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ORIGINAL PAPER

Time course of panic disorder and posttraumatic stress disorder onsets

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Abstract

Purpose Posttraumatic stress disorder (PTSD) often co-occurs with panic disorder (PD), with some etiological models positing a causal role of panic reactivity in PTSD onset; however, data addressing the temporal ordering of these conditions are lacking. The aim of this study was to examine the bi-directional associations between PD and PTSD in a nationally representative, epidemiologic sample of trauma-exposed adults.

Methods Participants were community-dwelling adults (62.6% women; M_{age} = 48.9, SD 16.3) with lifetime DSM-IV PTSD criterion A trauma exposure drawn from the 2001/2 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) and re-interviewed in 2004/5 (N = 12,467). Cox discrete-time proportional hazards models with time-varying covariates were used to investigate the bi-directional associations between lifetime PD and PTSD, accounting for demographic characteristics, trauma load, and lifetime history of major depression, generalized anxiety disorder, and social anxiety disorder.

Results PD was significantly associated with subsequent onset of PTSD (HR 1.210, 95%CI = 1.207–1.214, $p < .001$), and PTSD was significantly associated with onset of PD (HR 1.601, 95% CI 1.597–1.604, $p < .001$). The association between PTSD and subsequent PD was stronger in magnitude than that between PD and subsequent PTSD ($Z = -275.21$, $p < .01$). Men evidenced stronger associations between PD and PTSD compared to women.

Conclusions Results were consistent with a bidirectional pathway of risk, whereby PD significantly increased risk for the development of PTSD, and PTSD significantly increased risk for PD. Given the association between PTSD and subsequent PD, particularly among men, clinicians may consider supplementing PTSD treatment with panic-specific interventions, such as interoceptive exposure, to prevent or treat this disabling comorbidity.

Keywords Posttraumatic stress disorder · Panic disorder · Epidemiology · Panic attack · Trauma

Introduction

Exposure to a potentially traumatic event (PTE; e.g., physical or sexual assault, transportation accident, combat exposure) is a necessary condition for the diagnosis of posttraumatic stress disorder (PTSD) [1]. PTE exposure is quite common, with epidemiological studies estimating that up to 89% of the population will experience one or more PTEs over the course of their lifetime [2]; however, the lifetime prevalence of PTSD is 7–8% [2, 6], with the conditional probability of PTSD given PTE exposure ranging from 9 to 11% when not specifying a particular type of PTE exposure [2]. Further, PTE exposure also is associated with increased risk for a wide array of psychiatric conditions, including panic disorder, major depression, specific phobias, and substance use disorders [3–5], with many of these conditions

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often co-occurring with PTSD [6, 7]. Significant focus in the trauma literature has been devoted to comorbidity with panic-spectrum psychopathology. Multiple lines of evidence support a relationship between PTE exposure and/or PTSD with panic psychopathology. PTE exposure is related to increased incidence of panic attacks [8, 9], and approximately 69% of individuals seeking treatment for PTSD meet current criteria for panic attacks [10]. Similarly, individuals with panic disorder with or without agoraphobia (PD/PDA) often report histories of PTEs [11], and both clinical and epidemiologic samples indicate that PTSD and PD/PDA are highly comorbid [6, 12, 13].

In spite of high rates of co-occurrence between PTSD and panic-spectrum psychopathology, the nature of this co-occurrence is not well understood. Theoretical models suggest that panic attacks and panic reactivity (i.e., a tendency to endorse panic symptoms in response to physiological arousal) may play a causal role in PTSD etiology. Specifically, it has been hypothesized that peri-traumatic panic attacks (i.e., panic attacks experienced during a PTE) may facilitate trauma-relevant fear conditioning, subsequently increasing risk for PTSD [9, 14], with empirical evidence supporting a relationship between peri-traumatic panic attacks and increased likelihood of developing PTSD [15, 16]. However, the role of more severe panic psychopathology in PTSD etiology has received less attention in the literature. In addition, sex differences in PD/PDA and PTSD comorbidity are unclear. Investigating potential differences in comorbidity on the basis of sex is important, given that women are more likely than men to meet criteria for PD/PDA and PTSD, in spite of men and women experiencing comparable rates of PTEs [17, 18].

