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RESEARCH ARTICLE

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Cross-sectional association between posttraumatic stress and cognition is moderated by pulmonary functioning in world trade center responders

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Abstract

Background: Posttraumatic stress disorder (PTSD) symptomatology and poorer pulmonary function are highly prevalent psychiatric and medical conditions. In the present study, we tested for the individual, additive, and modifying associations of PTSD symptomatology and pulmonary function with cognitive performance.

Methods: In this cross-sectional study, a total of 1,401 World Trade Center (WTC) responders (mean age = 53, SD = 8 years, 92% males) participated in the study. Cogstate assessment measured cognitive performance. PTSD symptomatology was measured using the trauma-specific version of the posttraumatic stress disorder checklist (PCL-17) adapted for the WTC attacks. The 1-second forced expiratory volume and forced vital capacity (FEV1/FVC) ratio was used to measure pulmonary function. Linear regressions with cognitive performance as the outcome were conducted to assess individual, additive, and moderating associations of PTSD symptomatology and pulmonary function.

Results: Higher PTSD symptomatology and poorer pulmonary function were negatively associated with cognitive performance. A 10% increase on the FEV1/FVC ratio moderated the association between PTSD symptomatology and cognition, whereby its association with cognition was stronger when PTSD symptomatology was higher (est. = 0.01, 95%CI = 0.004, 0.01, $p < 0.001$). When stratified by responder type, these associations persisted in trained (est. = 0.01, 95%CI = 0.01, 0.02, $p < 0.001$), but not in non-trained (est. = 0.004, 95% C.I. = −0.01, 0.02, $p = 0.39$) responders.

Conclusions: In the presence of higher PTSD, better pulmonary functioning is associated with better cognitive performance. Early intervention efforts to mitigate preventable cognitive decline in high-risk populations should be studied, especially since intervention in one modality may have an impact on others.

KEYWORDS
cognitive function, posttraumatic stress, pulmonary function, World Trade Center responders

1 | INTRODUCTION

Cognitive function in the World Trade Center (WTC) responders is a clinically significant issue that will become more important in the coming years. Two decades of research since the September 11th 2001 terrorist attacks have shown that this cohort is experiencing rapid physical aging,[1] poor mental health outcomes,[2] and more recently, poor cognitive outcomes.[3] Chronic posttraumatic stress disorder (PTSD) and impaired pulmonary function are signature mental and physical health conditions that often co-occur in veterans and which have also been reported to occur separately [2,4–6] and comorbidly [7–10] in the WTC responders.

Increasing evidence on the associations between the exposures at the WTC and risk or incidence of mild cognitive impairment (MCI) is suggestive of two pathways by which exposures might affect cognition: a psychological distress pathway of unremitting post-traumatic stress, and a physiological pathway of inhalation of airborne neurotoxins and fine particulates affecting lung functioning among other physiological systems.[11,12] We previously reported prospective associations between prevalence of PTSD and incidence of MCI,[13] as well as dose–response prospective associations between exposure to dust and cognitive performance in WTC responders.[14] However, the extent to which the prevalence of one condition (PTSD symptomatology or impaired pulmonary function) may modify the other in its association with cognitive performance has not been investigated.

Our goal in this cross-sectional study was to extend prior work by exploring the potential individual, additive, and moderating associations of pulmonary function and presence of PTSD symptomatology with cognitive performance in responders exposed to the events of 9/11 and its aftermath. Figure 1 illustrates our conceptual model. Finding effect modification between more PTSD symptomatology and poorer pulmonary functioning on cognitive performance would indicate that individuals with high PTSD symptoms and poor pulmonary function need to be prioritized for intervention to reduce their joint disability burden to mitigate against cognitive impairment.

2 | MATERIALS AND METHODS

2.1 | Participants

Participants were recruited from the Stony Brook University (SBU) World Trade Center Health Program (WTC-HP). The WTC-HP is a clinical population supported by the National Institute for Occupational Safety and Health (NIOSH). WTC responders were recruited to clinics through extensive outreach campaigns at union meetings, postal questionnaires, media articles, and >50,000 telephone calls in multiple languages.[15] Stony Brook's clinic has enrolled >12,000 WTC responders living in Nassau and Suffolk counties on Long Island, NY, who worked in rescue and recovery operations during and after September 11th, 2001. Prior work has shown that responders at the SBU clinic are similar in exposure, PTSD burden, and age on September 11, 2001 to the rest of the general responder population, but the SBU responders include more law enforcement personnel,

