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The impact of neurotoxicant exposures on posttraumatic stress disorder trajectories: The Ft. Devens Gulf War Veterans Cohort

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Abstract

Gulf War veterans (GWVs) were exposed to neurotoxicants, including sarin nerve gas, anti–nerve agent pills, pesticides, oil well fires, and fumes from unvented tent heaters, all of which have been associated with subsequent adverse health. Posttraumatic stress disorder (PTSD) symptoms have also been associated with GW deployment; however, associations between exposures and PTSD symptoms have not been investigated. We assessed PTSD symptom trajectories and associations with neurotoxicant exposures in Ft. Devens Cohort (FDC) veterans (N = 259) who endorsed trauma exposure during deployment and completed the PTSD Checklist at three follow-ups (1992–1993, 1997–1998, 2013–2017). Results indicate that among veterans with more severe initial PTSD symptoms, symptoms remained significantly higher across follow-ups, Bs = −1.489–1.028, whereas among those with low initial PTSD symptoms, symptom severity increased significantly over time, Bs = 1.043–10.304. Additionally, neurotoxicant exposure was associated with a significant increase in PTSD symptoms, Bs = −1.870–9.003. Significant interactions between time and exposures were observed for PTSD symptom clusters, suggesting that among participants with high initial PTSD symptom, unexposed veterans experienced symptom alleviation, whereas

exposed veterans' PTSD symptoms remained high. In GWVs with low initial PTSD symptoms, both unexposed and exposed veterans experienced PTSD symptom exacerbations over time; however, this occurred at a faster rate among exposed veterans. These findings suggest that in the years following deployment, GWVs who were exposed to both traumatic events and neurotoxicants may experience more severe and chronic PTSD symptoms than those without neurotoxicant exposures.

Compared with nonmilitary populations, veterans report more traumatic experiences, which occur during both military training and deployment. As a result, some veterans develop PTSD (i.e., ~12% of Gulf War veterans; Kang et al., 2003). Veterans who suffer from PTSD report poorer health, lower health-related quality of life, and higher levels of disability compared to those without PTSD (Fang et al., 2015). There has been extensive research within veteran populations on predispositions for PTSD, including biological and psychosocial factors as well as specific characteristics of traumatic events, which has highlighted the heterogeneity of this disorder (see Able and Benedek, 2019, for a review). However, less attention has been given to evaluating change in individual PTSD symptoms and symptom clusters over time and examining which factors may influence chronicity.

Most research on PTSD symptom trajectories in veteran populations has focused on short-term follow-ups (i.e., 1–10 years). Although the results of these studies have been mixed, most have identified a subgroup of veterans who report a worsening or chronic trajectory of PTSD or experience an exacerbation of symptoms over time; however, in these studies, the number of veterans who experience this trajectory has been low (i.e., ~6%–10%; Mota et al., 2019; Vasterling et al., 2016). Few studies have surveyed PTSD symptoms for more than 10 years of follow-up. The findings from these studies suggest that the longer the follow-up period, the more likely an increase in PTSD symptomology is observed (Karstoft, 2013), with one study reporting that 20% of veteran participants exhibited a chronic trajectory of PTSD for over 20 years (Marmar et al., 2015).

Overall, most findings indicate that within short-term follow-up periods conducted in early adulthood, the rates of chronic PTSD symptom trajectories appear to be low. However, in studies with longer follow-up periods that extend into later life, these rates appear much higher, potentially due to the changes associated with aging, such as worsening cognitive function and additional stress (e.g., retirement, bereavement), which have been identified as possible predictors of late-life exacerbated, reactivated, or new-onset clinical PTSD symptomology (Davison et al., 2016; Mota et al., 2016).

Most longitudinal studies assessing PTSD symptomology have been conducted with veterans who served either during the Vietnam War era or in support of the recent conflicts in Iraq and Afghanistan, whereas few studies have assessed PTSD trajectories in 1991 Gulf War (GW) veterans. Overall, the rates of PTSD within GW veterans as assessed immediately following their return home have been shown to be relatively low, ranging from 3.3% to 7.2% (Research Advisory Committee on Gulf War Veterans' Illnesses [RAC-GWVI], 2008). One study of GW National Guard reservists from medical and police units found that PTSD symptoms increased significantly over the span of 2 years, with hyperarousal symptoms reported as the most severe among all measured symptoms at all assessment points (Southwick, 1995). Similarly, in cohorts of GW veterans from Louisiana, PTSD symptoms related to emotional numbing and hyperarousal were shown to significantly increase over the course of 1 year, whereas symptoms of reexperiencing and avoidance showed no change (Benotsch et al., 2000; Thompson et al., 2004). The longest assessment of PTSD symptoms to date within GW veterans (Orcutt, 2004) was conducted over a period of 6 years within the Ft. Devens Cohort (FDC), the longest-running cohort of GW veterans. The author found that PTSD symptoms following the GW were best categorized into two groups: one characterized by low levels of symptoms with little increase over time and one by higher levels of initial symptoms that increased significantly over time. These findings suggest that PTSD symptoms within GW veterans may not be homogenous and may, in fact, be related to other deployment-related factors, such as environmental hazards.

