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DISASTER PSYCHIATRY: TRAUMA, PTSD, AND RELATED DISORDERS (MJ FRIEDMAN, SECTION EDITOR)

Chromosomes to Social Contexts: Sex and Gender Differences in PTSD

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Abstract

Purpose of Review This review highlights recent research on sex- and gender-related factors in the prevalence, symptom expression, and treatment of PTSD. Further discoveries about the underlying mechanisms of sex and gender effects have the potential to shape innovative directions for research.

Recent Findings The prevalence of PTSD is substantially higher among women, but women show a modest advantage with respect to treatment response. There is evidence of greater heritability among females. Women are more likely to experience sexual and intimate violence, childhood trauma exposure, and repeated trauma exposures. Specific characteristics of social contexts act as gender-linked risks for PTSD. Among individuals diagnosed with PTSD, men and women are similar in phenotypic expression.

Summary Though research has yet to fully account for the factors that explain sex- and gender- related effects on PTSD, emerging research suggests these effects occur across multiple levels. Shared risk factors for trauma exposure and PTSD merit further investigation. Both social and biological contexts merit investigation to understand sex-linked differences in heritability.

Keywords Post-traumatic stress disorder · PTSD · Gender · Sex · Social context · Genetic

Introduction

Men and women differ markedly in their exposure to traumatic stressors and risk for PTSD. Women are more likely to experience certain toxic patterns of exposure and are at substantially higher risk for PTSD as compared to men. Yet, a reliable equifinality is observed, where men and women are quite similar in phenotypic expression of PTSD. Among individuals diagnosed with PTSD, women demonstrate a modest advantage with respect to treatment response. How do these findings regarding gender elucidate social and biological factors important to the prevention and treatment of traumatic stress? Research that produces a mere catalog of sex differences is not sufficient. This approach can lead to deterministic conclusions that emphasize unmodifiable risk factors and homogeneous categorical distinctions between men and women [1•]. But observations of the contexts and conditions where gender differences are (and are not) observed, and of the magnitude of those differences, have potential to yield insights into the cultural, social, and biological correlates of sex and gender that influence traumatic stress responses across populations.

Sex and gender are not mechanisms, but proxy variables for multi-level interdependent biological and social factors that research continues to reveal (Fig. 1). Research across human and animal studies challenges a purely binary conceptualization of sex, revealing multiple systemic influences on the expression of sex-linked characteristics of anatomy, hormones, chromosomes, and individual cells [2]. These studies reveal fascinating biological diversity within males and females that cast sex more as a spectrum of biological contexts than a

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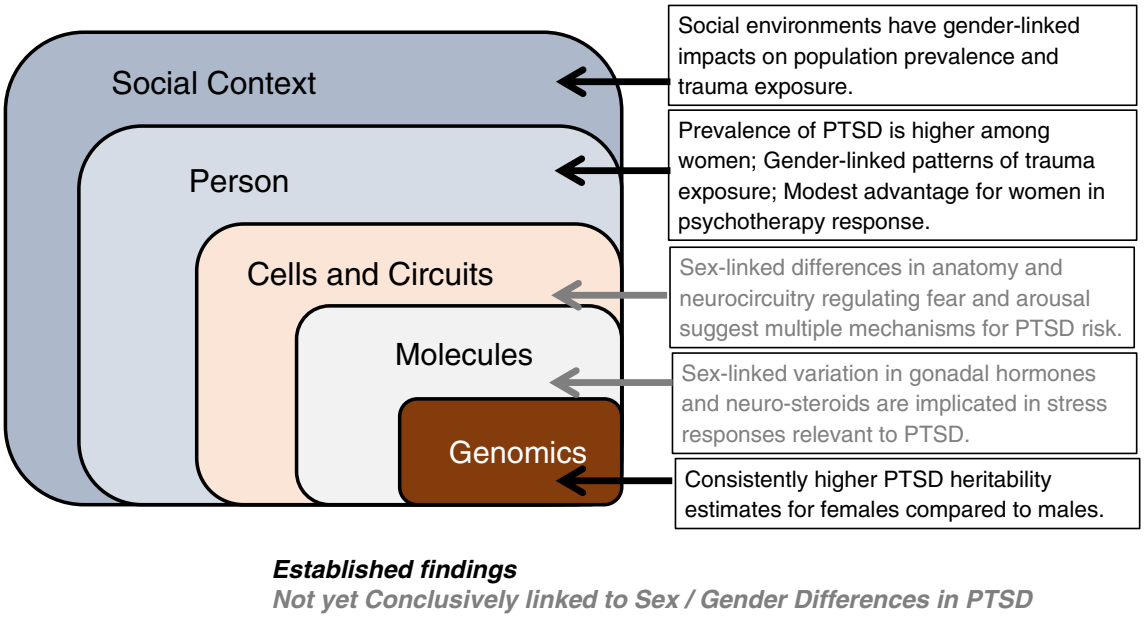

