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Mental Health Mediators of Subjective Cognitive Concerns among World Trade Center Responders

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Abstract

Decline in cognitive functioning among rescue and recovery workers who responded in the aftermath of the September 11, 2001, World Trade Center (WTC) attacks is of emerging interest. Responders are vulnerable to cognitive decline from exposure to airborne toxins present at the WTC site, as well as from WTC-related mental and physical health conditions. To better understand the relationship between occupational WTC exposure, mental health, physical health and subjective cognitive functioning, we examined the mediating role of health status in the association between exposure and subjective cognitive concerns in a multi-site, longitudinal investigation of the WTC General Responder cohort (n=16,380 responders; n=58,575 visits) for the period 2002 – 2015. Through latent class analyses, we identified a four-level marker of cognitive concerns based on information from a Self-Administered Mental Health Questionnaire. Using generalized linear mixed models with random intercepts, we observed that a higher intensity WTC exposure composite was associated with greater cognitive concerns, and that this

association was operating almost entirely through mental health comorbidities, not physical health comorbidities. In fully adjusted models, the inclusion of probable depression, anxiety, PTSD and use of psychotropic medications attenuated the association between highest WTC exposure and greatest cognitive concerns. Physical health did not appear to be on the pathway between WTC exposure and cognitive concerns. Understanding the underlying sources of cognitive concerns may help identify vulnerable members of the General Responder cohort and potentially aid clinical decision-making, such as treatment choice and enhanced screening options. Earlier diagnosis and symptom treatment may help preserve functional independence.

Keywords

September 11 Terrorist Attacks; Cognitive Dysfunction; Mental Health; Epidemiology; Occupational Health

INTRODUCTION

Some cognitive change is natural with aging, but cognitive and functional impairment is not part of the normal aging process (Harada et al., 2013). Cognitive decline can range from mild cognitive impairment to dementia (Jessen et al., 2014). Decline in cognitive functioning is emerging as a significant area of clinical concern and epidemiological investigation among rescue and recovery workers who responded in the aftermath of the September 11, 2001 World Trade Center (WTC) attacks (Daniels et al., 2021). Cognitive functioning has been assessed in the WTC Health Program's General Responder (Clouston et al., 2017; Clouston et al., 2016; Clouston et al., 2020; Clouston et al., 2019) and Fire Department of New York (FDNY) Responder (Singh et al., 2020a; Singh et al., 2020b) Cohorts and the WTC Health Registry (Alper et al., 2020; Seil et al., 2019), a longitudinal study of responders and community members.

Prevalence of cognitive concerns among WTC responders varies by cohort and assessment method. Objective measures of cognitive functioning have been examined only at a single clinical center monitoring the General Responder Cohort. In this subset (n=1,193) assessed in 2015–2016 using the computer-administered neuropsychological battery Cogstate, 14.8% presented with cognitive dysfunction (Clouston et al., 2017). Similarly, a longitudinal investigation at this same site using the Montreal Cognitive Assessment reported a cognitive impairment prevalence of 12.8% at baseline (n=813) in 2014–2015 (Clouston et al., 2016) and an incidence of 14.2% at follow-up (n=1800) 1–2.5 years later (Clouston et al., 2019). Subjective cognitive decline ranged from 8% in the FDNY cohort (n=7,875) (Singh et al., 2020a) to 22% in the WTC Health Registry (n = 14,574) (Seil et al., 2019). As comparison, the 2015–2017 Behavioral Risk Factor Surveillance System indicates that 11.1% of community-dwelling adults aged 45 years and older reported subjective cognitive decline (U.S. Centers for Disease Control and Prevention, 2019).

WTC responders' unique risk for cognitive decline is twofold (Figure 1). First, WTC responders may be at direct risk of cognitive decline because of their occupational exposure to numerous airborne toxins. The WTC attacks resulted in intense fire and building collapses, releasing particles and gases into the atmosphere that settled on surfaces and

structures (Liroy et al., 2002). Particles were re-suspended during rescue, recovery and cleanup operations, fine and ultrafine particles were well above normal urban background levels until mid-October and coarse particles were elevated until the fires were extinguished in December (Landrigan et al., 2004). Fine particulate matter is increasingly recognized as an important risk factor for neuropsychiatric problems (Dickerson et al., 2020; Hahad et al., 2020; Landrigan et al., 2018; Ventriglio et al., 2020), including cognitive deficit and neurodegenerative diseases (Chen and Schwartz, 2009; Power et al., 2011; Ranft et al., 2009; Weuve, 2014); hypothesized mechanisms include inflammation and oxidative stress (Calderon-Garciduenas et al., 2008; Hahad et al., 2020). Animal studies show increased brain inflammation in response to particulate matter exposure, (Campbell et al., 2005) with signs of blood-brain barrier dysfunction, neural degeneration, cerebrovascular pathology and apoptosis of glial cells (Calderon-Garciduenas et al., 2002). The olfactory pathway may have represented a relevant exposure route for the WTC responders, especially for fine particles that can bypass the blood-brain barrier (Lucchini et al., 2012b) targeting the brain directly.

Second, WTC responders may be at indirect risk of cognitive decline because they suffer from acute and long-term mental and physical health effects (Prevention, 2020) attributed to both the airborne toxins and psychological stressors from the work, such as long shifts, fear for personal safety and viewing human remains (Herbert et al., 2006; Lucchini et al., 2012a; Wisnivesky et al., 2011). While indirect, these mechanisms are also of concern. Depression, anxiety and post-traumatic stress disorder (PTSD), which have been persistent among WTC responders (Wisnivesky et al., 2011), can lead to cognitive dysfunction (Barnes et al., 2006; Barrett et al., 1996; Horner and Hamner, 2002; Johnsen and Asbjornsen, 2008; Jorm, 2000; Lopez et al., 2003; Marin et al., 2011). Physical health disorders prevalent in this population include asthma, sinusitis and spirometric abnormalities (Wisnivesky et al., 2011). Respiratory disease has also been linked to cognitive impairment (Hung et al., 2009; Mikkelsen et al., 2012). Additionally, some medications for treating these physical health conditions can have cognitive side effects (Agostini et al., 2001; Buffett-Jerrott and Stewart, 2002; Lupien and McEwen, 1997; Pasricha et al., 2006; Warrington and Bostwick, 2006).

