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Polygenic Liability, Exposure Severity, and Post-Traumatic Stress Disorder (PTSD) Predict Cognitive Impairment in World Trade Center Responders

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Abstract

BACKGROUND: There is a high incidence of cognitive impairment among World Trade Center (WTC) responders, comorbid with post-traumatic stress disorder (PTSD). Yet, it remains unknown whether genetic risk for Alzheimer's disease, PTSD, educational attainment, or for a combination of these phenotypes, is associated with cognitive impairment in this high-risk population.

OBJECTIVE: In a study of $n = 3997$ WTC responders, polygenic scores for Alzheimer's disease, PTSD, and educational attainment were used to test whether genome-wide risk for one or more of these phenotypes is associated with cognitive impairment, controlling for demographic factors, population stratification, and indicators of 9/11 exposure severity.

RESULTS: Polygenic scores for Alzheimer's disease and educational attainment were significantly associated with an increase and decrease, respectively, in the hazard rate of mild cognitive impairment. The polygenic score for Alzheimer's disease was marginally associated with an increase in the hazard rate of dementia, but only age, exposure severity, and symptoms of PTSD were significantly associated with an increase in the hazard rate of dementia.

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DISCLOSURES STATEMENT

The authors have no conflict of interest to disclose.

CONCLUSION: These results add to the emerging evidence that many WTC responders are suffering from mild cognitive impairments that resemble symptoms of Alzheimer's Disease, with severe impairments closely tied to PTSD and the type of work that responders completed during rescue and recovery efforts.

Keywords

Mild Cognitive Impairment; Dementia; Alzheimer's Disease; PTSD; Polygenic Score

INTRODUCTION

Alzheimer's Disease (AD) and Related Dementias (ADRD) are fatal and costly age-related neurodegenerative disorders [1]. The prodromal phase in ADRD begins with the gradual decline of cognitive ability [2], often characterized clinically by the presence of mild cognitive impairment (MCI) [3]. There is evidence that risk of mortality increases when cognitive impairments affect basic activities of daily living [4]. Consequently, a better understanding of the factors that predict MCI before the emergence of functional limitations is critical to understanding the etiology and pathogenesis of ADRD and crucial for the identification of individuals at heightened risk. Genetic liability is one risk factor for ADRD that can be measured reliably and remains stable across an individual's life course.

Extant research has uncovered many of the genetic underpinnings for ADRD [5–7]. The identification of risk alleles for ADRD in genome-wide association studies is broadly consistent with findings from biometric studies of cognitive function at midlife [8] and late adulthood [9], having reported heritability estimates ranging from 26%−54% [8, 9]. However, the extent to which genetic liabilities for AD, PTSD, educational attainment, or a combination of these phenotypes are risk factors for cognitive impairment in trauma-exposed populations remains unclear. An ongoing study of World Trade Center (WTC) responders has documented a high incidence of MCI [10], but less is known about the causes of incident MCI and to what degree it is a result of a severe trauma exposure versus aging. Nevertheless, previous work in the WTC population has reported that MCI is characterized by changes to biomarkers consistent with ADRD [11, 12]. Yet, it has also been found that MCI is precipitated by symptoms of post-traumatic stress disorder (PTSD) in WTC responders, consistent with chronically re-experiencing the stressful memories of a traumatic event [10, 13, 14], suggesting that MCI might sometimes be a sequela of PTSD. Moreover, a recent report highlighted educational attainment as a protective correlate of confusion and memory loss in WTC responders, irrespective of PTSD status [15].

It remains unknown whether genome-wide liability for AD, educational attainment, PTSD, or some combination of these pathological and non-pathological phenotypes predict incidence of cognitive impairment among WTC responders. The present study utilized data from WTC responders to conduct a polygenic risk score analysis of MCI and dementia to determine whether additive genetic liability for these phenotypes contributes to increased liability for cognitive impairment, after controlling for demographic factors, population structure, and risk and protective factors specific to the WTC rescue and recovery efforts.

Results have the potential to underscore underlying genetic risk for cognitive impairment and to help identify individuals at heightened risk in this unique cohort.

MATERIALS AND METHODS

Sample

The present study analyzed data from n = 3,997 WTC responders. Inclusion criteria included having (1) provided consent for genetic testing, (2) predominately European ancestry as determined by genetic principal components analysis (EUR > .80) (3) cognitive data, and (4) demographic information and self-reported symptoms of PTSD. The sample was middle-aged (mean = 38.20, SD = 8.03) and predominately male (~93%). See Table 1 for descriptive statistics and sample characteristics.

