis of risk factors without severity differences between women and men, only pre-traumatic depression symptoms were carried on to stage 2, all other risk factors were specified as zero. At stage 2, no mediation effect for pre-traumatic depression symptoms was identified (Supplementary Table S5).

Discussion

In a large cohort of nearly three thousand trauma survivors enrolled in the immediate aftermath of trauma, six of the candidate 16 risk factors for PTSD severity at 3-months post-trauma were either more prevalent (past trauma burden) or more severe (pre-trauma anxiety, neuroticism, anxiety sensitivity, peritraumatic distress, and acute stress disorder symptoms) in women than in men. Aiming to identify potential mediators in the pathway between sex and PTSD severity, multiple mediation analyses showed that acute stress disorder, neuroticism, lifetime sexual assault exposure, anxiety sensitivity, and pre-trauma anxiety symptoms uniquely contributed to the relationship between sex and 3-month PTSD severity. Our findings are similar to previous research suggesting higher levels of these five constructs in women than in men.[27–31] Yet, to the best of our knowledge this is the first study to systematically explore their combined impact on sex differences in PTSD severity.

A multiple mediation model has also been conducted by Christiansen and Hansen[32] who examined PTSD risk factors in a sample of Danish bank employees (N = 368) exposed to bank robbery. Their model included 10 potential mediators, of which four (depression, peritraumatic distress, neuroticism, anxiety sensitivity) overlap with mediators included in our model. For depression and peritraumatic distress, results of both studies have similar findings, i.e. both were identified as unique mediators under the specified models. Contrary to our model, neither neuroticism nor anxiety sensitivity emerged as a uniquely significant mediator in the Danish sample. However, because multiple mediation analyses determine the mediation effect of any given variable conditional on the presence of other mediators included in the model,[33] the results of the two studies are not directly comparable. Furthermore, Christiansen and Hansen[32] did not include a regularization component, and PTSD severity was assessed at 6-months post-trauma (compared to 3-months post-trauma in our sample). Differences in the sociodemographic features of the cohorts might further have contributed to these divergent results: While Christiansen and Hansen[32] examined a sample of relatively well-educated professionals with exposure to a traumatic event (bank robbery) less common among the general population, the present study included a much larger and diverse sample size with traumatic events that are more commonly experienced among the general population (e.g. motor vehicle accidents). In addition to the index event, the present

sample might be more representative with regard to prior traumatic event exposure, as in the Danish study only 2.7% of women and 0.7% of men reported lifetime sexual violence exposure, compared to 30.1% of women and 7.8% of men in the AURORA sample. Both studies emphasize the relevance of assessments beyond female sex as a simple risk factor and highlight how indirect effects can (partially) explain women's higher PTSD severity.

Five of six predictors in our model together fully mediated the association between sex and PTSD, i.e. they fully accounted for women's higher PTSD severity at 3-months post-trauma. In conjunction with another study by our team, which examined vulnerability differences in PTSD risk factors and identified particularly adverse effects of two risk factors in men (but none in women) in the same study sample from AURORA,[12] our results thus suggest that although men experience more negative reactions to some risk factors,[12] women are at higher risk for greater PTSD severity after acute trauma due to their disproportionally higher prevalence or severity of a number of risk factors.

Several findings stand out with regard to individual predictors in our model. First of all, most studies that examine the impact of sexual trauma focus on differences in the trauma type of the index event only,[34] but the role of past sexual trauma is less explored:[32] In line with recent evidence,[35] our study showed that prior sexual trauma is an important predictor of PTSD symptoms related to new trauma exposure. Secondly, while ASD symptoms were the most important predictor of 3-month PTSD symptoms, our supplementary analyses confirmed the relevance of the remaining mediators in explaining women's higher PTSD symptom load, offering further targets for prevention and intervention measures. In addition, while past research has suggested the relevance of peritraumatic experiences for sex differences in PTSD symptoms,[36] our results show that peritraumatic experiences alone could not explain as much of the indirect effect as the joint multiple mediation model.

