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**BRIEF COMMUNICATION**

# Apolipoprotein E (APOE) ϵ4 Allele Is Associated with Increased Symptom Reporting Following Sports Concussion

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**Abstract**

Exploring the relationship between genetic factors and outcome following brain injury has received increased attention in recent years. However, few studies have evaluated the influence of genes on specific sequelae of concussion. The purpose of this study was to determine how the ϵ4 allele of the apolipoprotein E (APOE) gene influences symptom expression following sports-related concussion. Participants included 42 collegiate athletes who underwent neuropsychological testing, including completion of the Post-Concussion Symptom Scale (PCSS), within 3 months after sustaining a concussion (73.8% were evaluated within 1 week). Athletes provided buccal samples that were analyzed to determine the make-up of their APOE genotype. Dependent variables included a total symptom score and four symptom clusters derived from the PCSS. Mann-Whitney *U* tests showed higher scores reported by athletes with the ϵ4 allele compared to those without it on the total symptom score and the physical and cognitive symptom clusters. Furthermore, logistic regression showed that the ϵ4 allele independently predicted those athletes who reported physical and cognitive symptoms following concussion. These findings illustrate that ϵ4+ athletes report greater symptomatology post-concussion than ϵ4– athletes, suggesting that the ϵ4 genotype may confer risk for poorer post-concussion outcome. (*JINS*, 2016, *22*, 89–94)

**Keywords:** APOE gene, Genetics, Mild traumatic brain injury, Post-concussion symptoms, Sports injuries, Collegiate athletes

## INTRODUCTION

Several theories have been proposed to explain the heterogeneity in recovery rates and outcome following traumatic brain injury (TBI). Given the complexity of the sequelae of these injuries, there does not yet appear to be a ready explanation that can account for the widespread variability in outcome observed after TBI. However, genetic factors may hold clues. There is growing evidence that the apolipoprotein E (APOE) gene may be linked to outcome following brain injury (Dardiotis et al., 2010; Jordan, 2007). APOE is a protein that is predominantly involved in the transportation of lipid molecules across tissues such as the central nervous system. A central function of APOE is to maintain and restore neuronal membranes and tissue after they have been compromised (Dardiotis et al., 2010). The APOE gene is polymorphic, meaning that it is comprised of three primary alleles (ϵ2, ϵ3, and ϵ4; Eisenberg, Kuzawa, & Hayes, 2010). Possession of at least one ϵ4 allele has been associated with unfavorable outcome following brain injury (for a review, see Dardiotis et al., 2010).

To date, many efforts have focused on establishing associations between the ϵ4 allele and *global* outcomes following TBI (Chiang, Chang, & Hu, 2003; Liaquat, Dunn, Nicoll, Teasdale, & Norrie, 2002; Teasdale, Murray, & Nicoll, 2005). However, few studies have examined more precise measures of outcome. Given that physical, cognitive, and affective difficulties have consistently been reported following mild TBI (Lovell et al., 2006; Silver, McAllister, & Arciniegas, 2009), genetic factors could be illuminating.

Studies that have evaluated the relationship between the APOE gene and symptom reporting following TBI have been mixed. Ariza et al. (2006) examined post-concussion symptoms in a sample of patients with *moderate to severe* TBI and found that ϵ4+ patients endorsed more symptoms at 6 months post-injury compared to ϵ4- patients. In contrast to Ariza and colleagues' (2006) findings, Chamelian, Reis, and Feinstein (2004) reported no symptom score differences between ϵ4+ and ϵ4- participants with *mild to moderate* TBI at 6 months post-injury. Moran et al. (2009) also evaluated

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the relationship between the ϵ4 allele and post-concussion symptom reporting in children between the ages of 8 and 15 who had sustained *mild* TBIs. Symptoms were evaluated at "baseline" (within 2 weeks following the injury), and at 3 and 12 months post-injury. Moran et al. (2009) reported no group differences at any of the time points assessed post-injury.

This brief review shows that the current literature regarding the APOE gene and post-concussion symptom reporting is still in its infancy. Thus far, heterogeneous samples have been studied, making it difficult to draw conclusions about the precise role that the APOE gene has on symptom reporting outcome. Furthermore, examination of genetic factors on specific outcomes following sports-related concussions, in particular, has largely gone unexplored. With these considerations in mind, the main objective of this study was to evaluate the relationship between the APOE ϵ4 allele and symptom reporting patterns following sports-related concussion in a sample of collegiate athletes. It was hypothesized that participants with the ϵ4 allele would show greater symptomatology following concussion than participants without the ϵ4 allele.

