Practice of Epidemiology

Professional Fighters Brain Health Study: Rationale and Methods


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Initially submitted August 23, 2012; accepted for publication November 12, 2012.

Repetitive head trauma is a risk factor for Alzheimer’s disease and is the primary cause of chronic traumatic encephalopathy. However, little is known about the natural history of, and risk factors for, chronic traumatic encephalopathy or about means of early detection and intervention. The Professional Fighters Brain Health Study is a longitudinal study of active professional fighters (boxers and mixed martial artists), retired professional fighters, and controls matched for age and level of education. The main objective of the Professional Fighters Brain Health Study is to determine the relationships between measures of head trauma exposure and other potential modifiers and changes in brain imaging and neurological and behavioral function over time. The study is designed to extend over 5 years, and we anticipate enrollment of more than 400 boxers and mixed martial artists. Participants will undergo annual evaluations that include 3-tesla magnetic resonance imaging scanning, computerized cognitive assessments, speech analysis, surveys of mood and impulsivity, and blood sampling for genotyping and exploratory biomarker studies. Statistical models will be developed and validated to predict early and progressive changes in brain structure and function. A composite fight exposure index, developed as a summary measure of cumulative traumatic exposure, shows promise as a predictor of brain volumes and cognitive function.

Abbreviations: CTE, chronic traumatic encephalopathy; MRI, magnetic resonance imaging; PFBHS, Professional Fighters Brain Health Study.

Repetitive head trauma is a reported risk factor for Alzheimer’s disease and is considered the primary cause of chronic traumatic encephalopathy (CTE) (1–3). The long-term effects of cumulative head trauma have come to public view with the revelation that many athletes who play contact sports, some of whom are rather young, have been found to have pathologically verified CTE (4). Yet, despite the attention that this issue has engendered, little is known about the natural history of, and risk factors for, CTE or about the means of early detection and intervention.

Professional fighters are a potentially informative cohort for studying the neurological sequelae of repeated head trauma. These athletes are on the receiving end of thousands of blows to the head over many years with their traumatic exposure scheduled and, in many ways, measurable. Previous studies have identified a variety of risk factors for CTE in boxers, including frequency and duration of fighting, fighting style, abnormalities on neuroimaging, and the apolipoprotein E4 genotype (5, 6).

Clinical manifestations of CTE can include motor deficits, affective and personality changes including a decline in impulse control, and impaired cognitive function. In regard to the latter, neuropsychological studies of former boxers indicate difficulties with memory, processing speed, complex attentional tasks, sequencing abilities, and frontal executive functions (7, 8). Similarly, various findings on magnetic resonance imaging (MRI) have been reported in active boxers, though these studies differ in the criteria used to identify abnormalities (9–14).

The relevance of previous studies of CTE in boxers to current athletes is limited by a number of methodological concerns. The following issues cloud the interpretation of...
prior work: 1) reliance on retrospective or cross-sectional design; 2) lack of, or inadequate, control groups; 3) evidence based on small sample sizes or case reports; 4) selection bias of boxers who are symptomatic or who have extraordinary amounts of exposure; and 5) use of retired fighters who may have competed under different regulations or tended to have greater exposures.

Among modern fighters, who usually have shorter careers and fewer fights per year, another relevant concern may be the future development of other neurodegenerative diseases such as Alzheimer’s disease and Parkinson’s disease (15–17). Head trauma is reported to induce overexpression of the amyloid precursor protein and could “prime the pump” for Alzheimer’s disease by premature deposition of β-amyloid. Little is known about what the risk of Alzheimer’s disease will be in contemporary fighters. However, the technology now exists to image amyloid in vivo by using positron emission tomography (18).

Repetitive head injury occurs in a wide variety of contact sports, as well as in those engaged in military activities. The precise incidence of CTE after repetitive head injury is unknown but is likely to be at least 20% (4, 19, 20). As in many neurodegenerative diseases, it is likely that there is a period of time when pathophysiological changes occur in the brain prior to initial symptoms, when intervention may be possible to delay clinical onset. Presently, though, we lack a biomarker or clinical indicator of CTE that can predict whether an individual exposed to recurrent head trauma is in danger of developing, or already in the midst of, a progressive neurodegenerative brain disorder.

