Apolipoprotein E gene polymorphism, trauma burden, and posttraumatic stress symptoms in U.S. military veterans: Results from the National Health and Resilience in Veterans Study

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Key words:

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ABSTRACT

Background: Previous research examining the association between apolipoprotein E (*APOE*) gene polymorphism and risk for posttraumatic stress disorder (PTSD) has been inconsistent due to the use of small and select samples. This study examined the relation between *APOE* genotype and PTSD symptoms in two nationally representative samples of U.S. military veterans. The potential effect of cumulative trauma burden and social support in moderating this association was also evaluated.

Methods: The main sample consisted of 1,386 trauma-exposed European American (EA) veterans (mean age: 62--63 years) who participated in the National Health and Resilience in Veterans Study (NHRVS) in 2011. The independent replication sample consisted of 509 trauma-exposed EA veterans from the 2013 NHRVS.

Results: *APOE* ε4 allele carriers reported significantly greater severity of PTSD symptoms than noncarriers in the main, but not the replication, sample. In both samples, the interaction of *APOE* ε4 carrier status and cumulative trauma burden was associated with greater severity of PTSD symptoms (*F* range = 2.53--8.09, all *P*'s < .01), particularly re-experiencing/intrusion symptoms (*F* range = 3.59--4.24, *P*'s < .001). Greater social support was associated with lower severity of PTSD symptoms among *APOE* ε4 allele carriers with greater cumulative trauma burden (β range −.27 to −.60, *P*'s < .05).

Conclusion: U.S. military veterans who are *APOE* ε4 allele carriers and exposed to a high number of traumas may be at increased risk for developing PTSD symptoms than ε4

noncarriers. Greater social support may moderate this association, thereby highlighting the potential importance of social support promoting interventions in mitigating the effect of ε4 × cumulative trauma burden on PTSD risk.

1 INTRODUCTION

Posttraumatic stress disorder (PTSD) affects 6.4--7.8% of trauma-exposed adults (Kessler, 2000; Pietrzak, Goldstein, Southwick, & Grant, 2011; Wisco et al., 2014). Myriad environmental and psychosocial risk and protective factors for PTSD have been identified in trauma-exposed populations, including military veterans (Andersen, Karstoft, Bertelsen, & Madsen, 2014; Wisco et al., 2014; Xue et al., 2015). There is also increasing interest in identifying genetic risk factors for PTSD and how these markers interact with environmental factors to predict PTSD risk (e.g., Grabe et al., 2009; Kilpatrick et al., 2007). Examining the interactive effects of candidate genes and environmental factors on mental disorders, as opposed to investigating genetic or environmental influences independently, can substantially further our understanding of the etiology of these conditions (Dick et al., 2015). To date, candidate gene studies have identified possible risk alleles mapped to genes implicated in PTSD (Almli, Fani, Smith, & Ressler, 2014), and several genome-wide significant associations between genes such as *AC068718* (rs10170218), *RORA* (rs8042149), *ANKRD55* (rs159572), and *ZNF626* (rs11085374) and PTSD (Guffanti et al., 2013; Logue et al., 2013; Stein et al., 2016).

c a growing body of research has evaluated whether polymorphisms in the apolipoprotein E (*APOE*) gene may contribute to PTSD risk (e.g., Kimbrel et al., 2015; Lyons et al., 2013), most studies have been small and focused on select samples of trauma survivors (e.g., Vietnam or Iraq/Afghanistan-era veterans). *APOE* is a protein-coding gene with three

functionally different alleles (ε2, ε3, ε4), with ε3 being the most frequently occurring in the general population. The *APOE* gene encodes the APOE protein, which plays a role in neuronal repair through its involvement in cholesterol metabolism, and transportation of cholesterol and other lipids to neurons. The *APOE* ε4 allele, however, has been linked to hippocampal atrophy and memory impairment (Pievani et al., 2011; Small, Rosnick, Fratiglioni, & Bäckman, 2004), reduced synaptic plasticity (Chen, Durakoglugil, Xian, & Herz, 2010), and a more robust systemic and central nervous system inflammatory response (Lynch et al., 2003). It has also been associated with greater likelihood of developing several neurological and neuropsychiatric disorders (e.g., Skoog et al., 2015), especially Alzheimer's disease (Bekris, Yu, Bird, & Tsuang, 2010; Kim, Basak, & Holtzman, 2009).

