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ORIGINAL RESEARCH

Sex Differences in Antihypertensive Medications and PTSD Incidence

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Purpose: Evidence suggests there may be a protective association between some antihypertensive medications and posttraumatic stress disorder (PTSD) incidence, but few samples are large enough to examine sex differences in these associations.

Methods: Data came from a trauma cohort established from the Danish national registries from 1994 to 2016. All cohort members experienced at least one of the seven potentially traumatic events (PTE). Those exposed redeemed prescriptions for antihypertensive medications (beta blockers, angiotensin II receptor blockers [ARBs], angiotensin-converting enzyme inhibitors [ACE-Is], and calcium channel blockers) within 60 days prior to PTE. For the unexposed group, three persons who never redeemed an antihypertensive medication prescription were matched to each exposed person on age, sex, and time of trauma. The outcome was incident PTSD over 22 years of follow-up (average follow-up time was 5–6 years). We conducted descriptive analyses followed by Cox proportional hazards regression adjusted for marital status, income, trauma group, Charlson Comorbidity Index score before the PTE, and comedication use of statins, non-steroidal anti-inflammatory drugs, and antidepressants to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Analyses were sex-stratified.

Results: We observed evidence of a protective association between calcium channel blockers and the development of PTSD for females (HR = 0.79; 95% CI = 0.29, 2.2) and males (HR = 0.49; 95% CI = 0.22, 1.1). For females, the adjusted association between ARBs and PTSD was 0.47 (95% CI = 0.11, 2.1); for males, the adjusted association was 1.4 (95% CI = 0.50, 3.6). A slight protective effect was also observed for beta-blockers among males, while these associations closer to the null were observed for females. For both sexes, associations with ACEs were closer to the null.

Conclusion: These results suggest possible sex differences in the potentially protective effects of antihypertensive medications on the development of PTSD, although imprecision in measurement indicates results should be interpreted with caution.

Keywords: posttraumatic stress disorder, PTSD, trauma, antihypertensive medication classes, sex differences

Introduction

Posttraumatic stress disorder (PTSD) is a potentially debilitating psychiatric disorder that can occur after a traumatic event.[1] It has been widely documented that PTSD increases risk for cardiovascular disease (CVD),[2–5] and accordingly, there is growing interest in the impact of antihypertensive medications for PTSD prevention and intervention. Studies to date have largely examined cross-sectional associations between antihypertensive use and PTSD prevalence;[6] antihypertensive use at any time and incident PTSD;[7] and antihypertensives given immediately after a traumatic event (e.g., in the emergency room) on PTSD[8–10] with mixed results. A smaller literature exists on antihypertensive medications taken prior to traumatic event occurrence and subsequent effects on PTSD incidence.[7,11] In our previous work using Danish national health registries, we documented a protective overall association between a single class of antihypertensive medication, calcium channel blockers, prescribed and filled within 60 days prior to a traumatic event and PTSD incidence.[11]

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Complicating this issue, however, sex differences are well documented in PTSD and CVD incidence, pathophysiology, and usage of antihypertensive medication.[12–14] Therefore, it is plausible that sex differences also exist in associations between antihypertensive medications and PTSD incidence. To date, however, only two studies have examined this possibility. In a cross-sectional study, Seligowski et al analyzed sex differences in antihypertensive medication use and prevalent PTSD among 840 individuals from the Grady Trauma Project and replicated their findings in more than 116,000 participants from the Partners Biobank. Overall, the authors observed some evidence for sex differences in PTSD prevalence for angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin II receptor blockers (ARBs).[6] More recently, Kang et al analyzed the association between renin–angiotensin system blockers (an antihypertensive medication class including both ARBs & ACE-Is) and PTSD incidence using data from the UK biobank, but no evidence of sex differences was observed in this dataset. The conflicting findings from these two studies could be attributed to several factors. Neither study assessed antihypertensive medication use relative to the time of trauma, although the Kang et al study was longitudinal and did ensure that antihypertensive medications were taken before PTSD. It is possible that antihypertensive medications have different effects on PTSD depending on when these medications are taken relative to traumatic experiences (i.e, temporal proximity to a traumatic event). In addition, it is possible that antihypertensive medications have a different effect on incident PTSD, which was examined by Kang et al, and PTSD maintenance, which was examined by Seligowski et al.[6,7] Finally, evidence suggests that different antihypertensive classes may have different effects on PTSD,[11] and Seligowski et al examined individual classes, while Kang et al combined ARBs & ACE-Is into one group, potentially obscuring class-specific associations.