Importantly, while our study used sex assigned at birth as the stratification variable, this might have served as a proxy for gender-related effects for some of the variables included. With the majority of our sample identifying as cis-gender (i.e. individuals with female sex who identify as women, or individuals with male sex who identify as men) we might have been picking up on effects of both sex and gender, even when we use a variable such as sex assigned at birth. We therefore discuss the implications of our findings in a broader context that acknowledges that both are closely intertwined[6] by referring to sex/gender when distinction is not clear. Investigating the relative impact of sex-related and gender-related diathesis respectively, will be a relevant goal for future research.

A better understanding of how risk factors differentially contribute to PTSD development in women and men can help to develop refined targeted interventions to improve trauma-related mental health outcomes. If replicated in future research, some of the mediators identified in this study might be viable targets for early intervention. For instance, with more women than men showing severe acute stress symptoms after trauma, early screening for acute stress symptoms in ED settings and implementation of post-traumatic interventions[37,38] might help to mitigate women's higher PTSD risk. Importantly, however, systematic screening for acute stress symptoms after trauma will not only benefit affected

women; the relatively fewer at-risk men may be identified along with the women at risk for developing PTSD.

The following study limitations should be considered in interpreting our study results. Selection bias could have contributed to who gets treated in the ED, limiting generalizability to other trauma populations. Not only are some trauma populations (e.g. victims of sexual assault) underrepresented in ED patients[39], data collection in the ED – i.e. shortly after trauma exposure – might furthermore be biased due to the recent trauma expose, as patients might still be under distress during the assessment. We invite researchers to use our openly available code to conduct replication studies in further trauma samples from prospective ED studies and beyond. Moreover, with nearly a decade of research showing that individuals with the dissociative subtype of PTSD show altered symptom patterns and pathophysiology compared to individuals without the dissociative subtype,[40,41] examining sex/gender differences in risk factors for PTSD among individuals with and without the dissociative subtype seems an exciting avenue for a more rigorous understanding of which PTSD risk factors affect whom and how. Furthermore, future research should investigate sex/gender-related mechanisms from a temporal perspective, including examinations of sex/gender-related factors for chronic or late-onset trajectories as well as spontaneous long-term remission. Neither were possible within the scope of this project. Finally, the model is based on a limited set of risk factors, and the impact of further aspects such as neuro-biological or sex-specific variables should be explored in more detail in future research. It was not possible to examine sex-specific factors such as menstrual cycle phase or other sex hormone-related information in the current data set, because these data were not collected for the sample investigated in this study. This gap in research seems to be in line with the broader scientific picture regarding limited evidence on women's health issues: A national evaluation of sex- and gender-based analysis mandates in Canada showed that in spite of institutional efforts to fill existing knowledge gaps, the percentage of grants investigating female-specific health issues did not change significantly from 2009 to 2020.[13] In addition, a systematic review on the role of sex and gender in trauma research showed that only 4% of prospective studies on PTSD risk factors investigated female-specific issues.[3] To better understand and address the prominent sex/gender differences in PTSD – as well as many other mental disorders[42] – increased focus on both sex/gender-dependent and sex/gender-specific risk factors is necessary.

A major strength of the current study is the introduction of a theoretical framework to classify sex/gender-differences in mental health risk factors. We hope such a systematic approach will help to advance our knowledge of sex/gender differences in PTSD risk factors, by better understanding and classifying the underlying risk mechanisms that contribute to sex/gender differences in PTSD outcomes (i.e. sex/gender-dependent risk factors including risk factors with prevalence/severity differences and risk factors with vulnerability differences, and sex-specific risk factors, which are restricted to one sex/gender only).The present approach can also be transferred to further mental disorders. In conjunction with a previous analysis from our study team[12] we give an example of how this framework can be applied to clinical psychological research to disentangle sex/gender-dependent differences in mental health risk factors. Focusing on sex-differences in the prevalence/severity of PTSD risk factors, this study benefits from the large and diverse

sample with high representation of both women and men as well as the prospective design, which is well suited for the multiple mediation analysis applied.