There is evidence for a common liability model of co-occurring PD/PDA and PTSD, as PTSD and PD/PDA share common genetic and unique environmental risk [19–22], indicating that shared liability may account for high rates of co-morbidity. Indeed, similarities exist with regard to underlying physiology of PTSD and PD/PDA. For example, PTSD and PD/PDA, but not other anxiety disorders, are associated with autonomic arousability [23], such that individuals with PTSD and PD/PDA have similar patterns of self-reported and physiological anxiety in response to laboratory-induced arousal [24]. Similarly, comparison of cortisol stress response in clinical and non-clinical samples indicates a cortisol hypo-responsiveness common to individuals with PTSD and PD [25]. Putative individual difference characteristics, such as anxiety sensitivity [26, 27] and distress tolerance [28, 29], also have been associated with both disorders. Finally, peripheral evidence from treatment-outcome research is consistent with a common liability model of PD/PDA and PTSD. Specifically, in a sample of patients with comorbid PD–PTSD, treatment of PTSD with cognitive behavioral methods demonstrated concurrent reduction in panic symptoms, even in the absence of panic-focused treatment [30].

Epidemiologic studies of PD/PDA and PTSD may be useful in evaluating the nature of the etiologic relationship between PD/PDA and PTSD. For example, evaluating the temporal associations between PD/PDA and PTSD and the strength of these associations would point to whether this relationship is primarily uni- or bi-directional. If the strength of the association between PTSD and subsequent PD/PDA is comparable to that of PD/PDA and subsequent PTSD, this bi-directional relationship would be consistent with the etiologic hypothesis that common underlying liability (i.e., genetic or environmental factors) shared by both conditions may be responsible for their co-occurrence. However, if the data are more consistent with a uni-directional relationship, for example, the risk of PTSD subsequent to PD/PDA is substantially greater than the risk of PD/PDA subsequent to PTSD, this would support an etiologic model of a direct, causal relationship, potentially related to the influence of panic psychopathology on fear conditioning. To our knowledge, no studies to date have examined the bi-directional association between PD/PDA and PTSD within a population-based sample.

The aim of this study was to examine the bi-directional association between PD/PDA and PTSD in a sub-set of trauma-exposed adults participating in a national epidemiologic research study. Specifically, we examined both the risk of PTSD associated with prior PD/PDA, and the risk of PD/PDA associated with prior PTSD. We hypothesized that the association between PD/PDA and subsequent PTSD would be stronger in magnitude than the reverse association, based on theory and existing literature highlighting panic processes as risk factors for PTSD. Given observed sex differences in the prevalence of PD/PDA and PTSD, we also examined whether associations between PD/PDA and PTSD differed by sex.

Method

Participants

The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) is a longitudinal, nationally representative population-based survey of community-dwelling US adults. Details of the study design have been described previously [31]. Briefly, baseline interviews were conducted in 2001/2 ($n = 43{,}093$, response rate: 81.0%), with a follow-up wave in 2004/5 ($n = 34{,}653$, response rate: 86.7%). Interviews were conducted in person by trained, lay interviewers. The current investigation is limited to participants who completed both waves of interviews ($N = 34{,}653$), with the primary analyses limited to the subset of the sample that

met lifetime DSM-IV PTSD criterion A trauma exposure ($N = 12,467$). This was necessary because only individuals with a criterion A trauma are eligible for a diagnosis of PTSD. The US Census Bureau and the US Office of Management and Budget reviewed and approved the research protocol and informed consent procedures. After complete description of the study to the subjects, written informed consent was obtained. 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

Psychiatric disorders were assessed using the NIAAA Alcohol Use Disorder and Associated Disabilities Interview Schedule, DSM-IV version [32]. The AUDADIS-IV has good test–retest reliability and moderate agreement against structured clinical interviews [33]. The AUDADIS-IV also was used to assess substance use and other psychiatric disorders.