To better understand the relationship between WTC exposures, mental health, physical health and subjective cognitive functioning, we examined the mediating role of health status in the association between WTC exposure and self-reported cognitive concerns in a multi-site, longitudinal investigation of the WTC General Responder Cohort. Understanding the underlying sources of cognitive concerns may help identify vulnerable members of the General Responder Cohort and potentially aid clinical decision-making, such as screening and treatment options.

MATERIALS AND METHODS

Study Population

The WTC Health Program General Responder Cohort is a self-selected, open cohort that includes non-FDNY responders who worked or volunteered in rescue, recovery, demolition, debris cleanup or related supportive services at the WTC sites and has been described in detail elsewhere (Dasaro et al., 2017; Herbert et al., 2006; Moline et al., 2008). In brief, the WTC Health Program provides medical monitoring and treatment for WTC-

certified conditions (U.S. Centers for Disease Control and Prevention, 2020), with an initial examination followed by annual monitoring examinations, including medical, mental health and exposure assessments. The Program began in 2002 (Dasaro et al., 2017), and enrollment into the program has been continuous. To minimize selection, recall and other biases that may arise as workers delayed entry into the Health Program, we restricted the study population to responders who enrolled by 2007 and returned for at least one monitoring visit after the initial exam. This study was classified as exempt human subjects research by the Mount Sinai Program for the Protection of Human Subjects.

Exposure Assessment

WTC exposure groupings reflect the intensity and duration of exposure to the dust, smoke and debris, as reported in the interviewer-administered Exposure Assessment Questionnaire (Wisnivesky et al., 2011). Group assignment was based on the total time spent working at the WTC sites, exposure to the cloud of debris from the collapse of the buildings and work on the debris pile (Wisnivesky et al., 2011). Very high exposure encompasses those who worked more than 90 days, were exposed to the dust cloud and worked on the pile. High exposure consists of those who were exposed to the dust cloud, but either worked fewer than 90 days or did not work on the pile. Intermediate exposure consists of those not exposed to the dust cloud and either worked between 40 and 90 days or worked on the pile. Low exposure consists of those who worked fewer than 40 days, were not exposed to the dust cloud and did not work on the pile. This four-level exposure metric has been associated with incidence of chronic disease (Wisnivesky et al., 2011) and cancer (Solan et al., 2013). To increase interpretability of results, maintain sample size across visits and to operationalize WTC exposure for the current analyses, we combined very high and high exposure into a single category to yield a three-level composite exposure measure (high, medium, low).

Mental Health

Mental health was assessed using validated screening instruments administered at monitoring visits (Stellman et al., 2008). We focused on depression, anxiety and PTSD because they are WTC-related conditions that could affect cognitive function. Depression was assessed with the 9-item Patient Health Questionnaire (PHQ-9) using a cut-point ≥ 10 to indicate probable depression (Kroenke et al., 2001; Manea et al., 2012; Spitzer et al., 1999). Anxiety was assessed with the 7-item General Anxiety Disorder scale (GAD-7) using a cut-point ≥ 10 to indicate probable anxiety (Spitzer et al., 2006). PTSD was assessed with the 17-item PTSD Symptom Checklist–Civilian (PCL) using a cut-point ≥ 44 to indicate probable PTSD (Blanchard et al., 1996; Weathers et al., 1993; Wilkins et al., 2011). Of note, screening for depression and anxiety began in September 2008, with near complete implementation by mid-2009; responders who participated in monitoring visits prior to this point are missing depression and anxiety data at those visits. To operationalize mental health comorbidities, we used time-varying, binary measures of probable depression (yes, no), probable anxiety (yes, no) and probable PTSD (yes, no) at each visit.

We also examined self-reported use of psychotropic medications (anti-depressants, sedatives, stimulants, non-stimulants, enhancers) at each monitoring visit as a proxy for severity, persistence and refractory nature of mood symptoms. To operationalize

psychotropic medication use, we created a time-varying, three-level variable (none, monotherapy, polytherapy) based on the number of distinct medications reported at each visit, regardless of medication class (Quon et al., 2020).

Physical Health

Physical health conditions of interest were WTC-certified conditions that could affect cognitive function, particularly in combination with treatment. We focused on sleep apnea, asthma, chronic obstructive pulmonary disease, lung scarring, rhinitis and sinusitis with corresponding use of antihistamines, inhaled glucocorticoids or oral steroids. At each visit, we searched for a self-reported diagnosis of any of the six conditions plus self-reported use of a medication in any of the three medication classes. We used this combination of diagnosis-plus-medication as a stringent marker of WTC-related physical health conditions. To operationalize physical health comorbidities, we created a time-varying, binary variable (yes, no) representing the presence or absence of any of these physical health conditions at each visit. We examined physical health comorbidities as a composite rather than differentiating by diagnosis, as done for mental health comorbidities, because the hypothesized association between physical health and cognitive function during the study period was primarily through concurrent medication use, and there is overlap in medications used for the comorbidities.

Cognitive Concerns

Cognitive functioning was not directly assessed in the full General Responder cohort. Consequently, we used six questions from the Self-Administered Mental Health Questionnaire (Supplemental Table 1) related to concerns about concentration, attention, and memory over the preceding two to four weeks in latent class analysis (performed with the SAS procedure PROC LCA (Lanza et al., 2007)) to identify four latent classes of cognitive concerns. We evaluated latent class models with three to six classes based on how cleanly separated the resultant classes appeared when viewing response-level probabilities (p) for each questionnaire item and whether the classes were intuitively meaningful (Supplemental Table 2). The five-level latent class model resulted in response-level probabilities distinctly separated and consistent across questionnaire items. The second and third lowest categories were not interpretable as distinct classes so we combined them into a single category representing low cognitive concerns. The benefit of collapsing the five-level latent class model rather than using the four-level latent class model was that the lowest class in the five-level model was more distinctly interpreted as no concerns for use as a referent in further modeling. To operationalize our marker of self-reported cognitive concerns, we used this time-varying, four-level latent class (none, low, medium, high) at each visit.

