ORIGINAL ARTICLE

Posttraumatic Stress Disorder and the Risk of Respiratory Problems in World Trade Center Responders: Longitudinal Test of a Pathway

Roman Kotov, PhD, Evelyn J. Bromet, PhD, Clyde Schechter, MD, Julie Broihier, MA, Adriana Feder, MD, George Friedman-Jimenez, MD, DrPH, Adam Gonzalez, PhD, Kathryn Guerrera, AS, Julia Kaplan, MPH, Jacqueline Moline, MD, Robert H. Pietrzak, PhD, Dori Reissman, MD, MPH, Camilo Ruggero, PhD, Steven M. Southwick, MD, Iris Udasin, MD, Michael Von Korff, ScD, and Benjamin J. Luft, MD

ABSTRACT

Objective: Posttraumatic stress disorder (PTSD) is associated with high medical morbidity, but the nature of this association remains unclear. Among responders to the World Trade Center (WTC) disaster, PTSD is highly comorbid with lower respiratory symptoms (LRS), which cannot be explained by exposure alone. We sought to examine this association longitudinally to establish the direction of the effects and evaluate potential pathways to comorbidity.

Methods: 18,896 responders (8466 police and 10,430 nontraditional responders) participating in the WTC–Health Program were first evaluated between 2002 and 2010 and assessed again 2.5 years later. LRS were ascertained by medical staff, abnormal pulmonary function by spirometry, and probable WTC-related PTSD with a symptom inventory.

Results: In both groups of responders, initial PTSD (standardized regression coefficient: $\beta = 0.20$ and 0.23) and abnormal pulmonary function ($\beta = 0.12$ and 0.12) predicted LRS 2.5 years later after controlling for initial LRS and covariates. At follow-up, LRS onset was 2.0 times more likely and remission 1.8 times less likely in responders with initial PTSD than in responders without. Moreover, PTSD mediated, in part, the association between WTC exposures and development of LRS ($p < .0001$). Initial LRS and abnormal pulmonary function did not consistently predict PTSD onset.

Conclusions: These analyses provide further evidence that PTSD is a risk factor for respiratory symptoms and are consistent with evidence implicating physiological dysregulation associated with PTSD in the development of medical conditions. If these effects are verified experimentally, treatment of PTSD may prove helpful in managing physical and mental health of disaster responders.

Key words: pulmonary health, PTSD, mental-physical comorbidity, occupational medicine, disaster, 9/11.

INTRODUCTION

Responders to the 2001 World Trade Center (WTC) attacks experienced multiple environmental exposures and psychological traumas during the rescue, recovery, and clean-up efforts at Ground Zero and nearby sites (1,2). Approximately 90,000 responders participated, including police and firefighters with training in disaster response

BMI = body mass index, **FVC** = forced vital capacity, **LRS** = lower respiratory symptoms, **PTSD** = posttraumatic stress disorder, **WTC** = World Trade Center

From the Departments of Psychiatry (Kotov, Bromet, Gonzalez) and Medicine (Broihier, Guerrera, Luft), Stony Brook University, Stony Brook, New York; Department of Family & Social Medicine (Schechter), Albert Einstein College of Medicine, New York, New York; Departments of Psychiatry (Feder, Pietrzak, Southwick) and Preventive Medicine (Kaplan), Mount Sinai School of Medicine, New York, New York; Departments of Population Health (Epidemiology), Medicine and Environmental Medicine (Friedman-Jimenez), New York University School of Medicine and Bellevue Hospital Center, New York, New York; Department of Population Health (Moline), North Shore–LIJ Health System, Great Neck, New York; Department of Psychiatry (Pietrzak, Southwick), Yale University School of Medicine, National Center for Posttraumatic Stress Disorder, VA Connecticut Healthcare System, West Haven, Connecticut; Office of the Director National Institute for Occupational Safety and Health (Reissman), Washington, DC; Department of Psychology (Ruggero), University of North Texas, Denton, Texas; Environmental and Occupational Health Sciences Institute (Udasin), University of Medicine & Dentistry of New Jersey, Piscataway, New Jersey; and Group Health Research Institute (Von Korff), Group Health Cooperative, Seattle, Washington.

Address correspondence and reprint requests to Roman Kotov, PhD, Department of Psychiatry, Stony Brook University, Stony Brook, NY 11794. E-mail: roman.kotov@stonybrook.edu

Received for publication March 3, 2014; revision received January 8, 2015.

DOI: 10.1097/PSY.0000000000000179

and individuals with no prior training, such as construction workers, electricians, and transportation workers. Ten percent to 30% of responders report emotional or medical problems (3–5). Nontraditional responders show particularly high rates, unlike police officers, many of whom were trained in disaster response (4,5). The psychiatric and physical conditions are frequently comorbid (4,6,7). The high comorbidity is consistent with studies of combat veterans (8), general population samples (9–12), and primary care patients (13–15).

Lower respiratory symptoms (LRS), pulmonary abnormalities, and posttraumatic stress disorder (PTSD) are the signature health problems in WTC responders (3–7,16–22). PTSD and pulmonary abnormalities were found to be unrelated (4,7), but correlations of PTSD symptoms with respiratory symptoms range from 0.27 (4) to 0.46 (7). The link between PTSD and respiratory complaints was reported previously, and three explanations were proposed. One is that chronic respiratory symptoms serve as recurrent reminders of the traumatic event (9/11 in our study population) and could trigger PTSD symptoms (23). Furthermore, pulmonary problems may impair daily functioning and complicate psychiatric care, contributing to persistence of PTSD. A second explanation is that PTSD is associated with sympathetic hyperactivity (24) and immune dysregulation (25,26), which may increase vulnerability to pulmonary inflammation and produce respiratory problems (27). Indeed, our previous cross-sectional analysis of a large responder cohort produced statistical evidence consistent with PTSD mediating some of the association between trauma and respiratory symptoms (4). Third, the comorbidity may be coincidental, resulting from shared risk factors (e.g., smoking, obesity, and WTC exposures (28).

Each of these explanations is plausible, and longitudinal investigations are needed to tease them apart. Although longitudinal studies cannot establish causality, they can help to narrow the list of alternative explanations. Unfortunately, few such studies have been conducted (2,29,30), and the available research has focused on cardiovascular symptoms (31) or medically unexplained somatic symptoms (32,33) rather than pulmonary problems. The limited longitudinal data on respiratory complaints suggest that PTSD contributes to the onset, persistence, and severity of these symptoms (7). Conversely, respiratory problems were found to predict PTSD onset, but this association was weaker (7). Thus, both the first and second explanations received support, but to our knowledge, only one study tested them longitudinally. Also, Niles et al. (7) examined this relationship in a specific population—WTC-exposed firefighters—and did not address the possibility that PTSD-LRS comorbidity could stem from shared risk factors (third explanation).