Fig. 1 Multi-level effects for sex and gender differences in PTSD

categorical distinction. Similarly, psychological research seldom finds that men and women are categorically distinct with respect to stereotypical psychological traits or cognitive styles, but overlapping populations across multiple continua [3]. Finally, at the population level, gender can be viewed as a social determinant of health, a proxy for multiple interacting effects of systemic social, economic, and political influences [4]. Our challenge then is to search for these sex- and gender-linked variables across molecular, personal, and societal levels to identify mechanisms for the observed gender differences in PTSD. In this review, we focus on the genomic-, person-, and societal-level effects, for the relatively strong evidence of sex and gender differences, and to highlight the inter-relationships among micro- and macro-effects. We use the term "sex" in discussions of molecular biological data but the term "gender" in discussing most other domains of research. The term "gender" is intended to refer broadly to the expression of sex-linked biological variables when moderated by social context (i.e., in vivo human research), as well as gender-linked variation in individual psychological differences and/or socioeconomic contextual influences.

Prevalence of PTSD

Women are approximately twice as likely to suffer from PTSD as compared to men: the prevalence of DSM-5 PTSD in the USA is estimated to be 6.1% among women and 3.2% among men. The 2:1 ratio for women's increased risk is similar for lifetime estimates of PTSD, with a prevalence of 8% among women and 4.1% among men [5]. This gender ratio is similar to population estimates using DSM-IV PTSD criteria [6], despite the significant changes to diagnostic criteria. The elevated risk for PTSD among women is observed across nations and cultures [7] and is evident in childhood [8], clearly present in adolescence and adulthood, but declines in older age [9]. In contrast to these consistent gender differences in the prevalence of PTSD, there are few gender differences in the age at onset or chronicity of PTSD [10–12].

Symptom Presentation

To what extent could the marked and persistent gender differences in the prevalence of PTSD be a function of gender differences in post-trauma symptom presentation? If the construct validity of PTSD differs by gender, gender differences may be an artifact of how we operationalize the diagnosis. Investigations of the underlying structure of PTSD symptoms tend to find good support for the DSM-5 model as well as a "hybrid" model blending transdiagnostic dimensions for positive-negative valence and internalizing-externalizing behaviors that is comprised of intrusions, avoidance, negative affect, anhedonia, externalizing behaviors, anxious arousal, and dysphoric arousal factors [13–16]. Though women frequently show greater symptom severity, both models of PTSD are robust to gender, demonstrating measurement invariance that indicates the underlying construct of PTSD is consistent for both men and women, or that if differences exist, they are relatively small and do not meaningfully impact prevalence [13, 17, 18•]. For example, one study with trauma-exposed adolescents in Malaysia found that, at similar PTSD severity levels, girls were slightly more likely to endorse emotional cue reactivity, and boys were slightly more likely to

endorse reckless or self-destructive behavior [18•], small but gender-role concordant effects on symptom expression. The dissociative subtype of DSM-5 PTSD, characterized by symptoms of derealization and depersonalization, does not appear to be more common among women as compared to men [19, 20]. The consistency of the DSM-5 PTSD construct for men and women is similar to results for DSM-IV PTSD, where the construct was found to be robust to gender and trauma type [21]. In summary, there is little evidence for gender-related divergence in the phenotypic expression of PTSD, nor evidence of significant gender-related bias in the construct.