Studies examining the relation between *APOE* gene and PTSD have been mixed. In a sample of 172 Vietnam veterans, Lyons et al. (2013) found that the presence of an *APOE* ε4 allele was associated with a greater number of PTSD symptoms, but not with PTSD diagnosis. They also observed that ε4 carriers with high combat exposure had greatest severity and risk for PTSD. More recently, a study of 859 non-Hispanic black veterans found that each additional *APOE* ε4 allele was associated with 60% greater likelihood of having a PTSD diagnosis and greater severity of PTSD symptoms, and that this finding was only observed among veterans with high levels of combat exposure; these effects were not observed in non-Hispanic white veterans (Kimbrel et al., 2015). *APOE* genotype was also unrelated to severity of postdeployment PTSD symptoms in 230 U.S. army soldiers (Dretsch et al., 2016). Other studies have found the *APOE* ε2 allele, but not ε4, to be associated with memory impairment and re-experiencing symptoms of PTSD (Freeman, Roca, Guggenheim, Kimbrell, & Griffin, 2005), PTSD diagnosis (Kim et al., 2013), and PTSD symptom severity

(Johnson et al., 2015), which is the opposite of the expectation based on the literature related to Alzheimer's disease.

Gene × environment (G × E) effects of *APOE* ε4 and environmental exposures are also poorly understood. Aside from combat exposure severity (e.g., Kimbrel et al., 2015; Lyons et al., 2013), it remains unknown whether ε4 carrier status may interact with cumulative trauma burden to predict PTSD risk, as has been observed for other genetic polymorphisms (e.g., *SLC6A4*: Grabe et al., 2009). Further, no known study has evaluated potentially modifiable moderators of the *APOE* ε4 × trauma burden interaction, such as social support, a robust protective factor for PTSD (Ozer, Best, Lipsey, & Weiss, 2003). A small number of studies have found low social support to interact with high trauma exposure and genetic risk factors to increase the likelihood of PTSD (Kilpatrick et al., 2007; Lian et al., 2014), suggesting that high levels of social support may buffer against genetic risk among trauma-affected individuals.

To address these gaps, we analyzed data from two nationally representative samples of trauma-exposed European American (EA) U.S. military veterans to evaluate two aims: (1) examine the relation between *APOE* ε4 carrier status, alone and interactively with cumulative trauma burden, and overall severity of PTSD symptoms and symptom clusters; and (2) determine whether levels of perceived social support may moderate any effects of *APOE* ε4 carrier status and the interaction of ε4 × trauma burden in predicting severity of PTSD symptoms.

2 MATERIALS AND METHODS

2.1 Participants

Participants were recruited from a research panel of over 50,000 U.S. households developed and maintained by GfK Knowledge Networks, Inc. (Menlo Park, CA), and representing approximately 98% of U.S. households. Participants in the research panel who answered affirmatively to the question, “Have you ever served on active duty in the U.S. Armed Forces, Military Reserves, or National Guard?” were eligible to participate in the National Health and Resilience in Veterans Study (NHRVS), a nationally representative study of U.S. veterans. The main sample consisted of 1,386 trauma-exposed EA U.S. military veterans from the NHRVS, conducted in 2011. Participants in the replication sample were an independent sample of 509 trauma-exposed EA U.S. military veterans from a second baseline cohort survey of the NHRVS conducted in 2013. Poststratification weights were applied based on the demographic distribution of veterans (age, sex, education, race/ethnicity, metropoloitan area, and Census region) in the GfK Knowledge Networks survey panel and calibrated against U.S. Census data. The NHRVS was approved by the Veterans Affairs (VA) Connecticut Healthcare System and the VA Office of Research & Development.

2.2 Assessments

2.2.1 APOE genotyping

Participants provided saliva for DNA extraction. Saliva was collected using Oragene DNA (OG-250) kits. DNA was extracted using prepIT-L2P reagent (DNA Genotek, Ontario, Canada) according to manufacturer's directions. Samples were genotyped with the PsychChip GWAS array. Genotypes were called using GenomeStudio software V2011.1 and genotyping module V1.8.4 (Illumina, San Diego, CA). Ninety samples with missing genotyping rate >5% were excluded from analysis. The following criteria were used for including SNPs: minor allele frequency (MAF) > .01%, missing genotyping rate per SNP < 5%, and Hardy--Weinberg equilibrium (HWE) *P*-value > 10^{-5}. This resulted in 423,415 autosomal SNPs and 2,737 samples. Duplicates were detected by estimating the genome-wide identity-by-descent (IBD) sharing for all pairwise samples in PLINK (Purcell et al., 2007) using 93,814 independent SNPs with MAF > .01. Nine duplicate pairs and 12 additional pairs with a high level of IBD sharing (>.1) were detected. We randomly removed one subject of the duplicate or related pairs, retaining 2,718 independent samples (2,270 EAs). We computed principal components (PC) for the GWAS data using EIGENSOFT (Price et al., 2006) based on a common set SNPs (64,219) with Hapmap3, which were in low linkage disequilibrium (LD) with one another and have a MAF > .01. We detected and removed 95 outlier EA samples from the PC analysis, defined as samples whose ancestry was at least three standard deviations from the mean on one of the two largest PCs. We then imputed 1,000 genomes variants into the EA samples following the best practice guidelines of IMPUTE2 (Howie, Donnelly, & Marchini, 2009). Prephasing was first performed with SHAPEIT (Delaneau, Marchini, & Zagury, 2012) to infer haplotypes for the EA samples based on 295,837 autosomal SNPs with MAF > .01. Imputation was then carried out on prephased haplotypes using IMPUTE2 against reference data from the 1000 Genomes Phase III integrated variant set. After postimputation QC (SNP missing rate <.05, MAF > .005, imputation quality score (info) >.5, and HWE > 10^{-6}), 10,377,932 SNPs remained. We extracted two *APOE* SNPs—rs429358 and rs7412—from the imputed data of EA samples