In the present study, we sought to advance understanding of the relationship between LRS and PTSD by a) examining this association over time to explicate the temporal sequence leading to this comorbidity, b) evaluating the role of WTC exposures, c) testing specificity of PTSD-LRS link compared with pulmonary abnormalities, and d) considering robustness of the findings between two populations: police and nontraditional responders. We tested three alternative explanations of comorbidity between WTC-related respiratory problems and PTSD: a) respiratory problems contribute to the onset and persistence of PTSD; b) PTSD contributes to the onset and persistence of respiratory problems; and c) the comorbidity reflects the influence of common risk factors. Alternatively, observed comorbidity may be an artifact arising from common method variance (i.e., responses biases common across self-report measures of health) (34,35) or nonspecific effects of negative affectivity (36). We controlled for such effects statistically.

METHODS

Sample

Data were obtained from the WTC–Health Program, a consortium of 5 Centers for Disease Control and Prevention–funded clinical programs in New York and New Jersey providing annual monitoring and treatment to WTC responders (4,19). The WTC–Health Program assesses and treats WTC-related conditions of responders with documented involvement in the WTC clean-up and recovery efforts, except for New York City firefighters because they are enrolled in a parallel program. The institutional review boards of all participating organizations monitor the study and review it annually. Written informed consent is obtained. Although participation in research is optional, more than 90% of responders consented for their monitoring data to be used in research.

The program began in July 2002, and enrollment remains open. The ascertainment period for the current study was July 2002 to July 2010. During that period, 26,965 responders enrolled in the program, and 18,896 (70.1%) completed a follow-up examination by July 2011 and comprise the analysis cohort. The excluded 8069 responders enrolled more than a year later, on average, and many of them are expected to complete the follow-up in the future. Otherwise, the participants without follow-up were very similar to the analysis cohort on probable PTSD, respiratory problems, demographics, and exposures (Table 1).

Nearly half of the analysis sample (n = 8466; 44.8%) worked in law enforcement (mostly police) and the others (n = 10,430; 55.2%) were nontraditional responders (construction, maintenance, and transportation workers, electricians, clergy, etc). These two groups differed in prior disaster training and on study variables, as shown previously (4,37) and in Table 2. Thus, we stratified the analyses by occupational group.

Measures

The primary outcome measures were WTC-related LRS, pulmonary abnormalities measured by forced vital capacity (FVC), and probable WTC-related PTSD. LRS were assessed by medical staff using questions derived from standard assessments (38–40). The symptoms included wheezing, chest tightness, cough, and shortness of breath. A lower respiratory symptom was defined as 1+ symptom occurring in the month before the examination; not occurring exclusively during a cold, flu, or upper respiratory infection; and not present in the year prior to 9/11. Because chest tightness and shortness of breath can be symptoms of anxiety, we also analyzed a composite of just wheezing or cough (LRS-2) to test whether symptom selection influenced the results. Indeed, wheezing and cough are not part of psychiatric phenomenology.

Pulmonary function was evaluated with the EasyOne spirometer (ndd Medical Technologies, Chelmsford, MA) using standard techniques (41–43).

TABLE 1. Comparison of the Analysis Sample to Responders Who Had Not Completed the Follow-Up by July 1, 2011

	Police			Nontraditional Responders		
Variable	No Follow-Up (*n* = 3930)	Analysis Sample (*n* = 8466)	Effect Size	No Follow-Up (*n* = 4139)	Analysis Sample (*n* = 10,430)	Effect Size
Years between 9/11 and initial visit, M (SD)	5.6 (2.4)	4.3 (2.2)	0.59	4.2 (2.4)	3.3 (2.1)	0.41
Age at initial visit, M (SD), y	40.7 (6.7)	40.9 (7.1)	−0.03	43.4 (10.0)	44.3 (9.7)	−0.09
Sex, % female	16.0	14.7	1.1	13.9	13.9	1.0
BMI, M (SD), kg/m^2	30.3 (5.2)	30.2 (4.9)	0.02	29.6 (5.5)	30.0 (5.4)	−0.07
Current cigarette smoker at initial visit, %	12.1	9.8	1.3	22.8	20.0	1.2
Worked in dust cloud, %	24.2	28.6	0.8	12.3	12.8	1.0
Long work on site, %	21.7	22.3	1.0	28.4	27.1	1.1
Probable PTSD at initial visit, %	6.0	6.3	0.9	22.1	21.3	1.0
Abnormal FVC at initial visit, %	22.7	25.6	0.9	21.8	23.3	0.9
Lower respiratory symptoms at initial visit, %	48.5	50.8	0.9	58.5	57.3	1.1

M = mean; SD = standard deviation; BMI = body mass index; PTSD = posttraumatic stress disorder; FVC = forced vital capacity.

Effect size for group comparison is Cohen *d* for continuous variables and odds ratio for dichotomous variables.

This article focused on restrictive breathing pattern as measured by FVC. Abnormal function was defined as scoring below the age-sex-race-height–specific lower limit of normal for FVC (44).

Probable PTSD was measured with the PTSD Checklist (45), a 17-item self-report inventory assessing the severity of DSM-IV (46) PTSD symptoms in the past month rated "in relation to 9/11" on a scale from 1 (not at all) to 5 (extremely). A cut-point of at least 50 was used to define probable PTSD (47). In a subsample of 2550 WTC–Health Program participants monitored at the Long Island site, we found high concordance between this cutoff and a research diagnosis of PTSD based on the Structured Clinical Interview for DSM-IV (48). Specifically, current prevalence rates were similar (11.1% for PTSD Checklist, 10.2% for interview), κ was

TABLE 2. Descriptive Characteristics of the Study Groups

Variable	Police (*n* = 8466)	Nontraditional (*n* = 10,430)	*p*
Age at index assessment, M (SD), y	40.9 (7.1)	44.3 (9.7)	<.001
Sex, % female	14.7	13.9	.151
Years from 9/11 to initial visit, M (SD)	4.3 (2.2)	3.3 (2.1)	<.001
Years from 9/11 to follow-up, M (SD)	6.8 (1.9)	5.9 (1.9)	<.001
Initial visit BMI, M (SD), kg/m^2	29.9 (4.9)	29.2 (5.1)	<.001
Current cigarette smoker at initial visit, %	9.8	20.0	<.001
Worked in dust cloud, %	28.6	12.8	<.001
Long work on site, %	22.3	27.1	<.001
Initial WTC-LRS, %	50.8	57.3	<.001
Follow-up WTC-LRS, %	40.1	51.9	<.001
Initial low FVC, %	25.6	23.3	.002
Follow-up low FVC, %	24.0	22.8	.070
Initial probable WTC-PTSD, %	6.3	21.3	<.001
Follow-up probable WTC-PTSD, %	8.2	24.7	<.001

M = mean; SD = standard deviation; BMI = body mass index; WTC = World Trade Center; LRS = lower respiratory symptoms; FVC = forced vital capacity; PTSD = posttraumatic stress disorder.

high (0.91), and the negative predictive value was excellent (95.7%). As expected, the positive predictive value was lower (57.4%), as symptomatic participants did not always meet full diagnostic criteria.