In conclusion, we present a systematic overview of how sex/gender-dependent and sex/gender-specific risk factors may contribute towards sex differences in PTSD severity. Taking a closer look at risk factors with sex differences in prevalence/severity in particular, we suggest that a combination of five of these risk factors could account for women's higher PTSD severity at 3-months post-trauma in a sample of acutely traumatized individuals. Our results demonstrate that sex/gender differences in mental health outcomes are driven by a complex interplay of multiple factors, and different mechanisms might shape the experience of women and men. Future research on sex/gender differences in PTSD risk factors is warranted to further disentangle how underlying mechanisms contribute towards vulnerability as well as resiliency. Identifying factors in the different causal pathways between sex, gender and PTSD risk has the potential to inform targeted preventive interventions and to mitigate health disparities.

Methods

Participants and Procedure

Recruitment for the AURORA study occurred from September 2017 through June 2021. The AURORA study procedures are described in detail elsewhere.[43] In brief, patients presenting to emergency departments (EDs) within 72 hours of trauma exposure were screened for eligibility at 29 study sites across the United States. Eligible events included motor vehicle collision, physical assault, sexual assault, mass casualty incidents, fall >10 feet or any other event in line with the DSM-5 definition of trauma,[44] as verified by a research assistant. Participants were included if they were 18–75 years old, fluent in spoken and written English, could provide informed consent to participate in the study, able to follow the enrollment protocol, and possessed a smartphone and e-mail address. Participants were excluded from data collection if they became pregnant or incarcerated. In addition, we excluded one participant with missing information on sex assigned at birth. An overview of individuals at each stage of study inclusion is depicted in Fig 3. 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 analyzed in this study were from these self-report assessments at baseline, 2 weeks, 8 weeks, and 3 months post-trauma. The Institutional Review Board (IRB) of the University of North Carolina (UNC) approved the study protocol (IRB #1707–03) and other sites created either reliance agreements or parallel IRBs. All participants provided written informed consent and received compensation for their participation in all assessments. Data for the present analysis was obtained by sending an analysis proposal to the AURORA executive committee, an internal mechanism for AURORA co-investigators to request a limited dataset and specify plans for analyses. Approval from the executive committee was obtained on October 18, 2022.

A total of n = 2942 individuals (n = 1124 men, n = 1818 women; age = 35.9 ± 13.3) were included in the data release used for the present analysis. The most common trauma type was motor vehicle collisions (n = 2194, 74.6%). Other traumatic events included assaults,

falls, animal-related trauma, non-motor vehicle collisions, burns, disasters, and poisoning. Detailed information on sample and trauma characteristics is provided in Haering et al.[12]

Measures

We assessed 16 pre-, peri-, and post-traumatic risk factors examined in our complementary analysis.[12] Detailed information on all measures is presented in Supplement 1.

Pre-traumatic predictors—Sex assigned at birth, age, race–ethnicity, marital status, education, income, and employment status were recorded in the ED. Race-ethnicity was assessed by two survey questions: 'Do you consider yourself to be Hispanic, Latino, or of Spanish origin?'. If the answer to this first question was 'yes' participants race/ethnicity was coded as Hispanic. If the answer to the first question was 'no', participants were asked' 'What race do you consider yourself to be?'. Answers were coded as Hispanic; Non-Hispanic White; Non-Hispanic Black; Non-Hispanic Other. For the present analyses, responses were aggregated towards a variable reflecting whether the participant was member of a marginalized group (including participants whose race/ethnicity was coded as Hispanic, Non-Hispanic-Black, Non-Hispanic Other) or not.

Pre-trauma depression symptoms (30 days prior to the ED visit) were assessed using the Patient-Reported Outcomes Measurement Information System (PROMIS) Depression Short-Form 8b,[45,46] and pre-trauma anxiety symptoms (30 days prior to the ED visit) were assessed using the PROMIS Anxiety Bank Items.[46] Anxiety sensitivity was assessed at week 2 follow-up by an abbreviated version of the Anxiety Sensitivity Index scale.[46] At week 2, participants further competed 8 items on neuroticism using the Big Five Personality Inventory (BFI).[47] Information on past traumatic experiences (trauma load) was collected at week 8 follow-up using the Life Events Checklist (LEC-5).[48,49] Due to their relatively stable nature with regards to the elapsed time between trauma and data collection, we consider anxiety sensitivity, neuroticism and trauma load pre-traumatic predictors.