With the goals of overcoming the methodological limitations of prior research and addressing some of the important unanswered questions in the field of cumulative head trauma, we have initiated the Professional Fighters Brain Health Study (PFBHS), an observational, longitudinal study of active professional fighters. In this article, we describe the objectives and design of the PFBHS, along with a characterization of our cohort through the first year.

The objectives of the PFBHS are 1) to quantify the associations between measures of head trauma exposure and other potential modifiers and changes in brain imaging and neurological function over time; 2) to determine the relationships between brain imaging and cognition and behavior in fighters; and 3) to identify biomarkers and other indicators that are associated with declining cognitive and neurological function in those exposed to repetitive head trauma.

**MATERIALS AND METHODS**

**Study design**

The PFBHS is a longitudinal observational study of unarmed professional combatants participating in boxing, mixed martial arts, or martial arts. The study will be performed over an 8-year period with recruitment of new subjects extending over 4 years. Subjects will be seen for a baseline evaluation and on an annual basis thereafter for at least 4 years.

**Study population and recruitment**

Participants will be drawn from those seeking initial licensure or renewing licensure to fight professionally in the state of Nevada. Subjects must be aged ≥18 years, have at least a fourth-grade reading level, be fluent in English or Spanish, and be able to undergo 3-tesla MRI of the brain.

The Nevada Athletic Commission (Las Vegas, Nevada) receives approximately 800 applications (initial and renewing) per year for licenses to participate in unarmed combat. We anticipate that approximately 160 applicants per year will enroll in the study.

Recruitment information for the study was distributed through several channels, including the following: the Nevada Athletic Commission, which posted a recruitment brochure on its website; communications with those involved in the management and training of fighters (e.g., promoters, managers, trainers); and direct outreach to fighters at local training facilities. Participants are allowed to submit, if they wish, any results of the testing performed in the study to the Nevada Athletic Commission to fulfill licensing requirements. Currently, fighters are required to undergo MRI and magnetic resonance angiography for their initial licensure and testing for human immunodeficiency virus and hepatitis B and C each year they are licensed.

**Procedures**

This study was approved by the local institutional review board. All initial and follow-up evaluations are performed at the Cleveland Clinic’s Lou Ruvo Center for Brain Health in Las Vegas, Nevada. Participants cannot have fought in a sanctioned professional or amateur competition during the 45 days prior to the study visits. All subjects are thoroughly informed of the risks and benefits of participation in the research study, and their informed consent is obtained. On the initial study visit, subjects undergo the following procedures in a standard order: With the assistance of the study coordinator, participants answer questionnaires that collect information on demographics, educational attainment, family and medical history, drug, alcohol, and tobacco use, and current medications. Subjects are asked about previous head trauma (both related and unrelated to athletic activities), prior involvement in other contact sports, fighting history (age when competitive fighting began and amateur record), whether they have fights scheduled within 2 weeks of the study visit, and training habits (customary sparring schedules, as well as sparring information over the 2 weeks prior to the study visit). Subjects are queried regarding any facial cuts or possible concussions experienced in training over the 2 weeks prior to the study visit. Subjects are instructed to consider as a concussion not only instances in which they were “knocked out” but also episodes in which they were “dazed,” “stunned,” or had their “bell rung.”

Before the study visit, the fighters’ professional records are obtained from commonly cited websites (http://www.boxrec.com for boxers and http://www.mixedmartialarts.com and http://www.sherdog.com for mixed martial arts fighters) to determine the number of years of professional fighting, number and outcome of professional fights, number of...
rounds fought, weight class of each fight, frequency of professional fighting, and number of times knocked out (which includes both knockouts and technical knockouts). This information is reviewed with the subjects for accuracy by the study coordinator.

Information about behavioral status of the subjects is obtained through 2 self-administered questionnaires, the Patient Health Questionnaire-9 (21) and the Barratt Impulsivity Scale-11 (22). The Patient Health Questionnaire-9 is a 9-question test that assesses the presence of depression. The Barratt Impulsivity Scale-11 is a 30-question test that assesses the presence and degree of impulsive behavior. The subjects complete the Epworth Sleepiness Scale and are asked to rate their average sleep times (23).