GW veterans are a unique cohort in that their deployment contained multiple potential exposures to neurotoxicants, including sarin nerve gas, pyridostigmine bromide pills (PB), pesticides, and combustion byproducts from oil well fires and unvented tent heaters (White et al., 2016). These exposures have since been associated with chronic

health symptoms that encompass multiple body systems including fatigue; pain; neurological, cognitive, and mood issues; and gastrointestinal, respiratory, and skin problems (Steele, 2000). Although neurotoxicant exposures may be the most notable feature of the 1991 Gulf War, veterans may have been exposed to other harmful experiences, such as mild traumatic brain injury (mTBI) and psychologically traumatic events. Recently, researchers have investigated a "multiple-hit" hypothesis, which posits that exposure to both mTBI and neurotoxicants is associated with increased rates of Gulf War Illness (GWI) and chronic medical conditions, when compared with either exposure alone or no exposure at all (Janulewicz et al., 2018). We similarly hypothesized that exposure to both traumatic events and neurotoxicants during deployment would be associated with increased rates of PTSD symptoms and/or increased symptom severity in a sample of GW veterans. To our knowledge, the present study was the first to investigate trajectories of PTSD symptoms over a 20-year follow-up period in GW veterans. The current study was a longitudinal analysis using the FDC's recent resurvey, conducted more than 20 years postwar (i.e., 2013–2017), and considered the potential impact of GW-specific neurotoxicant exposures on PTSD symptoms and trajectories.

METHOD

Participants and procedure

The FDC of GW veterans is the longest-running cohort of GW veterans and has been described in prior papers (Yee et al., 2020; Zundel et al., 2019). In summary, during the spring of 1991, active duty, reserve, and National Guard U.S. Army personnel who had been deployed to the GW and returned home through Ft. Devens in Massachusetts, were recruited to participate in a survey to assess psychological health and combat exposure. Subsequent questionnaires were mailed to participants in 1992 (Follow-Up 1), 1997–1998 (Follow-Up 2), and 2013–2017 (Follow-Up 3) to assess long-term health, psychological and functional well-being, and GW-specific environmental and combat exposures.

This study utilized a subset of individuals in the FDC who completed the baseline survey and all three follow-up surveys and had complete data for the PTSD Checklist (PCL; Weathers, 1991) at each assessment point. Relevant covariates from the baseline survey included age and gender. Of the 295 veterans who completed all three follow-up surveys, we excluded 19 who reported no traumatic event exposure and 17 who did not have sufficient data (i.e., missing most data points) for the PCL at all three follow-up surveys in which they participated; this resulted in an analytic sample of 259 GW veterans. Of these 259 veterans, 19 had one or two missing data points for the PCL on the follow-up surveys. Missing data points were replaced with the average of the other symptoms within the specific PTSD symptom cluster using a single-imputation method.

Because the first study to investigate PTSD symptom trajectories within the FDC found that the sample was best categorized into two groups (i.e., veterans with low vs. high initial symptoms; Orcutt, 2004), we stratified our analyses to assess whether the effect of neurotoxicant exposures was different for individuals with high levels of initial PTSD symptoms versus those with low levels of initial PTSD symptoms. These low and high initial PTSD symptom groups were determined by their PCL score at Follow-Up 1 such that participants with a score above 35 were considered to have high initial PTSD symptoms ($n = 46$), and those with a score of 35 or below were considered to have low initial PTSD symptoms ($n = 213$). These thresholds were implemented following the National Center for PTSD guidelines for *DSM-IV* PCL cutoffs for administration in a general, non–treatment-seeking population (National Center for PTSD, n.d.).

All demographic variables used as covariates in the analyses were taken from the baseline survey, which occurred in 1991. Before administering each survey, participants gave their informed consent for inclusion on each occasion. Prior to each survey distribution, approval was obtained from the Institutional Review Board at Veteran Affairs Boston Healthcare System and, when required, by the Human Research Protection Office at U.S. Army Medical Research & Development Command (USAMRDC).

Measures

PTSD symptoms

Because the FDC began in 1991, PTSD symptoms were defined using the prevailing definition from the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*; American Psychiatric Association [APA], 1994). To evaluate PTSD symptoms, we used the PCL (Weathers et al., 1991), a 17-item self-report questionnaire reflecting the PTSD criteria outlined in the *DSM-IV*. Participants were asked to rate how much they had been bothered by each symptom during the past month, with responses ranging from 1 (*not at all*) to 5 (*extremely*). Symptom ratings were summed for a total PTSD symptom severity score (range: 17–85), with a score of 36 or higher indicative of probable PTSD (National Center for PTSD, n.d.).