Peri-traumatic predictors—Peri-traumatic experiences were assessed in the ED. Peri-traumatic arousal was with a modified version of the Peritraumatic Distress Inventory (PDI),[50] and participants further rated how close they perceived that they came to dying during the trauma (from 0 'life was not threatened at all' to 10 'came very close to being killed or easily could have been killed').

Post-traumatic predictors—Social support in the two weeks between trauma and follow-up was measured by a modified version of the PROMIS Emotional Support-Short Form 4a.[45] Acute stress disorder (ASD) symptoms at two weeks post-trauma were measured using a modified version of the PCL-5,[51] and acute dissociative symptoms at two weeks post-trauma were assessed with the Brief Dissociative Experiences Scale (DES-B) – Modified.[52]

Outcome—PTSD symptom severity was quantified using the PTSD Symptom Checklist for DSM-5 (PCL-5) at the 3-month follow-up. The PCL-5 is a 20 item self-report questionnaire that assesses the presence and severity of various posttraumatic stress symptoms on a scale from 0 (*not at all*) to 4 (*extremely*).[51] Items are summed to create

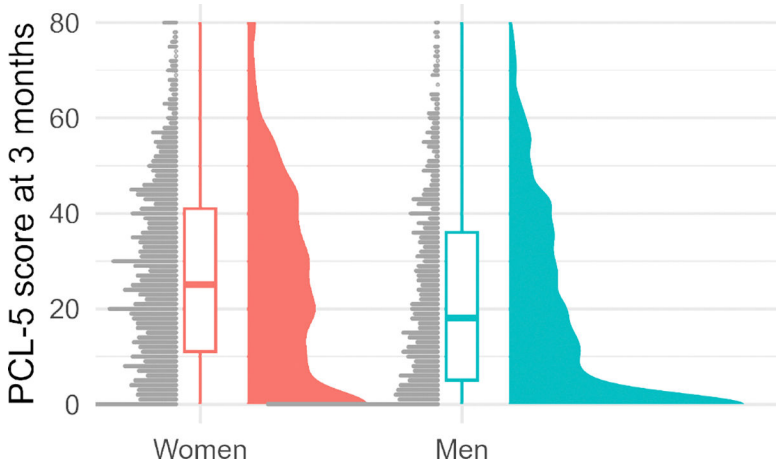
a total severity score. PTSD symptoms were rated in relation to the trauma associated with the baseline ED visit.

Statistical Methods

All analyses were conducted in R version 4.2.1 (RRID:SCR_001905). Because this analysis complements our previous analysis of vulnerability differences in women and men,[12] we used the same statistical assumptions for this investigation. We focused on sex assigned at birth (rather than gender) as our stratification variable and used the same data set from our aforementioned research for this analysis.[12] This process included multiple imputation with predictive mean matching via the *aregImpute* function of the Hmisc package (RRID:SCR_022497) for constructs that were assessed longitudinally in the AURORA study (i.e. PTSD severity, depressive symptoms, anxiety symptoms, dissociative symptoms and social support). Missing values for these variables were imputed using the respective longitudinal assessments of each construct as auxiliary variables. For details see manuscript and code of Haering et al.[12]