Measures

Demographics and WTC Factors.—Age in years at 9/11/2001, biological sex as determined by genotype, and self-reported educational attainment were included in inferential analyses as potential demographic correlates of cognitive impairment. Individual differences in WTC exposure were measured using two variables. On average, the more time spent working at Ground Zero, the greater the potential exposure to dust and fine particulate matter, as well as psychological and emotional trauma. Consequently, the number of weeks responders spent working at the WTC was used as an indicator of exposure duration. Exposure severity was also measured using a variable that was based on the type of work responders engaged in during rescue and recovery efforts and the likelihood of exposure to dust and air borne toxins based on that work. Examples of low-risk work for dust exposure are escorting pedestrians around the site, perimeter security, morgue work, and hazard material removal (due to the use of PPE). Examples of high-risk work for dust exposure include truck loading and unloading, sanitation work, bucket barrage, and mechanic work. Whether responders held a supervisory (1 = Yes, 0 = No) or volunteer role (1 = Yes, 0 = No) during the rescue and recovery efforts was also noted, as these features are putatively protective (supervisory role) and risk (volunteer role) factors for exposure severity.

Post-Traumatic Stress Disorder (PTSD) and Cognitive Impairment.—Symptoms of PTSD were measured using the trauma-specific version of the PTSD checklist (PCL-17) [16] adapted for the 9/11 WTC attacks. In the current study, this scale exhibited high internal consistency evaluated using classical (Cronbach's α = 0.95) and contemporary (ω_t = 0.96, ω_h = 0.84) psychometric approaches [17]. The presence of MCI and dementia were made consistent with diagnostic guidelines [3, 18], identified using the Montreal Cognitive Assessment (MoCA) [19]. The MoCA is a standard clinical assessment of executive function, memory, and spatiovisual capability, which is highly sensitive to detection of mild and severe deficits related to cognitive aging [20, 21]. At follow-up, among those who were deemed to be MCI/dementia free at baseline, scores 20 < MoCA ≤ 23 and MoCA ≤ 20 was used to detect MCI and dementia, respectively. By study design, symptoms of PTSD were measured before WTC responders completed the MoCA. Of the n = 3997 responders that met inclusion criteria for the present study, the baseline MoCA was completed approximately 8 years (mean = 7.98 years, range of dates for the baseline assessment =

January 2014 to June 2019) after having first completed the trauma-specific, WTC-adapted version of the PCL-17 (range of dates = July 2002 to September 2017).

Polygenic scores.—Blood draws were conducted from January 2012 to January 2019. DNA was extracted from peripheral blood mononuclear cells (PBMCs) and then genotyped using the Infinium Global Screening Array (Illumina, San Diego, CA, USA). Single nucleotide polymorphisms (SNPs) were then processed via established protocols for genotype calling, imputation, ancestry measurement, and the calculation of polygenic scores. Genotypes were imputed to 25,514,638 million SNPs using the Haplotype Reference Consortium reference panel on the Michigan Imputation Server pipeline v1.2.4. The analysis utilized a full list of SNPs after clumping (p-value threshold = 1).

Polygenic scores are a summation of the SNPs associated with a target phenotype, weighted by their effect size from a genome-wide association study. The effects of all SNPs were coded so higher polygenic scores are associated with higher values or greater incidence of the respective phenotype. The current study included polygenic scores for educational attainment [22], Alzheimer's disease (AD) [23] and PTSD [24], and also for re-experiencing symptoms of PTSD [24], as previous research on chronic PTSD supports the view that merely re-experiencing a significant trauma, absent other symptoms, can result in increased risk of ADRD [25]. To avoid the potential inflation of standard errors due to multicollinearity, polygenic risk scores for PTSD and re-experiencing symptoms were entered into models separately. Only findings from models that included the polygenic score for PTSD are reported in the results because conclusions remain unchanged when the polygenic score for reexperiencing symptoms was substituted for the polygenic score for PTSD.

Data Analytic Procedures

Data was imported into R Studio version 1.3.1056, and inferential analyses were conducted using the "survival" package [26] and "survminer" package [27] in R Studio. To begin, descriptive statistics were calculated for study variables. Next, Kaplan-Meier non-parametric survival analyses were used to examine the cumulative incidence of MCI and dementia, before estimating Cox proportional hazard models to provide insight into the effects of demographic factors, polygenic scores, and features of the WTC rescue and recovery efforts, including measures of exposure duration, symptoms of PTSD, and probable exposure to air borne toxins (low-risk or high-risk) based on the type of work responders completed at the WTC sites. Tied survival times were handled using the Breslow approximation [28]. A test of proportionality was conducted using Schoenfeld residuals [29], and stratified Cox models were estimated to allow for different baseline hazards for any variable that violated the proportionality assumption. To assess the explanatory power of study variables in predicting cognitive impairment, generalized coefficients of determination (R^2) were calculated for Cox models [30].

