Apolipoprotein E ε4 Associated With Chronic Traumatic Brain Injury in Boxing

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Context.—Given the similarities between Alzheimer disease and dementia pugilistica, we evaluated the relationship between apolipoprotein E (*APOE*) genotype and chronic traumatic brain injury (CTBI) in boxers to determine whether there is a genetic susceptibility to the effects of head trauma.

Objective.—To assess the relationship between CTBI and *APOE* genotype in boxers.

Design and Setting.—Clinical characterization of 24 volunteer and 6 referred boxers in an outpatient setting.

Participants.—Thirty professional boxers aged 23 to 76 years underwent neurologic and behavioral assessment in conjunction with *APOE* genotyping.

Main Outcome Measures.—Apolipoprotein E genotype was examined in relationship to measures of CTBI. A 10-point clinical rating scale (0-9), the Chronic Brain Injury (CBI) scale, was devised to assess the severity of traumatic encephalopathy associated with boxing. Boxers with abnormal CTBI scores were further classified on the basis of whether their impairments were possibly or probably related to boxing. Scores were analyzed in relation to boxing exposure (number of bouts) and *APOE* genotype.

Results.—Among the 30 boxers, 11 were found to be normal (CBI score=0), 12 showed mild deficits (CBI score=1-2), 4 were moderately impaired (CBI score=3-4), and 3 showed signs of severe impairment (CBI score >4). High-exposure boxers (ie, those with ≥12 professional bouts) had significantly higher CBI scores (mean [SD], 2.6 [1.9]) than low-exposure boxers (mean [SD], 0.3 [0.7]) ($P<.001$), indicating that neurologic impairment as measured by the CBI scale seems related to boxing exposure. The *APOE* genotype frequencies of the study population were approximately the same as those found in the general population. Boxers with low exposure had mean CBI scores of 0.33, irrespective of *APOE* genotype. However, high-exposure boxers with an *APOE* ε4 allele had significantly greater CBI scores (mean [SD], 3.9 [2.3]) than high-exposure boxers without *APOE* ε4 (mean [SD], 1.8 [1.2]) ($P=.04$). All boxers with severe impairment possessed at least 1 *APOE* ε4 allele. The tendency for greater CTBI among those with both high exposure and an ε4 allele was statistically significant at the $P<.001$ level.

Conclusions.—These preliminary findings suggest that possession of an *APOE* ε4 allele may be associated with increased severity of chronic neurologic deficits in high-exposure boxers.

JAMA. 1997;278:136-140

CHRONIC TRAUMATIC brain injury (CTBI) is the most serious public health concern in modern-day boxing.[1] Also known as dementia pugilistica or chronic traumatic encephalopathy, CTBI represents the long-term and cumulative neurologic consequences of repetitive head trauma. This syndrome has been most typically described in active or retired boxers after a long exposure to the sport. However, CTBI may also be anticipated in other sports such as American football, soccer, or ice hockey. Clinically, CTBI is characterized by a varied constellation of cognitive impairment, parkinsonism, ataxia, pyramidal tract dysfunction, and behavioral changes.[1-4] Pathologically, CTBI exhibits several features that are similar to those characteristic of Alzheimer disease (AD). These similarities include regional neurofibrillary tangle formation[5-10] with similar immunochemical characteristics,[8,9] diffuse β-amyloid plaques,[7] and reduced cholinergic activity in the basal forebrain.[3]

Investigations have identified apolipoprotein E (*APOE*) as a susceptibility gene for late-onset familial and sporadic AD.[11-13] The human *APOE* gene encodes a cholesterol carrier lipoprotein (apolipoprotein E) produced in the liver and brain. It is polymorphic and occurs in 3 common allelic forms designated *APOE* ε2, ε3, and ε4, which give rise to 6 possible genotype combinations. Possession of the *APOE* ε4 allele increases the risk of AD in a dose-dependent fashion and shifts the age at onset distribution to earlier ages.[12] *APOE* ε2 is underrepresented in AD populations and may protect against AD.[14,15]