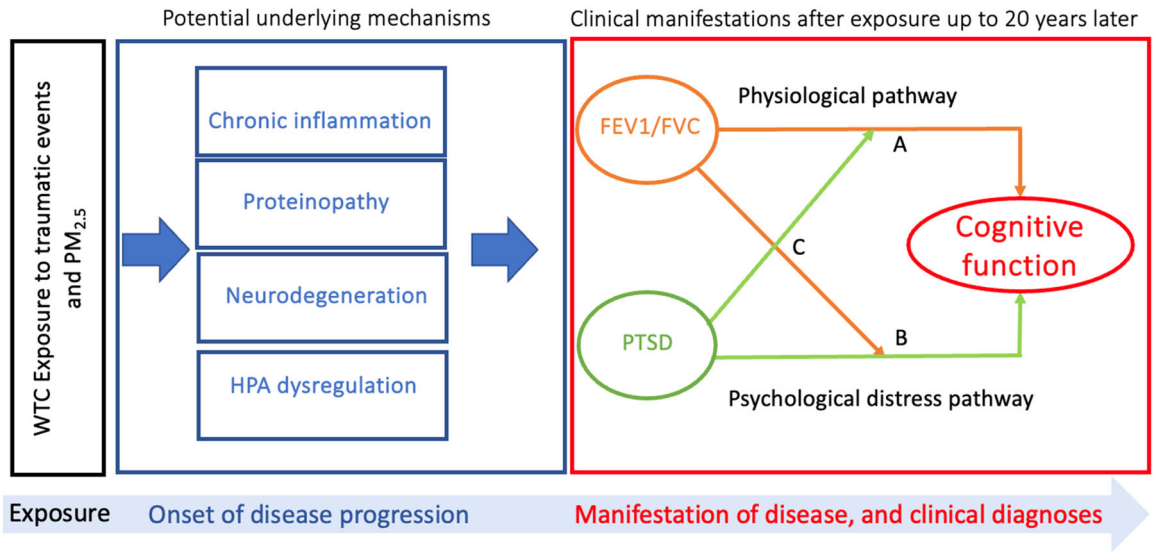

FIGURE 1 The figure illustrates a conceptual model representing associations between pulmonary function, posttraumatic stress, and cognitive function. In the black box on the left is the exposure. The blue box in the middle represents the latent period and represents potential underlying pathways that might be driving our predictor measures (i.e. pulmonary function and posttraumatic stress) that in this study, we are measuring ~1-2 decades after exposure. In the red box on the right are the clinical manifestations that we are studying 20 years after exposure. In this study we are only investigating the orange and green arrows: i) associations between forced expiratory volume in 1 s/forced vital capacity (FEV1/FVC) posttraumatic stress disorder (PTSD) symptomatology and cognition (green arrow B), iii) additive effects of FEV1/FVC and PTSD symptomatology and cognition (orange arrow A + green arrow B), iv) interaction of FEV1/FVC and PTSD symptomatology and cognition (orange and green arrows C).

more men, and fewer responders without a high school degree.[10] SBU runs the second largest clinical center, monitoring >8000 responders living on Long Island, NY. The SBU clinic started operating in 2002 and it began the first and only prospective study to date to assess neuropsychological performance during the monitoring visits.[16]

Eligibility criteria for this study are described elsewhere.[14] Briefly, the study cohort includes a random sample of individuals first seen in 2015, retrieved from a population monitoring program. The sample is closed to enrollment, though individuals who refused the initial wave were invited to participate in follow-up data collection efforts. It includes trained first responders and untrained construction and volunteer responders who helped in search, recovery, and clean-up operations following the terrorist attacks of September 11th, 2001. Responders were included in this analysis if upon enrollment they did not have a diagnosis of dementia, completed a validated neuropsychological assessment, and had valid information on spirometry and PTSD symptoms.

2.2 | Population for analysis

This study was cross-sectional and used only baseline data collected between January 01, 2014 and December 31, 2015 during regular monitoring visits among responders who were fluent in English. Thus, cognitive ability, posttraumatic stress symptomatology, and pulmonary function were based on responders' scores from their baseline evaluation in 2014/15. The response rate for the baseline neuropsychological assessment for eligible responders was 95.6%. For these analyses, we required participants to have passed the Quality Control Grade for pulmonary assessment at >1 which indicates that the test is acceptable. Of a total of 1499 participants who completed cognitive, mental health, and physical assessments, 98 did not pass quality control. Therefore, a total of 1401 responders who completed baseline evaluation were included in these analyses.

2.3 | Ethics

The Stony Brook University Institutional Review Board approved this study. Responders provided informed consent.

2.4 | Cognitive performance

Cognitive performance was the outcome of interest. It was measured using the CogState Brief Battery (www.cogstate.com), which is a computer-administered neuropsychological test that was developed to detect small changes in cognition across multiple domains.[17–19] It associates well with traditional paper-and pencil neuropsychological tests, with impairment status, and with Alzheimer's Disease biomarkers such as amyloid and tau.[20] It has shown high test-retest reliability and stability in individuals with no impairment, with mild cognitive impairment, and with dementia,[21] and high sensitivity and specificity in identifying MCI and AD dementia.[22] The Cogstate measures cognitive performance using three game-life tasks that involves repeated trials using a virtual deck of playing cards displayed on a green background. Participants first receive instructions and then interact with the games using two keys on a keyboard marked "Y" for yes, and "N" for no.

There are three tasks, each of which includes 30–88 independent trials, with overall measures being averaged across all trials within each task: The first task, *Detection*, is a simple reaction-time task, whereby one card at a time is flipped over and it asks the participant to tap the "Y" button as quickly as possible when the card is flipped and the Black Joker is displayed. The average speed (answers/second) in which detection tasks are completed was taken to measure **reaction speed**. The second task, *Identification*, is a choice-reaction time, whereby one card is flipped over and either a black or a red joker is displayed. The correct response is to as quickly as possible tap the "Y" button for the Red Joker, and to tap the "N" button for the Black Joker. The average number of correct answers (answers/second) was used to measure **processing speed**. The third task is an n-back task referred to as *One-Card Learning*, and it begins by sequentially flipping over a card that randomly displays one of the 52 cards found in the common deck of playing cards; participants had to answer whether they had seen that card before. The average arcsine probability of correct responses was used to measure **visual memory**. To create an overall index of cognitive performance, the measures were standardized using a mean of 0 and a standard deviation of 1, and the average across measures was used. A higher total score on the CogState composite score indicates better cognitive performance.

