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## **TRAUMATIC BRAIN INJURY**

### **Genetic interplay with soccer ball**

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**Mortality from neurodegenerative disease is high among professional soccer players, potentially associated with repeated head impacts during routine gameplay. New data suggest that the apolipoprotein E  $\epsilon$ 4 allele might exacerbate the effects of soccer ball heading on cognition. However, genotyping of athletes to determine their dementia risk remains a distant prospect.**

Refers to Hunter, L. E. et al. Associations of apolipoprotein E  $\epsilon$ 4 genotype and ball heading with verbal memory in amateur soccer players. *JAMA Neurol.* <https://doi.org/10.1001/jamaneurol.2019.4828> (2020).

Soccer is the world's most popular participation sport, with over a quarter of a billion active participants worldwide. Given such high participation numbers, concerns have been raised over the fact that mortality from neurodegenerative disease among former professional soccer players is ~3.5-fold higher than in matched population controls, ranging from a twofold increase in deaths with Parkinson disease to a fivefold increase in deaths with Alzheimer disease (AD)<sup>1</sup>. Furthermore, autopsy studies on former soccer players with dementia report chronic traumatic encephalopathy (CTE) neuropathologic change, a neurodegenerative pathology associated with exposure to traumatic brain injury (TBI) and repeated head impacts, in ~75% of cases<sup>2</sup>. Consequently, there is a

need to identify the factors that contribute to high neurodegenerative mortality in former soccer players, in particular, the role of head impact exposure.

Repeated head impacts through heading the ball are considered part of normal training and match play in soccer. Data show that a single session of heading can lead to immediate, short-lived cognitive impairment<sup>3</sup>, and self-reported exposure to football heading correlates with structural changes on brain imaging studies<sup>4</sup>; however, the late cognitive consequences attributable to soccer heading remain uncertain. A new report from the Einstein Soccer Study provides novel insight into how the interplay between exposure to heading and apolipoprotein E (*APOE*) genotype affects cognitive performance after extensive soccer participation<sup>5</sup>.

Reporting on a cohort of 352 amateur soccer players with at least 5 years of participation, the authors confirmed their previous observation<sup>6</sup> that verbal memory performance inversely correlates with history of self-reported exposure to ball heading. Specifically, performance on the delayed recall component of the International Shopping List Test (ISLT) was poorest for participants reporting the highest exposure to heading in the previous 12 months.

The authors went on to consider the influence of the *APOE* genotype on cognitive performance in this cohort. In isolation, possession of the *APOE\** $\epsilon$ 4 allele produced no measurable effect on ISLT delayed recall. However, in a subgroup analysis in which players were stratified by *APOE* genotype and extent of heading exposure, those with the *APOE\** $\epsilon$ 4 allele and highest heading exposures performed the worst out of all the groups. Notably, however, the observed effect size was small,

equivalent to recalling one item fewer on the shopping list than players in the low and moderate heading exposure groups.

Individuals carrying the *APOE\** $\epsilon$ 4 allele are known to be at increased risk of developing AD<sup>7</sup>. Furthermore, multiple levels of enquiry have demonstrated that following a single moderate or severe TBI, *APOE\** $\epsilon$ 4 carriers show evidence of poorer immediate and 6-month outcomes and greater long-term dementia risk than non-carriers<sup>7</sup>. Data regarding the influence of *APOE* genotype on outcomes from repetitive mild TBI are largely restricted to observations in small cohorts. However, possession of the *APOE\** $\epsilon$ 4 allele has been linked to neurological and cognitive impairment in former boxers<sup>8</sup> and American football players<sup>9</sup>.

An overwhelming majority of research on neurodegenerative outcomes in contact sport athletes has focused on the association with CTE. Preliminary consensus criteria for the neuropathological evaluation of CTE describe the pathognomonic pathology as abnormally deposited hyperphosphorylated tau in neurons and astrocytes, with CTE often referred to as a primary 'tauopathy'<sup>10</sup>. Nonetheless, amyloid- $\beta$  (A $\beta$ ) pathologies, which are more closely linked to *APOE\** $\epsilon$ 4 than tau pathologies, are also observed in individuals with CTE, with greater prevalence in those who are *APOE\** $\epsilon$ 4-positive<sup>7</sup>. In addition, possession of the *APOE\** $\epsilon$ 4 allele is associated with the development of diffuse A $\beta$  plaques shortly after moderate or severe TBI<sup>7</sup>. However, it remains unclear how *APOE* genotype might influence late pathologies, including CTE neuropathological change, in individuals exposed to head impacts and TBI.

As a cross-sectional study, the new report by Hunter and co-authors<sup>5</sup> provides little insight into whether the difference in cognitive performance between the highest

and lower heading-exposed soccer players is static or progressive. In addition, although the cohort was sizeable, notable demographic differences between the subgroups might have influenced the outcomes. For example, the highest heading exposure subgroup had fewer years of education and included more males than the other subgroups. Also of note, the authors did not consider race, which is known to modify the influence of *APOE* genotype on dementia risk, in their analysis. However, the ongoing Einstein Soccer Study provides scope to address these issues in future work through longitudinal evaluations and with an expanded cohort.

Notwithstanding these limitations, many of which the authors acknowledge, their approach has substantial strengths. Whereas many studies have reported observations on professional athletes only, this work focuses on outcomes in amateur soccer players. Therefore, data from this relatively large study population have greater relevance for the overwhelming majority of participants in the sport. Furthermore, by combining observations on the influence of heading exposure and *APOE* genotype, the study is the first to consider the interaction of two putative risk factors in determining cognitive outcomes in soccer players.

The authors suggest that their findings could inform an advanced approach to risk stratification for soccer players, based on heading exposure and *APOE* genotype. However, the data do not yet support such a strategy. No difference in outcome was observed between low and intermediate heading exposure subgroups, irrespective of stratification for *APOE* genotype. The only observed difference was in the highest exposure subgroup, with only a minimal effect noted, and the immediate and longer-

term clinical relevance — if any — of the marginal difference in performance observed in this single task is unclear.

In conclusion, these observations on amateur soccer players raise some important questions regarding the influence of multiple interacting risk factors on cognitive outcomes in contact sport athletes. However, much more research will be required to support the study authors' proposal that prospective genotyping might be used to identify an individual athlete's risk and, based on this, advise on safe limits for head impact exposure.

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### **Competing interests**

The authors declare no competing interests.