Head trauma has been implicated as a possible environmental trigger for AD. Several epidemiologic investigations have noted that head trauma increases the risk of AD,[16] especially in those harboring the *APOE* ε4 allele.[17,18] Neuropathological observations suggest the mechanism for this association may relate to widespread cerebral β-amyloid deposition following head trauma.[19-21] The β-amyloid precursor protein (βAPP) expression is increased following head injury, which suggests that βAPP is part of the brain's acute response to injury[21]; but βAPP may also be a marker of axonal injury secondary to traumatic brain injury.[22,23] Further, cerebral β-amyloid deposition may be prominent in those who harbor an *APOE* ε4 allele.[24] In support of such a model, we have reported the simultaneous occurrence of dementia pugilistica and fatal congophilic angiopathy in a retired boxer who had the ε3/ε4 genotype.[25]

In view of the above-mentioned clinical, pathological, and epidemiologic observations, the current investigation was undertaken to determine whether *APOE* genotype influences the risk of CTBI and its severity among boxers.

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METHODS

Subject Selection

Boxers were enrolled from several sources. The majority were local boxers in retirement who volunteered for neurologic examination and *APOE* genotyping. Five professional boxers were referred by the New York State Athletic Commission (NYSAC) for neurologic evaluation, and the 5 volunteered to undergo *APOE* genotyping. One additional boxer was referred directly for the evaluation of dementia.

Clinical Characterizations

Boxers underwent a detailed neurologic examination performed by 1 of 3 neurologists (B.D.J, N.R.R, A.R.J). Two examiners were present in 10% of cases to confirm interrater reliability. Impairments were rated using a new scale designed to assess the long-term consequences of brain injury, the Chronic Brain Injury (CBI) scale (Table 1). The CBI scale quantifies the clinical findings of motor, cognitive, and psychiatric deficits associated with boxing-related brain injury as outlined by Mendez.[3] Scores on the CBI scale range from 0 to 9, with higher scores reflecting greater impairment. The cognitive component incorporates the boxer's score on the Folstein Mini-Mental State Examination,[26] a widely used cognitive screening instrument. Assessment of behavioral manifestations of CTBI was based on observations during the examination as well as historical information provided by the boxer or the boxer's surrogate responder. The behavioral component of the CBI scale assesses the domains of psychopathology outlined in the Neuropsychiatric Inventory.[27]

Information was obtained about each boxer's past medical history, boxing exposure, family history, and social habits. In cognitively intact boxers, boxing exposure was obtained by self-report. In cases of significant cognitive impairment, boxing exposure was obtained from a surrogate responder or by boxing records. Overall boxing exposure was classified as high if the boxer participated in 12 or more professional bouts. The use of the 12-bout criterion of exposure was based on a prior study of a representative sample of 338 professional boxers, among whom the mean number of bouts was 12.2.[28] Amateur boxers with no history of professional bouts were classified as low exposure based on the lack of conclusive evidence for long-term neurologic sequelae in association with amateur boxing.[3]

Measures of severity of CTBI included the total CBI score and a categorical classification based on CBI score consisting of normal (CBI=0), mild (CBI=1-2), moderate (CBI=3-4), and severely impaired (CBI>4) ratings. For a separate analysis, boxers with abnormal CTBI scores were further classified on the basis of whether their impairments were possibly or probably related to boxing according to the diagnostic criteria described by Jordan.[29] Boxers classified as probable were those who exhibited clinical findings typical of boxing-related CTBI. Boxers classified as possible were those who exhibited a clinical syndrome consistent with CTBI but indistinguishable from other neurologic disorders (eg, typical Parkinson disease, AD, or alcoholic dementia).