Cognitive function is assessed by several computer-based and verbal tests. The computer-based assessment consists of 4 subtests of the CNS Vital Signs program (CNS Vital Signs, Morrisville, North Carolina) including verbal memory, symbol digit coding, the Stroop test, and a finger tapping test. Results from these tests are used to determine scores in various clinical domains (i.e., verbal memory, processing speed, psychomotor speed, and reaction time). The test battery is available in both English and Spanish with several versions of each section available for retesting. In addition, subjects take a computerized version of the Trails A and B test. The total computer test time is approximately 25 minutes and is performed by the subject with the study coordinator present to proctor the effort and answer questions. The study coordinator also administers and records the phonemic (letter F) and semantic (animals) tests of verbal fluency (24, 25).

A standard neurological examination is performed, including testing for ocular dysmetria and the 3-step Luria test (26). A speech sample is obtained from the participant by using a handheld voice recorder. The speech sample consists of reading a standard paragraph and a 1-minute extemporaneous description of the subject’s last fight.

An MRI scan of the brain is performed with a MAGNETOM Verio 3-tesla scanner (Siemens Medical Systems, AG, Erlangen, Germany). The MRI protocol includes whole-brain 3-dimensional high-resolution $T_1$-weighted, $T_2$-weighted, fluid-attenuated inversion recovery and susceptibility weighted imaging for anatomical information. Additionally, functional magnetic resonance measures are performed by using whole-brain pseudocontinuous arterial spin labeling for quantitative perfusion, whole-brain diffusion tensor imaging for measures of white matter integrity, and resting state functional connectivity as a measure of neuronal dynamic connectivity. The time required for MRI is approximately 50 minutes. If the participant is applying for initial licensure in Nevada, a magnetic resonance angiography of the Circle of Willis is performed at the fighter’s request.

The annual follow-up visits are scheduled within a window of 9–15 months from the previous visit but at least 45 days after a sanctioned professional competition if 1 had occurred. During the follow-up visit, the study coordinator updates any changes in the initial intake questionnaires, as well as the fight record and changes in training. The subject will complete the Patient Health Questionnaire-9, the Barratt Impulsivity Scale-11, the computerized cognitive battery, a neurological examination, a speech sample, and MRI of the brain.

Beginning in the second year of the study, participants will be given the option of undergoing venipuncture, with part of the sample sent for testing for the human immunodeficiency virus, hepatitis B, and hepatitis C. A portion of the remaining sample will be sent for DNA extraction and apolipoprotein E genotyping with multiple aliquots of plasma or serum prepared and stored.

Two other cohorts will be enrolled in the second year. One will be a control group matched for age and education but without any prior experience at a high school level or higher participating in a combat sport or a sport in which head trauma can be anticipated to occur, such as football, hockey, rugby, soccer, or rodeo. This group will be recruited from settings where physical fitness is emphasized, such as local YMCAs or city recreational leagues. The second group is retired fighters who have participated in at least 10 professional fights. Both groups will undergo the same procedures as for the active fighters and will be evaluated on an annual basis.

To ensure that the participants in the PFBHS do not differ significantly from all those who fight professionally, we reviewed results from every sanctioned professional fight in Nevada from January 1, 2011, to December 31, 2011, by using the Nevada Athletic Commission website (http://www.boxing.nv.gov). The age, professional record, number of years of professional fighting, and number of knockouts/technical knockouts were recorded for each fighter. Comparisons were made between study subjects and all fighters for each characteristic.

Of the initial 121 fighters enrolled, 58% were mixed martial artists. The mixed martial artists were more highly educated, older when they began competing, and more likely to be Caucasian, whereas boxers had more total fights and more years of fighting (Tables 1 and 2). Compared with all fighters licensed in Nevada during 2011–2012, the study participants were slightly younger and had a shorter professional career but were similar in their winning percentages and number of times being knocked out.