for a candidate gene analysis of *APOE* ε4 carrier status. These two SNPs define ApoE status and were selected in accordance with previous literature (e.g., Kim et al., 2013; Kimbrel et al., 2015). One SNP (rs7412) was directly genotyped by the PsychChip array and the other (rs429358) was imputed with high-quality score (info = .99). To determine *APOE* ε4 carrier status, we made hard genotype calls of the imputed SNP by applying a posterior genotype probability threshold of .9. There was no evidence of deviation from Hardy--Weinberg expectations for the *APOE* genotype in either the main (P = .14) or replication (P = .74) sample. A dichotomous variable of 0 versus 1 or 2 *APOE* ε4 alleles was created.

2.2.2 Sociodemographic and military characteristics

Age, sex, household income, education, employment status, marital status, combat veteran status, and number of years of military service were assessed.

2.2.3 Cumulative trauma burden

The *Trauma History Screen* (THS) assessed lifetime exposure to 13 potentially traumatic events (Carlson et al., 2011), including child and adult physical and sexual assault, natural disaster, and unexpected loss of a loved one. Events were summed to yield a measure of cumulative trauma burden.

2.2.4 PTSD symptoms

The PTSD Checklist (PCL) was used to assess lifetime and past-month PTSD symptoms based on respondents' worst reported traumatic event on the THS. The DSM-IV version

(PCL-Specific Stressor [PCL-S]) was used in the main sample (α = .94) and the DSM-5 version (PCL-5) was administered in the replication sample (α = .95). Veterans were classified as having probable PTSD if their PCL score was ≥50 on the DSM-IV version (Weathers, Litz, Herman, Huska, & Keane, 1993) and ≥38 on the DSM-5 version (Hoge, Riviere, Wilk, Herrell, & Weathers, 2014). Comparability of the symptom clusters on the two PCL versions was achieved by using the four-factor DSM-IV model of re-experiencing, avoidance, emotional numbing, and hyperarousal symptoms (King, Leskin, King, & Weathers, 1998), and the DSM-5 model of intrusions, avoidance, negative cognitions and mood, and alterations in arousal and reactivity. Responses on items comprising each symptom cluster were summed to yield severity measures.

2.2.5 Social support

Social support was assessed using a 5-item version of the Medical Outcomes Study Social Support Scale (Amstadter et al., 2010); items assessed emotional and instrumental support (α = .90 in main sample; α = .87 in replication sample). Veterans were asked how often each kind of support was available when needed, and items included, “Someone to get together with for relaxation” and “Someone to love and make you feel wanted.”

2.2.6 Other psychiatric disorders

The Mini International Neuropsychiatric Interview adapted for self-report was used to assess lifetime DSM-IV diagnoses of major depressive, alcohol, and drug use disorders (Lecrubier et al., 1997).

2.3 Data analysis

Descriptive statistics were used to summarize sociodemographic, trauma, and clinical variables of trauma-exposed veterans. A series of univariate analyses of covariance (ANCOVAs) were conducted to evaluate the relation between *APOE* ε4 allele carrier status, trauma burden, and their interaction, and severity of lifetime and past-month PTSD symptoms in the main and replication samples. Covariates included age, sex, top 10 PCs from population stratification analysis, combat exposure (i.e., combat veteran vs. noncombat veteran), and nature of "worst" traumatic event (i.e., assaultive vs. nonassaultive). To evaluate the role of social support in moderating the interaction between *APOE* ε4 allele carrier status × lifetime trauma burden, we incorporated an ε4 × trauma burden × social support interaction term into the ANCOVAs. To evaluate the relationship between *APOE* ε4 allele carrier status, cumulative trauma burden, and their interaction, and lifetime PTSD symptom clusters, we conducted a parallel series of univariate ANCOVAs with scores on each of the PTSD symptom clusters entered as dependent variables in separate analyses and other PTSD symptom clusters entered as additional covariates. A statistical significance threshold of $\alpha = .01$ was employed in analyses to reduce the likelihood of Type I error. These post-hoc analyses were limited to lifetime PTSD symptom clusters due to the low prevalence and variance of past-month PTSD symptom clusters. Reported raw frequencies are unweighted; means, percentages, and inferential statistics are poststratification weighted to reflect the general population of U.S. veterans. Analyses were conducted using SPSS version 22.