2.5 | Posttraumatic stress

Posttraumatic stress symptomatology was our first predictor of interest. It was assessed using the PTSD Checklist (PCL-17),[23] tailored to the WTC disaster to assess symptoms related to experiences at the WTC. The PCL-17 is a 17-item self-report measure assessing the criterion symptoms listed in the Diagnostic and Statistical Manuel of Mental Disorders (DSM-IV). Participants were asked to rate problems that they were bothered by in the past month in relation to 9/11 on a scale of 1 (not at all) to 5 (extremely). The scale was summed with scores ranging from 17 to 85, with higher scores reflecting more severe symptomatology.

2.6 | Pulmonary function

Pulmonary function was our second predictor of interest. It was evaluated with the EasyOne spirometer (ndd Medical Technologies) using standard techniques.[24–26] Spirometry is a simple and quick procedure where patients are asked to take maximal inspiration and then forcefully expel air for as long and as quickly as possible.[27] From spirometry we calculated forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), and the ratio of the two volumes (FEV_1/FVC). Higher spirometry values mean better pulmonary function.

2.7 | Covariates

Potential confounders which we adjusted for included age (days) at each visit, sex, height, and education. Since >98% of responders had a high school degree, we used completion of university as a dichotomous variable (yes/no to university degree) to represent education. We also considered other potential confounders including responder type which we categorized into trained responder versus non-trained responders for example construction and utility workers; smoking status (ever vs never); and comorbidity including history of hypertension, stroke, or heart attack.

2.8 | Statistical analysis

Data on responder demographics and potential risk factors were summarized as means and standard deviations for continuous variables and as frequencies and percentages for categorical variables. T-tests and χ^2 tests were used to compare continuous and categorical variables between responder types (trained vs. non-trained), respectively.

Multivariable linear regression models were employed to examine the baseline associations of pulmonary function and PTSD symptomatology with the overall index of the Cogstate, our outcome. In Models 1 and 2, the continuous PCL-17 score and FEV1/FVC ratio were main predictors, respectively. In Model 3, we included both the PCL-17 and the FEV1/FVC ratio to test additive associations, and in Model 4 we additionally included the interaction term of PCL-17 and FEV1/FVC ratio to test for effect-modification. All models were adjusted for the same covariates, noted above. Complete data were used and therefore participants missing in any of predictors, or covariates, included in the multivariable analysis were excluded.

To investigate the associations between pulmonary function and cognitive performance across various levels of psychological distress, in additional models, we analyzed the association between the continuous measure of the FEV1/FVC ratio and cognitive performance across three categories of posttraumatic stress symptomatology: no PTSD: PCL-17 ≤22), subsyndromal PTSD: PCL-17: 23–43, and probable PTSD: PCL-17≥44.

To examine whether the relationships of pulmonary function and PTSD symptomatology with cognitive performance varied by responder-type we also repeated all models by stratifying analyses into trained and non-trained responders. Prior literature[12] showed there might be a healthy-responder effect in that, trained responders in this instance, police officers, might be more resilient to potential physical and mental effects, than non-trained responders such as construction workers who helped in rescue and recovery, due to lack of prior exposures and training.

3 | RESULTS

3.1 | Descriptive characteristics

A total of 1401 responders (mean age = 53 years, 92% male, 32% with a university degree) were included in these analyses. The mean Cogstate score was 0.02 (SD = 0.6), mean on the PCL-17 was 28 (SD = 12.4) and the mean FEV1/FVC ratio was 82.1 (SD = 5.6). Most responders were non-smokers (67%) (Table 1). Cogstate was correlated with the PCL-17 ($r = -0.19$, $p < 0.001$) and with FEV1/FVC ($r = 0.07$, $p = 0.02$). The PCL-17 score and FEV1/FVC were not correlated with each other ($r = 0.02$, $p = 0.57$). When stratified by responder type, correlation coefficients were similar to the full

TABLE 1 Descriptive characteristics of the total study sample and stratified by responder type.

	Total (n = 1,401)	Trained responders (n = 1,080)	Non-trained responders (n = 321)
Age, y (SD)	53 (8.1)	51.5 (6.9)	57.8 (9.3)
Sex, M (%)	1,285 (91.7%)	981 (90.8%)	304 (94.7%)
University degree, (%)	448 (32.1%)	361 (33.4%)	87 (27.1%)
COGSTATE, sum (SD)	0.02 (0.6)	0.05 (0.6)	−0.1 (0.7)
PCL-17, sum (SD)	27.5 (12.4)	26.7 (12.0)	30.5 (13.4)
FEV1/FVC (SD)	82.1 (5.6)	82.4 (5.5)	81.2 (5.7)
Current smokers (%)	78 (6%)	55 (5.1%)	23 (7.2%)
Previous smokers (%)	390 (28%)	248 (23%)	142 (44.2%)
Never smokers (%)	933 (67%)	777 (71.9%)	156 (48.6%)
Hypertension (%)	355 (25%)	255 (23.6%)	100 (31.2%)
History of stroke (%)	13 (1%)	9 (0.8%)	4 (1.3%)
History of heart attack (%)	91 (7%)	62 (5.7%)	29 (9.0%)

Note. FEV1, Forced Expiratory Volume; FVC, Forced Vital Capacity; PCL, Posttraumatic checklist.

TABLE 2 Linear regression model examining the association of the higher posttraumatic stress disorder symptomatology using the PCL-17% and 10% increase in forced expiratory volume in 1 s/forced vital capacity ratio on the Cogstate performance in all responders and stratified by responder-type.