Two questions included in the cognitive concerns latent class analysis are drawn from the instruments used to identify responders with depression and PTSD. To evaluate the impact of including a single PHQ-9 question (Concentrate-1, used in determination of probable depression) and a single PCL-17 question (Concentrate-3, used in determination of probable PTSD) in the cognitive concerns latent class analysis (Supplemental Table 1), we calculated the number of visits (total visits $n=58,575$) where responders would shift probable depression or probable PTSD categories with responses to these questions set to

missing. PHQ-9 and PCL-17 scoring both have some tolerance for missing values so setting these questions to missing does not necessarily alter the total score. For example, on the PHQ-9, up to two missing values can be replaced with the average score of non-missing items (Kroenke et al., 2010). With the PHQ-9 question set to missing, n=361 visits shifted from probable to no depression, n=253 from no to probable depression and n=433 to missing. With the PCL-17 question set to missing, n=530 visits shifted from probable to no PTSD, n=41 from no to probable PTSD and n=241 to missing. Considering the overall sample size and magnitude of the observed associations between mental health and cognitive concerns, the relatively small number of visits that would change mental health status with these questions removed from PHQ-9 and PCL-17 scoring is likely insufficient to alter the overall findings. Consequently, to maximize generalizability we used these questions in determination of depression and PTSD diagnoses as well as cognitive concerns.

To appraise the overall utility of the cognitive concerns measure, we examined the association between cognitive concerns and scores from the 12-Item Short Form Survey (SF-12) (Ware et al., 1996) and the Sheehan Disability Scale (Leon et al., 1997). There was a clear relationship between increasing cognitive concerns and worsening SF-12 Mental and Physical Health Composite Scores. As cognitive concerns increased across the four classes, Mental Health Composite Scores worsened from mean (standard deviation (SD)) 55.5 (6.2) to 47.2 (9.8), to 36.6 (9.1), to 31.7 (8.6). A similar pattern was observed for Physical Health Composite Scores, with a reduction from mean 47.4 (9.2) with no cognitive concerns to mean 31.5 (8.9) with high cognitive concerns. Likewise, as cognitive concerns increased across the four classes, the Sheehan Disability Scale scores worsened from mean (SD) 2.1 (4.1), to 7.0 (6.4), to 13.6 (7.2), to 17.7 (7.9).

Statistical Analyses

Descriptive statistics were based on Cochran-Mantel-Haenszel statistics, Cochran-Armitage trend tests, Fisher's exact tests and general linear models, as appropriate. We calculated Spearman correlations between scores from the PHQ-9, GAD-7 and PCL-17 using linear mixed models on the ranked scores to account for repeated measures and non-normality (Hamlett et al., 2004; Huang and Railkar, 2019; Irimata et al., 2018; Lam et al., 1999).

To evaluate the mediating role of mental and physical health in the association between WTC exposure and cognitive concerns, we estimated adjusted odds ratios and 95% confidence intervals (CI) using generalized linear mixed models with random intercepts to account for the longitudinal data with PROC GLIMMIX in SAS. Study baseline is the first monitoring visit with an identified cognitive concerns latent class. We adjusted for an a priori set of covariates based on the literature. Stationary covariates included sex (male, female); race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other); primary language (English, other); educational attainment (less than high school degree, high school degree, some college, college degree, advanced degree); and pre-9/11 occupation (protective services, construction, other). Time-varying covariates included age (integer); clinic provider (Icahn School of Medicine at Mount Sinai; New York University School of Medicine; Northwell Health; Stony Brook University; Rutgers University); employment

status (working full or part-time, not working); smoking status (never, former, current); and time since September 11, 2001.

Models estimating associations for cognitive concerns or psychotropic medications assumed multinomial distributions. Models estimating associations for binary mediators assumed binomial distributions. With categorical outcomes and predictors, we could not decompose model coefficients into individual correlations for each path (Figure 1) between exposure and outcome (Breen et al., 2013). Consequently, we ran separate models to compare qualitatively the magnitude of effect across models with (a) direct effect of WTC exposure only; (b) direct effect of WTC exposure plus indirect effect of mental health; (c) direct effect of WTC exposure plus indirect effect of physical health; and (d) total effect of WTC exposure, mental health and physical health. We also assessed for independent associations between WTC exposure and mediators and between mediators and cognitive concerns. We conducted model-based complete case analyses so that visit-level missing data for mediators were permitted in models not including the mediator.

Secondary Analyses

We conducted secondary analyses to examine the robustness of our findings. To further understand mental health status as a mediator of the association between WTC exposure and cognitive concerns, we assessed mediation by each mental health marker in four separate models rather than in one combined model. To ensure that our findings were not an artifact of aging, we ran the mediation model restricting to the subset ≤ 55 years on 9/11/2001. To interrogate further the LCA outcome measure, which includes information from the depression and PTSD screeners, we ran the mediation models using two LCA component variables specifically addressing attention and memory.

RESULTS

From July 16, 2002 through December 30, 2007, 25,615 responders enrolled in the WTC Health Program, 22,382 (87%) consented to participate in research, and 18,304 (82% of consented) returned for at least one monitoring visit after their initial exam. Missing data (cognitive concerns $n=241$; WTC exposure $n=669$; demographics $n=1,014$) yielded an analytic sample of 16,380 responders (64% overall; 73% consented; 89% returned for monitoring) with follow-up data available through September 30, 2015. There were 58,575 monitoring visits (median 3, interquartile range (IQR) 2, 5) with a median follow-up time of 4.9 years (IQR 2.1, 6.9) (Figure 2). The mean (SD) age of responders was 39.3 (8.8) years on September 11, 2001 and 45.9 (8.8) years at the baseline visit (Table 1). The majority of responders was male (85.6%) and non-Hispanic white (61.9%). Prior to the WTC attacks, nearly half (44.5%) were employed in protective services. Most responders (65.8%) were categorized as having a medium level exposure to dust, smoke and debris from the WTC sites. At baseline, while the prevalence of probable depression (21.8%), probable anxiety (17.1%) and probable PTSD (21.0%) were all high, only 8.4% reported any use of psychotropic medications. The correlation across these three mental health conditions ranged from 0.7–0.8. Ten percent of responders met study criteria for physical health comorbidity. At baseline, 7.6% of responders were classified as having a high level of

cognitive concerns (Figure 3). WTC exposure was significantly associated with all study covariates except baseline measures of clinical care site ($p=0.22$), psychotropic medication use ($p=0.25$) and physical comorbidity ($p=0.16$). When the ordinal restriction for exposure was relaxed, exposure was generally associated with baseline clinical care site ($p<.001$).

There was a total effect of WTC exposure on longitudinal measures of cognitive concerns. In models adjusted for sex, race/ethnicity, primary language, educational attainment, pre-9/11 occupation, age (time-varying), clinic (time-varying), employment status (time-varying), smoking status (time-varying), and time since 9/11/2001, responders with high versus low WTC exposure had nearly four times the odds (OR 3.92, 95% CI 2.48, 6.21) of reporting high compared to no cognitive concerns (Table 2). In contrast, responders with high versus low WTC exposure had 1.33 (95% CI 1.09, 1.62) times the odds of reporting low compared to no cognitive concerns.