## METHOD

### Participants and Procedures

Participants included 42 college athletes who participated in a clinically based university sports-concussion management program. All participants in the present study sustained a mild TBI, or concussion, as defined by the following criteria: loss of consciousness lasting 30 min or less, loss of memory for events immediately before or after the injury lasting less than 24 hr, or any alteration in mental state at the time of injury (i.e., disorientation, confusion, etc.; Ruff, Iverson, Barth, Bush, & Broshek, 2009). Team physicians determined TBI status, and concussed athletes were referred for neuropsychological testing as soon as possible following the injury.

Study participants were selected from a sample of athletes who had sustained concussions between 2002 and 2014 and were subsequently referred for post-concussion neuropsychological testing. Briefly, to be included in the study, participants must have sustained a mild TBI or concussion, according to the criteria described above, *and* completed post-concussion testing within three months following their injury. The 3-month time frame was chosen because we were interested in examining the relationship between genetic factors and relatively acute outcome following concussion, while maintaining a sufficient sample size. Additionally, concussed athletes must have provided a buccal (cheek cell) sample that was successfully analyzed for their APOE genotype. Our clinically based concussion management program was initiated in 2002, but the genetics arm of the program did not begin until 2011. At the time of participant selection, 34 athletes had been recruited prospectively (i.e., at the time of their post-concussion assessment) for the genetics portion of the study, and another 31 athletes who had previously participated in post-concussion testing were contacted by phone or email and offered participation in the genetics portion of the study. Among these 31 participants, 18 declined participation due to lack of interest in participating in a follow-up study, and 13 consented; however, 5 of these 13 were eventually excluded because they had completed post-concussion testing more than 3 months after their concussive injury.

The final sample ($n = 42$) was comprised of mostly male athletes (83.3%) who had completed, on average, 13.5 years ($SD = 1.3$) of education. The average time tested post-injury was 9.8 days ($SD = 14.6$; Mdn = 4.0; Range = 0–72 days), and 73.8% of the athletes were tested within the *first week* following their concussion. All participants had sustained relatively mild concussions, as only 14.3% of the entire sample reported loss of consciousness.

This study was approved by our university's institutional review board, and eligible participants signed an informed consent form before participation in research.

### Laboratory Procedures

DNA extraction was performed on buccal samples using methods and materials as described by Freeman et al. (2003). The APOE genotype for each participant was determined by using two Taqman® Single Nucleotide Polymorphism (SNP) assays for the SNPs APOE112 and APOE158. The procedures outlined in Christensen et al. (2008) and Ingelsson et al. (2003) were used to define the different genotypes. Genotyping results could be any pair of ϵ2, ϵ3, and ϵ4 alleles.

### Measures

The Post-Concussion Symptom Scale (PCSS) was used to evaluate athletes' self-reported symptoms following concussion. The PCSS (Lovell et al., 2006) is a 22-item measure designed to evaluate the severity of commonly experienced post-concussion symptoms. Athletes are asked to rate their *current* symptoms using a 0–6 scale, where 0 represents no symptoms and 6 represents severe symptoms. The PCSS is administered through the ImPACT computer program, and all athletes individually completed the PCSS under the supervision of a trained doctoral student or undergraduate research assistant. The internal consistency of the PCSS is excellent, ranging from 0.89 to 0.94 (Lovell et al., 2006).

The PCSS was used to calculate several symptom-related outcome indices, including a total symptom score and four symptom clusters. Briefly, the total symptom score was calculated by adding the ratings of all 22 items on the PCSS (higher scores represent greater symptoms), and the symptom clusters were derived from previous factor analytic work (Merritt & Arnett, 2014) and were calculated as follows: physical symptoms (7 items; $\alpha = .85$; possible range = 0–42), cognitive symptoms (4 items; $\alpha = .94$; possible range = 0–24), affective

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**Table 1.** Sample characteristics by ϵ4 allele group.