Trauma Exposure

Trauma exposure is the defining risk factor for PTSD. The experience of trauma is widespread and frequent, though the subsequent development of PTSD is relatively rare. In the USA, most people, about 70%, experience at least one event consistent with the DSM-5 trauma criterion (Criterion A) at some point in their lives [5], with similar proportions among men and women [22•]. The similarity in DSM-5 trauma exposure for men and women found in the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) [5] is consistent with estimates for DSM-IV trauma exposure [6], but contrasts with other prior research using DSM-III-R and DSM-IV criteria [23] that find a higher prevalence of trauma exposure among men. Some researchers have hypothesized that enhancements to the scope and specificity and of trauma exposure items in modern epidemiological assessment instruments (e.g., specific queries for intimate partner violence, distinct from physical assault items) have led to more precise exposure estimates and attenuated gender differences [24].

The majority of trauma-exposed individuals have experienced multiple events, averaging 4–5 events worldwide [25•]. Using DSM-5 trauma exposure criteria, recent data suggest that men and women experience similar numbers of traumatic events. Approximately 48–58% of the US population reports a directly experienced traumatic event, with approximately 25% reporting a single event, 12–13% reporting to two different events, and 6–7% reporting three different events, and 5% exposed to four or more different types of traumatic events [22•].

Consistent gender differences emerge in the types of traumatic events men and women experience. Men are more likely to experience war-related events, accidental injury, serious illness, physical assault/mugging, terror attacks, and to witness injury [6]. Women are more likely to experience all forms of childhood maltreatment, sexual assault/rape, intimate partner violence (IPV), kidnapping, and stalking [6]. These events differ in subsequent risk for PTSD. Worldwide DSM-IV data indicate that approximately 4% of individuals who experience any type of traumatic event will develop PTSD in response to that event, but the proportions differ across events [25]. Rape has the greatest risk for PTSD, where 17.4% develop PTSD. Other events more common among women, such as kidnapping (11.3%) and stalking (8.4%), are also associated with substantially higher-than-average risk for PTSD. Though only 2.8% of individuals who are physically assaulted will develop PTSD, 9.4% of individuals who are physically assaulted by an intimate partner develop PTSD. Risk for PTSD is mixed among events more common among men: there is a higher-than-average prevalence of PTSD in response to torture (6.9%) and witnessing atrocities (8.7%), somewhat elevated risk for accidents (5.1%), but considerably lower-than-average risk in response to combat (1.9%), injury (1.7%), witnessing death or serious injury (1.6%), and mugging (2%) [25]. To date, there is little data examining the conditional risk, or proportions of individuals who meet the criteria for DSM-5 PTSD across different events. One notable exception is that in the US population, direct combat exposure appears to confer a higher-than-average risk for PTSD, though still substantially lower than risks for sexual assault. The most frequent types of trauma reported among men and women who meet the criteria for DSM-5 PTSD follow a similar pattern to those observed for DSM-IV [5].

In addition to conditional risk for individual events, the frequency and timing of trauma exposure also contribute to women's PTSD risk. Repeated exposure to violence and assault is associated with increased risk for PTSD [25], and the forms of violence more common among women (childhood abuse, partner violence) tend to be repeated, chronic forms of violence [5, 26]. Similarly, prior exposure to physical and sexual violence is associated with increased vulnerability to both subsequent trauma exposure [26] and PTSD following subsequent trauma [25], which may also exacerbate women's risk. Women's increased risk for childhood physical and sexual abuse may be particularly important: these events cluster with other childhood adversities that enhance risk for poor adult mental health, erode existing social resources, and impede development of new resources [27]. These adversities also increase risk for subsequent trauma exposure as well as the risk for PTSD following subsequent trauma [28].