		Whole sample $N = 1,401$			Trained responders $N = 1,080$			Non-trained responders $N = 312$		
		B (95%CI)	*β* (95%CI)	*p*	*B* (95%CI)	*β* (95%CI)	*p*	*B* (95%CI)	*β* (95%CI)	*p*
M1	PCL-17	**−0.01 (−0.01, −0.01)**	**−0.21 (−0.26, −0.15)**	**<0.001**	**−0.001 (−0.001, −0.01)**	**−0.20 (−0.26, −0.13)**	**<0.001**	**−0.01 (−0.02, −0.01),**	**−0.23 (−0.35, −0.12)**	**<0.001**
M2	FEV1/FVC	**0.08 (0.02, 0.15)**	**0.07 (0.02, 1.13)**	**0.01**	0.06 (−0.01, 0.14)	0.06 (−0.01, 1.12)	0.08	0.12 (−0.03, 0.27)	0.10 (−0.03, 0.23)	0.12
M3	PCL-17	**−0.01 (−0.01, −0.01)**	**−0.21 (−0.26, −0.15)**	**<0.001**	**−0.01 (−0.01, −0.01)**	**−0.20 (−0.26, −0.13)**	**<0.001**	**−0.01 (−0.02, −0.01)**	**−0.24 (−0.35, −0.13)**	**<0.001**
	FEV1/FVC	**0.09 (0.03, 0.15)**	**0.08 (0.02, 1.14)**	**0.01**	0.07 (−0.003, 0.14)	0.06 (−0.003, 1.24)	0.06	0.14 (−0.01, 0.28)	0.12 (−0.01, 0.25)	0.07
M4	PCL-17* FEV1/FVC	**0.01 (0.004, 0.014)**	**1.51 (0.66, 2.34)**	**<0.001**	**0.01 (0.004, 0.02)**	**1.71 (0.73, 2.69)**	**<0.001**	0.004 (−0.01, 0.02)	0.79 (−1.00, 2.59)	0.39

Note: Results show both the unstandardized (B) and standardized (β) betas and 95% confidence intervals (CI), and p-value.All models have been adjusted for age, sex, education, responder type, smoking history, hypertension, history of stroke, and history of heart attack. The regression coefficients of PTSD symptomatology indicate the change of cognitive performance by 1 score increase on the PCL-17. The regression coefficients of FEV1/FVC indicate the change of cognitive performance by 10% increase on the FEV1/FVC ratio. PCL-17*FEV/FVC indicates the interaction of the PCL-17 and FEV/FVC variables. Bold typeface was used to highlight statistically significant results.

Abbreviations: FEV1, Forced Expiratory Volume; FVC, Forced Vital Capacity; PTSD, posttraumatic stress disorder.

sample. About a quarter of responders had hypertension, and 6% had a myocardial infarction, but only a few responders had a stroke (1%).

When stratified by responder-type, non-trained responders ($N = 321$, 23%), were less likely to have completed college, had higher PCL-17 scores, had a lower FEV1/FVC ratio, and performed worse on the CogState as compared to trained responders. A higher percentage of non-trained responders were previous or current smokers as opposed to non-smokers (Table 1).

3.2 | Posttraumatic stress symptomatology, pulmonary function, and cognitive performance

In separate linear regression models, PTSD symptomatology and FEV1/FVC ratio were associated with cognitive performance; a one-point increase on the PCL-17 was associated with 0.01 points lower cognitive performance on the Cogstate; while a 10% increase on the FEV1/FVC ratio was associated with an increase of 0.08-point higher on the Cogstate. In standardized terms, this means that a standard deviation increase on the PCL-17 was associated with 0.21 standard deviations lower on the Cogstate, while a standard deviation increase on the FVE1/FVC ratio was associated with 0.07 higher standard deviations. When both the PCL-17 and the FEV1/FVC ratio were included in the same model, both predictors remained independently associated with cognitive performance, with the PCL-17 remaining a stronger predictor (one-point increase on PCL-17: est. = −0.01, 95% CI = (−0.01, −0.01), $p < 0.001$; 10% increase on FEV1/FVC ratio: est. = 0. 09, 95% CI = (0.03, 0.15), $p = 0.006$). In standardized terms, a standard deviation higher on the PCL-17 was associated with 0.21 standard deviations lower on the Cogstate while 1 standard deviation higher on the FEV1/FVC was associated with 0.08 standard deviations higher (Table 2). In Figure 2 we compare the results from the models; the slope of the PCL-17 became slightly steeper by adjusting for FEV1/FVC, from panel A (Model 1) to panel C-1 (Model 3) while the slope of FEV1/FVC became steeper by adjusting for PCL-17, from panel B (Model 2) to panel C-2 (model 3). Lastly, a significant interaction between PCL-17 and FEV1/FVC on cognitive performance was also found in that the association between a higher score on the PCL-17 and cognitive performance is reduced in the presence of higher FEV1/FVC (est. = 0.01, 95% CI = (0.004, 0.014); standardized est. = 1.51; 95% CI = 0.66, 2.34, $p < 0.001$) indicating effect-modification (Figure 3).