To adjust for population structure, the first twenty genetic principal components were included as covariates in all models. All predictors were estimated simultaneously so hazard ratios and relative risk ratios are adjusted for the effects of the other variables in

model. To help ease the computational burden on estimation algorithms and to facilitate the interpretation of parameter estimates, all continuous variables were standardized ($M = 0$, $SD = 1$) prior to estimating models. Finally, a sensitivity analysis was performed to evaluate the consistency of estimated effects across different analytic routines. Specifically, logistic regression models were estimated to predict the occurrence of cognitive impairment irrespective of the amount of time that lapsed between the WTC exposure and the onset of impairment. As estimated odds ratios differ from true risk ratios when the incidence of an outcome is common [31], adjusted odds ratios (aOR) from logistic regressions were transformed to risk ratios, $aRR = aOR/(1 - P_{ref}) + (P_{ref} \times aOR)$, where P_{ref} is the incidence of cognitive impairment when exposure duration and exposure severity equal zero.

RESULTS

Mild Cognitive Impairment

Results are reported in Table 2 and depicted in Figure 1, including Kaplan-Meier non-parametric survival functions for MCI. Older age was significantly associated with MCI, such that a standard deviation increase in age (~8 years) was associated with a 45% increase in the hazard rate of MCI. Compared to not finishing high school, having a college degree was associated with a 45% decrease in the hazard rate of MCI. Similarly, compared to males, females exhibited a 45% decrease in the hazard rate of MCI. Exposure severity due to engagement in high-risk work and symptoms of PTSD were also associated with a significant increase in the hazard rate of MCI, with an especially pronounced effect observed for the measure of exposure severity that sorted responders into low-risk and high-risk groups based on the type of work they completed at the WTC sites and probable exposure to air borne toxins due to that work. Finally, the polygenic scores for educational attainment and Alzheimer's disease were significantly associated with a 14% decrease and 10% increase in the hazard rate of MCI, respectively. Statistically significant ($p < .05$) effects are depicted in Figure 1.

The global proportional odds assumption was not upheld for the Cox model of MCI ($\chi^2 = 50.80$, $df = 35$, $p = .041$) because the measure of exposure severity violated the proportionality assumption ($\chi^2 = 19.50$, $df = 1$, $p < .001$). Therefore, a stratified Cox model was estimated that allowed for separate baseline hazards for high-risk and low-risk groups. A likelihood-ratio test indicated that stratification significantly improved model fit ($\chi^2 = 506.46$, $df = 1$, $p < .001$), and the global proportionality assumption was upheld for the stratified Cox model ($\chi^2 = 28.50$, $df = 34$, $p = .734$). Next, a stratified interaction model was estimated that also allowed the effects of study variables to differ for high-risk and low-risk groups, but the fit of the stratified interaction model did not differ significantly from the stratified model with no interaction ($\chi^2 = 42.03$, $df = 34$, $p = .162$). Moreover, the same pattern of results emerged from the stratified Cox models of MCI and dementia (Table S1 & S2), including the direction, size, and precision of estimates.

The generalized coefficient of determination indicated modest explanatory power for predicting incidence of MCI ($R^2 = 0.51$), with genetic principal components and polygenic scores accounting for only a moderate proportion of the total variance (5.41%). Notably, relative risk ratios from logistic regressions indicated that substantive conclusions remained

largely unchanged irrespective of whether the time to onset of MCI or MCI itself was specified as the outcome of interest. For example, the relative risk ratio for the polygenic score for AD indicated that a standard deviation increase in genetic liability for AD was associated with an 12% increase in the risk of MCI ($p = .015$).

Dementia

Results are reported in Table 3 and depicted in Figure 2, including Kaplan-Meier non-parametric survival functions. Compared to MCI, fewer variables were significantly associated with the hazard rate of dementia. Older age was significantly associated with dementia, such that a standard deviation increase in age (~8 years) was associated with a 63% increase in the hazard rate of dementia. Similar to MCI, the type of work responders completed at the WTC sites (low-risk or high-risk), and symptoms of PTSD were associated with increases in the hazard rate of dementia. Although the polygenic score for Alzheimer's disease was marginally associated with a 14% increase in the hazard rate of dementia ($p = .095$) and having a college education was marginally associated with a 51% decrease in the hazard rate of dementia ($p = .096$), no other variables were significantly associated with dementia. The proportional odds assumption was upheld for the Cox model of dementia ($\chi^2 = 36.20$, $df = 35$, $p = .413$), and the generalized coefficient of determination indicated appreciable explanatory power ($R^2 = 0.58$), with genetic principal components and polygenic scores accounting for 4.42% of the total variance. Finally, the effects of age, high-risk work, and PTSD remained largely unchanged in logistic models (Table 3).

