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Original article

Posttraumatic stress disorder, major depression, and mild cognitive impairment: A cohort study of world trade center responders

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ABSTRACT

Background: World Trade Center (WTC) responders have elevated risk of posttraumatic stress disorder (PTSD), major depressive episodes (MDEs), and mild cognitive impairment (MCI). In a sample of 337 WTC responders from the Fire Department of the City of New York (FDNY), we estimated the proportion of MCI cases explained by PTSD and MDE.
Methods: We fit quasi-Poisson regressions, adjusting for covariates, to estimate risk ratios (RRs) and population-attributable fractions (PAFs), and explored associations between a symptom count and MCI, as well as individual cognitive tests.
Measures: PTSD and MDE were diagnosed with the SCID-5. MCI was defined algorithmically using objective testing (HVLT subtests, COWA, SDMT, TMT-A/B), self-reported concern (CFI >0), and excluding severe naming impairment. The cohort was predominantly firefighters; occupational requirements preserve activities of daily living.
Results: PTSD (RR=1.90, 95 % CI = [1.53–2.36]), MDE (RR=1.62, 95 % CI = [1.16–2.27]), and comorbid PTSD/MDE (RR=2.31, 95 % CI = [1.74–3.06]) conferred higher risk of MCI. The combined PAF for PTSD, MDE, and their comorbidity was 11.7 % (95 % CI = [6.1 %–18.1 %]). Symptom burden was associated with higher MCI risk (RR = 1.11, 95 % CI = [1.08–1.14]), and worse visuospatial learning/recall and verbal recognition (ρ range = [−0.13 to −0.20]).
Conclusion: Over 20 years after the precipitating trauma, PTSD, MDE, and their comorbidity accounted for a meaningful share of MCI cases, although most cases (>85 %) were not attributable to these disorders. Findings highlight visuospatial learning and memory as most strongly linked to psychiatric symptoms in this cohort.

The terrorist attacks on the World Trade Center (WTC) that occurred on September 11, 2001, led to unprecedented exposure to traumatic events for thousands of rescue and recovery workers. Among these responders, members of the Fire Department of the City of New York (FDNY) have been the subject of extensive research due to the heightened severity of their exposures and risk of developing posttraumatic stress disorder (PTSD), major depression, and cognitive impairment (Chiu et al., 2011; Soo et al., 2011; Singh et al., 2020; Singh et al., 2020).

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PTSD and depression may share underlying mechanisms linked to mild cognitive impairment (MCI), a clinical entity characterized by complaints of cognitive decline and objective deficits while activities of daily living remain preserved (Jack et al., 2024). Building on prior research, this study investigates the intersection of PTSD, major depressive episodes (MDEs), and psychiatric symptom burden in relation to MCI and cognitive dysfunction in WTC-exposed FDNY responders.

1. PTSD and cognitive impairment

Extensive research has established that PTSD is negatively associated with cognitive function. A review of relevant studies highlighted deficits in memory, attention, and executive function among individuals with PTSD, beyond the effects of trauma alone (age range across studies: 19 – 81 years) (Qureshi et al., 2011). Impaired memory for everyday events has also been documented in PTSD patients (ages 18 – 50 years) (Pitts et al., 2022), underscoring the link between PTSD and cognitive function. Similarly, a recent review of the relationship between PTSD and working memory reported consistent impairments in patients with PTSD, spanning childhood to late adulthood (Norte et al., 2024). Providing further evidence for the link between PTSD and impaired memory, a meta-analysis investigating episodic memory among patients with PTSD (mean age = 38.75 years) found notable dysfunction when compared to both trauma-exposed and non-traumatized controls (Petzold and Bunzeck, 2022). In addition to these studies conducted predominately in Western nations, cognitive dysfunction has also been consistently linked to PTSD in East Asian cohorts (Narita-Ohtaki et al., 2018; Shin et al., 2017; Yang et al., 2014; Wu et al., 2015; Li et al., 2020). Together these findings indicate consistent PTSD-related impairments across memory and executive function spanning multiple ages, cohorts, and contexts.

2. Depression and cognitive impairment

Patients with major depressive disorder are also at a higher risk of cognitive impairment and decline (Bora et al., 2013; Ismail et al., 2017; Rock et al., 2014; Wei et al., 2025; Zhou et al., 2022; Yang et al., 2020; Dai et al., 2025; Kida et al., 2016; Kim, 2022; Choi et al., 2019; Baek and Yoon, 2023; Yatawara et al., 2016). A meta-analysis found impaired cognition among patients with major depression (ages 34 – 76 years), with the most pronounced deficits in verbal memory and processing speed for late-onset cases (Bora et al., 2013). Another meta-analysis reported 20 % to 40 % prevalence of depression among individuals with MCI (range of mean ages = 53 – 88 years) (Ismail et al., 2017), and other meta-analytic findings have revealed that cognitive impairment is not only a central aspect of depression, but deficits in memory, executive function, and attention can persist after remission (Rock et al., 2014). These findings suggest that cognitive dysfunctions related to depression may be enduring rather than temporary symptoms of depressive episodes. Similarly, across East Asian cohorts, depressive symptoms and diagnoses have been linked to worse cognition, faster decline, and future impairment (Wei et al., 2025; Zhou et al., 2022; Yang et al., 2020; Dai et al., 2025; Kida et al., 2016; Kim, 2022; Choi et al., 2019; Baek and Yoon, 2023; Yatawara et al., 2016). These findings indicate that depression is consistently associated with cognitive dysfunction, impairment, and heightened risk of cognitive decline across different age groups and cultures.