Despite widespread exposure to traumatic events in the general population, there is evidence of gender-linked patterns of exposure associated with an increased risk for PTSD that highlight the role of childhood trauma, sexual/gender-based violence, and repeated trauma exposures. Few studies have comprehensively addressed these dimensions of exposure as mechanisms for observed gender differences in PTSD, but extant data suggests that more detailed assessment of these dimensions better accounts for gender-linked risk. In a study using a US population sample that investigated gender differences in trauma type, but not timing or repeated exposures, women exhibited a greater risk for DSM-IV PTSD following almost all forms of trauma exposure, leading to conclusions

that minimized the role of exposure patterns as a mechanism of gender differences in PTSD prevalence [6]. In contrast, a study of the Australian general population that assessed sexual and gender-based violence in greater detail found no gender differences in PTSD risk for these events, suggesting that women's increased risk for sexual and gender-based violence underlies some, but not all of the observed gender differences in PTSD prevalence [29•]. Promising approaches to accounting for the interplay of qualitative and quantitative characteristics of trauma exposure are emerging, such as person-centered approaches that group individuals into qualitatively different subtypes of trauma exposure. Using this approach, a study of North American adults found three classes of exposure: a low-exposure group, primarily vicarious trauma and accidents; a moderate-exposure group characterized by witnessing violence and being threatened with a weapon; and a high-exposure group characterized by a high prevalence of interpersonal violence experiences and a high number of exposures [30]. This high-exposure group was significantly over-represented among women and was associated with higher DSM-5 PTSD symptoms scores as compared to the other classes. Such methods to quantify parsimonious but clinically meaningful ontologies of trauma exposure severity will further advance efforts to identify how trauma exposure accounts for gender-linked PTSD risks.

Genetic Risk

Genetic studies afford unique opportunities to understand individual differences in risk and resilience to PTSD and may be especially relevant for understanding sex differences. As this field advances, results can inform our understanding of sex differences in mechanisms underlying PTSD. Recent molecular genetic studies as well as twin studies conducted over the last two decades find that PTSD, similar to other mental health conditions such as schizophrenia and depression, is a highly polygenic phenotype. In genetics parlance, it is a "complex genetic phenotype," meaning that it is influenced by environmental factors and many genetic factors (i.e., likely thousands of polymorphisms). In examining the evidence for sex differences, we focus on twin studies and large-scale (i.e., $N >$ 20,000) genome-wide association studies (GWASs), given that these methods are known to yield reliable results. In contrast, we do not review candidate gene studies because abundant evidence suggests that nearly all polymorphisms implicated by candidate gene studies are false positives [31, 32]. Thus, while some candidate gene findings suggest sex-linked hypotheses about women's predisposition to PTSD, such as the sex-specific associations reported between ADCYAP1R1 polymorphisms and both PTSD symptoms and estrogen receptor binding [33], we caution that GWASs of other well-studied mental disorders, such as schizophrenia, have yielded little support for the most investigated candidate genes [32]. Given the highly polygenic nature of PTSD, the analysis of millions of genetic variants using sample sizes of at least tens of thousands of participants is necessary to achieve adequate statistical power. The sample sizes required to address hypotheses regarding trauma exposure in gene X environment interactions are likely to be even larger. Thus, large-scale sample collections, with detailed environmental exposure information, such as those developed through the efforts of the PTSD psychiatric genomic consortium initiative [34], are promising initiatives to shed further light on these sex differences.