WTC exposures were assessed at initial visit. We focused on two exposures previously found to have the most reliable links to LRS and PTSD: working in the dust cloud on 9/11 (22,49) and long duration of work on site, operationalized as being in the top quartile (>1353 hours) (4,22).

Covariates included in the analyses were age, sex, body mass index (BMI), current cigarette smoking, years from 9/11 to initial examination, and interval from initial to follow-up examination.

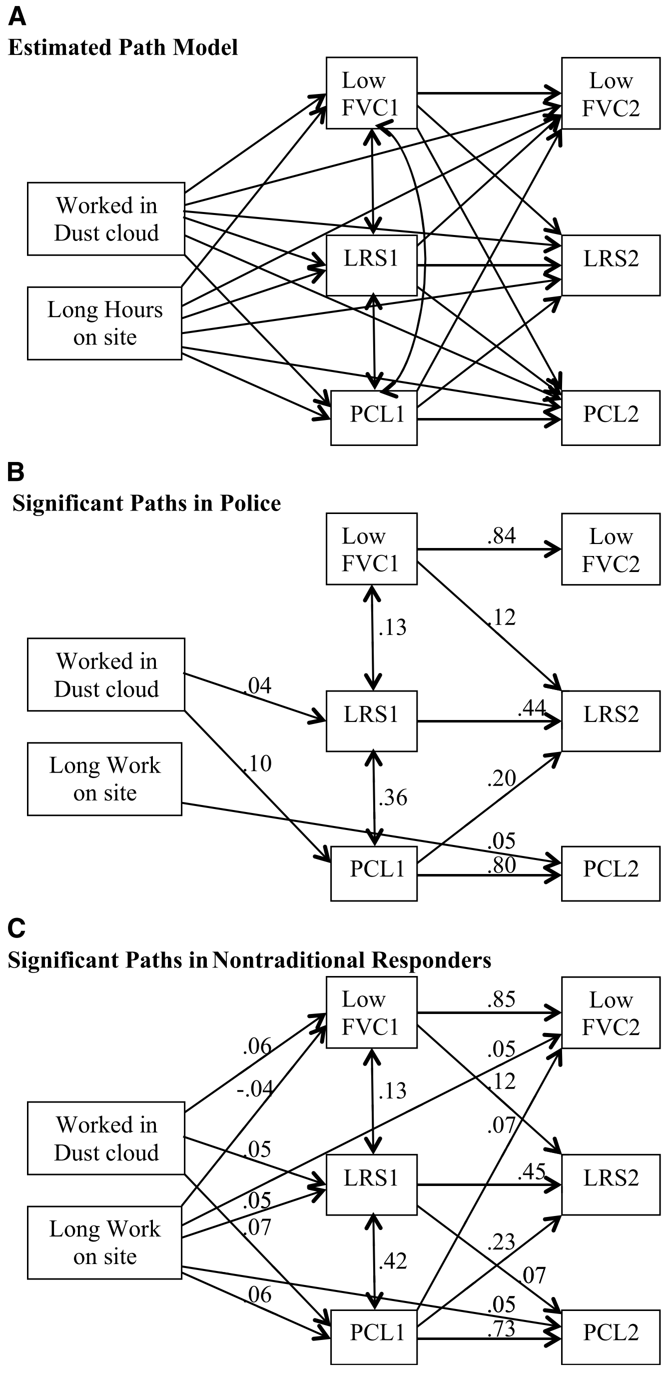

FIGURE 1. Path models. Path model shows all effects being estimated (A) and effects significant at $p < .01$ in police (B) and in nontraditional responders (C). Values are standardized regression coefficients. Analyses adjusted for age, sex, time to assessment, initial BMI, and initial smoking status (not shown), whenever they were significantly correlated with the outcome (Table 4). Directional arrows indicate regression paths; double-headed arrows indicate correlations. Correlations among predictors are not shown. The model fit the data extremely well with Comparative Fit Index > 0.99, Tucker-Lewis Index > 0.98, root mean square error of approximation < 0.02, and weighted root mean square residual < 0.50, all of which indicate excellent fit (52). BMI = body mass index; FVC = forced vital capacity; LRS = lower respiratory symptoms; PCL = Posttraumatic Stress Disorder Checklist.

Analyses

With the exception of time to examination, age, and BMI, study variables were categorical. Comparisons of police and nontraditional responders were performed using χ^2 tests. Bivariate associations were analyzed using polychoric correlations when continuous variables were involved and tetrachoric correlations when both variables were dichotomous to produce equivalent estimates for continuous variables, dichotomous variables, and a mix of the two. Polychoric and tetrachoric correlations have a clear interpretation, with $r < 0.20$ conventionally considered a small effect, $r = 0.20–0.50$ a medium effect, and $r > 0.50$ a large effect (50). Multivariate analyses were conducted using path analysis—a type of structural equation modeling—a system of multiple regressions that are estimated simultaneously (51). It was used to test study hypotheses by regressing outcomes at follow-up on WTC exposures and health status at initial visit (Fig. 1A). Given that each outcome was regressed on as many as five predictors, a conservative p value less than .01 was used to define statistical significance. Regression on initial health status was controlled for any nonspecific effects, such as common method variance. These analyses also adjusted for covariates (demographics, time to examination, initial BMI, and initial smoking) that were significant in the bivariate analysis. Follow-up BMI and smoking were not included because these characteristics were extremely stable between the two assessments. Mediation analyses tested whether exposures contributed to follow-up respiratory problems indirectly via initial PTSD and vice versa (53). The path analyses were performed using Mplus version 7 (54). We used the robust maximum likelihood estimator, which can handle nonnormal distributions. Other analyses were carried out in Stata version 13.1 (55).

RESULTS

Table 2 describes the relevant characteristics of study participants. The occupational groups differed on nearly all study variables. Most importantly, police had much lower rates of LRS and probable PTSD and slightly higher rates of abnormal FVC at both assessments.

Persistence, Remission, New Onset, Comorbidity

From initial to follow-up visit, the rate of LRS declined by 10.7% in police and 5.4% in nontraditional responders, and the rate of abnormal FVC declined by 1.6% and 0.5%, whereas probable PTSD increased by 1.9% and 3.4% (Table 2). As shown in Table 3, most conditions persisted. In police, the ratio of persistent to remitted ranged from 1.3:1 to 2:1 across outcomes. In nontraditional responders, persistence was even more common with ratios ranging from 2:1 to 2.5:1. New onsets were relatively rare. In police, the ratio of new onsets to unaffected was 1:3, 1:11, and 1:21 for LRS, abnormal FVC, and PTSD, respectively. In nontraditional responders, new onsets were more common with the corresponding ratios of 1:2, 1:11, and 1:7.

