A. OVERALL COVER PAGE

Project Title: Assessing Inflammatory and Behavioral Pathways Linking PTSD to Increased Asthma Morbidity in WTC Workers	
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Human Subjects: NA	**Vertebrate Animals:** NA
hESC: No	**Inventions/Patents:** No

B. OVERALL ACCOMPLISHMENTS

B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?

The major goals of this project are the following:
•Aim 1: Assess the relationship of PTSD with systemic and airway inflammatory patterns in WTC workers with asthma and evaluate the association with asthma control
•Aim 2: Examine the longitudinal association between PTSD and symptom perception in WTC workers with asthma
•Aim 3: Assess the relationship between PTSD and adherence to asthma SMB (medication adherence, trigger avoidance, and inhaler technique) in WTC workers and identify the pathways linking them
•Aim 4: Develop and pilot test an integrated intervention for asthma and PTSD by adapting the Relaxation Response Resiliency Program (3RP), a mind-body program, with counseling to promote asthma SMB, and education to correct over-perception of asthma symptoms

B.1.a Have the major goals changed since the initial competing award or previous report?

Yes

Revised goals:

Aim 4:
Develop and pilot test an integrated intervention for asthma and PTSD by adapting Cognitive Processing Therapy (CPT) with counseling to promote asthma SMB and education of asthma symptoms

We have modified the approach of the pilot study in Aim 4. Based on analyses of the data obtained for Aims 1-3, we found that over-perception was not significantly associated with PTSD. Similarly, Dr. Adam Gonzalez (consultant) recently completed a randomized controlled trial that showed limited effectiveness of the originally proposed Relaxation Resiliency Program (3RP) for PTSD in WTC workers. In the original proposal we indicated that the pilot intervention would be modified based on the above data. Therefore, we will use Cognitive Processing Therapy (CPT), an evidenced-based intervention for PTSD. CPT is based on a social cognitive theory of PTSD that focuses on how the traumatic event is construed and coped with by a person who is trying to regain a sense of mastery and control in his or her life. We integrated CPT with psychoeducation for asthma based on the effective program SAMBA.1 Both interventions were combined and adapted to address the main challenges faced by WTC workers with PTSD and asthma.

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

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B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

For this reporting period, is there one or more Revision/Supplement associated with this award for which reporting is required?

No

B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

NOTHING TO REPORT

B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST?

NOTHING TO REPORT

B.6 WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?

Not Applicable

FINAL PROGRESS REPORT

Title: Assessing Inflammatory and Behavioral Pathways Linking PTSD to Increased Asthma Morbidity in WTC Workers

Grant No.: 5 U01OH011312

PI: Juan P. Wisnivesky, MD, DrPH

Project Period: 09/01/2016 – 08/31/2022 (NCE)

Abstract

Purpose:

Asthma and post-traumatic stress disorder (PTSD) are the most common conditions in World Trade Center (WTC) rescue and recovery workers, affecting approximately 28% and 32% of individuals, respectively.[1] A large number of local residents and passersby also suffer from these conditions.[2] Moreover, a large number of workers with asthma continue to report symptoms years after exposure at the WTC site.[1,3,4] Thus, asthma is a major cause of morbidity and compromised quality of life among the WTC rescue and recovery worker population. Several studies show a strong association of PTSD with increased asthma morbidity, including worse disease control, increased acute resource utilization, and poorer quality of life in the WTC worker population.[3,5,6] However, the pathways underlying these associations are unknown and this knowledge gap is a major barrier for developing effective and highly needed interventions.

PTSD is associated with systemic inflammation (increased levels of interleukin [IL]-1α, IL-2, IL-6, tumor necrosis factor-alpha [TNF-α] and decreased IL-4, IL-5).[7-10] Some of these pro-inflammatory cytokines have been linked to more severe asthma phenotypes, potentially explaining the relationship between PTSD and worse asthma outcomes.[8,11-15] But biological pathways are only part of the drivers of asthma morbidity. Several observations suggest that PTSD has a stronger association with subjective (asthma symptoms, use of rescue medication, and quality of life) than objective (airflow limitation) markers of asthma morbidity,[16-20] suggesting over-perception of symptoms. Additionally, theory and empirical evidence suggest that inaccurate perception of asthma symptoms and maladaptive illness and medication beliefs in patients with PTSD may lead to lower adherence to asthma self-management behaviors (SMB), a key determinant of asthma outcomes.[21-24] With adherence to controller medications being low among asthma patients in general,[25-27] behavioral mechanisms may also contribute to the association between PTSD and increased asthma morbidity in WTC workers.

Our goal was to examine the interaction of biology and behavior in WTC workers with asthma and PTSD and use this information to design and pilot test an intervention to improve their care.

Methods: A cohort of WTC workers were recruited and enrolled. Participants were eligible if they: 1) were at least 18 years of age; 2) had a diagnosis of asthma made by a health care provider; and 3) spoke English or Spanish. WTC workers were excluded if they 1) had chronic obstructive lung disease (COPD) or other chronic respiratory illness; and/or 2) had a history of heavy smoking (≥15 pack-years) because of the possibility of undiagnosed COPD. Current smokers were eligible if their cumulative smoking history did not exceed this threshold.

Eligible individuals were consented and completed surveys at the time of enrollment (baseline), at 6-month and 12-month follow-ups. A subset of participants completed an additional visit for sputum collection. Blood samples were collected and a clinical interview completed by a psychologist or trainee to assess PTSD and other psychiatric diagnoses. Additional data was collected using electronic devices to monitor medication adherence and actual versus perceived peak expiratory flow (PEF).

A subset of participants from the cohort study were recruited for a pilot randomized controlled study to test a novel intervention for PTSD and asthma if they met the following criteria: 1) results of the Structured Clinical

Interview for DSM-5 Disorders (SCID) and/or PTSD Checklist (PCL-5) survey showing evidence of PTSD; 2) poorly controlled asthma based on an Asthma Control Questionnaire (ACQ) score between 0.75-1.5; 3) an Asthma Quality of Life Questionnaire (AQLQ) score less than 4.7; and 4) completion of observational study 12-month visit.

Results: In total, 361 participants completed a baseline interview. Of these, 101 (31%) met criteria for PTSD based on the SCID, and 61 (18%) met PTSD criteria based on the PCL-5. PTSD was significantly associated with worse asthma control ($p=0.002$), higher rates of emergency room (ER) visits ($p=0.0002$) and hospitalizations ($p=0.03$) and poorer asthma-related quality of life ($p<0.0001$). Participants with PTSD had different illness beliefs about asthma ($p<0.001$), believed their asthma medications were more necessary ($p=0.003$) and were more concerned about medication side effects ($p<0.001$) than those without PTSD, and had more catastrophic beliefs about asthma ($p<0.001$).

Aim 1: We found no significant association between blood or sputum cytokines with PTSD diagnosis or PCL-5 scores both in unadjusted and adjusted analyses (all $p>0.05$).

Aim 2: Adjusted analyses showed no significant differences in PEF among WTC workers with (351.9 ± 143.3 liters per minute) vs. without PTSD (364.6 ± 131.6 liters per minute, $p=0.55$). WTC workers with PTSD vs. those without PTSD had increased proportion of accurate perception ($67\%\pm37\%$ vs. $54\%\pm38\%$, $p=0.01$) and lower under-perception ($23\%\pm32\%$ vs. $39\pm38\%$, $p=0.004$) of airflow limitation during periods of airway obstruction. Similar results were obtained in adjusted analyses.

Aim 3: PTSD was not significantly associated with medication adherence (mean difference: -0.15; 95% confidence interval [CI]: -0.5 to 0.2), inhaler technique (mean difference: -0.12; 95% CI: -0.7 to 0.5), use of action plans (odds ratio [OR]: 0.8; 95% CI: 0.4 to 1.8), or trigger avoidance (OR: 0.9; 95% CI: 0.4 to 1.8).

Aim 4: There were no significant differences in asthma control, quality of life, medication adherence, medication beliefs, illness beliefs, PTSD, depression or anxiety symptoms between the intervention and control groups either before the trial, at 1-week follow-up, or at 3-month follow-up (all $p>0.05$).

Conclusions:

Aim 1: We found no major differences in asthma inflammatory markers in WTC workers with vs. without PTSD. These findings suggest that other mechanisms likely explain the association between PTSD and asthma control in WTC exposed individuals.

Aim 2: We found that WTC workers with and without PTSD had similar degrees of airflow limitation as evidenced by PEF values, suggesting equal asthma control. WTC workers with PTSD were more likely to accurately and less likely to under-perceive airflow limitation. Anxiety sensitivity may influence asthma perception in WTC workers with coexisting PTSD, making these individuals more attuned to and hyper-focused on their asthma symptoms, which over time, may lead to more accurate perception of airflow limitation.

Aim 3: PTSD was not significantly associated with medication adherence, inhaler technique, use of action, or trigger avoidance. Thus, behavioral pathways do not appear to mediate the association between PTSD and worse subjective asthma control.

Aim 4: The intervention piloted in this study did not demonstrate any significant differences in asthma-related beliefs and behaviors or in PTSD symptoms compared to the control protocol. Further research is needed to explore effective ways of managing comorbid PTSD and asthma in this complex population.

Specific Aims

Aim 1: Assess the relationship of PTSD with systemic and airway inflammatory patterns in WTC workers with asthma and evaluate the association with asthma control.

