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Effect of the APOE ϵ 4 Allele and Combat Exposure on PTSD among Iraq/Afghanistan-Era Veterans

Nathan A. Kimbrel, PhD^{1,2,3,a}, Michael A. Hauser, PhD^{4,5}, Melanie Garrett, MS^{4,5}, Allison Ashley-Koch, PhD^{4,5}, Yutao Liu, PhD^{4,5}, Michelle F. Dennis, BA^{1,2,3}, Rebecca C. Klein, PhD^{1,2,3}, Veterans Affairs Mid-Atlantic Mental Illness Research, Education, and Clinical Center Workgroup², and Jean C. Beckham, PhD^{1,2,3}

¹Durham Veterans Affairs Medical Center, Durham, NC

²The VA Mid-Atlantic Mental Illness Research, Education, and Clinical Center, Durham, NC

³Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC

⁴Department of Medicine, Duke University Medical Center, Durham, NC

⁵Duke Center for Human Genetics, Durham, NC

Abstract

Background—The apolipoprotein E (APOE) ϵ 4 allele has been implicated in a range of neuropsychiatric conditions. The present research examined if the ϵ 4 allele of the APOE gene moderated the effect of combat exposure on posttraumatic stress disorder (PTSD) among Iraq/Afghanistan-era veterans.

Method—Participants included 765 non-Hispanic White (NHW) and 859 non-Hispanic Black (NHB) Iraq/Afghanistan-era veterans. A structured interview established psychiatric diagnoses. Combat exposure and PTSD symptom severity were assessed *via* self-report.

Results—The most common lifetime diagnoses were depression (39.2%), PTSD (38.4%), and alcohol dependence (24.38%). After correcting for multiple comparisons, no significant effects were observed on any of the outcomes among the NHW sample; however, within the NHB sample, significant gene x environment (GxE) interactions were observed for lifetime PTSD ($p = .0029$) and PTSD symptom severity ($p = .0009$). In each case, the APOE ϵ 4 allele had no effect on the outcomes when combat exposure was low; however, when combat exposure was high, an additive effect was observed such that ϵ 4 homozygotes exposed to high levels of combat reported the highest rates of PTSD (92%) and the worst symptom severity scores on the Davidson Trauma Scale ($M = 79.5$).

Conclusions—While preliminary, these findings suggest that the APOE ϵ 4 allele, in conjunction with exposure to high levels of combat exposure, may increase veterans' risk for developing PTSD.

^aCorrespondence concerning this article should be sent to: Dr. Nathan A. Kimbrel, Durham Veterans Affairs Medical Center, 508 Fulton Street, Durham, NC, 27705. Phone: (919) 286-0411, ext. 6759. Nathan.Kimbrel@va.gov.

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Keywords

APOE; genetic; PTSD; depression; veteran; comorbidity

Iraq/Afghanistan-era veterans are at increased risk for anxiety, mood, and substance-use disorders.^{1–3} One obvious explanation for the high rates of psychiatric problems and psychiatric comorbidity observed among returning veterans is combat exposure, which has been associated with a variety of problems, including PTSD, depression, and substance use.^{1, 4–6} While the impact of combat exposure on post-deployment psychiatric adjustment is evident, genetic factors are also likely to play a role.^{7–13} Indeed, it is estimated that approximately 30% of susceptibility to PTSD among Vietnam Veterans is due to genetic factors.⁷ Behavioral genetics studies further suggest that genetic factors may partially explain the co-occurrence of other disorders observed among veterans, such as the comorbidity observed between PTSD and depression.⁸