**Statistical analysis**

The statistical analysis will be conducted in 3 stages. Predictors of changes in brain imaging, cognition, and behavior will be developed in stage 1, tested in stage 2, and validated in stage 3. Data from the first 300 fighters enrolled will be used to develop and test the models (training sample), and data from the last 100 fighters enrolled will be used to measure the accuracy of the models (validation sample). In stage 1, data plots and regression decision trees, along with expert opinion, will be used to develop fight exposure indices and to identify imaging biomarkers predictive of early and progressive brain changes. Potential predictors of structural and cognitive change, after adjustment for race, age, sex, and education, will be tested by using multiple-variable regression models in stage 2. By using an independent validation sample, we will estimate the sensitivity, specificity, and discrimination ability (e.g., area under the receiver operating characteristic curve) of the prediction models in stage 3.

On the basis of cross-sectional data from the first 146 fighters enrolled in the study, we created a composite fight
exposure index from a regression decision tree of the MRI-based brain volume data. The tree represents a collection of hierarchical nonparametric rules that segment the data into more homogeneous groups on the basis of a deviance score. Guided by the tree branch splitting values and deviance reduction values, we created a 5-point exposure composite score for predicting brain volume as a function of the total number of fights and the average number of fights per year (Table 3). A second composite score, based only on professional fighting exposure, is also under evaluation (Table 4). These indices show promise as independent predictors of thalamus, caudate, and amygdala volumes, which in turn are strong predictors of neurological processing scores.

**Sample size considerations**

Our sample size projections are based on our initial cross-sectional data. To detect a 3-unit difference in cognition scores (the difference observed in the current data) as a function of fight exposure index, approximately 300 fighters are needed in the training sample for 82.1% power and a 5% type I error rate. An additional 50 control subjects would permit detection of a 0.5-unit difference in brain volumes (i.e., 0.5 is half of the observed standard deviation) between subjects with low fight exposure versus no exposure (for 79% power and a 5% type I error rate). For our validation sample, a sample size of 100 fighters would allow us to rule out any prediction model with discrimination ability of <0.65 with 80% power and 5% type I error rate.

To date, we have enrolled boxers and mixed martial artists in nearly a 1:1 ratio, providing sufficient power to detect

**Table 1. Demographic Information for 121 Professional Fighters Initially Enrolled in the Professional Fighters Brain Health Study, Nevada, 2011–2012**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Boxers (n = 51)</th>
<th>Mixed Martial Artists (n = 70)</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) %</td>
<td>Mean (SD) %</td>
<td>Mean (SD) %</td>
<td>Mean (SD) %</td>
</tr>
<tr>
<td>Age, years</td>
<td>29.2 (8.6)</td>
<td>29.2 (5.0)</td>
<td>29.2 (6.7)</td>
</tr>
<tr>
<td>Years of education</td>
<td>13.0 (2.3)</td>
<td>14.1 (2.5)</td>
<td>13.66 (2.5)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>78.1 (17.0)*</td>
<td>75.7 (12.1)</td>
<td>76.7 (14.3)</td>
</tr>
<tr>
<td>Male sex</td>
<td>92.2</td>
<td>92.9</td>
<td>92.6</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>21.6</td>
<td>40.0**</td>
<td>32.2</td>
</tr>
<tr>
<td>Black</td>
<td>41.2**</td>
<td>11.4</td>
<td>24.0</td>
</tr>
<tr>
<td>Hispanic</td>
<td>25.5</td>
<td>17.1</td>
<td>20.7</td>
</tr>
<tr>
<td>Other contact sports</td>
<td>7.8*</td>
<td>4.3</td>
<td>5.8</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>15.7</td>
<td>37.1*</td>
<td>28.1</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>2.0</td>
<td>4.3</td>
<td>3.3</td>
</tr>
<tr>
<td>Family history of Alzheimer’s disease</td>
<td>11.8</td>
<td>11.4</td>
<td>11.6</td>
</tr>
</tbody>
</table>

Abbreviation: SD, standard deviation.
* P < 0.05; ** P < 0.005.

