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Polygenic Risk and Exposure Severity Predict Trajectories of PTSD: A Prospective Cohort Study

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Posttraumatic stress disorder (PTSD) is persistent over time, thus identifying risk factors for chronic PTSD is crucial for clinical research. Trauma exposure severity and polygenic liability are two established predictors of PTSD onset and severity, but their contributions to the long-term course of PTSD remain largely unknown. In this prospective longitudinal cohort study, we tested whether severity of trauma exposure and polygenic risk for symptoms of PTSD independently predict long-term trajectories of PTSD symptoms. Data included 49,402 observations, spanning July 2002 to December 2022, from $n = 5687$ World Trade Center responders who had predominately European ancestry (baseline mean age = 37.74, SD = 8.19, range = 16–75; 92.89% male). First, the best-fitting model of 20-year PTSD trajectories was determined. Next, a polygenic risk score and a sum score of traumatic exposures were included as predictors of individual differences in intercepts (initial levels) and slopes (rates of change), adjusting for demographic covariates. The polygenic risk score significantly predicted rates of change in PTSD symptoms, independent of the intercept, such that higher polygenic risk was associated with more rapid increases in the years after trauma and a steeper arch-shaped trajectory. Exposure severity predicted initial levels and rates of change in symptoms, with more pronounced effects on initial levels. These findings indicate that polygenic liability and exposure severity predict the long-term prognosis of PTSD and have the potential to inform future clinical studies in trauma-exposed populations.

Molecular Psychiatry; https://doi.org/10.1038/s41380-025-03235-2

INTRODUCTION

Posttraumatic stress disorder (PTSD) is a debilitating psychiatric condition, with a lifetime prevalence up to 8.6% in the general US population [1, 2], and up to 30% in at-risk occupational groups, including first responders and veterans [3–9]. PTSD is persistent [10], with symptoms characterized by avoidance (evading activities or situations because they remind the individual of trauma), hyperarousal (heightened startle responses, difficulty concentrating, or trouble sleeping due to being constantly "on edge"), and reexperiencing (repeated, disturbing memories, nightmares, or "flashbacks"). Over half of individuals diagnosed with PTSD do not remit within 3 years of trauma exposure [11, 12], and treatment does not result in full remission for most patients [13–15]. Risk factors for chronic PTSD are poorly understood, and chronic PTSD is more treatment resistant, with fewer efficacious interventions available than for acute PTSD [13]. Long-term costs of unresolved PTSD include increased rates of psychiatric and medical comorbidity, health care utilization, disability, and suicide [16–18]. Meta-analytic evidence points to intentional trauma— i.e., events involving deliberate actions intended to harm others, such as terrorist attacks, physical assault, or acts of war —as one unique risk factor for PTSD persistence up to 2 years following exposure [12]. However, there is a need to better understand risk factors for chronic PTSD course, independently of initial symptom severity, and over longer follow up periods.

PTSD is moderately heritable and advances in molecular genetics indicate that hundreds of genetic variants contribute to increased risk of PTSD [19]. These genetic variants can be aggregated into a polygenic risk score (PRS) to improve prediction of PTSD [20–22]. To date, several cross-sectional studies have demonstrated that PRS for PTSD (PRS-PTSD) predicts PTSD onset, symptom severity, and diagnosis [23–28]. However, research on whether PRS-PTSD predicts the course of PTSD is very limited. Our team found that PRS-PTSD predicts a severe PTSD trajectory class over 18-years of follow up in a moderately sized sample ($n = 1490$) of responders to the 9/11 disaster ($OR = 1.28$) [23]. Consistently, PRS-PTSD was associated with high symptom severity and increasing trajectories of PTSD in US Army soldiers over an approximately 9-month period after combat deployment, as

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Received: 17 June 2024 Revised: 4 August 2025 Accepted: 2 September 2025
Published online: 19 September 2025

determined using latent class analysis or growth mixture models ($OR = 1.23$ and $OR = 1.12$, respectively) [29]. Crucially, both studies employed an analytic approach that categorizes individuals into mutually exclusive groups that reflect their overall aggregate longitudinal symptom course. This approach is limited because it cannot provide information about whether PRS-PTSD predicts symptom course at the individual level, and whether prediction of symptom progression is independent of baseline symptom severity.

Although psychiatric PRS are known to capture environmental effects via active, evocative, and passive gene-environmental correlations [30], PRS-PTSD is associated with PTSD independently of trauma exposure [23, 24]. This is consistent with evidence that the effects of PRS and environmental exposures on psychiatric disorders are largely additive, even after accounting for correlations between PRS and environment [30]. Exposure severity, such as the duration and severity of traumatic events, is therefore another factor that can inform risk of chronic PTSD. Although the cross-sectional association between trauma exposure severity and higher PTSD severity is established [31, 32], the association between trauma severity and continuous variation in PTSD course (e.g., individual differences in rate of change) remains largely unknown.