Sensitivity Analyses

Two additional sensitivity analyses were conducted at the request of reviewers. First, MCI and dementia were combined into a single outcome, and Cox and logistic models were estimated to assess predictors of any cognitive impairment, including MCI and dementia (MoCA < 23). Second, to provide an estimate of a psychologically traumatic or emotionally salient exposure, whether responders saw blood or bodily fluids (Yes ~ 41%, No ~ 59%) during rescue and recovery efforts was included as an additional predictor of cognitive impairment. Results are reported in Table 4 and supplemental material (Tables S3–S7).

Briefly, the predictors of MCI and dementia were similar after adjusting for whether responders saw blood or bodily fluids during rescue and recovery efforts, which was itself not a significant predictor of MCI, dementia, or any cognitive impairment (p-values > .05). The predictors of any cognitive impairment (MoCA ≤ 23) were similar to the predictors of MCI, except the effect of the polygenic score for Alzheimer's Disease increased in magnitude. In Cox and logistic models, a standard deviation increase in the polygenic score for AD was associated with a 17% increase in the hazard rate ($p = .003$) and a 25% increase in the relative risk ($p < .001$) of any cognitive impairment.

DISCUSSION

The present study tested whether demographic factors, indicators of physical and traumatic exposure, and polygenic scores for AD, PTSD, and educational attainment were associated with incidence of MCI and dementia among WTC responders. The polygenic score for

educational attainment was significantly associated with a decrease in the hazard rate of MCI, while the polygenic score for AD was significantly associated with an increase in the hazard rate of MCI, as well as a marginally significant increase in the hazard rate of dementia. Although genetic factors in aggregate accounted for a moderate degree of variance in MCI (5.41%) and dementia (4.42%), including genetic principal components and polygenic scores, effect sizes were small for individual polygenic scores. For example, the polygenic score for educational attainment accounted for less than 1% of the total explanatory power of study variables predicting MCI. Similarly, the polygenic score for Alzheimer's disease accounted for approximately 1% of the total explanatory power of study variables predicting MCI and dementia. These small effect sizes indicate that polygenic scores alone provide limited utility in predicting the individuals who will suffer from cognitive impairment in this trauma-exposed cohort, despite highlighting potentially important pathogenic factors that are present at the time of gamete formation.

Critically, results of the current study further underscore the importance of individual differences in trauma exposure and long-term psychiatric sequalae in understanding the precipitously high incidence of cognitive impairment among WTC responders. Exposure severity was strongly associated with increases in the hazard rates of MCI and dementia, specifically when measured in terms of high-risk work at the WTC site that increased the likelihood of responders encountering dust and fine particulate matter that can infiltrate the brain to cause neuronal damage, potentially resulting in neurodegenerative disease. Importantly, the strong links between high-risk work and incidence of mild and severe cognitive impairments persisted after accounting for population stratification and genetic liability for Alzheimer's disease, PTSD, and educational attainment.

Symptoms of PTSD were also consistently linked with incidence of MCI and dementia. These finding are consistent with growing evidence that trauma exposure and PTSD may result in an AD-like disorder by causing early proliferation of tau protein and Aβ [32]. A notable finding has been the identification of the presence of physical functional limitations [33] alongside changes in proteins consistent with inter-neuronal damage in WTC responders with PTSD and MCI [34]. Taken together with the present findings, these results may suggest that persistent symptoms of PTSD are a risk factor for a heretofore unknown disease arising independently from Alzheimer's disease though having similar symptomatology.

While the polygenic score for AD was significantly associated with a higher incidence of MCI, it was only marginally associated with a higher incidence of dementia. This may come as a surprise as genetic liability for a severely debilitating neurodegenerative disease, like AD, might be expected to predict severe impairments more strongly than mild impairments. Indeed, the effect size of the polygenic score for AD was larger for dementia than MCI but estimated with less precision due to the lower incidence of dementia, in turn, resulting in insufficient power to detect a significant genetic signal. Consistent with this interpretation, the effect size of the polygenic score for AD was even larger when power was increased by combining MCI and dementia into a single outcome. Further, many of the WTC responders with cognitive impairments are currently at midlife, prior to the age at which symptoms of AD typically appear, and MCI has many potential causes and does not necessarily progress

to dementia. Therefore, it remains an open question whether genetic signal for AD will increase as WTC responders continue to age chronologically and cognitively.