Abnormal FVC was only weakly related to LRS and probable PTSD (Table 4). In contrast, the concurrent associations between LRS and PTSD were considerable and increased at follow-up (tetrachoric correlation from 0.38 to 0.49 in police and from 0.44 to 0.56 in nontraditional responders). This pattern suggests that comorbidity increased with time. We further tested this by stratifying the analyses by date of initial visit and controlling for demographic, exposure, and life-style factors (Table 5). At follow-up, the association remained unchanged across time intervals. The initial visit correlations were low in the first two strata, but by 2005, it reached levels observed in the follow-up.

TABLE 3. Health Status Across Initial and Follow-Up Assessments (in percent)

Condition	Persistent	Remitted	New Onset	Unaffected	Total
Police					
WTC-LRS	29.1	22.3	11.0	37.6	100.0
Abnormal FVC	17.3	7.9	6.2	68.6	100.0
Probable PTSD	3.8	2.4	4.2	89.6	100.0
Nontraditional					
WTC-LRS	39.8	19.8	12.1	28.4	100.0
Abnormal FVC	16.5	6.9	6.2	70.5	100.0
Probable PTSD	14.1	6.6	10.1	69.3	100.0

Persistent = condition present both at initial and at follow-up visits; Remitted = condition present at initial but not follow-up visit; New onset = condition absent at initial but present at follow-up visit; Unaffected = condition absent at initial and follow-up visits; WTC = World Trade Center; LRS = lower respiratory symptoms; FVC = forced vital capacity; PTSD = posttraumatic stress disorder.

Bivariate Longitudinal Associations

The demographic and life-style risk factors were weakly associated with the health outcomes (Table 4). The exception was abnormal FVC, which was substantially less common in women and more common in responders with larger BMI. Also, smoking was moderately correlated with LRS and probable PTSD. Exposure to the dust cloud was associated with all of the health outcomes, albeit weakly. Long work on site was related to elevated LRS and PTSD, but the correlation with abnormal FVC was negligible. Stability of LRS over the interval was substantial (r = 0.54–0.58), stability of PTSD was even higher (0.77–0.82), and FVC was the most stable (0.85–0.86). Longitudinal associations between LRS and PTSD were substantial, and initial PTSD predicted follow-up LRS somewhat better (0.39–0.44) than initial LRS predicted follow-up PTSD (0.34–0.40; $p < .001$). Longitudinal correlations of these variables with FVC were weak, other than initial FVC predicting follow-up LRS (0.20 in both samples).

Path Analyses

The bivariate analyses suggested the presence of predictive relations among the health variables. To test these effects more rigorously, we conducted path analyses. These models adjusted for all covariates significantly associated with a given outcome in the bivariate analyses.

TABLE 4. Correlations Among Study Variables in Police (Below Diagonal) and Nontraditional Responders (Above Diagonal)

Variable	Time to Initial	Time to Follow-Up	Age	Female	BMI	Smoker	Dust Cloud	Long Work	Initial LRS	Follow-Up LRS	Initial PTSD	Follow-Up PTSD	Initial FVC	Follow-Up FVC
Time to initial visit		**0.80**	0.17	0.03	0.07	−0.06	0.05	−0.15	0.17	0.01	0.10	0.05	0.05	0.10
Time to follow-up visit	**0.83**		0.09	0.02	0.06	−0.03	0.03	−0.11	0.14	0.02	0.08	0.07	0.01	0.09
Age at initial visit	**0.24**	0.14		−0.01	0.07	−0.14	0.04	−0.07	0.08	0.05	0.02	0.01	0.11	0.14
Female	0.05	0.06	0.01		−0.18	−0.18	−0.12	−0.04	0.13	0.13	0.19	0.16	−0.11	−0.12
BMI at initial visit	0.05	0.04	0.07	**−0.24**		−0.08	0.07	0.02	0.11	0.08	−0.01	0.00	**0.22**	**0.21**
Current smoker	−0.12	−0.09	−0.03	0.15	−0.12		−0.03	0.10	0.16	**0.22**	0.14	**0.20**	0.10	0.10
Dust cloud exposure	−0.17	−0.14	0.00	−0.05	0.01	0.03		0.07	0.09	0.05	0.10	0.04	0.10	0.11
Long work on site	−0.16	−0.11	−0.05	0.01	0.06	0.04	0.18		0.05	0.09	0.08	0.13	−0.05	0.02
Initial LRS	0.02	0.04	0.07	0.09	0.09	0.06	0.05	0.05		**0.58**	**0.44**	**0.40**	0.16	0.17
Follow-up LRS	−0.08	−0.06	0.09	0.09	0.10	0.14	0.10	0.09	**0.54**		**0.44**	**0.56**	**0.20**	**0.22**
Initial PTSD	0.04	0.02	0.15	0.07	0.07	0.14	0.14	0.07	**0.38**	**0.39**		**0.77**	0.03	0.11
Follow-up PTSD	−0.02	0.01	0.12	0.09	0.07	0.15	0.13	0.13	**0.34**	**0.49**	**0.82**		0.07	0.12
Initial low FVC	0.01	0.01	0.04	**−0.22**	0.18	0.04	0.06	0.03	0.14	**0.20**	0.06	0.06		**0.86**
Follow-up low FVC	0.02	0.03	0.06	**−0.21**	0.15	0.08	0.07	0.07	0.16	**0.21**	0.05	0.10	**0.85**	

BMI = body mass index at initial visit; Smoker = current smoker at initial visit; LRS = lower respiratory symptoms; PTSD = posttraumatic stress disorder; FVC = forced vital capacity.

Moderate associations ($r \geq 0.20$) are shown in bold. Stability correlations are underlined.

Correlations involving continuous variables are polychoric; all others are tetrachoric. Correlations greater than 0.04 are significant at $p < .01$ level.

TABLE 5. Associations Between Lower Respiratory Symptoms and Posttraumatic Stress Disorder, Stratified by Time of Enrollment

	Unadjusted Correlations		Adjusted Correlations	
Strata	Initial Visit *r*	Follow-Up Visit *r*	Initial Visit *β*	Follow-Up Visit *β*
Police				
7/2002–6/2003	0.26	0.50	0.33	0.46
7/2003–6/2004	0.11	0.42	0.03	0.29
7/2004–6/2005	0.44	0.51	0.42	0.47
7/2005–6/2006	0.40	0.56	0.35	0.51
7/2006–6/2007	0.43	0.47	0.40	0.41
7/2007–6/2008	0.32	0.54	0.26	0.56
7/2008–6/2010	0.41	0.49	0.38	0.42
Nontraditional				
7/2002–6/2003	0.27	0.50	0.25	0.44
7/2003–6/2004	0.30	0.55	0.23	0.48
7/2004–6/2005	0.46	0.64	0.41	0.56
7/2005–6/2006	0.54	0.55	0.45	0.54
7/2006–6/2007	0.52	0.64	0.42	0.51
7/2007–6/2008	0.51	0.50	0.42	0.42
7/2008–6/2010	0.49	0.53	0.30	0.46

r = tetrachoric correlation; *β* = semipartial tetrachoric correlation controlling for age, sex, dust cloud, long work on site, time to assessment, initial body mass index, and initial smoking status.