PTSD and trauma exposure were only assessed at wave 2. Within the PTSD module, respondents were queried on whether they had experienced a range of PTEs (e.g., motor vehicle accident, sexual assault, sudden death of a loved one, etc.). DSM-IV Criterion A for PTSD was assessed for participants' self-identified "worst" traumatic event, and all other PTSD symptoms were assessed in reference to this criterion A event. Age of onset of PTSD, based on individuals' "worst" event, was assessed for those who met diagnostic criteria for lifetime PTSD. For individuals with lifetime PTSD who were missing age of onset data (1.5%), the data were imputed based on the median age of onset of participants in the same age decade. A sum score of the number of PTE categories endorsed served as a covariate for the present analyses to ensure that observed associations between PD/PDA and PTSD were not better accounted for by differences in trauma load.

PD/PDA was initially assessed using three probe questions including: (1) "Have you ever had a panic attack, when all of a sudden you felt frightened, overwhelmed or nervous, almost as if you were in great danger, but really weren't?" (2) "Were you ever very surprised by a panic attack that happened totally out-of-the-blue, for no real reason, or in a situation where you did not expect to be frightened?" (3) "Did you ever think you were having a heart attack, but the doctor said it was just nerves or you were having a panic attack?" Respondents who endorsed at least one of these problems were queried further about the presence of DSM-IV panic attack symptoms (e.g., racing heart, shortness of breath), frequency of attacks, and interference in functioning. Agoraphobia was assessed using DSM-IV criteria by asking respondents about their avoidance of a number of situations (e.g., crowded places, closed spaces, flying, traveling on buses), whether panic attacks were associated with such specific situations, and whether the person experienced interference in their daily functioning because of their discomfort with the endorsed situations.

PD/PDA was assessed at both wave 1 and wave 2; however, age of onset was not obtained for new cases with onset occurring between waves 1 and 2. For those cases that onset after wave 1, age of onset for PD/PDA was imputed using date of birth and date of interview as: (1) mean age in the year prior to interview if onset occurred in the past year, or (2) mean age during that approximate 2 years window between wave 1 and the year prior to wave 2 if onset occurred after wave 1 but prior to the year of the wave 2 interview. For individuals with lifetime PD/PDA who were missing age of onset data (1.7%), the data were imputed based on the median age of onset of participants in the same age decade.

Lifetime major depressive disorder, generalized anxiety disorder, and social anxiety disorder also were assessed using the AUDADIS-IV. For the purposes of this study, lifetime history of each disorder was considered positive if a participant met criteria at either the wave 1 or wave 2 assessment. Each disorder was coded as 0 ("absent") or 1 ("present").

Data analytic plan

Descriptive statistics were conducted to examine the distribution of PD/PDA and PTSD age of onset, as well as the distribution of the difference in age of onset among individuals with histories of PD/PDA and PTSD (i.e., age of onset of PD/PDA—age of onset of PTSD). Analyses were conducted in the total trauma-exposed sample, as well as stratified by sex.

Two Cox proportional hazards (PH) models were conducted: (1) PD/PDA predicting PTSD onset; and (2) PTSD predicting PD/PDA onset. The predictor disorder represented a time-dependent covariate changing from 0 to 1 at the age of onset, with failure time for cases being the age of onset of the criterion disorder or censoring time (for non-cases) being the last observed age (i.e., wave 2 age). In cases where individuals met criteria for both disorders, but the outcome disorder preceded the predictor disorder, the time-dependent covariate remained at 0 (i.e., the cases were retained in the analyses but did not contribute to the estimate of the relative risk). The estimates of the hazard ratio (HR), an approximation of the relative risk, accounted for the influence of incomplete information from right-censored observations [e.g., individuals who were at-risk of developing PD/PDA (or PTSD) but did not prior to the end of the observation period]. All models were adjusted

for demographic characteristics relevant to the outcomes of interest [i.e., age (in years), sex (reference group = male), race/ethnicity (reference group = white), and education level (reference group = "less than high school")], number of PTE categories endorsed, and lifetime diagnoses (0, 1) of major depressive disorder, generalized anxiety disorder, and social anxiety disorder. Models also were run separately for men and women to evaluate potential sex differences in the associations between PD/PDA and PTSD. The determination of significant sex differences in the relationships between PD/PDA and PTSD was made by examining the difference between log relative risks, which produces a Z score and associated p value of the difference between the size of the hazard ratios for men and women.