3 RESULTS

Table 1 shows sociodemographic, military, and clinical characteristics of trauma-exposed veterans in the main and replication samples. On average, participants in both samples were 62--63 years of age, predominantly male, some college or higher educated, married/cohabitating, retired, had household incomes <$60,000, were noncombat veterans, and spent an average of 7 years in the military. On average, veterans in the samples reported experiencing 3.7--3.8 traumatic life events, with 7.1--10.0% screening positive for lifetime PTSD and 3.5--3.8% for past-month PTSD.

Table 2 shows results of analyses evaluating the relation between *APOE* ε4 carrier status, trauma burden, and their interaction, and PTSD symptoms.

In the main sample, *APOE* ε4 carrier status, number of traumas, and their interaction were associated with greater severity of lifetime and past-month PTSD symptoms. Figure 1 illustrates the interaction of *APOE* ε4 and trauma burden on severity of lifetime PTSD symptoms in the main sample. Among ε4 carriers, those with a greater number of traumas had greater PTSD symptoms. Incorporation of an *APOE* ε4 × lifetime traumas × social support interaction term into this ANCOVA revealed a significant association with lifetime (three-way interaction, $F = 3.01$, $P < .001$) and past-month (three-way interaction, $F = 4.35$, $P < .001$) PTSD symptoms. Adjusted post-hoc analyses among ε4 carriers with greater cumulative trauma burden revealed that greater levels of social support were associated with significantly reduced likelihood of lifetime ($\beta = -.48$, $t = 6.21$, $P \leq .001$) and past-month ($\beta = -.60$, $t = 7.89$, $P < .001$) PTSD symptoms. Among ε4 carriers with greater cumulative trauma burden (i.e., greater than the median number of three events, $n = 602$), those with

higher levels of perceived social support were less likely to screen positive for current PTSD (2.4% in highest tertile vs. 4.8% in middle tertile vs. 20.5% in lowest tertile; see Fig. 2).

In the replication sample, the interaction of *APOE* ε4 carrier status × cumulative trauma burden was significantly associated with lifetime and past-month PTSD symptoms; *APOE* ε4 carrier status was unrelated to these outcomes. Incorporation of an *APOE* ε4 × lifetime traumas × social support interaction term revealed a significant association with lifetime (F = 3.86, P < .001) and past-month (F = 4.55, P < .001) PTSD symptoms. Adjusted post-hoc multivariable linear regression analyses in ε4 carriers with greater cumulative trauma burden revealed that greater levels of social support were associated with significantly reduced likelihood of lifetime (β = −.27, t = 2.32, P ≤ .024) and past-month (β = −.37, t = 3.07, P = .003) PTSD symptoms. Among ε4 allele carriers with greater cumulative trauma burden, those with higher levels of social support were less likely to screen positive for current PTSD (0% in highest tertile vs. 8.3% in middle tertile vs. 11.8% in lowest tertile).

Adjustment for MDD and SUDs did not substantively change the results. In the main sample, the main and interactive effects of ε4 allele and ε4 allele × cumulative trauma burden remained significant for both lifetime PTSD symptoms: F = 20.77, P < .001 and F = 36.13, P < .001, respectively; and past-month PTSD symptoms: F = 22.76, P < .001; F = 30.10, P < .001, respectively. In the replication sample, the interaction of e4 allele × trauma burden also remained significant for past-month (F = 2.78, P = .003) but not for lifetime (F = 1.30, P = .23) PTSD symptoms.

Table 3 shows results of analyses examining the relationship between *APOE* ε4 carrier status, cumulative trauma burden, and the interaction of these variables, and lifetime PTSD symptom clusters. In the main sample, the interaction of *APOE* ε4 carrier status × lifetime traumas was significant for re-experiencing and avoidance symptoms. In the replication sample, ε4 carrier status was associated with greater severity of intrusions; and the interaction of *APOE* ε4 × cumulative trauma burden was significant for intrusion symptoms and alterations in arousal and reactivity.