Intermediate analyses showed evidence of direct associations between WTC exposure and all four mental health measures, but not physical comorbidity (Supplemental Table 3) and between all mental and physical health measures and cognitive concerns (Supplemental Table 4).

Mental health mediated most of the longitudinal association between WTC exposure and cognitive concerns. In adjusted models, the association for high versus low WTC exposure for high compared to no cognitive concerns was attenuated from OR=3.92 (95% CI 2.48, 6.21) to OR=1.42 (95% CI 0.85, 2.39) after accounting for markers of mental health (Table 3). In this model, the magnitude of the associations between probable depression, anxiety and PTSD as well as use of psychotropic medications increased in a step-wise manner as cognitive concerns increased. Responders with monotherapy versus no medication had 2.53 (95% CI 2.03, 3.14) times the odds of low compared to no cognitive concerns. In contrast, responders with polytherapy versus no medication had 9.54 (95% CI 5.22, 17.4) times the odds of high compared to no cognitive concerns.

Physical health did not mediate the longitudinal association between WTC exposure and cognitive concerns. In adjusted models, the association for high versus low WTC exposure for high compared to no cognitive concerns remained relatively unchanged (OR=3.97 95% CI 2.51, 6.27) from the total effect (OR=3.92, 95% CI 2.48, 6.21) after accounting for physical comorbidity (Table 4). This model did show, however, an independent association between physical comorbidity and cognitive concerns. In adjusted models, responders with physical comorbidity compared to those without had 2.18 (95% CI 1.75, 2.71) times the odds of high compared to no cognitive concerns.

Considering mental and physical health as joint mediators of the association between WTC exposure and cognitive concerns did not appreciably change the results from separately examining their mediating roles (Table 5). The primary difference was that the association between physical comorbidity and cognitive concerns was attenuated by the addition of the mental health mediators.

In secondary analyses, the overall pattern of results did not change substantially when running a separate model for each of the four mental health factors rather than a single

model that included all mediators (Supplemental Table 5). Of the four mental health factors, PTSD exerted the greatest impact on attenuating the magnitude of the effect of WTC exposure on cognitive concerns and use of psychotropic medication exerted the smallest impact. Restricting analyses to the 14,164 responders who were aged ≤ 55 years on 9/11/2001 did not alter the results of the full mediation model (Supplemental Table 6). The overall pattern of results across total effect and mediation models was unchanged from the main analyses when using two component questions of the LCA, Attention–2 and Memory–1, individually as the outcome rather than the LCA cognitive concerns classes (data not shown). The magnitude of the effects were attenuated from the main analyses, although remained objectively large.

DISCUSSION

In this large, longitudinal investigation of subjective cognitive concerns in the WTC General Responder Cohort, we observed that higher WTC exposure is associated with greater cognitive concerns and that this association is operating primarily through markers of mental, but not physical, health. In fully adjusted models, the inclusion of depression, anxiety, PTSD and psychotropic medication use attenuates the association between highest intensity WTC exposure and greatest cognitive concerns. The additional inclusion of physical comorbidities does little to further change the primary exposure–outcome association. While not on the pathway between WTC exposure and cognitive concerns, physical comorbidity directly impacts self-reported cognitive concerns, for example through medication side effects.

Cognitive dysfunction has been documented previously in cross-sectional (Clouston et al., 2017; Clouston et al., 2016) and longitudinal (Clouston et al., 2019) analyses in limited subsets of the General Responder Cohort as well as in the FDNY Responder cohort (Singh et al., 2020a) and WTC Health Registry (Alper et al., 2020; Seil et al., 2019). Similar to our study, in the FDNY cohort, PTSD symptoms and depressive symptoms mediated between 82% and 110% of the association between WTC exposure and subjective cognitive concerns (Singh et al., 2020b). In our study, however, we examined this association longitudinally through up to 11 years of monitoring visits, expanded mental health markers to include anxiety and use of psychotropic medications, and assessed the impact of physical comorbidity on cognitive concerns.

To date, the General Responder Cohort has not universally been assessed for objective or subjective cognitive functioning. Consequently, to examine this outcome of emerging interest we used the extensive detail available in the Self-Administered Mental Health Questionnaire (Dasaro et al., 2017) to create a latent class measure representing four levels of subjective cognitive concerns about concentration, attention, and memory. This measure is not a validated instrument and its latent structure is specific to this particular set of analyses. Nonetheless, our marker of subjective cognitive concerns was associated with age, level of educational attainment and smoking history in the expected directions. When compared to the Mental and Physical Health Composite Scores from the SF-12 and the Sheehan Disability Scale, worsening health was associated with increasing cognitive concerns on each scale. We have confidence that our measure of subjective cognitive

concerns is discriminating a sub-population experiencing a higher burden of concern about their cognitive functioning.

We did not observe a direct effect of environmental exposure on cognitive concerns after accounting for mental health; however this does not mean the relationship does not exist. First, there is no biomarker of WTC exposure in this population. A true measure of toxicant exposure may result in different findings. Second, while our qualitative composite exposure marker is sensitive to respiratory disease (Wisnivesky et al., 2011) and cancer (Solan et al., 2013), it is possible that a different qualitative focus could be more meaningful for cognitive function. Respiratory and cognitive diseases, however, have overlapping routes of exposure with both relying on inhalation. Similarly, the lack of an indirect path detected from WTC exposure through physical comorbidity to cognitive concerns may result from a poor marker of the relevant physical health diagnoses or our use of a composite physical health measure.

It is unsurprising that in this population cognitive concerns appear to be driven by mental health (Jorm, 2000). Considerable literature exists documenting associations between depression, anxiety, PTSD and use of psychotropic medication with cognitive functioning, across military (Barrett et al., 1996; Vasterling et al., 2002), traumatized (Brandes et al., 2002; Twamley et al., 2009) and general populations (Barnes et al., 2006; Lopez et al., 2003). A recent meta-analysis examined longitudinal associations between diagnoses of depression (n=31 studies), anxiety (n=4 studies) and PTSD (n=4 studies) with dementia (Kuring et al., 2020). The summary measure for the association between depression and dementia was OR 1.91 (95% CI 1.71, 2.12); for anxiety and dementia was OR 1.60 (95% CI 1.29, 2.00); and for PTSD and dementia was OR 2.55 (95% CI 0.43, 15.12). This meta-analysis focused exclusively on longitudinal studies with participants who were free from cognitive impairment at baseline, supporting the hypothesis that these mental health disorders are risk factors for later dementia, although whether the relationship is causal or prodromal remains uncertain.