Much of the psychiatric genetics research conducted with veterans to date has involved candidate gene studies aimed at identifying the genetic basis of PTSD;^{9–12} however, the molecular genetic basis of PTSD has remained elusive, leading some researchers to propose the need for more gene x environment (GxE) investigations of PTSD.¹³ For example, while it is clear that trauma severity—particularly combat exposure severity—is associated with the development of PTSD,^{1, 4–6} there is also substantial variability in response to traumatic events,¹⁴ which suggests the possibility of GxE interactions.¹⁵ Moreover, a number of studies have already found evidence for GxE effects on PTSD.^{13, 16–20} There is also evidence for GxE effects on other closely-related disorders, such as other anxiety disorders, depression, and alcohol use-disorders.^{21–24} To date, however, there has been only limited research on whether the apolipoprotein E (APOE) gene might moderate the effect of trauma exposure on PTSD and other closely-related disorders.^{20, 25}

The human APOE gene contains three polymorphic alleles, $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$, that are estimated to have worldwide frequencies of, 8.4%, 77.9% and 13.7%, respectively.²⁶ Apolipoprotein E (apoE) supports injury repair in the brain by transporting cholesterol and other lipids to neurons; however, the $\epsilon 4$ allele of the APOE gene is associated with a wide range of neurological problems, including apoptosis, cortical atrophy, abnormalities in the hippocampus, inflammation, increased amyloid- β (A β) peptide aggregation, decreased lipid and glucose metabolism, and decreased neurogenesis.^{26–27} The $\epsilon 4$ allele is also associated with cardiovascular disease, difficulty recovering from traumatic brain injuries (TBI), and Alzheimer disease (AD).^{26–31} Most notable are the additive genetic effects observed for the APOE $\epsilon 4$ allele on risk for AD. For example, among non-Hispanic Whites (NHW), the odds ratio (OR) of developing AD is 2.6 for $\epsilon 2/\epsilon 4$, 3.2 for $\epsilon 3/\epsilon 4$, and 14.9 among $\epsilon 4/\epsilon 4$ homozygotes relative to $\epsilon 3/\epsilon 3$ homozygotes.²⁶ Age of onset for AD is also affected by APOE $\epsilon 4$ in a dose-dependent manner.²⁶

These findings, in conjunction with prior research suggesting an increased risk for dementia among veterans with PTSD,³² recently lead Lyons and colleagues to examine whether the $\epsilon 4$ allele of the APOE gene might moderate susceptibility to PTSD in a sample of predominantly NHW male Vietnam-era veterans ($N = 172$).²⁰ Consistent with their

hypothesis, they found that $\epsilon 4$ carriers who scored highly on a self-report measure of combat exposure were significantly more likely to have PTSD symptoms and to meet criteria for PTSD.²⁰ While promising, the conclusions that can be drawn from this study are limited by its relatively small sample size, which prevented the authors from examining the potential additive effects of $\epsilon 4$ on PTSD.

An additional concern relates to disparate findings between this study and other studies on APOE and PTSD. The first such study examined the relationship between APOE genotype and PTSD symptoms among 54 male NHW combat veterans, all of whom met criteria for combat-related PTSD.³³ Carriers of the $\epsilon 2$ allele—which is associated with decreased risk for AD²⁶—reported more re-experiencing symptoms and worse memory functioning than the rest of the sample; however, the findings from this study are also limited by the small sample size and the fact that all of the participants met criteria for PTSD.

A more recent study examined the relationship between APOE, PTSD, and alcohol use in Korean veterans of the Vietnam War.²⁵ Absence of the $\epsilon 2$ allele was associated with decreased risk for PTSD in this study after accounting for combat exposure. In addition, a significant interaction between APOE $\epsilon 2$ and harmful drinking was observed, such that the $\epsilon 2$ non-carriers with harmful drinking were more likely to have PTSD compared with $\epsilon 2$ non-carriers without harmful drinking. While novel, this study was also limited by its small sample size ($N = 256$) and the small number of $\epsilon 4$ homozygotes present ($n = 3$).