We investigated this moderating effect further by stratifying participants into groups of no PTSD (PCL-17 ≤22), subsyndromal PTSD (PCL-17: 23–43), and probable PTSD (PCL-17 ≥44). The majority of participants were in the no-PTSD group ($n = 628$, 50%), followed by subsyndromal PTSD ($n = 494$, 39%), and probable PTSD ($n = 144$, 11%). We ran three linear regression models using the FEV1/FVC ratio as the predictor and the sum on the Cogstate as the outcome, and adjusting for the same covariates. Results indicated that the positive associations between higher pulmonary function and cognitive performance are stronger in individuals with higher PTSD symptomatology. Specifically, while there was no association between pulmonary function and cognitive performance in the no

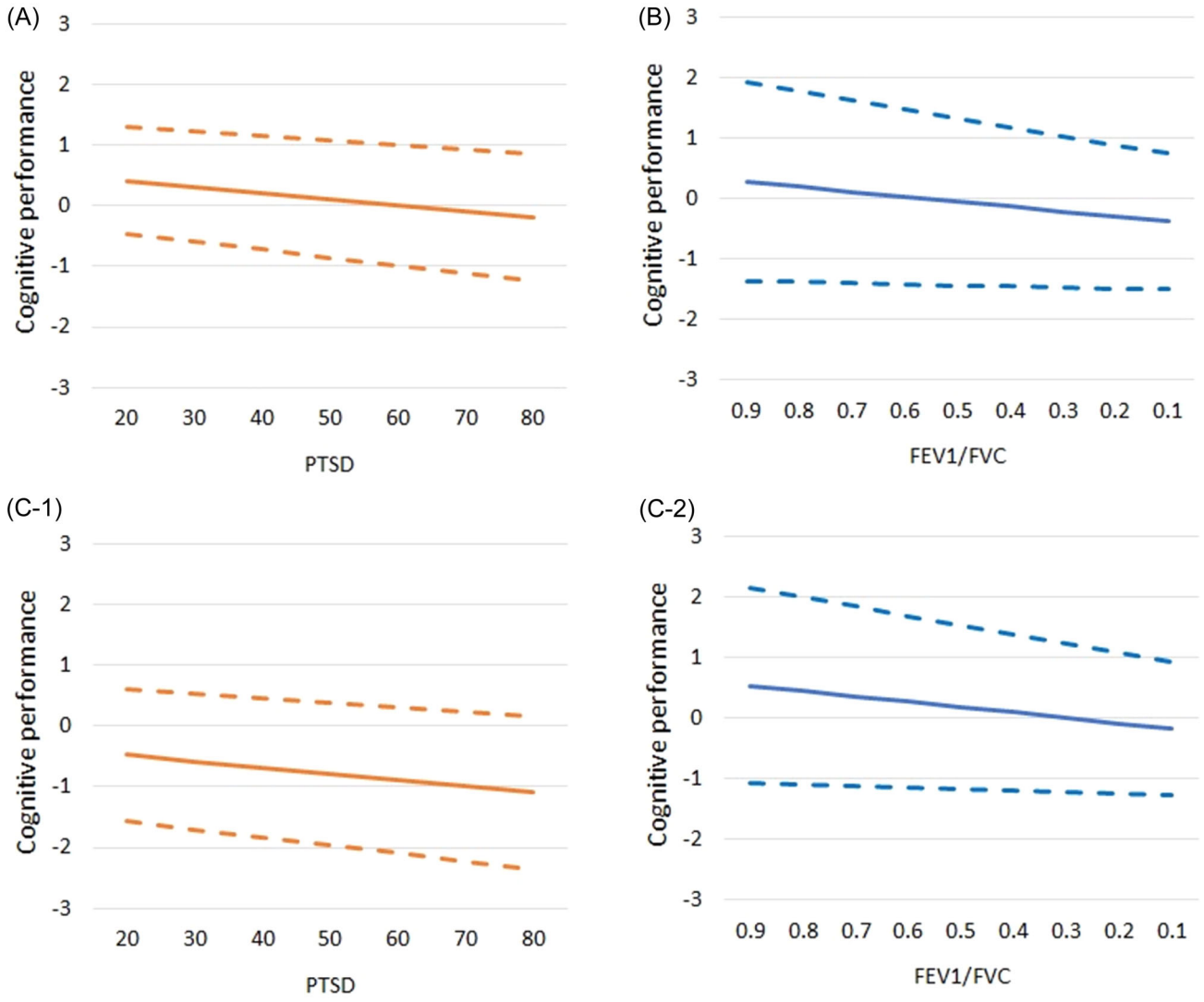

FIGURE 2 The y-axis is the predicted value for cognitive performance. The x-axis is posttraumatic stress disorder (PTSD) on panels A and C-1 and forced expiratory volume in 1 s/forced vital capacity (FEV1/FVC) on panels B and C-2. We reversed the value on FEV1/FVC from 0.9 to 0.1 on panels B and C-2 to make the slopes of regression lines in the same direction as those by PTSD on panels A and C-1. Solid line is the estimated regression lines and dashed lines are the corresponding 95% CI: (A) is from model 1 where the main predictor is PTSD; (B) is from model 2 with the main predictor being FEV1/FVC. (C-1 and C-2) are from model 3 where PTSD and FEV1/FVC are main predictors.

PTSD group, we found that in the subsyndromal PTSD group, as FEV1/FVC ratio increases by 10%, cognitive performance scores increase by 0.09 points although this association was not statistically significant (95% CI: −0.01, 0.18, $p = 0.07$). In the probable PTSD group, we found that for every 10% increase on the FEV1/FVC ratio, cognitive performance score increases by 0.25 points (est = 0.25, 95% CI = (0.03, 0.47) or in standardized terms, by 0.21 standard deviations (95%CI = 0.23, 4.88), $p = 0.03$).