Sampling weights, described in detail elsewhere [31], were applied to the Cox PH models. Statistical significance was defined as $p < .05$. All analyses were conducted in R 3.0 [34], with the Cox PH models being conducted using the *coxph* function in the *survival* package [35].

Results

Sample characteristics

Sample characteristics are presented in Table 1. Men had a younger age of first PTE compared to women and endorsed having experienced a greater number of PTE types compared to women. Women were more likely than men to meet criteria for lifetime PD/PDA and PTSD. Among individuals with a lifetime diagnosis of PD/PDA ($n = 1286$), the mean age of onset was 34.7 years (SD 14.6). Men and women did not significantly differ in their average age of onset of PD/PDA [$M = 33.8$ and $M = 35.1$, respectively; $t(570) = -1.36$, $p = .175$]. Among individuals with a lifetime diagnosis of PTSD ($n = 2463$), the mean age of onset was 29.2 years (SD 16.5). Men and women did not significantly differ in their age of onset of PTSD [$M = 28.2$ and $M = 29.5$, respectively; $t(1339) = -1.81$, $p = .071$]. Among individuals who met lifetime criteria for both PD/PDA and PTSD ($n = 804$), 27.4% reported initial onset of PD/PDA, 67.2% reported initial onset of PTSD, and 5.5% reported onset within the same year. Among men who met lifetime criteria for both disorders ($n = 175$), 33.7% reported initial PD/PDA onset, 59.4% initial PTSD onset, and 6.9% same-year onset; for women ($n = 629$), 25.6% reported initial PD/PDA onset, 69.3% initial PTSD onset, and 5.1% same year onset.

Cox proportional hazard models

See Table 2 for output from the Cox proportional hazard models and Fig. 1 for a graphical representation of hazard ratios for PD/PDA and PTSD predicting one another. A diagnosis of PD/PDA was associated with a 21% greater chance of developing PTSD, above and beyond the effect of the covariates. The association between PD/PDA and subsequent PTSD was stronger for men compared to women (test of gender comparison: $Z = 107.02$, $p < .01$). Specifically, men with compared to without PD/PDA evidenced a 67% increased chance of developing PTSD, whereas women with compared to without PD/PDA only evidenced an 11% increased chance of developing PTSD.

A diagnosis of PTSD was associated with a 60% increased chance of developing PD/PDA, above and beyond the effect of the covariates. The association between PTSD and subsequent onset of PD/PDA was stronger for men compared to women (test of gender comparison: $Z = 57.41$, $p < .01$). Men with compared to without PTSD evidenced a 72% greater chance of developing PD/PDA, whereas women with compared to without PTSD evidenced a 58% increased chance of developing PD/PDA.

We then assessed whether there were differences in magnitude for PD/PDA predicting PTSD compared to PTSD predicting PD/PDA. Contrary to expectation, the association between PTSD and subsequent PD/PDA was significantly greater than the association between PD/PDA and subsequent PTSD (test of comparison: $Z = 151.39$, $p < .01$). The same effect was detected for men ($Z = 9.96$, $p < .01$) and women ($Z = 178.81$, $p < .01$), although the difference in effect size was more pronounced for women compared to men. Finally, to evaluate whether sex differences in the total sample models were better accounted for by trauma type, models were re-run with categories of worst traumatic event (dummy coded 0 and 1) entered as covariates in the models. Neither the magnitude nor direction of effect changed with respect to the role of sex in the models or the respective associations between PD/PDA and PTSD, suggesting that sex differences likely are not reflecting differences in propensity for different types of trauma exposure.