Table 1.—Chronic Brain Injury Scale (CBI)

Motor (incoordination, dysarthria, parkinsonism, gait disturbance, or pyramidal signs)	
Normal	0
Mild	1
Moderate	2
Severe	3
Cognitive (deficits in mental speed, memory, attention, executive function, language, or visuospatial function)	
Normal (Mini-Mental State Examination [MMSE]=28-30)	0
Mild (MMSE=20-27)	1
Moderate (MMSE=10-19)	2
Severe (MMSE≤9)	3
Behavioral (agitation or aggression, delusions, hallucinations, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability or lability, or aberrant motor behavior)	
Normal	0
Mild	1
Moderate	2
Severe	3
Total CBI score (range, 0-9)	

APOE Genotyping

Informed consent for *APOE* genotyping was obtained in writing from all subjects in accordance with a protocol approved by the Cornell University Medical College Institutional Review Board. Consent was provided by legal representatives of 2 subjects who lacked decision-making capacity because of cognitive impairments, and testing was conducted with the subjects' assent and cooperation. Subjects were given the option of receiving their *APOE* genotype test results, contingent on pretest and posttest genetic counseling, following the guidelines of the National Institute on Aging and the Alzheimer's Association Working Group on APOE Genotyping in Alzheimer's Disease.[30] The *APOE* genotype was determined using a standard polymerase chain reaction protocol.[31] The DNA sample was extracted and purified (QIAGEN DNA Prep Kit, QIAGEN, Chatsworth, Calif) after centrifugation of ethylenediaminetetraacetic acid–treated whole blood to obtain the buffy coat. In 10 subjects, samples of DNA were sent anonymously to a certified testing laboratory (Athena Diagnostics, Worcester, Mass) for confirmation of genotype.

Table 2.—Characteristics of the Study Population*

Case	Age, y (Race)	Boxing Exposure	Amateur Bouts, No.	Professional Bouts, No.
1	70 (B)	High	NA	162
2	26 (H)	Low	14	8
3	48 (B)	High	NA	79
4	29 (B)	High	150	13
5	31 (B)	High	NA	34
6	29 (B)	Low	8	3
7	57 (W)	Low	100s	NA
8	57 (W)	Low	200	1
9	36 (W)	Low	32	0
10	59 (H)	High	50	71
11	39 (W)	Low	5	NA
12	70 (W)	High	26	22
13	65 (W)	High	31	31
14	76 (W)	High	21	29
15	69 (B)	High	47	45
16	67 (B)	Low	4	NA
17	64 (H)	High	32	117
18	37 (H)	High	105	58
19	41 (H)	High	33	20
20	35 (W)	High	15	28
21	64 (W)	High	1	40
22	60 (H)	High	41	56
23	68 (W)	Low	48	NA
24	47 (W)	Low	45	4
25	31 (B)	Low	20	2
26	39 (H)	High	110	23
27	30 (B)	Low	55	10
28	64 (B)	High	200	25
29	37 (H)	High	44	20
30	23 (H)	Low	25	0

*W indicates white; B, black; H, Hispanic; and NA, not available.

Statistical Analysis

Age comparisons were made with analysis of variance. The Fisher exact test was used to compare the frequency of *APOE* genotypes between groups. Statistical tests of trend[32] were used in the following 2 contexts: (1) to compare the severity of boxing-related impairment and *APOE* carrier frequency (the Jonckheere-Terpstra test) and (2) to compare the scores of boxers with and without the ε4 allele, stratified by boxing exposure (the Kruskal-Wallis test). The Mann-Whitney *U* test was used to assess the differences in CBI scores among the various groups of boxers.[33]

RESULTS

Characteristics of the 30 boxers who participated in the current investigation are presented in Table 2. Twenty-seven boxers were retired from boxing, and 3 were active. The average age was 49 years (SD, 16.5 years; range, 23-76 years). There were 11 whites, 10 blacks, and 9 Hispanics.

