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Comorbid Post-traumatic Stress Disorder and Major Depression Disorder Associated with Asthma Morbidity among WTC Workers

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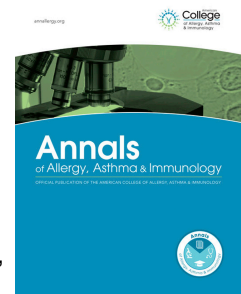
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Title: Comorbid Post-traumatic Stress Disorder and Major Depression Disorder Associated with Asthma Morbidity among WTC Workers

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Abbreviations: World Trade Center (WTC), Post-Traumatic Stress Disorder (PTSD), Asthma Control Questionnaire (ACQ); Asthma Quality of Life Questionnaire (AQLQ); World Trade Center Health Programs (WTCHP); Diagnostic and Statistical Manual (DSM) for Mental Disorders (SCID); Major Depressive Disorder (MDD);

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Background : World Trade Center (WTC) rescue and recovery workers suffer a high burden of asthma, comorbid post-traumatic stress disorder (PTSD) ,and depression. PTSD is associated with worse asthma outcomes.

Objective : In this study, we evaluated whether the relationship between PTSD and asthma morbidity is modified by depression.

Methods : We used data from a cohort of WTC workers with asthma. Asthma control (ACQ), resource utilization, and quality of life (AQLQ) were evaluated. We used regression analyses to evaluate the adjusted association of PTSD and depression with asthma control, resource utilization and quality of life.

Results : Of the study cohort of 293 WTC workers with asthma, 19% had PTSD alone, 2% had MDD alone and 12% had PTSD and MDD. Adjusted mean differences (95% CI) in ACQ scores were 1.32 (0.85 to 1.80) for WTC workers with PTSD and MDD, 0.44 (0.03 to 0.84) for those with PTSD alone, and 0.50 (-0.38 to 1.38) for workers with MDD alone compared to those without depression or PTSD. WTC workers with PTSD and depression, PTSD alone, and depression alone had mean (95% CI) adjusted differences in AQLQ scores of -1.67 (-2.22 to -1.12), -0.56 (-2.23 to -1.12), and -1.21 (-2.23 to -0.18) compared to workers without depression or PTSD. Similar patterns were observed for acute resource utilization.

Conclusion : PTSD and depression appear to have a synergistic effect that worsens asthma control and quality of life. Efforts to improve asthma outcomes in this population should address the negative impacts of these common mental health conditions.

1 Introduction

2
3 Asthma is one of the most common chronic conditions reported among rescue and recovery
4 workers and other populations exposed to the debris following the collapse of the World Trade
5 Center (WTC) towers on September 11, 2001 or ground zero during the subsequent months.^{1,2}
6 Over a follow-up period of >10 years, multiple studies have reported that up to one third of
7 exposed individuals have developed asthma.²⁻⁵ Research has also shown that asthma is a major
8 source of morbidity and poor quality of life among WTC-exposed populations as well as an
9 important contributor to health care costs.⁶⁻⁸

10
11 Post-traumatic stress disorder (PTSD) and depression are the most common mental health
12 conditions among WTC workers.⁹ Two systematic reviews of the health effects of the WTC
13 attacks documented that workers and first responders were >10 times more likely to have PTSD
14 symptoms compared to the general population.^{10,11} Similarly, symptoms of depression have been
15 documented in up to 15% of WTC workers and exposed local residents.¹² Moreover, many WTC
16 workers have comorbid PTSD and depression.¹²⁻¹⁴ PTSD is one of the strongest risk factors for
17 lack of asthma control, decreased asthma-related quality of life and increased healthcare resource
18 utilization among WTC-exposed populations.^{5,15,16} Similarly, depression (particularly, symptoms
19 of depression) is a risk factor for worse asthma outcomes in the general population; however, this
20 association has not been demonstrated in the setting of WTC exposure.¹⁷⁻¹⁹ Despite the high
21 prevalence and potential interrelationship among these mental health conditions, prior studies
22 have not evaluated the combined impact of PTSD and depression on asthma morbidity among
23 WTC workers.

24

25 In this study, we used data from a well-characterized cohort of WTC workers with asthma to
26 assess the interaction between PTSD and depression on asthma control, asthma-related resource
27 utilization and quality of life.

28

29 **Methods**

30

31 *Study Population*

32

33 We recruited a cohort of WTC rescue and recovery workers with a physician diagnosis of asthma
34 that were monitored and/or treated at the Mount Sinai Hospital or North Shore-Long Island
35 Jewish Health System/Queens College sites of the World Trade Center Health Programs
36 (WTCHP) Clinical Centers of Excellence. WTCHP-eligible general responders worked or
37 volunteered for ≥ 4 hours from September 11 to 14, 2001, ≥ 24 hours during September 2001, or
38 ≥ 80 hours from September to December 2001. Members of the Office of the Chief Medical
39 Examiner who processed human remains and workers from the Port Authority Trans Hudson
40 Corporation who were engaged in cleaning tunnels for ≥ 24 hours from September 11, 2001 to
41 July 1, 2002 are also eligible. Additional details about the WTCHP have been previously
42 reported.^{20,21}

43

44 Inclusion criteria included age ≥ 18 years, physician diagnosis of asthma, and ability to
45 communicate in English or Spanish. WTC workers with a history of significant tobacco exposure

(≥ 15 pack-years of smoking history), chronic obstructive lung disease, or other chronic respiratory illness were excluded from the study.