Discussion

The aim of this investigation was to determine the bidirectional association between PD/PDA and PTSD in a large, epidemiologic sample of trauma-exposed adults. To the best of our knowledge, this study represents the first of its kind to examine temporal ordering of PD/PDA and PTSD among community-dwelling individuals with a PTE history. Results of descriptive analyses indicated that ages of onset of PD/PDA and PTSD were similar, but that PTSD onset occurred, on average, slightly earlier than PD/PDA onset (approximately age 29 compared to age 35, respectively). Results of the Cox PH models identified bidirectional associations, whereby PD/PDA significantly increased likelihood of developing PTSD, and PTSD significantly increased

Table 1 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) wave 2 (2004–2005) trauma-exposed participants

	Total trauma-exposed sample ($N=12,467$)	Trauma-exposed men ($n=4666$)	Trauma-exposed women ($n=7801$)	Test of sex difference
Sex (% women)	62.6%	–	–	–
Race/ethnicity (%)				
White	60.6%	62.2%	59.6%	
African American	18.6%	15.9%	20.2%	
American Indian/Alaska Native	1.9%	2.0%	1.9%	
Asian/Native Hawaiian/Pacific Islander	2.4%	2.6%	2.3%	
Hispanic/Latino	16.5%	17.3%	16.0%	
Mean age (SD), in years	49.3 (16.3)	49.2 (16.0)	49.4 (16.6)	$t=-0.71$, $p=.475$
Highest level of education completed (%)				
Less than high school degree	14.0%	13.9%	14.1%	
High school or GED	28.4%	26.9%	29.3%	
Some college/2-year degree	32.2%	31.3%	32.8%	
Bachelor's degree	13.1%	14.9%	12.0%	
Some graduate school	12.4%	13.2%	11.9%	
"Worst" traumatic event endorsed				
Serious illness/injury of a loved one	27.7%	25.3%	29.2%	$\chi^2=22.26$, $p<.001$
Unexpected death of loved one	22.7%	20.7%	23.9%	$\chi^2=17.58$, $p<.001$
Indirect/direct experience of 9/11 or other terrorist attack	12.1%	11.9%	12.2%	$\chi^2=0.21$, $p=.644$
"Other" traumatic event	7.5%	6.5%	8.1%	$\chi^2=12.00$, $p=.001$
Witnessing death/serious injury	4.0%	5.6%	3.1%	$\chi^2=50.61$, $p<.001$
Life-threatening illness	3.7%	3.6%	3.8%	$\chi^2=0.58$, $p=.448$
Exposure to combat/war zone	3.4%	8.3%	0.5%	$\chi^2=545.17$, $p<.001$
Serious accident	3.3%	5.4%	2.1%	$\chi^2=99.38$, $p<.001$
Physical assault	2.7%	1.1%	3.6%	$\chi^2=73.90$, $p<.001$
Sexual assault	2.6%	0.3%	4.0%	$\chi^2=155.68$, $p<.001$
Witnessing violence as child	2.3%	1.9%	2.6%	$\chi^2=6.36$, $p=.012$
Threatened with a weapon	2.3%	3.8%	1.4%	$\chi^2=71.68$, $p<.001$
Natural disaster	2.0%	2.5%	1.7%	$\chi^2=9.92$, $p=.002$
Physical assault/neglect as a child	0.9%	1.0%	0.9%	$\chi^2=0.92$, $p=.337$
Kidnapped/stalked	0.9%	0.5%	1.1%	$\chi^2=13.11$, $p<.001$
Number of potentially traumatic event categories endorsed	4.38 (2.49)	4.67 (2.56)	4.20 (2.43)	$t=10.13$, $p<.001$
Mean age of first PTE (SD), in years	18.53 (14.71)	16.91 (12.61)	19.52 (15.77)	$t=9.47$, $p<.001$
Lifetime PD/PDA	10.3%	7.0%	12.3%	$\chi^2=87.02$, $p<.001$
Lifetime PTSD	19.8%	14.4%	22.9%	$\chi^2=132.69$, $p<.001$
Lifetime major depression	29.7%	21.7%	34.5%	
Lifetime generalized anxiety disorder	11.4%	7.8%	13.6%	
Lifetime social anxiety disorder	9.3%	8.2%	10.0%	

likelihood of developing PD/PDA. These findings are most consistent with past studies indicating the importance of common genetic and environmental vulnerabilities in understanding risk for co-occurring PD/PDA and PTSD [19–22].

