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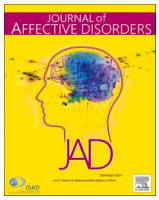

Research paper

Trajectories of post-traumatic stress disorder symptoms and subsequent risk of long COVID in the World Trade Center Health Registry

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ABSTRACT

Objective: Though the etiology of long COVID is not well-understood, pre-existing mental health conditions have been identified as risk factors. We examined associations between post-traumatic stress disorder symptoms (PTSS) and long COVID among individuals exposed to the World Trade Center disaster.
Methods: We used group-based trajectory modeling to identify five PTSS trajectories (resilient, low-stable, remitted, delayed onset, chronic-high) among enrollees in the World Trade Center Health Registry (2003–04 to 2020–2021). Among 5361 enrollees who reported a COVID-19 infection, we used modified Poisson regression to estimate risk ratios (RRs) and 95 % confidence intervals (95 % CI) for associations of PTSS trajectories with self-reported long COVID symptoms.
Results: In 2022–23, 41 % of enrollees reported long COVID symptoms. In models adjusted for sociodemographic characteristics and self-reported diagnosed physical health conditions and depression, associations with long COVID were observed for all trajectories compared to the resilient trajectory, which was characterized by very low PTSS at all points. RRs were similar among trajectory groups characterized by a high lifetime prevalence of probable PTSD ($RR_{remitted} = 1.83$, 95 % CI = 1.64, 2.04; $RR_{delayed} = 1.86$, 95 % CI = 1.67, 2.06; $RR_{chronic} = 1.80$, 95 % CI = 1.59, 2.03). Risk of long COVID was also elevated among individuals in the low-stable trajectory group, who had a lower lifetime prevalence of probable PTSD (RR = 1.46, 95 % CI = 1.35, 1.58).
Conclusion: Risk of long COVID is elevated among individuals with a history of PTSS, including among those whose symptoms have improved. Populations at high risk of PTSD, including those exposed to traumatic events, may benefit from targeted screening to identify those with long COVID.

1. Introduction

A proportion of individuals infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) experience symptoms that arise or persist beyond the acute infection period, a condition termed long COVID. Various definitions of long COVID have been used in clinical care, research, and public health surveillance; however, a committee of the National Academies of Science, Engineering and Medicine (NASEM), through an extensive engagement process with experts and stakeholders, has defined long COVID as an "infection-associated chronic condition that occurs after SARS-CoV-2 infection and is present for at least 3 months as a continuous, relapsing and remitting, or progressive disease state that affects one or more organ systems." (Ely et al., 2024).

Clinical presentations of long COVID are heterogeneous. Patients commonly report fatigue, post-exertional malaise, cognitive impairment ("brain fog"), chest pain and heart palpitations, orthostatic intolerance, shortness of breath, loss of smell and/or taste, and digestive symptoms (Davis et al., 2021; Thaweethai et al., 2023). Long COVID symptoms impact individuals' wellbeing and functioning, and are associated with high healthcare utilization, poor health-related quality of life, and risk of unemployment and housing insecurity (Carlile et al., 2024; Lapin et al., 2024; Packard and Susser, 2023; Perlis et al., 2023; Tartof et al., 2022). The etiology of long COVID is presently not well understood and may encompass a number of pathophysiologic mechanisms (Crook et al., 2021). However, previous research has identified associations between long COVID and severity of acute infection, female sex, older age, and pre-existing conditions (Subramanian et al., 2022; Thompson et al., 2022; Tsampasian et al., 2023; Wang et al., 2024).

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Among the pre-existing conditions that have been shown to be associated with increased risk for long COVID are mental health conditions, including depression and anxiety. In a 2023 meta-analysis, anxiety and depression were associated with a 20 % higher risk of long COVID among individuals with an acute COVID-19 infection (Tsampasian et al., 2023). Other mental health conditions have been less widely examined; however, some evidence suggests that post-traumatic stress disorder (PTSD) may also increase risk of long COVID. Prevalence of PTSD has been shown to be higher among those with long COVID compared to controls (Engelmann et al., 2024). However, many studies assess PTSD after long COVID symptom onset and cannot not rule out PTSD as a consequence of long COVID or severe COVID infection (Janiri et al., 2021; Kirchberger et al., 2024; Nagarajan et al., 2022). To date, only a small number of longitudinal studies have examined PTSD in relation to subsequent diagnosis of long COVID or onset of long COVID symptoms. Among four identified analyses that assessed pre-existing PTSD or adjustment disorders in relation to incident long COVID, three reported significant positive associations (Kostev et al., 2022; Nishimi et al., 2024; Wang et al., 2024), while a fourth reported no association (Ioannou et al., 2022). Each of these studies used diagnoses recorded in electronic health records to identify individuals with PTSD; however, this approach may misclassify those without a documented clinical diagnosis (Meltzer et al., 2012). Additionally, as PTSD symptoms may fluctuate over time (Santiago et al., 2013), a more nuanced investigation of PTSD symptom trajectories in relation to long COVID is warranted to better understand whether the timing and chronicity of symptoms is relevant to risk.

The aim of the present study was to investigate whether long-term symptoms following COVID-19 were associated with a history of post-traumatic stress disorder symptoms (PTSS) among individuals exposed to the World Trade Center (WTC) disaster, who have a high prevalence of PTSD. Leveraging over 15 years of longitudinal data, we defined PTSS trajectories prior to COVID-19 infection and examined whether these trajectories were associated with self-report of any long COVID symptom. Secondarily, we examined whether PTSS trajectories were associated with number of long COVID symptoms reported or with specific long COVID symptoms.

2. Methods

The World Trade Center Health Registry (Registry) is a closed, longitudinal cohort study established to monitor the physical and mental health effects of World Trade Center exposure. Enrollees include workers who participated in WTC rescue/recovery efforts, as well as exposed community members who lived, worked, went to school, or who were passersby in Lower Manhattan when the attacks occurred on September 11, 2001. All enrollees responded to a baseline survey in 2003–2004, and four additional wave surveys have since been administered (Wave 2 in 2006–07; Wave 3 in 2011–12; Wave 4 in 2015–16; and Wave 5 in 2020–21). The Wave 5 survey was launched in April 2020 among a sample that included all enrollees who responded to at least three previous surveys (i.e., baseline, Wave 2, and Wave 3 and/or Wave 4) and enrollees who had turned 18 years old after the baseline survey. In addition to these wave surveys, two supplemental surveys were administered to collect data on COVID-19 experiences and effects among the WTC-exposed population. These were the COVID-19 baseline survey, fielded between March 3 and August 27, 2021 among the Wave 5 sample, and the COVID-19 follow-up survey, fielded between December 26, 2022 and September 8, 2023. Among those who had responded to the COVID-19 baseline survey.