Potential study participants had already indicated willingness to be contacted for research were mailed an invitation and later contacted by research staff. Those interested in participating signed informed consent, underwent a short screening assessment and then completed a standardized in-person interview conducted in English or Spanish based on participant's preference. The study was approved by the Institutional Review Boards of the Icahn School of Medicine at Mount Sinai and that of Queens College, City University of New York.

Study Variables

Socio-demographic information including age, sex, race and ethnicity, education, income, marital status, and language was ascertained using validated tools.²² We also collected information regarding asthma history, asthma diagnosis in relation to WTC exposure, medication regimen and family history of asthma, and level of WTC exposure.²

We used the Structured Clinical Interview for Diagnostic and Statistical Manual (DSM) for Mental Disorders (SCID) Patient Edition Version Five to assess for the presence of PTSD and/or major depressive disorder (MDD).²³ The SCID is the gold standard for psychiatric interviews, has excellent reliability and validity and was administered by trained study personnel. Based on the results of this assessment, participants were classified into 4 groups: no PTSD or MDD, PTSD alone, MDD alone, and both PTSD and MDD.

Primary outcomes included asthma control, acute asthma-related resource utilization and asthma-related quality of life. The Asthma Control Questionnaire (ACQ) was used to assess the level of asthma control among study participants.²⁴ 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 prior week. The ACQ items are scored on a scale of 0 to 6 with higher scores indicating worse asthma control; the minimal clinically significance difference is 0.5 units.²⁵

Resource utilization related to acute asthma exacerbations was assessed based on self-reports of the number of emergency room (ER) visits or hospitalizations during the prior 12 months. We assessed asthma-related quality of life using the Mini Asthma Quality of Life Questionnaire (Mini-AQLQ). This validated 15-item tool assesses several domains of quality of life including physical, emotional, social and occupational limitations due to asthma in the prior 2 weeks.²⁶ Responses were generated on a Likert scale with higher scores indicating better quality of life.

Statistical Analysis

We used ANOVA and the chi-square test to compare the baseline characteristics of WTC workers according to the presence or absence of PTSD and/or MDD. We compared unadjusted ACQ and AQLQ scores among the four study groups using ANOVA. Unadjusted rates of ER visits and hospitalizations were compared using a chi-square test.

We fitted linear regressions models to compare ACQ and AQLQ scores for the four PTSD/MDD groups after controlling for age, sex, race/ethnicity, education, income, asthma onset pre vs. post 9/11, comorbidities, and WTC exposure. Adjusted rates of asthma-related resource utilization in the prior year were compared using logistic regression. We computed odds ratios and 95% confidence intervals for acute health care utilization, using the group of workers without PTSD or MDD as a reference group. Analyses were performed using SAS 9.4 (SAS, Inc., Cary, NC, USA) statistical software, using two-sided p-values.

Results

Between February 2017 and January 2020, we identified 130 individuals that were contacted and found ineligible during screening (23% reported no history of asthma, 23% had a history of COPD, 14% were non English or Spanish speakers, and 39% due to other reasons) and enrolled 307 eligible participants. Of these 307 WTC workers, three were found to be ineligible after enrollment and 11 dropped out after recruitment. Thus, our final cohort included 293 WTC workers with asthma. Overall, 19% of the study participants had PTSD alone, 2% had MDD alone and 12% had PTSD and MDD. Baseline characteristics of study participants without PTSD or MDD, with PTSD alone, MDD alone or PTSD and MDD are shown in Table 1. WTC workers with PTSD and MDD or PTSD alone were more likely to be Hispanic ($p=0.003$) and have a lower income ($p=0.002$) than those without PTSD or MDD. The percentage of patients with asthma onset after exposure to the WTC site was 90% for workers with PTSD and MDD, 85% for those with PTSD alone, 67% for those with MDD alone and 82% for workers without PTSD

or MDD ($p=0.4$). No significant differences in other baseline characteristics were observed among the four study groups ($p>0.05$).

Mean ($\pm$ SD) ACQ scores were 2.35 ± 1.12 for WTC workers with PTSD and MDD, 1.71 ± 1.10 for workers with PTSD alone, 1.61 ± 1.09 for workers with MDD alone and 1.19 ± 1.01 for workers with neither PTSD nor MDD (Table 2). Compared to workers without PTSD and depression, the unadjusted mean difference (95% confidence interval [CI]) in ACQ scores were 1.16 (0.76 to 1.55) for WTC workers with PTSD and MDD, 0.51 (0.21 to 0.82) for those with PTSD alone, and 0.42 (-0.43 to 1.27) for workers with MDD alone. Unadjusted AQLQ scores were also significantly different across study groups (mean $\pm$ SD: 3.87 ± 1.28 for WTC workers with PTSD and MDD, 4.73 ± 1.29 for those with PTSD alone, 4.23 ± 1.64 for those with MDD alone, and 5.41 ± 1.17 for workers with no PTSD or MDD). Compared with workers without PTSD or MDD, the mean difference (95% CI) in AQLQ scores was -1.54 (-2.01 to -1.08) for WTC workers with PTSD and MDD, -0.69 (-1.04 to -0.33) for those with PTSD alone, and 1.18 (-2.18 to -0.18) for workers with MDD alone. Similarly, rates of asthma-related ER visits or hospitalizations in the prior year were 42% for WTC workers with PTSD and MDD, 27% for workers with PTSD alone, 17% for those with MDD alone and 9% for workers with no PTSD or MDD. The unadjusted odds ratio (95% CI) for acute asthma-related healthcare resource utilization among workers with PTSD and MDD was 7.58 (3.15 to 18.26), for workers with PTSD alone was 3.91 (1.81 to 8.43), and for those with MDD alone was 2.1 (0.23 to 19.09) compared to workers without PTSD or MDD.