4 DISCUSSION

This study examined the association between *APOE* genotype, trauma exposure, and PTSD symptoms in two contemporary, nationally representative cohorts of EA military veterans. *APOE* ε4 allele carriers reported greater lifetime and past-month PTSD symptoms than noncarriers in the main sample, however, this association was not significant in our replication sample. This finding aligns with a recent meta-analysis supporting an association between ε4 carrier status and higher risk for combat-related PTSD (Roby, 2017). It is possible that the lack of a main effect in the replication sample was due to small sample size, and differences in sociodemographic factors and environmental exposures across samples may also partly account for the inconsistent findings. It is also possible that the discrepancy in findings between the main and replication samples may be attributable in part to the different PCL versions (DSM-IV vs. DSM-5) used; however, after recomputing a PCL-5 summary score by removing the new DSM-5 PTSD symptoms from the PCL-5 such that it more closely aligned with the PCL-S (DSM-IV), the main effect of ε4 allele carrier status remained nonsignificant for both lifetime (F = .44, P = .51) and past-month (F = .01, P = .92)

symptoms. Further evaluation of a possible association between *APOE* ε4 status and PTSD symptoms is needed in different trauma-exposed samples.

In both samples, *APOE* ε4 carriers with greater trauma burden reported greater lifetime and past-month PTSD symptoms. This finding is consistent with previous work linking ε4 allele carrier status to PTSD among veterans with high combat exposure (Lyons et al., 2013; Kimbrel et al., 2015), and extends it to demonstrate that cumulative trauma burden may also moderate the effect of ε4 allele carriage on PTSD symptoms. The *APOE* ε4 allele may hinder the neuronal repair and recovery that is necessary after injury related to extensive stress exposure (Lyons et al., 2013; Kimbrel et al., 2015). Trauma exposure across the lifespan can deleteriously affect brain structure and function, including reductions in hippocampal volume (Bremner, 2006; Woon, Sood, & Hedges, 2010) and dysregulation of the hypothalamic--pituitary--adrenal (HPA) axis (Bremner, 2006; Carpenter et al., 2007; Elzinga et al., 2008), which can increase risk for developing PTSD symptoms (Gilbertson et al., 2002; Pitman et al., 2012). *APOE* ε4 allele carriers are similarly at increased risk of several deficits relevant to PTSD, including hippocampal volume loss and amygdala atrophy (den Heijer et al., 2002; Goni et al., 2012) and greater cortisol levels (Gill-Bea et al., 2010), possibly further exacerbating PTSD vulnerability. Given that individuals with PTSD are at higher risk of dementia (Yaffe et al., 2010), it is also possible that the ε4 allele contributes to a shared mechanistic pathway for the development of both conditions, or that the development of dementia symptoms plays a role in the ε4-PTSD association. For example, a recent study found that Alzheimer's model mice displayed more exaggerated and frequent responses to a PTSD-like induction than control mice (Justice et al., 2015). Additional research utilizing prospective designs is needed to elucidate possible mechanisms linking ε4, PTSD, and cognitive decline and dementia in trauma-affected individuals.

Analyses of PTSD symptom clusters revealed that the *APOE* ε4 × trauma burden association was linked to greater re-experiencing and avoidance symptoms in the main sample, and greater intrusion symptoms and alterations in arousal and reactivity in the replication sample. In light of prior studies showing higher levels of cerebrospinal fluid cortisol among *APOE* ε4 carriers (Gil-Bea et al., 2010; Peskind, Wilkinson, Petrie, Schellenberg, & Raskind, 2001), it is possible that greater HPA axis reactivity among ε4 carriers may exacerbate hyperarousal symptoms among highly trauma-exposed individuals, which may in turn trigger re-experiencing/intrusion symptoms. Greater hippocampal atrophy and volume loss in ε4 carriers may also contribute to deficits in memory for fear extinction (den Heijer et al., 2002; Fanselow, 2000; Pievani et al, 2011), which can maintain re-experiencing/intrusion symptoms. Villasana, Weber, Akinyeke, and Raber (2016) found that mice carrying the ε4 allele had higher levels of heme oxygenase-1, a marker of stress, in the hippocampus, and also exhibited greater anxiety-related behaviors and conditioned fear responding. These findings suggest a possible mechanism linking ε4 carriage and intrusive symptoms among highly trauma-exposed veterans. Clearly, more research is needed to elucidate mechanisms underlying this association.

