Apolipoprotein E4 as a Predictor of Outcomes in Pediatric Mild Traumatic Brain Injury

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Abstract

The $\epsilon 4$ allele of the apolipoprotein E (*APOE*) gene has been linked to negative outcomes among adults with traumatic brain injury (TBI) across the spectrum of severity, with preliminary evidence suggesting a similar pattern among children. This study investigated the relationship of the *APOE* $\epsilon 4$ allele to outcomes in children with mild TBI. Participants in this prospective, longitudinal study included 99 children with mild TBI between the ages of 8 and 15 recruited from consecutive admissions to Emergency Departments at two large children's hospitals. Outcomes were assessed acutely in the Emergency Department and at follow-ups at 2 weeks, 3 months, and 12 months post-injury. Among the 99 participants, 28 had at least one $\epsilon 4$ allele. Children with and without an $\epsilon 4$ allele did not differ demographically. Children with an $\epsilon 4$ allele were significantly more likely than those without an $\epsilon 4$ allele to have a Glasgow Coma Scale score of less than 15, but the groups did not differ on any other measures of injury severity. Those with an $\epsilon 4$ allele exhibited better performance than children without an $\epsilon 4$ allele on a test of constructional skill, but the groups did not differ on any other neuropsychological tests. Children with and without an $\epsilon 4$ allele also did not differ on measures of post-concussive symptoms. Overall, the findings suggest that the *APOE* $\epsilon 4$ allele is not consistently related to the outcomes of mild TBI in children.

Key words: APO E; neuropsychology; pediatric brain injury

Introduction

OF THE APPROXIMATELY 500,000 traumatic brain injuries (TBIs) that occur each year among children 14 years of age and younger (Bazarian et al., 2005), 80–90% are classified as mild (Kraus, 1995). The outcomes of mild TBI remain a topic of debate (Yeates and Taylor, 2005). Although previous research suggests that children with mild TBI do not consistently demonstrate deficits on standardized cognitive tests, they do display a variety of cognitive, somatic, emotional, and behavioral problems, often labeled post-concussive symptoms, that are more frequent, severe, and persistent than those reported by children with injuries not involving the head (Yeates et al., 2009).

One possible explanation for the inconsistent findings is that the effects of mild TBI are moderated by various factors, one of which may be genetics. A number of genes have been identified as potentially playing a role in the brain's response to injury (Jordan, 2007). For instance, the apolipoprotein E (*APOE*) gene codes for a lipid transporter protein expressed throughout the brain. The *APOE* gene has three alleles: $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$. Possession of the *APOE* $\epsilon 3$ allele appears to be neuroprotective, while possession of the $\epsilon 4$ allele is associated with deleterious health effects. In adults, the $\epsilon 4$ allele predicts poorer outcomes and increased mortality following ischemic stroke and cardiopulmonary arrest, as well as an earlier age of onset of Alzheimer's disease (Eichner et al., 2002; Higgins et al., 1997; Strittmatter and Roses, 1995). In children,

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possession of the $\epsilon 4$ allele is associated with higher risk of and increased impairment in cerebral palsy (Kuroda et al., 2007). The mechanism by which *APOE* is thought to influence recovery from brain injury is not entirely clear, but it has been implicated in beta amyloid accumulation, oxidative stress response, inflammatory responses, growth and branching of neurites, glial activation, and excitotoxicity (Jofre-Monseny et al., 2008; Laskowitz and Vitek, 2007; Lynch et al., 2001; Miyata and Smith, 1996; Wang et al., 2007).

APOE may also be related to the outcomes of TBI. The prior literature on *APOE* and TBI has focused largely on adults. Studies have suggested that possession of the *APOE* $\epsilon 4$ allele is associated with more severe injuries (Liaquat et al., 2002; Nicoll et al., 1995; Teasdale et al., 1997) and possibly with a greater risk of neurological deterioration (Jiang et al., 2006). However, a recent meta-analysis failed to find support for a relationship between possession of the $\epsilon 4$ allele and injury severity (Zhou et al., 2008). The relationship between the *APOE* $\epsilon 4$ allele and neurobehavioral outcomes is less clear. Some studies have found a negative influence of $\epsilon 4$ allele possession on memory, executive function, and fine motor control (Ariza et al., 2006; Crawford et al., 2002), and a recent meta-analysis showed a negative association with broad functional outcomes (Zhou et al., 2008). In contrast, other studies have not found a significant association with neuropsychological outcomes or rate of improvement over time (Chamelian, et al., 2004; Ponsford et al., 2007). One study even suggested that possession of the $\epsilon 4$ allele confers a beneficial effect on post-injury neuropsychological test performance (Han et al., 2007). Several studies have focused specifically on adults with mild TBI and obtained more consistent results, such that the presence of the *APOE* $\epsilon 4$ allele was associated with poorer neurobehavioral outcomes (Liberman et al., 2002; Sundström et al., 2004, 2007).