Enrollment in the WTC Health Program is voluntary and continuous so self-selection into the program may decrease the generalizability of results. Likewise, attrition is a concern in any longitudinal cohort. To minimize selection and recall bias we limited the analytic population to responders who enrolled, completed their initial examination by 2007, and then returned for at least one monitoring visit, which was this study's baseline. All of our measures, too, were based on self-report, although assessment of depression, anxiety and PTSD relied on validated screening instruments. Information on use of alcohol and drugs of abuse could have further informed the analyses, but given the magnitude of the observed associations would have been unlikely to alter the overall findings. In secondary analyses, we tested corollaries to our conceptual model and ensured our findings were not an artifact of an aging cohort by restricting the sample ≤ 55 years on 9/11/2001.

WTC responders may be at heightened risk for cognitive decline. While there may be a direct effect of WTC exposure to airborne toxins on cognitive function that was not identifiable through this study, we did find that depression, anxiety, PTSD, use of psychotropic medications, and to a lesser extent physical comorbidities – all relatively common among responders – are clearly and strongly related to self-reported cognitive

concerns. This information is important for the WTC Health Program to consider when implementing screening and treatment plans as well as for initiating conversations with responders attending monitoring visits. Nearly 20 years after September 11, 2001 the mean age of rescue and recovery workers is approaching 60 years. If this population is vulnerable to cognitive decline then now is the time to implement screening programs and plan for symptom management, especially for individuals with complex comorbidities requiring intensive medical supervision. For these individuals, earlier diagnosis and symptom treatment can help maintain functional independence for longer (de Vugt and Verhey, 2013).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Cognitive functioning among rescue and recovery workers who responded in the aftermath of the September 11, 2001 World Trade Center attacks is of emerging interest
- Self-reported cognitive concerns in this population are common
- Associations between higher intensity World Trade Center exposure composite and greater cognitive concerns appear to be driven primarily by mental health comorbidities, not physical health comorbidities

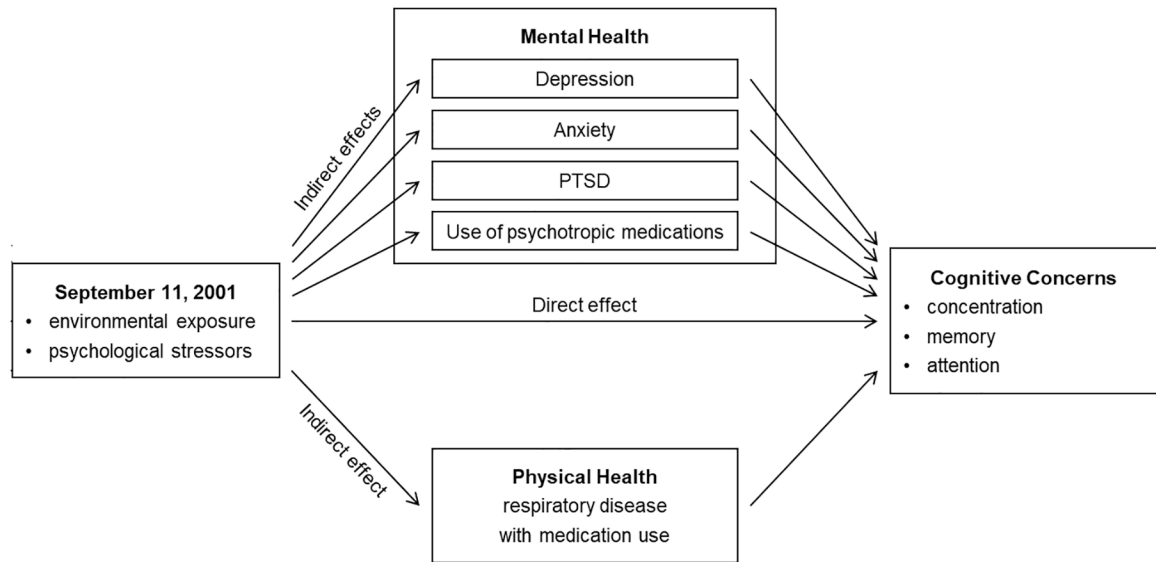


Figure 1.
Hypothesized Association between World Trade Center Exposures and Cognitive Concerns