Stratification was based on time of initial visit. Last stratum is 2 years due to smaller number of participants in 2009 and 2010. Initial and follow-up correlations were computed on the same people (14 strata).

In police, both initial FVC and probable PTSD predicted follow-up LRS above and beyond initial LRS, even after adjusting for covariates (Fig. 1B), but the effect was stronger for PTSD ($\beta = 0.20$) than FVC (0.12). In contrast, initial LRS did not predict follow-up PTSD or FVC. WTC exposures did not contribute to follow-up health directly, except for a very weak association between long hours and PTSD. Exposure to the dust cloud was associated with initial PTSD. We also found a significant indirect effect of dust cloud exposure on follow-up LRS via initial PTSD ($p < .0001$). The parallel effect for long work was not significant ($p = .066$). Neither exposure indicator had an effect on follow-up PTSD via initial LRS ($p > .277$).

All of these associations were also observed in the nontraditional responders (Fig. 1C). In particular, initial PTSD predicted follow-up LRS above and beyond initial LRS and the covariates ($\beta = 0.23$), and the effect of initial FVC on follow-up LRS was also significant (0.12), and dust cloud exposure had an indirect link with follow-up LRS via initial PTSD ($p < .0001$). Several other effects were significant in this group, but all were small and did not replicate in police.

We repeated the path analyses substituting LRS-2 (wheezing and cough) for the full LRS composite, and the pattern of results was unchanged. This suggests that the present findings are not due to similarities of content between respiratory and PTSD measures.

To better understand the PTSD-LRS link, we examined a) LRS onset among responders who were initially free of LRS and b) LRS remission among responders with initial LRS, stratified by initial PTSD. Responders with initial PTSD had double the onsets and half the remissions of responders without PTSD (Fig. 2).

DISCUSSION

In this longitudinal analysis of 18,896 WTC responders, PTSD emerged as a risk factor for LRS and statistically mediated some of the association between disaster exposures and LRS. Our evaluation of the association over time extends previous cross-sectional and initial longitudinal observations (4,7). We found that common risk factors and method variance, potential overlap between anxiety and respiratory symptoms, and contributions from LRS to future PTSD could not fully explain PTSD-LRS comorbidity, whereas PTSD predicted both more onsets and fewer remissions of LRS. The effects were substantial, placing PTSD among the top risk factors for LRS. Furthermore, we found that PTSD-LRS comorbidity grew over time, until about 2006. If PTSD reduces remission and increases late-onset LRS, whereas the natural course of WTC-LRS is to largely

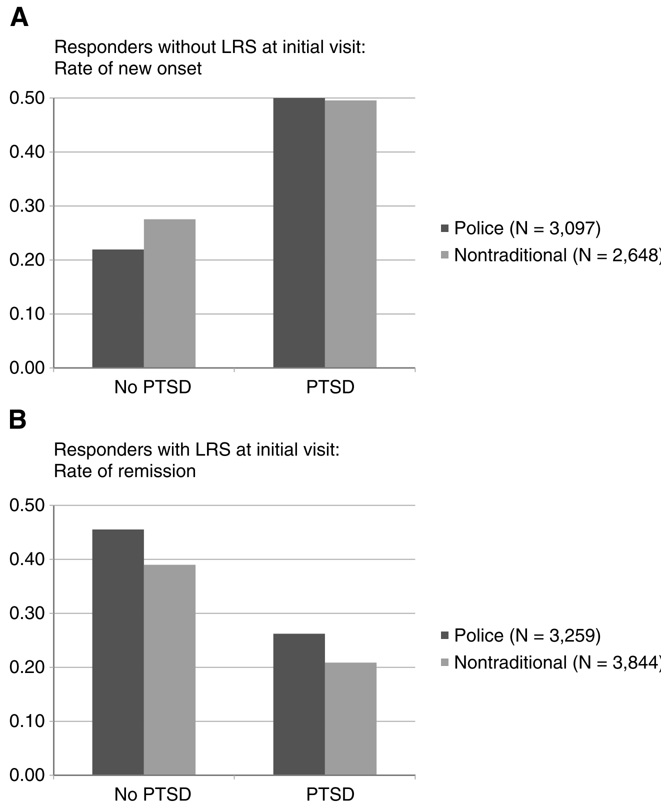

FIGURE 2. New-onset and remission of LRS across visit stratified by probable PTSD at initial visit. In police who had no initial LRS, the new-onset rate was 0.50 given initial PTSD and 0.22 given no initial PTSD; in nontraditional responders who had no initial LRS, the rates were 0.50 and 0.28, respectively. In police who had initial LRS, the remission rate was 0.26 given initial PTSD and 0.46 given no initial PTSD; in nontraditional responders who had initial LRS, the rates were 0.21 and 0.39, respectively. LRS = lower respiratory symptom; PTSD = posttraumatic stress disorder.

remit within 4 years after exposure, this growth of comorbidity is entirely expected. Of note, the comorbidity increased not only with the date of enrollment into the WTC–Health Program but also over the follow-up in the same responders.

Overall, these analyses suggested a pathway where WTC exposures triggered initial LRS and PTSD, and then PTSD contributed further to maintenance and development of LRS, so the effect of exposures on LRS may be mediated, in part, by PTSD. Nevertheless, the present study is observational and cannot evaluate causality in the observed paths. Randomized clinical trials of PTSD treatments are being conducted at Long Island WTC-HP to test the causal connection with LRS experimentally. It also should be noted that negative affectivity and reporting biases affect both PTSD and LRS (34–36) and inflate the apparent association. We controlled for these effects statistically and found that they cannot explain the PTSD-LRS link fully.

Also, here we evaluated statistical relationships and have not examined biological processes underlying these links. One possibility is that PTSD is associated with sympathetic hyperactivity (24) and immune dysregulation (25,26), which can increase vulnerability to pulmonary inflammation, and that in turn may produce respiratory problems (27). Furthermore, recent studies of PTSD found epigenetic changes in immune system genes that may contribute to this pathway (56,57). Immunologic and epigenetic studies of WTC responders are underway to evaluate these possibilities. If such studies confirm this pathway, PTSD treatment should be considered in prevention of LRS and management of ongoing respiratory problems.