**Table 2. Mean Values of Fight Exposure Variables for 121 Professional Fighters Initially Enrolled in the Professional Fighters Brain Health Study, Nevada, 2011–2012**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Boxers (n = 51), mean (SD)</th>
<th>Mixed Martial Artists (n = 70), mean (SD)</th>
<th>Combined, mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age when started fighting, years</td>
<td>16.2 (8.3)</td>
<td>19.9 (6.3)*</td>
<td>18.3 (7.4)</td>
</tr>
<tr>
<td>Total years of fighting</td>
<td>13.1 (7.5)*</td>
<td>9.4 (7.2)</td>
<td>11.0 (7.5)</td>
</tr>
<tr>
<td>No. of fights per year</td>
<td>5.5 (4.0)</td>
<td>4.4 (8.3)</td>
<td>4.9 (6.8)</td>
</tr>
<tr>
<td>Total no. of fights</td>
<td>90.0 (89.5)**</td>
<td>24.1 (17.6)</td>
<td>48.4 (58.5)</td>
</tr>
<tr>
<td>Years as amateur</td>
<td>7.4 (5.5)**</td>
<td>4.4 (5.7)</td>
<td>5.7 (5.7)</td>
</tr>
<tr>
<td>Years as professional</td>
<td>5.7 (6.2)</td>
<td>5.0 (4.5)</td>
<td>5.3 (5.3)</td>
</tr>
<tr>
<td>No. of knockouts</td>
<td>1.3 (2.4)</td>
<td>0.9 (1.4)</td>
<td>1.05 (1.9)</td>
</tr>
</tbody>
</table>

Abbreviation: SD, standard deviation.
* P < 0.05; ** P < 0.005.
Table 4. Composite Fight Exposure Score for Predicting Volume From Professional Fighting Exposure, Professional Fighters Brain Health Study, Nevada, 2011–2012

<table>
<thead>
<tr>
<th>Total No. of Professional Fights</th>
<th>0 Professional Fights Per Year</th>
<th>0.1–1 Professional Fights Per Year</th>
<th>&gt;1 Professional Fights Per Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>1–15</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>&gt;15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

fairly small differences of 3%–4% between these 2 groups in brain volume in some structures (e.g., the thalamus). As enrollment continues, we will monitor this ratio and adjust our sample requirements with stratification of these 2 types of fighters if needed.

**DISCUSSION**

According to the Centers for Disease Control and Prevention (Atlanta, Georgia), nearly 1 million individuals experience a concussion each year, frequently in the setting of organized sports (27). Moreover, there has been increasing recognition in the scientific and lay media of retired athletes who have died with pathologically confirmed CTE (3). Yet little is known about how repeated concussions or subconcussive blows to the head lead to a chronic neurodegenerative condition such as CTE. There are no existent biological markers for early detection of CTE, our knowledge of the risk factors for development of CTE is limited, and we know little of the spectrum of other brain disorders that may be related to cumulative head trauma (2, 4, 5–7).

The PFBHS is designed to begin accumulating information about the evolution of CTE and perhaps other long-term brain disorders related to head trauma. Because the pathogenesis of CTE, like other neurodegenerative diseases such as Alzheimer’s disease and Parkinson’s disease, may begin years before clinical symptoms become noticeable, we have chosen to begin longitudinal assessment of active fighters. A practical aim of the study is to identify a marker, either through MRI of the brain or changes over time in cognitive or speech measures or blood constituents, that may identify early disease and/or track disease progression.

The group of fighters initially enrolled in the study appears to represent a relatively broad range of fighting experience. It also seems that the participating cohort, though not a random sample of fighters, is generally representative of professional fighters, being only slightly younger with slightly fewer years of fighting compared with all licensed professional fighters in Nevada. However, there is a danger of a selection bias arising in those who remain for the duration of the study.

Among the major challenges in the field of traumatic brain injury, particularly for a longitudinal study of fighters, is the quantification of exposure. In the absence of a direct measure of the cumulative trauma each subject experiences, there are several potential surrogates that can be used, such as the total number of fights, the number of fights per year, the number of knockouts, and the years of fighting; however, each of these variables may actually have a slightly different influence on the development of CTE. The total number of fights, for example, may act as a proxy for the amount of training. Some have postulated that the effects of repeated blows to the head, even at a subconussive level, that occur during sparring may play as important a role as the match itself in causing cumulative brain injury (28, 29). Furthermore, frequency of fighting may be a complementary variable that requires consideration; fighting more frequently may reduce the time the brain has to fully recover from prior trauma and may be a risk factor that interacts with the total number of fights.