Hypotheses

Based on the recent findings from Lyons et al.²⁰ as well as prior research demonstrating additive effects for $\epsilon 4$ on AD,²⁶ we hypothesized that the $\epsilon 4$ allele would moderate the effect of combat exposure on PTSD in an additive fashion, such that $\epsilon 4$ homozygotes exposed to high levels of combat would exhibit the highest rate of PTSD and have the worst symptom severity. In addition, given previous findings suggesting that much of the comorbidity observed between PTSD and other psychiatric disorders is due to genetic factors⁸ as well as evidence for GxE effects on other closely-related disorders, such as other anxiety disorders, depression, and alcohol use-disorders,^{21–24} we further hypothesized that the APOE $\epsilon 4$ x combat interaction would be associated with psychiatric comorbidity in general, such that $\epsilon 4$ homozygotes exposed to high levels of combat would also exhibit the highest overall rates of psychiatric comorbidity.

Methods

Participants

Participants were drawn from an ongoing multi-site research study known as the Veterans Affairs (VA) Mid-Atlantic Mental Illness Research, Education and Clinical Center (MIRECC) Repository. To be eligible, participants had to have served in the United States military after September 11, 2001. Additional inclusion criteria for the current analyses included: (1) being either a NHW or non-Hispanic Black (NHB) Iraq/Afghanistan-era veteran; (2) having data available regarding level of combat exposure; (3) completion of the diagnostic interview; and (4) being genotyped for APOE. The final sample of participants

(total $N = 1624$) included 765 NHW and 859 NHB Iraq/Afghanistan-era veterans. Note that the current analyses were restricted to NHB and NHW veterans because they represented the two largest subgroups of participants (1624/1686 or 96.3%) with genetic data available for analysis from the Repository at the time of the study. The final sample was predominantly male (79.5%), although females were also well-represented (20.5%). The majority of participants had served in Iraq (82.5%). A substantial proportion had also served in Afghanistan (49.8%). Approximately 41.6% of the sample had served in both Iraq and Afghanistan.

Procedures

Participants were recruited through fliers, advertisements, VA clinic referrals, and invitation letters from four VA Medical Centers located in the mid-Atlantic region of the United States. Approval was obtained from each site's Institutional Review Board (IRB) prior to data collection. After a complete description of the study was provided to participants, written informed consent was obtained. Following informed consent procedures, a structured diagnostic interview was administered to participants along with a battery of self-report measures. A peripheral blood sample was obtained through venipuncture.

Genotyping

Genomic DNA was extracted from the blood samples using standard salting techniques (Gentra, Minneapolis, MN, USA). APOE genotypes for rs429358 and rs7412 were determined with TaqMan-based allelic discrimination assays by use of Assays-On-Demand products. Products were run on the ViiA7 Realtime PCR system with 384-well block according to the standard protocols from the manufacturer (Applied Biosystems, Foster City, CA).³⁴ Genotype frequencies for the NHB sample ($n = 859$) were as follows: $\epsilon 2/\epsilon 2$ ($n = 6$), $\epsilon 2/\epsilon 3$ ($n = 117$), $\epsilon 3/\epsilon 3$ ($n = 414$), $\epsilon 4/\epsilon 2$ ($n = 33$), $\epsilon 4/\epsilon 3$ ($n = 254$), and $\epsilon 4/\epsilon 4$ ($n = 35$). Genotype frequencies for the NHW sample ($n = 765$) were as follows: $\epsilon 2/\epsilon 2$ ($n = 8$), $\epsilon 2/\epsilon 3$ ($n = 89$), $\epsilon 3/\epsilon 3$ ($n = 459$), $\epsilon 4/\epsilon 2$ ($n = 16$), $\epsilon 4/\epsilon 3$ ($n = 175$), and $\epsilon 4/\epsilon 4$ ($n = 18$). Thus, there were approximately twice as many $\epsilon 4$ homozygotes among the NHB sample as in the NHW sample. Neither distribution varied from Hardy-Weinberg equilibrium (p 's $> .05$).