As seen in Table 3, adjusted analyses showed significant differences in asthma control among WTC workers with PTSD and MDD (mean adjusted difference [95% CI] in ACQ scores 1.32 [0.85 to 1.80]) and with PTSD alone (mean adjusted difference [95% CI]: 0.44 [0.03 to 0.84]), but not with MDD alone (mean adjusted difference [95% CI]: 0.50 [-0.38 to 1.38]) compared to those without PTSD or MDD. Similarly, WTC workers with PTSD and MDD (mean adjusted difference [95% CI]: -1.67 [-2.22 to -1.12]), PTSD alone (mean adjusted difference [95% CI]: -0.56 [-2.23 to -1.12]), and MDD alone (mean adjusted difference [95% CI]: -1.21 [-2.23 to -0.18]) had lower AQLQ scores compared to workers without PTSD or MDD. Adjusted odds for acute resource utilization was higher (7.61, 95% CI: 2.21 to 26.21) among workers with PTSD and MDD vs. those without PTSD or MDD. However, no statistically significant increase in acute resource utilization was observed among WTC workers with PTSD alone (OR: 2.98, 95% CI: 0.91 to 9.73) or MDD alone (OR: 1.88, 95% CI: 0.15 to 24.31).

Discussion

Asthma is the single most common physical health condition and remains a major source of morbidity for WTC workers almost 20 years after exposure to the debris caused by the collapse of the WTC towers. Prior literature shows a consistent association between PTSD and poor asthma control and worse quality of life.^{5,6,27,28} Depression, however, while a risk factor for worse asthma outcomes in the general population, has not yet identified as a predictor of poor asthma control in WTC responders. In this study, we found that many WTC workers with asthma have comorbid PTSD and MDD. Moreover, workers with PTSD and MDD had worse asthma morbidity than those with only one of these mental health comorbidities.²⁹ These results

highlight a group of WTC workers at high risk for poor asthma outcomes and suggest that mental health treatments should be an integral component of the management of asthma in these patients.

Prior studies have reported a high level of asthma in WTC workers and exposed community members, with reports of poorly-controlled disease in >70% of these populations.²⁹ High levels of resource utilization for asthma exacerbations as well as major impacts on asthma-related quality of life in WTC workers with asthma have also been described, providing additional evidence of the substantial impact on wellbeing and the healthcare costs associated with this chronic respiratory condition.²⁹ PTSD has been consistently associated with increased asthma morbidity in WTC workers, firefighters, and local residents.^{29,30} WTC workers with more severe PTSD symptoms are at increased risk of new onset asthma as well as more severe disease;^{31,32} however, even WTC exposed individuals with subthreshold PTSD may be at increased risk of worse asthma outcomes.²⁸ The relationship between asthma morbidity and PTSD has also been reported among veterans and individuals in the general population with asthma.^{16,33–35}

Depression is also a common mental health condition diagnosed in many first responders, recovery workers, and community residents exposed to the WTC debris.²⁷ The impact of depression on asthma morbidity is considerable. Studies in the general population of patients with asthma have shown that depression is associated with poorer quality of life, worse pulmonary function, increased health care utilization and use of rescue medications.^{36–40} However, in WTC-exposed populations, depression has heretofore not shown a consistent link with worse asthma outcomes. In this study, we found that approximately one third of WTC

workers with asthma and PTSD had a coexisting diagnosis of MDD. Moreover, we found that the workers with comorbid PTSD and MDD had significantly worse asthma control, increased resource utilization and poorer quality of life.

Several mechanisms may explain the observed association between mental health conditions and asthma morbidity. PTSD affects multiple organ systems as a consequence of changes in the hypothalamic-pituitary axis, the autonomic nervous system, and the immune system.^{41,42} PTSD is associated with a state of basal, low-grade, systemic inflammation, which, in turn, may modulate airway inflammation, a central feature of asthma. Cognitive and behavioral mechanisms may also play a role. First, PTSD has been more strongly correlated with subjective rather than objective measures of asthma control. Thus, misinterpretation and over perception of symptoms may be more common among WTC workers with PTSD and may contribute to increased asthma morbidity.⁴³ Asthma self-management behaviors encompass several complex behaviors such as adherence to controller medications, adequate inhaler technique, use of action plans, allergen avoidance, and avoiding tobacco exposure that are critical for adequate asthma control. Studies conducted in the general population and in WTC workers with asthma have shown that only 50% of patients adhere to controller therapy.⁴⁴⁻⁴⁶ PTSD, has been strongly associated with low treatment adherence in multiple chronic diseases,^{47,48} thus, suggesting another potential pathway for the association between PTSD and worse asthma morbidity. Depression is also associated with systemic inflammation.⁴⁹ Moreover, research in multiple chronic diseases, including asthma, has shown that patients with comorbid depression have lower rates of adherence to treatment.⁵⁰ Thus, biobehavioral mechanisms may also explain the relationship between depression and worse asthma control in WTC rescue workers. Taken together, the combined