| | Positive ϵ4 allele group ($N$ = 15) | | Negative ϵ4 allele group ($N$ = 27) | | |
|---|---|---|---|---|---|
| Variables | *M* | *SD* | *M* | *SD* | *p*-Value |
| Age | 19.93 | 1.39 | 20.00 | 1.59 | .893 |
| Education | 13.87 | 1.41 | 13.37 | 1.21 | .237 |
| Days tested post-injury | 7.67 | 11.64 | 11.04[a] | 16.08 | .480 |
| | *N* | % | *N* | % | *p*-Value |
| Sex | | | | | |
| Male | 12 | 80.0 | 23 | 85.2 | |
| Female | 3 | 20.0 | 4 | 14.8 | .686 |
| Ethnicity | | | | | |
| Caucasian | 10 | 66.7 | 20 | 74.1 | |
| Other | 5 | 33.3 | 7 | 25.9 | .726 |
| Concussion history | | | | | |
| 0 | 5 | 33.3 | 9 | 33.3 | |
| 1 | 6 | 40.0 | 10 | 37.0 | |
| 2 or more | 4 | 26.7 | 8 | 29.7 | .974 |
| History of ADHD | | | | | |
| Yes | 2 | 13.3 | 1 | 3.7 | |
| No | 13 | 86.7 | 26 | 96.3 | .287 |
| Sport[b] | | | | | |
| Contact | 9 | 60.0 | 21 | 77.8 | |
| Limited contact | 6 | 40.0 | 6 | 22.2 | .292 |
| Loss of consciousness | | | | | |
| Yes | 3 | 20.0 | 3 | 11.1 | |
| No | 12 | 80.0 | 24 | 88.9 | .649 |
| Retrograde amnesia | | | | | |
| Yes | 3 | 20.0 | 3 | 11.1 | |
| No | 12 | 80.0 | 24 | 88.9 | .649 |
| Anterograde amnesia | | | | | |
| Yes | 5 | 33.3 | 13 | 48.1 | |
| No | 10 | 66.7 | 14 | 51.9 | .517 |

[a]There was an outlier in the negative ϵ4 allele group (one athlete was tested 72 days post-injury). When the outlier was removed, the results did not significantly change; thus, the outlier was used in the analyses.
[b]Contact sports include football, hockey, lacrosse, and rugby; limited contact sports include basketball, golf, and soccer.

symptoms (4 items; α = .76; possible range = 0–24), and sleep symptoms (4 items; α = .80; possible range = 0–24).

## RESULTS

### Descriptive Statistics

Participants were divided into two groups based on ϵ4 allele status: 15 athletes (35.7%) were ϵ4 positive and 27 (64.3%) were ϵ4 negative. Descriptive statistics, including basic demographic and injury severity variables, are presented in Table 1 by group. As indicated in the table, the allele groups were well-matched, as there were no significant differences between the two groups on any of the demographic or injury severity variables examined.

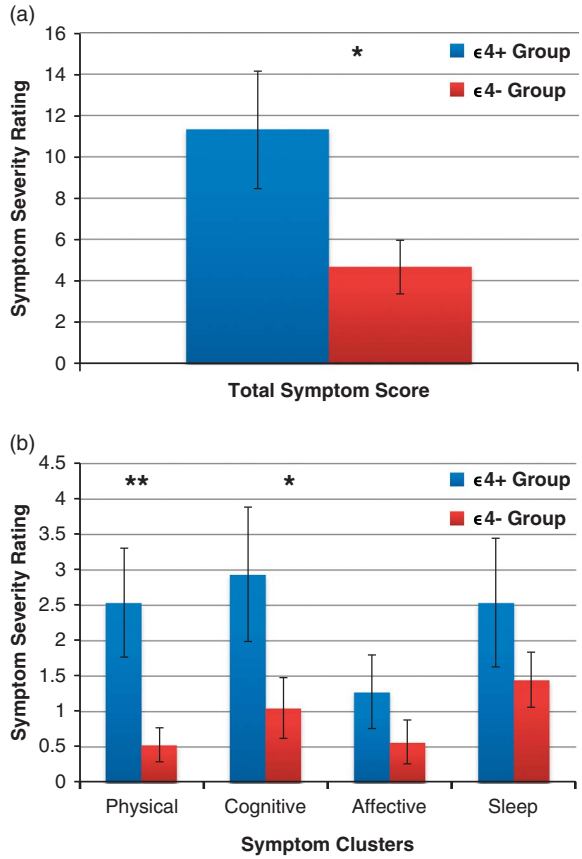


**Fig. 1.** Means and standard errors of each symptom variable are presented in the figure, according to ϵ4 allele group. Total symptom score comparisons are illustrated in Figure 1a and symptom cluster comparisons are illustrated in Figure 1b. The total symptom score is comprised of all 22 items on the PCSS, and the symptom clusters were derived from a previous factor analysis of the PCSS (Merritt & Arnett, 2014). $*p < .05$, $**p < .01$. Total symptom score: Cohen's $d = 0.73$, medium-large effect; physical symptom cluster: Cohen's $d = 0.87$, large effect; cognitive symptom cluster: Cohen's $d = 0.60$, medium effect.