Aim 2: Examine the longitudinal association between PTSD and symptom perception in WTC workers with asthma.

Aim 3: Assess the relationship between PTSD and adherence to asthma SMB (medication adherence, trigger avoidance, and inhaler technique) in WTC workers and identify the pathways linking them.

Aim 4: Develop and pilot test an integrated intervention for asthma and PTSD by adapting Cognitive Processing Therapy (CPT) with counseling to promote asthma SMB and education of asthma symptoms.

Study Design

Eligibility:

A cohort of WTC workers were recruited and enrolled across two sites in New York City: Mount Sinai Hospital and Queens College. Potential participants were identified through the WTC Health Program clinics at these sites. Participants were eligible if they: 1) were at least 18 years of age; 2) had a diagnosis of asthma made by a health care provider; and 3) spoke English or Spanish. WTC workers were excluded if they 1) had a diagnosis of COPD or other chronic respiratory illness; or 2) had a history of heavy smoking (≥15 pack-years) because of the possibility of undiagnosed COPD. Current smokers were eligible if their cumulative smoking history did not exceed this threshold. Individuals deemed eligible based on medical records were contacted via a mailed letter and followed up with a phone call to assess interest and verify eligibility through a brief screening questionnaire. Interested and eligible patients completed an informed consent either in-person or over the phone.

Design of Observational Cohort Study:

Eligible individuals were consented and completed 3 surveys at in-person or phone-based interviews with a trained research coordinator: one at the time of enrollment (baseline), at 6-month and 12-month follow-ups. A subset of participants completed an additional visit for sputum collection at which several survey measures were repeated. Blood samples were collected and a clinical interview completed by a psychologist or trainee to assess PTSD and other psychiatric diagnoses. Additional data was collected using electronic adherence monitoring devices and an AM2 device tracking actual versus perceived asthma symptoms.

Measures:

We collected information on sociodemographic characteristics and smoking history, and comorbidities. The extent of exposure to the WTC site was categorized based on prior criteria developed using data on using on the total amount of time spent at the WTC site, the level of exposure to the WTC cloud, and history of working on the pile.[28]

We also collected information regarding asthma history, asthma diagnosis in relation to WTC exposure, medication regimen, and family history of asthma.[29]

Assessment of PTSD: A trained research staff member administered the SCID patient edition version 5 to assess for the presence of PTSD.[30] Other analyses utilized the PCL-5, another clinical measure that is validated in English and Spanish to assess for PTSD symptoms.[31-32]

The SCID-5 was also used to assess current and past major depressive episodes. Additionally, self-reported depressive symptoms were collected using the 9-item Patient Health Questionnaire (PHQ-9).[33]

Inflammatory Markers: Peripheral blood was collected in EDTA tubes to measure plasma cytokines levels. After collection, the plasma was separated via centrifugation (1400xg) for 15 minutes at 4˚C. The plasma supernatant was then collected and stored at -80˚C until further processing for cytokine protein level. Sputum was induced adopting methodology used by the National Heart, Lung and Blood Institute-sponsored asthma networks.[34] Briefly, participants performed baseline spirometry and then received 360 micrograms of short-acting bronchodilator prior to induction. Subjects received nebulized hypertonic saline (3%) for 12 minutes, over three 4-minute intervals to induce sputum. Sputum was processed by the whole sputum method.[35,36] Cytospins were prepared and stained with Diff-Quick (Dade Diagnostics of PR, Aguada, PR) for differential cell

counts. The sputum cell differential was determined by counting at least 500 white blood cells on the cytospin slides, excluding samples with a cell viability <50% and >20% squamous cells.

Sputum supernatant and plasma were assayed for a panel of cytokines using a multiplex assay (Milliplex, Billerica, MA) according to manufacturer's instructions. Briefly, samples, standards, and controls were added to the appropriate wells. The premixed magnetic beads were added to each well and incubated on a plate shaker for 16 to 18 hours at 4°C. After washing, detection antibody was added and incubated on a plate shaker for 1 hour at room temperature, followed by Strepaviden-Phycoerythrin for 30 minutes. The plate was run on the Luminex 200 system (Luminex Corp., Austen, TX) and data analyzed using the MILLIPLEX Analyst Software (EMD Millipore Corp., Billerica, MA).

Perception of Airflow Limitation: We used the AM2 programmable peak flow monitor (ERT Corporation, Philadelphia, PA) to assess perception of airflow limitation by comparing actual and perceived (i.e., guessed) PEF values measured daily in the morning and evening for 6 weeks. Following a validated protocol,[37] research staff trained participants to enter their guessed PEF into the AM2 device and then to perform three PEF measurements. Each PEF guess was characterized as being in the accurate (guessed PEF ≤10% lower or higher than the measured PEF), under-perception (guessed PEF >10% higher than measured), or over-perception (guessed PEF <10% lower than measured) of airflow limitation zone using a validated asthma risk grid.[38] It is unlikely that participants would report under-perception of asthma symptoms during periods without airflow limitation (as participants would have to guess a supranormal PEF to be classified as experiencing under-perception). Thus, we also calculated the percent of the time each participant spent in the under-, over-, and accurate perception zones while they had airflow limitation (i.e., the PEF was <80% predicted).

Asthma Control: The ACQ was used to assess the level of asthma control among study participants.[39] The ACQ is a well-validated tool that has been extensively used in epidemiologic studies and clinical trials to assess asthma symptoms and use of rescue medications over the previous week. The ACQ items are scored on a scale of 0 to 6, with higher scores indicating worse asthma control; the minimal clinically significant difference is 0.5 units.[40]

Resource utilization related to acute asthma exacerbations was assessed on the basis of self-reports of the number of ER visits or hospitalizations during the previous 12 months. We assessed the asthma-related quality of life using the mini AQLQ. This validated 15-item tool assesses several domains of quality of life, including physical, emotional, social, and occupational limitations because of asthma in the previous 2 weeks.[41] Responses were generated on a Likert scale with higher scores indicating better quality of life.

Self-management Behaviors: The Medication Adherence Reporting Scale (MARS) is a 10-item self-reported medication adherence scale that has been adapted to inhaled medications and has been validated against objective measures on electronic devices.[42] A score greater than 4.5 is considered a marker of good adherence.[42]

We also used the Adherence Starts with Knowledge-12 (Ask-12), a 12-item self-report questionnaire developed to identify patient-specific barriers to medication adherence within 3 domains: inconvenience/forgetfulness, treatment beliefs, and behavior. Items are scored on a 5-point scale, and total scores range from 12 to 60, with higher scores representing greater adherence barriers.[43]

Other self-management behaviors assessed included inhaler technique, use of asthma action plans, adherence to trigger avoidance behaviors, and annual influenza vaccination.

Disease Beliefs: The Brief Illness Perception Questionnaire (BIPQ) was used to measure asthma-related beliefs among WTC workers.[44] This validated scale was expanded with WTC-specific items from a prior study.[1] Beliefs about asthma medications were assessed using the Asthma Beliefs About Medicines Questionnaire (BMQ), a 10-item validated tool assessing medication necessity and concerns.[45]

Statistical Methods

Analyses for Observational Study:

We used descriptive statistics such as mean, standard deviation, median, interquartile range and percentage to report the distributional characteristics of study participants at cohort baseline.

Aim 1:

We compared the baseline characteristics of WTC workers with and without PTSD using a t-test, Wilcoxon test, or chi-square test, as appropriate. The unadjusted association of PTSD with blood and sputum cytokines levels and sputum cell counts was evaluated using a Wilcoxon test. The unadjusted relationship between PCL-5 scores and cytokine levels were calculated using the Spearman correlation coefficient. We used linear regression models to assess the adjusted association of PTSD with blood and sputum cytokines or sputum cell counts after controlling for age, sex, race/ethnicity, income, WTC exposure, smoking history, asthma history and regimen, and depression. Similar analyses were used to evaluate the adjusted association of PCL-5 scores with blood and sputum inflammatory makers or sputum cell counts.

Aim 2:

Unadjusted actual and predicted PEF values were compared among WTC workers with and without PTSD using a linear mixed model with a participant random intercept to incorporate clustering due to repeated measures within individuals. Airflow limitation perception scores in WTC workers with vs. without PTSD were compared using a t-test. We used the Pearson correlation coefficient to assess the unadjusted relationship between PCL-5 scores and perception of airflow limitation.

The adjusted associations of PTSD with ACQ, AQLQ and PEF measures were evaluated using linear regression or mixed linear models (random participant intercept), respectively, controlling for sociodemographic characteristics, asthma history, comorbidities, and level of WTC exposure. Similar models were used to assess the association of PTSD with under-, accurate or over-perception of airflow limitation after adjusting for age and sex but not for other markers of asthma control (as symptom perception was conceptualized as being in the pathway between PTSD and asthma outcomes). We repeated the analyses, limiting to data points obtained during periods of airflow limitation.

Aim 3:

We compared unadjusted MARS, Ask-12, and inhaler technique scores according to the presence or absence of PTSD using a t-test. Rates of adherence to controller medication (based on the MARS cut-off of >4.5), good inhaler technique, use of asthma action plans, trigger avoidance, and influenza vaccination were compared among WTC workers with and without PTSD using a chi-square test.