Although the *DSM-IV* contains three symptom clusters, with avoidance and numbing symptoms grouped together, there is growing evidence that these aspects of PTSD may

represent two distinct symptom groups, wherein avoidance is a more strategic and effortful mechanism, and numbing is a more automatic response to hyperarousal (APA, 1994; Asmundson et al., 2000; Foa et al., 1992). Thus, several factor analytic studies have been conducted on the PTSD criteria in the *DSM-IV* and concluded that an individual's symptoms load on to four separate factors: reexperiencing, avoidance, numbing, and hyperarousal (Asmundson et al., 2000; King et al., 1998); the fifth edition of the *DSM* (*DSM-5*) has since incorporated this change (APA, 2013). Therefore, we chose to investigate a four-factor model of PTSD. For the present study, we scored the PCL both for total PTSD symptom severity and for the four factor-based subscales: Reexperiencing (Items 1–5), Avoidance (Items 6–7), Numbing (Items 8–12), and Hyperarousal (Items 13–17). The symptom cluster scores were derived by adding up the individual ratings, ranging from 1 to 5, for each symptom cluster.

GW environmental exposures

FDC veterans were asked about their environmental exposures specific to GW deployment at Follow-Up 2 and Follow-Up 3. To reduce potential recall bias, exposure data were taken from the Follow-Up 2 survey, which was administered 6 years postdeployment. The neurotoxicant exposures of interest were pesticide smell, oil smell, diesel smell, tent heater combustion byproducts, PB pills, and chemical warfare (i.e., number of times on formal alert), based on prior research with the FDC (Proctor et al., 1998; Proctor et al., 2006; White et al., 2016; Wolfe et al., 1998; Wolfe et al., 2002; Yee et al., 2020; Zundel et al., 2019). Participants were asked whether they had experienced a pesticide smell, oil smell, or diesel smell as well as if they had a heater or stove in the area in which they slept; each was coded as a "yes" or "no" response.

Participants were asked to indicate how many anti–nerve gas (i.e., PB) pills they took in the GW, with response options of 0, 1–2, 3–10, 11–21, and more than 21. Responses were coded into whether they took any PB pills ("yes") or never took PB pills ("no"), as previous FDC studies have found significant health effects using this grouping (Yee et al., 2020; Zundel et al., 2019). Additionally, as a separate variable, responses were coded into whether participants took more than 21 PB pills, dichotomized into "yes" (fewer than 21) and "no" (21 or more) responses, as the blister pack given to troops included 21 pills, which was the equivalent of taking the recommended doses for more than 7 days (Keeler et al., 1991; RAC-GWVI, 2008). Additionally, several studies have reported associations between taking more than 21 PB pills and a significantly increased risk for GWI, whereas taking fewer than 21 has been associated with only a modestly increased risk (RAC-GWVI, 2008). Similarly, participants were asked to indicate how many times they were on "formal alert" for a chemical attack (e.g., had to put on full Mission Oriented Protective Posture [MOPP] gear), with response options of 0, 1–2, 3–10, 11–20, and 20 or more times. Responses were coded into whether they were ever on formal alert (i.e., more than 0 times; "yes") or never on "formal alert" (i.e., one or more times; "no"). As a separate variable, if they were on formal alert more than 20 times, which was dichotomized into "yes" for more than 20 times "no" for fewer than 20 times, as the self-reported frequency of chemical alarms has been associated with adverse effects on brain structure, with the strongest effects observed for both 7–30 days and 30 days or more of hearing chemical alarms (Chao et al., 2016).

Data analysis

Descriptive statistics were calculated to compare the demographic, military, and exposure characteristics of the full FDC, after removing the current sample, with the current sample as well as participants with high versus low initial PTSD symptom levels (see Table 1). Repeated linear regressions using the generalized estimation equations (GEE) approach, stratified by low and high initial PTSD symptom status, were used to analyze the PTSD symptom outcomes (i.e., total score, four symptom cluster scores) over time. GEE, introduced by Zeger (1986), is used to analyze repeated-measures data while accounting for the within-subject correlation inherent in these data (Ballinger, 2004). Each model contained time as a categorical variable (Follow-Ups 1, 2, or 3), one of the exposure measures as a factor, and baseline age and gender as covariates. Interaction terms for Follow-Up 2 for each exposure and Follow-Up 3 for each exposure were initially included in each model; nonsignificant terms were removed from final models. In reporting the results, beta values were used to indicate the unstandardized slopes from the regression models. This study utilized a subset of the FDC composed of individuals who completed the baseline survey and all three follow-up surveys and had complete data for the PCL at each survey; thus, there were no missing data. We considered p values less than .05 to be significant. False discovery rate correction was applied for multiple comparisons to the main effect models of the four cluster scores as well as the total score outcomes. Because of sample size issues, we did not perform adjustments for interactions terms; instead, unadjusted p values are presented, as these results are more exploratory. All analyses were performed using SPSS (Version 25).