3. Biological mechanisms

Imaging studies have further illuminated the potential neural mechanisms underlying cognitive deficits in patients with PTSD. For example, a review of MRI studies highlights disruptions in key brain regions associated with memory and emotional regulation, including irregular activity in subcortical regions (e.g. hippocampus, amygdala, thalamus) and the cerebellum (Dossi et al., 2020). A systematic review of imaging studies on the link between PTSD and cognitive impairment highlight “bilateral frontal (e.g., prefrontal, orbitofrontal, cingulate cortices), temporal (particularly in those with damage to the hippocampi), and parietal (e.g., superior and precuneus) regions” (de Araujo et al., 2023). Neuroimaging studies of WTC responders have reported cortical atrophy (Clouston et al., 2022) and white matter changes (Kritikos et al., 2022) among those with cognitive impairment, and reduced cortical complexity (Kritikos et al., 2021) and gray-white matter contrasts (Zhou et al., 2025) in responders with PTSD.

Depression also has putatively causal pathways to cognitive decline and MCI (Diniz et al., 2013). Major depression is associated with HPA-axis dysregulation and glucocorticoid exposure that affects hippocampal and prefrontal circuitry (Belleau et al., 2019; Oei et al., 2007). Depression is also linked to heightened systemic inflammation and microglial activation (Osimo et al., 2020; Eggerstorfer et al., 2022), vascular–metabolic dysregulation consistent with the ‘vascular depression’ hypothesis (Taylor et al., 2013), impaired synaptic plasticity (Duman et al., 2016), and circadian disturbance (de Leeuw et al., 2023; Germain and Kupfer, 2008). Depression is further intertwined with lifestyle and cardiometabolic risk factors that influence cognition (Geraets et al., 2022; Zhao et al., 2024). Some studies have also connected depression to neurodegenerative biomarkers (Babulal et al., 2020; Chan et al., 2020) and accelerated brain and biological aging (Han et al., 2021; Protsenko et al., 2021), although reciprocal and reverse causation remain possible (Yin et al., 2024; Gao et al., 2022). Nevertheless, these overlapping pathways with PTSD suggest that psychiatric comorbidity may confer additive risk for MCI (Flatt et al., 2018; Wallensten et al., 2023), motivating our tests of independent and joint associations between psychiatric diagnoses and MCI, and between psychiatric symptom burden and individual cognitive tests.

4. PTSD, depression, and cognitive impairment in WTC responders

Extant research has consistently linked PTSD and depression to cognitive impairment in WTC responders. For example, PTSD and major depression among police and volunteer responders were found to be significantly associated with MCI (Clouston et al., 2016). Moreover, reexperiencing symptoms of PTSD have been shown to prospectively predict increased risk of incident MCI in WTC responders (Clouston et al., 2016; Clouston et al., Dec 2019). Among WTC-exposed responders from the FDNY, PTSD is significantly associated with subjective cognitive concerns (Singh et al., 2020). PTSD and depressive symptoms have also been shown to mediate the link between WTC exposure and cognitive concerns among FDNY responders, highlighting a putative etiological pathway from trauma exposure to concerns about cognitive decline (Singh et al., 2020).

Other work in this population has reported a 16 % to 20 % prevalence of clinically elevated symptoms of PTSD three-to-five years post-exposure (Chiu et al., 2011). Further, prevalence trends of probable PTSD and depression have been documented in WTC-exposed firefighters over a decade after the 9/11 attacks, reinforcing the chronic nature of PTSD and linking PTSD to respiratory symptoms, alcohol use, and health behaviors (Soo et al., 2011). Echoing the chronicity of PTSD symptoms in WTC responders, a recent trajectory analysis found a 10 % annual prevalence of clinically elevated symptoms two decades after the WTC attacks (Mann et al., 2025).

5. Study rationale & aims

PTSD and major depression often co-occur in trauma-exposed populations (Rytwinski et al., 2013; Flory and Yehuda, 2015), and comorbidity is associated with greater symptom severity and persistence (Shalev et al., 1998; Post et al., 2011), functional impairment (Flory and Yehuda, 2015; O’Donnell et al., 2009; Nichter et al., 2019), sleep disturbance (Leskin et al., 2002), and higher medical burden (Nichter et al., 2019; Frayne et al., 2004). Converging evidence implicates mechanisms relevant to cognition—including stress physiology (Golier et al., 2003; McEwen and Gianaros, 2011), neuroinflammatory and vascular–metabolic pathways (Miller and Raison, 2016; Passos et al., 2015; Dedert et al., 2010), and fronto-hippocampal circuit disruption (Fenster et al., 2018; Logue et al., 2019; Logue et al., 2018)—suggesting that comorbid PTSD and depression may pose a higher risk for cognitive dysfunction than either condition alone (Nijdam et al., 2013; Scheiner et al., 2014; Koopowitz et al., 2021).

Building on this rationale, we test both categorical diagnoses and a comorbidity symptom count in relation to MCI and domain-specific cognitive tests. Given the established links between PTSD and depression with cognitive impairment, this study aims to explore how these psychiatric disorders jointly contribute to risk for cognitive impairment in WTC-exposed FDNY responders. By leveraging validated diagnostic tools and objective assessments of cognitive function, this study is well situated to clarify the interplay between trauma-related psychiatric symptoms and cognitive impairment in this vulnerable population. For psychiatric diagnoses and MCI, we quantify context-specific population-attributable fractions (PAFs) for PTSD, MDD, and their comorbidity. For symptom counts and individual cognitive tests we evaluate rank-based and linear associations, as well as potential non-linearity. This approach extends prior studies of WTC responders by quantifying comorbidity-specific risk for cognitive impairment and by testing associations between categorical and continuous measures of psychiatric symptoms with categorical and continuous measures of MCI and cognitive dysfunction in the most highly exposed population of WTC responders—firefighters and EMS from the FDNY.

6. Methods

6.1. Sample

The sample for this study ($n = 337$) included participants enrolled in a large cohort of WTC-exposed responders from the FDNY. Participants were recruited through a multi-stage process involving random selection from a source population of eligible responders and outreach by mail and telephone. More details on participant recruitment and data collection can be found elsewhere (Mann et al., 2024). Inclusion criteria included documented presence at the WTC disaster site for at least one day between September 11, 2001, and July 24, 2002, and fluent English proficiency. Exclusion criteria included current or past diagnosis of a known neurological condition that could affect cognitive function, including and not limited to Alzheimer's disease, Parkinson's disease, epilepsy, brain tumors, stroke, and traumatic brain injury (TBI). Participants provided written informed consent, and the study was approved by the Stony Brook University Institutional Review Board (IRB: 2021–00,295). Data collection occurred from November 2021 to December 2023.