Research on the effects of *APOE* in pediatric TBI is extremely limited. Only two studies have been published to date, neither of which was specific to children with mild TBI. The first was a post-mortem study of 165 children with severe TBI, most of whom did not survive more than 4 days post-injury (Quinn et al., 2004). No differences were found between those with and without an $\epsilon 4$ allele on measures of injury severity (e.g., amount of ischemic damage, brain swelling). In the second study, Teasdale et al. (2005) collected data from close to 1000 participants of all ages and severities. They discovered a significant interaction between age, presence of the *APOE* $\epsilon 4$ allele, and poorer outcomes, as measured by the Glasgow Outcome Scale (GOS) (Jennett and Bond, 1975), such that younger individuals, especially those under the age of 15, showed greater susceptibility to the adverse effects of the $\epsilon 4$ allele than older individuals. Some unpublished data summarized by Blackman et al. (2005) suggested that, among children with moderate to severe TBI, those with the $\epsilon 4$ allele showed better outcomes than children without the allele. The authors suggest that, in children, possessing the $\epsilon 4$ allele may actually confer protection for the brain.

In summary, adults with TBI, even those with mild TBI, appear to be at risk for poorer outcomes if they possess the *APOE* $\epsilon 4$ allele, while no clear conclusions can be drawn regarding the relationships of the $\epsilon 4$ allele to outcomes for children with TBI. The current study aimed to elucidate the role of *APOE* in mild TBI in children. We hypothesized that, in children with mild TBI, the presence of the *APOE* $\epsilon 4$ allele would

be associated with more severe injuries, as well as poorer neuropsychological functioning and more post-concussive symptoms, particularly at earlier post-injury assessments.

Methods

Participants

Participants were recruited from the Emergency Departments at Nationwide Children's Hospital in Columbus, Ohio, and Rainbow Babies and Children's Hospital in Cleveland, Ohio. All children from 8 to 15 years of age who presented for evaluation of blunt head trauma were screened to determine if they met criteria for participation. Children were eligible to participate if their injury was associated with a loss of consciousness (LOC), or a Glasgow Coma Scale (GCS) (Teasdale and Jennett, 1974) score of 13 or 14, or two or more acute signs or symptoms of concussion as noted by Emergency Department personnel. Acute symptoms included post-traumatic amnesia, vomiting, nausea, headache, diplopia, dizziness, disorientation, or any other indications of mental status change (i.e., dazed, foggy, slow to respond, lethargic, confused, sleepy). Children were not eligible if they demonstrated a LOC lasting more than 30 min, any GCS score of less than 13, any delayed neurological deterioration (i.e., a decline in GCS below 13 following admission or any emergent neurosurgical intervention), or any medical contraindication to magnetic resonance imaging (MRI). Children were not required to have undergone a computed tomography (CT) scan to be eligible to participate. Children who had an acute CT scan were not excluded from the study if they demonstrated intracranial lesions or skull fractures, as long as they did not require surgical intervention. Other exclusion criteria included any associated injury with an Abbreviated Injury Severity (AIS) (American Association for Automotive Medicine, 1990) score greater than 3; any surgical interventions; previous head injury requiring medical treatment; history of severe psychiatric illness resulting in hospitalization; premonitory neurological disorders or mental retardation; hypoxia, hypertension, or shock during or following the injury; injury resulting from child abuse or assault; or injuries that would interfere with neuropsychological testing (e.g., fracture of preferred upper extremity).

Of the 387 children eligible to participate, 186 (48%) agreed to enroll in a larger prospective, longitudinal study of mild TBI (Yeates and Taylor, 2005). Participants and non-participants did not differ significantly in age, sex, or ethnic/racial minority status; they also did not differ in census tract measures of socioeconomic status (i.e., mean family income, percentage of minority heads of household, and percentage of households below the poverty line).