In a first step, sex differences in the prevalence of all 16 predictors were examined using two-sided Student's t-tests for continuous variables and Chi-squared tests for categorical variables, with a Bonferroni correction for multiple testing. An adjusted alpha level of 0.0031 (determined by dividing the original alpha by the number of comparisons, i.e., 0.05/16) was used to determine significance for all sixteen statistical tests performed to compare risk factor prevalence or severity among women and men. In a second step, predictors with significant ($p < .0031$) severity differences in men and women were examined in a multiple mediation model. Mediation models can explain how or through which means a relationship between two variables (e.g. sex and PTSD) occurs.[33] While research to date on testing a simple mediation hypothesis is large and growing, multiple mediation (i.e. simultaneous mediation by multiple variables) received less attention so far,[33] in spite of its clear potential (see Preacher & Hayes[33] for a detailed discussion). A major advantage of multiple mediation models (compared to separate simple mediation models) is determining the mediation effect of any given variable conditional on the presence of other mediators included in the model.[33] For the present study, we conducted an exploratory multiple mediation analysis via regularization (Xmed), as suggested by Serang et al.[53] The analysis is particularly suitable if available theory is limited. Xmed comprises two stages to identify a set of potential mediators. At stage 1, a structural equation model comprising all potential mediators of interest is fitted. A regularization component is implemented, and lasso penalties are imposed to determine the optimal tuning parameter lambda. The model is then refitted under the chosen lambda value. All nonzero specific indirect effects are chosen as potential mediators, specific indirect effects which are estimated to be zero are not carried on in the analysis. At stage 2 of the mediation analysis, the model is refitted without any regularization, using only the variables that were identified as potential mediators in stage 1. Eventually, we used bias-corrected bootstrapping to conduct 95% confidence intervals (CI) of the effects. Variables were standardized for the analyses. Finally, we performed supplementary models to test the robustness of our results (see OSF markdown), including an analysis where we repeatedly (i=1000) re-sampled our cohort of women to match the number of men (n = 1124 women and men respectively), to avoid a sex imbalance.

Extended Data



Extended Data Fig. 1.
Distribution of PTSD symptoms 3-months post-trauma by sex.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability

Data and/or research tools used in the preparation of this manuscript were obtained from the National Institute of Mental Health (NIMH) Data Archive (NDA). NDA is a collaborative informatics system created by the National Institutes of Health to provide a national resource to support and accelerate research in mental health. Dataset identifier(s): NIMH Data Archive Digital Object Identifier (DOI) 10.15154/c01s-jy79. This manuscript reflects the views of the authors and may not reflect the opinions or views of the NIH or of the Submitters submitting original data to NDA.

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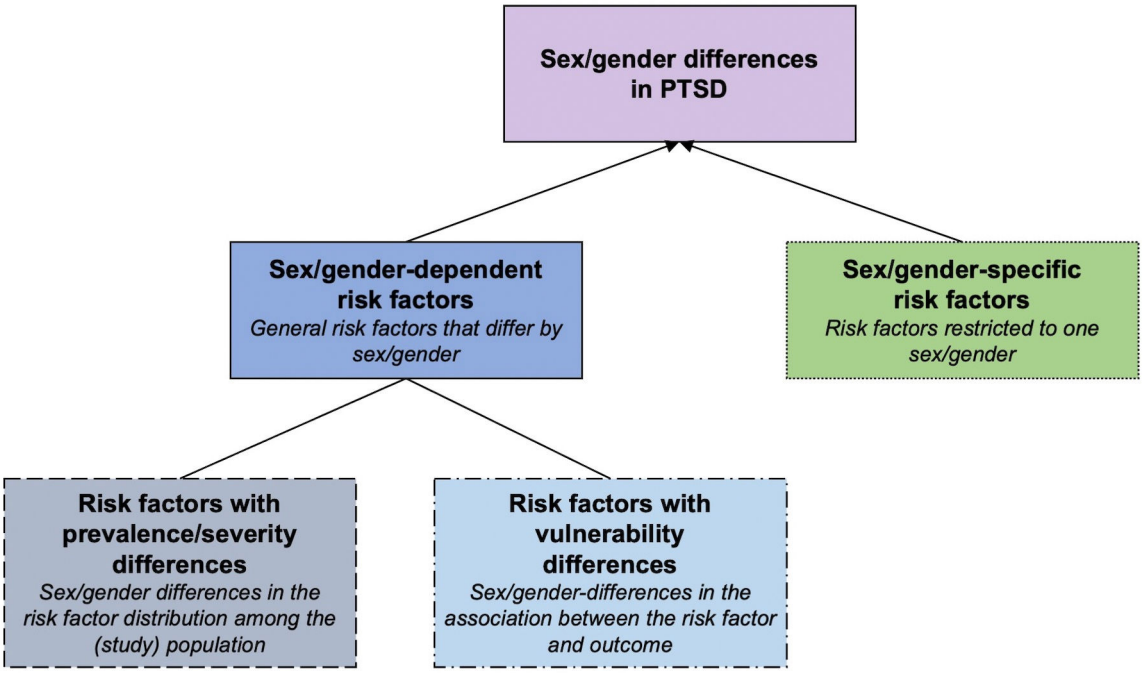