The current study addressed these knowledge gaps by investigating whether PRS-PTSD and severity of trauma exposure predict the 20-year course of PTSD symptoms in a large longitudinal sample of responders to the 9/11 terrorist attacks. To our knowledge, this is the longest and largest prospective cohort of trauma-exposed patients who are genotyped and assessed annually for PTSD symptoms beginning shortly after exposure. In a separate paper, we report PTSD trajectories in 9/11 responders over this time period [33], and this study extends this work to evaluate two putative etiologic factors in PTSD symptom course. This study is the first to investigate associations between PRS-PTSD and rates of change in PTSD symptoms, to inform whether polygenic risk predicts symptom progression. Crucially, analyses separate initial-levels from rates of change to test whether PRS-PTSD contributes to the course of PTSD symptom severity independently of baseline symptoms. Moreover, trauma severity is included as a predictor in the same model, to clarify the independent role of trauma exposure controlling for genetic liability. Finally, this study addressed the heterogeneous presentation of PTSD by relating trajectories of PTSD symptom clusters to trauma exposure severity and cluster-specific PRS-PTSD.

METHODS

Sample

Data include 49,402 observations, spanning July 2002 to December 2022, from $n = 5687$ World Trade Center (WTC) responders with predominately European ancestry as determined by genetic principal components analysis (EUR > 0.80). 98.49% self-identified as White, 1.23% as multi-racial, 0.02% as Black, 0.23% as Native American, and 0.02% as Asian. 96.45% reported non-Latino ethnicity. Biological sex was determined by genotype, and the sample was mostly male (92.9%). The median age of responders on 9/11/2001 was 37 years old (*mean* = 37.74, *SD* = 8.19 years, minimum = 16, maximum = 75). All responders reported the severity of PTSD symptoms at least once, 99.5% and 96.7% completed at least one and two follow-up assessments, respectively. 76.92% completed five or more follow-up assessments, and 33.67% completed 10 or more. The median time between assessments was approximately 1 year (median = 1.07, IQR = 0.33). Informed oral and written consent was obtained from all study participants. The Institutional Review Board at Stony Brook University approved procedures for health monitoring visits (Number of ethical approval: 604113; WTC Health & Wellness Study).

Measures

Polygenic risk for PTSD. DNA was extracted from blood samples and genotyped using the Infinium Global Screening Array (Illumina, San Diego, CA, USA). Single nucleotide polymorphisms (SNPs) were processed following standard protocols for genotype calling, quality control, imputation to the 1000 Genomes reference panel, and ancestry measurement using principal component analysis (PCA). Polygenic risk scores (PRS) were generated using PRScs, a Bayesian regression framework that incorporates linkage disequilibrium (LD) patterns[34]. This method applies continuous shrinkage priors to adjust SNP effect sizes based on summary statistics, producing individual PRS by summing allele counts weighted by these adjusted effect sizes, yielding a continuous measure of genetic risk[34]. Weights for SNPs were derived from genome-wide association summary statistics from the Million Veterans Program (MVP), a large-scale study of PTSD symptom severity and its clusters measured using the PTSD Checklist (PCL) [35]. Polygenic scores for PCL total score and reexperiencing, avoidance, and hyperarousal cluster scores were coded so higher scores were associated with higher liability for symptoms. Finally, polygenic scores (PRS) were standardized (mean = 0, SD = 1) to ease interpretation of effects.

Trauma exposure severity. While all responders experienced 9/11 exposure, a composite score of trauma severity was the sum of eight binary exposures (0 = Not exposed, 1 = exposed) that were associated with increased risk of PTSD in prior studies [8, 36, 37]. Exposures included: early arrival to ground zero (i.e., arrival on 9/11 or 9/12; 73.4% exposed), being beside or near the WTC towers when they collapsed (83.7%), caught in the dust cloud (79.4%), sleeping at ground zero (16.9%), contact with blood or bodily fluids (41.6%), witnessing or handling human remains (68.7%), knowing someone who was injured on 9/11 (56.0%), and death of a colleague, family member or friend on 9/11 (68.9%). The resulting sum scores were approximately normally distributed.

Symptoms of PTSD. The severity of PTSD symptoms was measured using the trauma specific version of the PCL for the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV), adapted for the WTC attacks. The PCL asks respondents to rate how much they have been bothered by seventeen symptoms of PTSD in the past month, with responses ranging from (1) "Not at all" to (5) "Extremely". The total severity score is a sum of the 17 items, with possible scores ranging from 17–85. Subscale scores were also calculated for symptoms of reexperiencing, avoidance, and hyperarousal. Table 1 displays descriptive statistics for PCL total scores at each year of data collection. Descriptive statistics for PCL subscale scores are reported in the supplement, as are the items that comprise each subscale.

Data analysis. Multi-level models were estimated using different packages in RStudio [38] to ensure consistency of findings, including 'lme4' [39], 'nlme' [40] and 'lcmm' [41], and estimates were identical to the second decimal place. To determine the average trajectory, a series of models were estimated, including an intercept-only model and models that estimated fixed and random linear rates of change, and different forms of non-linear change. In these models the outcome variable was the repeatedly measured WTC responders' PCL score from 2002 to 2022, and the timing variable was years since 9/11/2001. Residual errors were assumed to be independent and normally distributed. Models were estimated using full information maximum likelihood, and information criteria were compared to determine the preferred model, including Akaike information criteria (AIC), Bayesian information criteria (BIC), and sample-size adjusted BIC (SSBIC). A quadratic model was preferred, which included fixed and random intercepts, linear slopes, and quadratic slopes (Table S4). PCL trajectories are detailed in a larger sample of WTC responders ($n = 12{,}822$), and the results are reported in a different publication [33]. Additional information on the interpretation of longitudinal multi-level models can be found elsewhere [42].