Both COVID-19 surveys queried whether enrollees had ever been sick with an illness they thought might be COVID-19 (baseline survey) or whether they had ever had COVID-19 (follow-up survey); enrollees were asked to provide the month and year of their first illness or infection. We considered reported months of March 2020 or later to be valid. To reduce potential misclassification, we used the month reported on the COVID-19 baseline survey, when available, as the date of first COVID-19 infection. Enrollees were also asked whether they had tested positive for COVID-19 infection and date of their positive test; however, to align with NASEM's long COVID definition, we did not restrict main analyses to those who reported a positive COVID-19 test (Ely et al., 2024). Enrollees who indicated that they had ever had COVID-19 and reported at least one symptom of their acute infection on the follow-up COVID-19 survey were asked to indicate whether they had ever had any of the following symptoms >12 weeks after their COVID-19 illness started: unusual tiredness or fatigue; difficulty breathing, shortness of breath or cough; altered sense of taste or smell; confusion/trouble thinking or concentrating/brain fog; muscle or joint pain; trouble sleeping; lightheadedness upon standing; anxiety or depression; other problem; or no symptoms. Enrollees were considered to have ever had long COVID if they selected at least one problem from the checklist.

Probable 9/11-related post-traumatic stress disorder symptoms (PTSS) were assessed beginning at the baseline survey wave using the PTSD Checklist-Specific (PCL-S), which included 17 items about symptoms related to 9/11 and corresponds to DSM-IV criteria for PTSD. In Wave 5, PTSS were assessed with the PTSD Checklist 5 (PCL-5), which included 20 items and corresponded to updated DSM-V criteria for PTSD. We used a previously developed crosswalk (Moshier et al., 2019) to convert PCL-S scores from the four earlier waves to PCL-5 scores. This approach has shown to have high intraclass correlation (>0.95) between observed and predicted PCL-5 scores among US Veterans. Individuals with scores of 33 or higher were considered to have probable PTSD, based on recommended thresholds (Bovin et al., 2016).

Among enrollees who responded to all five wave surveys and both COVID-19 surveys, who had at least two complete PCL measurements, and who were 18 or older at 9/11 ($N = 14{,}756$), we used group-based trajectory modeling to identify groups of enrollees whose PTSS followed similar longitudinal patterns (Nagin and Odgers, 2010). Details of the modeling procedure can be found in the Appendix. Five PTSS trajectory groups were identified: 1.) resilient, characterized by very low PTSS at all time points; 2.) low-stable, characterized by low PTSS at all time points; 3.) delayed onset, characterized by initially low PTSS that increased over time; 4.) remitted, characterized by initially high PTSS that decreased over time; and 5.) chronic, characterized by high PTSS at all time points (Fig. 1).

Fixed sociodemographic characteristics, including date of birth, sex, and race/ethnicity were queried at baseline. Time-varying sociodemographic characteristics, including educational attainment, household income, and employment status were assessed on baseline surveys and on subsequent surveys. Enrollees' 9/11 experiences were assessed at baseline and Wave 2, and WTC exposure was quantified by summing up to eleven self-reported experiences (e.g., sustaining an injury, witnessing horrific events, exposure to the dust cloud). Smoking status was queried at each wave beginning at baseline, and body mass index was calculated using height and weight reported beginning at Waves 3. Self-reported diagnosis of physical and mental health conditions, including year of diagnosis, were assessed at each wave.

The current study includes enrollees who responded to all five wave surveys and both COVID-19 surveys ($N = 14{,}888$). We excluded those <18 years old at 9/11 ($N = 116$), those with fewer than two complete PCL measurements ($N = 16$), those who indicated that they had never had COVID-19 on the COVID-19 follow-up survey ($N = 6174$) or who were missing data on COVID-19 infection at that survey ($N = 90$). As the long COVID survey question asked about symptoms experienced at least 12 weeks after acute infection, we additionally excluded enrollees who did not report a valid date of infection ($N = 564$) or whose first infection occurred within 12 weeks of their follow-up COVID-19 survey date ($N = 1038$). As COVID-19 infection may have impacted enrollees' covariates or Wave 5 PCL scores, we additionally excluded 1028 enrollees who reported a date of COVID-19 infection that preceded their Wave 5 survey completion date. Lastly, we removed 501 enrollees who did not answer the long COVID survey question, including 405 enrollees who did not

