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The Effects of Psychosocial and Traumatic Stressors on MCI Diagnosis

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Background and Objective: Toxic stress exposure can have effects across the lifespan. Studies of civilians and veterans suggest a connection between psychosocial and traumatic stressor exposure in adulthood and a diagnosis of dementia later in life. The objective of this study was to investigate the impact of psychosocial and traumatic stressors on rates of MCI (Mild Cognitive Impairment) diagnosis in Vietnam Era Twin Study of Aging participants. **Methods:** 1,237 twin participants from the VETSA study were aged 61.72 ± 2.44 years at the time of data collection. Traumatic stress was measured by clinical interviewing, with psychosocial stressors quantified by self-report measures. Neuropsychological assessment determined MCI diagnosis. Previously conducted genotyping determined ApoE genotype. Mixed model analysis was used to determine effects on MCI diagnosis. **Results:** Our results from the mixed model analysis did not find a significant relationship between psychosocial and traumatic stress exposure and MCI diagnosis. PTSD diagnosis, measured by the DIS-III-R, collected for the Harvard Drug Study in 1996 ($F = 0.249$, $p = 0.618$) does not have a significant effect on MCI diagnosis. Life stress exposure, measured by Holmes and Rahe (1967), ($F = 0.249$, $p = 0.618$) does not have a significant effect on MCI diagnosis. Significant associations were determined using the Type III fixed effects. Associations were considered statistically significant at $p < 0.05$, two-tailed. **Implications:** Few subjects in Wave 2 of VETSA had MCI ($n = 147$), due in part to the age of the participants at the time (Mean 61.72 ± (2.44 years)). This led to a lack of power in our analysis. Future studies should examine all available VETSA data.

Keywords: veterans, mild cognitive impairment, psychosocial stress, traumatic stress

There is no single cause of mild cognitive impairment (MCI), a neurodegenerative condition defined as "clinically significant memory impairment that does not meet the criteria for dementia" (Petersen, 2011, p. 2). MCI is an amnestic disorder representing an intermediate stage between normative aging and Alzheimer's dementia. Though all MCI demonstrate neuropsychological impairment, diagnosis can be broken into subtypes amnestic or non-amnestic (Rountree et al., 2007) for more stable estimates of prevalence and rates of returning to normal cognitive functioning (Jak et al., 2009).

As age increases, so does the risk of developing MCI. A lifetime's worth of factors and exposures can affect the risk of developing this unhealthy form of cognitive decline. Apolipoprotein genotype (Tang et al., 2023), education (Tervo et al., 2004), and general cognitive ability during adulthood (Corbo et al., 2023) have been associated with an increased risk of developing MCI, but neither the exact causes of MCI nor the influence of a lifetime of stressors is completely understood. There is no known cure for MCI, thus the identification of modifiable risk factors is important for prevention and earlier detection of those at risk. Although research on MCI risk factors is extensive, the identification of the role of stress is incomplete and has never been investigated in a sample of twins.

Exposure to stress in adulthood and midlife has been shown by previous studies to increase the likelihood of an MCI diagnosis on the neurobiological level (Kritikos et al., 2023; Song et al., 2020). Stress occurs during a threat and when environmental demands exceed adaptive capacity, with threat associated external and internal stimuli eliciting the reactions defined as stressors. Potential stressors encountered during adulthood include a long list of adverse psychosocial and physical forces. A psychosocial factor is defined by Hemingway and Marmot (1999) as phenomena that are "potentially related to the social environment and to pathophysiologic changes...Psychosocial factors may act alone or combine in clusters and may exert effects at different stages of the life course" (p. 2). The stressor can be a discrete event such as the death of a spouse, or a prolonged exposure, such as racial discrimination experienced by minority Americans (Turner et al., 2017). In the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; DSM-4), Criterion A1, traumatic events are defined as "an event that involves actual or threatened death or serious injury, or other threat to one's personal integrity" and includes "learning about the unexpected or violent death, serious harm, or threat of death or injury experienced by a family member or other close associate" (First et al., 2004, p. 14).