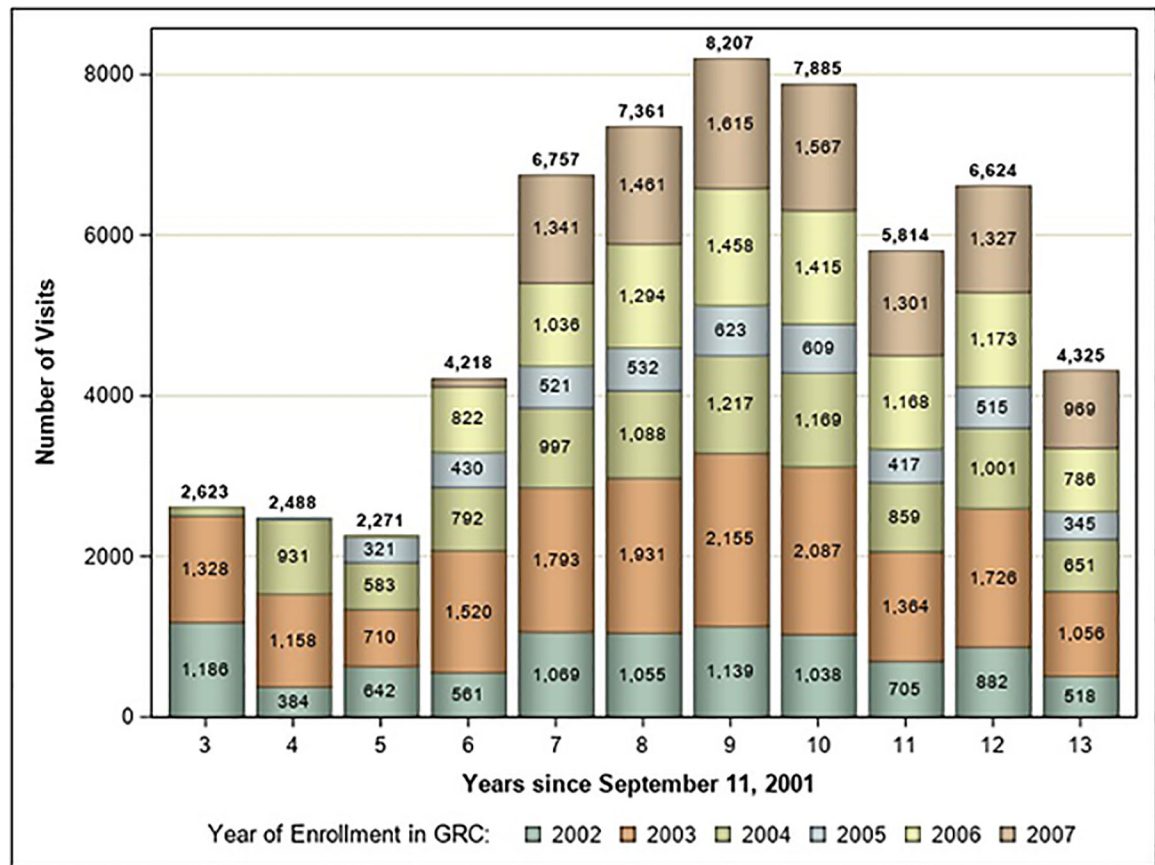


Figure 2.
Number of Visits per Enrollment Cohort by Years since September 11, 2001, World Trade Center Health Program General Responder Cohort, 2002 – 2015 (n=16,380 responders; n=58,575 visits). GRC, general responder cohort

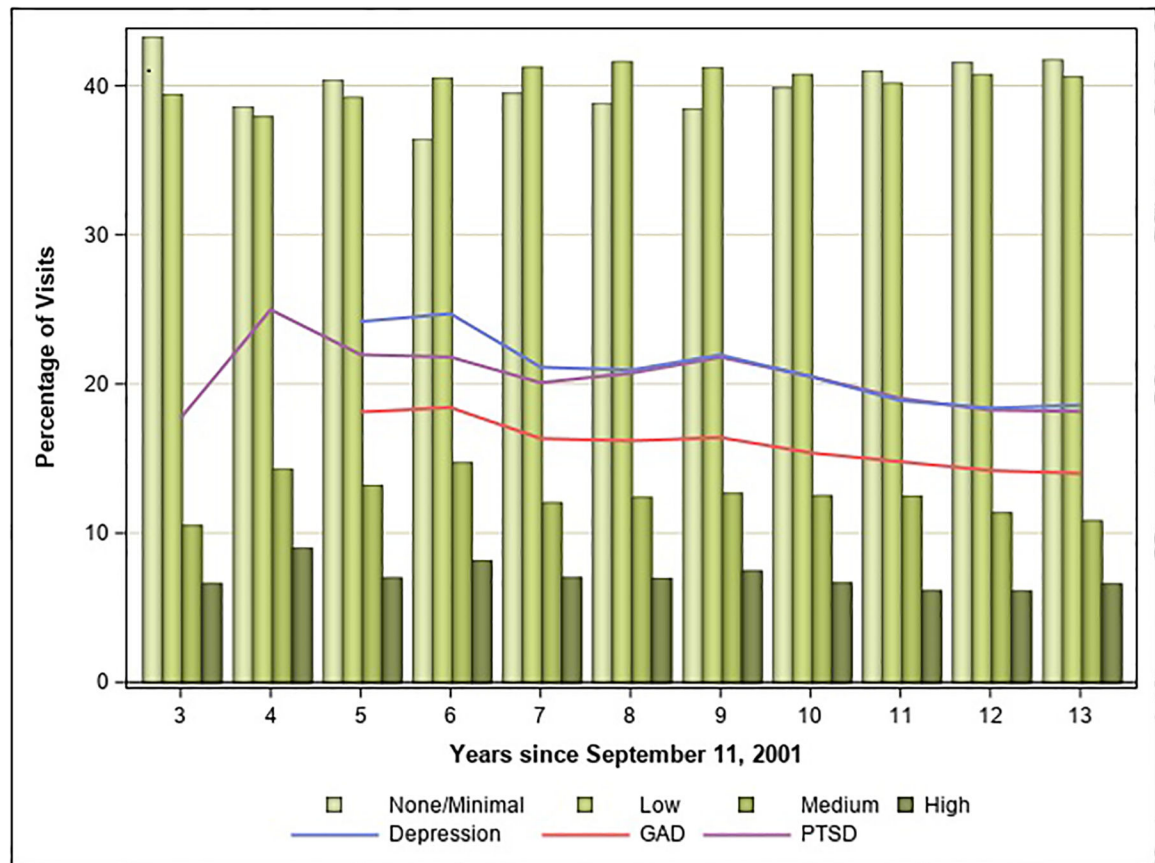


Figure 3.
Distribution of Cognitive Concerns Class, Probable Depression, Probable Anxiety, and Probable PTSD by Years since September 11, 2001, World Trade Center Health Program General Responder Cohort, 2002 – 2015 (n=16,380 responders; n=58,575 visits)

Table 1.

Characteristics of World Trade Center Health Program General Responder Cohort, 2002 – 2015, Overall and by Exposure (n=16,380)