To date, there is consistent evidence of higher heritability of PTSD among females as compared to males. Twin studies demonstrate moderate heritability for PTSD (between ~30 and 70%) [35], and adequately powered molecular genetic studies yield findings that are consistent with these estimates [34, 36•]. Twin studies show a trend for higher heritability in samples with higher proportions of women. These heritability estimates are bounded by data from females at the high end of the moderate range with an estimate of 71% [37] and data from males as the low end of the moderate rage with an estimate of 24% [35]. Results from twin studies, with designs that capture effects of all genetic variations, are expected to be substantially higher than results from molecular genetic studies, which capture only common genetic variation (and further, many common genetic variations are measured imperfectly). A recent large-scale GWAS of PTSD has replicated the gender differences observed in twin studies, finding estimates of PTSD heritability that are higher among females (29%) as compared to males (7%) [36•].

The causes of sex differences in heritability are not well understood, but several plausible hypotheses exist. Heritability estimates are bounded by the reliability of measures, and the most parsimonious explanation may be gender differences in the psychometric reliability of PTSD assessment measures. However, this explanation is unlikely because the consistent evidence of gender-related factorial and measurement invariance across DSM-IV and DSM-5 (as discussed earlier in this review) implies similar reliabilities. Sex differences in heritability may also stem from differences in environmental influences. Notably, if PTSD-inducing environmental factors, such as high-risk trauma exposure, are more uniform among females, then genetics may be more relevant in determining which women develop PTSD. In contrast, if relevant environmental influences are more variable among men, then genetics would account for less of the variation in development of PTSD among men. Finally, these results could be due to sex-linked biological contexts that mediate genetic risk. If biological mechanisms vary with sex hormones [34] or other sex-linked differences in biological environments in response to traumatic stress [38, 39], the phenotypic consequences of genetic variation may be more pronounced among women or dampened among men.

To date, no sex-specific individual risk variants for PTSD have been identified in large-scale GWASs. However, 2018 was a pivotal year in PTSD genetics, because the first high-confidence individual loci for PTSD were discovered [34, 40]. Notably, these discoveries required samples of approximately 100,000 participants. Consequently, even larger sample sizes will likely be necessary to conclusively identify genetic loci separately for females and males, and therefore subgroup analyses should be viewed with caution (at this point in time). Though translation of GWAS loci into risk variants, identification of mechanisms, and translation into prevention and treatment efforts may span decades, these discoveries have potential to yield powerful insights, both regarding biologically based sex-linked risks for PTSD as well as their interaction with environmental events and contexts.

Social Context

Extant studies of individual risk factors do not fully explain women's increased risk for PTSD relative to men, but the impact of these risk factors may depend on the individual's social context. When gender is viewed as socially constructed, it follows that social contexts contribute gender-related risks for PTSD, where characteristics of a neighborhood, community, state, or country influence individual outcomes. This evidence is gleaned from study designs that account for ecological factors such as geographic variation or effects of shared contexts while modeling individual outcomes.

Emerging evidence suggests that some contextual qualities may have a more potent impact on women's health compared to men's. For example, environments characterized by greater socioeconomic disadvantage and lower social connectedness are linked to higher mortality rates, with robust gender differences demonstrating a more deleterious impact among women [41, 42]. For women, these social context characteristics are more strongly linked to mortality rates than individual characteristics, where the impact of social context for men is relatively small in comparison to individual demographic and behavioral characteristics. Social contextual effects are relevant to understanding gender differences in patterns of trauma exposure as well as PTSD. Worldwide epidemiological data indicates that most traumatic events are not randomly distributed across populations [26], and though gender-linked patterns of trauma exposure are well documented, the consistency of these gender differences across environments and populations is not well understood. Likewise, the prevalence ratio of (DSM-IV) PTSD in women relative to men varies significantly across countries [7], with few hypotheses regarding social determinants, though the gender disparity in depression is more pronounced in countries with greater gender inequality [43]. In this section, we highlight aspects of social context that have potential to explain gender differences in trauma exposure and PTSD prevalence.