Posttraumatic stress disorder (PTSD) is a disorder that can be present at any age. It is triggered by either witnessing or experiencing an event that presents a threat to one's safety. Symptoms may include flashbacks, nightmares, severe anxiety, and uncontrollable

thoughts about the event (Hathaway et al., 2010). It is also associated with cognitive impairments unique to the condition in the domains of verbal learning, speed of information processing, attention, working memory, and verbal memory (Scott et al., 2015). A neurobiological pathway has been proposed to describe how PTSD influences dementia, with traumatic exposure triggering persistent over-activation of the hypothalamic-pituitary-adrenal (HPA) axis and the adrenergic system (Leister & Menke, 2020).

The literature on the impact of psychosocial and traumatic stress on MCI outcomes has been mixed. A study by Wang et al., (2018) of non-military elders of both sexes found a significant dose-dependent relationship between PTSD symptom severity and developing dementia later in life. A study by Peavy et al., (2009) also found that chronic stress and stressful life events led to general memory decline in cognitively normal (CN) individuals as well as those diagnosed with MCI. As for conversion from CN to MCI, Peavy et al., (2012) did not find an association between stressful experiences and change to MCI. These findings could result from the variability of ways that stress and PTSD were operationalized.

Although research with elderly veteran participants varies from that of elderly civilian participants, most VETSA participants were not exposed to combat (Kremen et al., 2013). However, veterans are exposed to factors that are unique to military service (Sibener, 2014). In a study of 181,093 elderly veterans by Yaffe et al. (2010), the 7-year cumulative incident dementia rate amongst veterans with PTSD was 10.6% while those without PTSD had a rate of 6.6%. While Yaffe et al. (2010) did not specify the veterans' era, in another study greater incidence of MCI was observed specifically in Vietnam Era veterans who had also been diagnosed with PTSD (Weiner et al., 2017).

Previous studies have indicated that psychosocial factors such as racism (Moon et al., 2019), workplace adversity (Nabe-Nielsen, et al., 2019), and divorce (Eriksson, 2015) are risk factors for dementia. But in a meta-analysis of 24 longitudinal studies examining categories of toxic psychosocial and trauma-related stress, Bougea et al. (2022) found suggestive, yet non-robust evidence that psychosocial and traumatic types of stress are associated with increased risk of dementia in later life.

As VETSA participants have aged, the focus of the multi-institutional VETSA study has shifted from a focus on substance use to early identification of risk for MCI and Alzheimer's disease (AD). VETSA participants are all part of the Vietnam Era Twin Registry. VETSA selection criteria were (1) being in one's fifties at the time of recruitment and (2) that both twins in a pair had to be willing to participate in the baseline assessment (Kremen et al., 2013). A narrow subject age range of participants enhances VETSA's ability to examine within-individual differences and change over time. Another key aspect of the study design was an extensive neuropsychological test battery. The study is also unique in that we have cognitive assessment scores from participants when they were inducted into the military at the age of 17 to 25 years old. The present study was designed to investigate the influence of psychosocial and traumatic stressors on MCI diagnosis. It is hypothesized that participants with exposure to psychosocial and traumatic stressors would be more likely to have developed MCI.

Methods

Participants

VETSA participants were recruited from the Harvard Drug Study (Tsuang et al., 2001). 1,237 twins participated (349 monozygotic pairs, 265 dizygotic pairs, and 9 unpaired). Attrition-replacement participants were included as a subset of the Wave 2 participants. The attrition-replacement participants are twin pairs from the Vietnam Era Twin Registry in the same age range as the returning Wave 2 participants. At Wave 2 of data collection, the mean age of participants was 61.72 ± (2.44 years). All VETSA participants were in the military sometime between 1965 and 1975. The majority did not see combat or serve in Vietnam. The sample was entirely male and 95.4% (n = 712) white. Black Americans made up 4% (n = 30), Hispanics represented 0.3% (n = 2) and 0.3% were missing information on race (n = 2). The average lifetime education was 12.4 (± 1.3 years) (see Appendix).

Instrumentation

Holmes and Rahe Stress Scale

Life stressors were measured using the Holmes and Rahe Social Readjustment Rating Scale. The Holmes and Rahe Social Readjustment Rating Scale is a 100-item questionnaire (α = .8458), composed of 43 life events. An individual's total score measures the amount of stress the individual has experienced in the past year. The tool has been exten-

sively studied, and its reliability and validity are well established. Cronbach's alpha for various populations ranges from 0.82 to 0.90 (Holmes & Rahe, 1967).