TABLE 1 Demographic and baselinea characteristics of the full Ft. Devens Cohort (FDC) and the study sample

Characteristic	FDC with study sample removed ($N = 2,690$)		Study sample ($N = 259$)			High initial PTSD symptoms ($n = 46$)		Low initial PTSD symptoms $n = 213$)		
	M	*SD*	*M*	*SD*	*p*[b]	*M*	*SD*	*M*	*SD*	*p*[b]
Age (years)	29.94	8.37	32.43	8.60	< .001	32.09	9.03	32.50	8.53	.770
	n	%	*n*	%		*n*	%	*n*	%	
Male	2467	91.7	226	87.3	.016	36	78.3	190	89.2	.045
Caucasian	2202	81.9	241	93.1	< .001	42	91.3	199	93.4	.613
Activity duty[c]	781	29.0	42	16.2	< .001	5	10.9	37	17.4	.279
Trauma type[d]										
Combat/mopping up	697	25.9	95	36.7	< .001	21	45.7	74	34.7	.161
Exposure to noncombat life-threatening event	121	4.5	19	7.3	.043	3	6.5	16	7.5	.814
Personal domestic violence	647	24.1	49	18.9	.043	7	15.2	42	19.7	.481
Anticipation of life threat	236	8.8	30	11.6	.060	8	17.4	22	10.3	.173
Attributes of war zone environment	219	8.1	19	7.3	.651	0	0	19	8.9	.036
Intraunit hassles/personal performance	455	16.9	47	18.1	.624	7	15.2	40	18.8	.567
No event	307	11.4	0	0	< .001	0	0	0	0	1.000

Note: PTSD = posttraumatic stress disorder.

[a]As assessed in 1991. [b]For continuous variables an independent samples t-test was used and for nominal variables, a chi-squared test was used to determine statistical significance. [c]Versus reserve or National Guard. [d]Descriptions of each traumatic event category can be found in Wolfe et al. (1993).

RESULTS

Demographic, baseline, and exposure characteristics

Demographic comparisons between the full FDC and the study sample, as well as between participants with high versus low initial PTSD symptom levels, are summarized in Table 1. The study sample differed from the full FDC by age, gender, race, active duty status during the GW, and trauma type. Most participants ($n = 259$) were male (87.3%) and White (93.1%), with 16.2% reporting active duty status at the time of the GW. The mean participant age in 1991 (i.e., baseline survey administration) was 32.43 years. The most commonly reported traumatic event was combat or "mopping up", which entailed suiting up in full MOPP gear in the advent of a chemical attach (~36.7%), followed by personal/domestic (~18.9%). At Follow-Up 2 (i.e., 1997–1998), 68.3% of veterans reported exposures to a diesel smell as well as unvented tent heaters, 70.3% reported exposure to an oil smell, and 33.4% reported exposure to an insecticide or pesticide smell. Moreover, 18.5% of veterans reported taking more than 21 PB pills and 25.1% reported hearing 20 or more chemical alarms. Exposure characteristics are also summarized in Supplementary Table S1.

Change in PTSD symptoms over time

Among participants with high initial PTSD symptom levels (17.8% of the sample), there were no significant changes to the four PTSD symptom cluster scores or the total symptom score across the study period, *p*s = .238–.816, indicating that there was no significant increase in or the resolution of symptoms over time. In veterans with low initial PTSD symptom levels (82% of the sample), both PTSD symptom cluster scores and total scores significantly increased over time, *p*s < .001 except for scores on the Avoidance subscale, which did not increase from Follow-Up 1 to Follow-Up 2, $p = .240$, but did significantly increase from Follow-Up 1 to Follow-Up 3, $p < .001$. Correlations between cluster scores and total scores across follow-ups, stratified initial PTSD symptom level status, are reported in Supplementary Tables S2 and S3.

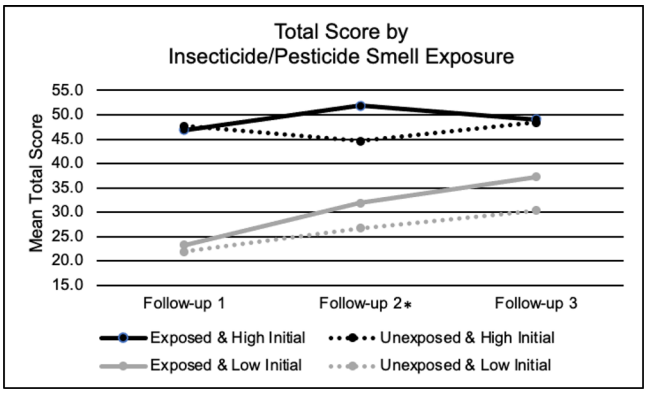

FIGURE 1 Significant Time x Pesticide Smell Exposure interactions for the total score. Note. Significant *p* values represent the difference between groups (exposed vs. unexposed) at that follow-up point. This figure is exemplary of all other significant interactions. $^{*}p < .05$

Longitudinal associations between GW neurotoxicant exposures and PTSD symptom scores

In veterans with high initial PTSD symptom levels, no significant main effects of exposure were observed for diesel smell, oil smell, unvented tent heaters, insecticide or pesticide smell, exposure to more than 20 chemical attack alerts, for any PTSD symptom cluster score or total score, *p*s = .460–.896. A significant main effect of exposure to more than 21 PB pills was observed for the total PTSD symptom score as well as the subscale scores for Reexperiencing, Avoidance, and Hyperarousal. Among veterans who reported exposure to more than 21 PB pills, there was at least one additional symptom reported in each cluster or an increase in severity of one symptom from each cluster, *p*s = .030–.044. No significant main effect of exposure to more than 21 PB pills was observed for the Numbing subscale score, $p = .667$. Additionally, a significant main effect of any PB pill exposure was observed for the Numbing subscale score such that exposed participants reported more than two additional symptoms or increased symptom severity, $B = 2.530$, 95% CI [0.740, 4.320], $p = .030$. No significant main effects of exposure to any PB pills were observed for the Reexperiencing, Avoidance, or Hyperarousal subscales or for the total score, *p*s = .130–474.