### Symptom Reporting and ϵ4 Allele Status

Given that the post-concussion PCSS symptom scores were not normally distributed, non-parametric statistics were used to compare the various symptom indices across the two ϵ4 allele groups. Figure 1 displays the means and standard errors of each symptom variable by ϵ4 allele group. Mann-Whitney *U* tests showed that athletes with the APOE ϵ4 allele reported greater symptoms than athletes without the ϵ4 allele on all of the symptom indices evaluated, with significant differences found on the following indices: the PCSS total symptom score, the physical symptom cluster, and the cognitive symptom cluster (all *p* at least $< .05$; see Figure 1).

Logistic regression analyses were then used to further examine the relationship between ϵ4 allele status and post-concussion symptom reporting. Specifically, the physical and cognitive symptom clusters were each dichotomized into "symptoms present" *versus* "symptoms absent" groups, and each served as a criterion variable in separate logistic

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**Table 2.** Participants classified as "symptoms present" and "symptoms absent" by ϵ4 allele group

| Physical symptoms | | |
|---|---|---|
| ϵ4 Status | Symptoms absent | Symptoms present |
| ϵ4- | 21 | 6 |
| ϵ4+ | 6 | 9 |
| **Cognitive symptoms** | | |
| ϵ4 Status | Symptoms absent | Symptoms present |
| ϵ4- | 19 | 8 |
| ϵ4+ | 5 | 10 |

regressions. Symptom groups were calculated as follows: athletes with a physical symptom score of "0" were classified into the "symptoms absent" group ($n = 27$; 64.3%), and athletes with a physical symptom score of "≥1" were classified into the "symptoms present" group ($n = 15$; 35.7%). Similarly, athletes with a cognitive symptom score of "0" were classified into the "symptoms absent" group ($n = 24$; 57.1%), and athletes with a cognitive symptom score of "≥1" were classified into the "symptoms present" group ($n = 18$; 42.9%). Table 2 shows the breakdown of participants who were classified as "symptoms present" and "symptoms absent" by ϵ4 allele group for the physical and cognitive symptom clusters.

With respect to physical symptoms, ϵ4 allele status was a significant predictor of the "symptoms present" group, such that ϵ4+ athletes were more likely to endorse physical symptoms than ϵ4- athletes, $\chi^2(1, N = 45) = 5.95$, $p = .015$ (Nagelkerke's $R^2 = .18$; odds ratio = 5.25; 95% CI = 1.33–20.76). As for cognitive symptoms, ϵ4 allele status was also a significant predictor of the "symptoms present" group, such that ϵ4+ athletes were more likely to endorse cognitive symptoms than ϵ4– athletes, $\chi^2(1, N = 45) = 5.45$, $p = .020$ (Nagelkerke's $R^2 = .16$; odds ratio = 4.75; 95% CI = 1.23–18.41).

## DISCUSSION

Given that several previous studies have evaluated the relationship between the APOE ϵ4 allele and gross outcome following TBI, the main purpose of our study was to narrow the focus and evaluate whether there may be an association between the ϵ4 allele and more specific outcomes following TBI. To our knowledge, this is the first study to have specifically examined the relationship between the APOE ϵ4 allele and post-concussion symptom reporting patterns among concussed collegiate athletes. The PCSS was used as the primary outcome measure, and several symptom-related variables were derived from the PCSS, including a total symptom score and four symptom clusters (physical, cognitive, affective, and sleep). It was hypothesized that ϵ4 positive participants would show greater symptomatology following concussion as compared to ϵ4 negative participants, and the results largely supported our hypothesis. Specifically, ϵ4 positive athletes reported significantly more symptoms than ϵ4 negative athletes across the following symptom indices: the PCSS total symptom score, the physical symptom cluster, and the cognitive symptom cluster, indicating that ϵ4 positive participants may be at greater risk for experiencing poorer post-concussion outcomes.

When placing our findings within the context of the broader TBI literature, as noted previously, there are few studies available for comparison. Ariza et al. (2006) examined adult patients with moderate to severe TBI and reported that ϵ4+ patients reported greater symptoms than ϵ4– patients at 6 months post-injury. Findings from Ariza et al. (2006) are consistent with our results, as both studies indicate that APOE ϵ4 allele carriers show greater symptomatology after sustaining a brain injury than do non-ϵ4 allele carriers. However, in contrast to our findings and the results of Ariza et al. (2006), other studies have found no differences between ϵ4+ and ϵ4– patients with respect to symptom reporting when assessing patients with mild to moderate TBI (Chamelian et al., 2004; Moran et al., 2009).