We repeated all analyses stratifying the sample by responder type. In total, we had data for 1080 trained responders, and 321 non-trained responders. Trained responders were younger than non-trained responders (mean age = 51.5, SD = 6.9 vs. 57.8, SD = 9.3) and had a healthier profile; specifically fewer current smokers (5% vs 7%), lower hypertension rates (23% vs. 31%), and lower history of heart attack (5% vs. 9.0%)). Trained responders also scored higher on the CogState (mean = 0.05, SD = 0.6 vs. mean = −0.1 SD = 0.7), had better pulmonary function (FEV1/FVC max = 82.4 SD = 5.5 vs. 81.2 SD = 5.7) and reported less PTSD symptomatology (mean = 26.7, SD = 12.0, vs. mean = 30.5, SD = 13.3).

We found that in trained responders, the association between a 10% higher on FEV1/FVC ratio and cognition was not statistically significant (est. = 0.06, 95% CI = (−0.01, 0.14), $p = 0.08$), while a one-point increase on the PCL-17 was associated with lower cognitive performance (est. = −0.001, 95% CI = (−0.001, −0.01), standardized estimate = −0.20, 95%CI = −0.26, −0.13, $p < 0.001$). When entered together in the same model, the PCL-17 remained associated with lower cognitive performance (PCL-17: est. = −0.010, 95% CI = (−0.01, −0.01), standardized estimate = −0.20, 95%CI = −0.26,

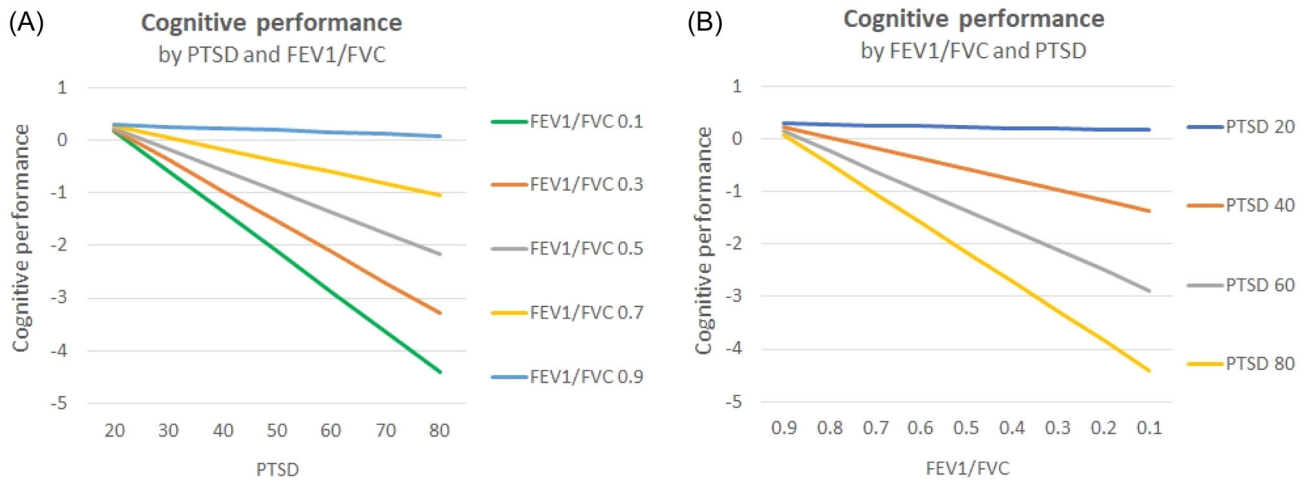

FIGURE 3 The y-axis is the predicted value for cognitive performance. Solid lines are the regression lines estimated from model 4 with the interaction of posttraumatic stress disorder (PTSD) and forced expiratory volume in 1 s/forced vital capacity (FEV1/FVC). 95% CIs not presented to ease visualization. (A) The x-axis is posttraumatic checklist total score (B) The x-axis is FEV1/FVC reversed from 0.9 to 0.1 to make the slopes of regression lines in the same direction as those by PTSD on panel A. Panel A shows the association of PTSD and cognitive performance by different FEV1/FVC values while Panel B shows the association of FEV1/FVC and cognitive performance by different PTSD scores.

−0.13 $p < 0.001$; 10% on FEV1/FVC: est. = 0.07, 95% CI = (−0.03, 0.14), standardized estimate for 1 standard deviation high on FEV1/FVC = 0.06, 95%CI = −0.003, 1.24, $p = 0.06$). When including the interactive effect of PCL-17 and FEV1/FVC with cognitive function in trained responders, results were statistically significant (est. = 0.01, 95% CI = (0.004, 0.02), standardized estimate = 1.71, 95%CI = 0.73, 2.69, $p < 0.001$, Table 3).

We further investigated this association by stratifying the participants into three PTSD groups as described above, although when we stratified further, the number of observations was relatively low, so parameters were estimated with comparatively low precision. Overall, we found a similar pattern of results to the full sample. Specifically, we found no association of pulmonary function on cognitive performance in the no PTSD group for both trained and non-trained responders, but the association of pulmonary function on cognition became stronger with more PTSD severity. Specifically in trained responders, we found that for subsyndromal PTSD, a 10% increase on FEV1/FVC was associated with better cognitive performance (est. = 0.11, 95% CI = (0.01, 0.21), $p = 0.03$; i.e. a 1 standard deviation higher on FEV1/FVC ratio was associated with 0.12 high standard units on the Cogstat, 95%CI = 0.01, 0.22), and in non-trained responders, we found an association in the probable PTSD group (est. = 0.46, 95% CI = (0.11, 0.81), standardized estimate = 0.49, 95%CI = 0.12, 0.86; $p = 0.01$) (Table 3).