DIS-III-R

Subjects were interviewed using the Diagnostic Interview Schedule Version III Revised (DIS-III-R), a structured interview employed in epidemiological research. Interviews were performed over the telephone by the Institute for Survey Research at Temple University. Responses to the DIS-III-R were used to diagnose psychiatric disorders according to the revised third edition of the Diagnostic and Statistical Manual of Mental Disorders (Coopers and Michels, 1988).

PTSD Checklist (PCL-R)

The PTSD Checklist (PCL) is a self-report rating scale for assessing posttraumatic stress disorder. It consists of 17 items (α = 0.87) which correspond to the DSM-III symptoms of PTSD. Examinees are instructed to indicate how much they have been bothered by each symptom in the past month using a 5-point (1-5) scale. The anchors for the severity ratings range from "Not at all" to "Extremely." The PCL can be used as a continuous measure of PTSD symptom severity by summing scores across the 17 items.

AFQT

The Armed Forces Qualification Test (AFQT) is a 50-minute paper-and-pencil test consisting of 100 multiple-choice items (α = .88) that was administered just prior to military induction (Bayroff & Anderson, 1963). The items equally represent the four domains of vocabulary, arithmetic word problems, knowledge of tools and mechanical or electrical equipment, and spatial visualization, which involves matching folded and unfolded box patterns (Uhlaner & Bolanovich, 1952). Originally intended as a measure of military trainability, further research has found the AFQT to be a highly g-loaded test (Orme et al., 2001), with g being the construct of general intelligence (Humphreys, 1979). VETSA investigators received permission from the United States Department of Defense to re-administer a version of the AFQT that is similar to the AFQT versions that had been administered to VETSA subjects just prior to their induction into the military (1965–1975). This version has been used in previous research (Grafman et al., 1988). Scores from the time of induction are also available to VETSA investigators.

Genotyping

ApoE genotype is integral in AD and MCI research as it accounts for as much as 50% of the attributable risk for AD in many populations (Ashford, 2004). As per Lyons et al. (2013), ApoE genotyping was conducted for the 1,237 VETSA participants at either the Boston University or University of California, San Diego site. ApoE genotype was determined using previously described conditions (Emi et al., 1988; Hixson & Vernier, 1990). Due to the low rate of participants that possessed e4 allele, homozygous and heterozygous carriers were grouped.

Jak-Bondi MCI

This study uses VETSA data that utilized the Jak-Bondi (Jak, et al., 2009) operationalization of MCI. Conservative criteria were used in VETSA, such that it requires impairment on two measures within a domain, with impairment identified as 1.5 *SD* below normative data (Jak et al., 2009). According to these standardized criteria, individuals in VETSA were classified as normal if, at most, performance on one measure within one or two cognitive domains fell more than 1.5 *SD* below age-appropriate norms.

Procedure

Mixed modelling was used to test the association between demographic factors, psychosocial and traumatic variables, and MCI diagnosis.

All analyses were conducted in SPSS 29.0.0.0. All measures were assessed at the individual level. Because our sample consisted of twins, we used a linear mixed modelling approach to account for the clustering of twins within families by including a family ID variable as a random effect. Separate analyses were performed for each measure. Standardized scores were used for all outcome measures and for AFQT, education, and performance on neuropsychological tests.

Model 1 tested whether age at testing date for Wave 2 (61.72 ± 2.44 years) had an effect on MCI outcome. Model 2 tested the association of intelligence, as measured by AFQT performance upon military induction (collected between 1965–1975) with MCI outcome. Model 3 tested the association of ApoE e4 allele status on MCI outcome. Model 4 examined the correlation between years of education on MCI outcome. Model 5 tested the association of race on MCI outcome. Model 6 tested the association of ethnicity (Hispanic/Non-Hispanic) on MCI outcome. Model 7 tested the association of PTSD diagnosis at Harvard Drug Study (Tsuang, et al., 2001) data collection date (1996) as measured by the DIS-III-R on MCI out-

come. Model 8 tested the association of psychosocial stressors over the last two years before the Wave 2 testing date on MCI outcome. Model 9 tested the association of PTSD symptoms at Harvard Drug Study (Tsuang, et al., 2001) data collection date (1996), as measured by the DIS-III-R collection on MCI outcome. Significant associations were determined using the type III fixed effects. Associations were considered statistically significant at $p < 0.05$, two-tailed.