Fig. 1 |. Possible pathways of how risk factors can contribute to sex differences in posttraumatic stress disorder (PTSD)

The figure summarizes how sex/gender-related aspects in risk factors may contribute to sex/gender differences in PTSD. Risk factors may either be sex/gender-dependent or sex/gender-specific: Sex/gender-dependent risk factors refer to quantitative differences by sex/gender, whereas sex/gender-specific risk factors refer to qualitative differeances. Sex/gender-specific risk factors are associated with risk only in one sex/gender. Sex/gender-dependent risk factors can be further classified into risk factors with prevalence or severity differences, and risk factors with vulnerability differences by sex/gender. Risk factors with prevalence or severity differences refer to predictors with sex/gender differences in the distribution within the (study) population. Risk factors associated with vulnerability differences describe predictors with sex/gender-differential effects i.e., sex/gender moderates the association between a certain risk factor and PTSD. The two sex/gender-dependent sub-groups are not mutually exclusive.

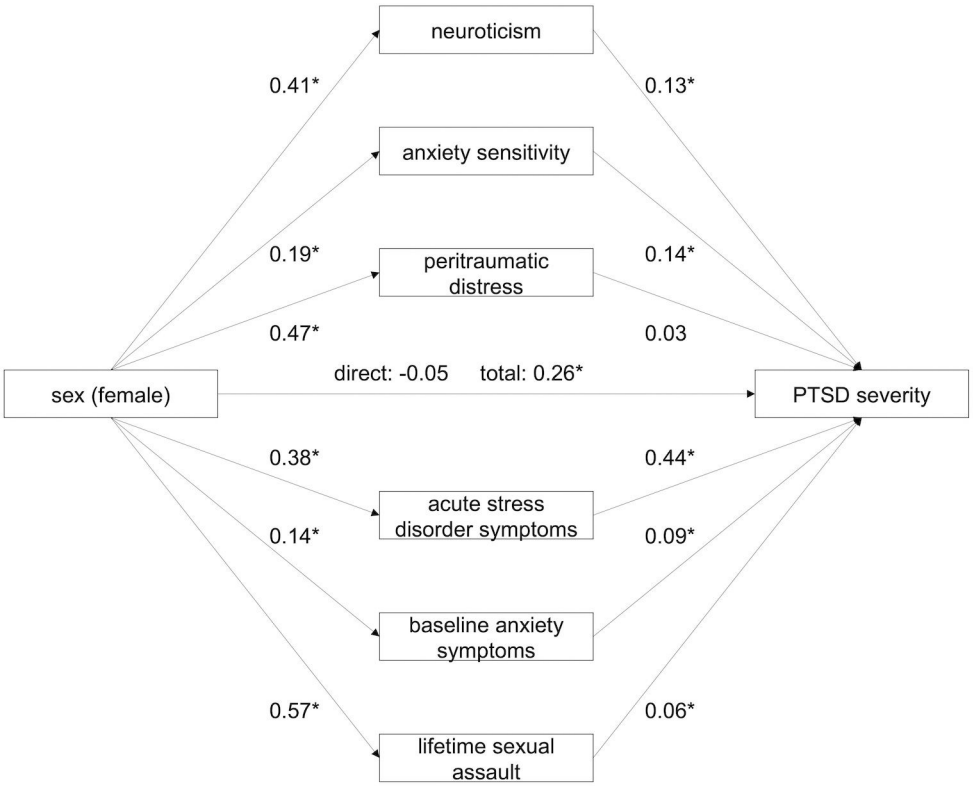

Fig. 2 |. Multiple mediation model for PTSD severity comparing female and male participants. The figure shows the estimates by the multiple mediation model with regularization predicting 3-month PTSD severity. Coefficients are standardized to facilitate comparisons of mediation path direction and magnitude. *Indicates statistical significance based on 95% confidence interval.