Linear regression assessed the adjusted association between PTSD with medication adherence and inhaler technique scores, controlling for age, sex, race and ethnicity, education, socioeconomic status, asthma onset, and presence or absence of comorbid depression. The adjusted association between PTSD and rates of medication adherence, good inhaler technique, use of asthma action plans, trigger avoidance, and influenza vaccination in WTC workers was evaluated using logistic regression. We compared BIPQ and BMQ responses in WTC workers with and without PTSD using a t-test and calculated Cohen effect sizes. We used multiple imputation methods to address missing data.

Pilot Randomized Study (Aim 4):

Eligibility: A subset of participants from the cohort study were recruited for the pilot study if they met the following criteria: 1) results of the SCID and/or PCL-5 showing evidence of PTSD; 2) poorly controlled asthma based on ACQ score between 0.75-1.5; 3) an AQLQ score less than 4.7; and 4) completion of observational study 12-month visit.

Design of the Pilot Study: The original plan to use the Relaxation Resiliency Program (3RP) was based on preliminary data from Dr. Adam Gonzalez (consultant) showing that this intervention could be effective for WTC workers with PTSD and lower respiratory symptoms. Since then, Dr. Gonzalez completed a fully powered randomized controlled trial that showed that 3RP did not significantly improve the outcomes (i.e., PTSD

symptoms and respiratory symptoms) for this population. As such, in consultation with Dr. Gonzalez, the team has worked to adapt an established PTSD treatment, Cognitive Processing Therapy (CPT) to target 9/11 PTSD symptoms and asthma management and asthma related-quality of life. Additionally, the original plan was to use data collected in Aims 1-3 to revise and tailor the pilot intervention to be tested in Aim 4. Analyses of the data obtained for Aims 1-3, showed that PTSD was not significantly associated with over-perception of asthma symptoms. Thus, the pilot study did not focus on addressing symptom over-perception as a strategy to improve asthma control in WTC workers with PTSD. We integrated CPT with psychoeducation for asthma based on the effective program.

The final pilot design involved the randomization of participants to one of 2 arms: an intervention consisting of CPT and asthma psychoeducation, or an attention-control program consisting of general supportive psychotherapy, emotional support, and asthma education. Arm assignment was conducted using block randomization to place the same number of participants in each arm.

Participants in both arms completed 10 sessions via Zoom with a trained interventionist, lasting approximately 10 weeks. Participants in the intervention group completed the PCL-5 at the beginning of each session to assess current PTSD symptoms and guide intervention activities. Graduate students in clinical psychology were trained to deliver the intervention by Dr. Gonzalez. Dr. Gonzalez provided weekly supervision and review audio-taped sessions for treatment fidelity.

Outcome Assessment: A follow-up survey 4 weeks after the last session will be administered to assess PTSD symptoms (SCID count and PCL-5), ACQ and AQLQ scores, medication adherence (MARS), and illness and medication beliefs (BIPQ and BMQ).

Analysis for Pilot Study (Aim 4): Asthma self-management behaviors, asthma severity, beliefs about asthma and medications, and mental health outcomes were compared between intervention and control groups at each time point (pre-intervention, 1-week post-intervention, and 3 months post-intervention) using the t-tests and Wilcoxon-Rank test.

All analyses were performed using Statistical Analysis System version 9.4 (SAS Institute, Inc., Cary, North Carolina) statistical software, using 2-sided p-values.

Results and Significance

Observational Study Results:

Recruitment: Between February 2017 and January 2020, we contacted WTC workers with diagnosis of asthma enrolled in the WTCHP program through the Mount Sinai Hospital and Queens College sites. Of these, 177 were found ineligible during screening (23% reported no history of asthma, 23% had COPD, 14% were not English or Spanish speakers, and 40% due to other reasons). A total of 364 eligible individuals consented to participate; however, 3 were found to be ineligible after consent, and thus 361 participants were enrolled and completed a baseline interview. Seventy-six participants from this cohort completed sputum induction. Retention was 72% at 6 months and 77% at 12 months.

Baseline Characteristics: In the final cohort of 361 participants, the average age was 55.4 (SD=8.1), 28% were female, 33% identified as white non-Hispanic, 21% as Black non-Hispanic, 32% as Hispanic or Latino, and 14% as another race or ethnicity (Table 1). A majority (60%) of participants were married, 28% had only a high school education or less, and 31% had a household income below $3,000/month. The majority reported never smoking (77%) and having asthma onset after WTC exposure (86%).

At baseline, 31% (N=101) of participants met criteria for PTSD based on the SCID. Participants with PTSD were significantly more likely to be younger ($p=0.03$), Hispanic or other race ($p=0.01$), and low income ($p<0.001$) than those who did not meet PTSD criteria. Participants with PTSD were also more likely to express more depressive symptoms based on the PHQ-9 ($p<0.001$) and to meet clinical criteria for comorbid major depression based on the SCID ($p<0.001$). There were no other significant differences between other sociodemographic characteristics ($p>0.05$ for all comparisons).

PTSD was significantly associated with worse asthma control (p=0.002), higher rates of ER visits (p=0.0002) and hospitalizations (p=0.03) and poorer asthma-related quality of life (p<0.0001). Participants with PTSD had significantly different illness beliefs about asthma (p<0.001), believed their asthma medications were more necessary (p=0.003) and had more concerns about side effects (p<0.001) than those without PTSD, and had more catastrophic beliefs about asthma (p<0.001).

Adherence and symptom perception data collected from monitoring devices at each visit time point are displayed in Table 1b.

Aim 1:

Table 2 shows the unadjusted association of PTSD with blood and sputum cytokines. Overall, there were no significant association between PTSD and any of the blood cytokines assessed in the study (p<0.05 for all comparisons). Similarly, sputum cytokines were not significantly associated with presence or absence of PTSD (p<0.05 for all comparisons). In secondary analyses, we found that the severity of PTSD symptoms (PCL-5 scores) was not significantly correlated with blood (p<0.05 for all comparisons) or sputum (p<0.05 for all comparisons) cytokine levels.

Adjusted analyses showed no significant association between PTSD and blood cytokine levels or sputum cytokine levels (Table 3). Similarly, the severity of PTSD symptoms was not significantly associated with blood levels of any cytokine after adjusting for confounders except for IL-1β (mean difference: 0.03 units per 1 unit increase in PCL-5 score, 95% CI: 0.01-0.06), IL-2 mean difference: 0.03 units per 1 unit increase in PCL-5 scores, 95% CI: 0.01-0.06), and VEGF (mean difference: 1.4 units per 1 unit increase in PCL-5 score, 95% CI: 0.6-2.3) (Table 5). There were no significant associations of PTSD symptoms with sputum cytokine levels in adjusted analyses.

Aim 2:

Unadjusted analyses showed no significant differences in mean PEF measures (351.92±143.25 liters per minute vs. 364.62±131.62 liters per minute, p=0.55) or predicted PEF (73±30% vs. 76±27%, p=0.78) in WTC workers with vs. without PTSD (Table 6). In terms of perception of airway obstruction, WTC workers with PTSD had decreased rates of under-perception (16.0±24.7% vs. 22.4±25.2%, p=0.02) compared to those without PTSD. Moreover, during periods of airflow limitation, WTC workers with PTSD were more likely to have accurate (67.0±37.2% vs. 53.5±38.1%, p=0.01) and less likely to have under-perception (23.3±32.1% vs. 38.9±37.5%, p=0.004) compared to workers without PTSD. PTSD was not associated with over-perception overall (22.4±32.2% vs. 15.6±23.8%, p=0.3) or during periods of airflow limitation (4.5±18.2% vs. 3.2±14.6%, p=0.4). Similarly, higher PCL-5 scores were significantly positively correlated with accurate perception (r= 0.2, p=0.004) and negatively correlated with under-perception (r= -0.2, p=0.005) during periods of airflow limitation.

Adjusted analyses showed that PTSD was significantly associated with worse asthma control (mean difference [95% CI]: 0.9 [0.5 to 1.3]) and poorer quality of life (mean difference [95% CI]: -1.4 [-1.9 to -1.0]) after controlling for potential confounders (Table 7). However, there was no significant association between PTSD and PEF (mean difference [95% CI]: -10.5 [-47.3 to 26.4] liters per minute) or predicted PEF (mean difference [95% CI]: -3 [-10 to 5%]). While there were no significant differences in symptom perception among groups overall, PTSD was significantly associated with accurate (mean difference [95% CI]: 13.5 [0.8 to 26.3%]) and less likely associated with under-perception (mean difference [95% CI]: -14.8 [-27.0 to -2.7%]) during periods of airway obstruction. Similarly, PCL-5 scores were significantly associated with increased accurate perception (mean difference [95% CI]: 5.9 [1.9 to 9.9] % per 10 units difference in PCL-5) and lower rates of under-perception (mean difference [95% CI]: -5.6 [-9.4 to -1.8] % per 10 units difference in PCL-5) but not with over-perception (mean difference [95% CI]: -0.1 [-1.8 to 1.5] % per 10 units difference in PCL-5) during periods of obstruction after controlling for confounders. Adjusted analyses using perception assessments based on individual PEF measures as the outcome also showed that PTSD was associated with increased odds of accurate perception overall (OR [95% CI]: 2.0 [1.1 to 3.6]) and during periods of airway obstruction (OR [95% CI]: 2.2 [1.0 to 4.9]).