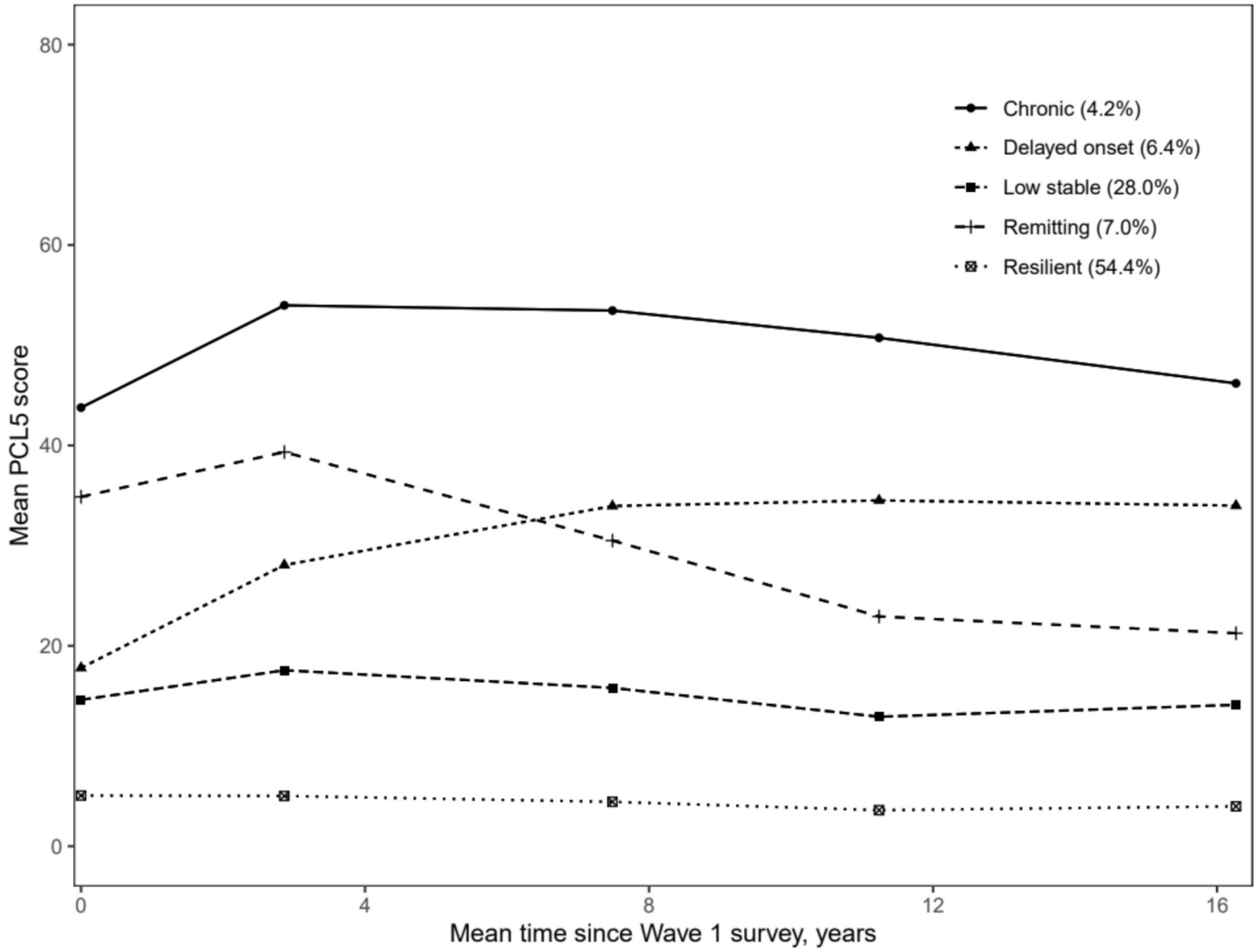

Fig. 1. Line chart showing mean observed PCL-5 score by time since Wave 1 survey by trajectory group, among World Trade Center Health Registry enrollees who responded to all wave surveys and both COVID-19 surveys, and who were ≥ 18 years old at 9/11. Note that PCL-S scores were converted to PCL-5 scores for survey waves 1–4, using crosswalk developed by Moshier et al., 2019.

report a symptomatic acute infection. The final sample eligible for analyses was 5361 enrollees (see Appendix for eligibility flow chart). The Registry protocol was approved by the US Centers for Disease Control and Prevention (CDC) and the New York City Department of Health and Mental Hygiene (DOHMH) institutional review boards.

First, we examined the univariate prevalence of each long COVID symptom reported. Second, we examined sociodemographic characteristics, 9/11 experiences, and health risk factors and outcomes among our study sample stratified by whether they reported at least one long COVID symptom. To assess whether PTSS trajectories were associated with long COVID, we used modified Poisson regression models with robust standard errors to estimate risk ratios (RRs) and 95 % confidence intervals (95 % CI) (Zou, 2004). Model 1 adjusted for sociodemographic characteristics and 9/11 experiences, including age category at baseline COVID-19 survey, sex, race/ethnicity, household income category, educational attainment, employment status, WTC rescue/recovery worker status, and WTC exposure category. Model 2 additionally adjusted for health risk factors and outcomes hypothesized to be associated with both PTSD and long COVID risk, including BMI category, smoking status, and lifetime diagnosis of asthma, GERD, sleep apnea, hypertension, COPD, cardiovascular conditions, stroke, cancer, or any autoimmune condition. Model 3 additionally adjusted for lifetime diagnosis of depression; we opted to include lifetime diagnosis as we hypothesized that depression symptoms at Wave 5 might mediate associations between PTSS trajectory group and long COVID risk (Gradus, 2018). Time-varying covariates were assessed at Wave 5. When covariate data were missing at Wave 5, we carried forward data one survey cycle (e.g., from Wave 4). A complete case analysis approach was then employed for multivariable-adjusted models, excluding up to 164 enrollees (3 %) with missing data on any covariates.

In secondary analyses, we used modified Poisson regression models to examine the association between PTSS trajectories and specific long COVID symptoms. We additionally used multinomial logistic regression to estimate odds ratios (ORs) and 95 % CI for the association of PTSS trajectories with the number of long COVID symptoms reported (0, 1–2, ≥3). All analyses were conducted in SAS v. 9.4 (Cary, NC).

We conducted several sensitivity analyses to assess the robustness of our main findings. First, we restricted analyses to enrollees who reported that they had a positive COVID-19 test (polymerase chain reaction (PCR) or antigen). Second, although the NASEM definition of long COVID recognizes mood disorders as symptoms, we excluded anxiety and depression from the definition of long COVID, to ensure that correlates of PTSD were not being reported as long COVID symptoms. Third, we excluded enrollees whose reported date of most recent COVID-19 infection occurred within 12 weeks of their COVID-19 follow-up survey, to reduce the possibility that symptoms reported were due to acute COVID-19 infection. Fourth, we examined associations between PTSD trajectories and long COVID among those currently experiencing

symptoms at the time of the COVID-19 follow-up survey. Lastly, main analyses included lifetime diagnosed depression as a covariate rather than depression measured at the timepoint prior to COVID-19 infection; however, we ran a sensitivity analysis that instead included probable depression at Wave 5, defined as a score of ≥10 on the Patient Health Questionnaire-8.

3. Results

Table 1 shows the prevalence of long COVID symptoms among the study sample. A total of 40.9 % of enrollees reported ever experiencing at least one long COVID symptom. Overall, 17.2 % of enrollees in the study sample reported currently experiencing long COVID symptoms; among those who reported ever having long COVID symptoms, 42.6 % reported currently experiencing them. Those who reported any symptoms reported a median of two symptoms (mean = 2.5). The most commonly reported symptom was unusual tiredness or fatigue (24.3 % of all enrollees), followed by difficulty breathing, shortness of breath or cough (12.6 %), and muscle or joint pain (12.3 %).