Measures

Trained clinical interviewers administered the *Structured Clinical Interview for DSM-IV-TR Axis I Disorders* (SCID-I)³⁵ to determine psychiatric diagnoses. Reliability among clinical interviewers ($N = 22$) scoring seven SCID-I training videos was excellent for both current and lifetime diagnoses (Fleiss' kappa = 0.94). For the purposes of the current analyses, lifetime mood (depression, bipolar I, bipolar II), anxiety (PTSD, panic disorder, social anxiety disorder, obsessive-compulsive disorder, specific phobia), and substance use disorders (alcohol, sedatives, cannabis, stimulants, opioid, cocaine, hallucinogens) were summed to create a lifetime psychiatric comorbidity variable. Psychotic (schizophrenia lifetime prevalence = 0.2%) and eating disorders (anorexia lifetime prevalence = 0.3%; bulimia lifetime prevalence = 0.3%) were excluded from the analyses due to low base rates. On average, participants had 1.5 lifetime psychiatric disorders ($SD = 1.3$; range = 0 – 9). The

most common diagnoses were major depression (39.2%), PTSD (38.4%), and alcohol dependence (24.4%).

The *Combat Exposure Scale (CES)*⁶ is a brief self-report measure used to assess combat exposure. The scoring procedures outlined by Keane et al.⁶ were followed in the current study. The mean score on the CES was 11.4 ($SD = 10.5$; $Range = 0-40$). To maximize interpretability of the findings, a median split was used to classify level of combat exposure as either high or low, such that scores from 0 to 5 were recoded as 0 (low) and scores from 6 to 40 were recoded as 1 (high). Internal consistency for the CES was good ($\alpha = .86$).

The *Davidson Trauma Scale (DTS)*³⁶ was used to assess PTSD symptom severity. It contains 34 items that allow participants to rate each of the 17 DSM-IV-TR PTSD symptoms on frequency and severity. The full range of possible DTS scores was observed ($Range = 0-136$; $M = 39.4$; $SD = 39.1$). Internal consistency was excellent ($\alpha = .98$).

Data Analysis Plan

The NHW and NHB samples were examined separately to help protect against potential population stratification effects. Binary logistic regression was used to examine the effects of the APOE $\epsilon 4$ allele and combat exposure on PTSD diagnosis. Due to small cell counts for higher numbers of psychiatric disorders, number of psychiatric disorders was truncated at 3. Ordinal logistic regression was used to examine the relationship between the APOE $\epsilon 4$ allele and combat exposure on number of psychiatric disorders (0, 1, 2 or 3), whereas linear regression was utilized to study the relationship between the APOE $\epsilon 4$ allele, combat exposure, and PTSD symptom severity, as determined by the DTS. For each model, the main effects of APOE and combat exposure were entered into the model along with the interaction term. An additive genetic model was employed and therefore APOE was considered continuously in all of the analyses (0, 1 or 2 copies of the $\epsilon 4$ allele). Contrasts were specified within each model to inspect the relationship between APOE $\epsilon 4$ and the outcome at each level of combat exposure; $CES < 6$ was considered to be low combat exposure and $CES \geq 6$ was considered to be high combat exposure. Because a total of three hypotheses were tested in two different samples (6 total tests), a Bonferroni correction was used and alpha was set at 0.0083. Statistical tests were performed using SAS version 9.2 (SAS Systems, Cary, NC).

Results

As can be seen in Table 1, no significant GxE effects were observed within the NHW sample. In contrast, significant GxE effects were observed for all three of the main outcomes examined in the NHB sample (all p 's < 0.0083). A significant interaction between APOE and combat exposure was observed for lifetime PTSD diagnosis ($p = 0.0029$). For each additional $\epsilon 4$ allele, the odds of having a lifetime PTSD diagnosis increased by 1.61, but only among those with high combat exposure ($p = .0077$). The rates of lifetime PTSD among the high combat exposure group were 49.3% for participants with no $\epsilon 4$ alleles, 56.4% for those with one $\epsilon 4$ allele, and 92.3% for those with two $\epsilon 4$ alleles (Figure 1). APOE and combat exposure also interacted to predict current PTSD symptom severity ($p = 0.0009$). Again, as the number of $\epsilon 4$ alleles increased, the mean severity score on the DTS

increased by 10.25 points, but only among those with high combat exposure ($p = .0011$, Figure 2).