Significant interactions between time and insecticide or pesticide smell exposure in veterans with high initial PTSD symptom levels were observed for the reexperiencing cluster, $B = 3.767$, 95% CI [0.670-6.913], $p = .019$, and total score, $B = 7.998$, 95% CI [0.094-15.902], $p = .047$. The total score interactions are displayed in Figure 1. A significant interaction was observed between time and exposure to more than 21 PB pills for the numbing score, $B = 4.105$, 95% CI [1.067, 7.143], $p = .008$. Although a very small number of veterans who had high initial PTSD symptom levels reported no exposure to chemical attack alarms ($n = 4$), those who were exposed appeared to report increases in PTSD symptoms (i.e., all clusters and total score) over time, whereas unexposed participants recovered or appeared to have a decrease in symptoms over time. These data are not reported due to low statistical power. The effects of exposure in participants with high initial PTSD symptom levels are summarized in Table 2.

Among participants with low initial PTSD symptom levels, no significant main effects of exposure were observed for diesel smell, tent heaters, insecticide or pesticide smell, any PB pill ingestion, more than 20 chemical attack alerts, any chemical attack alerts, for all PTSD symptom cluster scores, or PTSD total score, *p*s = .060–.917. Oil smell exposure was associated with a significant score increase on the Avoidance subscale, $B = 0.425$, 95% CI [0.079, 0.772], $p = .030$; Hyperarousal subscale, $B = 0.711$, 95% CI [0.228, 1.194, $p = .020$; and total PTSD symptom score, $B = 1.652$, 95% CI [0.321, 2.984], $p = .030$. No significant associations were observed between oil smell exposure and scores on the reexperiencing or numbing subscales, *p*s = .110–300. Exposure to more than 21 PB pills was associated with a significant score increase on the Reexperiencing, $B = 1.303$, 95% CI [0.409, 2.197], $p = .020$; Avoidance, $B = 0.537$, 95% CI [0.088, 0.985], $p = .038$; or Numbing subscales, $B = 1.100$, 95% CI [0.152, 2.048], $p = .038$. No association was observed for exposure to more than 21 PB pills and Hyperarousal subscale score, $p = .635$.

There were significant results for the interactions between time and insecticide or pesticide smell exposure among participants with low initial PTSD symptom levels for the Reexperiencing subscale, $B = 0.896$, 95% CI [0.074, 1.718], $p = .033$; Numbing subscale, Follow-Up 2: $B = 1.310$, 95% CI [0.259, 2.361], $p = .015$, Follow-Up 3: $B = 1.677$, 95% CI [0.103, 3.251], $p = .037$; Hyperarousal subscale, Follow-Up 2: $B = 1.221$, 95% CI [0.157, 2.286], $p = .025$, Follow-Up 3: $B = 2.139$, 95% CI [0.724, 3.553], $p = .003$; and total scores, Follow-Up 2: $B = 3.740$, 95% CI [1.072, 6.409], $p = .006$, Follow-Up 3: $B = 5.409$, 95% CI [1.087, 9.730], $p = .014$. The total score interactions are displayed in Figure 1. A significant interaction between time and exposure to more than PB pills was observed for the hyperarousal subscale, $B = 1.625$, 95% CI [0.240, 3.010], $p = .021$, and total scores, $B = 3.870$, 95% CI [0.286, 7.454, $p = .034$. These interactions are displayed in Supplementary Figure S1, Panels B and C. Significant interactions between time and diesel smell exposure were observed for the reexperiencing, $B = 1.871$, 95% CI [0.833, 2.909], $p < .001$; avoidance, Follow-Up 2: $B = 0.486$, 95% CI [0.043, 0.930], $p = .032$, Follow-Up 3: $B = 0.836$, 95% CI [0.211, 1.462, $p = .009$

TABLE 2 Associations between neurotoxicant exposures and Posttraumatic Stress Disorder Checklist symptom cluster scores