Sociodemographic characteristics, WTC exposures, and health risk factors and outcomes of our population, stratified by self-report of any long COVID symptoms, are shown in Table 2. Compared to enrollees who reported no long COVID symptoms, enrollees who reported at least one symptom were more likely to be female (39.4 % v. 34.2 %), have BMI ≥35 kg/m^2 (15.1 % vs. 9.1 %), report currently smoking cigarettes (5.6 % vs. 3.7 %), report high WTC exposure (5 to 11 WTC experiences: 16.6 % vs. 11.4 %), and to have performed WTC rescue and recovery work (51.5 % vs. 44.6 %). Compared with those reporting no symptoms, those reporting long COVID symptoms were less likely to be <50 years old (9.0 % vs. 11.3 %), be non-Hispanic white (74.8 % v. 84.1 %), to have graduated from college (53.5 % v. 65.6 %), and to have annual household incomes of $150,000 or more (29.2 % vs. 43.1 %). Prevalence of most self-reported, pre-existing health conditions was higher among those reporting long COVID symptoms. For example, 26.7 % of enrollees reporting at least one long COVID symptom reported ever being diagnosed with depression, compared to 17.6 % of enrollees without symptoms, and prevalence of asthma among those with and without long COVID symptoms was 30.2 % and 20.1 %, respectively. Those with long COVID symptoms were more likely than those without symptoms to be in the chronic high (6.8 % vs. 1.5 %), delayed onset (9.9 % vs. 3.3 %), remitting (9.5 % vs. 3.5 %) and low stable (33.0 % vs. 25.6 %) PTSS trajectory groups, and less likely to be in the resilient PTSS trajectory group (40.7 % vs. 66.1 %).

In unadjusted models, PTSS trajectory groups were differentially

Table 1
Prevalence of long COVID symptoms reported by World Trade Center Health Registry enrollees who self-reported a COVID-19 infection.

	n	%
Total	5361	100
Reported long COVID symptoms		
Any symptom	2191	40.9 %
Unusual tiredness or fatigue	1302	24.3 %
Difficulty breathing, shortness of breath or cough	675	12.6 %
Confusion/trouble thinking or concentrating/brain fog	572	10.7 %
Altered sense of taste or smell	522	9.7 %
Muscle or joint pain	662	12.3 %
Trouble sleeping	600	11.2 %
Lightheadedness upon standing	371	6.9 %
Anxiety or depression	441	8.2 %
Other problem	241	4.5 %
Currently experiencing long COVID symptoms[a]		
Among all enrollees	918	17.2 %
Among enrollees reporting any symptom	918	42.6 %

[a] Excludes 34 enrollees with missing data on current symptoms.

Table 2
Sociodemographic characteristics, 9/11 exposures, and health risk factors and conditions among World Trade Center Health Registry enrollees who self-reported a COVID-19 infection, by long COVID symptoms reported (any v. none).

	Did not report any long COVID symptoms		Reported ≥1 long COVID symptoms		P_{chisq}
	N	%	N	%	
Total (row %)	3170	59.1 %	2191	40.9 %	
Age at baseline COVID-19 survey, years					
<50	358	11.3 %	197	9.0 %	*0.0031*
50–59	825	26.0 %	650	29.7 %	
60–69	1158	36.5 %	802	36.6 %	
≥70	829	26.2 %	542	24.7 %	
Sex					
Male	2087	65.8 %	1328	60.6 %	*<0.0001*
Female	1083	34.2 %	863	39.4 %	
Race/ethnicity					
Non-Hispanic White	2665	84.1 %	1638	74.8 %	*<0.0001*
Non-Hispanic Black	136	4.3 %	149	6.8 %	
Hispanic	205	6.5 %	254	11.6 %	
Non-Hispanic Asian	110	3.5 %	90	4.1 %	
Non-Hispanic other	54	1.7 %	60	2.7 %	
Educational attainment					
High school graduate or less	338	10.7 %	322	14.7 %	*<0.0001*
Some college	752	23.7 %	696	31.8 %	
College graduate	2079	65.6 %	1173	53.5 %	
Employment status					
Employed	1873	59.1 %	1229	56.1 %	*0.0282*
Not employed	1296	40.9 %	962	43.9 %	
Annual household income					
<$25,000	72	2.3 %	108	5.0 %	*<0.0001*
$25,000- < $50,000	180	5.8 %	218	10.1 %	
$50,000- < $75,000	307	9.9 %	302	14.0 %	
$75,000- < $150,000	1211	38.9 %	896	41.6 %	
≥$150,000	1342	43.1 %	629	29.2 %	
Eligibility category					
Rescue/recovery worker	1414	44.6 %	1128	51.5 %	*<0.0001*
Community member	1756	55.4 %	1063	48.5 %	
Number of 9/11 experiences reported[a]					
0 to 1	1130	35.6 %	683	31.2 %	*<0.0001*
2 to 4	1679	53.0 %	1145	52.3 %	
5 to 11	361	11.4 %	363	16.6 %	
Smoking status					
Never	2006	63.3 %	1341	61.2 %	*0.0030*
Former	1043	33.0 %	726	33.2 %	
Current	117	3.7 %	123	5.6 %	

(continued on next page)

Table 2 (*continued*)

	Did not report any long COVID symptoms		Reported ≥1 long COVID symptoms		P_{chisq}
	N	%	N	%	
Body mass index (BMI) category, kg/m^2					
<25	939	29.7 %	496	22.8 %	*<0.0001*
25- < 30	1309	41.5 %	799	36.7 %	
30–35	621	19.7 %	555	25.5 %	
≥35	288	9.1 %	329	15.1 %	
Self-reported diagnosed health conditions					
Depression					
Yes	559	17.6 %	586	26.7 %	*<0.0001*
Asthma					
Yes	637	20.1 %	661	30.2 %	*<0.0001*
Chronic obstructive pulmonary disease (COPD)					
Yes	307	9.7 %	416	19.1 %	*<0.0001*
Gastroesophageal reflux disorder (GERD)					
Yes	826	26.1 %	862	39.6 %	*<0.0001*
Diabetes					
Yes	339	10.7 %	343	15.8 %	*<0.0001*
Autoimmune condition					
Yes	246	7.8 %	255	11.7 %	*<0.0001*
Hypertension					
Yes	1282	40.5 %	1052	48.2 %	*<0.0001*
Cardiovascular disease (CVD)					
Yes	271	8.6 %	266	12.2 %	*<0.0001*
Stroke					
Yes	72	2.3 %	61	2.8 %	*0.2241*
Sleep apnea					
Yes	613	19.4 %	655	30.1 %	*<0.0001*
Cancer					
Yes	663	21.0 %	468	21.4 %	*0.6847*
Post-traumatic stress disorder symptom (PTSS) trajectories					
Trajectory group					
Resilient	2094	66.1 %	892	40.7 %	*<0.0001*
Low stable	811	25.6 %	724	33.0 %	
Remitting	112	3.5 %	209	9.5 %	
Delayed onset	104	3.3 %	217	9.9 %	
Chronic high	49	1.5 %	149	6.8 %	

Unless otherwise noted, time-varying covariates were assessed at the Wave 5 survey (2020–2021); missing values were carried forward from the Wave 4 survey (2015–2016), where available.