6.2. Measures

Mild Cognitive Impairment (MCI): Participants completed a battery of validated neuropsychological tests to evaluate multiple domains of cognitive function. Verbal memory and learning was assessed by the Hopkins Verbal Learning Test (Benedict et al., 1998), which includes measures of total recall, delayed recall, verbal recognition, and verbal retention. Executive functions were measured using the Trail Making Test (TMT) (Gaudino et al., 1995) and the Symbol Digit Modalities Test (SDMT) (Benedict et al., 2017). Verbal fluency was measured by the Controlled Oral Word Association (COWA) test (A Singh et al., 2020). Severe impairments of visual recognition, word acquisition, and verbal expression were assessed using the Boston Naming Test (BNT) (Mack et al., 1992). All neurocognitive assessments were administered to participants by trained research staff.

From these assessments, a binary variable indicating MCI was operationalized algorithmically using the National Institute on Aging-Alzheimer's Association (NIA-AA) criteria (Jack et al., 2024)—using published age-adjusted norms for each test, we coded scores falling in the borderline/impaired–to-profound ranges as "impaired" and classified participants as having MCI if they showed impairment on two or more tests, together with self-reported cognitive concerns (Cognitive Function Instrument > 0), and the absence of severe impairments indicated by 3 or more errors on the Boston Naming Task. More details on the descriptive statistics and prevalence of domain-specific impairments measured by individual tests have been published elsewhere. (Mann et al., 2024)

We additionally administered the CogState™ computerized battery, which has demonstrated sensitivity to dementia-related changes in older adults (Hammers et al., 2011; Mielke et al., 2015). The battery comprised the Groton Maze Learning Test, Detection, Identification, One Card Learning, Continuous Paired Associate Learning, and the GMLT-Delayed. From these tasks, domain scores were derived capturing episodic memory, working memory, reaction speed, processing speed, cognitive throughput, and visuospatial learning and recall.

Psychiatric Disorders: Posttraumatic Stress Disorders (PTSD) and Major Depressive Episode (MDE) were assessed using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (SCID) (First et al., 2015). The SCID is a widely used, semi-structured interview designed to diagnose major psychiatric disorders according to the criteria outlined in the DSM-5. It involves a series of questions that allow trained experimenters to systematically assess the presence, severity, and duration of mental health conditions. For the present study, the SCID modules for PTSD and MDE were administered on the same day as the other study assessments.

Physical Health Covariates. Electronic health records were utilized to capture physical health conditions, including physician's diagnosis (coded 0 = not diagnosed, 1 = diagnosed) of asthma, cardiovascular disease, diabetes, and hypertension. Body Mass Index (BMI), calculated as weight in kilograms divided by height in meters squared, was determined using responders' height and weight measurements.

6.3. Data analysis

Missing Data. Analyses were conducted using RStudio Version 2023.12.0 + 369. To evaluate whether the data were missing completely at random (MCAR), a distribution free non-parametric test (Jamshidian and Jalal, 2010) was conducted using all study variables. The nonsignificant result ($p = 0.374$) is consistent with the null hypothesis that data are MCAR. This suggests the small number of missing observations for psychiatric and MCI diagnoses ($n = 6$ [1.74 %] participants from a sample of 343 participants) are unlikely to be related to observed variables. Consequently, listwise deletion of missing data (i.e. complete case analysis) was deemed suitable for inferential analyses.

Age Trends for Cognitive Tests. Age-related trends for each cognitive test were examined, with scores standardized to z-scores to ease interpretation. For each cognitive test, we fit two covariate-adjusted models: a linear model with age entered continuously and a natural cubic spline to allow curvature ($df = 3$), both adjusting for prespecified covariates (gender, race/ethnicity, education, occupation, asthma, BMI, cardiovascular disease, hypertension, and diabetes). Next, we obtained model-based means for both continuous-age curves and binned-age summaries using estimated marginal means with proportional weighting, which averages over the empirical distribution of categorical covariates and holds continuous covariates at their sample means. Predicted trends with 95 % confidence intervals were plotted across the observed age range, and adjusted bin means (with matching 95 % CIs) were computed for 5-year age intervals (from 45–70 years). Natural spline and linear trends were then visualized alongside the adjusted age-bin means to facilitate comparison of linear and non-linear trends for each cognitive test.

Prevalence and Associations of PTSD, MDE, and MCI. Crude prevalence was calculated with Clopper-Pearson intervals (Clopper and Pearson, 1934) for binary variables (PTSD, MDE, & MCI) and Goodman intervals (Goodman, 1965) for multinomial groups (PTSD only, MDE only, comorbid PTSD/MDE). Bivariate associations between psychiatric diagnoses and MCI were assessed using Fisher's exact test. To adjust for the potentially confounding or suppressing effects of covariates, multivariable, robust, quasi-Poisson regressions were adopted for overdispersion due to using a binary MCI outcome and accommodating its small counts in certain categories. Covariates included age, sex, race/-ethnicity, level of education, occupation, and physical health variables (asthma, BMI, cardiovascular disease, diabetes, and hypertension). Multivariable regressions adjusted for demographics and occupation only, before additionally adjusting for physical health variables.