	Reexperiencing score		Avoidance score		Numbing score		Hyperarousal score		Total score	
Exposure	**Slope**	***SE***	**Slope**	***SE***	**Slope**	***SE***	**Slope**	***SE***	**Slope**	***SE***
High initial PTSD symptoms ($n = 46$)										
Diesel smell	0.519	1.557	0.869	0.758	0.551	1.414	1.941	1.152	3.879	4.300
Oil smell	0.545	1.735	−.424	0.817	−.167	1.480	1.674	1.295	0.628	4.789
Unvented tent heaters	0.983	1.230	0.807	0.614	0.392	1.032	−.306	1.026	1.876	3.363
Insecticide/pesticide smell	−.870*	1.190	0.367	0.562	0.525	0.995	0.988	0.927	−.846*	2.660
> 21 pyridostigmine bromide pills	**2.969**	**1.400**	**1.262**	**0.599**	0.550*	1.278	**2.212**	**0.920**	**9.003**	**3.275**
Any pyridostigmine bromide pills	1.811	1.259	1.173	0.667	**2.530**	**0.913**	0.814	1.138	6.328	3.256
On alert for chemical attack (> 20)	1.409	1.151	0.186	0.559	0.266	1.043	1.285	0.878	3.146	3.116
Low initial PTSD symptoms ($n = 213$)										
Diesel smell	0.281*	0.207	−.059*	0.155	0.656	0.437	−.113*	0.290	0.344*	0.715
Oil smell	0.209*	0.202	**0.425**	**0.177**	0.765	0.448	**0.711***	**0.246**	**1.652***	**0.679**
Unvented tent heaters	0.492	0.329	−.163*	0.163	0.367	0.459	−.032*	0.311	2.037	1.227
Insecticide/pesticide smell	0.338*	0.239	0.520	0.208	0.203*	0.358	0.537*	0.301	1.324*	0.792
> 21 pyridostigmine bromide pills	**1.303**	**0.456**	**0.537**	**0.229**	**1.100**	**0.484**	0.187*	0.395	1.150*	1.023
Any pyridostigmine bromide pills	0.412	0.342	0.279	0.170	0.603	0.429	0.701	0.396	1.995	1.188
On alert for chemical attack (> 20)	0.870	0.433	0.101	0.206	0.216	0.467	0.698	0.490	1.886	1.441
On alert for chemical attack (any)	−.190	0.535	0.103	0.273	0.672	0.659	0.701	0.501	1.286	1.826

Note: All analyses included baseline age, gender, and time as covariates. Slope refers to the unstandardized slopes of the main effect of exposure from the regression models. Bold font indicates a significant main effect at $p < .05$.

*$p < .05$ for interactions between time and exposure.

and hyperarousal clusters, $B = 1.628$, 95% CI [0.304, 2.952], $p = .016$; as well as for the total score, $B = 5.234$, 95% CI [1.602, 8.865]. These interactions are displayed in Supplementary Figure S2. Significant interactions between time and oil smell exposure were observed for the reexperiencing, $B = 1.960$, 95% CI [.886, 3.035], $p < .001$; hyperarousal, $B = 1.955$, 95% CI [0.668, 3.243], $p = .003$; and total scores, $B = 5.275$, 95% CI [1.559, 8.992], $p = .005$. These interactions are displayed in Supplementary Figure S3. Significant interactions between time and unvented tent heater exposure were observed for the avoidance, $B = 0.566$, 95% CI [0.117, 1.016], $p = .013$, and hyperarousal scores, Follow-Up 2: $B = 1.472$, 95% CI [0.441, 2.503], $p = .005$, Follow-Up 3: $B = 1.635$, 95% CI [0.271,3.000], $p = .019$. These interactions are displayed in Supplementary Figure S4. The effects of exposure in participants with low initial PTSD symptom levels are summarized in Table 2.

DISCUSSION

To our knowledge, this was the first study of its kind to examine changes in PTSD symptom clusters over time in GW veterans and investigate the impact of neurotoxicant exposures on such changes. The results suggest that among veterans with low initial PTSD symptom levels at Follow-Up 1, PTSD symptom cluster scores significantly increased over the span of 25 years but remained below the clinical cutoff suggestive of PTSD. These findings support those from research conducted in other veteran cohorts demonstrating increases in PTSD symptoms over time (Mota et al., 2016; Vasterling et al., 2016). These prior studies have focused solely on veterans with a PTSD diagnosis and have not included veterans who may have subclinical symptom levels. Because the current study included all veterans regardless of whether they report low or high levels of

initial PTSD symptoms, the findings highlight that individual symptoms or symptom clusters may change over time regardless of whether relevant scores exceed a cutoff suggestive of a PTSD diagnosis. This gives credence to the need for consistent follow-up of psychiatric issues in postdeployed veterans.

PTSD symptoms may increase over time for several different reasons. Factors related to aging, such as late-life stressors and life changes contribute to increases in posttraumatic stress symptoms over time (Davison et al., 2016; Mota et al., 2016; Vasterling et al., 2016). Late-life stressors that come with normal aging may include changes in employment, poorer physical health, and illness and death in friends and family. Additionally, with age, many individuals begin to reminisce about their life and may return to memories of their traumatic experiences, causing a subsequent increase in symptoms. Therefore, it appears that GW veterans follow a trajectory similar to those seen in other veteran cohorts wherein PTSD symptoms increase across time.