Of note, *APOE* ε2 carriage has been found to be associated with memory impairment, more re-experiencing symptoms, and greater overall PTSD symptoms in small samples of humans (Freeman et al., 2005; Johnson et al., 2015), while stress-exposed mice carrying the ε2 allele have been found to have impairments in fear memory extinction (Johnson et al., 2015; Olsen, Agam, Davis, & Raber, 2012). However, a meta-analysis did not find support for an effect of the e2 variant on risk for combat-related PTSD (Roby, 2017). Further research in

larger samples is needed to help resolve these inconsistent findings regarding *APOE* genotype and PTSD (Johnson et al., 2015; Rogers & Weeber, 2008).

Higher levels of social support were found to be associated with lower PTSD symptoms among *APOE* ε4 allele carriers with greater cumulative trauma burden. This finding adds to a small literature demonstrating an effect of social support in moderating the association between other genetic polymorphisms (Kilpatrick et al., 2007; Lian et al., 2014) and PTSD, depressive symptoms, and suicidal ideation (Chen et al., 2011; Kilpatrick et al., 2007; Kim et al., 2014). Social support has been linked with lower cortisol levels (McQuaid et al., 2016; Rosal, King, Ma, & Reed, 2004), improved cardiovascular and immune functioning (Uchino, 2006), and less-threatening appraisal of stressful events (Sippel, Pietrzak, Charney, Mayes, & Southwick, 2015), suggesting a potential role in buffering the impact of trauma-related stress responses. It is also possible, however, that veterans with more PTSD symptoms engage in behaviors that lead to less social support (e.g., avoidance, social isolation) or may inaccurately perceive their social support (e.g., Platt, Lowe, Galea, Norris, & Koenen, 2016). Nonetheless, assuming that social support may help buffer against the development of PTSD symptoms, facilitating the enhancement of social support networks (e.g., one-to-one mentorship programs, peer support groups, social/relationship skills interventions, Vet-to-Vet programs) among highly trauma-exposed veterans at elevated genetic risk for PTSD may be an important aspect of prevention initiatives (e.g., Hogan, Linden, & Najarian, 2002; Pietrzak et al., 2009; Resnick & Rosenheck, 2008; Williams, Bambara, & Turner, 2012).

The current findings should be considered in light of several limitations. First, PTSD symptoms were assessed via self-report, and it is unclear whether results would be

comparable if PTSD symptoms were assessed using a structured clinical interview such as the Clinician Administered PTSD Scale (CAPS). However, statistically significant and large magnitude associations have been observed between total scores on the PCL and on the CAPS (Macdonald, Greene, Torres, Frueh, & Morland, 2013; Monson et al., 2008). Second, the main sample was larger than the replication sample and different versions of the PCL (i.e., DSM-IV vs. DSM-5) were used in these samples; thus, it is unclear whether differences in patterns of associations between the samples may be related to reduced statistical power or versions of the PCL. Third, the sample was comprised predominantly of male EA veterans. Further research is needed to examine the role of *APOE* ε4 carrier status on risk for PTSD among more diverse samples of veterans and other trauma-affected populations. Fourth, given the strong association between *APOE* ε4 carrier status and poorer cognitive functioning and dementia (e.g., Engelborghs et al., 2003; Wisdom et al., 2011), it remains to be determined whether cognitive impairment might influence the association between ε4 and PTSD, as formal neuropsychological testing was not conducted in this cohort of veterans. Fifth, there have been a number of limitations raised with respect to G × E research with candidate genes, including the lack of replication of some findings, publication bias, and the frequent use of underpowered samples (e.g., Dick et al., 2015). However, the current study incorporated a number of recommendations made for improving the rigor of G × E studies, including having an adequately powered main sample, an independent replication sample, and a priori selection of candidate genes (i.e., *APOE*) and environmental factors (i.e., trauma exposure) based on theoretical rationale and existing literature (Dick et al., 2015). A recent review also recommended additional research examining the effect of positive exposures (i.e., social support) on psychopathology (Leighton, Botto, Silva, Jimenez, & Luyten, 2017).

5 CONCLUSION

Results of the present study suggest that *APOE* ε4 carrier status interacts with cumulative trauma burden to predict severity of PTSD symptoms, particularly re-experiencing/intrusive symptoms, in U.S. military veterans. Further, greater social support is associated with lower severity of PTSD symptoms in ε4 allele carriers with greater cumulative trauma burden. Further research is needed to examine the complex relationship and mechanistic pathways between *APOE* genotype, PTSD, and cognitive decline and dementia (Lee et al., 2008; Meziab et al., 2014; Peavy et al., 2007; Yaffe et al., 2010); evaluate how *APOE* and other gene polymorphisms are linked to transdiagnostic aspects of trauma-related psychopathology (e.g., Mota et al., 2015); and examine the efficacy of interventions to enhance social support in mitigating PTSD symptoms among at-risk trauma survivors.