Aim 3:

Unadjusted analyses showed no significant differences in medication adherence based on MARS scores in WTC workers with or without PTSD (34% vs 41%; p=.4; Table 8). However, Ask-12 scores showed lower rates of adherence among WTC workers with versus without PTSD (24.0 ± 5.9 vs 22.1 ± 5.5, respectively; p=.01). Inhaler technique scores (6.6 ± 1.7 vs 6.5 ± 1.6; p= .6) as well as the proportion of WTC workers who showed adequate technique (80% vs 75%; p=4) were not significantly different among the 2 groups. Similarly, we found no significant differences in the proportion of WTC workers who used an asthma action plan (49% vs 42%; p=.2), avoided asthma triggers (55% vs 47%; p=.2) or received the influenza vaccine (62% vs 59%; p=.7) in those with or without PTSD.

Adjusted analyses showed that PTSD was not associated with MARS scores (mean difference [95% CI]: -0.15 [-0.5 to 0.2]), percentage adherence based on MARS scores of 4.5 or greater (OR [95% CI]: 2.5 [0.9 to 6.8]), or ASK-12 scores (mean difference [95% CI]: 1.7 [-0.3 to 3.6]; Table 9) after controlling for age, sex, race and ethnicity, education, income, asthma onset pre- versus post-9/11, depression, and other comorbidities. Similarly, WTC workers with and without PTSD did not have significant differences in inhaler technique scores (mean difference [95% CI]: -0.11 [-0.7 to 0.5]) or in odds of showing an adequate inhaler technique (OR [95% CI]: 0.9 [0.4 to 2.3]). Use of asthma action plans (OR [95% CI]: 0.8 [0.4 to 1.8]), trigger avoidance (OR [95% CI]: 0.9 [0.4 to 1.8]), and influenza vaccination (OR [95% CI]: 0.7 [0.3 to 1.5]) were not significantly different according to PTSD status after controlling for potential confounders.

Whereas self-management was similar in both groups, we evaluated potential differences in illness and medication beliefs known to be associated with adherence among WTC workers with and without PTSD (Table 10). The WTC workers with PTSD were significantly more likely to have emotional responses to their asthma, such as reporting that thinking about asthma makes them sad (4.5 vs 1.4; p<.0001), worried about their future (3.0 vs 2.3; p<.0001), feeling that nothing will ever improve their asthma (4.6 vs 2.6; p<.0001), and reporting that asthma affects them emotionally (5.6 vs 2.9; p<.0001). They also were more likely to report asthma consequences, such as that asthma affects their lives (6.3 vs 4.8; p=.0001) and they experience a lot of asthma symptoms (5.9 vs 5.2; p=.04). Beliefs about medication necessity (3.1 vs 2.9; p=.1) and concerns (3.0 vs 2.9; p=.2) were not significantly different in those with or without PTSD.

Pilot Study Results (Aim 4)

Recruitment: Between August 2020 and December 2021, we recruited a subset of eligible study participants for the pilot randomized trial. During this window, 48 participants were identified as eligible at the time of their 12-month follow-up; of these, 43 consented to participate in the pilot. We randomized 43 individuals; 5 participants were found to be ineligible, resulting in a total of 38 individuals participating in the pilot. Nineteen were randomized to the intervention and 19 to the control arm. In total, 79% of pilot participants completed the first follow-up survey 1 week after completing the 10th session and 74% completed a second follow-up 3 months after the 10th session.

Characteristics: Participants in the pilot had a mean age of 54.2 (SD: 8.4), and 39% were female (Table 11). Twenty-five percent of participants identified as Black or African American, 25% as White, 36% as Hispanic/Latino, and 14% as other race or ethnicity. Over half (56%) had at least some college education, 50% were married, and 52% had a household income less than $3,000 per month. Participants in the control group were significantly more likely to be married (69% vs. 25%, p=0.02), but otherwise did not differ from the intervention group.

There were no significant differences between the intervention and control groups either before the trial, at 1-week follow-up, or at 3-month follow-up in asthma control, asthma-related quality of life, medication adherence, beliefs about illness or medications, or mental health status (all p>0.05; Table 12).

Discussion/Summary

Aim 1:

PTSD has been consistently associated with increased asthma morbidity in studies of WTC-exposed individuals as well as other populations.[46,47] Overall, we did not find significant associations of PTSD with the levels of blood or sputum inflammatory makers. These findings suggests that other mechanisms, like symptom

perception, mental health comorbidities, or behavioral factors, may explain the relation between PTSD and worse asthma control in WTC workers.

Aim 2:

PTSD has been more strongly associated with subjective compared to objective asthma morbidity markers, suggesting potential differences in symptom perception.[48] In this study, we found that WTC workers with and without PTSD had similar degrees of airflow limitation as evidenced by PEF values, thus suggesting equal asthma control. However, despite similar objective measures of asthma control, those with PTSD had worse ACQ and AQLQ scores. Our study highlights that symptom perception may partially explain the difference in subjective asthma morbidity markers as WTC workers with PTSD were more likely to accurately and less likely to under-perceive airflow limitation. Thus, poorer self-reported asthma control among WTC workers with vs. without PTSD may be partially explained by more accurate recognition of episodes of airflow limitation.

Aim 3:

Our study showed that PTSD was not associated with adherence rates to key self-management behaviors in WTC workers with asthma. These findings suggest that behavioral pathways are unlikely to explain the relationship between PTSD and increased asthma morbidity. Nevertheless, we found that many WTC workers were not adherent to asthma self-management, suggesting a potential target for future interventions to improve asthma control.

Additionally, our results showed that WTC workers with PTSD reported different illness beliefs. In particular, WTC workers with PTSD were significantly more likely to be emotionally affected by their asthma. They also were more likely to report feeling a lack of control over their health and worried about their future because of their asthma. According to the SRM and empirical data, disease beliefs are strong modifiable predictors of self-management adherence.[49] Thus, these data can help physicians identify and address potential barriers to medication adherence in WTC workers with asthma. In addition, these beliefs could be the target of behavioral interventions to improve asthma self-management, given that almost half of participants reported low adherence to self-management.

Aim 4:

The intervention piloted in this study did not demonstrate any significant differences in asthma-related beliefs and behaviors or in PTSD symptoms compared to the control protocol. Further research is needed to explore effective ways of managing comorbid PTSD and asthma in this complex population.

E. Publications and Presentations

Publications

1. Wisnivesky JP, Markowitz SB, James S, Stone K, Dickens B, Busse P, Crowley L, Federman A, Katz C, Gonzalez A. Comorbid posttraumatic stress disorder and major depressive disorder are associated with asthma morbidity among World Trade Center workers. *Ann Allergy Asthma Immunol*. 2021;*126*:278-283. https://doi.org/10.1016/j.anai.2020.10.007
2. Wisnivesky JP, Becker JH, Ankam A, Markowitz SB, Doernberg M, Dickens B, Busse P, Crowley L, Federman A, Katz C, Weiss JJ, Gonzalez A. The relationship between post-traumatic stress disorder and self-management behaviors in World Trade Center workers with asthma. *J Allergy Clin Immunol Pract*. 2021;*10*(1):242-249. https://doi.org/10.1016/j.jaip.2021.08.035
3. Wisnivesky JP, Agrawal A, Ankam J, Gonzalez A, Federman A, Markowitz SB, Birmingham JM, Busse PJ (In prep). Inflammatory markers in World Trade Center workers with asthma: Associations with post-traumatic stress disorder.

4. Silverstein GD, Castaño K, Ankam J, Muellers KA, Wisnivesky JP, Gonzalez A (In prep). Post-traumatic Stress Disorder Symptom Clusters and Asthma Outcomes amongst World Trade Center Rescue and Recovery Workers.
5. Wisnivesky JP, Agrawal N, Ankam J, Gonzalez A, Busse P, Lin J, Federman A, Feldman J, Weiss JJ, Markowitz SB (Under review). Perception of Airway Obstruction in World Trade Center Workers with Asthma and Post-traumatic Stress Disorder

Presentations

1. Wisnivesky J, James S, Stone K, Muellers M, Federmann E, Crowley L, Gonzalez A, Federman A, Markowitz S, Busse P, Katz C. Post-traumatic Stress Disorder, Depression and Asthma Morbidity among World Trade Center Workers. American Thoracic Society Annual Conference, 2020.