Although prior theoretical and empirical studies have suggested a potentially causal role of panic psychopathology in relation to PTSD [15, 16], presumably by way of peri-traumatic panic attacks strengthening fear conditioning processes [9, 14], the current study did not find support for this model when considering this more severe form of panic psychopathology (e.g., full diagnosis of PD/PDA). In fact, a stronger association was evidenced for PTSD predicting PD/PDA compared to the reverse. Given that panic attacks are known to convey general risk for psychopathology, broadly defined (e.g., 36), future studies would benefit from evaluating bidirectional associations between panic attacks and PTSD in epidemiological samples. It may be the case that different factors promote risk for panic attacks compared to PD/PDA, and that panic attacks compared to PD/PDA convey risk for different conditions.

Table 2 Cox proportional hazard model output: patterns of association between panic disorder (with and without agoraphobia; PD/PDA) and posttraumatic stress disorder (PTSD) in an epidemiological sample

	Total trauma-exposed sample ($N=12,467$)	Trauma-exposed men ($n=4666$)	Trauma-exposed women ($n=7801$)
Factors predicting PTSD			
PD/PDA[a]	1.210* (1.207–1.214)	1.670* (1.662–1.678)	1.112* (1.108–1.115)
Wave 2 age	0.976* (0.976–0.976)	0.977* (0.976–0.977)	0.975* (0.975–0.976)
Sex (0 = male, 1 = female)	1.628* (1.625–1.630)	–	–
Race/ethnicity (0 = white, 1 = nonwhite)	1.143* (1.142–1.145)	1.049* (1.047–1.052)	1.188* (1.186–1.190)
Education (1: high school/GED)[b]	0.797* (0.796–0.799)	1.019* (1.016–1.023)	0.713* (0.711–0.714)
Education (2: some college)	0.743* (0.741–0.744)	0.786* (0.783–0.788)	0.704* (0.702–0.706)
Education (3: Bachelor's degree)	0.710* (0.709–0.712)	0.692* (0.689–0.694)	0.721* (0.719–0.722)
Education (4: some graduate school)	0.631* (0.629–0.632)	0.547* (0.544–0.549)	0.672* (0.670–0.673)
Number of potentially traumatic event categories endorsed	1.161* (1.161–1.161)	1.148* (1.147–1.149)	1.172* (1.171–1.172)
Major depressive disorder (MDD)	2.102* (2.099–2.105)	2.008* (2.003–2.013)	2.079* (2.076–2.082)
Generalized anxiety disorder (GAD)	1.579* (1.576–1.581)	2.006* (2.000–2.012)	1.502* (1.499–1.505)
Social anxiety disorder (SAD)	1.324* (1.321–1.326)	1.367* (1.363–1.372)	1.385* (1.382–1.388)
Factors predicting PD/PDA			
PTSD[a]	1.601* (1.597–1.604)	1.721* (1.714–1.729)	1.580* (1.576–1.583)
Wave 2 age	0.975* (0.975–0.976)	0.977* (0.976–0.977)	0.975* (0.975–0.975)
Sex (0 = male, 1 = female)	1.424* (1.422–1.427)	–	–
Race/ethnicity (0 = white, 1 = nonwhite)	0.927* (0.925–0.929)	0.767* (0.764–0.770)	0.976* (0.974–0.978)
Education (1: high school/GED)[b]	0.740* (0.738–0.742)	0.777* (0.773–0.781)	0.728* (0.725–0.730)
Education (2: some college)	0.835* (0.832–0.837)	1.012* (1.007–1.017)	0.781* (0.779–0.784)
Education (3: bachelor's degree)	0.690* (0.688–0.692)	1.000* (0.995–1.005)	0.610* (0.610–0.612)
Education (4: some graduate school)	0.629* (0.627–0.631)	0.802* (0.797–0.806)	0.583* (0.581–0.586)
Number of traumatic event categories endorsed	1.075* (1.074–1.075)	1.108* (1.108–1.109)	1.073* (1.073–1.073)
Major depressive disorder (MDD)	2.105* (2.101–2.109)	2.197* (2.189–2.204)	1.998* (1.994–2.002)
Generalized anxiety disorder (GAD)	1.868* (1.864–1.871)	1.931* (1.924–1.939)	1.856* (1.852–1.860)
Social anxiety disorder (SAD)	1.951* (1.947–1.955)	1.918* (1.911–1.926)	1.979* (1.974–1.983)