Due to missing data, category-specific numbers may not sum to total.

[a] 9/11 experiences include: being in WTC tower; witnessed 3 or more traumatic events; thought might be killed/injured; lost family member; lost friend or acquaintance; lost coworker; intense dust cloud exposure; damage to workplace or home; sustained injury; had to evacuate home; lost job.

associated with risk of reporting at least one long COVID symptom (Fig. 2). Compared to enrollees in the resilient trajectory group, enrollees in all other trajectory groups had higher risk of any long COVID symptoms. As additional covariates were added to models, associations attenuated but remained significant. In models adjusted for all covariates, including self-reported diagnosed depression, enrollees in the low stable trajectory group had nearly 50 % higher risk of long COVID symptoms than those in the resilient trajectory group (RR = 1.46, 95 % CI: 1.35, 1.58). Among enrollees in the remitting, delayed onset and chronic high trajectory groups, risk ratios were similarly elevated relative to those in the resilient trajectory group (e.g., RR for remitting = 1.83, 95 % CI: 1.64, 2.04; RR for delayed onset = 1.86, 95 % CI: 1.67, 2.06; RR for chronic high = 1.80, 95 % CI: 1.59, 2.03).

The results of several sensitivity analyses did not materially change our main findings (see Appendix for full results). However, when we included probable depression at Wave 5 in our analysis, associations were attenuated for associations with the chronic high trajectory group (RR = 1.60, 95 % CI: 1.40, 1.84), and to a somewhat lesser extent for the associations with the remitted and delayed onset trajectory groups (e.g., RR = 1.74, 95 % CI: 1.55, 1.95 for remitting; RR = 1.68, 95 % CI: 1.50, 1.89 for delayed onset).

PTSS trajectories were also associated with the number of long COVID symptoms reported (Fig. 3). Notably, in multivariable-adjusted models, enrollees in the chronic high trajectory group were more than nine times more likely than those in the resilient trajectory group to report three or more symptoms (OR = 9.14, 95 % CI: 5.99, 13.96); the likelihood of reporting one or two symptoms was approximately two times higher (OR = 1.95, 95 % CI: 1.25, 3.04). Compared to those in the resilient trajectory group, enrollees in the remitting and delayed onset trajectory groups were each more than seven times more likely to report at least three long COVID symptoms (e.g., OR = 7.26, 95 % CI: 5.19, 10.17for delayed onset), while the magnitude of association was lower for those in the low stable trajectory group (OR = 2.82, 95 % CI: 2.28, 3.48).

In multivariable-adjusted models examining PTSS trajectories with specific long COVID symptoms, associations were strongest for anxiety and depression symptoms (Fig. 4). For example, those in the chronic high trajectory group had 8.74 times higher risk (95 % CI: 6.09, 12.56) than those in the resilient trajectory group of reporting anxiety or depression symptoms, while those in the low stable group had a three-fold higher risk (RR = 3.14, 95 % CI: 2.36, 4.18). Significant associations between PTSS trajectories and all other long COVID symptoms included on the survey were observed, though the magnitudes of associations were lower than those with anxiety and depression. Relative risks tended to be higher for those in the chronic high trajectory group; however, confidence intervals were generally overlapping between the chronic high, remitting, and delayed onset trajectory groups. For example, compared to those in the resilient trajectory group, those with chronic high trajectories were nearly two and a half times more likely to report shortness of breath or cough (RR = 2.41, 95 % CI: 1.82, 3.20), while RRs were below two for those in the remitted (RR = 1.70, 95 % CI: 1.31, 2.22), delayed onset (RR = 1.86, (95 % CI: 1.41, 2.44), and low stable (RR = 1.47, 95 % CI: 1.23, 1.76) trajectory groups.

4. Discussion

Among individuals exposed to the World Trade Center disaster who reported a COVID-19 infection, we examined associations between trajectories of 9/11-related PTSS over 15+ years and subsequent risk of long COVID symptoms. Compared to those who had very low PTSS across all measured time points, risks were elevated among individuals in trajectory groups characterized by high lifetime prevalence of PTSD, even among those whose symptoms had improved. This includes individuals with chronically high PTSS (lifetime PTSD prevalence: 100 %) and delayed onset or remitted PTSS (lifetime PTSD prevalence: 93 % for both). Relative to enrollees in the resilient trajectory group, long COVID risk was also increased among those with low-stable PTSS, who had a lifetime PTSD prevalence of 18 %, though the magnitude of the association was lower. Similar patterns were observed when examining associations between PTSS trajectories and individual long COVID