effects of PTSD and MDD may compound the biological and psychological impact of these conditions on asthma morbidity and control. The co-occurrence of PTSD and MDD has been consistently linked with worse outcomes in other chronic conditions. For example, a nationally representative survey revealed that veterans with co-occurring PTSD and MDD were more likely to be diagnosed with a cardiovascular disease, migraine, fibromyalgia and rheumatoid arthritis than those with MDD alone, and, had greater odds of having a diagnosis of hypercholesterolemia and hypertension than those with PTSD alone.⁵¹ In the same population-based study, those with comorbid PTSD-MDD were more likely to endorse current suicide ideation, lifetime suicide attempts, probable generalized anxiety and social anxiety disorders, and poor cognitive and mental health functioning and quality of life than veterans with either PTSD or MDD alone.⁵² There is a growing literature aimed at understanding factors that might help explain the experience of comorbid PTSD-MDD. Researchers have identified certain personality characteristics, namely high neuroticism (negative affectivity) and low extraversion, that may be specifically linked to co-occurring PTSD and MDD.⁵³ Based on shared diagnostic symptoms and biological correlates, it has also been theorized that the experience of PTSD-MDD comorbidity may actually be a phenotypic subtype of PTSD.⁵⁴ Additional information about both the inflammatory and cognitive-behavioral pathways explaining our findings would be critical to further the understanding of the phenomenology of PTSD-MDD comorbidity and to develop targeted biological therapies and cognitive-behavioral interventions to improve the outcomes of these patients.

Our study has strengths and limitations. We enrolled a well-characterized population of WTC workers with asthma and used the gold standard of the SCID to assess for PTSD and MDD.

Moreover, our measures of asthma control and quality of life are well-validated tools. Acute asthma-related resource utilization was obtained by self-report; however, prior studies have shown validity in using this approach.^{55,56} Our study included only WTC workers enrolled in the WTCHP, and, therefore, the study results cannot be generalized to other exposed populations such as firefighter or local community members such as residents, students business and service members. We did not include a sample of unexposed patients with asthma; thus, we could not assess if the rates of PTSD and/or depression are increased among WTC workers. However, multiple prior studies have documented the association between WTC exposure and higher rates of mental health conditions.^{9,57,58} The cohort included a small number of WTC workers with MDD alone; thus, our estimates of asthma morbidity in this group could show a lack of precision and should be confirmed by additional studies. While with assessed for PTSD symptoms in relation to WTC exposures, we did not capture the date of onset of PTSD or MDD. Finally, the study used a cross-sectional design, which does not allow establishing causal relationships between PTSD and/or MDD with asthma morbidity. It may be possible that the physical and social limitation of poor asthma control can lead to or worsen symptoms of MDD and/or PTSD. However, prior studies of WTC-exposed workers showed a PTSD symptoms preceded development of asthma.³¹

In summary, this study showed that WTC workers with comorbid PTSD and MDD are at the highest risk for poor asthma outcomes. These results have direct implications for the management of WTC workers, a population experiencing a high burden of asthma. First, it highlights the importance of screening for mental health conditions, in particular for symptoms of PTSD and MDD among WTC workers with uncontrolled asthma. Relatively brief screening

tools are available for these conditions, which can easily be integrated into the routine care of these patients. Second, it suggests the importance of adequately addressing mental health problems as a complementary strategy for achieving good asthma control. Further research is needed to better understand the potential biological and cognitive-behavioral pathways underlying the relationships between PTSD and MDD with increased asthma morbidity. Established treatments for depression, specifically behavioral activation, and those for PTSD, namely, cognitive processing therapy and prolonged exposure therapy, have been successful in reducing both PTSD and MDD symptoms.⁵⁹⁻⁶² Integrated treatments focused on behavioral activation and exposure have also shown promise for treating comorbid PTSD and MDD.^{63,64} Future studies should also evaluate the effectiveness of integrated asthma-mental health interventions for improving the outcomes of WTC workers.