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Table 1. Sociodemographic, Military, and Trauma and Clinical Characteristics of the Main and Replication Samples of Trauma-Exposed U.S. European-Ancestry Military Veterans

	Main Sample (*n* = 1,386)	Replication Sample (*n* = 509)
	Weighted Mean (*SD*) or *n* (Weighted %)	Weighted Mean (*SD*) or *n* (Weighted %)
Sociodemographic characteristics		
Age	62.6 (14.3)	62.4 (15.6)
Male sex	1,260 (92.8%)	457 (90.7%)
Some college or higher education	1,183 (66.0%)	428 (65.4%)
Married/living with partner	1,084 (74.9%)	379 (72.3%)
Currently employed	536 (36.1%)	152 (30.3%)
Household income ≥$60,000/year	728 (42.4%)	255 (44.0%)
Military characteristics		
Combat veteran	479 (32.7%)	213 (42.0%)
Number of years in military	6.8 (7.5)	7.0 (7.2)

Trauma and clinical characteristics		
Number of lifetime traumatic events	3.8 (2.5)	3.7 (2.5)
Index traumatic event		
Sudden death of close family member of friend	451 (34.4%)	151 (32.7%)
Life-threatening illness or injury	226 (16.6%)	84 (14.2%)
Military-related trauma	113 (7.9%)	42 (9.5%)
Child physical or sexual abuse	59 (3.2%)	23 (5.4%)
Other traumatic event	537 (37.9%)	209 (38.2%)
Lifetime PCL score[a]	28.4 (11.4)	15.2 (15.2)
Positive screen for lifetime PTSD	95 (7.1%)	44 (10.0%)
Past-month PCL score[a]	24.2 (10.1)	9.4 (12.1)
Positive screen for past-month PTSD	41 (3.8%)	15 (3.5%)
Lifetime major depressive disorder	244 (18.2%)	60 (25.6%)
Lifetime alcohol use disorder	659 (48.6%)	212 (41.7%)
Lifetime drug use disorder	200 (14.6%)	63 (12.3%)
APOE ε4 allele carrier	334 (24.1%)	133 (25.6%)

0 alleles	1,052 (75.9%)	376 (74.4%)
1 allele	318 (22.9%)	124 (23.7%)
2 alleles	16 (1.2%)	9 (1.9%)

Note. PCL, PTSD Checklist; PTSD, posttraumatic stress disorder.

[a]The DSM-IV version of the PCL was used in the main sample (score range = 17--85) and the DSM-5 version of the PCL was used in the replication sample (score range = 0--80).

Table 2. Results of Analyses Evaluating Relation Between *APOE* ε4 Allele Carrier Status, Cumulative Trauma Burden, and Lifetime and Past-Month PTSD Symptoms

	Main Sample (*n* = 1,386)			
	Lifetime PTSD Symptoms		Past-Month PTSD Symptoms	
	F	*P*	*F*	*P*
APOE ε4 carrier	16.11	<.001	6.75	.010
Cumulative trauma burden	28.31	<.001	22.48	<.001
APOE ε4 × cumulative trauma burden	6.08	<.001	8.09	<.001
	Replication Sample (*n* = 509)			
	Lifetime PTSD Symptoms		Past-Month PTSD Symptoms	
	F	*P*	*F*	*P*
APOE ε4 carrier	.41	.52	.04	.84
Cumulative trauma burden	11.97	<.001	8.66	<.001

APOE ε4 × cumulative trauma burden	2.53	.006	3.06	.001

Note. PTSD, posttraumatic stress disorder; *APOE* ε4, apolipoprotein epsilon 4.

Analyses are adjusted for age, sex, ancestral proportion scores, combat veteran status, and type of index trauma (assaultive vs. nonassaultive).

Table 3. Results of Analyses Evaluating Relation Between *APOE* ε4 Allele Carrier Status, Cumulative Trauma Burden,

and Lifetime PTSD Symptom Clusters

Main Sample (*n* = 1,386)								
	Re-experiencing		Avoidance		Emotional Numbing		Hyperarousal	
	F	*P*	*F*	*P*	*F*	*P*	*F*	*P*
APOE ε4 carrier	4.12	.043	5.98	.015	2.32	.13	4.11	.043
Cumulative trauma burden	9.08	<.001	3.30	<.001	4.05	<.001	3.09	<.001
APOE ε4 × cumulative trauma burden	4.24	<.001	3.01	.001	1.63	.085	2.14	.016
Replication Sample (*n* = 509)								
	Intrusions		Avoidance		Negative Cognitions and Mood		Alterations in Arousal and Reactivity	
	F	*P*	*F*	*P*	*F*	*P*	*F*	*P*
APOE ε4 carrier	14.99	<.001	.22	.64	5.29	.022	1.96	.16
Cumulative trauma burden	3.89	<.001	.74	.71	1.12	.34	2.96	.001

APOE ε4 × cumulative trauma burden	3.59	<.001	.86	.57	1.47	.15	5.30	<.001

Note. PTSD, posttraumatic stress disorder; *APOE* ε4, apolipoprotein epsilon 4.