Next, two time-invariant predictors of random intercepts and slopes were included to test study hypotheses. These predictors capture departures from the average initial-level of symptoms and the average rates of change in symptoms, including the PRS (for PCL total or cluster score corresponding to the dependent variable) and the measure of exposure severity, indicating the reported number of traumatic exposures, written as:

$$PCL_{ti} = b_{1i} + b_{2i} \times (time) + b_{3i} \times \left(time^2\right) + e_{ti} \quad (1)$$

$$\begin{aligned} b_{1i} &= \beta_{01} + \beta_{11} \times (PRS) + \beta_{21} \times (Exposure) + d_{1i} \\ b_{2i} &= \beta_{02} + \beta_{12} \times (PRS) + \beta_{22} \times (Exposure) + d_{2i} \\ b_{3i} &= \beta_{03} + \beta_{13} \times (PRS) + \beta_{23} \times (Exposure) + d_{3i} \end{aligned} \quad (2)$$

Study hypotheses were tested by determining whether β_{11}, β_{21}, β_{12}, β_{22}, β_{13} and β_{23} were significantly different from zero

Table 1. Descriptive Statistics and Internal Consistency Coefficients for PCL Total Scores.

	Descriptive Statistics								Internal Consistency		
Year	***n***	***M***	***Med.***	***SD***	***Min.***	***Max.***	***Skew***	***Kurtosis***	**α**	**ω_T**	**ω_H**
2002	161	29.28	25	11.79	17	70	1.19	0.70	0.93	0.95	0.73
2003	526	27.67	24	10.78	17	78	1.39	1.93	0.93	0.94	0.79
2004	437	26.93	23	11.31	17	80	1.93	4.41	0.95	0.96	0.80
2005	464	27.55	23	12.56	17	85	1.86	3.62	0.95	0.96	0.84
2006	638	29.08	24	13.30	17	85	1.54	2.01	0.95	0.96	0.82
2007	1000	28.55	24	12.81	17	85	1.60	2.38	0.95	0.96	0.81
2008	998	28.80	24	13.45	17	83	1.58	2.07	0.96	0.96	0.87
2009	1814	27.81	23	13.10	17	85	1.67	2.55	0.96	0.96	0.85
2010	2099	28.20	23	13.41	17	85	1.64	2.40	0.96	0.96	0.85
2011	2110	29.96	24	14.66	17	85	1.38	1.25	0.96	0.97	0.86
2012	2299	28.88	24	13.68	17	85	1.44	1.44	0.96	0.96	0.84
2013	2655	28.58	23	13.48	17	85	1.42	1.37	0.95	0.96	0.85
2014	3163	28.37	23	13.44	17	85	1.51	1.75	0.96	0.96	0.86
2015	2814	28.15	23	13.36	17	84	1.52	1.82	0.96	0.96	0.88
2016	3663	28.38	23	13.26	17	85	1.50	1.83	0.96	0.96	0.86
2017	3657	28.59	23	13.51	17	84	1.45	1.59	0.96	0.96	0.84
2018	4221	27.61	22	12.76	17	85	1.57	2.06	0.95	0.96	0.84
2019	4342	27.45	22	12.65	17	83	1.62	2.35	0.95	0.96	0.87
2020	3704	26.76	22	12.42	17	85	1.75	2.84	0.95	0.96	0.85
2021	4435	26.37	22	12.01	17	85	1.74	2.85	0.95	0.96	0.84
2022	4202	25.95	21	11.63	17	85	1.75	2.92	0.95	0.96	0.83
	Descriptive Statistics								**Internal Consistency**		
Wave	***n***	***M***	***Med.***	***SD***	***Min.***	***Max.***	***Skew***	***Kurtosis***	**α**	**ω_T**	**ω_H**
1	5687	27.88	23	13.12	17	85	1.60	2.22	0.95	0.96	0.85
2	5660	27.86	23	13.14	17	85	1.57	2.06	0.96	0.96	0.86
3	5502	27.76	22	13.14	17	85	1.62	2.28	0.96	0.96	0.85
4	5301	27.65	22	13.07	17	83	1.61	2.10	0.96	0.96	0.86
5	4922	27.77	23	13.02	17	85	1.61	2.19	0.96	0.96	0.85
6	4375	27.87	23	12.95	17	85	1.52	1.89	0.95	0.96	0.84
7	3809	27.81	23	12.95	17	85	1.59	2.21	0.95	0.96	0.86
8	3273	27.85	23	12.82	17	85	1.52	1.85	0.95	0.96	0.84
9	2792	27.98	23	13.00	17	85	1.56	2.03	0.95	0.96	0.86
10	2337	27.93	23	13.00	17	85	1.57	2.14	0.95	0.96	0.85
11	1915	27.33	23	12.44	17	85	1.67	2.64	0.95	0.96	0.84
12	1509	27.77	23	12.63	17	82	1.63	2.47	0.95	0.96	0.85
13	1073	27.49	23	11.99	17	82	1.51	1.95	0.95	0.96	0.82
14	700	27.77	23	12.48	17	80	1.56	2.25	0.95	0.96	0.82
15	367	27.99	23	13.48	17	84	1.65	2.35	0.96	0.97	0.81
16	145	28.77	23	13.83	17	81	1.41	1.40	0.96	0.97	0.85
17	35	26.65	23	11.19	17	64	1.89	3.46	0.94	0.96	0.70

n sample size, M arithmetic mean, Med median, SD standard deviation, Min minimum observed score, Max maximum observed score, Skew Fisher's skewness, Kurtosis excess kurtosis, α Cronbach's alpha, ω_T Omega total, ω_H Omega hierarchical.