Finally, APOE and combat exposure were found to also interact to predict lifetime psychiatric comorbidity ($p = 0.0065$) among NHB veterans, such that the odds of having a greater number of lifetime psychiatric disorders increased by 1.55 for each additional $\epsilon 4$ allele, but only among those with high combat exposure ($p = .0053$, Figure 3). To determine if the latter finding was being driven by the presence or absence of a PTSD diagnosis, a post-hoc analysis was conducted in which PTSD diagnosis was removed from the calculation of the lifetime psychiatric comorbidity score. The interaction term continued to be statistically significant in this follow-up analysis ($p = .0202$). In addition, contrasts indicated that the odds of having a greater number of lifetime psychiatric disorders other than PTSD increased by 1.50 (1.10, 2.03) with each additional $\epsilon 4$ allele, but only among those with high combat exposure ($p = .0098$). When this analysis was repeated with lifetime PTSD diagnosis included as a covariate, the interaction term was no longer significant ($p = .1853$). However, examination of the contrasts revealed a similar, albeit non-significant, pattern as the previous models. For example, among those with high combat exposure, the odds of having a greater number of lifetime psychiatric disorders other than PTSD increased by 1.30 (0.96, 1.78, $p = .0925$) with each additional $\epsilon 4$ allele. Notably, more than half (53.8%) of $\epsilon 4$ homozygotes with high combat exposure met criteria for 3 or more disorders other than PTSD, whereas only 11.2% of non- $\epsilon 4$ carriers and 12.8% of $\epsilon 4$ heterozygotes exposed to high combat had three or more disorders other than PTSD.

Discussion

The present findings provide mixed support for the hypothesis that the $\epsilon 4$ allele interacts with combat exposure in an additive manner to predict PTSD and psychiatric comorbidity among Iraq/Afghanistan-era veterans. Specifically, whereas significant GxE effects were observed among NHB Iraq/Afghanistan-era veterans for both PTSD and psychiatric comorbidity, no such effects were found among NHW veterans. Thus, the present study represents only a partial replication of the recent study by Lyons and colleagues,²⁰ which found that $\epsilon 4$ carriers (most of whom were NHW) who scored highly on a self-report measure of combat exposure were significantly more likely to have PTSD symptoms and to meet criteria for PTSD than non- $\epsilon 4$ carriers exposed to similar levels of combat.²⁰

It is particularly interesting that the present study did not find an effect for APOE among the NHW sample, but did find the hypothesized effect among the NHB sample. One potential explanation for these disparate findings is that whereas Lyons et al.²⁰ tested a dominant genetic model, the present study was primarily interested in testing for additive genetic effects for APOE on PTSD risk because of previous research indicating strong additive effects for the $\epsilon 4$ allele on AD.²⁶ There were also only about half as many $\epsilon 4$ homozygotes in the NHW sample than in the NHB sample in the present study, which may have limited our power to some degree to adequately test for an additive interaction effect within this sample. However, follow-up post-hoc analyses revealed that the hypothesized interaction effects were also not observed among the NHW sample when dominant or recessive models were used, whereas statistically significant interactions continued to be observed among the

NHB sample when dominant and recessive models were tested. As a result, it appears that the discrepant findings in the current study are unlikely to simply be due to the type of genetic model that was tested. Instead, these differences appear to be largely driven by race. Thus, it is clear that additional research on the association between APOE $\epsilon 4$ genotype, combat exposure, and PTSD with large and diverse samples of veterans is needed.