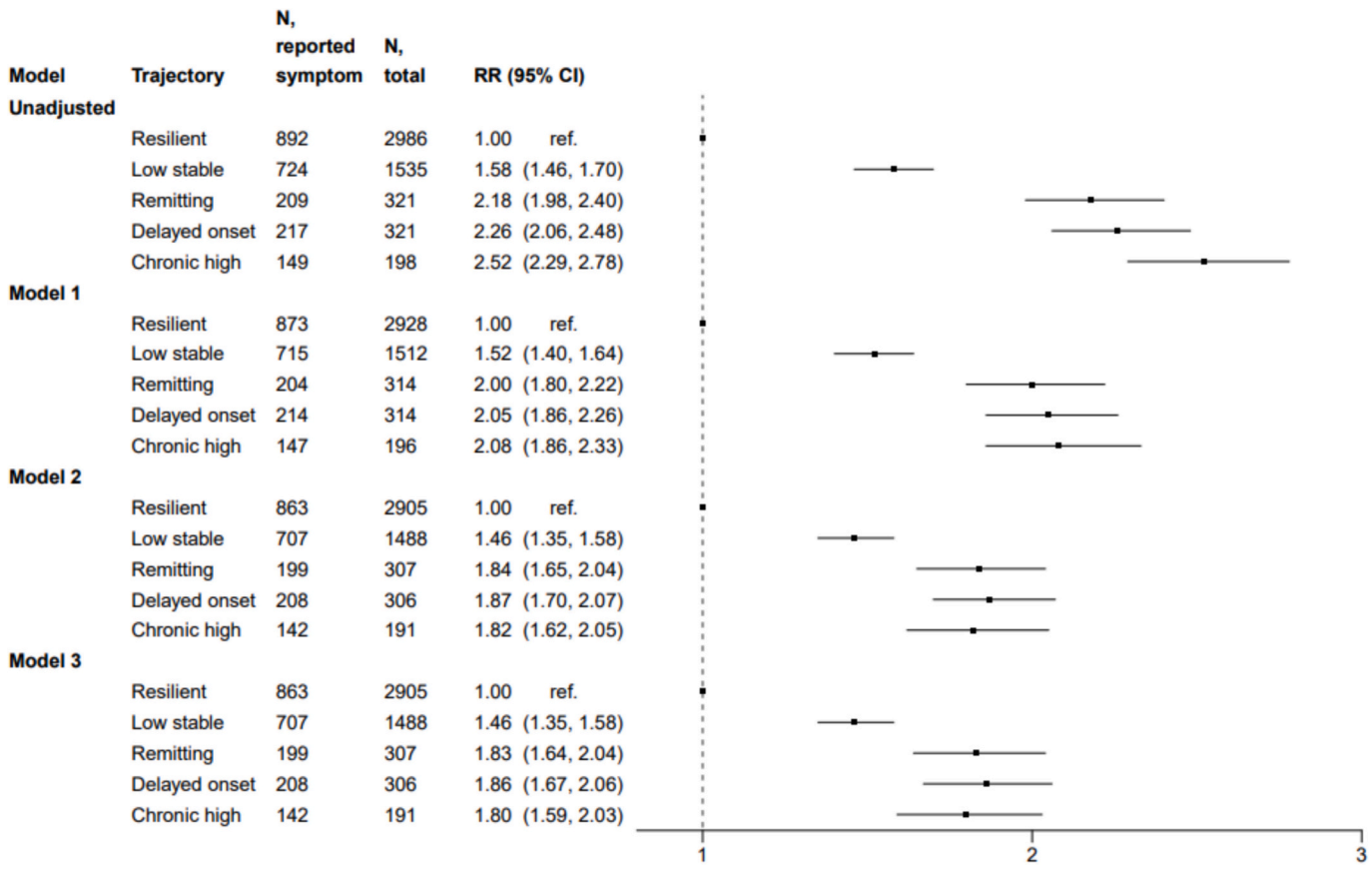

Fig. 2. Forest plot of risk ratios (RRs) and 95 % confidence intervals (95 % CI) for associations between any long COVID symptom and PTSD symptom trajectories among World Trade Center Health Registry enrollees who self-reported a COVID-19 infection. Model 1 is adjusted for age, sex, race/ethnicity, household income, educational attainment, employment status, number of 9/11 experiences reported, eligibility category. Model 2 is adjusted for Model 1 covariates and smoking status, BMI category, self-reported diagnosed physical health conditions. Model 3 is adjusted for Model 2 covariates and self-reported diagnosed depression.

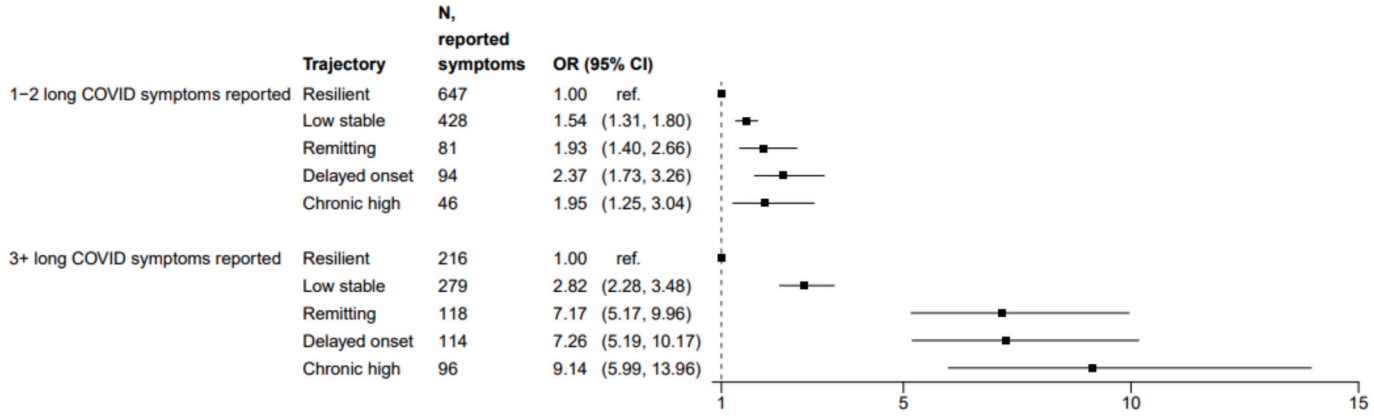

Fig. 3. Forest plot of odds ratios (ORs) and 95 % confidence intervals (95 % CI) for associations between number of long COVID symptoms reported and PTSD symptom trajectories among World Trade Center Health Registry enrollees who self-reported a COVID-19 infection. Models are adjusted for age, sex, race/ethnicity, household income, educational attainment, employment status, number of 9/11 experiences reported, eligibility category, smoking status, BMI category, self-reported diagnosed physical health conditions, and self-reported diagnosed depression.

symptoms, suggesting that results were not driven by a specific symptom or cluster of symptoms. While the effect size was larger for anxiety and depression, sensitivity analyses which removed mental health symptoms from the study outcome revealed that these symptoms did not have a substantial impact on the results of the main analysis. Trajectory groups defined by high PTSS symptoms at any timepoint were also more likely to report more long COVID symptoms. This may similarly suggest that a history of PTSS is associated with an elevated risk for multiple physical symptoms rather than specific symptom clusters, or may suggest an elevated risk for more severe illness.

Our results are in line with a recent longitudinal analysis by Nishimi et al., which found that US veterans who with PTSD had a 55 % higher risk of subsequently being diagnosed with long COVID compared to those without PTSD (Nishimi et al., 2024). Another population-based study also reported significant associations between previously diagnosed adjustment disorders, including PTSD, and diagnosis of conditions