	Overall	World Trade Center General Responder Cohort Exposure Index			
	Total n (percent)	Low n (percent)	Medium n (percent)	High n (percent)	p-value
Participants	16,380	2,071 (12.6)	10,783 (65.8)	3,526 (21.5)	
Cognitive Concerns Class: Baseline					<0.001
None	6,466 (39.5)	860 (13.3)	4,096 (63.3)	1,510 (23.3)	0.20 ^d
Low	6,571 (40.1)	813 (12.4)	4,413 (67.2)	1,345 (20.5)	
Medium	2,094 (12.8)	261 (12.5)	1,424 (68.0)	409 (19.5)	
High	1,249 (7.6)	137 (11.0)	850 (68.0)	262 (21.0)	
Cognitive Concerns Class: Worst					<0.001
None	4,119 (25.1)	549 (13.3)	2,601 (63.1)	969 (23.5)	0.44 ^d
Low	7,146 (43.6)	915 (12.8)	4,710 (65.9)	1,521 (21.3)	
Medium	2,807 (17.1)	366 (13.0)	1,875 (66.8)	566 (20.1)	
High	2,308 (14.1)	241 (10.4)	1,597 (69.2)	470 (20.3)	
Age on 9/11/2001 (mean, SD)	39.3 (8.8)	40.6 (9.5)	39.2 (8.9)	39.1 (8.3)	<.001
Age at Baseline (mean, SD)	45.9 (8.8)	47.5 (9.4)	45.7 (8.9)	45.7 (8.3)	<0.001
Time since 9/11/2001 (mean, SD) ^a	9.2 (2.7)	9.4 (2.6)	9.2 (2.7)	9.3 (2.7)	<0.001
Sex					<0.001
Female	2,352 (14.4)	379 (16.1)	1,558 (66.2)	415 (17.6)	
Male	14,028 (85.6)	1,692 (12.1)	9,225 (66.8)	3,111 (22.2)	
Race/Ethnicity					0.009
Non-Hispanic white	10,137 (61.9)	1,254 (12.4)	6,621 (65.3)	2,262 (22.3)	
Non-Hispanic Black	1,754 (10.7)	242 (13.8)	1,115 (63.6)	397 (22.6)	
Hispanic	4,063 (24.8)	514 (12.7)	2,780 (68.4)	769 (18.9)	
Other	426 (2.6)	61 (14.3)	267 (62.7)	98 (23.0)	
Primary Language					<0.001
English	14,241 (86.9)	1,771 (12.4)	9,045 (63.5)	3,425 (24.1)	
Other	2,139 (13.1)	300 (14.0)	1,738 (81.3)	101 (4.7)	
Educational Attainment					<0.001 ^d
Less than high school degree	1,186 (7.2)	181 (15.3)	877 (73.9)	128 (10.8)	
High school degree	3,713 (22.7)	450 (12.1)	2,557 (68.9)	706 (19.0)	
Some college	6,612 (40.4)	768 (11.6)	4,319 (65.3)	1,525 (23.1)	
College degree	3,034 (18.5)	372 (12.3)	1,936 (63.8)	726 (23.9)	
Advanced degree	1,835 (11.2)	300 (16.3)	1,094 (59.6)	441 (24.0)	
Pre-9/11 Occupation					<0.001
Protective Services	7,292 (44.5)	780 (10.7)	4,302 (59.0)	2,210 (30.3)	
Construction	4,099 (25.0)	514 (12.5)	3,144 (76.7)	441 (10.8)	

	Overall	World Trade Center General Responder Cohort Exposure Index			
	Total n (percent)	Low n (percent)	Medium n (percent)	High n (percent)	p-value
Other	4,989 (30.5)	777 (15.6)	3,337 (66.9)	875 (17.6)	
Time-varying Characteristics: Baseline					
Clinic Site					0.22
Mount Sinai Health System	11,365 (69.4)	1,368 (12.0)	7,685 (67.6)	2,312 (20.3)	
NYU Langone Health	431 (2.6)	56 (13.0)	260 (60.3)	115 (26.7)	
Northwell Health	1,049 (6.4)	166 (15.8)	611 (58.3)	272 (25.9)	
Rutgers University	810 (4.9)	86 (10.6)	566 (69.9)	158 (19.5)	
Stony Brook University	2,725 (16.6)	395 (14.5)	1,661 (60.9)	669 (24.5)	
Employment Status					0.02
Working full or part time	12,285 (75.0)	1,554 (12.7)	8,012 (65.2)	2,719 (22.1)	
Not working	4,095 (25.0)	517 (12.6)	2,771 (67.7)	807 (19.7)	
Smoking Status					0.002 ^d
Never	9,623 (58.7)	1,209 (12.6)	6,192 (64.3)	2,222 (23.1)	
Former	4,588 (28.0)	645 (14.1)	3,043 (66.3)	900 (19.6)	
Current	2,169 (13.2)	217 (10.0)	1,548 (71.4)	404 (18.6)	
PHQ-9 Score (mean, SD) ^b	5.7 (6.5)	5.3 (6.0)	5.8 (6.6)	5.4 (6.5)	0.03
Probable Depression (PHQ-9 ≥10)					0.01
Yes	1,510 (21.8)	194 (12.9)	1,021 (67.6)	295 (19.5)	0.86 ^d
No	5,424 (78.2)	802 (14.8)	3,441 (63.4)	1,181 (21.8)	
GAD-7 Score (mean, SD) ^b	4.1 (5.7)	3.8 (5.4)	4.2 (5.7)	4.0 (5.9)	0.11
Probable Anxiety (GAD-7 ≥10)					0.045
Yes	1,173 (17.1)	143 (12.2)	780 (66.5)	250 (21.3)	0.15 ^d
No	5,666 (82.9)	845 (14.9)	3,613 (63.8)	1,208 (21.3)	
PCL-17 Score (mean, SD)	33.1 (16.4)	30.8 (15.2)	33.5 (16.6)	33.1 (16.5)	<0.001
Probable PTSD (PCL-17 ≥44)					<0.001
Yes	3,386 (21.0)	344 (10.2)	2,338 (69.1)	704 (20.8)	0.06 ^d
No	12,723 (79.0)	1,686 (13.3)	8,265 (65.0)	2,772 (21.8)	
Psychotropic Medication Use					0.25 ^d
None	15,005 (91.6)	1,898 (12.7)	9,897 (66.0)	3,210 (21.4)	
Monotherapy	1,033 (6.3)	130 (12.6)	671 (65.0)	232 (22.5)	
Polytherapy	342 (2.1)	43 (12.6)	215 (62.9)	84 (24.6)	
Physical Comorbidity ^c					0.16
Yes	1,601 (10.0)	224 (14.0)	1,043 (65.1)	334 (20.9)	
No	14,464 (90.0)	1,806 (12.5)	9,551 (66.0)	3,107 (21.5)	

SD, standard deviation; PHQ, Patient Health Questionnaire; GAD, Generalized Anxiety Disorder scale; PCL, PTSD Symptom Checklist

^aMean time since 9/11/2001 reported at visit (n=58,575) rather than participant level; mean time by outcome represents cognitive concerns by visit rather than baseline

^b Screening for depression and anxiety began in September 2008, with near complete implementation by mid-2009, so responders who completed their baseline monitoring visit prior to this point have missing data for depression and anxiety at baseline

^c Physical comorbidity: diagnosis with sleep apnea, asthma, chronic obstructive pulmonary disease, lung scarring, rhinitis or sinusitis paired with self-reported use of antihistamines, inhaled glucocorticoids or oral steroids

^d p-value for test of a linear trend

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Table 2.