To date, no study has explored sex differences in multiple individual classes of antihypertensive medications (including beta blockers, ARBs, ACE-Is, and calcium channel blockers) taken at the time of trauma and PTSD incidence. The current study fills this gap in the literature using data from a population-based sample with up to 22 years of follow-up.

Method

Sample

The sample for this study originated from a population-based cohort of 1.4 million people in Denmark who had experienced a potentially traumatic event (PTE) from 1994 to 2016. This dataset was sourced from population-wide Danish registries, including Danish National Patient Registry, Danish Psychiatric Central Research Registry, Danish Medical Birth Registry, Civil Registration System, and Cause-of-Death Registry.[15–18] Denmark provides universal medical care to all residents, which is catalogued in an extensive registry system that captures diagnoses, treatments, and social variables. These national registries can be linked using a unique personal identification number assigned to each resident of Denmark at birth or immigration. The data sources have been described in further detail elsewhere.[11,19]

Within the nationwide registries, we identified PTEs based on ICD-10 and transportation accident E codes including: fire/explosion, transportation accident, exposure to toxic substance/medical complications, traumatic brain injury (TBI), assault with or without a weapon, pregnancy-related trauma, suicide death of a family member, or multiple traumas (experiencing more than one of these events on the same day). The definition of certain events like pregnancy-related trauma and transportation accidents was augmented to include subsequent hospitalization to increase the probability that these events constituted traumatic experiences, rather than general stressors. For the current study, the cohort was restricted to individuals who did not have a recorded psychiatric disorder between 1994 and the date of the PTE.

Analytic Variables

Our exposure was filling a prescription of one of the four classes of antihypertensive medications within 60 days prior to the PTE. The antihypertensive medication classes were identified using Anatomical Therapeutic Chemical (ATC) codes, including calcium channel blockers (ATC Code: C08), ACE-Is (ATC Code: C09AA), ARBs (ATC Code: C09CA), and beta blockers (ATC Code: C07). We matched each exposed person with up to three unexposed persons who did not fill an antihypertensive medication prescription within 60 days prior to their PTE on sex, year of birth, and date of PTE. Unexposed participants who later filled a prescription for an antihypertensive medication were moved to the exposed cohort at that time. The final sample for the present analysis included 203,615 females and 194,331 males.

For all analyses, the primary outcome of interest was incident diagnosis of PTSD (ICD-10 code: F43.1) over the 22-year follow-up period (average length of follow-up was 5–6 years).[1] These data were obtained from the Danish National Patient Registry (capturing all of Denmark's inpatient and outpatient care occurring at nonpsychiatric hospitals) and Danish Psychiatric Central Research Register (capturing all of Denmark's inpatient and outpatient care occurring in psychiatric hospitals), with all primary and secondary diagnoses included.[20] Follow-up ended when the participant was diagnosed with PTSD, emigrated from Denmark or died, or at the end of the study period.

Confounders were chosen based on the literature and included marital status and income at the time of the PTE (obtained from the Civil Registration System) and prescription of antidepressants (ATC Code: N06A), non-steroidal anti-inflammatory drugs (ATC Code: M01A), or statins (ATC Code: C10AA) filled within 60 days before the PTE. Additionally, we included Charlson Comorbidity Index (CCI)[21] score before trauma (determined by prior diagnoses recorded in the Danish National Patient Registry), and PTE type.

Analytic Approach

We conducted descriptive analyses according of age group, marital status, income quartile, PTE type, and CCI score by antihypertensive medication class and in the unexposed group. Second, we calculated the incidence rate of PTSD per 100,000 person-years as well as the cumulative incidence of PTSD over the entire study period, for the exposed and unexposed groups. Finally, we conducted a Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between each class of antihypertensive medication and PTSD incidence. We estimated both crude models and models adjusted for the matching factors and confounders named above. All analyses were sex-stratified.