When evaluating the above studies, considerable methodological differences are observed across the studies with regard to the sample studied (i.e., adult *vs*. child, mechanism of injury, severity of TBI), the timing of the post-injury assessment, and the method of evaluating post-concussion symptoms. These methodological differences likely contribute to the disparate findings that have resulted, and suggest a need for a more fine-tuned approach for evaluating the influence of genetic factors on outcome following TBI. For instance, given the proposed pathophysiological differences across mild, moderate, and severe TBI (Blennow, Hardy, & Zetterberg, 2012), it may be beneficial to examine these populations as unique cohorts to more precisely understand how genetics influence response to brain injury. Furthermore, the timing of the post-injury evaluation is another important variable that could impact conclusions. A major advantage to the current study was that our sample was relatively homogeneous—all participants were collegiate athletes with similar ages and levels of education, all had sustained concussions as a result of sports participation, and the majority of the sample was assessed within one week of sustaining a concussion. Thus, our findings extend current knowledge by illustrating how genetic factors impact relatively acute symptom expression following sports-related concussion.

In addition to examining symptom severity differences between ϵ4+ and ϵ4– athletes, we also evaluated the extent to which the ϵ4 allele could predict those individuals who specifically endorsed physical and cognitive symptoms post-concussion. Results showed that the ϵ4 allele significantly predicted the presence of both physical and cognitive symptoms. With respect to physical symptoms, the ϵ4 allele explained 18% of the variance; for cognitive symptoms, it explained 16% of the variance. Importantly, past research has suggested that several pre-morbid and injury-specific variables

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influence the presence and duration of post-concussion symptoms (Lange et al., 2013; Merritt & Arnett, 2014). Our findings suggest that, in addition to these variables, genetic factors play a significant role in post-concussion symptom reporting, and that both physical and cognitive symptoms may be especially susceptible to the effects of the ϵ4 allele.

One limitation of the present study is the small sample size. However, there is a precedent in the literature for conducting genetics-related studies using similar sample sizes (Bazarian, Zemlan, Mookerjee, & Stigbrand, 2006; Sundström et al., 2004). Another limitation concerns the generalizability of our findings. In the present study, we specifically focused on collegiate athletes who had sustained concussions, or mild TBIs; thus, our findings may be less generalizable to other populations such as adolescents or older adults, as well as to samples with more severe brain injuries. However, as discussed above, given the disparate findings that have resulted in the literature with respect to the APOE gene and outcome following brain injury, it is necessary to examine more homogeneous TBI samples (i.e., limit sample to a specific group who has sustained similar injury severities such as concussed athletes) so that we may develop a more nuanced understanding of such relationships. Furthermore, given the widespread interest and concern over the effects of sports-related concussions, it is thought that our findings will still be relevant and clinically meaningful to a broad population. Another limitation with respect to the generalizability of our findings is that our results may not be as applicable to athletes who do not have a history of concussion, as approximately two-thirds of the sample had at least one prior concussion. Finally, our study was restricted to the evaluation of self-reported sequelae of concussion. Future studies would benefit from not only evaluating self-reported symptoms, but to also assess the relationship between the ϵ4 allele and other measures of impairment following concussion.

Although these results will need to be replicated in a larger sample, our findings indicate that, compared to athletes without the ϵ4 allele, athletes with the ϵ4 allele have a propensity to report greater symptomatology post-concussion, particularly within the domain of physical and cognitive symptoms. Future studies examining the role of the ϵ4 allele in concussion outcome are warranted.

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## REFERENCES

Ariza, M., Pueyo, R., del M Matarín, M., Junqué, C., Mataró, M., Clemente, I., … Sahuquillo, J. (2006). Influence of APOE polymorphism on cognitive and behavioral outcome in moderate and severe traumatic brain injury. *Journal of Neurology, Neurosurgery, & Psychiatry*, *77*(10), 1191–1193.

Bazarian, J.J., Zemlan, F.P., Mookerjee, S., & Stigbrand, T. (2006). Serum S-100B and cleaved-tau are poor predictors of long-term outcome after mild traumatic brain injury. *Brain Injury*, *20*(7), 759–765.

Blennow, K., Hardy, J., & Zetterberg, H. (2012). The neuropathology and neurobiology of traumatic brain injury. *Neuron*, *76*(5), 886–899.