Hazard ratios presented with 95% confidence intervals

*$p < .001$

[a]Time-dependent covariate

[b]Reference group = 0: "less than high school"

While our findings are most consistent with a common liability model of comorbid PD/PDA and PTSD, other etiologic models of this relationship may be operating and investigation of multiple etiological pathways to comorbid PD/PDA–PTSD is needed. Additionally, studies of specific risk mechanisms linking PD/PDA and PTSD are needed, such as investigations of genetic and environmental factors underlying fear conditioning processes, as well as subjective and physiological reactivity to interoceptive cues (e.g., change in heart rate) [24]. Examining the role of cognitive risk factors (e.g., anxiety sensitivity) relevant to both disorders also would be fruitful [28, 29]. Further, it is possible that a different pattern of findings would emerge for nonclinical panic attacks, particularly peri-traumatic panic attacks, and PTSD; however, due to high rates of missing age of onset data for panic attacks among individuals without full PD/PDA, we were not able to examine these associations within the current investigation.

Our data indicate that there are significant sex differences in the relationships between PD/PDA and PTSD. Specifically, although women were more likely than men to meet criteria for either disorder, men had stronger associations between these disorders relative to women, particularly with regard to PD/PDA predicting PTSD. It may be that men who met PD/PDA had more severe symptomology than women, consistent with different gender thresholds for meeting diagnostic criteria. Alternatively, it may be the case that the observed sex differences in the relationship between PD/PDA and PTSD are better explained by differences in trauma characteristics, such as type of trauma (e.g., interpersonal versus accidental) [37]; however, the current follow-up analyses did not support this hypothesis. Men and

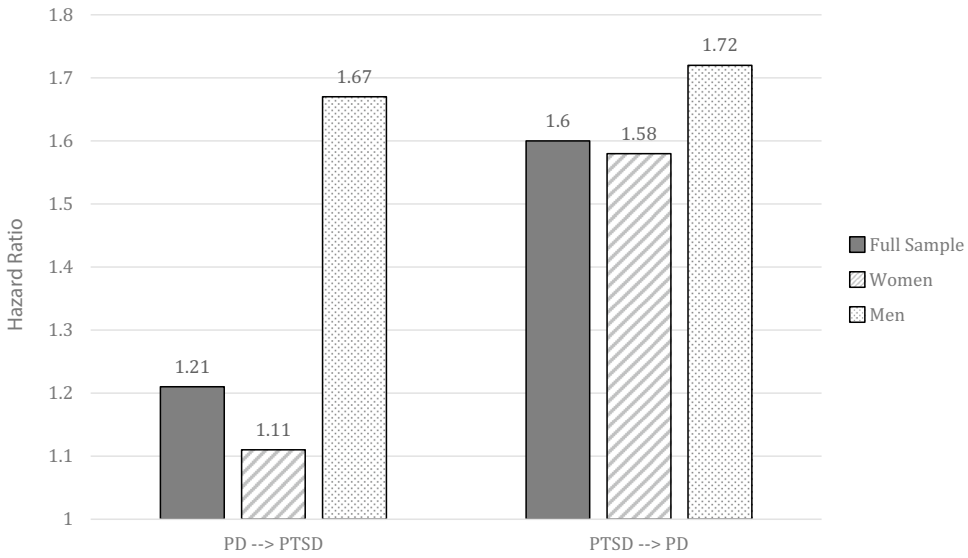

Fig. 1 Associations between panic disorder (PD) and posttraumatic stress disorder (PTSD)