Statistical power was calculated separately for each sex, and we had 80% power to detect an HR of 1.5 at an alpha level of 0.05, given our sample sizes. However, in accordance with recommendations against null-hypothesis significance testing for evaluating results,[22–25] we interpret our results with regard to the level of evidence provided by these point estimates and confidence intervals. Importantly, we present all results so that readers may reach their own conclusions about the strength of evidence provided by this study. All analyses were conducted in SAS version 9.4. This work was approved by the Danish Data Protection Agency [2015-57-0002]. The Institutional Review Board at Boston University Medical Campus reviewed this study and classified it as "non-human subjects research" because the Boston University study team did not have access to any participant identifiers or any information that could link data back to the identity of participants, removing the need for further ethics board approval at their institution. Data and code can be accessed by request to Statistics Denmark.

Results

Sex-specific descriptive statistics are presented in Tables 1 and 2. Most participants were over 50 years old, aligning with the typical age for antihypertensive medication prescriptions, and most study participants were married or widowed. The majority of participants were in the second lowest income quartile, but males were more likely to be in the highest income quartile than females. Among both sexes, the most common PTE was exposure to toxic substances/medical complications.

Table 1 Female Descriptive Characteristics of Individuals Exposed vs Unexposed to Antihypertensive Medications Before PTE Exposure

	Females							
	Calcium Channel Blockers		ACE Inhibitors		Beta Blockers		Angiotensin II Receptor Blockers	
	Exposed (N=16,439)	Unexposed (N=41,821)	Exposed (N=13,004)	Unexposed (N=34,831)	Exposed (N=20,558)	Unexposed (N=50,717)	Exposed (N=6,728)	Unexposed (N=19,517)
Age group								
<30	0.7	0.8	0.5	0.5	4.7	5.7	0.3	0.3
30–50	4.8	5.6	4.9	5.5	9.9	12	4.6	4.7
50+	95	94	95	94	85	82	95	95

(*Continued*)

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Table 1 (Continued).

	Females							
	Calcium Channel Blockers		ACE Inhibitors		Beta Blockers		Angiotensin II Receptor Blockers	
	Exposed (N=16,439)	Unexposed (N=41,821)	Exposed (N=13,004)	Unexposed (N=34,831)	Exposed (N=20,558)	Unexposed (N=50,717)	Exposed (N=6,728)	Unexposed (N=19,517)
Marital status								
Married/ partnered	39	41	39	42	41	43	42	43
Single/ unknown	6.6	7.8	6.6	7.1	11	13	6.1	6.6
Divorced	12	13	12	14	11	13	13	14
Widowed	42	38	42	37	38	32	39	37
Income quartile								
1 (lowest)	25	23	25	23	25	22	25	26
2	49	46	50	45	45	41	47	45
3	17	19	17	19	19	21	18	18
4 (Highest)	8.3	13	8.2	12	9.7	15	10	11
Child (no income)	0	0.1	0.1	0.1	0.1	0.1	-	-
Unknown	0.2	0.3	0.2	0.4	0.3	0.6	0.2	0.2
Antidepressants	15	11	14	11	13	9.6	14	11
NSAIDs	17	15	16	16	14	14	18	15
Statins	20	7.3	23	7.8	21	6.7	24	11
CCI Score								
0	36	53	31	52	40	57	35	48
1–2	41	34	43	35	38	31	40	36
3+	23	13	26	14	23	12	25	17
PTE type								
Fire/explosion	2.7	3.9	2.7	3.7	2.3	3.8	3.1	3.3
Transport accident	3.2	3.5	3.1	4	2.3	3.5	3.3	4.2
Exposure to toxic substance/ medical complication	74	66	76	67	68	60	74	69
TBI	18	22	17	22	18	19	18	20
Assault	0.2	0.4	0.3	0.4	0.2	0.5	0.4	0.5
Pregnancy-related	1.2	2.6	0	1.8	8.5	11	-	1.4
Family suicide	0.6	1.2	0.5	1.1	0.6	1.1	0.8	1
Multiple events	0.5	0.6	0.5	0.6	0.4	0.5	0.5	0.7

Notes: All numbers are presented as percentages.
Abbreviations: ACE, angiotensin-converting enzyme inhibitors; NSAID, nonsteroidal anti-inflammatory drug; CCI, Charlson comorbidity index; PTE, potentially traumatic event; TBI traumatic brain injury.