References

1. Kim H, Baidwan NK, Kriebel D, Cifuentes M, Baron S. Asthma among world trade center first responders: A qualitative synthesis and bias assessment. *Int J Environ Res Public Health*. 2018;15(6). doi:10.3390/ijerph15061053
2. Wisnivesky JP, Teitelbaum SL, Todd AC, et al. Persistence of multiple illnesses in World Trade Center rescue and recovery workers: A cohort study. *Lancet*. 2011;378(9794):888-897. doi:10.1016/S0140-6736(11)61180-X
3. Kim H, Herbert R, Landrigan P, et al. Increased rates of asthma among World Trade Center disaster responders. *Am J Ind Med*. 2012. doi:10.1002/ajim.21025
4. Wheeler K, McKelvey W, Thorpe L, et al. Asthma diagnosed after 11 September 2001 among rescue and recovery workers: Findings from the World Trade Center Health Registry. *Environ Health Perspect*. 2007. doi:10.1289/ehp.10248
5. Brackbill RM, Hadler JL, DiGrande L, et al. Asthma and posttraumatic stress symptoms 5 to 6 years following exposure to the world trade center terrorist attack. *JAMA - J Am Med Assoc*. 2009;302(5):502-516. doi:10.1001/jama.2009.1121
6. Brite J, Friedman S, de la Hoz RE, Reibman J, Cone J. Mental health, long-term medication adherence, and the control of asthma symptoms among persons exposed to the WTC 9/11 disaster. *J Asthma*. 2019. doi:10.1080/02770903.2019.1672722
7. Rojano B, West E, Ferdermann E, et al. Allergen sensitization and asthma outcomes among world trade center rescue and recovery workers. *Int J Environ Res Public Health*. 2019;16(5). doi:10.3390/ijerph16050737
8. Miller-Archie SA, Jordan HT, Alper H, et al. Hospitalizations for asthma among adults exposed to the September 11, 2001 World Trade Center terrorist attack. *J Asthma*. 2018;55(4):354-363. doi:10.1080/02770903.2017.1337787
9. Chen C, Salim R, Rodriguez J, et al. The burden of subthreshold posttraumatic stress disorder in world trade center responders in the second decade after 9/11. *J Clin Psychiatry*. 2020;81(1). doi:10.4088/JCP.19m12881
10. Lowell A, Suarez-Jimenez B, Helpman L, et al. 9/11-related PTSD among highly exposed populations: A systematic review 15 years after the attack. *Psychol Med*. 2018;48(4):537-553. doi:10.1017/S0033291717002033
11. Chatterjee A, Banerjee S, Stein C, Kim M-H, DeFerio J, Pathak J. Risk Factors for Depression Among Civilians After the 9/11 World Trade Center Terrorist Attacks: A Systematic Review and Meta-Analysis. *PLoS Curr*. 2018;10. doi:10.1371/currents.dis.6a00b40c8ace0a6a0017361d7577c50a
12. Caramanica K, Brackbill RM, Liao T, Stellman SD. Comorbidity of 9/11-Related PTSD and Depression in the World Trade Center Health Registry 10-11 Years Postdisaster. *J Trauma Stress*. 2014;27(6):680-688. doi:10.1002/jts.21972
13. Chiu S, Niles JK, Webber MP, et al. Evaluating risk factors and possible mediation effects in posttraumatic depression and posttraumatic stress disorder comorbidity. *Public Health*

- Rep. 2011;126(2):201-209. doi:10.1177/003335491112600211
14. Stellman JM, Smith RP, Katz CL, et al. 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(9):1248-1253. doi:10.1289/ehp.11164
 15. Lippmann M, Cohen MD, Chen LC. Health effects of World Trade Center (WTC) Dust: An unprecedented disaster's inadequate risk management. *Crit Rev Toxicol.* 2015;45(6):492-530. doi:10.3109/10408444.2015.1044601
 16. Xu KY, Goodman E, Goswami R, et al. Determinants of asthma morbidity in World Trade Center rescue and recovery workers. *Ann Allergy, Asthma Immunol.* 2016;117(5):568-570. doi:10.1016/j.anai.2016.08.033
 17. Yonas MA, Marsland AL, Emeremni CA, Moore CG, Holguin F, Wenzel S. Depressive symptomatology, quality of life and disease control among individuals with well-characterized severe asthma. *J Asthma.* 2013;50(8):884-890. doi:10.3109/02770903.2013.810750
 18. Wang G, Zhou T, Wang L, et al. Relationship between current psychological symptoms and future risk of asthma outcomes: A 12-month prospective cohort study. *J Asthma.* 2011;48(10):1041-1050. doi:10.3109/02770903.2011.631238
 19. Kullowatz A, Kannies F, Dahme B, Magnussen H, Ritz T. Association of depression and anxiety with health care use and quality of life in asthma patients. *Respir Med.* 2007;101(3):638-644. doi:10.1016/j.rmed.2006.06.002
 20. Moline JM, Herbert R, Levin S, et al. WTC medical monitoring and treatment program: Comprehensive health care response in aftermath of disaster. *Mt Sinai J Med.* 2008;75(2):67-75. doi:10.1002/msj.20022
 21. Dasaro CR, Holden WL, Berman KD, et al. Cohort profile: World trade center health program general responder cohort. *Int J Epidemiol.* 2017. doi:10.1093/ije/dyv099
 22. NHIS - National Health Interview Survey,. <https://www.cdc.gov/nchs/nhis/index.htm>. Accessed April 27, 2020.
 23. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. American Psychiatric Association; 2013. doi:10.1176/appi.books.9780890425596
 24. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J.* 1999. doi:10.1034/j.1399-3003.1999.14d29.x
 25. Juniper EF, Svensson K, Mörk AC, Ståhl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med.* 2005;99(5):553-558. doi:10.1016/j.rmed.2004.10.008
 26. Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health related quality of life in asthma: Development of a questionnaire for