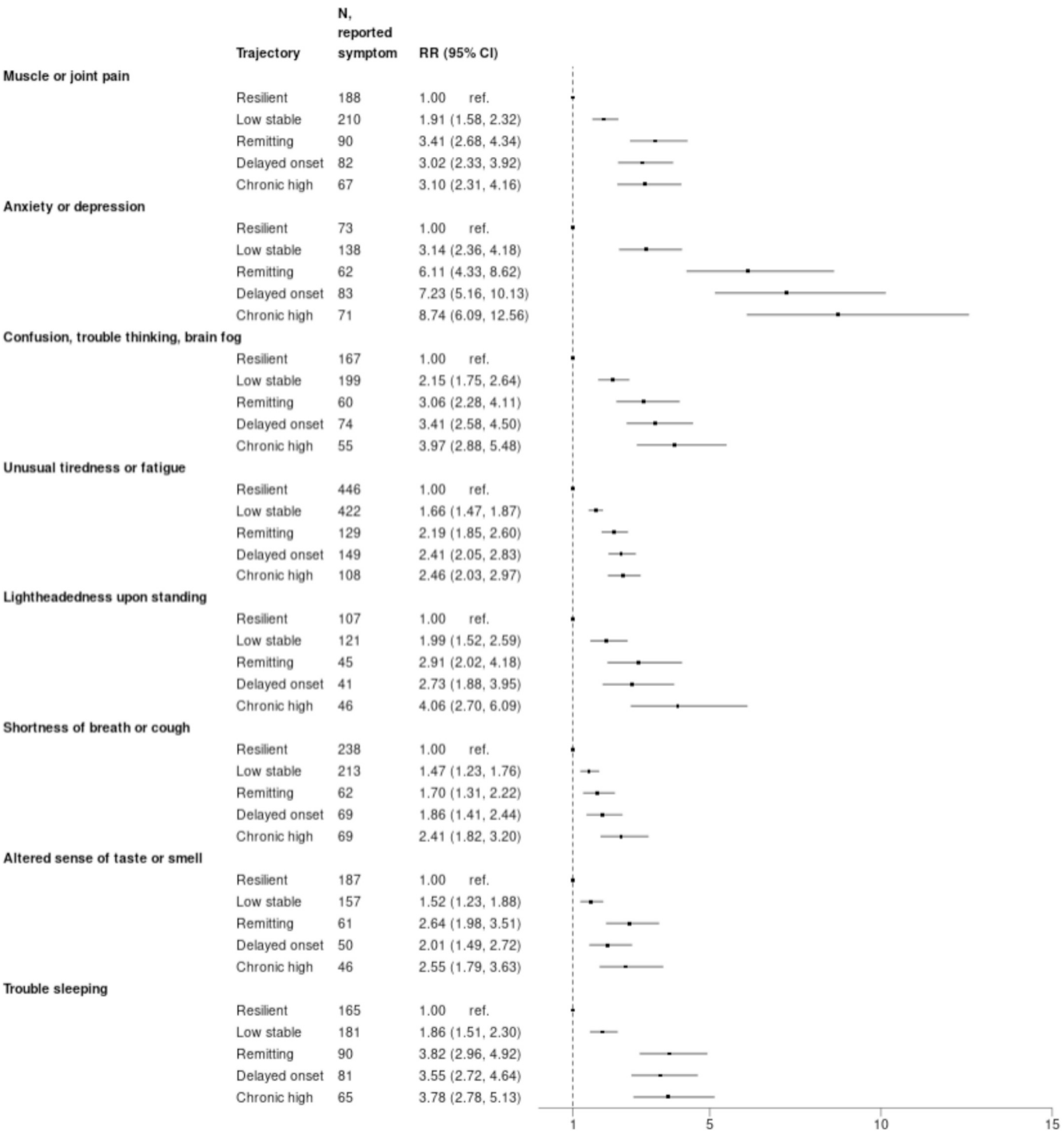

Fig. 4. Forest plot of risk ratios (RRs) and 95 % confidence intervals (95 % CI) for associations between specific long COVID symptoms and PTSD symptom trajectories among World Trade Center Health Registry enrollees who self-reported a COVID-19 infection. Models are adjusted for age, sex, race/ethnicity, household income, educational attainment, employment status, number of 9/11 experiences reported, eligibility category, smoking status, BMI category, self-reported diagnosed physical health conditions, and self-reported diagnosed depression.

associated with long COVID (Kostev et al., 2022). However, two studies that examined relationships between pre-existing health conditions and diagnostic codes indicative of COVID-19 in veterans and patients in the United Kingdom reported null and inverse associations with diagnosed PTSD, respectively (Ioannou et al., 2022; Wang et al., 2024). Each of these analyses used EHR data, and relied on recorded diagnoses of PTSD and long COVID or conditions that would indicate COVID-related care. The proportion of individuals in each study with diagnostic codes for long COVID and associated conditions were low (between 1.4 and 13.5 %); because long COVID may be under-documented or documented inconsistently by clinicians, individuals in these studies may not be entirely representative of the long COVID patient population (Henderson et al., 2024; Pfaff et al., 2023; Zhang et al., 2023). This is the first study to examine associations between PTSS and long COVID among a cohort of WTC-exposed individuals, who have a high prevalence of PTSD. While one previous study examined WTC-related

conditions in relation to long COVID risk among WTC responders, PTSD was not included as a predictor (Lhuillier et al., 2022).

Understanding how PTSD may be related to the risk of long COVID requires contextualizing these results in both the proposed pathophysiological mechanisms of long COVID and prior research on the role of PTSD in relation to other health conditions. Emerging evidence suggests that multiple and potentially overlapping mechanisms may underlie long COVID, including viral persistence of SARS-CoV-2 and reactivation of other latent viruses, immune system dysregulation and inflammation, autoimmunity, and endothelial dysfunction (Ahamed and Laurence, 2022; Al-Aly et al., 2024; Swank et al., 2023; Yin et al., 2024). The biological mechanisms linking PTSD to physical health outcomes, including cardiovascular disease and mortality (Edmondson et al., 2013; Giesinger et al., 2020; Nilaweera et al., 2023), are also not definitely known. PTSD is associated with dysregulation of hypothalamic pituitary adrenal axis and autonomic nervous system (Katrinli et al., 2022; Neigh and Ali, 2016; Sumner et al., 2023), and individuals with PTSD have been found to have elevated markers of inflammation and immune dysfunction compared to those without PTSD (Meewisse et al., 2007; Muniz Carvalho et al., 2021; Passos et al., 2015; Sumner et al., 2020; Yang and Jiang, 2020). It has been hypothesized that these changes may be related to increased susceptibility to infectious diseases, including COVID-19. Jiang and colleagues found that PTSD was associated with a higher risk of 28 different incident infections in a registry-based cohort of adults in Denmark (Jiang et al., 2019), and it has been suggested that stress-induced inflammation and immune response may predispose individuals to more frequent or more severe COVID-19 infections (Lamontagne et al., 2021). It is possible that impaired immune response related to chronic stress could increase the risk of developing long-term symptoms after a COVID-19 infection, as insufficient immune response and clinical severity of acute illness have both been identified as risk factors for long COVID (Garcia-Abellan et al., 2021; Wu et al., 2024; Xie et al., 2021). Additionally, previous studies of PTSD and CVD have identified genetic variants that increase the risk of both conditions; some of the association between PTSD and long COVID may similarly be due to common genetic factors (Lukas et al., 2025; Seligowski et al., 2022). Lastly, individuals with PTSD also have higher prevalence of health risk factors, including some that have been linked to long COVID risk, like high BMI and cigarette smoking (van den Berk-Clark et al., 2018). These factors may, to some extent, mediate observed associations between PTSD and long COVID (Subramanian et al., 2022; Whitaker et al., 2022). As knowledge about the pathophysiology of long COVID advances, determining whether associations with PTSD are causal may help inform future efforts to prevent this condition.