The contribution of psychiatric conditions, including PTSD, MDE, and their comorbidity to MCI was estimated using the population-attributable fraction (PAF) to account for both the strength of association and the prevalence of each psychiatric condition in the sample (Levin, 1953; Rockhill et al., 1998; Shield et al., 2016). Notably, the PAF serves as a counterfactual tool in cross-sectional studies, even when evidence of causation cannot be established, as it quantifies the proportion of an outcome that could hypothetically be prevented if the putative explanatory variables were absent, providing insights into potential improvements for public health. The multivariable quasi-Poisson regression was used to obtain the adjusted relative risks for MCI associated with three categories of diagnostic status: (1) PTSD only, (2) MDE only, and (3) comorbid PTSD and MDE (with unimpaired as the reference group), adjusting for all the covariates listed above. The adjusted RRs and sample proportions of categories were used to obtain PAF estimates, which were validated using model-based predicted risk. A nonparametric bootstrap procedure (Davison and DV., 1997) with 1000 resamples was used to generate 95 % confidence intervals for the PAF estimates.

Exploratory Dimensional Analysis. Finally, to conduct complementary exploratory analyses, we operationalized comorbid symptom burden as a count score derived from SCID item responses coded to indicate the presence or absence of a symptom. The binary MCI variable was then regressed on the SCID symptom count, before and after adjusting for study covariates. In addition, for each cognitive measure we quantified rank-based, monotonic, associations with the SCID symptom count using partial Spearman correlations with FDR adjustment for multiple testing (Benjamini and Hochberg, 1995). In parallel, we estimated linear slopes from ordinary least squares models of each cognitive measure on symptom count and covariates, reporting the per-symptom coefficient with p-values derived from non-parametric bootstrapping with 1000 resamples. Departure from linearity was assessed by comparing a natural cubic spline for symptom count ($df = 3$) against the linear model using a nested F-test.

7. Results

7.1. Sample characteristics and age trends

Descriptive statistics (summarized in Table 1) indicate that participants were predominantly male (98.5 %) and employed as firefighters (89.6 %), with additional representation from emergency medical service providers (8.0 %) and supervisory roles within these occupational categories. The educational attainment of the sample varied, with over half (51.6 %) having completed some college or technical school, while 30.3 % held a bachelor's degree, 7.4 % completed graduate-level education, and none reported having less than a high school diploma. Asthma (36.5 %) and hypertension (26.1 %) were common physical health conditions, while cardiovascular disease (9.5 %) and diabetes (5.0 %) were less common.

The average age of participants was 59.6 years ($SD = 6.3$), and 19.3 % of the sample was over 65 years old (n = 65). As expected, cognitive performance was negatively associated with age across experimenter-administered and computerized tests, with the exceptions of verbal retention measured by the HVLT, and verbal fluency measured by the COWA, which were comparatively flat, with the natural spline and binned-age means departing from N linearity for the COWA (see Supplemental Figure S1). Age differences were most evident for speeded and executive processing tasks (e.g., TMT-A/B and SDMT), with linear and non-linear declines overlapping closely. Age differences for tests of verbal memory (HVLT) were similar for total and delayed recall but smaller for retention and recognition. For computerized tests, age-related declines were most pronounced for visuospatial recall and episodic memory. Apart from the COWA (Table S5), non-linear splines did not improve fit relative to linear trends (p-values > 0.05, q-values > 0.10).

Table 1
Sample characteristics.

n = 337	*n/M*	%/*SD*
Age (years)	59.56	6.28
Gender		
Male	332	98.52
Female	5	1.48
Race/Ethnicity		
Non-Latino White	316	93.76
Other Race/Ethnicity	21	6.23
Level of Education		
High School Diploma	36	10.68
Some College/Tech. School	174	51.63
Bachelor's Degree	102	30.27
Graduate School	25	7.42
Occupation		
Firefighter	302	89.61
EMS	27	8.01
Supervisor	8	2.37
Physical Health		
Asthma	123	36.49
Body Mass Index	29.85	4.65
Cardiovascular Disease	32	9.49
Diabetes	17	4.96
Hypertension	88	26.11
Psychiatric Disorders		
Major Depressive Episode (MDE)	18	5.34
Posttraumatic Stress Disorder (PTSD)	51	15.13
(Comorbidity Groups)		
Neither MDE nor PTSD	280	83.09
MDE only	6	1.78
PTSD only	39	11.57
PTSD and MDE	12	3.56
Mild Cognitive Impairment (MCI)		
MCI	153	45.40

Notes. n = frequency. M = mean, % = percent. SD = standard deviation.

7.2. Crude prevalence

Unadjusted prevalence (reported in Fig. 1) indicated that PTSD was relatively common in this population more than two decades after exposure (51 cases, 15.1 %) and MCI was even more common (153 cases, 45.4 %), while MDE was evident in fewer participants (18 cases, 5.3 %). Notably, while 76.5 % of PTSD cases were not diagnosed with comorbid MDE, 66.6 % of those with MDE were also diagnosed with comorbid PTSD. MCI was especially common among participants diagnosed with PTSD (78.4 %) and MDE (72.2 %). Yet, among participants with MCI, only 26.1 % and 8.5 % were diagnosed with PTSD and MDE, respectively.

7.3. Categorical analyses

Results are summarized in Fig. 2 and reported comprehensively in supplemental material (Tables S1-S4). Several results are noteworthy. First, Fisher's exact test indicated that diagnosis of PTSD was significantly associated with MCI ($p < 0.001$). After multivariable adjustment

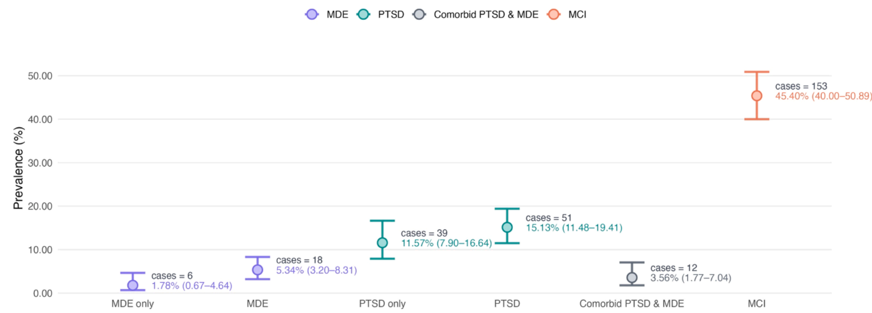

Fig. 1. Crude Prevalence of Psychiatric Diagnoses and Mild Cognitive Impairment
Notes. n = 337. Crude prevalence (%) is plotted and vertical bars indicate 95 % confidence intervals (Clopper–Pearson for binary and Goodman for multinomial variables). Text labels report the estimate, 95 % confidence interval, and case count. Colors group phenotypes: MDE & MDE only (violet), PTSD & PTSD only (teal), comorbid PTSD & MDE (gray), and MCI (orange). "MDE only" indicates cases of MDE without comorbid PTSD. PTSD only indicates cases of PTSD without comorbid MDE.