women may also differ in their subjective and physiological reactions to trauma. Available research on the occurrence of peri-traumatic panic attacks has not found support for sex differences, or differences as a function of trauma type [10, 16]. Finally, it is possible that sex moderates the factor structure of PTSD, which could influence the observed associations [38]. Further investigation of mechanisms accounting for sex differences in post-trauma reactions and patterns of comorbidity are needed.

There are three key clinical implications of our findings. First, it is possible that identification of common risk factors may inform the development of transdiagnostic prevention efforts. For example, a brief interoceptive exposure intervention after experiencing a PTE to decrease reactivity to symptoms of physiological arousal [39] may be beneficial for prevention of both PD/PDA and PTSD. Indeed, the cognitive behavioral treatment (CBT) literature has been moving in the direction of transdiagnostic interventions (i.e., combined treatments), which are centered on the premise that phenotype-specific treatment manuals have shared components that can be distilled into one protocol to address symptoms across related conditions simultaneously [40]. Second, our results suggest that clinicians should be educated regarding the potential increased risk for PD/PDA associated with a PTSD diagnosis and vice versa, particularly among men. For example, assessment and monitoring of panic attacks and associated worry would be useful for patients presenting with trauma histories and/or PTSD symptoms. Finally, the highly comorbid nature of PTSD and PD/PDA and the increased risk that these disorders confer into one another introduce the potential clinical utility of incorporating PD/PDA treatment principles into PTSD treatment and vice-versa. Given the pattern of sex differences observed in the present study, combined PD/PDA and PTSD treatment may be particularly suitable for male patients. Future research will be necessary to address combined treatment options and outcomes for individuals presenting comorbid PD/PDA and PTSD.

Our results should be interpreted in light of study limitations. First, trauma exposure and PTSD were only assessed at wave 2, and lifetime diagnoses and self-reported ages of onset were used. As such, we are limited by our reliance on retrospective reporting. Additionally, as is often the case in the PTSD literature, criterion A status and associated PTSD symptoms were only assessed for individuals' self-identified "worst" traumatic events; therefore, temporal ordering of multiple criterion A events could not be considered. Additionally, given that we only have information on PTSD symptoms related to the "worst" event, it is possible that individuals could have met criteria for PTSD based on an earlier trauma, in which case, effect size estimates could be skewed. Longitudinal studies are needed that are able to accommodate multiple trauma and sets of associated symptoms. Second, because of data limitations we were unable to assess the role of nonclinical panic attacks or panic reactivity in relation to PTSD; panic attacks are more common than PD/PDA and also are relevant to existing theoretical models of panic–PTSD. Therefore, future investigation of the longitudinal relationships between panic attacks and PTSD are needed. Similarly, we were not able to examine the role of potential vulnerability factors (e.g., HPA axis reactivity, anxiety sensitivity, interoceptive conditioning) accounting for comorbidity between PD/PDA and PTSD in this sample. Future investigations should incorporate measures of potential biological and environmental risk characteristics that could explain the observed patterns of comorbidity in the

current study. Third, it is possible that individuals evidenced sub-clinical symptoms of these disorders prior to meeting full criteria. Future studies would benefit from evaluating patterns of onset of early symptoms, in addition to evaluating when individuals met full criteria for disorders. Finally, the current study focused on PD/PDA and PTSD comorbidity, due to theoretical and preliminary empirical evidence suggesting a potential causal role of panic psychopathology in the etiology of PTSD. As such, a full analysis of the patterns of onset of multiple anxiety and mood disorders was not within the scope of this project. Future investigations of temporal ordering of multiple axis I disorders would be useful for understanding more broad patterns of comorbidity among trauma-exposed individuals.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to disclose.

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