Crucially, the statistically significant association of the polygenic score for AD with MCI should not be interpreted as definitive evidence that cognitively impaired WTC responders are suffering from early-onset Alzheimer's disease. This is because polygenic risk scores are often associated with a target, sometimes called a 'proxy phenotype', that is different from the phenotype for which the PRS was developed [35]. In other words, a polygenic risk score based on one phenotype may be predictive of a trait that is similar in clinical presentation or genetically correlated with the phenotype for which the polygenic score was constructed. Moreover, as previously noted, the effect size of the polygenic score for AD was small and overshadowed by the effects of high-risk work and PTSD, indicating that the clinical presentation of cognitive impairments among WTC responders bears a resemblance to AD but with etiology more closely tied to the severity of a traumatic exposure than inherited pathogenic variants.

Exposure severity based on probable exposure to air born toxins was strongly associated with cognitive impairment in the present study, both MCI and dementia, even after controlling for genetic liability for risk and protective phenotypes, including Alzheimer's disease, PTSD, and educational attainment. On the other hand, exposure to blood and bodily fluids was neither associated with MCI nor dementia. However, exposure to blood and bodily fluids by no means comprehensively captures the myriad of toxic and traumatic exposures endured by the heroes who facilitated rescue and recovery efforts after the 9/11 attacks. For example, many responders saw people fall or jump from the Twin Towers and are now charged with reliving those horrific memories for the rest of their lives. Others suffered injury while excavating debris to search for survivors, and others had a relative, friend, or co-worker killed and were (and continue to be) taxed with the emotional and physiological burden of bereavement. Finally, others witnessed the destruction of their homes, places of work, and community at large. Understanding how these emotional and physical traumas combine and intersect with dust exposure, as well as other environmental toxins and psychosocial factors that contribute to cumulative stress [36], will be crucial to better characterizing the exposome of PTSD and Alzheimer's disease- i.e., the totality of pathogenic exposures over the life course that lead to the expression of psychiatric symptoms and accelerated cognitive decline [37]. This will include discerning the common and unique features of the exposomes for PTSD and Alzheimer's disease.

Limitations

The present study is not without limitations. As the study design was observational, drawing causal conclusions from the reported findings is not warranted. Moreover, as all WTC responders were exposed to some level of trauma, the current study lacks a proper control group to better understand and contextualize the effect sizes documented in the current study. The residents of the NYC greater metropolitan area, including many WTC responders, differ from the general population in important ways, including greater exposure to airborne pollutants due to high population density. Additionally, the demographic

characteristics of WTC responders do not correspond with the demography of the general U.S. population, with most emergency responders being white and male.

As genome-wide association studies have largely been conducted with participants of predominately European ancestry, polygenic risk scores based on those studies lack validity in more diverse populations. Therefore, using European-derived polygenic scores that may have clinical implications in diverse ethnicities has the potential to further exacerbate racial and ethnic health disparities [38]. There is a need to expand genome-wide discovery efforts in non-European populations to improve our understanding of existing racial/ethnic disparities in ADRD [39, 40]. Thus, it remains unclear whether the current study findings generalize to other trauma-exposed populations, particularly those that are more diverse. Nevertheless, the current study adds to the emerging evidence that many WTC responders are suffering from AD-like cognitive impairments by documenting links between genetic liability for Alzheimer's disease and incidence of cognitive impairment.