The boxers in the current investigation had a varied exposure to the sport. Among the 30 boxers, 18 (60%) were considered high exposure. The high-exposure boxers tended to be older (mean [SD] age, 53.4 [15.7] years; range, 29-76 years) compared with those with low exposure (mean [SD]

Table 3.—Results of Diagnostic Evaluations*

Case	Neurologic Examination	MMSE Score	CBI Score	CTBI Classification	Comment
1	Severe dementia; severe spasticity; agitation; dysarthria; gait ataxia	3	8	Probable	
2	Normal	28	0	Normal	Referred for evaluation by the New York State Athletic Commission (NYSAC); magnetic resonance imaging (MRI) scan showed a paraventricular cyst, mild atrophy, and cavum septum pellucidum; admitted to use of recreational drugs; normal electroencephalogram (EEG)
3	Posturing on stressed gait; decreased simple and complex attention; mild dysarthria	28	2	Probable	Normal computed tomography (CT) scan and EEG; referred by the NYSAC
4	Normal	29	0	Normal	Experienced a prolonged postconcussion syndrome with 24 h of amnesia; also had unexplained syncopal episodes; normal MRI and EEG
5	Difficulty with Tandem gait	N/A	1	Probable	Complained of difficulties with balance; referred by the NYSAC; 1 episode of head trauma outside the ring
6	Normal	30	0	Normal	Referred by the NYSAC; abnormal EEG; normal CT scan
7	Normal	29	0	Normal	One episode of head trauma outside the ring secondary to a motor vehicle accident (experienced a few seconds of unconsciousness)
8	Normal	28	0	Normal	Magnetic resonance imaging scan showed nonspecific white matter changes consistent with focal ischemia
9	Normal	30	0	Normal	...
10	Mild dysarthria	27	2	Possible	Regular alcohol use
11	Normal	30	0	Normal	Occasional recreational drug use; regular alcohol use
12	Normal	27	1	Possible	History of meningitis as a child and history of schizophrenia that preceded boxing; regular alcohol use
13	Difficulty with tandem gait; positive Romberg sign	25	2	Possible	History of alcohol abuse
14	Mild-moderate memory impairment	24	2	Possible	Regular alcohol use
15	Severe dysarthria; slight increased tone in lower extremities; ataxic gait; slight dysmetria on left	22	4	Probable	Hospitalized once after a fight secondary to a concussion
16	Normal	29	0	Normal	...
17	Mild hyperreflexia on left; resting tremor and mild cogwheel rigidity	27	2	Possible	...
18	Flat affect with pseudobulbar-type laughing outbursts; dysarthria; mild paratonia of right upper extremity; ankle clonus; slowed rapid alternating movements; ataxic gait; memory impairment	20	5	Probable	MRI scan: moderate cortical atrophy and periventricular white matter changes; EEG showed diffuse slowing
19	Mild pseudobulbar affect; dysarthria; memory impairment; dysmetria; ataxic gait	17	5	Probable	...
20	Normal	29	0	Normal	Normal EEG and MRI
21	Moderate dysarthria and incoordination; slight increased tone in right lower extremity with wide based ataxic gait; hyperreflexia in right upper extremity	30	2	Probable	CT scan: mild cerebellar atrophy
22	Difficulty with sharpened Romberg sign	27	2	Probable	...
23	Mild tremor with titubation	29	1	Possible	...
24	Mild dysarthria and cogwheel rigidity	30	1	Probable	Remote history of polio
25	Mild dysmetria and difficulty with Romberg sign; hypomania and increased talkativeness	28	2	Possible	One episode of head trauma outside of the ring with loss of consciousness; still boxing; history of drug abuse
26	Anisocoria; abducens palsy diplopia on lateral gaze; dysmetria; ataxia; pseudobulbar affect and behavioral disinhibition	29	3	Probable	History of alcohol abuse; cavum septum on CT
27	Normal	29	0	Normal	...
28	Mild dysarthria; gait ataxia; resting tremor	25	3	Probable	...
29	Slight increased tone in lower extremities; abnormal sharpened Romberg sign; mild rigidity; mild depression	27	3	Probable	Complained of memory loss
30	Normal	29	0	Normal	...

*MMSE indicates Mini-Mental State Examination; CBI, chronic brain injury; and CTBI, chronic traumatic brain injury.

age, 42.6 [16.2] years; range, 23-68 years; P=.08). The high-exposure boxers had significantly higher CBI scores (mean=2.6, SD=1.9) compared with low-exposure boxers (mean=0.3, SD=0.7, P <.001).