($p_{(two\text{-}tailed)} < 0.05$). This model was also estimated after adjusting for the effects of age at 9/11/2011, biological sex, self-reported race/ethnicity, and the first ten genetic principal components. To decrease model complexity and facilitate convergence, PCL scores were regressed on these covariates, and standardized residuals were saved as the outcome variable. Statistically significant findings were depicted by plotting trajectories across levels of significant predictors with 95% confidence bands.

Additional analyses were conducted to determine the sensitivity of findings to underlying assumptions of multi-level models, including linearity, normality, and independence of residuals. First, an auto regressive (AR1) correlational structure was added to the linear multi-level model, which predicts the residuals of repeated measures by the prior value in the time series. Second, a generalized multi-level model with a log-link and Gamma distribution was estimated using penalized quasi-likelihood, which is appropriate for non-normally distributed outcomes. Third, a final sensitivity analysis was conducted using a zero-inflated mixed effects model to account for the left-censored distribution of PCL scores (i.e., the floor effect, where many individuals scored at the minimum possible value of 17).

RESULTS

Table 1 reports estimates of internal consistency for PCL total scores. The observed distributions of PRS-PTSD, exposure severity, and PCL total scores are depicted in Fig. 1. At each year and measurement occasion, the PCL exhibited excellent internal consistency (e.g., range of Cronbach's α =0.93–0.95; range of McDonald's $\omega_{total} = 0.94–0.97$). The PRS-PTSD was not associated with exposure severity ($r = 0.01$ [−0.03, 0.02], $p = 0.604$). Similarly, the PRSs for reexperiencing ($r = 0.01$ [−0.02, 0.03], $p = 0.538$), avoidance ($r = 0.01$ [−0.02, 0.04], $p = 0.468$), and hyperarousal symptoms ($r = 0.00$ [−0.03, 0.03], $p = 0.956$) were not associated with exposure severity.

Table 2 displays estimates from multi-level models. Results indicate that a responder with average genetic risk ($PRS = 0$) who reported the lowest level of exposure severity was predicted to have a PCL score of approximately 20 to 21 points in 2001, immediately following the 9/11 attacks ($\beta_{01} = 20.31$, $p < 0.001$), and the average rates of change in symptoms (linear and quadratic; β_{02} & β_{03}) were approximately zero, indicating an flat average trajectory of symptom severity for responders with average genetic risk and no traumatic exposures. Responders with high genetic risk for PTSD symptoms (+1 *SD*) were predicted to have marginally higher PCL total scores in 2001 ($\beta_{11} = 0.59$, $p = 0.059$), which increased more rapidly ($\beta_{12} = 0.11$, $p = 0.025$), such that PCL scores were predicted to increase linearly by 0.11 points each year following the WTC attacks, peaking in 2012 and remaining elevated in 2022, despite gradually decreasing over time, as genetic risk for PTSD symptoms was also negatively associated with quadratic rates of change ($\beta_{13} = -0.004$, $p = 0.032$). Similarly, each traumatic exposure reported by responders was significantly associated with a 1.21-point higher PCL total score in 2001 ($\beta_{21} = 1.21$, $p < 0.001$). Exposure severity also predicted more rapid linear rates of change ($\beta_{22} = 0.08$, $p < 0.001$) and negatively predicted quadratic rates of change ($\beta_{23} = -0.005$, $p < 0.001$), yet these effects balanced each other out, such that predicted PCL first increased and then decreased back to initial levels after 20 years.

The results of hypothesis tests remained unchanged after adjusting estimates for the effects of age, biological sex, self-reported race/ethnicity, and the first ten genetic principal components (Table 2). Predicted trajectories unadjusted (panels A & C) and adjusted for covariates (panels B & D) with 95% confidence bands are depicted in Fig. 2. The PRS for reexperiencing, avoidance, and hyperarousal symptom clusters were also significant predictors ($p < 0.05$) of rates of change in their corresponding PCL subscale scores, but not initial levels. Alternatively, exposure severity was a significant predictor of initial levels in PCL subscale scores ($p < 0.001$) and had significant but less pronounced effects on rates of change. These effects are depicted in Fig. 3 and reported comprehensively in the supplement (Tables S8 to S22). Of note, the trajectories of hyperarousal symptoms mirrored PCL total scores, whereas reexperiencing decreased and avoidance increased (Fig. 2). Effect sizes and hypothesis tests were similar after adjusting for covariates in sensitivity analyses, except for the PRS for avoidance symptoms, for which results were either marginally significant ($p < 0.10$) or not significant ($p > 0.10$) across models. Finally, the interaction between PRS-PTSD and exposure severity on initial-levels and rates of change were not statistically significant (*p*-values > 0.05).