Conclusions

Genetic liability for multiple phenotypes can help us to understand the unique factors through which clinical entities might be emerging in this trauma-exposed population. To date, the extent that WTC responders, who were heavily exposed to traumatizing events and to airborne materials expelled from the Twin Towers after the collapse, are suffering from early-onset AD or another unknown condition is unclear. This study suggests that genetic liability for Alzheimer's disease was a significant correlate of MCI. This work also identified genetic liability for educational attainment as an independent correlate of MCI in responders after adjusting for the significant effects of polygenic risk for AD and the highest level of education completed by responders. This suggests that polygenic liability for educational attainment is a protective factor for MCI via pathways independent of academic achievement which remain unknown. In sum, results of the present study suggest the potential for more than one ongoing process including AD and non-AD pathogenesis linked to exposure severity and persistent symptoms of PTSD in WTC responders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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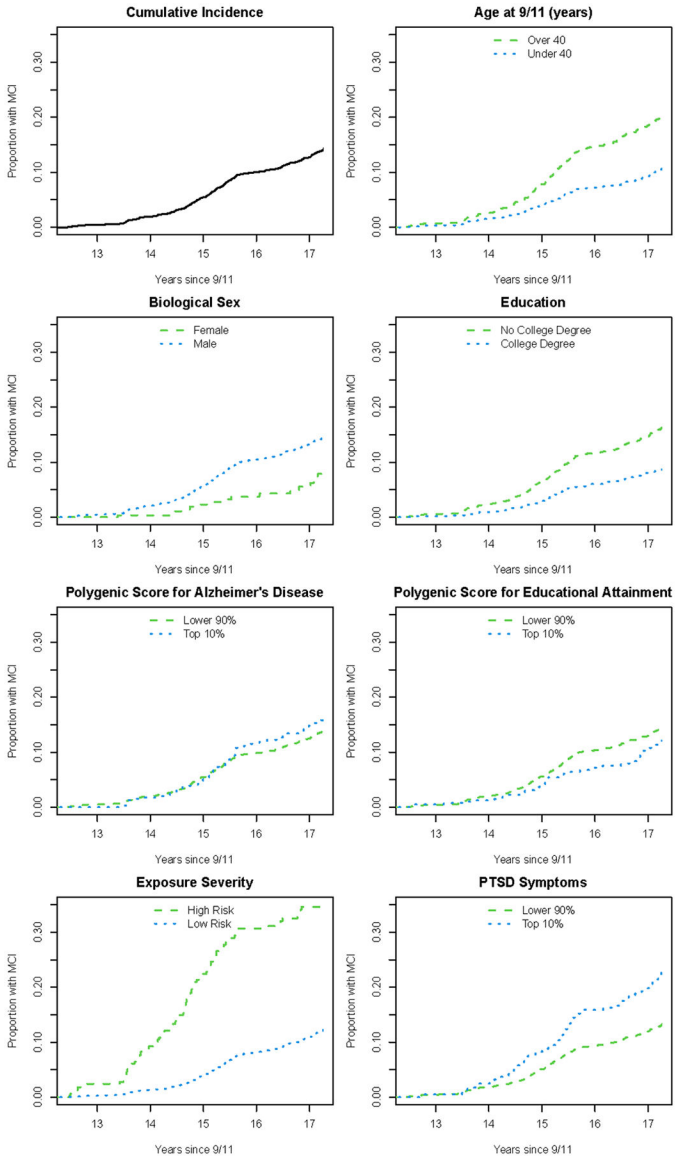

Figure 1.

Cumulative Hazards of Mild Cognitive Impairment

Notes. Kaplan-Meier non-parametric survival functions are plotted.

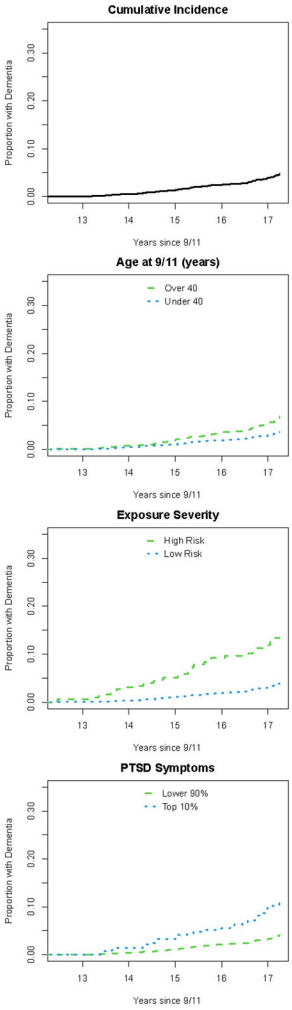

Figure 2.

Cumulative Hazards of Dementia

Notes. Kaplan-Meier survival functions are plotted.

Table 1.