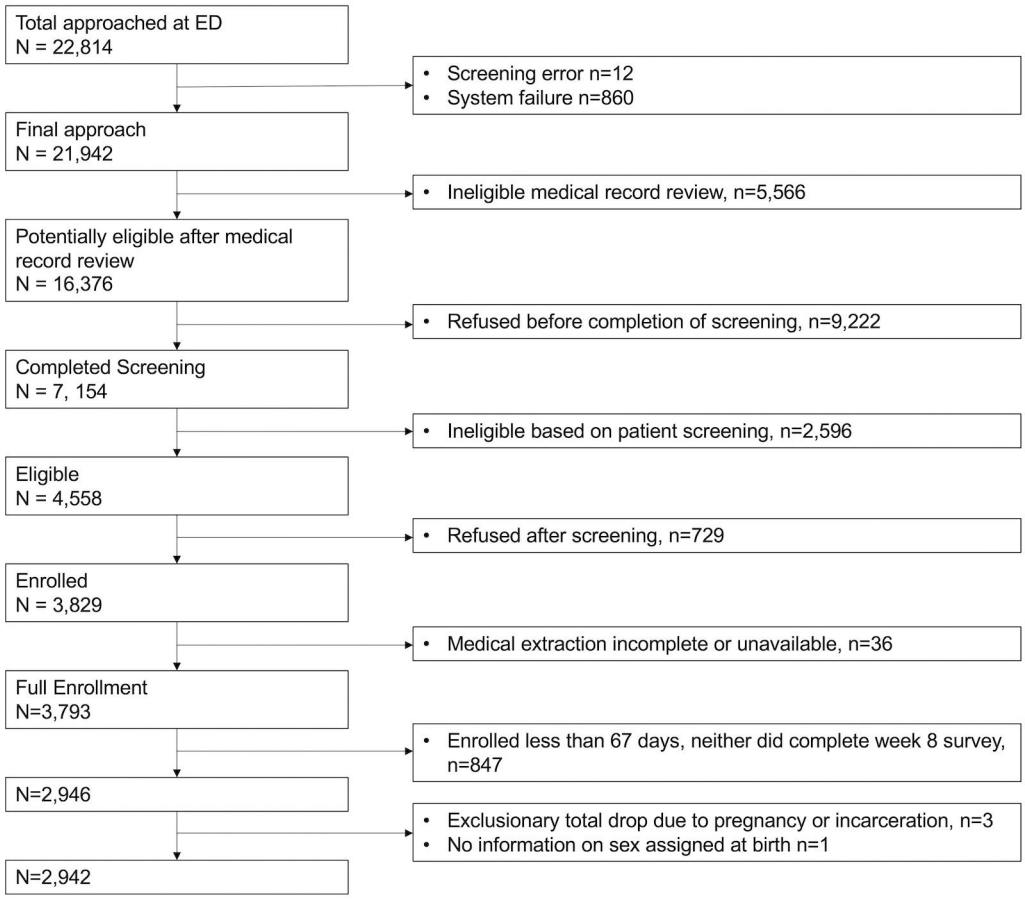

Fig. 3 |. Flowchart of AURORA participants included in the present analysis.
The chart shows the flow of participants from recruitment to follow-up.

Table 1

Demographic and trauma characteristics

Characteristic	N=2942	
	Mean	**SD**
Age	35.9	13.3
	N	**%**
Sex assigned at birth		
Female	1818	61.8
Male	1124	38.2
Gender identity		
Cis Women	1810	61.5
Cis Men	1118	38.0
Trans Women	6	0.2
Trans Men	5	0.2
Non-binary	3	0.1
Race/Ethnicity [a]		
Hispanic	341	11.6
Non-Hispanic Black	1458	49.6
Non-Hispanic White	1020	34.7
Race/Ethnicity not listed	111	3.8
Highest degree [b]		
Less than high school	339	11.5
High school	1971	67.0
College	623	21.2
Family income/year [c]		
Less than 19k	850	28.9
Between 19k and 35k	794	27.0
More than 35k	937	31.8
Index trauma		
Motor vehicle collision	2194	74.6
Physical assault	271	9.2
Fall, <10 feet	161	5.5
Animal-related	63	2.1
Nonmotorized collision(e.g.bike)	53	1.8
Fall, ≥10 feet	51	1.7
Sexual assault	17	0.6
Burns	14	0.5
Other	118	4.0

Note. Data available for [a]99.6%, [b]99.7%, [c]87.7%, of the sample, respectively.