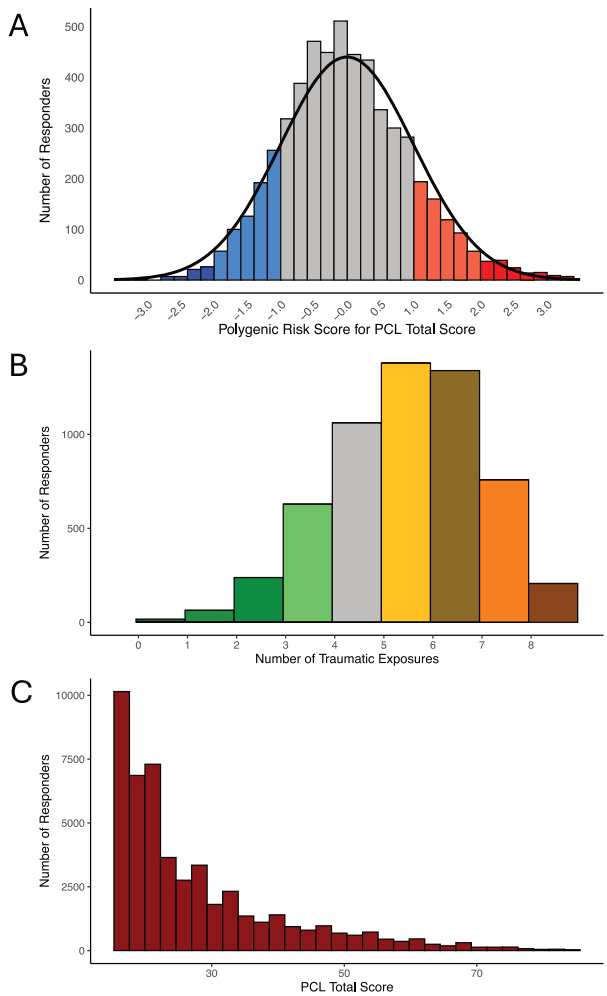

Fig. 1 Distributions of Focal Predictors and Outcome Variables. Histograms are depicted for polygenic risk scores (**A**), number of traumatic exposures (**B**), and self-reported PTSD symptom severity (**C**).

DISCUSSION

This study is the first to find that genetic liability significantly predicted continuous variation in the course of PTSD symptom severity, over and above the initial level of symptom severity. Responders with higher PRS did not initially differ from those with lower liability, but their symptoms became worse over time. In contrast, traumatic exposures predicted initial levels and had less pronounced effects on symptom change. Overall, genetic vulnerability and exposure severity conferred additive risks for chronic PTSD. These findings come from a large prospective study of a trauma-exposed occupational cohort and have important implications for clinical research of PTSD.

Only two studies to date have reported associations between PRS-PTSD and longitudinal assessments of PTSD [23, 29]. Both studies modeled two to four broad trajectory classes rather than participants' individual rates of change in symptoms and did not tease apart baseline levels from rates of change [23, 29]. The first study included a subset of participants from the current study [23], while the second study utilized a military sample to investigate PTSD over the first nine months post combat deployment [29]. The present study advances this literature by separating effects of genetic vulnerability on initial levels and subsequent change. This revealed that PRS predicts individual differences in change. For instance, responders in the highest strata of PRS-PTSD (+2 *SD*) worsened more rapidly over time, peaking 10 to 12 years after exposure, and gradually declining thereafter, with symptom severity at the 20-year follow up higher than the first assessment. Conversely, responders in the lowest PRS-PTSD strata (-2 SD) had low PTSD symptoms at baseline, and further improved over the 20-year follow up. Interestingly, the PRS-PTSD predicted linear and quadratic rates of change, the former positively and the latter

Table 2. Maximum Likelihood Estimates from Linear Multi-Level Models.

Unadjusted Model								
Level 1	***b***	***SE***	**Wald**	***p***	***b***	***SE***	**Wald**	***p***
Intercept	20.310	0.622	32.659	<0.001	−0.548	0.092	−5.978	<0.001
Linear Slope	0.001	0.003	0.351	0.726	−0.007	0.014	−0.504	0.615
Quadratic Slope	0.003	0.001	2.280	0.023	0.001	0.001	1.009	0.313
Level 2	***β***	***SE***	**Wald**	***p***	***β***	***SE***	**Wald**	***p***
PRS → Intercept	0.587	0.311	1.887	0.059	0.032	0.025	1.271	0.204
PRS → Linear Slope	0.105	0.047	2.234	0.025	0.012	0.004	3.124	0.002
PRS → Quadratic Slope	−0.004	0.002	−2.145	0.032	−0.001	0.000	−3.122	0.002
Exposure → Intercept	1.214	0.125	9.677	<0.001	0.085	0.017	4.999	<0.001
Exposure → Linear Slope	0.084	0.009	9.693	<0.001	0.008	0.003	2.989	0.003
Exposure → Quadratic Slope	−0.005	0.000	−11.074	<0.001	−0.001	0.000	−4.154	<0.001
Random Effects	Intercept	Linear Slope	Quadratic Slope		Intercept	Linear Slope		Quadratic Slope
σ^2	178.323	4.523	0.007		1.083	0.028		< 0.001

Model 1 is unadjusted for the effects of covariates and coefficients are unstandardized (*b*). Model 2 is adjusted for the effects of covariates, including the first ten genetic principal components, age, biological sex determined by genotype, and self-report race/ethnicity, and coefficients are standardized (β; STDY).
SE standard error, Wald test statistic, *p* probability of obtaining a test statistic equal to or more extreme than observed, assuming the null hypothesis is true. σ^2 variance. PRS polygenic risk score for PCL total score, Exposure count of eight traumatic WTC-related exposures.

negatively. Thus, PRS-PTSD not only predicted increases in symptoms but also a gradual decline after symptoms peaked. One interpretation of this finding is that genetics predispose an individual to a particular level of a trait or syndrome, in this case, symptoms of PTSD. Although illness can begin soon after exposure, it often takes many years to unfold, so PRS predicted both the initial progression of symptoms, and as more people reached or exceeded their trait level, the PRS also predicted gradual decline to maintain or return to their trait level. Overall, the finding that PRS contribute to symptom change is novel yet consistent with evidence from longitudinal twin studies of dynamic genetic effects over time [43–45], informing a theoretical understanding of the role of genetics in shaping the long-term course of illness.