Area social capital (i.e., social support, resources, and connectedness) is a well-established determinant of health outcomes, where lower social capital is associated with poor health [44]. Lower social capital is associated with an increased past-year incidence of interpersonal violence among women, but not men [45]. Higher levels of social capital are associated with a decreased risk for PTSD [46], and remission from PTSD [45]. Similarly, area socioeconomic status and neighborhood disorder status (e.g., physical decay, vandalism, vacant buildings) are associated with increased incidence of interpersonal violence, such as fatal assault, gun violence, and interpersonal partner violence (IPV) [47, 48]. These same neighborhood contextual variables are associated with lifetime PTSD among trauma-exposed individuals, even after adjusting for individual characteristics [46]. The effects of social capital are not always protective, however. Adolescent sexual assault is prospectively influenced by both individual risk and the assault risk of those with whom a young woman has social network ties [49]. Cohesive communities can maintain social norms that that have negative health effects or affect individuals differently across the community [50]. Most notably, social contexts with norms that support stricter gender roles show increased rates of child abuse, intimate partner violence, and sexual violence [51]. Preliminary data suggests these effects may be mediated by lower levels of violence perpetration by males in more gender-egalitarian communities [52].

Social and economic inequalities have also been identified as contextual influences on health. Income inequality and racial inequalities at the neighborhood level are associated with increased rates of violent assault [48]. The prevalence of past-year PTSD is lower among women residing within US states where policies reflect greater reproductive rights (an indicator of gender equality), as compared to women in states with greater gender inequality [53]. Greater state-level income inequality is associated with a higher incidence of PTSD among both men and women [54•].

These studies illustrate that the risks for PTSD are influenced not only by individual characteristics but those of our social environments as well. These effects may influence gender differences by two major pathways. First, women's trauma exposure may be more strongly shaped by social context than men's, where the distribution of traumatic events such as assault, IPV, child abuse, and sexual assault across communities shows reliable associations with characteristics of the social environment. Second, gender-specific impacts of gender roles and social and economic inequalities may be particularly relevant to explain aspects of women's vulnerability to PTSD that are not accounted for by individual risks or exposures. While more research is needed to fully understand the most important aspects of social contexts and the pathways by which they influence PTSD risk, these studies reinforce the

utility of considering both individual and environmental correlates of gender.

Response to Psychotherapy

In the USA, approximately half of individuals with a lifetime history of DSM-5 PTSD ever seek treatment (59.4%), most often from formal health care or mental health care settings [5]. Women are more likely to seek treatment (60.4% vs. 52.3%) as compared to men, and somewhat more likely to seek psychotherapy or counseling (55.1% vs. 48.2%), though pharmacotherapy treatment rates are similar (32.7% vs. 30.5%) [55]. Most individuals presenting for formal treatment present with chronic PTSD, with an average time since the onset of PTSD of 4.5 years [5].

Clinical practice guidelines in the USA recommend individual trauma-focused psychotherapy as the first-line treatment for PTSD [56, 57]. Meta-analyses suggest that trauma-focused psychotherapies are more effective for women as compared to men, though differences in treatment effectiveness are not large. Women demonstrate greater treatment-related symptom reduction as compared to men, at post-treatment and follow-up [58]. When these effect sizes are viewed in terms of the probability of treatment benefit [59], women have an approximately 78% chance of benefit from trauma-focused PTSD psychotherapies, whereas men have approximately a 68% chance of benefit. Earlier reviews also noted enhanced treatment effects among psychotherapy and pharmacotherapy trials with greater proportions of women [60], noting that the majority of trials with men focused on Veteran populations, where effect sizes were lower. Recent studies, however, document similar treatment efficacy among Veterans as compared to non-Veterans [61], as well as among men and women in trials with Veterans or military populations [62]. Women's better outcomes, though these effects are not large, do not appear to be a generalized advantage in psychotherapy, though relatively few meta-analyses of psychotherapy effectiveness have addressed gender in subgroup analyses. A recent meta-analysis of psychotherapy trials for depression did not find evidence of gender differences in treatment effectiveness [63], suggesting that gender-linked advantages may be specific to PTSD treatment.