In contrast, among participants with high initial PTSD symptom levels at Follow-Up 1, PTSD symptom cluster scores did not significantly change over 25 years. In fact, scores remained relatively high and stayed significantly higher than scores in veterans with lower initial symptom levels. Although we did not investigate treatment use, these data suggest that veterans who reported more severe initial PTSD symptoms at Follow-Up 1 did not experience symptom alleviation or resolution over time. Although rates of PTSD for GW veterans are relatively low (Kang et al., 2003), there is still a need for continued screening and clinical evaluation of veterans deemed to be at risk of PTSD in this group.

The present findings suggest that GW veterans, especially those who experienced multiple neurotoxicant exposures during deployment, may be unique as compared to veterans of other conflicts in that participants showed an increase in or chronicity of PTSD symptoms. We found that self-reported neurotoxicant exposures were associated with increased PTSD symptom cluster scores in veterans with both low and high initial PTSD symptom levels at Follow-Up 1. For example, among veterans with more severe symptoms, those with reported PB pill exposure scored, 2.5 points higher, on average, on the Numbing subscale than those who were unexposed, suggesting two additional reported symptoms or a 2-point increase in symptom severity. Among participants with low initial symptom levels, those who reported exposure to 21 or more PB pills scored an average of 1.3 points higher on the Reexperiencing subscale than those who were unexposed, suggesting one additional reported symptom or a 1-point increase in symptom severity. Regardless of initial symptom severity, the findings indicate that these neurotoxicant exposures exert adverse effects on PTSD symptoms. This is similar to observations reported by Janulewicz et al. (2018), who investigated a multiple-hit hypothesis regarding the impact of neurotoxicant exposures and mTBI on increased health-related symptoms and chronic medical conditions.

Importantly, our results are also consistent with those related to the survivors of the 1995 Tokyo sarin terrorist attack. Sarin nerve gas is an acetylcholinesterase inhibitor and, thus, depletes levels of cholinesterase, leading to excess acetylcholine in synapses and a chronic state of hyperexcitability (Golomb et al., 2008). Research on this population has found that survivors exhibit persistent patterns of PTSD symptoms, with hyperarousal symptoms the most frequently reported, and that these patterns are correlated with serum cholinesterase levels as measured shortly after the attack (Araki et al., 2005; Ohtani et al., 2004; Tochigi et al., 2005). Tochigi et al. (2005) concluded that these findings could have been due to higher degrees of psychological trauma in individuals who experience severe situations associated with more exposure to sarin or that higher levels of sarin exposure cause more severe damage to the brain, leading to more severe posttraumatic stress symptoms.

Researchers have recently hypothesized that environmental and occupational exposures, such as those experienced during the GW prime individuals to react adversely to traumatic events via an increased proinflammatory state, thus increasing the risk for and symptoms of PTSD (Georgopoulos et al., 2018; Walker et al., 2016). This is similar to hypotheses posited in the mTBI literature suggesting that neuroinflammation resulting from brain injury underlies the high rates of comorbid mTBI and PTSD (Kaplan et al., 2018). In fact, elevated levels of proinflammatory cytokines and chemokines have been observed in GW veterans. For example, Butterick et al. (2019) observed elevated levels of interleukin-6 and C-reactive proteins, markers of proinflammatory processes, in blood samples of GW veterans obtained nearly 30 years postwar. Recently, evidence of in vivo neuroinflammation, as assessed using a positron emission tomography radioligand that binds to active microglial and astrocytes, was observed in GW veterans, suggesting active inflammatory processes occurring nearly 30 years after potential neurotoxicant exposure (Alshelh et al., 2020). Therefore, it is possible that GW veterans exposed to neurotoxicants and traumatic events during deployment may be experiencing a multiple hit of proinflammatory responses, which, in turn, increases the severity or longevity of PTSD symptoms.

We observed several significant interactions between neurotoxicant exposures and time on PTSD symptom cluster scores. These interactions were observed at Follow-Up 2 and Follow-Up 3, which occurred 6–7 years and 20 years, respectively, after the war. This suggests that as time goes

on, exposed veterans exhibit distinct trajectories of PTSD symptoms as compared to unexposed veterans. Among participants with high initial PTSD symptom levels, unexposed veterans were shown to experience a decrease in PTSD symptom severity over time, whereas exposed veterans experienced no significant change but maintained a relatively high symptom level. For example, among veterans with more severe initial symptoms, those who reported exposure to more than 21 PB pills endorsed nearly five more symptoms or an increase in symptom severity on the PCL Numbing subscale by end of the follow-up period as compared to those who did not report this exposure. In participants with low less severe initial symptom levels, both exposed and unexposed veterans experienced an increase in PTSD symptoms over time; however, exposed veterans showed a much steeper and earlier increase in symptom severity. For example, among veterans with low initial PTSD symptom levels, those who reported insecticide or pesticide smell exposure endorsed more than two symptoms or an increase in symptom severity on the PCL Hyperarousal subscale by the end of the follow-up period as compared to those who did not report this exposure.