To incorporate these various aspects of exposure into a single measure, we created 2 novel composite fight exposure indices. These indices were developed by using brain volume as the outcome. One takes into account the total fight exposure (amateur and professional), and the other is based on the number of professional fights only (because amateur records are difficult to ascertain). On the basis of its performance over time in our cohort, 1 of the composite fight exposure indices may turn out to be a useful summary measure of exposure in future research and a tool for regulatory agencies in setting standards for surveillance of fitness to compete in combat sports.

In constructing the composite fight indices, we combined data from both boxers and mixed martial artists. Although there are clearly differences between the 2 sports (e.g., glove size, scheduled length of fights, means of striking a blow, and scoring) it is unclear whether the exposures to head trauma during training and competition are similar. Initial cross-sectional analysis of our first-year cohort did not reveal significant differences between the 2 groups in the relationship between exposure and brain volumes. As the PFBHS moves forward, the type of fighting will be entered into analyses, and differences between the 2 sports may emerge; however, studies comparing forces on the head (via helmet or mouthpiece sensors) between the 2 sports may provide the best comparative information.

An issue inherent in following athletes who are still active in their sports, particularly combat sports, is differentiating whether outcome measurements reflect chronic change or are influenced by recent acute injury. The design of the PFBHS excludes subjects who have had a sanctioned competition during the 45 days prior to the study visit; the intention of this exclusion is to allow sufficient time for resolution of any acute effects on MRI-determined cerebral blood flow, resting state connectivity, or cerebral edema and performance measures (cognitive testing). Dealing with the potential acute effects of sparring is more problematic. It is not feasible in this cohort to restrict sparring for a designated period before the study visit. Therefore, characteristics of the subjects’ training and exposure for the 2 weeks prior to the study visit are recorded. Ideally, these data could be coupled with information derived from planned studies that examine the immediate effects of sparring by using MRI and other tests to determine which measures are least influenced by acute trauma.

Several other potential limitations of the PFBHS need to be highlighted. Though subjects’ professional records are verified from standard databases, information regarding amateur fighting experience and traumatic brain exposures outside the ring is

self-reported. Moreover, a certain degree of variability of the cognitive testing must be anticipated. Fighters have their study visits at various time points related to upcoming competitions. A subject whose study visit is several days before a match is likely to be “cutting weight,” that is, trying to lose a certain amount of weight prior to the official weigh-in. At this point, the subject may be volume depleted and fatigued. If the same subject comes for a follow-up visit at a date not closely related to a fight, his or her performance may be better. Though it is difficult to control for the effects of volume depletion, fatigue, and training, the study coordinator proctoring the testing does encourage the participants and notes any obvious lapses in effort. Finally, it is currently unknown whether it is possible to detect significant changes in biomarkers or performance measures over a 5-year period of follow-up in relatively young athletes. Without pathological verification, there is no way to know if changes in biomarkers reflect the development of a disease such as CTE.

Although the definitive means to protect athletes from developing CTE would be to restrict blows to the head, this is not realistic given the current structure of many contact sports. However, more knowledge of the natural history of, risk factors for, and biomarkers of CTE would assist regulatory agencies in developing objective guidelines and advising athletes of their status in the hope of preventing long-term neurological complications. Output from studies such as the PFBHS may help provide such information.

ACKNOWLEDGMENTS

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Funding for this study was provided by the Linck Foundation.

We would like to thank Triny Cooper, Isacc Santa Ana, Brittany Mayer, and Michelle Sholar for their contributions to this study.

Conflict of interest: Charles Bernick is a member of the speakers bureaus for UCB Inc., Teva Pharmaceutical Industries, Ltd., and Novartis Pharmaceuticals Corp. No other authors have reported conflicts of interest.

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