- use in clinical trials. *Thorax*. 1992;47(2):76-83. doi:10.1136/thx.47.2.76
27. Jordan HT, Osahan S, Li J, et al. Persistent mental and physical health impact of exposure to the September 11, 2001 World Trade Center terrorist attacks. *Environ Heal A Glob Access Sci Source*. 2019;18(1). doi:10.1186/s12940-019-0449-7
 28. Mindlis I, Morales-Raveendran E, Goodman E, et al. Post-traumatic stress disorder dimensions and asthma morbidity in World Trade Center rescue and recovery workers. *J Asthma*. 2017;54(7):723-731. doi:10.1080/02770903.2016.1263650
 29. Jordan HT, Stellman SD, Reibman J, et al. Factors associated with poor control of 9/11-related asthma 10-11 years after the 2001 World Trade Center terrorist attacks. *J Asthma*. 2015;52(6):630-637. doi:10.3109/02770903.2014.999083
 30. Fagan J, Galea S, Ahern J, Bonner S, Vlahov D. Relationship of Self-Reported Asthma Severity and Urgent Health Care Utilization to Psychological Sequelae of the September 11, 2001 Terrorist Attacks on the World Trade Center among New York City Area Residents. *Psychosom Med*. 2003;65(6):993-996. doi:10.1097/01.PSY.0000097334.48556.5F
 31. De La Hoz RE, Jeon Y, Miller GE, Wisnivesky JP, Celedón JC. Post-traumatic stress disorder, bronchodilator response, and incident asthma in World Trade Center rescue and recovery workers. *Am J Respir Crit Care Med*. 2016;194(11):1383-1391. doi:10.1164/rccm.201605-1067OC
 32. Kotov R, Bromet EJ, Schechter C, et al. Posttraumatic stress disorder and the risk of respiratory problems in world trade center responders: Longitudinal test of a pathway. *Psychosom Med*. 2015;77(4):438-448. doi:10.1097/PSY.0000000000000179
 33. Goodwin RD, Fischer ME, Goldberg J. A twin study of post-traumatic stress disorder symptoms and asthma. *Am J Respir Crit Care Med*. 2007;176(10):983-987. doi:10.1164/rccm.200610-1467OC
 34. Dobie DJ, Kivlahan DR, Maynard C, Bush KR, Davis TM, Bradley KA. Posttraumatic Stress Disorder in Female Veterans: Association with Self-reported Health Problems and Functional Impairment. *Arch Intern Med*. 2004;164(4):394-400. doi:10.1001/archinte.164.4.394
 35. O'Toole BI, Catts S V. Trauma, PTSD, and physical health: An epidemiological study of Australian Vietnam veterans. *J Psychosom Res*. 2008;64(1):33-40. doi:10.1016/j.jpsychores.2007.07.006
 36. Patel PO, Patel MR, Baptist AP. Depression and Asthma Outcomes in Older Adults: Results from the National Health and Nutrition Examination Survey. *J Allergy Clin Immunol Pract*. 2017;5(6):1691-1697.e1. doi:10.1016/j.jaip.2017.03.034
 37. Krauskopf KA, Sofianou A, Goel MS, et al. Depressive symptoms, low adherence, and poor asthma outcomes in the elderly. *J Asthma*. 2013;50(3):260-266. doi:10.3109/02770903.2012.757779
 38. Ross JA, Yang Y, Song P XK, Clark NM, Baptist AP. Quality of life, health care utilization, and control in older adults with asthma. *J Allergy Clin Immunol Pract*.

- 2013;1(2):157-162. doi:10.1016/j.jaip.2012.12.003
39. Balkrishnan R, Christensen DB, Bowton DL. Self-reported health status, prophylactic medication use, and healthcare costs in older adults with asthma. *J Am Geriatr Soc*. 2002;50(5):924-929. doi:10.1046/j.1532-5415.2002.50221.x
 40. Vanderbilt D, Young R, MacDonald HZ, Grant-Knight W, Saxe G, Zuckerman B. Asthma severity and PTSD symptoms among inner city children: A pilot study. *J Trauma Dissociation*. 2008;9(2):191-207. doi:10.1080/15299730802046136
 41. Hori H, Kim Y. Inflammation and post-traumatic stress disorder. *Psychiatry Clin Neurosci*. 2019;73(4):143-153. doi:10.1111/pcn.12820
 42. Dennis PA, Dedert EA, Van Voorhees EE, et al. Examining the Crux of Autonomic Dysfunction in Posttraumatic Stress Disorder: Whether Chronic or Situational Distress Underlies Elevated Heart Rate and Attenuated Heart Rate Variability. *Psychosom Med*. 2016;78(7):805-809. doi:10.1097/PSY.0000000000000326
 43. Feldman JM, Steinberg D, Kutner H, et al. Perception of Pulmonary Function and Asthma Control: The Differential Role of Child Versus Caregiver Anxiety and Depression. *J Pediatr Psychol*. 2013;38(10):1091-1100. doi:10.1093/jpepsy/jst052
 44. Choi TN, Westermann H, Sayles W, Mancuso CA, Charlson ME. Beliefs about asthma medications: Patients perceive both benefits and drawbacks. *J Asthma*. 2008;45(5):409-414. doi:10.1080/02770900801971834
 45. Bender BG, Bender SE. Patient-identified barriers to asthma treatment adherence: Responses to interviews, focus groups, and questionnaires. *Immunol Allergy Clin North Am*. 2005;25(1):107-130. doi:10.1016/j.iac.2004.09.005
 46. Horne R. Compliance, adherence, and concordance: Implications for asthma treatment. In: *Chest*. Vol 130. American College of Chest Physicians; 2006:65S-72S. doi:10.1378/chest.130.1_suppl.65S
 47. Kronish IM, Edmondson D, Li Y, Cohen BE. Post-traumatic stress disorder and medication adherence: Results from the Mind Your Heart Study. *J Psychiatr Res*. 2012;46(12):1595-1599. doi:10.1016/j.jpsychires.2012.06.011
 48. Kronish IM, Lin JJ, Cohen BE, Voils CI, Edmondson D. Posttraumatic stress disorder and medication nonadherence in patients with uncontrolled hypertension. *JAMA Intern Med*. 2014;174(3):468-470. doi:10.1001/jamainternmed.2013.12881
 49. Raison CL, Miller AH. Is depression an inflammatory disorder? *Curr Psychiatry Rep*. 2011;13(6):467-475. doi:10.1007/s11920-011-0232-0
 50. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med*. 2000;160(14):2101-2107. doi:10.1001/archinte.160.14.2101
 51. Nichter B, Norman S, Haller M, Pietrzak RH. Physical health burden of PTSD, depression, and their comorbidity in the U.S. veteran population: Morbidity, functioning, and disability. *J Psychosom Res*. 2019. doi:10.1016/j.jpsychores.2019.109744