Total Effect. Adjusted^a Association between World Trade Center Exposure and Longitudinal Cognitive Concerns, World Trade Center Health Program General Responder Cohort, 2002 – 2015 (n=16,380)

	Cognitive Concerns Class				
	None	Low	Medium	High	
	Adjusted ^a Odds Ratio (95% Confidence Interval)				p-value
WTC Exposure Index					
Low	1.0	1.0	1.0	1.0	<0.001
Medium	1.0	1.19 (1.00, 1.41)	1.35 (1.03, 1.76)	1.89 (1.27, 2.80)	
High	1.0	1.33 (1.09, 1.62)	2.16 (1.58, 2.95)	3.92 (2.48, 6.21)	

^aAdjusted for sex, race/ethnicity, primary language, educational attainment, pre-9/11 occupation, clinic (time-varying), age (time-varying), employment status (time-varying), smoking status (time-varying), time since 9/11/2001

Table 3.

Mediation by Mental Health. Adjusted^a Association between World Trade Center Exposure and Longitudinal Cognitive Concerns, World Trade Center Health Program General Responder Cohort, 2002 – 2015 (n=14,869)

	Cognitive Concerns Class				
	None	Low	Medium	High	
	Adjusted ^a Odds Ratio (95% Confidence Interval)				p-value
WTC Exposure Index					
Low	1.0	1.0	1.0	1.0	0.06
Medium	1.0	1.16 (0.96, 1.39)	0.97 (0.74, 1.27)	1.10 (0.71, 1.70)	
High	1.0	1.26 (1.01, 1.56)	1.12 (0.82, 1.54)	1.42 (0.85, 2.39)	
Probable Depression					
No	1.0	1.0	1.0	1.0	<0.001
Yes	1.0	9.03 (6.59, 12.4)	113 (82.0, 157)	602 (395, 920)	
Probable Anxiety					
No	1.0	1.0	1.0	1.0	<0.001
Yes	1.0	4.38 (3.13, 6.14)	25.7 (17.9, 36.8)	93.0 (62.0, 139)	
Probable PTSD					
No	1.0	1.0	1.0	1.0	<0.001
Yes	1.0	14.4 (10.7, 19.6)	57.1 (41.3, 78.9)	98.8 (67.1, 145)	
Psychotropic Use					
None	1.0	1.0	1.0	1.0	<0.001
Monotherapy	1.0	2.53 (2.03, 3.14)	3.25 (2.44, 4.34)	4.52 (3.16, 6.46)	
Polytherapy	1.0	4.99 (3.10, 8.05)	6.39 (3.72, 11.0)	9.54 (5.22, 17.4)	

^a Adjusted for sex, race/ethnicity, primary language, educational attainment, pre-9/11 occupation, clinic (time-varying), age (time-varying), employment status (time-varying), smoking status (time-varying), time since 9/11/2001

Table 4.

Mediation by Physical Health. Adjusted^a Association between World Trade Center Exposure and Longitudinal Cognitive Concerns, World Trade Center Health Program General Responder Cohort, 2002 – 2015 (n=16,311)

	Cognitive Concerns Class				
	None	Low	Medium	High	
	Adjusted ^a Odds Ratio (95% Confidence Interval)				p-value
WTC Exposure Index					
Low	1.0	1.0	1.0	1.0	<0.001
Medium	1.0	1.19 (1.01, 1.42)	1.36 (1.04, 1.78)	1.93 (1.30, 2.86)	
High	1.0	1.34 (1.10, 1.63)	2.19 (1.60, 3.00)	3.97 (2.51, 6.27)	
Physical Comorbidity ^b					
No	1.0	1.0	1.0	1.0	<0.001
Yes	1.0	1.38 (1.23, 1.53)	1.65 (1.41, 1.94)	2.18 (1.75, 2.71)	

^a Adjusted for sex, race/ethnicity, primary language, educational attainment, pre-9/11 occupation, clinic (time-varying), age (time-varying), employment status (time-varying), smoking status (time-varying), time since 9/11/2001

^b Physical comorbidity: diagnosis with sleep apnea, asthma, chronic obstructive pulmonary disease, lung scarring, rhinitis or sinusitis paired with self-reported use of antihistamines, inhaled glucocorticoids or oral steroids

Table 5.

Mediation by Mental and Physical Health. Adjusted^a Association between World Trade Center Exposure and Longitudinal Cognitive Concerns, World Trade Center Health Program General Responder Cohort, 2002 – 2015 (n=14,821)

	Cognitive Concerns Class				
	None	Low	Medium	High	
	Adjusted ^a Odds Ratio (95% Confidence Interval)				p-value
WTC Exposure Index					
Low	1.0	1.0	1.0	1.0	0.052
Medium	1.0	1.16 (0.97, 1.40)	0.99 (0.76, 1.30)	1.15 (0.74, 1.78)	
High	1.0	1.27 (1.02, 1.58)	1.15 (0.84, 1.58)	1.48 (0.88, 2.50)	
Probable Depression					
No	1.0	1.0	1.0	1.0	<0.001
Yes	1.0	9.12 (6.64, 12.5)	112 (80.8, 155)	597 (390, 915)	
Probable Anxiety					
No	1.0	1.0	1.0	1.0	<0.001
Yes	1.0	4.41 (3.13, 6.21)	25.9 (18.1, 37.3)	94.7 (63.0, 143)	
Probable PTSD					
No	1.0	1.0	1.0	1.0	<0.001
Yes	1.0	14.2 (10.4, 19.2)	56.2 (40.7, 77.7)	97.9 (66.4, 144)	
Psychotropic Use					
None	1.0	1.0	1.0	1.0	<0.001
Monotherapy	1.0	2.48 (2.00, 3.09)	3.17 (2.37, 4.22)	4.32 (3.01, 6.18)	
Polytherapy	1.0	4.75 (2.93, 7.67)	6.14 (3.56, 10.6)	9.01 (4.91, 16.5)	
Physical Comorbidity ^b					
No	1.0	1.0	1.0	1.0	<0.001
Yes	1.0	1.32 (1.17, 1.50)	1.35 (1.11, 1.65)	1.63 (1.23, 2.15)	

^aAdjusted for sex, race/ethnicity, primary language, educational attainment, pre-9/11 occupation, clinic (time-varying), age (time-varying), employment status (time-varying), smoking status (time-varying), time since 9/11/2001

^bPhysical comorbidity: diagnosis with sleep apnea, asthma, chronic obstructive pulmonary disease, lung scarring, rhinitis or sinusitis paired with self-reported use of antihistamines, inhaled glucocorticoids or oral steroids