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Table 1. Baseline Characteristics

Characteristic	Total* N = 361 (100)
Age, Years, Mean (SD)	55.4 (8.1)
Female, No. (%)	100 (27.7)
Race/Ethnicity, No. (%)	
White	118 (32.7)
Black	76 (21.1)
Hispanic	116 (32.1)
Other	51 (14.1)
Married, No. (%)	204 (59.7)
Education, High school or less, No. (%)	96 (28.1)
Income, ≤$3,000 per month, No. (%)	96 (30.9)
Body Mass Index, Mean (SD)	31.5 (6.4)
Smoking History, No. (%)	
Current	4 (1.2)
Former	74 (21.9)
Never	260 (76.9)
Post 9/11 Asthma Onset, No. (%)	277 (85.5)
WTC Exposure, No. (%)	
Low	26 (10.5)
Intermediate	160 (64.5)
High	36 (14.5)
Very high	26 (10.5)
Sensitized to Aeroallergens (at least one), No. (%)	80 (35.9)
Asthma Action Plan, Have or used one, No. (%)	127 (40.4)
Vaccinated for Influenza this season, No. (%)	201 (59.1)
History of Intubation, No. (%)	6 (1.7)
Hospitalized for Asthma in the Past Year, No. (%)	15 (4.3)
Emergency Room Visit for Asthma in the Past Year, No. (%)	50 (14.4)
Oral Steroids use in the Past Year, No. (%)	101 (29.0)
Asthma Control (ACQ), No. (%)	
Well controlled	115 (32.9)
Uncontrolled	64 (18.3)
Very poorly controlled	170 (48.7)
Poor Asthma-related Quality of Life, No. (%)	131 (37.6)
Beliefs about Asthma Medications, Necessity, Mean (SD)	16.9 (4.6)
Beliefs about Asthma Medications, Concerns, Mean (SD)	14.6 (4.0)
Brief Illness Perception, Mean (SD)	36.1 (13.5)
Catastrophizing about Asthma Scale, Mean (SD)	29.8 (26.3)
Patient Health Questionnaire-9, Depressed, No. (%)	60 (17.1)
SCID PTSD, No. (%)	101 (31.1)
PTSD Checklist for DSM-5, No. (%)	61 (17.7)
On Controller Medications, No. (%)	219 (60.7)
Non-Adherent Medication Adherence Response Scale (MARS), No. (%)	123 (58.8)
Adherence Starts with Knowledge-12, Mean (SD)	22.6 (5.9)
Asthma Self-Efficacy (Modified), Mean (SD)	5.9 (1.9)
Comprehensive Environmental Control Practices, No. (%)	161 (46.7)
Incorrect Metered Dose Inhaler Technique, No. (%)	70 (25.1)
Forced Expiratory Volume in first second% Predicted, Mean (SD)	78.7 (22.2)
Comorbidities, No. (%)	
Gastric Esophageal Reflux Disorder	233 (64.5)
Chronic Sinusitis	203 (56.2)
Diabetes	61 (16.9)
Hypertension	152 (42.1)
Major depression (SCID)	92 (28.3)

Table 1b. Device Data

Device Characteristics	Baseline	6 Months	12 Months
Asthma Symptom Perception, Mean (SD)	**N = 222**	**N = 90**	**N = 75**
% Time in Over-Perception Zone	62.1 (26.84)	61.63 (26.44)	61.52 (30.28)
% Time in Accurate Perception Zone	20.73 (25.01)	19.77 (22.36)	22.51 (28.48)
% Time in Under-Perception Zone	17.06 (25.84)	17.92 (26.66)	16.23 (24.8)
Valid Data Points	45.92 (12.77)	46.38 (16.47)	45.75 (13.57)
Asthma Symptom Perception when Obstructed (PEF <80) Mean, (SD)	**N = 217**	**N = 84**	**N = 70**
% Time in Over-Perception Zone	56.91 (38.2)	62.92 (36)	58.66 (41.09)
% Time in Accurate Perception Zone	35.23 (36.79)	31.17 (34.35)	32.28 (38.38)
% Time in Under-Perception Zone	3.44 (15.29)	1.85 (9.15)	1.95 (11.78)
Valid Data Points	22.15 (16.39)	22.25 (16.55)	23.89 (17.86)
Peak Expiratory Flow measures, Mean (SD)	**N = 217**	**N = 90**	**N = 75**
Actual Peak Expiratory Flow	364.16 (134.96)	358.14 (134.41)	350.83 (135.21)
Guessed Peak Expiratory Flow	391.21 (109.23)	385.04 (102.91)	395.11 (96.87)
Predicted Peak Expiratory Flow % (Ratio of Actual PEF and Predicted PEF)	75 (28)	73 (26)	70 (28)
Quick Relief Dosers, Mean (SD)	**N = 146**	**N = 96**	**N = 79**
Rescue Usage per week	1.95 (2.04)	1.48 (1.67)	1.59 (1.73)

Abbreviations: PEF: Peak Expiratory Flow; PTSD: Post-traumatic Stress Disorder; SD: Standard Deviation

Table 2. Unadjusted Associations between Post-Traumatic Stress Disorder with Serum and Sputum Cytokine Levels in World Trade Center Workers with Asthma

Cytokine	Blood			Sputum		
	No PTSD	PTSD	P-value	No PTSD	PTSD	P-value
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
IL-1α	107.6 (340.8)	97.5 (306.2)	0.63	102.2 (138.2)	115.2 (127.8)	0.66
IL-1β	0.6 (1.1)	1.1 (2.6)	0.35	15.6 (23.4)	13.1 (11.5)	0.63
IL-2	0.5 (0.9)	1 (2.3)	0.41	0.2 (0.6)	0.1 (0.3)	0.88
IL-3	0.6 (0.6)	0.7 (0.6)	0.25	0.07 (0.2)	0.1 (0.3)	0.84
IL-4	141.6 (584.0)	165.9 (529.8)	0.35	12.5 (14.6)	12.2 (18.9)	0.55
IL-5	3 (8.7)	3.7 (7.9)	0.54	1.7 (1.5)	1.0 (1.0)	0.034
IL-6	14.9 (52.1)	14.2 (39.1)	0.72	14.3 (20.3)	17.4 (13.3)	0.054
IL-7	1 (2.8)	2.4 (6.5)	0.42	13.8 (10.6)	13.5 (9.2)	0.97
IL-8	8.4 (21.7)	9.3 (19.3)	0.84	1204.5 (1265.2)	992.0 (1306.7)	0.43
IL-10	6.6 (17.4)	5.7 (12.7)	0.57	3.2 (2.8)	4.2 (4.5)	0.59
IL-12	11.3 (19.4)	12.3 (27.4)	0.81	1.8 (5.9)	1.2 (2.1)	0.74
IL12p70	5.2 (28.7)	3.1 (6.4)	0.34	3.5 (7.5)	2.6 (1.9)	0.93
IL-13	30.7 (118.2)	30.0 (93.5)	0.7	4.7 (3.4)	3.7 (2.4)	0.51
IL-15	2.4 (4.2)	2.1 (3.5)	0.73	3.5 (4.4)	3.2 (2.4)	0.6
IL-17α	3.6 (13.9)	4.9 (18.6)	0.46	1.2 (2.7)	0.7 (1.1)	0.42
IL-1Rα	19.5 (29.0)	22.4 (31.9)	0.55	4119.6 (2321.1)	3864.8 (2616.7)	0.52
G-CSF	22.1 (22.8)	26.4 (31.7)	0.92	236.1 (415.9)	407.2 (518.9)	0.2
GM-CSF	4.5 (7.0)	5.3 (8.3)	0.78	1.5 (1.2)	1.2 (0.8)	0.65
IP10	468.2 (446.7)	438.4 (293.6)	0.94	3023.7 (3781.5)	3843.1 (4045.1)	0.18
IFN-α2	17.7 (26.0)	18 (30.5)	0.67	11.6 (8.7)	12.2 (11.3)	0.95
IFN–γ	4.3 (8.3)	8.9 (30.6)	0.94	2.3 (2.1)	2.5 (2.7)	0.64
Eotaxin	118.5 (82.0)	135.6 (90.7)	0.24	19.2 (24.5)	16.3 (15.5)	0.68
EGF	25.1 (28.7)	19.7 (19.6)	0.26	546.6 (394.5)	441.6 (173.6)	0.65
MCP1	374.8 (186.6)	383.7 (176.7)	0.58	971.7 (1010.5)	626.0 (387.0)	0.38
MIP1-α	4.9 (16.0)	4.7 (12.2)	0.53	27.0 (53.0)	27.3 (29.0)	0.8
MIP1-β	14.6 (15.1)	13.6 (16.3)	0.5	42.3 (104.7)	34.2 (48.4)	0.57
RANTES	3066.1 (2254.7)	2688.8 (1654.1)	0.62	7.3 (5.5)	8.1 (7.4)	0.85
TNF-α	9.1 (5.7)	10.8 (7.8)	0.21	5.8 (10.1)	5.4 (4.9)	0.64
TNF-β	59.6 (221.7)	51.2 (153.5)	0.97	0.5 (2.1)	0.1 (0.4)	0.37
VEGF	23.6 (34.9)	39.3 (85.5)	0.66	665.6 (926.1)	522.0 (377.8)	0.51
Eosinophils (%)	-	-	-	3.7 (4.0)	6.8 (8.9)	0.17
Neutrophils (%)	-	-	-	8.8 (7.2)	19.1 (17.5)	0.047
Macrophages (%)	-	-	-	86.6 (9.0)	73.3 (23.9)	0.14
Lymphocytes (%)	-	-	-	0.9 (0.7)	0.8 (0.5)	0.64

Abbreviations: PTSD: Post Traumatic Stress Disorder, IL: interleukin, G-CSF: granulocyte colony stimulating factor, GM-CSF: granulocyte-macrophage colony-stimulating factor, IP: interferon gamma

inducible protein, IFN: interferon, EGF: MIP: TNF: tumor necrosis factor, VEFG: vascular endothelial growth factor

Table 3. Adjusted Mean Differences in Blood and Sputum Cytokine Level in World Trade Center Workers with vs. without Post-Traumatic Stress Disorder