Table 2

Risk factor characteristics by sex

	Men (N=1124)	Women (N=1818)	Odd's Ratio	p-value
Marital status [a]				
Currently married	874 (77.8%)	1444 (79.4%)	0.91	.352
Employment status [b]				
Currently unemployed	180 (16.0%)	293 (16.1%)	0.95	.676
Family income/year [c]				
Less than 19k	304 (27.0%)	546 (30.0%)	1.09	.340
Member of marginalized group [d]	722 (64.2%)	1188 (65.3%)	1.05	.579
Lifetime sexual assault exposure [e]	88 (7.8%)	547 (30.1%)	4.91	<.001
	Men (N=1124)	**Women (N=1818)**	**Cohen's *d***	**p-value**
Age				
Mean (SD)	36.1 (13.1)	35.8 (13.4)	−0.02	.586
Trauma load [f]				
Mean (SD)	9.87 (9.96)	9.73 (9.03)	−0.02	.723
Chance of dying				
Mean (SD)	5.76 (3.32)	5.93 (3.44)	0.05	.194
Peritraumatic distress [g]				
Mean (SD)	11.8 (7.09)	15.2 (7.08)	0.48	<.001
Pre-trauma depression symptoms				
Mean (SD)	48.7 (10.7)	49.5 (11.0)	0.07	.059
Pre-trauma anxiety symptoms				
Mean (SD)	4.90 (4.55)	5.47 (4.75)	0.12	.001
Acute stress disorder symptoms [h]				
Mean (SD)	5.87 (4.73)	7.59 (4.48)	0.38	<.001
Acute dissociative symptoms				
Mean (SD)	1.69 (2.12)	1.80 (2.14)	0.05	.166
Social support				
Mean (SD)	10.2 (3.25)	10.3 (3.33)	0.02	.604
Anxiety Sensitivity [i]				
Mean (SD)	2.88 (3.09)	3.37 (3.26)	0.15	<.001
Neuroticism [j]				
Mean (SD)	2.51 (1.25)	3.04 (1.27)	0.42	<.001

Note. Two-sided t-tests were used to assess sex differences for continuous variables. Two-sided chi2-tests were used to assess sex differences for categorical variables. Bonferroni-corrected alpha level threshold for multiple comparisons is $p < 0.031$. Odd's ratio >1 indicates higher odds in women. Cohen's d>0 indicates higher mean values in women.

Data available for [a]99.3% and 99.5%, [b]85.7% and 89.8%, [c]85.2% and 89.3%, [d]99.6% and 99.6%, [e]79.1% and 85.9%, [f]78.9% and 85.8%, [g]94.9% and 94.1%, [h]85.1% and 88.2%, [i]84.5% and 88.8%, [j]84.4% and 88.5% of men and women, respectively.

Table 3

Total, direct, and indirect effects of sex on PTSD severity through the five mediators

	Estimate	SE	z	Bootstrap CI		*p*
				lower	upper	
Total effect of sex (c)	0.259	0.040	6.477	0.181	0.337	<.001
Direct effect of sex (c')	−0.050	0.037	−1.375	−0.122	0.021	0.169
Acute stress disorder symptoms	0.167	0.021	7.950	0.126	0.208	<.001
Neuroticism	0.055	0.009	6.132	0.038	0.073	<.001
Lifetime sexual assault exposure	0.033	0.010	3.379	0.014	0.052	.001
Anxiety sensitivity	0.027	0.007	3.816	0.013	0.041	<.001
Peritraumatic distress	0.014	0.008	1.809	−0.001	0.029	.070
Pre-trauma anxiety symptoms	0.013	0.005	2.673	0.003	0.022	.008

Note. Estimates show the results of a multiple mediation model with regularization, $df = 15$.