To our knowledge, the present research is also the first study to examine the interactive effects of APOE and combat exposure on psychiatric comorbidity. Consistent with our hypothesis, among the NHB sample, $\epsilon 4$ homozygotes with high levels of combat exposure reported significantly more lifetime psychiatric disorders than other veterans exposed to similarly high levels of combat (Figure 3). In contrast, no such effects were observed among the NHW sample. While preliminary, these findings suggest that the APOE $\epsilon 4$ allele, in conjunction with exposure to high levels of combat exposure, might also contribute to higher levels of psychiatric comorbidity among NHB veterans; however, post-hoc analyses revealed that the effect of the APOE x combat exposure interaction on psychiatric comorbidity was no longer significant when PTSD was included as a covariate in the model. Thus, it is likely that this effect was primarily due to the interactive effects of APOE and combat on PTSD. In addition, given that this finding was not observed within NHW sample, this finding should also be considered preliminary until it is replicated in another sample.

While the findings from the present research are of interest, they are unable to speak to the precise mechanisms by which APOE might influence the effect of combat exposure on PTSD and other psychiatric disorders among NHB veterans; however, one potential explanation for our findings is that the APOE $\epsilon 4$ allele may negatively impact neuronal recovery from the chronic stress associated with combat exposure.²⁰ Such an explanation would be in keeping with APOE's known role in neuronal repair^{20, 26–28} as well as prior research demonstrating that the APOE $\epsilon 4$ allele is associated with poor recovery from neuronal insult.³⁷ Such an explanation would also be in keeping with the extensive literature that suggests that prolonged stress leads to prolonged release of glucocorticoids which can, in turn, lead to hippocampal atrophy.³⁸ There is also recent evidence that APOE may interact with psychosocial factors to influence cognitive function.³⁹ Thus, one potential explanation for the present findings is that NHB veterans who carry the $\epsilon 4$ allele are at greater risk for the development of PTSD and other neuropsychiatric disorders following exposure to high levels of combat because they have a reduced capacity to recover from the prolonged glucocorticoid release that would be presumably associated with exposure to high levels of combat; however, additional research is needed to explicitly test this hypothesis.

Study Limitations and Future Directions

The current study had several limitations that should be noted when interpreting the data. The first concerns our method of trauma assessment. In the present study, we focused on the effects of combat-related trauma. Thus, it is unclear the degree to which the present findings might translate to other samples with other types of traumatic experiences (e.g., child abuse, domestic violence). We also did not consider TBI in the current analysis. Future studies should consider potential TBI x APOE effects on PTSD as well, as there is evidence that the $\epsilon 4$ allele is associated with difficulty recovering from TBI.³¹ In addition, although

psychiatric diagnoses were based on structured clinical interviews, level of combat exposure and PTSD symptom severity were based on self-report. Future studies should consider using more objective measures of trauma exposure and clinician-administered symptom severity scales. An additional limitation of the present research was that we were unable to differentiate between lifetime disorders with onset before and after combat exposure due to the manner in which the data were collected and coded in our databases. As a result, we are unable to rule out the possibility of reverse causality. A final limitation of the present study was that three different statistical approaches (binary logistic regression, ordinal logistic regression, and linear regression) were used to test the hypotheses. A consequence of this approach is that different statistical approaches were used to model the interactions. Specifically, whereas the logistic models tested for supra-multiplicative interactions, the linear model tested for a supra-additive interaction.

Summary and Conclusions

In summary, the findings from the present research provide mixed support for the hypothesis that the $\epsilon 4$ allele of the APOE gene interacts with combat exposure in an additive manner to predict PTSD and psychiatric comorbidity among Iraq/Afghanistan-era veterans. Whereas no significant GxE effects were observed among NHW veterans, significant GxE effects were observed for lifetime PTSD diagnosis, PTSD symptom severity, and lifetime psychiatric comorbidity among NHB veterans. In each case, the APOE $\epsilon 4$ allele had no effect on the outcomes when combat exposure was low; however, when combat exposure was high, an additive effect was observed such that $\epsilon 4$ homozygotes exposed to high levels of combat reported the highest rates of PTSD, the most psychiatric comorbidity, and the worst symptom severity. Given that the hypothesized effects were only observed in the NHB sample and not in the NHW sample, these findings should be considered preliminary until they are replicated in an independent sample.