In contrast to respiratory symptoms, abnormal pulmonary function was not related to PTSD. Furthermore, spirometry and LRS correlated only modestly. Both findings were observed in this population previously (4,7), and the dissociation between spirometry and symptom indices is an established phenomenon found in various populations (58,59). Spirometry is less sensitive than symptoms to the presence of respiratory problems (60). Furthermore, typical LRS has an episodic course, and one-time spirometry is not effective at capturing such conditions, consistent with our results. The observed pattern suggests that PTSD is associated with more subtle and fluctuating changes in airways rather than with chronic restriction or obstruction.

Along with previous studies of WTC responders (4,5,17), we observed substantially lower rates of mental and physical health problems in police. This effect may be explained by distinct characteristics of the police group, including selection, training, previous exposure to traumatic events, availability of social support and mental health services, and underreporting due to concerns about retaining employment. Nevertheless, the pattern of associations in police seems unaffected and largely parallels that observed in nontraditional responders, indicating robustness of our findings.

The present findings are likely generalizable to other responder populations, given similar evidence of mental-physical comorbidity in military and civilian samples (29). In Gulf war veterans, for example, PTSD was strongly associated with a variety of physical symptoms (33,61). Similar links were found in soldiers returning from Iraq (8). In community samples, PTSD was associated with a range of medical conditions, including respiratory illness (62). Even stronger connections were observed in primary care populations, where anxiety and depressive disorders were linked to greater medical morbidity, and treatment of psychiatric disorders produced improvement in comorbid medical conditions, such as diabetes and coronary heart disease (63). This research suggests that PTSD likely contributes to a range of health problems in WTC-exposed populations also. Furthermore, these studies suggest that the observed link is not unique to PTSD, but other anxiety disorders and depression may similarly contribute to LRS. There is indirect support for this possibility in WTC-exposed individuals (6). Future studies need to evaluate associations of LRS to a range of psychiatric disorders in WTC responders.

Strengths of the present study include a very large sample of WTC responders, a comprehensive catchment area, and rigorous ascertainment of WTC-related physical and mental health conditions. On the other hand, the study had several limitations. First, participants enrolled in the WTC–Health Program voluntarily. Thus, our prevalence estimates must be treated with caution (64). However, it is unlikely that factors determining enrollment would bias the longitudinal associations that are the focus of this report. Second, the present study focused on respiratory problems and PTSD, the most prevalent sequelae of WTC disaster, and did not consider the specificity of PTSD-LRS link. In future research, it will be important to examine a range of physical and psychiatric symptoms to better understand the nature of this connection. Third, although responders who had not yet completed the follow-up did not differ from the analysis sample on initial PTSD and LRS, health changes during the follow-up may have influenced participation and inflated observed comorbidity rates. Fourth, WTC exposures were assessed retrospectively—a nearly ubiquitous shortcoming of disaster research—reducing reliability of these measures (65). The exposures predicted health conditions nevertheless, but the magnitude of the effects was likely underestimated, and the direct path from exposures to follow-up LRS may have been weakened and became nonsignificant. Fifth, the analysis was limited to two exposure measures previously found to have the most reliable links to WTC-related conditions (4,22). Future research should consider exposures more comprehensively. Sixth, PTSD was measured by a self-report inventory and the disorder was considered probable, although the inventory shows high agreement with interview-based diagnosis. Last, the timing of assessments varied due to the open enrollment into the program. We sought to mitigate time differences by controlling them statistically and stratifying some analyses on enrollment time.

CONCLUSIONS

In conclusion, LRS remained common in WTC responders a decade after the disaster. PTSD is a major risk factor for onset and chronicity of LRS and may be contributing to its continued morbidity. The present study provides epidemiologic evidence of a potential pathway leading from exposures to PTSD to LRS. Underlying biological processes and the causal role of PTSD remain to be tested, but if the pathway is confirmed, aggressive PTSD treatment should be considered for responders with this comorbidity. Indeed, a range of effective treatments for PTSD are available, such as selective serotonin reuptake inhibitors and exposure therapy (66,67), and additional treatments may become indicated (e.g., anti-inflammatory drugs) as we learn about the mechanisms involved. Overall, these findings are consistent with the effort to develop healthcare systems that treat mental and physical conditions jointly to produce an optimal outcome.

We are extremely grateful to the WTC rescue and recovery workers who gave themselves so readily in response to the WTC attacks and agreed to participate in this ongoing research effort. We also thank the clinical staff of the WTC–Health Program for their dedication and the labor and community organizations for their continued support.

Source of Funding and Conflicts of Interest: This work was supported by the Centers for Disease Control and Prevention and the National Institute for Occupational Safety and Health, Contract 200-2011-39410 (R.K., E.J.B., C.S., and B.J.L.) and Grants U10 OH008232 (J.K.), U10 OH008225 (S.M.S.), U10 OH008216 (J.B., K.G., and B.J.L.), U10 OH008223 (G. F.), U10 OH008239 (I.U.), and U10 OH008275 (J.M.). The authors declare that they have no competing interests.

REFERENCES

1. Landrigan PJ, Lioy PJ, Thurston G, Berkowitz G, Chen LC, Chillrud SN, Gavett SH, Georgopoulos PG, Geyh AS, Levin S, Perera F, Rappaport SM, Small C, NIEHS World Trade Center Working Group. Health and environmental consequences of the world trade center disaster. Environ Health Perspect 2004;112:731–9.
2. Neria Y, DiGrande L, Adams BG. Posttraumatic stress disorder following the September 11, 2001, terrorist attacks: a review of the literature among highly exposed populations. Am Psychol 2011;66:429–46.