The collection of DNA for the present study began approximately midway through the larger parent project. Of the 186 participants, 99 were genotyped. Genotyped and non-genotyped participants did not differ significantly in age, sex, or socioeconomic status. Children who were genotyped were significantly more likely than non-genotyped children to be Caucasian. This difference reflects the selective recruitment of Caucasian children for the mild TBI group during the latter half of the study, in order to balance ethnic status across the mild TBI group and a comparison group of children with orthopedic injuries recruited as part of the larger study.

Procedure

Children who met all inclusion/exclusion criteria and whose parents agreed to participate were scheduled for an initial assessment that typically occurred within 2 weeks of their injury ($M = 11.62$ days, $SD = 3.40$). They completed follow-up assessments at 3 and 12 months post-injury. The assessments included neuropsychological testing and ratings of post-concussive symptoms. DNA samples were collected at the 12-month post-injury assessment. Institutional Review Board approval, and informed parental consent and child assent were obtained prior to participation.

APOE genotyping

For each participant, a buccal swab sample was obtained from each cheek, and DNA was isolated with the Puregene DNA isolation kit (Qiagen). APOE genotyping was performed using the INNO-LiPA ApoE kit from Innogenetics. The protocol was modified to include an additional 25 cycles of polymerase chain reaction (PCR) for a total of 60. For samples that did not yield interpretable results during the initial PCR amplification ($n = 38$), the DNA was amplified using the GenomePlex Complete Whole Genome Amplification (WGA) kit (Qiagen) prior to genotyping. To rule out any allelic discrimination, all WGA-amplified samples were analyzed in duplicate (i.e., both left and right cheeks). Two children had DNA from only one side amplify, and for one child, the results were not the same for DNA from the left and right cheek. No results are included for these three children. All children that were homozygous for the $\epsilon 4$ allele were confirmed by PCR with only 35 cycles, to decrease the possibility of background bands and misinterpretation.

Neuropsychological testing

In children, TBI frequently results in deficits in processing speed, visual-motor skills, memory, and executive functions (Yeates, 2000). Participants therefore completed several standardized tests designed to assess their neuropsychological functioning in those domains. Verbal learning and memory was assessed using the California Verbal Learning Test-Children's Version (CVLT-C) (Delis et al., 1994). The primary measure used in this study was the T-score for total recall across the five learning trials. The Developmental Test of Visual-Motor Integration (VMI) (Beery, 1989), which requires children to copy progressively complex geometric figures, measured visual-motor skills. The total standard score was analyzed for this study. Finally, four subtests from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Sahakian and Owen, 1992) were completed: Motor Screening, which assesses simple reaction time; Pattern Recognition Memory, which assesses visual recognition memory; Stockings of Cambridge, which is a disk transfer task that assesses planning skills; and Spatial Working Memory, which is a self-ordered pointing test that assesses working memory.

Measures of intellectual ability and academic achievement were also administered to assess whether the groups differed in those general areas. General intellectual functioning was assessed using the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999), with the Full Scale IQ used as the dependent variable. Academic achievement in the domains of

reading, spelling, and arithmetic was measured by the Wide Range Achievement Test (WRAT-3) (Wilkinson, 1993). Standard scores for each domain were analyzed for this study.

Post-concussive symptoms

Post-concussive symptoms (e.g., headaches, inattention, mood changes) were assessed via two measures, the Post-Concussive Symptom Interview (PCS) (Mittenberg et al., 1997a,b) and Health Behavior Inventory (HBI) (Yeates et al., 1999). For both the PCS and HBI, separate ratings were obtained from the parent and child. The PCS is a structured interview assessing the presence/absence of 15 symptoms, similar to those listed for Post-Concussion Syndrome in the ICD-10 (World Health Organization, 1992) and for Post-concussional Disorder in the DSM-IV (American Psychiatric Association, 1994). The PCS yields a score representing total number of symptoms reported over the past week and displayed satisfactory internal consistency for the larger study sample at each of the three assessments (Cronbach's $\alpha = 0.78-0.82$). The HBI is a 50-item self-report inventory rating the frequency of occurrence of post-concussive symptoms using a four-point Likert-type scale ranging from *never* to *often*. Scales representing somatic and cognitive symptoms, derived from factor analyses (Ayr, 2007), were used as dependent variables. Both the cognitive and somatic symptom scores demonstrated high internal consistency among the entire study sample across raters and assessment occasions (Cronbach's $\alpha = 0.85-0.94$).