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The VA Mid-Atlantic MIRECC workgroup for this publication includes: Mira Brancu, Patrick S. Calhoun, Eric B. Elbogen, John A. Fairbank, Jeffrey M. Hoerle, Kimberly T. Green, Harold S. Kudler, Christine E. Marx, Scott D. Moore, Rajendra A. Morey, Jennifer C. Naylor, Jennifer J. Runnals, Larry A. Tupler, Richard D. Weiner and Elizabeth E. Van Voorhees from the Durham (NC) VA Medical Center; Marinell Miller-Mumford from the Hampton (Va.) VA Medical Center; Scott D. McDonald and Treven C. Pickett from the Richmond (Va.) VA Medical Center; Robin A. Hurley, Jared Rowland, Katherine H. Taber and Ruth E. Yoash-Gantz from the Salisbury (NC) VA Medical Center.

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Figure 1.

Plot of the APOE x combat exposure interaction on lifetime PTSD diagnosis ($p = .0029$) among the non-Hispanic Black (NHB) sample ($n = 859$). For each additional $\epsilon 4$ allele, the odds of having lifetime PTSD increased by 1.61, but only among those with high combat exposure ($p = 0.0077$).

Figure 2.

Plot of the APOE x combat exposure interaction on PTSD symptom severity ($p = 0.0009$) among the non-Hispanic Black (NHB) sample ($n = 859$). As the number of $\epsilon 4$ alleles increased, the mean severity score on the Davidson Trauma Scale increased by 10.25 points, but only among those with high combat exposure ($p = 0.0011$).

Figure 3.

Plot of the APOE x combat exposure interaction effect on lifetime psychiatric comorbidity ($p = 0.0065$) among the non-Hispanic Black (NHB) sample ($n = 859$). For each additional $\epsilon 4$ allele, the odds of having a greater number of lifetime psychiatric disorders increases by 1.55, but only among those with high combat exposure ($p = 0.0053$).

Table 1
Summary of the APOE x Combat Exposure Interaction Effects Observed among Iraq/Afghanistan-Era Veterans

Non-Hispanic White (NHW) Iraq/Afghanistan-Era Veterans (N = 765)					
Outcome Variable	APOE* CES <i>p</i> -value	CES level	Odds Ratio/Beta*	95% Confidence Interval	Contrast <i>p</i> -value
Lifetime PTSD	0.4532				
		<6	1.22	0.65, 2.29	0.5310
		6	0.93	0.66, 1.31	0.6761
Number of Lifetime Psychiatric Disorders	0.6952				
		<6	1.12	0.72, 1.73	0.6200
		6	1.00	0.74, 1.36	0.9799
PTSD Symptom Severity	0.8246				
		<6	2.74	-6.41, 11.90	0.5553
		6	1.49	-4.80, 7.78	0.6416
Non-Hispanic Black (NHB) Iraq/Afghanistan-Era Veterans (N = 859)					
Outcome Variable	APOE* CES <i>p</i> -value	CES level	Odds Ratio/Beta*	95% Confidence Interval	Contrast <i>p</i> -value
Lifetime PTSD	0.0029 [†]				
		<6	0.67	0.42, 1.06	0.0867
		6	1.61	1.13, 2.28	0.0077
Number of Lifetime Psychiatric Disorders	0.0065 [†]				
		<6	0.85	0.63, 1.15	0.2963
		6	1.55	1.14, 2.11	0.0053
PTSD Symptom Severity	0.0009 [†]				
		<6	-4.22	-10.13, 1.68	0.1601
		6	10.25	4.09, 16.41	0.0011

[†]Meets Bonferroni correction

* Odds Ratio for categorical outcomes; beta for continuous outcome.