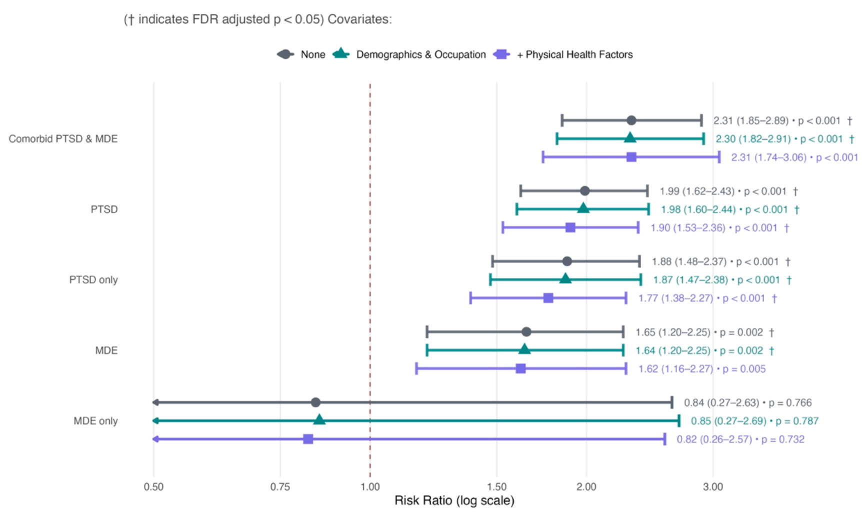

Fig. 2. Risk Ratios for Mild Cognitive Impairment by Psychiatric Diagnoses
Notes. n = 337. Unadjusted and adjusted risk ratios (RRs) obtained from quasi-Poisson regressions are plotted, controlling for demographics and occupation, and additionally controlling for physical health covariates. 95 % confidence intervals were calculated using Huber-White sandwich standard errors. RRs are displayed on a logarithmic scale, with points denoting RRs and horizontal bars the 95 % confidence interval. Numeric estimates and p-values are printed to the right of each bar.

for demographic and occupational covariates, this association remained statistically significant (adjusted $RR = 1.98$, 95 % CI = [1.60, 2.44], $p < 0.001$), and again after further adjusting for physical health covariates (adjusted $RR = 1.90$, 95 % CI = [1.53, 2.36], $p < 0.001$). Second, Fisher's exact test indicated that diagnosis of MDE was significantly associated with MCI ($p = 0.027$) and after multivariable adjustment for demographic and occupational covariates (adjusted $RR = 1.64$, 95 % CI = [1.20, 2.25], $p = 0.002$), as well as physical health covariates (adjusted $RR = 1.62$, 95 % CI = [1.16, 2.27], $p = 0.005$).

Third, the comorbidity of PTSD and MDE was examined as a putative correlate of MCI. Fisher's exact test indicated statistically significant differences in MCI across diagnostic groups ($p < 0.001$). After multivariable adjustment for demographics and occupation, diagnosis of MDE only was not significantly associated with MCI ($p = 0.787$). However, this null effect is likely due to the small number of responders ($n = 6$) who were diagnosed with MDE only. Diagnosis of only PTSD was significantly associated with MCI (adjusted $RR = 1.87$, 95 % CI = [1.47, 2.38], $p < 0.001$). Finally, the comorbidity of PTSD and MDE was also significantly associated with MCI (adjusted $RR = 2.30$, 95 % CI = [1.82, 2.91], $p < 0.001$) .[1] After additionally adjusting for physical health covariates, diagnosis of only PTSD remained significantly associated with MCI (adjusted $RR = 1.77$, 95 % CI = [1.38, 2.27], $p < 0.001$), as did comorbid PTSD and MDE (adjusted $RR = 2.31$, 95 % CI = [1.74, 3.06], $p < 0.001$).

PAFs are summarized in Fig. 3. PTSD without MDE accounted for approximately 8 % of MCI cases after adjusting for demographic, occupational, and physical health covariates (7.8 %, 95 % CI = [3.5 %, 13.1 %]). In contrast, MDE without PTSD did not contribute to MCI risk (PAF = −0.3 %; 95 % CI = [−1.8 %, 1.5 %]), consistent with the results of multivariable regressions and the small number of responders diagnosed with MDE only. Comorbid PTSD and MDE accounted for an additional 4.1 % of MCI cases (95 % CI = [1.7 %, 7.9 %]). When considering the combined contributions of PTSD, MDE, and their comorbidity, the total PAF was approximately 12 % (11.7 %, 95 % CI = [6.1 %, 18.1 %]).

[1] Note, the reference group for these adjusted RRs consists of responders without PTSD or MDE, while in the models examining the effects of PTSD and MDE, the reference groups included individuals who did not have PTSD but may have MDE and vice versa.