Statistical analysis

Chi-square and independent sample *t*-tests (or Wilcoxon summed rank tests for data determined to be non-normally distributed) were used to test for differences between the groups on demographic factors and various indices of injury severity. A series of multivariate, repeated-measures analyses of variance (MANOVA) were conducted to evaluate group differences in neuropsychological test performance, and parent- and child-reported post-concussive symptoms.

Results

APOE genotypes

The participants demonstrated the following APOE genotypes, in order of frequency: $\epsilon 3/3 = 56$ (56.6%); $\epsilon 3/4 = 21$ (21.2%); $\epsilon 2/3 = 15$ (15.2%); $\epsilon 4/4 = 4$ (4.0%); and $\epsilon 2/4 = 3$ (3.0%). Thus, 28 participants had at least one $\epsilon 4$ allele, and they were compared to the remaining 71 participants who did not have an $\epsilon 4$ allele. The distribution of alleles did not differ from the Hardy-Weinberg equilibrium. Group characteristics are summarized in Table 1. Children with and without an $\epsilon 4$ allele did not differ in age, sex, ethnic status, socioeconomic status, or mechanism of injury.

Injury severity

Children with an $\epsilon 4$ allele were no more likely than those without an allele to demonstrate intracranial abnormalities on MRI, skull fractures on CT or MRI, or LOC (Table 2). Additionally, the groups did not differ on the Modified Injury Severity Score (Mayer et al., 1980). However, children with an $\epsilon 4$ allele were more likely than those without an allele to have

TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF CHILDREN WITH AND WITHOUT AN *APOE* ϵ 4 ALLELE

Variable	ϵ 4 group (n = 28)	Non- ϵ 4 group (n = 71)
Age at injury, mean (SD)	11.73 (2.04)	12.06 (2.21)
Sex (% male)	71%	69%
Race (% Caucasian)	82%	82%
SES, mean (SD)	0.18 (0.96)	0.10 (0.91)
Mechanism of injury		
Falls	14%	22%
Sports/recreation	64%	59%
Transportation	11%	13%
Other	11%	6%

SES, socioeconomic status (a standardized Z-score composite of maternal education, median family income for census tract, and the Duncan occupational status index).

All p 's > 0.05.

a GCS score less than 15, $\chi^2(df = 1) = 4.82$, $p < 0.03$, odds ratio (OR) = 3.61, 95% confidence interval (CI) = 1.09–11.94.

Neuropsychological functioning

As shown in Table 3, analyses of neuropsychological test performance yielded limited evidence of group differences in outcome. Participants with an ϵ 4 allele exhibited consistently better performance on the VMI across time than children without the allele, $F(1,95) = 6.2$, $p < 0.02$, $\eta^2 = 0.06$. However, the groups did not differ on any of the other measures (i.e., WASI, WRAT-3, CVLT, CANTAB) in terms of either between-group differences or different within-group trends over time.

Post-concussive symptoms

Analyses of post-concussive symptom ratings did not reveal any differences between participants with and without an ϵ 4 allele. The groups did not differ based on either parent- or child-reported symptoms (Table 4), again in terms of either between-group differences or different within-group trends over time.

Discussion

The present study is the first of which we are aware that examines the association of the *APOE* ϵ 4 allele with outcomes of mild TBI in children and adolescents. As expected, the

presence of an *APOE* ϵ 4 allele was associated with lower GCS scores in our sample, reflecting more severe injury among those with the allele. However, this relationship did not extend to any other measures of injury severity. The GCS reflects the brain's response to trauma, and in that sense is not a direct measure of severity, but instead is an indicator of early functional response to injury. Our finding is therefore consistent with a recent study in adults that found an association between the ϵ 4 allele and early responses to TBI (Jiang et al., 2006). Although our study cannot speak directly to potential mechanisms, acute processes such as oxidative stress (Miyata and Smith, 1996) or glial activation (Laskowitz and Vitek, 2007; Wang et al., 2007) might underlie these adverse, early responses to injury.

We attempted to decompose the nature of the neurological abnormalities associated with lower GCS scores. Unfortunately, a detailed breakdown of GCS scores themselves was not possible, because scores were not reported for all three components in many medical records. However, in post hoc analyses, we examined the acute signs and symptoms of concussion documented by Emergency Department personnel that were used to determine eligibility for inclusion in the mild TBI group. Persistent post-traumatic amnesia, disorientation, other mental status changes, transient neurological deficits, and nausea were significantly more common in the presence of lower GCS scores; however, those characteristics did not differentiate the ϵ 4 positive and negative groups, nor did any of the other signs/symptoms. Thus, the aspects of neurological function that account for the association between the *APOE* ϵ 4 allele and lower GCS scores are not entirely clear.