3. Pietrzak RH, Schechter CB, Bromet EJ, Katz CL, Reissman DB, Ozbay F, Sharma V, Crane M, Harrison D, Herbert R, Levin SM, Luft BJ, Moline JM, Stellman JM, Udasin IG, Landrigan PJ, Southwick SM. The burden of full and subsyndromal posttraumatic stress disorder among police involved in the World Trade Center rescue and recovery effort. J Psychiatr Res 2012;46:835–42.
4. Luft BJ, Schechter C, Kotov R, Broihier J, Reissman D, Guerrera K, Udasin I, Moline J, Harrison D, Friedman-Jimenez G, Pietrzak RH, Southwick SM, Bromet EJ. Exposure, probable PTSD and lower respiratory illness among World Trade Center rescue, recovery and clean-up workers. Psychol Med 2012;42:1069–79.
5. Wisnivesky JP, Teitelbaum SL, Todd AC, Boffetta P, Crane M, Crowley L, de la Hoz RE, Dellenbaugh C, Harrison D, Herbert R, Kim H, Jeon Y, Kaplan J, Katz C, Levin S, Luft B, Markowitz S, Moline JM, Ozbay F, Pietrzak RH, Shapiro M, Sharma V, Skloot G, Southwick S, Stevenson LA, Udasin I, Wallenstein S, Landrigan PJ. Persistence of multiple illnesses in World Trade Center rescue and recovery workers: a cohort study. Lancet 2011;378:888–97.
6. Nair HP, Ekenga CC, Cone JE, Brackbill RM, Farfel MR, Stellman SD. Co-occurring lower respiratory symptoms and posttraumatic stress disorder 5 to 6 years after the World Trade Center terrorist attack. Am J Public Health 2012;102:1964–73.
7. Niles JK, Webber MP, Gustave J, Cohen HW, Zeig-Owens R, Kelly KJ, Glass L, Prezant DJ. Comorbid trends in World Trade Center cough syndrome and probable posttraumatic stress disorder in firefighters. Chest 2011;140:1146–54.
8. Hoge CW, Terhakopian A, Castro CA, Messer SC, Engel CC. Association of posttraumatic stress disorder with somatic symptoms, health care visits, and absenteeism among Iraq war veterans. Am J Psychiatry 2007;164:150–3.
9. Eaton WW, editor. Medical and Psychiatric Comorbidity Over the Course of Life. Arlington, VA: American Psychiatric Publishing; 2005.
10. Von Korff MR, Scott KM, Gureje O, editors. Global perspectives on mental-physical comorbidity in the WHO World Mental Health Surveys. New York, NY: Cambridge University Press; 2009.
11. Scott KM, Von Korff M, Ormel J, Zhang MY, Bruffaerts R, Alonso J, Kessler RC, Tachimori H, Karam E, Levinson D, Bromet EJ, Posada-Villa J, Gasquet I, Angermeyer MC, Borges G, de Girolamo G, Herman A, Haro JM. Mental disorders among adults with asthma: results from the World Mental Health Survey. Gen Hosp Psychiatry 2007;29:123–33.
12. Spitzer C, Barnow S, Völzke H, John U, Freyberger H, Grabe HJ. Trauma, posttraumatic stress disorder, and physical illness: findings from the general population. Psychosom Med 2009;71:1012–7.
13. Üstün TB, Sartorius N. Mental Illness in General Health Care: An International Study. Chichester, England: John Wiley & Sons, Ltd; 1995.
14. Bruce SE, Weisberg RB, Dolan RT, Machan JT, Kessler RC, Manchester G, Culpepper L, Keller MB. Trauma and posttraumatic stress disorder in primary care patients. J Clin Psychiatry 2001;3:211–7.
15. Lecrubier Y. Posttraumatic stress disorder in primary care: a hidden diagnosis. J Clin Psychiatry 2004;65(suppl 1):49–54.
16. Aldrich TK, Gustave J, Hall CB, Cohen HW, Webber MP, Zeig-Owens R, Cosenza K, Christodoulou V, Glass L, Al-Othman F, Weiden MD, Kelly KJ, Prezant DJ. Lung function in rescue workers at the World Trade Center after 7 years. N Engl J Med 2010;362:1263–72.
17. Perrin MA, DiGrande L, Wheeler K, Thorpe L, Farfel M, Brackbill R. Differences in PTSD prevalence and associated risk factors among World Trade Center disaster rescue and recovery workers. Am J Psychiatry 2007;164:1385–94.
18. Brackbill RM, Hadler JL, DiGrande L, Ekenga CC, Farfel MR, Friedman S, Perlman SE, Stellman SD, Walker DJ, Wu D, Yu S, Thorpe LE. Asthma and posttraumatic stress symptoms 5–6 years following exposure to the WTC terrorist attack. JAMA 2009;302:502–16.
19. Herbert R, Moline J, Skloot G, Metzger K, Baron S, Luft B, Markowitz S, Udasin I, Harrison D, Stein D, Todd A, Enright P, Stellman JM, Landrigan PJ, Levin SM. The World Trade Center disaster and the health of workers: five-year assessment of a unique medical screening program. Environ Health Perspect 2006;114:1853–8.
20. Stellman JM, Smith RP, Katz CL, Sharma V, Charney DS, Herbert R, Moline J, Luft BJ, Markowitz S, Udasin I, Harrison D, Baron S, Landrigan PJ, Levin SM, Southwick S. Enduring mental health morbidity and social function impairment in World Trade Center rescue, recovery, and cleanup workers: the psychological dimension of an environmental health disaster. Environ Health Perspect 2008;116:1248–53.
21. Prezant DJ, Weiden M, Banauch GI, McGuinness G, Rom WN, Aldrich TK, Kelly KJ. Cough and bronchial responsiveness in firefighters at the World Trade Center site. N Engl J Med 2002;347:806–15.
22. Webber MP, Glaser MS, Weakley J, Soo J, Ye F, Zeig-Owens R, Weiden MD, Nolan A, Aldrich TK, Kelly K, Prezant D. Physician-diagnosed respiratory conditions and mental health symptoms 7–9 years following the World Trade Center disaster. Am J Ind Med 2011;54:661–71.
23. Yellowlees PM, Kalucy RS. Psychobiological aspects of asthma and the consequent research implications. Chest 1990;97:628–34.
24. Pole N. The psychophysiology of posttraumatic stress disorder: a meta-analysis. Psych Bull 2007;133:725–46.
25. Yehuda R. Status of glucocorticoid alterations in post-traumatic stress disorder. Ann N Y Acad Sci 2009;1179:56–69.
26. Spitzer C, Barnow S, Völzke H, Wallaschofski H, John U, John U, Freyberger HJ, Löwe B, Grabe HJ. Association of posttraumatic stress disorder with low-grade elevation of C-reactive protein: evidence from the general population. J Psychiatr Res 2010;44:15–21.
27. Pace TW, Heim CM. A short review on the psychoneuroimmunology of posttraumatic stress disorder: from risk factors to medical comorbidities. Brain Behav Immun 2011;25:6–13.
28. Fu SS, McFall M, Saxon AJ, Beckham JC, Carmody TP, Baker DG, Joseph AM. Post-traumatic stress disorder and smoking: a systematic review. Nicotine Tob Res 2007;9:1071–84.
29. McFarlane AC. The long-term costs of traumatic stress: intertwined physical and psychological consequences. World Psychiatry 2010;9:3–10.
30. Pacella ML, Hruska B, Delahanty DL. The physical health consequences of PTSD and PTSD symptoms: a meta-analytic review. J Anxiety Disord 2013;27:33–46.
31. Coughlin SS. Post-traumatic stress disorder and cardiovascular disease. Open Cardiovasc Med J 2011;5:164–70.
32. Andreski P, Chilcoat H, Breslau N. Post-traumatic stress disorder and somatization symptoms: a prospective study. Psychiatry Res 1998;79:131–8.
33. Engel CC Jr., Liu X, McCarthy BD, Miller RF, Ursano R. Relationship of physical symptoms to posttraumatic stress disorder among veterans seeking care for Gulf war-related health concerns. Psychosom Med 2000;62:739–45.