PRS-PTSD has previously been found to be associated with PTSD independently of trauma exposure [23, 24]. This study extends this knowledge by demonstrating that PRS-PTSD and trauma severity constitute uncorrelated risk factors that independently predict PTSD course, both for total PTSD symptom severity and symptom clusters. This is in line with evidence for largely additive effects of genetic liabilities and environments on psychiatric disorders [30], and with the 9/11 attacks constituting a chance event with limited opportunity for evocative or active gene-environment correlation. This study is also the first to demonstrate an association specifically between trauma exposure and PTSD course, accounting for baseline PTSD symptom severity and controlling for genetic liability, indicating the lasting impact of traumatic exposures. Moreover, the PRS and exposure predictions remained when investigating the trajectories of each PTSD cluster separately, particularly for reexperiencing and hyperarousal symptoms.

PTSD symptom clusters exhibited distinct longitudinal patterns influenced by both PRS and trauma exposure levels. Higher PRS levels were consistently associated with elevated symptoms across clusters, indicating a persistent genetic vulnerability, while greater trauma exposures also corresponded to higher symptom severity, reflecting the cumulative effects of traumatic exposures. However, the trajectories exhibited subtle differences in how symptoms change over time. Hyperarousal symptoms show relatively stable yet slightly increasing patterns at higher PRS and exposure levels, suggesting that high risk resulted in persistent hyperarousal. In contrast, reexperiencing symptoms exhibited declines in lower-risk groups with comparatively sustained trajectories at higher levels of PRS and exposure severity. On the other hand, avoidance symptoms displayed more notable increases among those with higher PRS and greater exposure severity. These patterns highlight the significant heterogeneity in PTSD symptoms and demonstrate that analyses of symptom clusters can reveal divergent trends over time with differential links to etiologic factors.

Clinical implications

This study provides evidence for the utility of PRS-PTSD in predicting long-term symptom course, over and above baseline information on PTSD severity, demographic characteristics, and trauma exposure. As such, PRS-PTSD may be useful in future clinical research for identifying individuals, among those exposed to trauma, who are at risk of chronic PTSD because their symptoms are likely to worsen over time. Exposure severity is also a unique risk factor for chronic PTSD, but it contributes primarily to initial symptom severity. Symptoms tend to fluctuate around this baseline, but over many years they can improve or worsen substantially [33]. These factors are additive, so that individuals with the greatest PRS and traumatic exposure are at highest risk for chronicity, people with the lowest PRS and exposure are low risk, and those with elevation in one domain are in the middle. If identified early on, individuals at-risk for chronic PTSD could receive early prevention, resiliency training, treatment,