GW neurotoxicant exposures have been hypothesized to induce accelerated aging patterns (Proctor et al., 2006; Zundel et al., 2019). Accelerated aging is the phenomenon in which individuals may experience symptoms of aging, including medical conditions like diabetes and high blood pressure or symptoms like sleep dysregulation or joint pain, much earlier than their same5aged peers (Proctor et al., 2006; Zundel et al., 2019). The apparent increase in PTSD symptoms seen in the later years of follow-up among participants with low initial PTSD symptom levels who reported exposure to neurotoxicants may, in part, be due to an accelerated aging pattern. This could explain why the increase in PTSD symptoms commonly observed in other veteran cohorts over time appeared to be occurring at a faster rate in exposed groups versus unexposed groups.

The present findings suggest that neurotoxicant exposures may play a role in increased PTSD symptoms over time within a GW veteran cohort. Although exposure to traumatic events or neurotoxicants alone has been shown to induce inflammatory responses and the subsequent risk of posttraumatic stress or health-related symptoms, together, these two insults may result in both symptom exacerbation and a prolonged course of symptoms. Therefore, clinicians who treat veterans should be aware of other possible neurobiological factors, such as neurotoxicant exposure, that may impact their patients' experience with PTSD. Doing so may benefit treatment plans for mood disturbances and other chronic health issues reported by GW veterans.

Study limitations should be noted. First, study dropout and selection bias are inherent in longitudinal studies, as individuals with more health problems may be more likely to remain in the study than healthy individuals; alternatively, longitudinal studies may exclude the sickest veterans, who are either too ill to participate or may have died during the course of the study. Thus, the study sample differed from the full FDC on several key demographic characteristics and, as such, the reported findings may not be generalizable to the full FDC nor to the entire GW veteran population. Second, although we examined PTSD symptoms using a self-report measure, clinical PTSD diagnosis cannot be confirmed. Third, it is unknown whether the posttraumatic stress symptoms observed in this study resulted from wartime trauma or index traumatic events that occurred after deployment. Additionally, the results of the study may be confounded by the fact that veterans who experienced neurotoxicant exposures may have also experienced more traumatic events during or after deployment, which may independently lead to more severe or chronic PTSD trajectories. Fourth, information regarding participants' involvement in psychological or physical health–related treatments were not included in the surveys. It is possible that treatment could have affected both how symptoms changed and symptom trajectories over time. Additionally, patients with unexplained illnesses may have an increased incidence of PTSD due to the poor treatment they receive by the medical community as well as the stigma surrounding these illnesses and a general lack of support (Weir et al., 2014). This may, in part, explain why PTSD symptoms have been found to increase for many GW veterans who continue to be told that their chronic symptoms are psychosomatic (National Academies of Sciences, Engineering, and Medicine, 2016). Next, self-reported exposures to neurotoxicant exposures were used, as no objective measures of war-related exposures are available. However, recall bias was minimized by using exposure data from Follow-Up 2, which was less than 5 years following participants' return from the GW and before many exposure-outcome reports had been made public. Further, the survey's neurotoxicant data were dichotomized into "yes" and "no" responses, limiting our ability to investigate dose–response relationships. Additionally, it is unknown whether neurotoxicant exposure before or after the GW may have influenced the current findings. Future studies should include lifetime neurotoxicant exposure history.

Further research should focus on examining the mechanisms by which neurotoxicant exposure impacts PTSD symptoms. Specifically, studies examining the association between cognitive dysfunction and PTSD symptoms are needed, as elevated neuroinflammatory responses can also affect cognitive processes, including deficits in executive function, attention, and learning and memory, which may interfere with trauma-exposed individuals' ability to

process their experience, leading to an increased risk of developing PTSD symptoms (Quinones et al., 2020). Further, future studies should investigate normal aging stressors (e.g., retirement, declines in physical health) and their impact on PTSD symptoms over time, which would enable the nature of the effects in the current study to be further delineated (i.e., increases in symptoms due to normal aging or due to neurotoxicants). Additionally, future researchers should investigate whether there are specific treatment-resistant PTSD symptoms (e.g., irritability) that are prominent within neurotoxicant-exposed populations, and additional studies examining PTSD trajectories between those who do and do not receive treatment are warranted. Moreover, the interaction between time and PTSD symptom cluster scores suggests that longitudinal studies should be conducted to examine the trajectories of reported symptoms in all neurotoxicant-exposed populations, not just within GW veterans.

OPEN PRACTICES STATEMENT

The study reported in this article was not formally preregistered. Neither the data nor the materials have been made available on a permanent third-party archive; Department of Veterans Affairs (VA) privacy and data security policies and regulatory constraints provide that only aggregate summary data may be removed from the VA for publication. The authors have provided detailed results of these analyses in the paper. These restrictions are in place to maintain patient privacy and confidentiality. Access to these data can be granted to persons who are not an employee of the VA; however, there is an official protocol that must be followed for doing so. The authors invite individuals who wish to access the raw data that were used for this analysis to contact Dr. Maxine Krengel (Maxine.Krengel@va.gov) to discuss the details of the VA data access approval process.

AUTHOR NOTE

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SUPPORTING INFORMATION

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