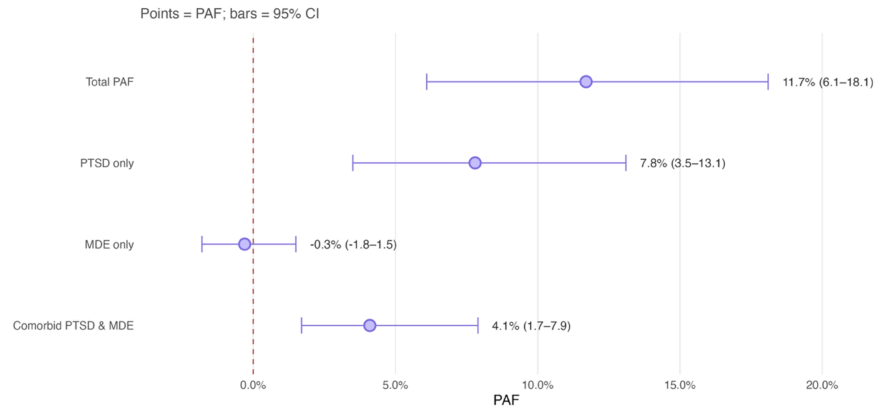

Fig. 3. Population-Attributable Fractions (PAF) for Mild Cognitive Impairment by Psychiatric Diagnoses
Notes. n = 337. PAFs were derived from a multivariable quasi-Poisson regression predicting MCI from psychiatric status (reference: Unimpaired; categories: Depression only, PTSD only, Comorbid PTSD+MDE), adjusting for age, sex, race/ethnicity, education, occupation, asthma, BMI, cardiovascular disease, hypertension, and diabetes. For each category, we combined the adjusted risk ratio with its crude prevalence to obtain a category-specific PAF. A total PAF was then computed to reflect the joint contribution across categories. Estimates were then validated three ways: (1) using model-based predicted risks, (2) using a multiplicative formula for the total PAF, and (3) using a summation-based formula for the total PAF. For all approaches, 95 % percentile intervals were obtained via nonparametric bootstrapping. Results were highly concordant across methods (values matched to two decimals). The figure reports the summation-based method for the total PAF with corresponding individual contributions. PAFs are presented as hypothetical or counterfactual summaries. See the discussion for assumptions and interpretive caveats.

7.4. *Exploratory dimensional analysis*

Greater comorbid symptom burden (*mean* = 2.53, *range* = [0, 18]) was significantly associated with risk of MCI (*RR* = 1.11, 95 % *CI* = [1.08, 1.13], $p < 0.001$), such that a one-symptom increase was associated with an 11 % increase in MCI risk. This association remained

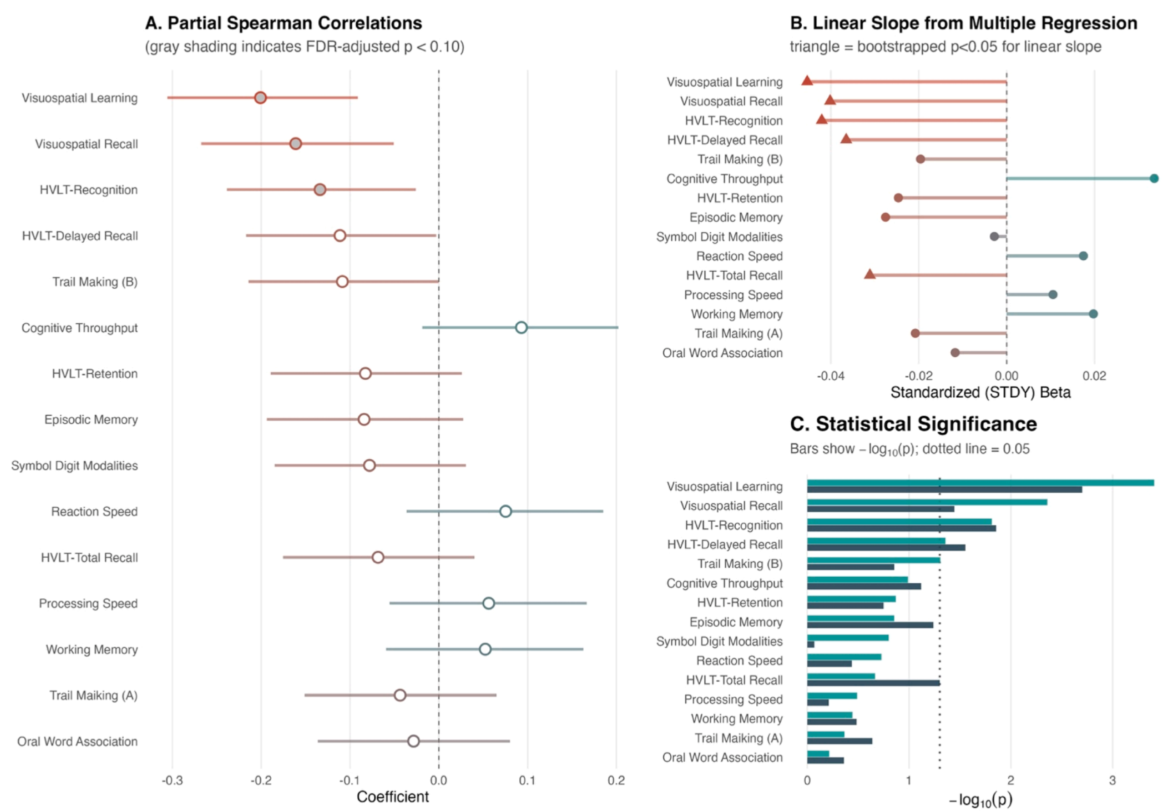

Fig. 4. Exploratory Associations Between Psychiatric Symptom Burden and Cognitive Tests
Notes. n = 337. **Panel A** depicts partial Spearman correlations (ρ) between psychiatric symptom burden and individual cognitive test scores, adjusted for study covariates, with horizontal bars denoting 95 % confidence intervals. The vertical dashed line marks ρ = 0. Gray shading flags coefficients with $p < 0.10$ after FDR correction. Values left of zero indicate worse performance with more symptoms (for Trail Making A/B, scores were reverse coded, so lower scores indicate worse performance). **Panel B** depicts the beta coefficients from ordinary least squares models that regressed cognitive test scores on the symptom-count index and study covariates. Standard errors and p-values were obtained using a non-parametric bootstrap procedure. Segments display the standardized (STDY) slope per +1 symptom (x-axis), and triangles flag coefficients that are statistically significant. **Panel C** reports −log10(p-values) for Spearman correlations (depicted in Panel A) and linear slopes (depicted in Panel B). The dotted line marks $p = 0.05$. Larger bars indicate stronger evidence for an association.

unchanged after adjusting for demographics and occupation (adjusted $RR = 1.11$, 95 % $CI = [1.08, 1.14]$, $p < 0.001$) and after additionally adjusting for physical health covariates (adjusted $RR = 1.11$, 95 % $CI = [1.08, 1.13]$, $p < 0.001$).