Chamelian, L., Reis, M., & Feinstein, A. (2004). Six-month recovery from mild to moderate traumatic brain injury: The role of APOE-epsilon4 allele. *Brain*, *127*(12), 2621–2628.

Chiang, M.-F., Chang, J.-G., & Hu, C.-J. (2003). Association between apolipoprotein E genotype and outcome of traumatic brain injury. *Acta Neurochirurgica*, *145*(8), 649–654.

Christensen, H., Batterham, P.J., Mackinnon, A.J., Jorm, A.F., Mack, H.A., Mather, K.A., … Easteal, S. (2008). The association of APOE genotype and cognitive decline in interaction with risk factors in a 65–69 year old community sample. *BMC Geriatrics*, *8*(1), 14–24.

Dardiotis, E., Fountas, K.N., Dardioti, M., Xiromerisiou, G., Kapsalaki, E., Tasiou, A., & Hadjigeorgiou, G.M. (2010). Genetic association studies in patients with traumatic brain injury. *Neurosurgical Focus*, *28*(1), E9:1–12.

Eisenberg, D.T.A., Kuzawa, C.W., & Hayes, M.G. (2010). Worldwide allele frequencies of the human apolipoprotein E gene: Climate, local adaptations, and evolutionary history. *American Journal of Physical Anthropology*, *143*(1), 100–111.

Freeman, B., Smith, N., Curtis, C., Huckett, L., Mill, J., & Craig, I.W. (2003). DNA from buccal swabs recruited by mail: Evaluation of storage effects on long-term stability and suitability for multiplex polymerase chain reaction genotyping. *Behavior Genetics*, *33*(1), 67–72.

Ingelsson, M., Shin, Y., Irizarry, M.C., Hyman, B.T., Lilius, L., Forsell, C., & Graff, C. (2003). Genotyping of apolipoprotein E: Comparative evaluation of different protocols. *Current Protocols in Human Genetics*, *Chapter 9*, Unit 9.14.

Jordan, B.D. (2007). Genetic influences on outcome following traumatic brain injury. *Neurochemical Research*, *32*(4-5), 905–915.

Lange, R.T., Brickell, T., French, L.M., Ivins, B., Bhagwat, A., Pancholi, S., & Iverson, G.L. (2013). Risk factors for postconcussion symptom reporting after traumatic brain injury in U.S. military service members. *Journal of Neurotrauma*, *30*(4), 237–246.

Liaquat, I., Dunn, L.T., Nicoll, J.A.R., Teasdale, G.M., & Norrie, J.D. (2002). Effect of apolipoprotein E genotype on hematoma volume after trauma. *Journal of Neurosurgery*, *96*(1), 90–96.

Lovell, M.R., Iverson, G.L., Collins, M.W., Podell, K., Johnston, K.M., Pardini, D., … Maroon, J.C. (2006). Measurement of symptoms following sports-related concussion: Reliability and normative data for the post-concussion scale. *Applied Neuropsychology*, *13*(3), 166–174.

Merritt, V.C., & Arnett, P.A. (2014). Premorbid predictors of postconcussion symptoms in collegiate athletes. *Journal of Clinical and Experimental Neuropsychology*, *36*(10), 1098–1111.

Moran, L.M., Taylor, H.G., Ganesalingam, K., Gastier-Foster, J.M., Frick, J., Bangert, B., … Wright, M. (2009). Apolipoprotein E4 as a predictor of outcomes in pediatric mild traumatic brain injury. *Journal of Neurotrauma*, *26*(9), 1489–1495.

Ruff, R.M., Iverson, G.L., Barth, J.T., Bush, S.S., & Broshek, D.K. (2009). Recommendations for diagnosing a mild traumatic brain injury: A National Academy of Neuropsychology education paper. *Archives of Clinical Neuropsychology*, *24*(1), 3–10.

Silver, J.M., McAllister, T.W., & Arciniegas, D. (2009). Depression and cognitive complaints following mild traumatic brain injury. *American Journal of Psychiatry*, *166*(6), 653–661.

Sundström, A., Marklund, P., Nilsson, L.G., Cruts, M., Adolfsson, R., Van Broeckhoven, C., & Nyberg, L. (2004). APOE influences on neuropsychological function after mild head injury: Within-person comparisons. *Neurology*, *62*(11), 1963–1966.

Teasdale, G.M., Murray, G.D., & Nicoll, J.A.R. (2005). The association between APOE ε4, age and outcome after head injury: A prospective cohort study. *Brain*, *128*(11), 2556–2561.