Results

Table 1 shows that Age ($F = 3.879$, $p = 0.05$) did not have a significant effect on MCI diagnosis, although it exhibited a trend towards a predictive effect. Intelligence, measured by the AFQT taken between ages 18-25, was found to have no significant impact on MCI diagnosis ($F = 3.523$, $p = 0.061$). The ApoE e4 allele(s) status ($F = .236$, $p = 0.628$) was also found to have no significant impact on MCI diagnosis. Education, however, ($F = 4.667$, $p = 0.031$) was found to have a significant effect on MCI diagnosis. Neither Race ($F = 2.195$, $p = 0.139$) , nor Ethnicity ($F = 2.252$, $p = 0.134$) had a significant effect on MCI diagnosis. PTSD diagnosis, as measured by the DIS-III-R (Coopers and Michel, 1988), collected for the Harvard Drug Study in 1996 ($F = 0.249$, $p = 0.618$) did not have a significant effect on MCI diagnosis. Life stress exposure, as measured by the Holmes and Rahe (1967), ($F = 0.249$, $p = 0.618$) also did not have a significant impact on MCI diagnosis. Lastly, Table 1 shows that PTSD symptoms ($F = 0.006$, $p = 0.936$) did not have a significant impact on MCI diagnosis.

Discussion

Our findings in a mixed model analysis of VETSA Wave 2 did not support the hypothesis. No significant associations between the stress factors we examined and MCI diagnosis in Wave 2 was observed. A significant relationship between education and MCI was observed, but is not surprising, as epidemiological studies consistently report that a high level of education is associated with a reduced risk of cognitive impairment (Anttila et al., 2002; Fratiglioni & Wang, 2007; Ngandu et al., 2007). The results of these studies indicate that education might reflect the extent of early cognitive stimulation of the brain which may influence global cognitive abilities. The average lifetime education of the participants was 12.4 (± 1.3 years; see Appendix A).

Previous studies investigated the relationship between psychosocial and traumatic stressor activities with cognitive decline. We hypothesize that our results may vary from those obtained by Yaffe et al. (2010) because their study tracked health records over a period of seven years, while our analysis looked at new MCI diagnoses over a shorter time span between each VETSA data collection point. Further, their subjects were more racially diverse and included women. Our study only investigated the onset of MCI, while their study included all types of dementias, including end-stage Alzheimer's Disease. Most importantly, the mean baseline age of their veteran subjects was 68.8 years.

The study by Weiner et al. (2017) primarily aimed to establish the relationship between traumatic brain injury, PTSD, and Alzheimer's Disease biomarkers. Their study's conceptualization of PTSD may have been more relevant to finding the connection between traumatic exposure and cognitive impairment, as it accounted for current and lifetime PTSD instead of PTSD status at one point in 1996. Another feature of their study that contributed to their finding was that their subjects had a mean age of 67.8.

As for Peavy et al. (2009), their operationalization of MCI was the less stringent Peterson et al. (1999) criteria. In one study by Oltra-Cucarella et al. (2018) criteria for MCI misclassified 24% of the sample compared to the more conservative Jak-Bondi MCI criteria (Jak et al., 2009) used for the current study. Stress was also measured as a cortisol rating and from responses to the Life Events and Difficulties Schedule (Brown & Harris, 1978), which quantified events over the participants' entire adult life instead of within the last two years before the study visit. Stressful events were also self-reported every six months, at which time cortisol was measured. This data was collected for two to three years. Aside from this difference in operationalization of toxic stress, the mean age of participants was 78.8 years old, making their participants much older than ours.