Descriptive Statistics and Sample Characteristics

***n* = 3997**	**Continuous Variables**					
	M	**SD**	**Min.**	**Max.**	**Skew**	**Kurtosis**
Age at 9/11 (years)	38.20	8.03	16.84	70.20	0.51	0.27
PCL Score	27.98	12.64	17.00	85.00	1.63	2.42
PRS – PTSD	0.00	1.00	−3.63	6.89	0.83	2.72
PRS – Alzheimer's Disease	0.00	1.00	−4.30	3.89	0.01	0.06
PRS – Educational Attainment	0.00	1.00	−3.71	3.29	0.02	−0.08
Exposure Duration (weeks)	8.25	9.25	0.00	58.00	1.47	1.54
Exposure Severity	0.14	0.30	0.00	1.00	2.18	3.20
Time-to-Event: MCI	15.44	1.38	12.44	17.79	0.09	−0.81
Time-to-Event: Dementia	15.81	1.43	12.45	17.79	−0.31	−1.06
	Ordinal & Categorical Variables					
Exposure Severity						
High-Risk Work	329 (8.23%)					
Low-Risk Work	3668 (91.77%)					
Supervisory Role						
Yes	736 (18.41%)					
No	3261 (81.59%)					
Volunteer Role						
Yes	1115 (27.90%)					
No	2882 (72.10%)					
Biological Sex						
Female	280 (7.01%)					
Male	3717 (92.99%)					
Level of Education						
< High School Diploma	139 (3.48%)					
High School Diploma	729 (18.24%)					
Some College	1884 (47.14%)					
College Degree	1158 (28.97%)					
Other/Unknown	87 (2.18%)					
Cognitive Impairment Status						
No Impairment	3331 (83.34%)					
Mild Cognitive Impairment	503 (12.58%)					
Dementia	163 (4.08%)					

Notes. *n* = sample size. M = mean. SD = standard deviation. Min. = minimum observed value. Max. = maximum observed value. Frequencies and percentages in parentheses are reported for categorical variables. Time-to-event variables represent the number of years after 9/11 when responders exhibit cognitive testing scores indicative of MCI or dementia.

Table 2.

Results of Cox and Logistic Regression Models Predicting Mild Cognitive Impairment

	Cox Model				Logistic Model			
Mild Cognitive Impairment	***aHR***	***Lower 95%***	***Upper 95%***	***p***	***aRR***	***Lower 95%***	***Upper 95%***	***p***
Demographics:								
Age (linear)	1.45	1.29	1.61	<.001	1.43	1.30	1.59	<.001
Age (quadratic)	1.07	0.97	1.17	.168	1.05	0.96	1.14	.325
Biological Sex (female)	0.55	0.34	0.88	.014	0.58	0.36	0.92	.021
High School Diploma	1.37	0.82	2.27	.227	1.68	1.05	2.55	.031
Some College	0.90	0.55	1.49	.684	1.11	0.68	1.75	.672
College Degree	0.55	0.32	0.95	.030	0.71	0.41	1.19	.203
Other Education/Unknown	1.31	0.67	2.59	.430	1.59	0.82	2.81	.160
Polygenic Scores:								
Post-Traumatic Stress	1.03	0.90	1.17	.709	1.01	0.89	1.14	.888
Alzheimer's Disease	1.10	1.00	1.20	.040	1.12	1.02	1.22	.015
Educational Attainment	0.86	0.79	0.95	.002	0.89	0.81	0.97	.012
WTC-Related Factors:								
Supervisor Role	0.81	0.63	1.04	.096	0.81	0.63	1.04	.096
Volunteer Role	0.99	0.80	1.22	.917	1.02	0.83	1.24	.852
Exposure Duration	1.03	0.95	1.12	.485	1.00	0.92	1.09	.986
High-Risk Work	4.12	3.31	5.13	<.001	3.17	2.66	3.71	<.001
PTSD Symptoms	1.24	1.14	1.34	<.001	1.19	1.10	1.29	<.001

Notes. MCI defined by 20 < MoCA ≤ 23. Effects were estimated simultaneously and additionally adjusted for the first twenty genetic principal components. *aHR* = adjusted hazard ratio. *aRR* = adjusted relative risk ratio calculated by correcting the adjusted odds ratio for incidence of cognitive impairment, specifically $\mathrm{aRR} = \mathrm{a}OR/\left[(1 - P_{ref}) + (P_{ref} \times aOR)\right]$, where P_{ref} is the incidence of mild cognitive impairment when exposure duration and high-risk activity for dust exposure equal zero. Lower and upper 95% denote confidence intervals for adjusted hazard ratios and relative risk ratios.

Table 3.