Eleven boxers (37%) had normal neurologic findings (CBI=0), while 19 boxers (63%) exhibited abnormalities. Of the 19 boxers with CBI score greater than 0, 12 boxers were classified as probable CTBI, and 7 boxers were classified as possible CTBI. Among the 7 possible CTBI cases, 4 boxers had mild to moderate cognitive impairment with or without minor motor disturbances (eg, mild dysarthria, difficulty with tandem gait, abnormal Romberg sign) in the setting of regular alcohol usage (ie, alcohol ingestion at least 4 times per week). A fifth boxer had a history of crack cocaine abuse and exhibited mild psychiatric disturbances along with mild dysmetria and an abnormal Romberg sign. The sixth boxer in the "possible" group had mild mental status changes and symptoms consistent with parkinsonism. The seventh exhibited essential tremor.

The results of the neurodiagnostic evaluation are presented in Table 3. Twelve boxers (40%) had mild CTBI (CBI=1-2). Four boxers (13%) were moderately impaired (CBI=3-4), and 3 boxers (10%) were severely affected (CBI>4). Neurologic findings in the boxers with mild CTBI included mild cognitive impairment (7 cases), mild dysarthria (4 cases), mild gait disturbances (4 cases), positive Romberg sign (3 cases), mild parkinsonism (2 cases), and mild pyramidal tract impairments (ie, hyperreflexia, mildly in-

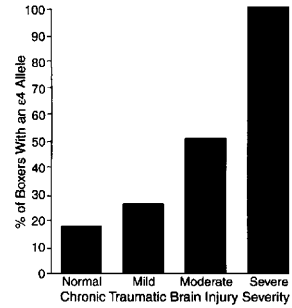

Figure 1.—Frequency of apolipoprotein E ε4 carrier frequency according to severity of chronic traumatic brain injury.

creased tone) (2 cases). One boxer with mild CTBI was diagnosed with bipolar disorder during his boxing career and displayed hypomania and increased talkativeness during the examination. In the 7 boxers with moderate to severe CTBI, the predominant features were dementia, dysarthria, and ataxia. Three boxers with severe CTBI also exhibited psychiatric manifestations.

Nineteen boxers (63%) were homozygous for *APOE* ε3/ε3. There were 7 boxers (23%) with an ε3/ε4 genotype, 2 (7%) with ε2/ε4, 1 (3%) with ε4/ε4, and 1 (3%) with ε2/ε3. Among the 12 boxers classified as probable CTBI, 6 (50%) had either *APOE* ε3/ε4 or ε4/ε4 compared with 3 (11%) of the 18 boxers labeled as normal or possible CTBI (P=.004).

All 3 boxers (100%) who exhibited severe CTBI had at least 1 copy of the *APOE* ε4 allele. This is compared with 50% (2 of 4) of those with moderate CTBI, 25% (3 of 12) with mild CTBI, and 18% (2 of 11) with normal examinations (Figure 1). This trend of higher CBI scores with the ε4 allele was statistically significant (P =.01). The mean CBI score for the 10 boxers with an *APOE* ε4 allele was 2.8 (SD, 2.6), compared with a mean of 1.2 (SD, 1.2) among the 20 boxers without an *APOE* ε4 allele. This difference did not reach statistical significance (P=.06).

Boxers were stratified according to boxing exposure and presence or absence of the ε4 allele. Table 4 shows mean, median, and ranges of CBI scores and age according to boxing exposure and *APOE* genotype. Low-exposure boxers with and without the ε4 allele had a mean CBI score of 0.3 (SD=0.7). High-exposure boxers with an *APOE* ε4 allele had a mean CBI score of 3.9 (SD=2.3) compared with 1.8 (SD=1.2) in high-exposure boxers without the ε4 allele. This difference was statistically significant (P=.04) (Table 5). The tendency for greater CTBI symptoms among those with increased exposure and an ε4 allele was statistically significant (P<.001) (Figure 2).