Despite the evidence that the ϵ 4 allele may predict early response to mild TBI, the early effects do not appear to lead to long-term effects on neuropsychological outcomes. Contrary to our hypotheses, children with an ϵ 4 allele did not display worse neurocognitive test performance or more post-concussive symptoms than children without the allele. Indeed, the only difference between groups reflected better performance on the VMI among children with the allele. Other studies have reported better neuropsychological test performance among individuals with the ϵ 4 allele following TBI (Blackman et al., 2005; Han et al., 2007), and some researchers posit that the allele may serve a protective function during neurodevelopment (Oria et al., 2005; Wright et al., 2003). However, our findings of a positive effect are limited to only one cognitive outcome measure, and hence may not be robust. Indeed, the difference would not be significant if a correction for multiple comparisons were applied.

The most salient limitation of the current investigation was the unavailability of DNA for all 186 children with mild TBI from the larger parent study. The only difference between those who were genotyped and those who were not was in ethnic status, with proportionally fewer Caucasian children among participants who were not genotyped. Given that the *APOE* ϵ 4 allele is more common in minorities of African descent (Corbo and Scacchi, 1999), the complete sample would have likely included a greater proportion of participants with an ϵ 4 allele, as well as a greater sample size overall. The complete sample also may have enabled us to compare children with only one versus two ϵ 4 alleles, to determine if children who are homozygous show especially poor outcomes. It also would have increased the statistical power of the current analyses. Although statistical power given the

TABLE 2. MEASURES OF INJURY SEVERITY FOR CHILDREN WITH AND WITHOUT AN *APOE* ϵ 4 ALLELE

Variable	ϵ 4 group	Non- ϵ 4 group
GCS score <15 ^a	25%	8%
Intracranial abnormalities on MRI	18%	20%
Skull fracture on CT or MRI	11%	8%
Loss of consciousness	36%	41%
Modified Injury Severity Score, mean (SD)	4.93 (5.67)	4.42 (4.60)

^a $p < 0.05$.

GCS, Glasgow Coma Scale.

TABLE 3. NEUROPSYCHOLOGICAL ASSESSMENT OF CHILDREN WITH AND WITHOUT AN *APOE* ϵ 4 ALLELE ACROSS TIME

Variable	Baseline		3-month		12-month	
	ϵ 4 group	Non- ϵ 4 group	ϵ 4 group	Non- ϵ 4 group	ϵ 4 group	Non- ϵ 4 group
WASI						
Full-Scale IQ	105.04 (12.63)	101.86 (13.55)	—	—	106.89 (12.04)	103.59 (14.01)
WRAT-3						
Reading	104.04 (9.48)	103.73 (14.18)	—	—	105.00 (9.87)	104.35 (13.62)
Spelling	101.21 (11.46)	102.93 (14.80)	—	—	102.46 (10.63)	102.80 (15.82)
Arithmetic	104.29 (13.94)	102.77 (14.56)	—	—	101.36 (12.45)	102.33 (16.34)
CVLT-C						
Total Words T score	50.19 (10.42)	49.83 (9.09)	55.41 (9.94)	54.97 (10.53)	52.22 (9.13)	53.34 (10.85)
VMI ^a	99.19 (14.10)	92.81 (11.82)	95.26 (14.38)	89.57 (10.69)	96.78 (12.95)	91.19 (11.95)
CANTAB						
MST: Latency (msec)	823.18 (337.92)	739.39 (189.98)	724.95 (178.22)	735.05 (181.57)	694.13 (182.52)	737.54 (295.97)
PRM: Number correct	21.04 (2.66)	20.31 (3.03)	22.04 (1.76)	22.17 (1.86)	22.19 (1.72)	21.39 (2.68)
SOC: Problems solved in minimum moves	7.50 (1.68)	7.41 (2.10)	8.65 (1.92)	8.36 (1.98)	8.62 (2.02)	8.83 (1.94)
SWM: Between errors	35.04 (19.83)	32.14 (16.88)	27.04 (19.58)	29.34 (18.89)	28.12 (18.94)	26.43 (18.23)

^a $p < 0.05$.