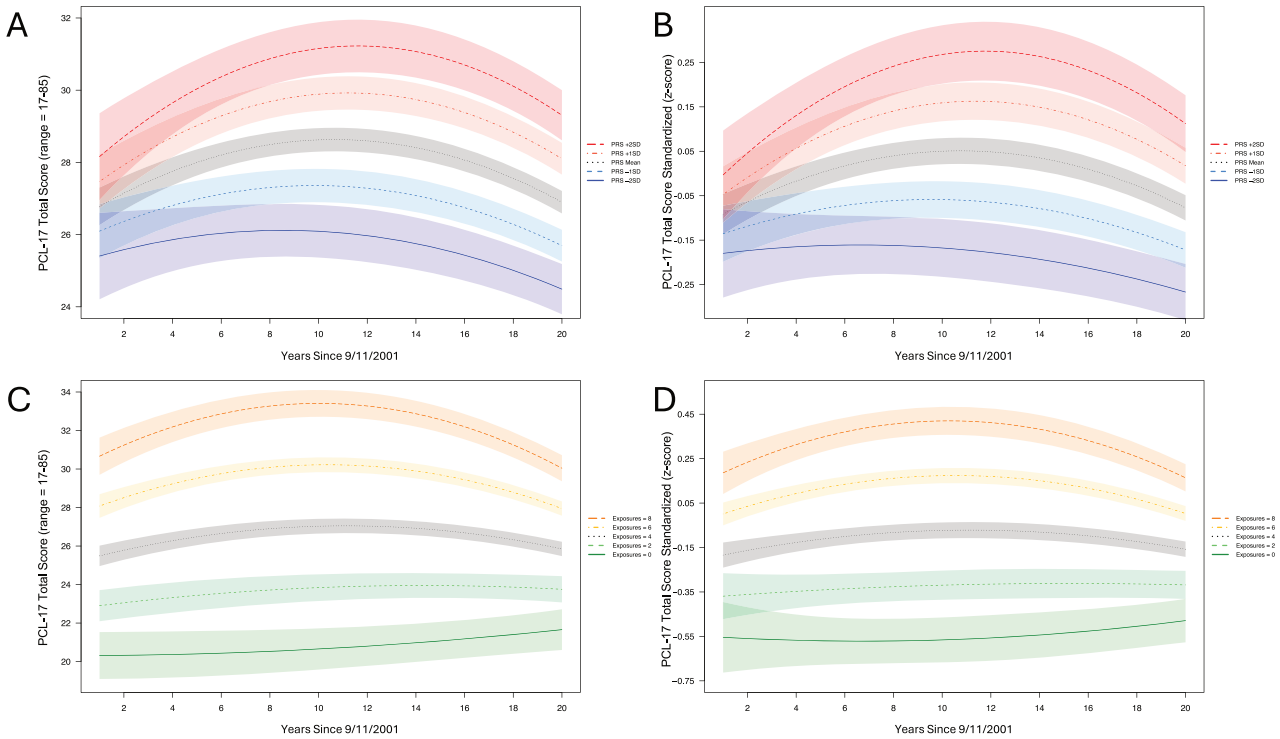

Fig. 2 Effects of Polygenic Risk and Exposure Severity on PCL Total Score. Predicted trajectories of PTSD symptom severity are plotted across levels of polygenic risk scores (-2 SD to+2 SD). **A** and **C** – Predicted trajectories with 95% confidence bands are unadjusted so the scale of the y-axis corresponds to PCL total scores for clinical reference, with possible values ranging from 17–85. **B** and **D** - Predicted trajectories with 95% confidence bands are adjusted for the effects of the first ten genetic principal components, age, biological sex, and self-reported race/ethnicity, and the scale of the y-axis is standardized (i.e., z-score units). PRS polygenic risk score for PCL total scores, SD standard deviation, Exposure count of eight psychologically traumatic WTC-related exposures.

and more attentive monitoring. With further research, present findings may be useful in guiding the selection of patients to participate in such research programs.

Limitations

This study benefits from a large sample and a prospective design with repeated clinical assessments spanning 20 years following trauma. However, we note several limitations. First, our analyses were restricted to participants of European ancestry, as WTC responders have predominately European ancestry, and the majority self-identify as White non-Latino race/ethnicity. The number of responders with non-European ancestry was insufficient to explore stratification or moderation by ancestry. Moreover, gene discovery efforts have been focused on European populations to date, decreasing the validity of PRS in more diverse populations [46, 47]. Consequently, the documented genetic effects may not generalize to individuals of other ancestries. Second, the WTC responder population is predominantly male, consistent with gender distributions among occupational cohorts of emergency responders and combat veterans. Thus, the number of females was also insufficient to explore moderation by biological sex, and the current findings might not generalize to other types of traumas, like natural disasters or interpersonal violence. Third, although the effects of polygenic risk scores on rates of change in PTSD symptoms were statistically significant, their magnitude is too small for direct clinical applications; however, they provide valuable insights for advancing clinical research on the long-term trajectory of PTSD. Moreover, future GWAS will likely produce even stronger PRS. Fourth, the current study did not detect PRS by environment interactions, which remain debated, generally yielding inconsistent results and very small effect sizes [30, 48, 49]. Fifth, data collection began approximately nine months after response efforts concluded, when the fires from the destruction of the WTC were finally extinguished. However, this study cannot speak to the effect of polygenic liability and exposure severity on symptoms during and immediately following trauma exposure. The number of observations per participant also varied substantially, ranging from 1 to 17. However, our analytic approach was specifically designed to accommodate this variability, ensuring no loss of information in the analysis. Finally, the measurement of exposure intensity and PTSD symptoms focused on the index event (i.e., the 9/11 terrorist attacks on the WTC). However, subsequent trauma exposure is likely in emergency responders and might impact the course of PTSD symptoms. Future studies will benefit from measuring trauma exposure as a time-varying predictor, that is, beyond the severity of the triggering trauma.

CONCLUSIONS

This prospective study in a large sample of 9/11 responders demonstrated that PRS-PTSD predicts long-term PTSD course, even after disentangling baseline symptoms from rates of change and adjusting for exposure severity, demographic characteristics, and population structure. Genetic vulnerabilities and trauma exposure conferred additive risks for more severe courses of PTSD. Future molecular genetic studies of PTSD will need to move beyond static phenotypes to capture the full potential of PRS-PTSD prediction to further illuminate etiology and prognosis for individual patients.