34. Meade AW, Craig SB. Identifying careless responses in survey data. Psychol Methods 2012;17:437–55.
35. Rammstedt B, Farmer RF. The impact of acquiescence on the evaluation of personality structure. Psychol Assess 2013;25: 1137–45.
36. Smith TW, MacKenzie J. Personality and risk of physical illness. Annu Rev Clin Psychol 2006;2:435–67.
37. Pietrzak RH, Feder A, Singh R, Schechter CB, Bromet EJ, Katz CL, Reissman DB, Ozbay F, Sharma V, Crane M, Harrison D, Herbert R, Levin SM, Luft BJ, Moline JM, Stellman JM, Udasin IG, Landrigan PJ, Southwick SM. Trajectories of PTSD risk and resilience in World Trade Center responders: an 8-year prospective cohort study. Psychol Med 2014;44:205–19.
38. Burney PG, Laitinen LA, Perdrizet S, Huckauf H, Tattersfield AE, Chinn S, Poisson N, Heeren A, Britton JR, Jones T. Validity and repeatability of the IUATLD (1984) Bronchial Symptoms Questionnaire: an international comparison. Eur Respir J 1989;2:940–5.
39. National Center for Health Statistics. NHANES III Reference Manuals and Reports. Hyattsville, MD: Centers for Disease Control and Prevention; 1996.
40. NIOSH (National Institute for Occupational Safety and Health) Health Hazard Evaluations Program, 2006. Available at: http://www.cdc.gov/niosh/hhe/HHEprogram.html.
41. Enright P, Skloot G, Herbert R. Standardization of spirometry in assessment of responders following manmade disasters: World Trade Center worker and volunteer medical screening program. Mt Sinai J Med 2008;75:109–14.
42. Enright PL, Skloot GS, Cox-Ganser JM, Udasin IG, Herbert R. Quality of spirometry performed by 13,599 participants in the World Trade Center Worker and Volunteer Medical Screening Program. Respir Care 2010;55:303–9.
43. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J. ATS/ERS Task Force. Standardisation of spirometry. Eur Respir J 2005;26:319–38.
44. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med 1999;159:179–87.
45. Weathers F, Litz B, Herman D, Huska J, Keane T. The PTSD checklist (PCL): reliability, validity, and diagnostic utility. Paper presented at the Annual Convention of the International Society for Traumatic Stress Studies, San Antonio, TX; 1993.
46. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: American Psychiatric Association; 1994.
47. Terhakopian A, Sinaii N, Engel CC, Schnurr PP, Hoge CW. Estimating population prevalence of posttraumatic stress disorder: an example using the PTSD checklist. J Trauma Stress 2008;21:290–300.
48. Spitzer RL, Williams JB, Gibbon M, First MB. The Structured Clinical Interview for DSM-III-R (SCID). I. History, rationale, and description. Arch Gen Psychiatry 1992;49:624–9.
49. Wheeler K, McKelvey W, Thorpe L, Perrin M, Cone J, Kass D, Farfel M, Thomas P, Brackbill R. Asthma diagnosed after 11 September 2001 among rescue and recovery workers: findings from the World Trade Center Health Registry. Environ Health Perspect 2007;115:1584–90.
50. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum; 1988.
51. Kline RB. Principles and Practice of Structural Equation Modeling. 3rd ed. New York: Guilford Press; 2011.
52. Marsh HW, Hau KT, Wen Z. In search of golden rules: Comment on hypothesis-testing approaches to setting cutoff values for fit indexes and dangers in overgeneralizing Hu and Bentler's (1999) findings. Struct Equ Model 2004;11:320–41.
53. Preacher KJ, Hayes AF. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. Behav Res Methods 2008;40:879–91.
54. Muthen LK, Muthen BO. Mplus. Statistical Analyses with Latent Variables. User's Guide. 7th ed. Muthen & Muthen: Los Angeles; 2012.
55. StataCorp. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP; 2013.
56. Uddin M, Aiello AE, Wildman DE, Koenen KC, Pawelec G, de Los Santos R, Goldmann E, Galea S. Epigenetic and immune function profiles associated with posttraumatic stress disorder. Proc Natl Acad Sci U S A 2010;107:9470–5.
57. Smith AK, Conneely KN, Kilaru V, Mercer KB, Weiss TE, Bradley B, Tang Y, Gillespie CF, Cubells JF, Ressler KJ. Differential immune system DNA methylation and cytokine regulation in post-traumatic stress disorder. Am J Med Genet B Neuropsychiatr Genet 2011;156B:700–8.
58. Curtis JR, Patrick DL. The assessment of health status among patients with COPD. Eur Respir J 2003;21(41 suppl):36s–45s.
59. Tsiligianni I, Kocks J, Tzanakis N, Siafakas N, van der Molen T. Factors that influence disease-specific quality of life or health status in patients with COPD: a review and meta-analysis of Pearson correlations. Prim Care Respir J 2011; 20:257–68.
60. Skloot G, Goldman M, Fischler D, Goldman C, Schechter C, Levin S, Teirstein A. Respiratory symptoms and physiologic assessment of ironworkers at the World Trade Center disaster site. Chest 2004;125:1248–55.
61. Kelsall HL, McKenzie DP, Sim MR, Leder K, Forbes AB, Dwyer T. Physical, psychological, and functional comorbidities of multisymptom illness in Australian male veterans of the 1991 Gulf War. Am J Epidemiol 2009;170:1048–56.
62. Sledjeski EM, Speisman B, Dierker LC. Does number of lifetime traumas explain the relationship between PTSD and chronic medical conditions? Answers from the National Comorbidity Survey-Replication (NCS-R). J Behav Med 2008;31:341–9.
63. Katon WJ, Lin EH, Von Korff M, Ciechanowski P, Ludman EJ, Young B, Peterson D, Rutter CM, McGregor M, McCulloch D. Collaborative care for patients with depression and chronic illnesses. N Engl J Med 2010;363:2611–20.
64. Savitz DA, Oxman RT, Metzger KB, Wallenstein S, Stein D, Moline JM, Herbert R. Epidemiologic research on man-made disasters: strategies and implications of cohort definition for World Trade Center worker and volunteer surveillance program. Mt Sinai J Med 2008;75:77–87.
65. Southwick SM, Morgan CA 3rd, Nicolaou AL, Charney DS. Consistency of memory for combat-related traumatic events in veterans of Operation Desert Storm. Am J Psychiatry 1997;154:173–7.
66. North CS, Pfefferbaum B. Mental health response to community disasters: a systematic review. JAMA 2013;310:507–18.
67. Benedek DM, Fullerton C, Ursano RJ. First responders: mental health consequences of natural and human-made disasters for public health and public safety workers. Annu Rev Public Health 2007;28:55–68.