Data represent means (with SD). WASI, Wechsler Abbreviated Scale of Intelligence; WRAT-3, Wide Range Achievement Test-3rd edition; CVLT-C, California Verbal Learning Test-Children's Version; VMI, the Developmental Test of Visual-Motor Integration; CANTAB, Cambridge Neuropsychological Test Automated Battery; MST, Motor Screening Test; PRM, Pattern Recognition Memory; SOC, Stockings of Cambridge; SWM, Spatial Working Memory.

current sample size approached the size needed to detect medium effect sizes with acceptable power, the effects of genes on behavior are typically more modest and may have gone undetected in our sample. A much larger sample would be needed to have adequate power to detect small effect sizes. On the other hand, our sample size was comparable to that of many published studies and many group differences were not in the predicted direction (i.e., children with an ϵ 4 allele did not always exhibit poorer outcomes), suggesting that statistical power may not have been a critical problem.

Another limitation is that the neurocognitive tests used in the study may not have been sensitive to mild TBI, especially in the long-term. But mild TBI does not tend to result in long-term deficits on standardized cognitive tests (Yeates and Taylor, 2005). However, our initial assessment occurred about 12 days post-injury, at which point cognitive deficits associated with mild TBI often are still present. Moreover, we found a significant difference between children with and

without the ϵ 4 allele on the VMI that persisted across time. We would also emphasize that ratings of post-concussive symptoms are sensitive to the longer-term effects of mild TBI (Yeates et al., 2009). Yet children with and without the ϵ 4 allele did not differ on such ratings. Thus, we believe that our outcome measures were sensitive enough to detect abnormalities in children with mild TBI and to differentiate children with and without the ϵ 4 allele.

Another potential study shortcoming was the exclusion of children with delayed neurological deterioration from participation. This criterion ruled out individuals who did not meet the usual definition of mild TBI. However, the ϵ 4 allele could be related to clinical deterioration following TBI (Jiang et al., 2006), and our exclusion criteria precluded the study of whether *APOE* is related to the likelihood of delayed neurological deterioration in children with TBI. A final shortcoming is that the sample was predominantly male and Caucasian. Although children with and without an ϵ 4 allele did not differ

TABLE 4. POST-CONCUSSIVE SYMPTOMS IN CHILDREN WITH AND WITHOUT AN *APOE* ϵ 4 ALLELE ACROSS TIME

Variable	Baseline		3-month		12-month	
	ϵ 4 group	Non- ϵ 4 group	ϵ 4 group	Non- ϵ 4 group	ϵ 4 group	Non- ϵ 4 group
Parent-reported symptoms						
PCS Interview	4.41 (3.43)	4.71 (3.59)	2.15 (2.25)	2.57 (2.52)	1.74 (3.11)	2.16 (2.38)
HBI cognitive symptoms	8.00 (8.33)	9.50 (7.78)	8.81 (7.12)	11.46 (7.65)	9.41 (7.67)	9.84 (7.91)
HBI somatic symptoms	5.22 (5.74)	6.53 (5.81)	2.52 (3.12)	3.87 (4.29)	2.70 (3.99)	3.10 (3.95)
Child-reported symptoms						
PCS Interview	5.04 (2.81)	5.27 (3.16)	4.15 (2.61)	4.07 (3.38)	4.48 (3.06)	4.16 (3.19)
HBI cognitive symptoms	10.19 (8.24)	12.26 (7.61)	9.52 (6.66)	10.46 (7.37)	11.37 (6.48)	11.67 (7.71)
HBI somatic symptoms	7.81 (5.57)	8.87 (5.89)	5.59 (5.34)	6.49 (5.74)	6.15 (5.94)	6.71 (5.58)

Data represent means (with SD). PCS, post-concussive symptom; HBI, Health Behavior Inventory.

All p 's > 0.05 .

on age, sex, ethnic status, or socioeconomic status, the findings may not generalize readily to females or ethnic minorities.

In summary, the current study suggests that in children the APOE $\epsilon 4$ allele has little impact on the severity or functional outcomes of mild TBI, although it may be associated with a somewhat more negative early response to injury. Future research will be needed to assess the potential moderating influence of other genes implicated in neural recovery or protection. Although APOE is the most extensively studied gene in TBI, a variety of other genes warrant additional investigation (e.g., interleukin, catechol-o-methyltransferase, dopamine D2 receptor) (Jordan et al., 2007).

Acknowledgments

Portions of the data were presented at the annual meeting of the Pediatrics Academic Societies in San Francisco in 2006. This work was supported by the National Institutes of Health (grants HD44099 and HD39834, to the senior author, K.O.Y.).

Author Disclosure Statement

No competing financial interests exist.

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