Table 2 Male Descriptive Characteristics of Individuals Exposed vs Unexposed to Antihypertensive Medications Before PTE Exposure

	Males							
	Calcium Channel Blockers		ACE Inhibitors		Beta Blockers		Angiotensin II Receptor Blockers	
	Exposed (N=14,977)	Unexposed (N=39,146)	Exposed (N=15,299)	Unexposed (N=39,939)	Exposed (N=18,446)	Unexposed (N=44,846)	Exposed (N=5,516)	Unexposed (N=16,162)
Age group								
<30	0.7	0.8	0.7	0.8	1	1.2	0.5	0.5
30–50	6.7	7.7	7.5	8.6	7	8.5	7.3	7.4
50+	93	92	92	91	92	90	92	92
Marital status								
Married/ partnered	64	63	62	64	63	62	67	64
Single/ unknown	10	11	11	12	11	12	9.3	11
Divorced	12	14	13	13	12	14	11	13
Widowed	14	12	15	12	14	12	12	12

(*Continued*)

Table 2 (Continued).

	Males							
	Calcium Channel Blockers		ACE Inhibitors		Beta Blockers		Angiotensin II Receptor Blockers	
	Exposed (N=14,977)	Unexposed (N=39,146)	Exposed (N=15,299)	Unexposed (N=39,939)	Exposed (N=18,446)	Unexposed (N=44,846)	Exposed (N=5,516)	Unexposed (N=16,162)
Income quartile								
1 (lowest)	20	18	20	19	22	19	20	21
2	38	35	38	34	37	34	34	34
3	19	19	19	20	19	19	20	19
4 (Highest)	22	27	22	27	21	27	26	26
Child (no income)	0.1	0.1	0.1	0.1	0.1	0.1	-	-
Unknown	0.2	0.3	0.2	0.4	0.2	0.4	0.3	0.4
Antidepressants	9.1	6.1	9.3	6.2	8.9	6.1	9.1	6.2
NSAIDs	14	12	13	12	12	12.3	14	12
Statins	25	9	29	8.5	32	8.1	29	13
CCI Score								
0	31	51	25	53	25	53	30	47
1–2	41	33	43	33	41	32	39	34
3+	28	16	32	15	34	15	31	19
PTE type								
Fire/explosion	3.5	6.1	3.8	6.1	2.8	6.2	4.4	5.3
Transport accident	2.8	3.9	2.6	4.3	2.3	4.3	3	4.1
Exposure to toxic substance/ medical complication	73	62	73	62	75	62	72	65
TBI	19	25	19	25	19	25	19	23
Assault	0.5	1.1	0.5	1.2	0.5	1.2	0.5	1.2
Pregnancy-related	0.1	0.2	0.1	0.2	0.1	0.2	0.1	0.1
Family suicide	0.4	0.6	0.3	0.6	0.2	0.5	0.5	0.5
Multiple events	0.7	1	0.8	1	0.7	1	0.8	0.9

Notes: All numbers are presented as percentages.
Abbreviations: ACE, angiotensin-converting enzyme inhibitors; NSAID, nonsteroidal anti-inflammatory drug; CCI, Charlson comorbidity index; PTE, potentially traumatic event; TBI, traumatic brain injury.

Compared to unexposed individuals, persons on antihypertensive medications had higher CCI scores prior to PTE exposure and were more likely to be on antidepressant and statin medications 60 days before the PTE for both sexes.

Incidence rates of PTSD per 100,000 person-years and cumulative incidence of PTSD by antihypertensive medication class are presented in Table 3. Among females, the highest incidence rate for PTSD was for persons prescribed beta blockers (19/100,000 person-years). For males, the highest incidence rate for PTSD was among persons prescribed ARBs

Table 3 Incidence Rates of PTSD Diagnosis per 100,000 Person-Years by Antihypertensive Medication Class Among Females and Males