Results of Cox and Logistic Regression Models Predicting Dementia

	Cox Model				Logistic Model			
	aHR	***Lower 95%***	***Upper 95%***	***p***	***aRR***	***Lower 95%***	***Upper 95%***	***p***
Demographics:								
Age (linear)	1.63	1.32	2.01	<.001	1.67	1.36	2.05	<.001
Age (quadratic)	0.98	0.83	1.17	.857	0.95	0.80	1.12	.552
Biological Sex (female)	1.07	0.56	2.05	.842	1.14	0.59	2.13	.699
High School Diploma	0.95	0.43	2.12	.904	1.19	0.53	2.57	.665
Some College	0.63	0.28	1.39	.251	0.78	0.35	1.70	.541
College Degree	0.49	0.21	1.14	.096	0.60	0.26	1.39	.241
Other Education/Unknown	0.85	0.26	2.72	.780	1.07	0.33	3.26	.908
Polygenic Scores:								
Post-Traumatic Stress	1.12	0.89	1.41	.324	1.11	0.89	1.39	.349
Alzheimer's Disease	1.14	0.98	1.34	.095	1.13	0.97	1.33	.118
Educational Attainment	0.94	0.80	1.11	.458	0.97	0.82	1.14	.714
WTC-Related Factors:								
Supervisor Role	0.80	0.52	1.22	.299	0.81	0.53	1.25	.349
Volunteer Role	1.00	0.70	1.44	.981	1.02	0.72	1.46	.894
Exposure Duration	1.01	0.87	1.17	.888	0.97	0.83	1.13	.701
High-Risk Work	4.71	3.28	6.76	<.001	4.06	2.91	5.54	<.001
PTSD Symptoms	1.33	1.16	1.52	<.001	1.27	1.11	1.45	<.001

Notes. Dementia defined by MoCA ≤ 20. Effects were estimated simultaneously and additionally adjusted for the first twenty genetic principal components. *aHR* = adjusted hazard ratio. *aRR* = adjusted relative risk ratio calculated by correcting the adjusted odds ratio for incidence of cognitive impairment, specifically $\mathrm{aRR} = \mathrm{a}OR/[(1 - P_{ref}) + (P_{ref} \times aOR)]$, where P_{ref} is the incidence of dementia when exposure duration and high-risk activity for dust exposure equal zero. Lower and upper 95% denote confidence intervals for adjusted hazard ratios and relative risk ratios.

Table 4.

Results of Cox and Logistic Regression Models Predicting Any Cognitive Impairment

	Cox Model				Logistic Model			
Any Cognitive Impairment (MCI or Dementia)	***aHR***	***Lower 95%***	***Upper 95%***	***p***	***aRR***	***Lower 95%***	***Upper 95%***	***p***
Demographics:								
Age (linear)	1.52	1.34	1.73	<.001	1.62	1.40	1.87	<.001
Age (quadratic)	1.03	0.93	1.14	.517	1.03	0.92	1.16	.592
Biological Sex (female)	0.53	0.31	0.90	.019	0.53	0.30	0.94	.029
High School Diploma	1.79	0.86	3.71	.119	2.75	1.25	6.06	.012
Some College	1.28	0.62	2.62	.506	1.78	0.82	3.86	.147
College Degree	0.85	0.40	1.79	.670	1.18	0.53	2.64	.678
Other Education/Unknown	2.41	1.00	5.84	.052	3.99	1.48	10.79	.006
Polygenic Scores:								
Post-Traumatic Stress	1.01	0.87	1.17	.937	1.01	0.86	1.20	.872
Alzheimer's Disease	1.17	1.06	1.30	.003	1.25	1.11	1.41	<.001
Educational Attainment	0.89	0.80	0.99	.030	0.90	0.80	1.02	.090
WTC-Related Factors:								
Supervisor Role	0.76	0.57	1.01	.059	0.73	0.53	1.00	.048
Volunteer Role	0.99	0.78	1.27	.959	1.02	0.77	1.34	.893
Exposure Duration	1.05	0.95	1.16	.305	1.03	0.93	1.15	.558
High-Risk Work	3.79	2.91	4.94	<.001	4.09	2.95	5.66	<.001
PTSD Symptoms	1.24	1.12	1.37	<.001	1.21	1.08	1.35	.001
Blood Exposure	1.02	0.83	1.26	.838	1.00	0.79	1.27	.972

Notes. Any cognitive impairment defined by MoCA ≤ 23. Effects were estimated simultaneously and additionally adjusted for the first twenty genetic principal components. *aHR* = adjusted hazard ratio. *aRR* = adjusted relative risk ratio calculated by correcting the adjusted odds ratio for incidence of cognitive impairment, specifically $\mathrm{aRR} = \mathrm{a}OR/\left[(1 - P_{ref}) + (P_{ref} \times aOR)\right]$, where P_{ref} is the incidence of dementia when exposure duration and high-risk activity equal zero. Lower and upper 95% denote confidence intervals for adjusted hazard ratios and relative risk ratios. Multiple imputation was used for missing data. Details on the multivariate imputation model and the results of a complete cases analysis are reported in supplemental material.