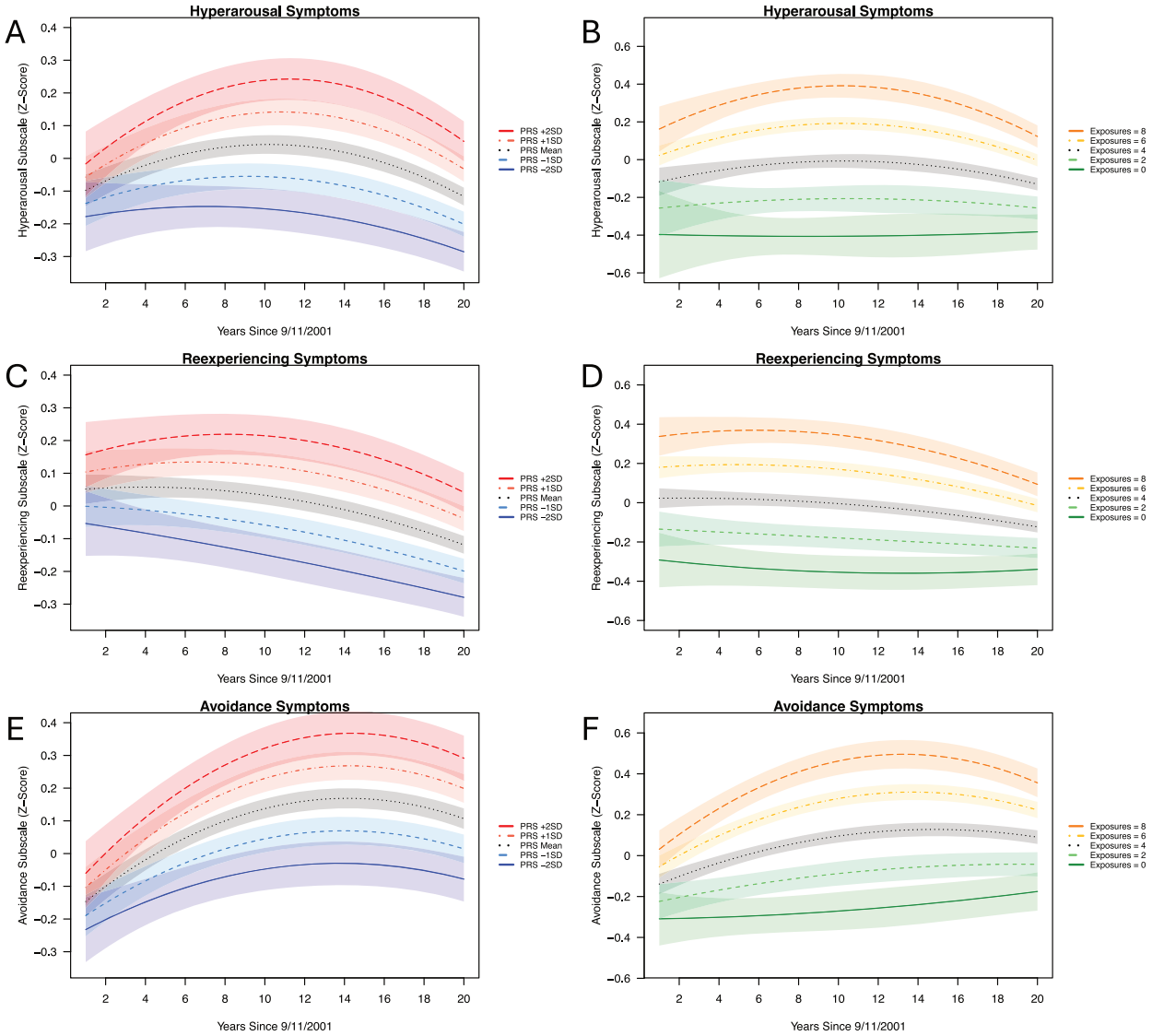

Fig. 3 Effects of Polygenic Risk and Exposure Severity on PCL Subscale Scores. Predicted trajectories are adjusted for the effects of the first ten genetic principal components, age, biological sex, and self-reported race/ethnicity. The scale of the y-axis is standardized (i.e., z-score units). PRS polygenic risk score for PCL subscale scores, SD standard deviation, exposure count of eight psychologically traumatic WTC-related exposures. Panels **A** and **B** depict the effects of polygenic risk and exposure count, respectively, on hyperarousal symptoms; Panels **C** and **D** depict the effects of polygenic risk and exposure count on reexperiencing symptoms. Panels **E** and **F** depict the effects of polygenic risk and exposure count on avoidance symptoms. The prediction of avoidance symptoms by the polygenic risk score was only marginally significant ($p < 10$) or not statistically significant ($p > 10$) across sensitivity analyses. Therefore, the results depicted in panel E should be interpreted with circumspection.

DATA AVAILABILITY

Data not provided in the article because of space limitations are not publicly shared due to ethical considerations. Study participants provided consent for their data to be analyzed by study personnel. To respect the autonomy and privacy of the WTC responders, the data underlying the reported results will be made available to qualified investigators whose proposed use of the data has been approved by an internal review committee and the Institutional Review Board at Stony Brook University. This access will be granted up to 4 years after publication of this study following rigorous de-identification of sensitive information. Requests for data access will be reviewed, and a response will be provided within 60 days of submission.

CODE AVAILABILITY

Correspondence concerning this article should be addressed to the first author, frank.mann@stonybrookmedicine.edu, including requests for a copy of the code that was used to conduct analyses.

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ACKNOWLEDGEMENTS

We thank the WTC responders from the General Responder Cohort whose participation was integral to this work. Data collection was funded by CDC 2011-200-39361 awarded to B.J.L. and U01OH011864 awarded to M.A.W, and by the SUNY Research Foundation. The analyses were partially funded by R21AG074705-01 awarded to F.D.M.

AUTHOR CONTRIBUTIONS

BJL, RK and MAW designed the study. BJL, MAC, and XY. coordinated and supervised data collection. AAS. and ARD. calculated polygenic risk scores. In consultation with RK, FDM. conducted the primary analyses, created tables and figures, and drafted the methods and results. MAW drafted the introduction and discussion. SAP, EJB, BPM, AAS, ARD, PK, MAC, XY, BJL and RK provided critical feedback and revisions, and all authors approved a final version of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS

Data collection was performed in accordance with ethnical guidelines approved by the Institutional Review Board at Stony Brook University (ethical approval number: 604113; WTC Health and Wellness Study) and all participants provided informed written consent. The participants were provided free screening and treatment for WTC-related health conditions and were not compensated otherwise.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41380-025-03235-2.

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