4 | DISCUSSION

In this cross-sectional study, we sought to investigate the individual, additive, and moderated associations of posttraumatic stress and pulmonary function on cognitive performance in 9/11 WTC responders. We found evidence for effect-modification, in that the negative association between higher PTSD symptomatology and cognitive performance was stronger among responders with lower pulmonary function, such that there was no relationship between more PTSD symptomatology and cognitive performance among responders with better pulmonary function. Put differently, the positive associations between better pulmonary function and higher cognitive performance were stronger in participants with more posttraumatic stress. Therefore, our results are supportive of an interactive model of co-morbidity,[28] implying that the presence of higher physical ability (or disability), might alter the association of higher psychological distress with cognitive outcomes. Results are also broadly consistent with a diathesis-stress model of cognitive dysfunction,[29] whereby the effect of an exogenous stressor, captured by individual differences in PTSD symptomatology, depends on one or more underlying vulnerability, for example, compromised pulmonary function.

Prior work from our team has shown that up to a quarter of WTC responders have comorbid chronic PTSD and pulmonary abnormalities[7–10]; and that these conditions adversely impact cognition independently.[3,14,16] Further work has shown associations between dust exposures on and after 9/11 and increased risks of cognitive impairment[30] and incidence of dementia[31] Indeed, co-occurrence of PTSD and pulmonary abnormalities might indicate shared risk factors, such as exposure to the event or time worked onsite. Prior work reporting high associations between the frequency of these two conditions has shown that responders who were severely exposed to the dust cloud were more likely to experience co-morbid pulmonary abnormalities and PTSD than either condition alone.[7] Our results are consistent with the growing body of literature supporting evidence for a close and synergistic association between mental health and

TABLE 3 Linear regression models examining the association of 10% increase of forced expiratory volume in 1 s/forced vital capacity max ratio with the Cogstate performance by posttraumatic stress disorder categories, in all responders and in trained responders.

	Whole sample *N* = 1,401			Trained responders *N* = 1,080			Non-trained responders N = 321		
PCL-17	*N*	*B* (95%CI)	*β* (95%CI)	*p*	N	*B* (95%CI)	*β* (95%CI)	*p*	N	*B* (95%CI)	*β* (95%CI)	*p*
≤22	622	0.03 (−0.06, 0.12)	0.03 (−0.05, 0.11)	0.52	507	0.001 (−0.01, 0.10)	0.001 (−0.09, 0.09)	0.99	115	0.16 (−0.06, 0.38)	0.15 (−0.05, 0.34)	0.15
23– 43	469	0.09 (−0.01, 0.18)	0.09 (−0.07, 1.76)	0.07	335	**0.11 (0.01, 0.21)**	**0.12 (0.01, 0.22)**	**0.03**	134	−0.06 (−0.29, 0.17)	−0.05 (−0.24, 0.14)	0.61
≥44	**127**	**0.25 (0.03, 0.47)**	**0.21 (0.23, 4.88)**	0.03	88	0.19 (−0.09, 0.47)	0.14 (−0.07, 0.35)	0.19	38	**0.46 (0.11, 0.81)**	**0.49 (0.12, 0.86)**	**0.01**

Note.& Results show both the unstandardized (B) and standardized (β) betas and 95% confidence intervals (CI), and p-value.All models have been adjusted for age, sex, education, smoking history, hypertension, history of stroke, and history of heart attack. The model in the whole sample was further adjusted for responder type that is trained or untrained. Bold typeface used to highlight statistically significant results.

physical illness,[32–36] specifically between compromised pulmonary function and PTSD in the WTC cohort.[7–9]

Our results are supportive of the buffering hypothesis, which refers to a protective (buffering) factor that weakens the association between an adverse risk factor and an outcome.[37] The resilience field conceptualizes physiologic resilience as the capacity to cope, adapt, or recover in response to changes in physiologic demands, and is phenotypically referred to as robustness.[38] Within this context, a more robust physiological system might be better able to circumvent the negative consequences of added stress on the brain.[38] Indeed, our results indicated that the positive association between higher pulmonary function and cognitive performance become observable in the presence of more PTSD symptomatology. These results were further supported when we stratified responders into PTSD groups, which revealed evidence for a threshold where the benefit of having some physiological reserve capacity to modify the outcome might be effective. Further, it might be useful to think of other physiological systems that might modify associations, and whether, similar to exposure therapy, individuals might be trained to increase physiologic resilience by building stress resistance via intentional exposure to stressors to gain immunity.[39] Indeed, while we noted evidence for a healthier profile in the trained responders, given the small sample size of the non-trained responders, we were probably underpowered to adequately detect associations. However, prior work has shown differential prevalence rates of PTSD and respiratory symptoms in trained and non-trained responders, owing to potential qualitative differences between these two populations which might be explained via the healthy-worker model with trained responders possibly having some added resilience due to continuous training and prior exposure to trauma.[9] Being a non-trained responder, whom in our sample consisted mainly of construction workers, might also reflect other broader risk factors that were not measured here, such as poorer access to health care both before and after 9/11, and physical health risks such as exposure to airborne dust and other pollutants that might have happened before 9/11.