For certain cognitive tests, greater comorbid symptom burden was associated with worse performance. Results are depicted in Fig. 4. Partial Spearman correlations were negative for statistically significant associations—largest for visuospatial learning and recall (FDR-adjusted q-values $< 0.0.05$) and verbal recognition (FDR-adjusted q-value < 0.10)—with relatively modest but directionally consistent magnitudes (range of $\rho \sim -0.13$ to -0.20). Similarly, linear models indicated that each additional symptom was associated with a ~0.03–0.04 SD decrease in cognitive test performance across these domains, with the strongest associations observed for visuospatial learning and verbal recognition. Delayed recall and executive function measured by the TMT-B were also negatively associated with comorbid symptom burden (p-values < 0.05) but were no longer significant after adjusting for FDR (q-values > 0.10). A few speeded and attention measures showed weak or null associations, and the measure of cognitive throughput displayed a modest positive trend that was not statistically significant ($p > 0.05$). F-tests comparing spline-versus-linear models provided no evidence of significant curvature (q-values > 0.50; Table S6). These results indicate robust relationships between increased symptom burden and individual tests of cognitive function, especially tests of visuospatial learning/recall and verbal recognition.

8. Discussion

This study found that PTSD was common (~15 %) and MDE was comparatively uncommon (~5 %) among WTC-exposed members of the FDNY approximately two decades after the precipitating trauma. Moreover, PTSD, MDE, and their comorbidity were linked to a higher risk of MCI, which was quite common (~45 %) when operationalized using subjective cognitive concern and the application of NIA-AA guidelines to objective cognitive tests. While MDE alone (absent comorbid PTSD) was not significantly associated with MCI, this finding likely reflects the small number of responders who were diagnosed with MDE only (only 6 cases; <2 %). Crucially, although MCI was very common among participants with PTSD (~78 %) and MDE (~72 %), most MCI cases (>85 %) could not be attributed to these psychiatric conditions, suggesting that other factors, such as physical exposures, cumulative stress, undiagnosed medical conditions, or environmental toxins play a major role in the etiology of MCI in this population. Thus, these findings suggest that PTSD and its comorbidity with MDE contribute meaningfully to the population burden of MCI in WTC-exposed FDNY responders, but most cases of MCI cannot be attributed to these psychiatric disorders.

Consistent with this interpretation, a recent study reported occupational differences in the prevalence of MCI among WTC responders, with members of the FDNY exhibiting a higher prevalence of MCI than law enforcement officers (Mann et al., 2024). Moreover, other studies in non-FDNY WTC responders, have linked probable exposure to fine particulate matter to early onset dementia (Clouston et al., 2024) and expounded the pathophysiology of neurotoxic exposures for WTC-related cognitive impairment (Clouston et al., 2022). Nevertheless, previous studies of WTC responders have consistently reported that PTSD is a risk factor for MCI (Clouston et al., 2017; Mann et al., 2023). Combined with the results of the present study, these findings highlight psychiatric diagnoses and symptom burden as robust correlates of cognitive impairment.

Beyond replicating associations in a heavily exposed firefighter cohort, PAF estimates provide a public-health lens on burden and impact—illustrating how reductions in PTSD and MDE could hypothetically translate into fewer MCI/cognitive dysfunction cases in this occupational setting. These cohort specific estimates, presented with confidence intervals and interpreted cautiously given subgroup sizes, quantify the upper limits of public health gains: the proportion of MCI cases that could be averted if PTSD and MDE were prevented, assuming these disorders are causes of MCI. Similarly, dimensional analyses show a negative relationship between comorbid symptom severity and visuospatial learning and recall, as well as verbal recognition, whereas other domains of cognition were not significantly associated. These findings highlight the domains of cognitive function that might be expected to improve from incremental symptom reduction *if a causal relationship exists*.

8.1. Limitations

First, the cross-sectional design precludes inferences about causality or the temporal sequence of PTSD, MDE, and MCI. Thus, the present study cannot discern whether PTSD and MDE precede, follow, or co-occur with MCI. Moreover, the lack of longitudinal follow-up precludes insights into the potential for recovery or remission of PTSD and MDE, as well as reversion of MCI and progression to more severe impairments indicative of dementia. The moderate sample size ($n = 337$) and small number of MDE cases resulted in wide confidence intervals, limiting what can be concluded about the link between MDE and cognitive impairment in the absence of comorbid PTSD. We recommend that future studies increase sample size and conduct longitudinal follow-up to assess temporal order and the potential progression and reversion of MCI.

Second, although the PAF does not reflect causality in a cross-sectional study, it serves a valuable role in a hypothetical or counterfactual framework by quantifying the proportion of cases that *might* be avoided if the explanatory variables were removed, granting the possibility that a causal link is present (Mansournia and Altman, 2018). A causal interpretation would require stronger evidence—including exchangeability (no unmeasured confounding after adjustment), positivity (non-zero probability of exposure within levels of covariates), response to manipulation (a well-defined intervention that modifies psychiatric symptoms), correct model specification, and temporal ordering of exposure before outcome, which cannot be verified here.

Third, this cohort comprises predominantly male, non-Latino White FDNY firefighters subject to fitness-for-duty requirements. Accordingly, results may not generalize to women, racial/ethnic minorities, and non-FDNY responder groups (e.g., law enforcement, construction workers, volunteers), or non-U.S. settings. Because population-attributable fractions reflect the exposure prevalence and covariate structure of the source population, our PAF estimates should only be interpreted within the context of WTC responders from the FDNY. We recommend replication in more diverse cohorts—with adequate power for subgroup analyses and tests of effect modification by sex, gender, and race/ethnicity—and encourage harmonized cognitive assessments and MCI definitions to facilitate cross-study comparability.