	Blood		Sputum	
Cytokine	**Mean Difference**	**95% CI**	**Mean Difference**	**95% CI**
IL-1α	-46.4	-196.9 to 104	-0.4	-122.3 to 121.6
IL-1β	0.4	-0.5 to 1.3	0.6	-17.6 to 18.9
IL-2	0.4	-0.3 to 1.2	-0.3	-0.8 to 0.3
IL-3	0.1	-0.2 to 0.3	-0.08	-0.3 to 0.1
IL-4	46.6	-269.6 to 362.9	-3.1	-10.6 to 4.4
IL-5	-0.006	-4.2 to 4.2	-0.9	-2.3 to 0.4
IL-6	-3.3	-27.7 to 21.2	15.7	-4.3 to 35.6
IL-7	1.6	-0.2 to 3.6	-0.5	-10.1 to 9.1
IL-8	-0.2	-10.6 to 10	388.0	-1004.7 to 1780.7
IL-10	-0.4	-7.5 to 6.7	0.6	-3.1 to 4.3
IL-12	-5.1	-14.5 to 4.3	-1.5	-7.5 to 4.4
IL12p70	-1.2	-14.8 to 12.3	-1.9	-8.2 to 4.4
IL-13	-11.4	-63.8 to 41.1	-2.2	-5.6 to 1.2
IL-15	-0.5	-2.6 to 1.6	-0.6	-4.8 to 3.6
IL-17α	1.5	-6.8 to 9.8	0.03	-2.7 to 2.8
IL-1Rα	4.4	-9.9 to 18.8	-530.7	-2839.9 to 1778.5
G-CSF	6.9	-4.7 to 18.5	313.5	-135.3 to 762.4
GM-CSF	0.8	-3.0 to 4.6	-0.3	-1.5 to 0.9
IP10	-114.4	-310.1 to 81.2	1445	-2186.2 to 5076.2
IFN-α2	-4.4	-17.1 to 8.2	-3.2	-10.8 to 4.5
IFN–γ	4	-5.5 to 31.5	0.1	-2.4 to 2.7
Eotaxin	-3.5	-38.5 to 31.4	-0.8	-24.7 to 23
EGF	-7.1	-19.6 to 5.4	-33.6	-348.4 to 281
MCP1	-12.2	-91.8 to 67.3	-322.8	-1223.1 to 577.5
MIP1-α	-2.5	-9.5 to 4.6	4.7	-48.4 to 57.9
MIP1-β	-1.3	-7.6 to 4.9	2.0	-102.1 to 106.1
RANTES	-490.4	-1430.7 to 449.5	2.2	-3.6 to 8.1
TNF-α	2	-0.8 to 4.8	2.5	-7.1 to 12.2
TNF-β	-15.6	-112.7 to 81.4	-0.5	-2.6 to 1.5
VEGF	14.6	-15.7 to 44.9	-172.9	-964.2 to 618.3
Eosinophils (%)	-	-	0.7	-6.0 to 7.3
Neutrophils (%)	-	-	0.1	-18.1 to 18.2
Macrophages (%)	-	-	-0.8	-21.8 to 20.1
Lymphocytes (%)	-	-	0.1	-1.2 to 1.4

Abbreviations: CI: Confidence Interval; PTSD: Post Traumatic Stress Disorder; IL: interleukin; G-CSF: granulocyte colony stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; IP: interferon gamma inducible protein; IFN: interferon; EGF: epidermal growth factor; MIP: Macrophage Inflammatory Protein; TNF: tumor necrosis factor; VEFG: vascular endothelial growth factor

Table 4. Correlations Between Blood and Sputum Cytokine Levels and PTSD Checklist for DSM-5 Scores

Cytokine	Blood		Sputum	
	Correlation Coefficient	p-value	Correlation Coefficient	p-value
IL-1α	-0.1	0.47	0.1	0.52
IL-1β	0	0.52	0.1	0.66
IL-2	0.1	0.38	0	0.73
IL-3	0.1	0.14	0.1	0.63
IL-4	0.1	0.24	0	0.85
IL-5	0	0.78	-0.1	0.56
IL-6	0.1	0.19	0	0.92
IL-7	0.1	0.25	0.1	0.34
IL-8	0.1	0.41	-0.2	0.13
IL-10	0	0.86	0.2	0.22
IL-12	0	0.88	0.2	0.24
IL12p70	0	0.68	0.1	0.25
IL-13	0	0.75	-0.2	0.16
IL-15	0	0.95	0.2	0.12
IL-17α	-0.1	0.5	-0.1	0.48
IL-1Rα	0.1	0.33	-0.1	0.63
G-CSF	0.1	0.2	0.1	0.41
GM-CSF	0	0.68	0	0.93
IP10	0	0.93	0.3	0.02
IFN-α2	0.1	0.41	0.1	0.52
IFN–γ	0.1	0.2	0.1	0.69
Eotaxin	0.1	0.16	0.1	0.23
EGF	-0.1	0.47	0	0.73
MCP1	0.1	0.32	-0.1	0.64
MIP1-α	-0.1	0.3	0	0.79
MIP1-β	0	0.95	0	0.89
RANTES	-0.1	0.08	0.1	0.52
TNF-α	0.1	0.22	0	0.94
TNF-β	0.1	0.39	0	0.77
VEGF	0	0.55	0.1	0.58
Eosinophils (%)	-	-	0.3	0.07
Neutrophils (%)	-	-	0.3	0.1
Macrophages (%)	-	-	-0.2	0.19
Lymphocytes (%)	-	-	0.1	0.39

Abbreviations: PTSD: Post Traumatic Stress Disorder; IL: interleukin; G-CSF: granulocyte colony stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; IP: interferon gamma inducible protein; IFN: interferon; EGF: epidermal growth factor; MIP: Macrophage Inflammatory Protein; TNF: tumor necrosis factor; VEFG: vascular endothelial growth factor

Table 5. Adjusted Association between Blood and Sputum Cytokine Levels and PTSD Checklist for DSM-5 Scores

Cytokine	Blood		Sputum	
	Mean Difference	95% CI	Mean Difference	95% CI
IL-1α	-1.0	-5.4 to 3.3	-1.1	-5.3 to 3.0
IL-1β	0.03	0.01 to 0.06	-0.4	-1.0 to 0.2
IL-2	0.03	0.01 to 0.06	-0.01	-0.03 to 0.01
IL-3	0.01	-0.001 to 0.01	0.002	-0.01 to 0.01
IL-4	3.5	-6.2 to 13.3	0.1	-0.2 to 0.3
IL-5	0.01	-0.1 to 0.1	-0.02	-0.1 to 0.02
IL-6	0.03	-0.7 to 0.7	0.02	-0.7 to 0.7
IL-7	0.1	0.02 to 0.1	0.2	-0.1 to 0.5
IL-8	0.1	-0.2 to 0.4	-19.3	-66.2 to 27.6
IL-10	0.1	-0.1 to 0.3	0.1	-0.01 to 0.2
IL-12	-5.1	-14.5 to 4.3	-0.1	-0.3 to 0.1
IL12p70	-0.02	-0.4 to 0.4	-0.1	-0.3 to 0.1
IL-13	-0.2	-1.7 to 1.3	-0.1	-0.2 to 0.05
IL-15	0.03	-0.03 to 0.09	-0.04	-0.2 to 0.1
IL-17α	0.2	-0.04 to 0.4	-0.03	-0.1 to 0.1
IL-1Rα	4.4	-9.9 to 18.8	-45.0	-121.7 to 31.7
G-CSF	0.3	-0.001 to 0.7	4.0	-11.5 to 19.4
GM-CSF	0.01	-0.1 to 0.1	-0.0	-0.1 to 0.03
IP10	-3.2	-8.8 to 2.4	101.6	-18.3 to 22.15
IFN-α2	0.1	-0.3 to 0.4	0.02	-0.2 to 0.3
IFN–γ	0.3	0.05 to 0.6	0.1	-0.02 to 0.1
Eotaxin	0.7	-0.3 to 1.7	0.2	-0.6 to 1.1
EGF	-0.1	-0.4 to 0.3	-2.0	-12.6 to 8.6
MCP1	0.6	-1.6 to 2.9	1.7	-28.9 to 32.3
MIP1-α	-0.1	-0.2 to 0.1	0.2	-1.6 to 2.0
MIP1-β	-1.3	-7.6 to 4.9	0.1	-3.4 to 3.6
RANTES	-24.6	-51.2 to 2.0	0.1	-0.1 to 0.3
TNF-α	0.1	0.02 to 0.2	-0.02	-0.3 to 0.3
TNF-β	-0.2	-3.0 to 2.5	-0.01	-0.1 to 0.1
VEGF	1.4	0.6 to 2.3	8.8	-17.9 to 35.5
Eosinophils (%)	-	-	0.1	-0.2 to 0.4
Neutrophils (%)	-	-	-0.5	-1.3 to 0.3
Macrophages (%)	-	-	0.4	-0.6 to 1.3
Lymphocytes (%)	-	-	0.03	-0.03 to 0.09

Abbreviations: CI: Confidence interval; PTSD: Post Traumatic Stress Disorder; IL: interleukin; G-CSF: granulocyte colony stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; IP: interferon gamma inducible protein; IFN: interferon; EGF: epidermal growth factor; MIP: Macrophage Inflammatory Protein; TNF: tumor necrosis factor; VEFG: vascular endothelial growth factor