Table 4.—Chronic Brain Injury (CBI) Score Stratified by *APOE* ε4 Status and Boxing Exposure*

Variables	Low Exposure: ε4 Absent (n=9)	Low Exposure: ε4 Present (n=3)	High Exposure: ε4 Absent (n=11)	High Exposure: ε4 Present (n=7)	P Value
Age, y					
Mean (SD)	44.0 (18.0)	38.3 (9.0)	59.6 (14.5)	43.6 (12.7)	P>.05†
Median (range)	36.0 (24-68)	39.0 (29-47)	64.0 (29-76)	39.0 (31-70)	
CBI					
Mean (SD)	0.3 (0.7)	0.3 (0.6)	1.8 (1.2)	3.9 (2.3)	P<.001‡
Median (range)	0.0 (0-2)	0.0 (0-1)	2.0 (0-4)	3.0 (1-8)	

*APOE ε4 indicates the type 4 allele of apolipoprotein E; and SD, standard deviation.
†P value determined using the t test.
‡P value determined using the Kruskal-Wallis test.

Table 5.—Pairwise Comparisons of Groups: Genotype and Boxing Exposure

Comparison	P Value*
Genotype	
ε4 Absent vs ε4 present (low exposure)	>.05
ε4 Absent vs ε4 present (high exposure)	=.04
Exposure	
Low exposure vs high exposure (ε4 absent)	<.001
Low exposure vs high exposure (ε4 present)	=.001

*Mann-Whitney U test used to determine P value.

Three boxers had an *APOE* ε2 allele. All 3 had high exposure to boxing (range, 34-79 professional bouts), and 2 had the *APOE* ε4 allele in combination with *APOE* ε2. However, none showed significant evidence of CTBI (ie, scores suggesting moderate or severe deficits). Although the mean CBI score for the 3 boxers with the ε2 allele was lower (1.67) than the CBI score for high-exposure boxers without an *APOE* ε2 allele (2.8), this difference did not reach statistical significance (P=.30).

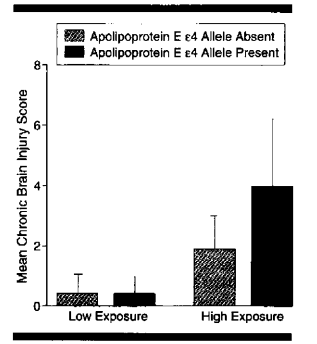

Figure 2.—Chronic traumatic brain injury scores of boxers by apolipoprotein E genotype and exposure. The bars represent the standard deviation.

COMMENT

The results of this preliminary investigation suggest that the APOE ε4 allele may predispose a boxer to developing CTBI, especially in those with high exposure to the sport. Boxers who were *APOE* ε4 positive with a high exposure to boxing had the highest scores on the CBI. Despite their greater overall impairment, the high-exposure boxers with the *APOE* ε4 allele tended to be younger (average age, 45.2 years) than high-exposure boxers without the *APOE* ε4 allele (average age, 56.5 years). This age difference approached statistical significance. While it is plausible that the *APOE* ε4 allele may be associated with a younger age of onset of CTBI, the age difference may reflect a self-selection bias toward younger *APOE* ε4–positive boxers in our volunteer population. It is possible that fewer older, high-exposure boxers who carry *APOE* ε4 were available owing to the greater burden of disease among such individuals.

The frequency of the *APOE* ε4 allele was noted to be highest (67%) in boxers with typical traumatic encephalopathy related to boxing (probable CTBI). The *APOE* ε4 allele was also overrepresented in those boxers with severe CTBI (100%) and moderate CTBI (50%). These findings are statistically significant and support the hypothesis that *APOE* ε4 is associated with CTBI in high-exposure boxers. There may be no association between *APOE* ε4 and CTBI in low-exposure boxers, or the lack of an observed effect may be due to the small sample size in our study.