Notably, though only 13 % individuals in the remitting PTSS trajectory had probable PTSD at Wave 5, shortly before their acute COVID-19 infection, they had an increased risk of long COVID comparable to enrollees with chronic high or delayed onset PTSS trajectories, of whom 85 % and 54 % had probable PTSD at Wave 5, respectively. Lifetime prevalence of probable PTSD among these groups was similar (93–100 %), suggesting that having high PTSS at any point following exposure to a traumatic event may have consequences for physical health that persist even once these symptoms have decreased. Previous research in the Registry has found that individuals with chronic, remitting, and delayed onset PTSS trajectories had similarly increased risk of self-reported confusion or memory loss compared to those with a resilient trajectory, and that probable PTSD at study enrolment in 2003–04 was associated with risk of heart disease hospitalizations assessed through 2010 and mortality assessed through 2016 (Giesinger et al., 2020; Jordan et al., 2013; Seil et al., 2023). In other populations, however, improvements in PTSS were associated with lower risk of type 2 diabetes, while inconsistent findings have been reported for cardiovascular disease (Gilsanz et al., 2017; Scherrer et al., 2019; Scherrer et al., 2020). Some research also suggests that PTSS that do not meet the criteria for full PTSD may also be associated with poor physical health outcomes and functioning (El-Gabalawy et al., 2018; Pietrzak et al., 2011), and a 2022 study found that subclinical symptoms of depression and anxiety were each shown to increase risk of long COVID relative to individuals with low or no symptoms (Wang et al., 2022).

Estimates of long COVID prevalence can vary widely based on the population examined and the definition used. Among US adults who reported a COVID-19 infection, recent population-based estimates of the proportion who report ever experiencing long COVID symptoms range from 18 % to 30 % (Adjaye-Gbewonyo et al., 2023; Statistics, 2024; Wu et al., 2024). The lifetime prevalence of any self-reported long COVID symptoms in our population was higher than these national estimates. Methodological differences may partially explain these findings: for example, our long COVID survey item specified timing of symptoms, but not duration, while national surveys specified symptoms lasting 3 months or longer. Additionally, while national surveys used a binary survey question asking about any long-term COVID-19 symptoms, the Registry used a checklist of multiple long COVID symptoms. High prevalence of long COVID in the Registry may also be attributable to a high prevalence of conditions linked both to WTC exposure and long COVID risk, including COPD and asthma. Recent work from the Registry indicates that WTC-exposed individuals have poorer health-related quality of life compared to the general population, potentially due to higher prevalence of mental and physical health conditions (Sisti et al., 2025). As long COVID is also associated with poorer functioning and QOL, efforts to address long COVID in this population may be warranted to prevent further decrements in wellbeing.

Our study benefits from longitudinal design, with systematic collection of repeated measures for over nearly 20 years prior to the COVID-19 pandemic. In contrast to previous EHR studies that relied on clinician diagnosis of PTSD, we used self-reported data on PTSS, which enabled us to examine subclinical symptoms that may still be relevant to long COVID risk. However, limitations of our study must be acknowledged. First, our survey question assessing long COVID queried a relatively limited number of specific symptoms, and omitted several that have been found to be part of one or more long COVID clinical phenotypes, including post-exertional malaise and cardiovascular and gastrointestinal symptoms. Many of the specific long COVID symptoms included in our survey overlap with somatic symptoms that have been shown to be increased among individuals with PTSD (e.g., fatigue, insomnia, muscle pain) (Gupta, 2013); however, associations between remitted PTSS and long COVID risk suggests that the observed associations cannot be fully explained by somatic symptoms that are experienced as a result of PTSD. We also did not specify duration of symptoms, while NASEM's recent definition requires symptoms to be present for at least three months to meet criteria for long COVID. Lastly, we relied on self-reported data to identify enrollees with a COVID-19 infection, which may lead to misclassification, particularly of cases occurring early in the pandemic when testing was less widely available, and which may have excluded enrollees with less severe acute infections.

5. Conclusions

Among a WTC-exposed population with over 15 years of follow-up, our analyses showed that individuals who experienced high PTSS were at an increased risk of experiencing long COVID symptoms. Although there are no currently approved treatments for long COVID, a number of long COVID care clinics have been established to provide multidisciplinary care to affected individuals. Our findings suggest that populations who are exposed to trauma or who have high prevalence of PTSD (e.g., disaster survivors or veterans) may benefit from enhanced screening for long COVID, as well as integrated therapies to improve quality of life. For example, new or worsening physical and/or mental health complaints in individuals with a history of PTSD may warrant additional investigation to determine whether long COVID may explain these symptoms. As long COVID itself may exacerbate mental health symptoms, individuals with both long COVID and a history of PTSD may benefit from strategies aimed at reducing mental health impacts.

Additionally, education about reducing risk of acute COVID-19 infection may be particularly important for trauma-exposed populations, to reduce incidence of long COVID in these individuals. Our findings highlight the need for additional research on the potential casual mechanisms underlying associations between PTSS and long COVID, and to identify potential moderators of these associations, both to identify particularly vulnerable individuals and to develop interventions aimed at reducing risk.

Institution and ethics approval and informed consent

The Registry protocol was approved by the US Centers for Disease Control and Prevention (CDC) and the New York City Department of Health and Mental Hygiene (DOHMH) institutional review boards (#02-058). Informed consent was obtained verbally from enrollees at the time of their enrollment.

CRediT authorship contribution statement

Julia S. Sisti: Visualization, Methodology, Conceptualization, Writing – original draft, Software, Formal analysis. **Samuel E. Packard:** Conceptualization, Writing – review & editing. **Janette Yung:** Conceptualization, Writing – review & editing. **Janna Metzler:** Writing – review & editing, Conceptualization, Supervision.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Registry survey documents and de-identified data limited to specific surveys and variables are available at: https://www.nyc.gov/site/911health/about/wtc-health-registry.page. Complete data are not publicly available due to privacy or ethical restrictions; however, additional data may be made available to researchers following review of applications to the Registry.

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