Table 6. Unadjusted Associations of Post-traumatic Stress Disorder with Measures of Asthma Control, Airway Obstruction and Symptom Perception

Outcome	PTSD	No PTSD	p-value
PEF in liters per minute, Mean (SD)	351.92 (143.25)	364.62 (131.61)	0.55
Predicted Peak Expiratory Flow, Mean % (SD)	73 (30)	76 (27)	0.78
Asthma Symptom Perception, Mean (SD)			
% Time in Over-Perception Zone	22.4 (32.2)	15.6 (23.8)	0.3
% Time in Accurate Perception Zone	61.6 (31.7)	62.0 (25.6)	0.6
% Time in Under-Perception Zone	16.0 (24.7)	22.4 (25.2)	0.02
Symptom Perception when Obstructed (PEF<80), Mean (SD)			
% Time in Over-Perception Zone	4.5 (18.2)	3.2 (14.6)	0.4
% Time in Accurate Perception Zone	67.0 (37.2)	53.5 (38.1)	0.01
% Time in Under-Perception Zone	23.3 (32.1)	38.9 (37.5)	0.004

Abbreviations: PEF: Peak Expiratory Flow; PTSD: Post-traumatic Stress Disorder; SD: Standard Deviation

Table 7. Adjusted Associations between Post-traumatic Stress Disorder, Peak Expiratory Flow, Symptom Perception in World Trade Center Workers with Asthma

Outcome	Mean Difference PTSD vs. No PTSD	95% Confidence Interval
Asthma Control Questionnaire, Mean (SD)[a]	0.9	0.5 to 1.3
Asthma Quality of Life Questionnaire, Mean (SD)	-1.4	-1.9 to -1.0
Peak Expiratory Flow, liters per minute	-10.5	-47.3 to 26.4
Predicted Peak Expiratory Flow (%)	-3	-10 to 5
Asthma Symptom Perception, Mean (SD)[b]		
% Time in Over-Perception Zone	6.2	-2.1 to 14.5
% Time in Accurate Perception Zone	0.1	-8.6 to 8.9
% Time in Under-Perception Zone	-6.5	-14.5 to 1.6
Symptom Perception when Obstructed (PEF<80), Mean (SD)		
% Time in Over-Perception Zone	1.4	-3.8 to 6.6
% Time in Accurate Perception Zone	13.5	0.8 to 26.3
% Time in Under-Perception Zone	-14.8	-27.0 to -2.7

Abbreviations: PTSD: post-traumatic stress disorder; SD: standard deviation; PEF: peak expiratory flow
[a]Adjusted for age, sex, race/ethnicity, smoking status, income, post 9/11 asthma, use of controller medications, and comorbidities
[b]Adjusted for age, sex, and race/ethnicity

Table 9. Unadjusted Associations between PTSD and Self-Management Behaviors among WTC Workers with Asthma

Self-management behavior	No PTSD (n=192)	PTSD (n=84)	p-value
Medication adherence			
MARS score, mean (SD)	4.0 (0.8)	4.1 (0.7)	0.7
MARS percent adherent, n (%)	54 (41)	18 (34)	0.4
ASK-12 score, mean (SD)	22.0 (5.5)	24.0 (5.9)	0.01
Inhaler technique			
Inhaler technique, mean (SD)	6.5 (1.6)	6.6 (1.7)	0.6
Adequate inhaler technique, n (%)	132 (75)	62 (80)	0.4
Use action plan, n (%)	76 (42)	35 (49)	0.2
Trigger avoidance, n (%)	89 (47)	44 (55)	0.2
Influenza vaccination, n (%)	110 (59)	49 (62)	0.5

Abbreviations: PTSD: post-traumatic stress disorder; MARS: Medication Adherence Rating Scale; ASK: Adherence Starts with Knowledge questionnaire; SD: standard deviation

Table 10. Adjusted Associations between PTSD and Self-Management Behaviors among WTC Workers with Asthma*

Self-management Behavior	Adjusted Mean Difference (95% CI) or adjusted OR (95% CI)
Medication adherence	
MARS score, mean difference (95% CI)	-0.15 (-0.5 to 0.2)
MARS percent adherent, OR (95% CI)	2.5 (0.9 to 6.8)
ASK-12 score, mean difference (95% CI)	1.70 (-0.3 to 3.6)
Inhaler technique	
Inhaler technique, mean difference (95% CI)	-0.12 (-0.7 to 0.5)
Adequate inhaler technique, OR (95% CI)	0.9 (0.4 to 2.3)
Use action plan, OR (95% CI)	0.8 (0.4 to 1.8)
Trigger avoidance, OR (95% CI)	0.9 (0.4 to 1.8)
Influenza vaccination, OR (95% CI)	0.7 (0.3 to 1.5)

Abbreviations: CI: confidence interval; OR: odds ratio; MARS: Medication Adherence Rating Scale; ASK: Adherence Starts with Knowledge questionnaire
*Adjusted for age, sex, race and ethnicity, education, income, asthma onset post 9/11, and comorbidities.

Table 11. Disease and Medication Beliefs among WTC Workers with Asthma with and without PTSD

Belief	No PTSD Mean (SD)	PTSD Mean (SD)	p-value	Effect Size
Illness beliefs				
Timeline				
Asthma will continue for a very long time/forever	7.7 (3.4)	8.1 (3.1)	0.4	0.1
Have asthma all the time, not only with symptoms	2.6 (1.4)	2.7 (1.4)	0.4	0.1
Cause				
Asthma is due to WTC exposure	3.43 (0.9)	3.35 (0.9)	0.5	-0.1
Asthma is due to inadequate protection at WTC site	3.40 (0.9)	3.32 (1.0)	0.5	-0.1
Control				
Lack personal control over asthma	3.4 (2.7)	4.3 (3.0)	0.02	0.3
Treatment does not help control asthma	1.6 (2.0)	2.4 (2.5)	0.01	0.3
Hard to know when asthma is starting to get worse	1.9 (0.9)	2.2 (0.9)	0.05	0.2
Managing asthma is difficult	3.4 (2.7)	4.1 (3.0)	0.1	0.3
WTC-related asthma is more severe	2.9 (0.8)	3.0 (0.8)	0.2	0.2
Consequences				
Asthma affects my life	4.8 (2.8)	6.3 (2.5)	0.0001	0.6
Experience a lot of asthma symptoms	5.2 (2.6)	5.9 (2.5)	0.04	0.3
Emotional responses				
Concerned about asthma	6.6 (3.4)	7.5 (2.8)	0.05	0.3
Asthma affects emotionally	2.9 (2.9)	5.6 (3.3)	<.0001	0.9
Always not feeling well	2.4 (2.9)	4.8 (3.4)	<.0001	0.8
Nothing will ever improve the asthma	2.6 (3.2)	4.6 (3.6)	<.0001	0.6
Thinking about asthma makes me sad	1.4 (2.3)	4.5 (3.8)	<.0001	1.1
Worry when asthma is starting to get worse	2.7 (1.2)	3.3 (1.1)	0.0005	0.5
Worry about future because of asthma	2.3 (1.4)	3.0 (1.5)	<.0001	0.5
Coherence				
Don’t understand asthma well	2.3 (2.6)	2.9 (3.0)	0.09	0.2
Medication beliefs				
Necessity	2.9 (0.9)	3.1 (0.8)	0.1	0.2
Concerns	2.9 (0.8)	3.0 (0.8)	0.2	0.2
Self-efficacy				
Confident in ability to control asthma	16.7 (4.4)	18.3 (3.8)	0.004	0.4
Confident in ability to use controller medicines	14.0 (3.8)	16.1 (3.8)	0.0003	0.5
Feel control over future health	1.8 (0.9)	1.6 (0.8)	0.07	-0.2

Abbreviations: PTSD: post-traumatic stress disorder; SD: standard deviation; WTC: World Trade Center

Table 12. Comparison of Pilot Baseline Characteristics by Study Arm

Characteristics	Total	Intervention	Control	p-value
Enrolled and Eligible, %	38 (100)	19 (100)	19 (100)	-
Age, Mean (SD)	54.2 (8.4)	57.3 (7.7)	51.9 (8.3)	0.09
Gender, Female, %	39.3	41.7	37.5	0.99
Race, %				
Black or African American	25.0	41.7	12.5	
White	25.0	25.0	25.0	0.20
Other	14.3	16.7	12.5	
Hispanic/Latino, %	35.7	16.7	50.0	
Insurance, %				
Medicare	25.0	33.3	18.7	
Medicaid	17.9	16.7	18.7	
Medicare and Medicaid	7.1	8.3	6.3	0.80
Private	35.8	25.0	43.7	
Other	7.1	8.3	6.3	
Unknown or Not reported	7.1	8.4	6.3	
Education, %				
Some High School	7.4	0.0	12.5	
High School Graduate or GED	18.5	18.2	18.7	
Any College	55.6	63.6	50.0	0.66
College Graduate	11.1	18.2	6.3	
Higher Degree	7.4	0.0	12.5	
Monthly Income, %				
Less than $3000	51.9	50.0	53.3	0.86
More than $3000	48.1	50.0	46.7	
Married, %	50.0	25.0	68.7	**0.02**
Language, Mostly English, %	75.0	91.7	62.5	0.28
Ever smoked, %	28.0	40.0	20.0	0.38
Hospitalization in the Past 12 Months, %	11.1	9.1	12.5	0.99
Emergency Visit in the Past 12 Months, %	14.3	8.3	18.7	0.61
Posttraumatic Stress Disorder for Structured Clinical Interview for DSM-5, %	74.1	72.7	75.0	0.99