Elucidating the mechanisms of how the respiratory system moderates the association between higher reporting of PTSD symptomatology and cognitive outcomes is an important gap in knowledge. Chronic inflammation of the lungs can release cytokines into the blood, resulting in neuronal damage to negatively impact cognitive function.[40–42] The associations of PTSD and pulmonary function with cognition might also be reflective of shared underlying neurodegenerative mechanisms. While these links are not fully understood, the latency period between WTC exposure and emerging cognitive impairment two decades later,[14,16] is suggestive of an insidious cascade of underlying mechanisms. Abnormal spirometry and PTSD are thought to operate via the same underlying neurobiological mechanisms that eventually affect cognition. Potential mechanisms include oxidative stress pathways that affect the central nervous systems leading to adverse health outcomes,[43–45] inflammatory disease pathways that alter inflammatory processes, such as c-reactive protein, a marker of systemic inflammation,[46,47] and immunological pathways that solicit a chronic immune response

which may alter DNA methylation patterns potentially associated with peripheral immune dysregulation.[48,49] PTSD is thought to operate via several biological pathways, including genes hypothesized to play a role in the hypothalamic pituitary adrenal (HPA) axis and the autonomic nervous system, causing physiological dysregulation of allostasis and high "allostatic load"[50,51]; pathways regulating synaptic plasticity, oxytocin signaling, altered inflammatory processes, and pathways related to cardiovascular and metabolic disease, the nervous system, and cancer.[52] These hypotheses suggest that PTSD is possibly better defined as an pathological neurobiological stress response that results in psychological symptoms, rather than being defined by the psychological symptoms themselves. Indeed the moderation of better pulmonary function in the presence of worse symptomatology support the notion that possibly prior system integrity, or the tendency for complex systems in the body to respond more efficiently to high "allostatic load," might mitigate consequences of neurobiological stress on cognition, better respond to challenges, and return to equilibrium.[53] Future research will need to elucidate further common mechanisms that might be driving physical and mental health pathways.

The study has some limitations. The results of this study were limited by its cross-sectional design and thus we cannot infer causation; we also cannot rule out reverse causation i.e. that participants with lower cognition function are at higher risk of experiencing PTSD symptomatology and worse physical health; however in prior work within this cohort we have shown that PTSD was associated with the onset of incident cognitive impairment[3] ruling out potential reverse causality. Nonetheless, investigating these variables longitudinally would better inform on the potential consequences of poor health on cognitive outcomes over time. Longitudinal analyses in this cohort are ongoing, thus there will be opportunity for future analyses. Further, most responders were professionally trained, with only a subset being non-trained volunteers. Consequently, statistical power might have been an issue for the non-trained group, especially when considering stratified analyses, and thus associations were estimated with low precision. Analyses should be replicated in larger samples.

Understanding the complex associations and interactions of PTSD symptomatology and pulmonary function on cognitive health necessitates the investigation of shared risk factors that influence these variables, such as duration and intensity of exposure while on site. Prior work has shown that risk for psychopathology was greater for individuals who were more proximate to the site of a terrorist attack,[54] and those with severe dust exposure in the aftermath of 9/11 were more likely to have co-morbid respiratory symptoms and PTSD, than either condition alone.[7] Further, there might be qualitative differences between responders who worked at the site for a longer duration than those who never returned. Our study is limited in that we did not investigate these findings in relation to the duration of exposure. Future research is urged to investigate the effects of duration of exposure on physical, mental, and cognitive outcomes, and elucidate underlying biological mechanisms in populations with varying exposures.

Considering the above limitations, our results still have several clinical implications. First, our findings emphasize the association between more severe PTSD symptomatology and cognitive function in all first responders, thereby highlighting the importance of maintaining and understanding mental health outcomes. Yet, we also found that reduced pulmonary functioning was associated with lower cognitive performance, especially in the presence of PTSD, highlighting the potential for PTSD to engender or identify vulnerability to medical comorbidities. While better pulmonary functioning seems to have protective effects, individuals with comorbid pulmonary abnormalities and posttraumatic stress might need more immediate intervention. Second, responders who have not been professionally trained to deal with traumatic events might be a higher-risk group in displaying worse outcomes, particularly impairment operating via physical and mental health pathways, which could be prevented. Third, PTSD has been previously associated with higher risk of death.[55] Given the high proportions of comorbid PTSD and pulmonary abnormalities in the WTC, as well as emerging cognitive problems, our findings reinforce the need to adequately manage care especially in vulnerable groups experiencing comorbid conditions by integrating medical and psychiatric health.

AUTHOR CONTRIBUTIONS

Jaeun Choi: Methodology; analysis, and interpretation of data; final approval of version to be published; writing—original draft; project administration. **Charles B. Hall:** Conceptualization; methodology; acquisition of data; analysis, and interpretation of data; final approval of version to be published; writing—original draft; supervision; project administration; funding acquisition. **Sean A.P. Clouston:** Methodology; conceptualization; acquisition of data; final approval of version to be published; data curation; writing—review and editing; project administration; funding acquisition. **Krystal L. Cleven:** Final approval of version to be published; writing—review and editing. **Frank D. Mann:** Final approval of version to be published; writing—review and editing. **Benjamin J. Luft:** Acquisition of data; final approval of version to be published; writing—review and editing. **Andrea R. Zammit:** Conceptualization; methodology; analysis, and interpretation of data; final approval of version to be published; writing—original draft; project administration; funding acquisition.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

DISCLOSURE BY AJIM EDITOR OF RECORD

John Meyer declares that he has no conflict of interest in the review and publication decision regarding this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS APPROVAL STATEMENT

The Stony Brook University Institutional Review Board approved this study. Responders provided informed consent.

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