Fourth, while we found that MDE alone (i.e. absent PTSD) was not a significant risk factor for MCI, it is worth noting that MDE without comorbid PTSD was uncommon, only evident in a total of six participants. Consequently, this finding should be interpreted with appropriate circumspection. Although statistical adjustments were made for key demographic, occupational covariates, BMI, and physical health conditions, residual third-variable confounding (i.e., potential omitted variable bias) remains possible.

Related, while PTSD and MDE accounted for a relatively small share of MCI cases in this highly exposed firefighter cohort (~12 %), the residual burden likely reflects environmental, occupational, inflammatory, lifestyle, and vascular contributors not measured and modeled here. Future work in this cohort will prioritize integration of systemic inflammatory and proteomic markers, cumulative occupational stressors, alongside lifestyle and genetic risks, to evaluate joint and pathway-specific effects. Because PAFs depend on the exposure distribution and covariates, future research should re-estimate PAFs in these expanded models.

Finally, this study did not measure activities of daily living or include a non-FDNY or unexposed control group. Therefore, we cannot determine whether the prevalence of PTSD, MDE, or MCI in this cohort is higher than in other clinical and community populations, nor can we investigate whether PTSD, MDE, or MCI interfere with activities of daily living. Any contextual comparisons to prior studies should be interpreted cautiously given differences in sampling, assessment instruments, and operational definitions. Thus, our findings should be viewed as within-cohort associations in a highly exposed firefighter population, and population-attributable fractions are correspondingly context-specific.

8.2. Strengths

This study focused on a well-defined cohort—WTC-exposed FDNY responders—offering an invaluable opportunity to explore the long-term psychiatric and cognitive effects of trauma in a unique occupational group. The use of well validated diagnostic interviews and neurocognitive assessments ensured high-quality diagnoses. This study also sheds light on the combined effects of PTSD and MDE, demonstrating a significant association with MCI and highlighting the importance of dual diagnoses in trauma-exposed populations. The inclusion of non-parametric bootstrapping to obtain confidence intervals for PAF estimates and careful adjustment for demographic, occupational, and physical health covariates further enhances the credibility of findings. In sum, the present study addresses critical issues at the intersection of mental health and cognitive impairment in a population exposed to significant occupational trauma, making the findings relevant to clinicians, policymakers, and researchers.

9. Conclusions

This study provides valuable insights into the prevalence and associations between PTSD, MDE, and MCI among WTC-exposed FDNY responders. Categorical analyses showed that PTSD—and especially its comorbidity with MDE—was associated with higher MCI risk. Complementing these findings, dimensional analyses demonstrated a monotonic association between psychiatric symptoms and cognitive dysfunction: each additional DSM-defined symptom was linked to small but consistent decrements in cognition (≈ -0.04 SD per symptom on average), with significant effects on visuospatial learning/recall and verbal recognition. There was no evidence these trends were non-linear (natural splines did not significantly improve model fit) and trends remained significant for associated domains after controlling the false discovery rate. Together, the categorical and dimensional results suggest that cognitive risk increases across the spectrum of symptom burden rather than only at diagnostic thresholds, underscoring the potential cognitive benefit of reducing psychiatric symptoms, even when symptoms fall short of clinical thresholds for diagnosis. Nonetheless, most MCI cases could not be attributed to PTSD, MDE, or their comorbidity, highlighting the need to delineate additional etiologic pathways—including exposures to environmental and occupational toxins, sleep disturbance, and other inflammatory processes and lifestyle factors. The use of validated interviews, neurocognitive testing, and robust categorical and dimensional modeling provides a strong foundation for longitudinal work to map mechanisms and identify modifiable targets to preserve cognitive health.

In sum, findings from the present study are consistent with an occupational health approach that pairs targeted screening with stepped intervention and longitudinal monitoring. Individuals with both PTSD and MDE warrant prioritization for additional psychiatric and cognitive screening, with positive screens triggering comprehensive neuropsychological assessment and evidence-based care. Thus, the present findings provide a context-specific lens for program planning, highlighting comorbidity and high-symptom strata as key targets for prevention and intervention in this highly exposed cohort.

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Declaration of AI-Assisted technologies

During the preparation of this work the first author used GPT-4o and Genimi 2.5 Pro to assist in literature searches, proofreading, and identify color schemes that are accessible to readers who are color blind. After using these tools, the first author reviewed and edited the content as needed and takes full responsibility for the content of the published article.

CRediT authorship contribution statement

Frank D. Mann: Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Conceptualization. **Sean A.P. Clouston:** Writing – review & editing, Funding acquisition, Conceptualization. **Jaeun Choi:** Writing – review & editing, Validation. **Charles B. Hall:** Writing – review & editing, Validation, Funding acquisition, Conceptualization. **Rachel Zeig-Owens:** Writing – review & editing, Project administration. **Christopher Christodoulou:** Writing – review & editing, Project administration. **Alicia M. Fels:** Writing – review & editing, Project administration. **Matthew D. Fajfer:** Writing – review & editing, Project administration. **Onix A. Melendez:** Writing – review & editing, Project administration. **Christina M. Hennington:** Writing – review & editing, Project administration. **Candace W. Arneaud:** Writing – review & editing, Project administration. **Yang Fan Zou:** Writing – review & editing, Project administration. **Ashley E. Fontana:** Writing – review & editing, Project administration. **Alissa Barber:** Writing – review & editing, Project administration. **Alexandra K. Mueller:** Writing – review & editing, Project administration, Data curation. **Melissa A. Carr:** Writing – review & editing, Project administration. **David J. Prezant:** Writing – review & editing, Funding acquisition, Conceptualization. **Benjamin J. Luft:** Writing – review & editing, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors have nothing to declare.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2025.116827.

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