Abbreviations: SD: standard deviation; GED: general educational development; DSM-5: Diagnostic and Statistical Manual, 5th edition
Percentages may not add to 100% due to rounding

Table 13. Comparison of Pilot Baseline (Pre-Intervention) and 1-Week and 3-Month Post-Intervention by Study Arm

Outcome	Baseline (Pre-Intervention)			1 Week Post-Intervention			3 Months Post-Intervention		
	Intervention	Control		Intervention	Control		Intervention	Control	
	Mean (SD)	Mean (SD)	P	Mean (SD)	Mean (SD)	P	Mean (SD)	Mean (SD)	P
Asthma Control Questionnaire	2.1 (1.1)	2.1 (0.4)	0.9	1.7 (1.0)	2.0 (0.7)	0.3	1.9 (1.5)	2.1 (0.9)	0.6
Asthma Quality of Life Questionnaire	3.7 (1.1)	3.7 (0.8)	0.9	4.3 (1.2)	3.9 (1.0)	0.5	4.4 (1.6)	3.8 (1.0)	0.2
Medication Adherence Reporting Scale	4.4 (0.8)	4.5 (0.7)	0.9	4.5 (0.6)	4.5 (1.1)	0.5	4.6 (0.6)	4.5 (0.8)	0.9
Illness Beliefs Questionnaire	47.0 (14.3)	46.8 (12.3)	1.0	41.4 (10.3)	44.0 (12.3)	0.6	42.7 (13.1)	44.6 (12.9)	0.7
Beliefs about Medication Questionnaire									
Necessity Score	20.1 (2.8)	19.5 (3.2)	0.9	20.7 (1.8)	19.4 (4.1)	0.7	19.5 (3.5)	18.8 (3.7)	0.7
Concerns Score	16.3 (2.7)	17.2 (4.0)	0.5	16.0 (3.7)	16.9 (4.4)	0.6	17.1 (4.6)	16.0 (4.3)	0.7
Posttraumatic Stress Disorder Checklist for DSM-5,	39.2 (10.3)	36.4 (9.6)	0.4	32.9 (14.7)	34.3 (11.3)	0.8	29.8 (17.4)	30.9 (9.1)	0.8
Patient Health Questionnaire-9	12.9 (5.4)	10.9 (4.9)	0.2	9.7 (4.6)	10.4 (6.4)	0.8	10.1 (7.5)	9.7 (5.8)	0.9
Generalized Anxiety Disorder-7	11.1 (5.1)	9.4 (4.6)	0.3	10.1 (5.6)	8.9 (5.7)	0.6	9.3 (7.8)	8.1 (5.2)	0.6

Abbreviations: SD: standard deviation; DSM-5: Diagnostic and Statistical Manual, 5th edition

C. OVERALL PRODUCTS

C.1 PUBLICATIONS

Are there publications or manuscripts accepted for publication in a journal or other publication (e.g., book, one-time publication, monograph) during the reporting period resulting directly from this award?

Yes

Publications Reported for this Reporting Period

Public Access Compliance	Citation
N/A: Not NIH Funded	Wisnivesky JP, Markowitz SB, James S, Stone K, Dickens B, Busse P, Crowley L, Federman A, Katz C, Gonzalez A. Comorbid posttraumatic stress disorder and major depressive disorder are associated with asthma morbidity among World Trade Center workers. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2021 March;126(3):278-283. PubMed PMID: 33098982; DOI: 10.1016/j.anai.2020.10.007.

C.2 WEBSITE(S) OR OTHER INTERNET SITE(S)

NOTHING TO REPORT

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

C.4 INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES

Have inventions, patent applications and/or licenses resulted from the award during the reporting period? No

If yes, has this information been previously provided to the PHS or to the official responsible for patent matters at the grantee organization? No

C.5 OTHER PRODUCTS AND RESOURCE SHARING

NOTHING TO REPORT

D. OVERALL PARTICIPANTS

D.1 WHAT INDIVIDUALS HAVE WORKED ON THE PROJECT?

Commons ID	S/K	Name	Degree(s)	Role	Cal	Aca	Sum	Foreign Org	Country	SS
JWISNIVESKY	Y	WISNIVESKY, JUAN P	MPH,DPH,MD	PD/PI	1.4	0.0	0.0			NA
	N	Birmingham, Janette		Technician	2.6	0.0	0.0			NA
	N	Castano, Katerina		Non-Student Research Assistant	4.6	0.0	0.0			NA
	N	Crawford, Ginger		Non-Student Research Assistant	2.2	0.0	0.0			NA
	N	Dickens, Brittany		Non-Student Research Assistant	6.0	0.0	0.0			NA
	N	Budinoska, Tamara		Non-Student Research Assistant	2.4	0.0	0.0			NA
	N	Ankam, Jyoti		Non-Student Research Assistant	1.3	0.0	0.0			NA
	N	Herrera-Moreno, Julia		Non-Student Research Assistant	2.3	0.0	0.0			NA
	N	Silverstein, Gabriella		Graduate Student (research assistant)	5.1	0.0	0.0			NA
	N	Busse, Paula	MD	Co-Investigator	1.3	0.0	0.0			NA
	N	Dicker, Elisa		Non-Student Research Assistant	2.2	0.0	0.0			NA

Glossary of acronyms:
S/K - Senior/Key
Cal - Person Months (Calendar)
Aca - Person Months (Academic)
Sum - Person Months (Summer)
Foreign Org - Foreign Organization Affiliation
SS - Supplement Support
RS - Reentry Supplement
DS - Diversity Supplement
OT - Other
NA - Not Applicable

D.2 PERSONNEL UPDATES

D.2.a Level of Effort

Not Applicable

D.2.b New Senior/Key Personnel Not Applicable
D.2.c Changes in Other Support Not Applicable
D.2.d New Other Significant Contributors Not Applicable
D.2.e Multi-PI (MPI) Leadership Plan Not Applicable

E. OVERALL IMPACT

E.1 WHAT IS THE IMPACT ON THE DEVELOPMENT OF HUMAN RESOURCES? Not Applicable
E.2 WHAT IS THE IMPACT ON PHYSICAL, INSTITUTIONAL, OR INFORMATION RESOURCES THAT FORM INFRASTRUCTURE? NOTHING TO REPORT
E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER? Not Applicable
E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)? NOTHING TO REPORT

G. OVERALL SPECIAL REPORTING REQUIREMENTS SPECIAL REPORTING REQUIREMENTS

G.1 SPECIAL NOTICE OF AWARD TERMS AND FUNDING OPPORTUNITIES ANNOUNCEMENT REPORTING REQUIREMENTS

NOTHING TO REPORT

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

G.4.a Does the project involve human subjects?

Not Applicable

G.4.b Inclusion Enrollment Data

File(s) uploaded:
WTCPTSD RPPR 2022 Inclusion Enrollment pdf.pdf

G.4.c ClinicalTrials.gov

Does this project include one or more applicable clinical trials that must be registered in ClinicalTrials.gov under FDAAA?

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

NOT APPLICABLE

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

Does this project involve human embryonic stem cells (only hESC lines listed as approved in the NIH Registry may be used in NIH funded research)?

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT No foreign component
G.10 ESTIMATED UNOBLIGATED BALANCE Not Applicable
G.11 PROGRAM INCOME Not Applicable
G.12 F&A COSTS Not Applicable

Cumulative Inclusion Enrollment Report

This report format should NOT be used for collecting data from study participants.

Study Title: Assessing Inflammatory and Behavioral Pathways Linking PTSD to Increased Asthma Morbidity in WTC Workers

Comments:

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native	0	2	0	0	0	0	0	0	0	**2**
Asian	4	9	0	0	0	0	0	0	0	**13**
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0	**0**
Black or African American	26	50	0	0	0	0	0	0	0	**76**
White	18	100	0	0	0	0	0	0	0	**118**
More Than One Race	2	4	0	0	1	0	0	0	0	**7**
Unknown or Not Reported	13	11	0	37	83	0	0	1	0	**145**
Total	**63**	**176**	**0**	**37**	**84**	**0**	**0**	**1**	**0**	**361**

I. OVERALL OUTCOMES

I.1 What were the outcomes of the award?

Findings resulting from this award have been disseminated in several ways. First, results have been presented annually at World Trade Center Investigator meetings throughout the award period. Additionally, analyses of the relationship between post-traumatic stress disorder and comorbid major depressive disorder with asthma outcomes were accepted for presentation at the 2020 American Thoracic Society national conference – and while the event was cancelled due to COVID-19, the abstract was disseminated via the Society's website. Third, this award has resulted in two peer-reviewed publications (in Annals of Allergy, Asthma & Immunology and the Journal of Allergy and Clinical Immunology Practice), with two additional manuscripts currently under review and one in preparation for submission. These publications will be used to present pertinent findings under Aims 1, 2 and 3 to audiences in allergy and immunology and mental health care professions. Finally, results from the clinical trial in Aim 4 will be developed into an additional manuscript.