52. Nichter B, Norman S, Haller M, Pietrzak RH. Psychological burden of PTSD, depression, and their comorbidity in the U.S. veteran population: Suicidality, functioning, and service utilization. *J Affect Disord.* 2019. doi:10.1016/j.jad.2019.06.072
53. Spinhoven P, Penninx BW, van Hemert AM, de Rooij M, Elzinga BM. Comorbidity of PTSD in anxiety and depressive disorders: Prevalence and shared risk factors. *Child Abus Negl.* 2014. doi:10.1016/j.chiabu.2014.01.017
54. Flory JD, Yehuda R. Comorbidity between post-traumatic stress disorder and major depressive disorder: Alternative explanations and treatment considerations. *Dialogues Clin Neurosci.* 2015;17(2):141-150. www.dialogues-cns.org. Accessed September 21, 2020.
55. Short ME, Goetzel RZ, Pei X, et al. How accurate are self-reports? Analysis of self-reported health care utilization and absence when compared with administrative data. *J Occup Environ Med.* 2009;51(7):786-796. doi:10.1097/JOM.0b013e3181a86671
56. Bhandari A, Wagner T. Self-reported utilization of health care services: Improving measurement and accuracy. *Med Care Res Rev.* 2006;63(2):217-235. doi:10.1177/1077558705285298
57. Hamwey MK, Gargano LM, Friedman LG, Leon LF, Petrsoric LJ, Brackbill RM. Post-traumatic stress disorder among survivors of the september 11, 2001 world trade center attacks: A review of the literature. *Int J Environ Res Public Health.* 2020;17(12):1-19. doi:10.3390/ijerph17124344
58. Smith EC, Holmes L, Burkle FM. The Physical and Mental Health Challenges Experienced by 9/11 First Responders and Recovery Workers: A Review of the Literature. *Prehosp Disaster Med.* 2019;34(6):625-631. doi:10.1017/S1049023X19004989
59. Wagner AW, Jakupcak M, Kowalski HM, Bittinger JN, Golshan S. Behavioral Activation as a Treatment for Posttraumatic Stress Disorder Among Returning Veterans: A Randomized Trial. *Psychiatr Serv.* 2019;70(10):867-873. doi:10.1176/appi.ps.201800572
60. Van Minnen A, Harned MS, Zoellner L, Mills K. Examining potential contraindications for prolonged exposure therapy for PTSD. *Eur J Psychotraumatol.* 2012;3(1):18805. doi:10.3402/ejpt.v3i0.18805
61. Schumm JA, Dickstein BD, Walter KH, Owens GP, Chard KM. Changes in posttraumatic cognitions predict changes in posttraumatic stress disorder symptoms during cognitive processing therapy. *J Consult Clin Psychol.* 2015;83(6):1161-1166. doi:10.1037/ccp0000040
62. Resick PA, Nishith P, Weaver TL, Astin MC, Feuer CA. A comparison of cognitive-processing therapy with prolonged exposure and a waiting condition for the treatment of chronic posttraumatic stress disorder in female rape victims. *J Consult Clin Psychol.* 2002;70(4):867-879. doi:10.1037/0022-006X.70.4.867
63. Gros DF, Price M, Strachan M, Yuen EK, Milanak ME, Acierno R. Behavioral Activation and Therapeutic Exposure: An Investigation of Relative Symptom Changes in PTSD and Depression During the Course of Integrated Behavioral Activation, Situational Exposure,

and Imaginal Exposure Techniques. *Behav Modif.* 2012;36(4):580-599.
doi:10.1177/0145445512448097

64. Nixon RD V., Nearmy DM. Treatment of comorbid posttraumatic stress disorder and major depressive disorder: A pilot study. *J Trauma Stress.* 2011;24(4):451-455.
doi:10.1002/jts.20654

Table 1. Baseline Characteristics of World Trade Center Workers with Asthma According to Post-traumatic Stress Disorder and Depression Status