Conclusions and Future Directions

Quantifying gender-related variation is important to understanding PTSD and traumatic stress responses at molecular, individual, and community levels of analysis. Research confirms that the multi-level influences that engender risk and resilience to traumatic stress reactions appear to be remarkably similar across men and women. Accounting for sex- and gender-linked factors in genetic risk will be critical in future study designs and in the eventual translational work towards precision medicine. Yet, interpreting sex differences in heritability may require better understanding of gender-linked environmental influences and genotype interactions with sex-linked biological contexts. Trauma exposure is an environmental influence that imparts gender-linked risks for PTSD through trauma type, repeated exposures, and timing of exposure(s). In particular, childhood exposure to interpersonal trauma, which is often repeated and episodic, is hypothesized to spark a cascade of psychological, neurobiological, and epigenetic changes that enhance risk for subsequent mental health comorbidities [64], highlighting the potential complexity of the interacting, gender-linked mechanisms that underlie women's elevated PTSD risk. Risk for childhood trauma, and other forms of interpersonal violence, is in turn influenced by larger environmental conditions of the individual's social context, pointing to hypotheses regarding gender as a proxy for specific patterns of socially determined trauma exposure.

Multi-level studies of the characteristics of social contexts define gender-linked, shared risk factors, such as inequalities or disadvantage, that increase risk for both specific types of traumatic events and for PTSD. Methodologically, an "omitted variable bias" occurs when variables that predict both exposures and outcomes are not accounted for, yielding inflated estimates of effects for related predictors that act as proxy variables, such as gender. Research across multiple levels has potential to further elucidate gender-related risks, and to inform macro-level interventions with potential to enhance trauma recovery at the community level.

We found relatively few studies that addressed the intersectional effects of gender and other social identities, but note that such studies would undoubtedly be important in understanding the ways in which social context shapes vulnerability to traumatic stress. For example, sex-adjusted rates of PTSD are higher among African-American individuals as compared to non-Latinx Whites, a difference partly accounted for by trauma type and frequency [65], and linked to social context characteristics such as disadvantaged, high-crime environments and racial discrimination [66]. Gender nonconformity and minority sexual orientation are linked to increased rates of trauma exposure, especially in childhood [67], with high rates of interpersonal and sexual violence that is so inextricably tied to gendered expectations that it is commonly referred to as "gender-based violence" [68]. Better understanding of multiple social identities and the individual and contextual-level factors that promote or impede resilience to traumatic stress in high-risk populations would undoubtedly enhance individual treatment and community prevention efforts.

Other gender differences are less clear in their clinical significance, and may best be interpreted cautiously to avoid over-interpreting small but statistically significant effects where men and women may be more similar than different.

Women show a modest advantage with respect to benefit from psychotherapy, but the clinical significance of the effect is not large, and these differences may be due to other gender-related differences in perceived need for care, delay in treatment seeking, or other factors. This difference is notable in that it is one of the few gender-related differences to suggest greater resilience, rather than vulnerability to traumatic stress, for women as compared to men.

In PTSD and other domains, research on gender-related effects is particularly vulnerable to biased interpretations [69]: investigators are not immune to cultural influence and implicit associations, and essentialist explanations are often more concise and intuitively appealing than the nuanced complexities across biological, psychological, and social systems that account for the effects of sex and gender. Research is unlikely to identify a single factor that accounts for gender differences in PTSD risk and resilience. Systematic consideration of the multiple levels at which sex and gendered effects are evident can diminish the utility of assumptions regarding homogeneous gender-related vulnerability, and shape hypotheses that highlight the wide array of potential mechanisms in traumatic stress responses.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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