	Antihypertensive Medication Class							
	Calcium Channel Blockers		ACE Inhibitors		Beta Blockers		Angiotensin II Receptor Blockers	
	Events/ # at risk	IR per 100,000 person-years (95% CI)	Events/ # at risk	IR per 100,000 person-years (95% CI)	Events/ # at risk	IR per 100,000 person-years (95% CI)	Events/ # at risk	IR per 100,000 person-years (95% CI)
Females								
Exposed	<10/16,439	7.6 (3.0, 14)	<10/13,004	9.9 (4.0, 19)	24/20,558	19 (12, 28)	<10/6728	8.4 (1.7, 20)
Unexposed	27/41,821	10 (6.6, 14)	29/34,831	13 (8.8, 18)	78/50,717	22 (18, 28)	22/19,517	21 (13, 30)
Males								
Exposed	12/14,977	15 (7.5, 24)	19/15,299	24 (14, 35)	22/18,446	23 (14, 33)	<10/5516	26 (10, 48)
Unexposed	51/39,146	21 (16, 27)	50/39,939	20 (15, 26)	70/44,846	25 (20, 32)	18/16,162	21 (13, 32)

Abbreviations: ACE, angiotensin-converting enzyme; CI, confidence interval; IR, Incidence rate; PTSD, posttraumatic stress disorder.

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Table 4 Rate of Developing PTSD Among Persons on Antihypertensive Medications at the Time of Trauma Compared to Those Not on Antihypertensive Medications at the Time of Trauma

		Antihypertensive Medication Class							
		Calcium Channel Blockers		ACE Inhibitors		Beta Blockers		Angiotensin II Receptor Blockers	
	Model	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Females	Unadjusted	0.70	(0.28, 1.7)	0.84	(0.36, 2.0)	0.89	(0.56, 1.4)	0.41	(0.12, 1.4)
	Adjusted	0.79	(0.29, 2.2)	1.1	(0.39, 3.0)	0.92	(0.56, 1.5)	0.47	(0.11, 2.1)
Males	Unadjusted	0.66	(0.35, 1.3)	1.1	(0.65, 1.9)	0.96	(0.59, 1.6)	1.0	(0.43, 2.5)
	Adjusted	0.49	(0.22, 1.1)	0.94	(0.49, 1.9)	0.85	(0.47, 1.5)	1.4	(0.50, 3.6)

Notes: Adjusted models accounted for marital status, income, CCI score, antidepressants, NSAIDs, and statin use.
Abbreviations: ACE, angiotensin-converting enzyme; CI, Confidence Interval; HR, Hazard Ratio.

(26/100,000 person-years). For both males and females, the lowest PTSD incidence rate was among persons prescribed calcium channel blockers (15/100,000 person-years and 7.6/100,000 person-years, respectively).

Results from the Cox proportional hazards regression are shown in Table 4. In males, the strongest association was found for calcium channel blockers and PTSD incidence (adjusted HR [aHR]=0.49, 95% CI = 0.22, 1.1). For males who filled prescriptions for ARBs, there was some evidence of an increased incidence of PTSD relative to unexposed males (aHR = 1.4, 95% CI = 0.50, 3.6). A slight protective association was observed for beta blockers and PTSD incidence (aHR = 0.85, 95% CI = 0.47, 1.5), but the adjusted association for ACE-Is and PTSD incidence was near null. Among females, the strongest association was found for ARBs and PTSD (aHR = 0.47, 95% CI = 0.11, 2.1). Evidence of a protective association with PTSD incidence was also found for calcium channel blockers (aHR = 0.79, 95% CI = 0.29, 2.2). The adjusted associations for the other antihypertensive medication classes and PTSD incidence were near null. However, it is important to note that the 95% CIs for almost all observed associations indicate that these associations are imprecisely measured.

Discussion

We examined sex differences in the association between four classes of antihypertensive medications filled within 60 days prior to potentially traumatic event exposure and incident PTSD. In our prior study in the same sample, we documented evidence that calcium channel blockers had a protective association with PTSD incidence.[11] Consistent with that work, we found a protective association between calcium channel blockers and incident PTSD for both males and females in the current study. However, this study extends this work by documenting that, among males specifically, calcium channel blockers had a stronger protective association with PTSD incidence, indicating that the previously observed overall protective association between calcium channel blockers and PTSD incidence may have been strongly influenced by the association among males. In addition, we observed a protective association between ARBs and incident PTSD in females, and an increased incidence of PTSD among males on ARBs compared with unexposed males, although the confidence intervals for these associations indicates imprecise estimation. Overall, these results suggest that there may be nuanced sex differences in the effects of antihypertensive medications and PTSD incidence that warrant further investigation.