Characteristic	PTSD and MDD	PTSD Alone	MDD Alone	No PTSD/Depression	P-value
Age, years, mean±SD	53.6±7.5	53.7±9.9	52.0±4.6	56.2±7.9	0.5
Male, No. (%)	22 (71)	40 (68)	4 (67)	140 (77)	0.5
Race/Ethnicity, No. (%)					
Black	6 (19)	9 (16)	1 (17)	44 (24)	0.003
White	3 (9.7)	21 (36)	2 (33)	71 (39)	
Hispanic	12 (38.7)	23 (40)	2 (33)	51 (28)	
Other	10 (32.3)	5 (9)	1 (17)	16 (9)	
Education, No. (%)					
Some high school	2 (7)	11 (19)	0 (0)	13 (7)	0.2
High school graduate	7 (23)	5 (8)	2 (33)	39 (21)	
Some College	13 (42)	22 (38)	2 (33)	65 (35)	
College Graduate	9 (29)	19 (33)	2 (33)	67 (36)	
Monthly Income, No. (%)					
≤US\$3,000	13 (48)	24 (48)	1 (20)	41 (24)	0.002
>US\$3,000	14 (52)	26 (52)	4 (80)	131 (76)	
WTC Exposure, No. (%)					
Low	2 (8)	5 (13)	1 (17)	16 (12)	0.3
Intermediate	15 (60)	20 (53)	4 (67)	93 (70)	
High	2 (7)	9 (24)	1 (17)	18 (13)	
Very High	6 (27)	4 (11)	0 (0)	12 (9)	
Ever Smoked, No. (%)	22 (73)	48 (79)	4 (67)	132 (75)	0.8
Asthma Onset Post 9/11, No. (%)	28 (90)	49 (85)	4 (67)	134 (82)	0.4
History of Intubation, No. (%)	3 (10)	1 (2)	1 (17)	0 (0)	0.002
Oral Steroids in the Last Year, No. (%)	10 (35)	22 (37)	2 (33)	49 (27)	0.4
On Asthma Controller Medication, No. (%)	20 (59)	35 (56)	5 (83)	115 (61)	0.7
Comorbidities, No. (%)					
GERD	19 (56)	40 (64)	5 (83)	125 (66)	0.6
Chronic Sinusitis	20 (59)	31 (49)	3 (50)	106 (56)	0.8
Diabetes	7 (21)	10 (16)	2 (33)	34 (18)	0.6
Hypertension	12 (35)	24 (38)	3 (50)	91 (48)	0.4

PTSD: Post-traumatic Stress Disorder, MDD: Major Depressive Disorder, GERD: Gastroesophageal Reflux Disease

Table 2. Unadjusted Asthma Outcomes among World Trade Center Workers with Post-traumatic Stress Disorder and/or Depression

Characteristic	PTSD and Depression		PTSD Alone		Depression Alone		No PTSD/ Depression
	Mean±SD	Difference (95% CI)	Mean±SD	Difference (95% CI)	Mean±SD	Difference (95% CI)	Mean±SD
ACQ Score	2.35±1.12	1.16 (0.76 to 1.55)	1.71±1.10	0.51 (0.21 to 0.82)	1.61 ± 1.09	0.42 (-0.43 to 1.27)	1.19 ±1.01
AQLQ Score	3.87±1.28	-1.54 (-2.01 to -1.08)	4.73±1.29	-0.69 (-1.04 to -0.33)	4.23± 1.64	-1.18 (-2.18 to -0.18)	5.41 ± 1.17
	Percentage	OR (95% CI)	Percentage	OR (95% CI)	Percentage	OR (95% CI)	Percentage
Resource Utilization	42%	7.58* (3.15-18.26)	27%	3.91* (1.81 to 8.43)	17%	2.1* (0.23 to 19.09)	9%

PTSD: Post-traumatic Stress Disorder, ACQ: Asthma Control Questionnaire, AQLQ: Asthma Quality of Life Questionnaire, OR: odds ratio, CI: confidence interval

*Reference group is the group of workers without PTSD or depression.

Table 3. Adjusted Differences in Asthma Outcomes among World Trade Center Workers with Post-traumatic Stress Disorder and/or Depression

Outcome	PTSD and Depression	PTSD Alone	Depression Alone
	Mean Difference (95 % CI)	Mean Difference (95 % CI)	Mean Difference (95 % CI)
ACQ Scores	1.32 (0.85 to 1.80)	0.44 (0.03 to 0.84)	0.50 (-0.38 to 1.38)
AQLQ Scores	-1.67 (-2.22 to -1.12)	-0.56 (-2.23 to -1.12)	-1.21 (-2.23 to -0.18)
	Odds Ratio (95% CI)	Odds Ratio (95% CI)	Odds Ratio (95% CI)
Acute Resource Utilization	7.61* (2.21 to 26.21)	2.98* (0.91 to 9.73)	1.88* (0.15 to 24.31)

PTSD: Post-traumatic Stress Disorder, ACQ: Asthma Control Questionnaire, AQLQ: Asthma Quality of Life Questionnaire, CI: confidence interval
Controlling for age, sex, race/ethnicity, education, income, asthma onset pre vs. post 9/11, comorbidities, and WTC exposure

*Reference group is the group of workers without PTSD or depression.