Wang et al. (2018) studied non-military elders and found a significant dose-dependent relationship between PTSD symptom severity and developing dementia later in life. Though the average age of their participants was 55.44 years, PTSD severity was indicated by the frequency of psychiatric clinic visits for PTSD. This operationalization of PTSD is not through clinically supported or uniform diagnosis criteria. As for psychosocial and trauma-related

stress, Bougea et al. (2022) may have found results that differed from ours because they used a wide variety of conceptualizations of psychosocial stress. For dementia diagnosis, one included study used self-report responses to quantify dementia. All participant data examined was for people 65 years or older.

One of the main limitations of the current study was the small number of people that met the diagnostic criteria for MCI, which in total was only 147 after adjusting for age, education, and practice effects. This small number resulted in a lack of statistical power. Additional issues with the analysis may be from our operationalization of psychosocial and traumatic stressors. The measure of psychosocial stress used, the Holmes and Rahe (1967), only pertained to the two years of the participant's life prior to test administration. A measure that accounts for the entirety of adulthood, from 18 years old onwards, would more accurately quantify the total adult stress burden. As for using the PTSD diagnosis conferred in 1996, the literature supports that just one incidence of PTSD permanently alters the brain (Hendrickson & Raskind, 2016). The mechanism is that trauma causes permanent neuronal changes that harm learning, habituation, and stimulus discrimination. Some of these neuronal changes that have a continuing impact do not even depend on actual exposure to reminders of the trauma for expression (Van der Kolk, 2003). Even so, a diagnosis back in 1996 may not be as relevant to cognitive status during the data collection period of VETSA Wave 2, which occurred in the 2010's (between 2009 and 2014).

Our insignificant findings are still relevant to MCI risk factor research. Our limitations highlight the importance of subject selection and support existing research on the typical age of onset for MCI (Howieson et al., 2008). Future analyses should be conducted with VETSA study data that covers a longer period of the twins' lives. Future analyses should also include data collected when the participants were older. These two suggestions should be followed so that a longer period of toxic stress exposure can be quantified and so that the subjects will be older, giving more time for MCI to develop. Higher rates of MCI can be expected to emerge as the participants age. The results did not indicate that toxic psychosocial stress exposure and/or traumatic stress had an impact on rates of MCI diagnosis within a subject pool of veterans from the VETSA study. Monitoring the health of veterans as they age is important for addressing the epidemic of cognitive impairment in the general population. Even those with primarily non-combatant roles are at risk for adverse health outcomes due to their service. Veterans have made great sacrifices and the scientific community must ensure that their unique healthcare needs are met.

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Table 1

Mixed Model Tests of Fixed Effects on MCI Diagnosis

Predictor Variable	Effect Size	*df*	*F*	Sig.
Intercept	-.0996630	424.991	.033	.855
Age	.012825	354.861	3.879	.050
Intelligence (AFQT)*	.041172	611.258	3.523	.061
APOE4 Genotype**	-.015053	494.713	.236	.628
Education	-.014630	627.474	4.667	.031
Race	-.083152	464.379	2.195	.139
Ethnicity (Hispanic/Non-Hispanic)	.095098	394.071	2.252	.134
PTSD Diagnosis***	-.006674	651.445	.056	.813
Life Stress Exposure****	.002229	667.789	.249	.618
PTSD Symptoms***	-.000481	656.508	.006	.936

Note. Dependent Variable: MCI diagnosis at VETSA Wave 2.
*at ages 17–25 years, as measured by the AFQT upon military induction between 1965–1975, collected for the Harvard Drug Study
**no e4 allele vs. homo- or heterozygous for e4
*** as measured by the DIS-III-R, collected for the Harvard Drug Study in 1996
**** measured over the last two years from testing date by the Holmes and Rahe (1967).

Appendix A

	VETSA subjects (Total $n = 746$)
Age at induction (years)	19.9 ± 1.4 (17—25) ($n = 746$)
Race	
White	95.4% ($n = 712$)
Black	4.0% ($n = 30$)
Hispanic	0.3% ($n = 2$)
Missing	0.3% ($n = 2$)
Marital status in 1991—1993	
Married	78.3% ($n = 584$)
Single	8.3% ($n = 62$)
Widowed	0.7% ($n = 5$)
Separated	1.9% ($n = 14$)
Divorced	10.9% ($n = 81$)
Education at induction (years)	12.4 ± 1.3 (7—20) ($n = 740$)

Note. Subject demographic data from Lyons et al. (2013).