The 3 boxers who had an *APOE* ε2 allele had relatively mild CTBI scores, despite high boxing exposure. This finding is consistent with the literature, which suggests that the *APOE* ε2 allele may convey protection against neurodegenerative disorders such as AD.[14,15]

The *APOE* carrier frequencies and the odds ratio of developing AD as a function of *APOE* genotype have been reported to vary as a function of national origin or race.[14] Our study population contained approximately equal numbers of whites, blacks, and Hispanics. It is unlikely that the effects of *APOE* ε4 pos-

session on CTBI that we observed are due to the heterogeneity of the racial origin of our study subjects. We cannot entirely exclude this possibility or discern differences in the magnitude of the effect owing to our limited sample size.

As observed by Roberts,[2] we found that high boxing exposure is associated with increased risk of boxing-related chronic neurologic injury. In the current investigation, the mean CBI score for high-exposure boxers was significantly greater than that for low-exposure boxers, independent of *APOE* status. This finding suggests that low exposure to boxing (ie, amateur status and/or fewer than 12 professional bouts) is associated with less brain injury, consistent with previous reports.[35,36]

According to the CTBI scale developed in this investigation, 7 boxers (23%) exhibited moderate to severe CTBI. This is comparable with estimates of a 17% prevalence of traumatic encephalopathy among a representative sample of retired professional boxers.[2] The predominant features of the moderate to severe group in the current series consisted of dysarthria, ataxia, and dementia. Boxers with mild CTBI (CBI score = 1-2) tended to display mild cognitive impairment and mild motor impairment (eg, dysarthria, abnormal Romberg sign, mild gait disturbance) in the absence of behavioral disturbances. Although behavioral or psychiatric manifestations can occur during any phase of CTBI, these disturbances are typically a late consequence.[37]

Although the findings of this preliminary investigation suggest that there may be a genetic susceptibility for development of CTBI in boxers, our results should be interpreted with caution. Since the majority of these boxers were either referred or volunteered, there is a potential self-selection bias. It is conceivable that more symptomatic boxers may come to medical attention or may volunteer to participate. Although the *APOE* allele frequencies in our study population are comparable with those reported in several large population studies, our sample size is relatively small. The confirmation of our findings requires *APOE* genotyping in a large, representative sample of boxers with appropriate attention to other variables such as age, boxing exposure, national origin, and other putative risk factors for CTBI and dementia.

The hypothesis that *APOE* ε4 conveys a genetic predisposition to CTBI potentially has extraordinary ramifications for the regulation of health and safety in boxing and other high-risk sports including American football, soccer, and ice hockey. Boxers who are at high risk could conceivably undergo more detailed neurologic evaluations and therefore be better advised regarding future participation. The presence of an *APOE* ε4 allele in a boxer would not necessarily preclude a boxer from participation but could be an indication to minimize or more strictly limit exposure to the sport (eg, excessive number of bouts, long duration of career, or numerous knockouts).

These preliminary findings suggest that the *APOE* ε4 allele may be associated with the pathophysiology of CTBI secondary to boxing. The magnitude of this effect as well as its precise mechanisms remain to be elucidated. In light of the established role of *APOE* ε4 as a risk factor for late-onset forms of AD, the current findings lend further support to the hypothesis that both AD and dementia pugilistica are complex disorders arising from the interaction of inherited susceptibilities and environmental exposures, including (but not limited to) *APOE* genotype and head trauma.

Dr Jordan received research funding from the Sports Neurology Boxing Fund, New York, NY; Drs Relkin, Ravdin, Jacobs, and Gandy received grants from the C.V. Starr Foundation, New York, NY; and Dr Relkin received a grant from the Hoyt Foundation, Cranbury, NJ.

The authors would like to thank Margaret Peterson, PhD, for statistical assistance and Greta Strong for her assistance in preparing the manuscript. Study coordination by Carmen Sanchez, MPH, is gratefully acknowledged. The technical assistance of Benjamin Lewis, Julia Tsai, and Celine Brockman, MS, in carrying out *APOE* genotyping is appreciated.

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