Analyses are adjusted for age, sex, ancestral proportion scores, combat veteran status, nature of index trauma

(assaultive vs. nonassaultive), and other PTSD symptom clusters.

The DSM-IV version of the PCL was used in the main sample and the DSM-5 version of the PCL was used in the replication sample.

Figure 1. Interaction of *APOE* ε4 allele carrier status and cumulative trauma burden in predicting lifetime severity of PTSD symptoms in the main sample (*n* = 1,386).

Note. PTSD, posttraumatic stress disorder; *APOE* ε4, apolipoprotein epsilon 4. PTSD Checklist score range = 17--85. Lines represent fitted regression lines adjusted for age, sex, ancestral proportion scores, combat veteran status, and nature of index trauma (assaultive vs. nonassaultive). Slopes and 95% confidence intervals for ε4 allele noncarriers = 1.93 (1.72--2.15) and 3.31 (2.96--3.66) for ε4 allele carriers.

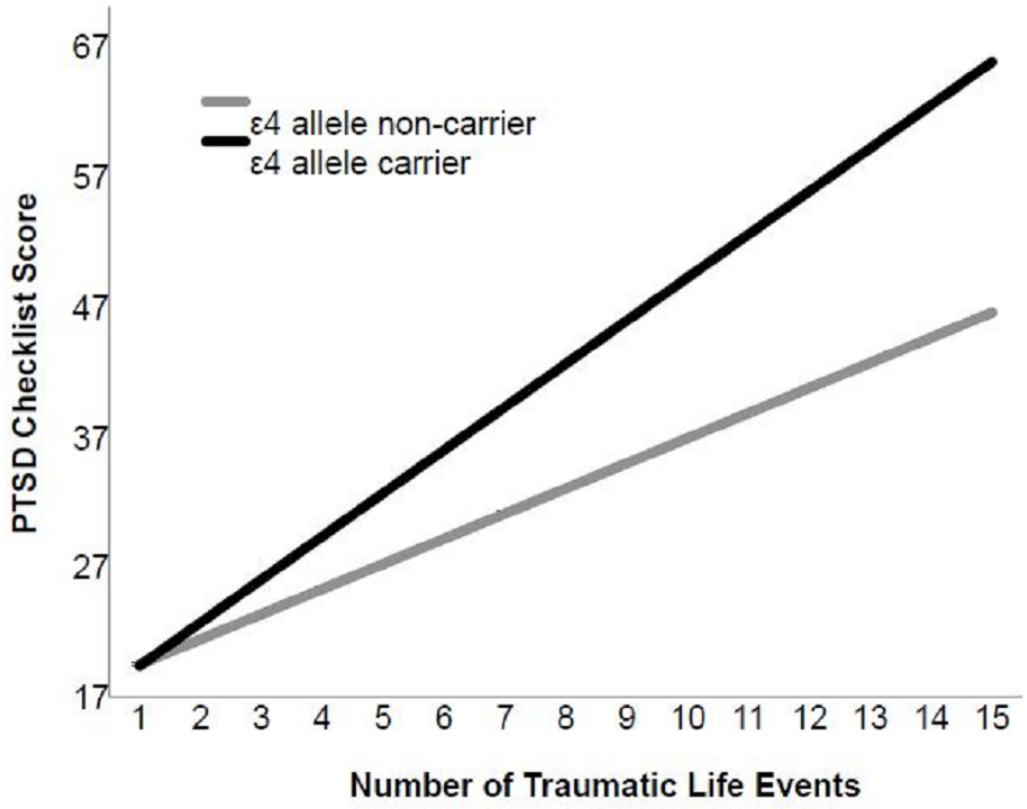

Figure 2. Prevalence of current PTSD in highly trauma-exposed veterans by ε4 carrier status and level of perceived social support in the main sample (*n* = 602).

Note. Current PTSD was identified as a score ≥50 on the DSM-IV version of the PTSD Checklist. Low, moderate, and high levels of perceived social support reflect tertiles of total scores on the 5-item version of the Medical Outcomes Study Social Support Scale.

*Statistically significantly greater prevalence than ε4 allele carriers with moderate and high levels of perceived social support, $\chi^2(2) = 9.83$, $P = .007$.