Our results differ from another large-scale study of sex differences, which found that ARBs were associated with fewer PTSD symptoms specifically in males, whereas ACE-Is were associated with fewer PTSD symptoms for both males and females.[6] In our study, there is some evidence that ARBs are associated with a slightly increased rate of PTSD among males and a decreased rate among females relative to unexposed groups. However, it should be noted that the width of the confidence intervals indicates that these estimates are imprecisely estimated, which warrants caution in interpretation. One explanation for these discrepant findings is the differences in the primary outcomes. Our study examined PTSD incidence, whereas the study by Seligowski et al examined PTSD maintenance, and it is possible that antihypertensive medications have different effects on the incidence and maintenance of PTSD.[6] Another recent large study by Kang et al found no evidence of sex differences in the association between antihypertensive medication use and PTSD.[7] However, that study assessed antihypertensive medication use in the 6 to 10 years prior to PTSD diagnosis (regardless of the timing of trauma exposure). Therefore, it is possible that this wider window of time does not capture the etiologically relevant exposure window for the impact of antihypertensive

medications on PTSD incidence. Further, that study examined ACE-Is and ARBs as one combined medication group and assessed PTSD via a six-item scale in an online survey, which may also obscure associations.

Research has demonstrated that ARBs may reduce PTSD symptoms due to the role of the renin–angiotensin system.[7,26,27] This system reacts to stress with the release of renin, which in turn produces angiotensin; specifically, angiotensin II has a number of functions, including constricting blood vessels and promoting sodium and water retention and norepinephrine release.[6,28] The protective associations between calcium channel blockers and PTSD incidence we found among females and males may be due to the general, non sex-specific, efficacy of calcium channel blockers on the physiological symptoms of PTSD. Calcium channel blockers work by blocking calcium from entering the cells of the heart and arteries, allowing blood vessels to relax, which increases blood flow and decreases blood pressure.[29] Future research investigating the possible mechanisms of sex differences is warranted.

The comprehensive Danish national registries allowed for examining sex differences in the association between antihypertensive medications and PTSD incidence in a longitudinal sample with minimal loss to follow-up. Another strength of the study is that the medication registry data include filled prescriptions and provide an additional level of assurance that medications were taken beyond the receipt of the prescription itself; however, we cannot assure individuals were adherent to medications nor the duration or dosage of medication usage. Our emphasis on prescriptions obtained within the 60 days preceding PTE exposure was a choice made to strike a balance between sensitivity and specificity in our ability to capture all antihypertensive medication that was being taken at the time of trauma. However, alternative time frames for antihypertensive medication prescriptions before PTE exposure may have etiological importance. Additionally, patients may be on more than one antihypertensive medication at a time; these individuals were included separately in each medication class for analysis. Future research should explore how distinct combinations of antihypertensive medications at the time of trauma may exert interactive effects on PTSD incidence. Although we began with a relatively large original study cohort of over 1.4 million individuals, the restrictions needed to perform the current analyses reduced our final sample size substantially, leading to large confidence intervals for some associations, indicating imprecise estimates. This study comprehensively harnessed data from over two decades (1994–2016); however, it is still possible individuals may have experienced trauma or been on antihypertensive medications prior to the beginning of our study period. Thus, it remains unclear how cumulative trauma load across the lifespan might play a role in the link between antihypertensive medication usage and PTSD development. Given the homogenous population of Denmark, as well as their policy of universal healthcare, these findings must be replicated for generalizability in other large and diverse populations from different geographical locations. This work may also benefit from the use of more complex causal methods, such as propensity score matching.

Conclusions

This study adds to the literature as the first longitudinal examination of sex differences in the associations between four classes of antihypertensive medications and the incidence of PTSD. We found evidence of potentially nuanced sex differences in these associations, however differences across studies in the use of prevalent or incident PTSD outcomes has also yielded mixed results within the literature. Accordingly, mechanisms of potential sex differences should be elucidated in larger and more diverse samples.

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Disclosure

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