Fluid biomarkers and risk of neurodegenerative disease in retired athletes with multiple concussions: results from the International Concussion and Head Injury Research Foundation Brain health in Retired athletes Study of Ageing and Impact-Related Neurodegenerative Disease (ICHIRF-BRAIN study)

Owen James Swann,1, Michael Turner,2 Amanda Heslegrave,1,3 Henrik Zetterberg1,4

ABSTRACT
Objectives To investigate the association and utility of blood plasma markers of neurodegeneration in a population of retired athletes self-reporting multiple concussions throughout a sporting career. It is hypothesised that this type of athletic history would cause an increased prevalence of neurodegenerative disease, as detected by biomarkers for neurodegenerative disease processes.

Methods One hundred and fifty-nine participants were recruited (90 males, 69 females, mean age 61.3±9.3 years), including 121 participants who had retired from playing professional or semiprofessional sports and self-reported ≥1 concussion during their careers (range 1–74; mean concussions=10.7). The control group included 38 age-matched and sex-matched controls, with no history of concussion. We measured neurofilament light (NFL) and tau (neurodegeneration markers), glial fibrillary acidic protein (GFAP) (astrocytic activation marker) and 40 and 42 amino acid-long amyloid beta Aβ40 and Aβ42 (Alzheimer-associated amyloid pathology markers) concentrations using ultrasensitive single molecule array technology.

Results We found retired athletes reporting one or more concussions throughout an athletic career showed no significant changes in NFL, tau, GFAP and Aβ40 and Aβ42 concentrations in comparison to a control group. No correlations were found between biomarkers and number of concussions (mean=10.7). A moderate correlation was found between NFL concentration and age.

Conclusion No difference in blood concentrations of neurodegeneration markers NFL, tau, GFAP and Aβ40 and Aβ42 was found in retired athletes with a history of concussion compared with controls. An increased prevalence of neurodegenerative diseases is not detected by biomarkers in a population self-reporting multiple concussions.

Trial registration number ISRCTN 11312093

WHAT IS ALREADY KNOWN ON THIS TOPIC
⇒ Little is known about neurofilament light, tau, glial fibrillary acidic protein and Aβ40 and Aβ42 blood plasma concentrations many years after competing in sports that carry a risk of concussion/mild traumatic brain injury. This study was done to assess whether experiencing repetitive concussions throughout an athlete’s lifetime leads to any changes in various biomarker concentrations that may indicate an increased risk of long-term neurodegenerative disease.

WHAT THIS STUDY ADDS
⇒ This study found no significant differences in any of the biomarker concentrations between retired athletes with concussion and a control group without a history of concussion.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY
⇒ Our study does not refute that lifetime concussions may induce neurodegeneration and/or reduce resilience to neurodegenerative disease, but the usefulness of fluid biomarkers alone as a predictor of long-term neurodegenerative disease risk may be limited.

INTRODUCTION
Multiple concussions/mild traumatic brain injury (mTBI) or repetitive subconcussive head impact in athletes is a growing concern due to an association with impaired mental health, cognitive impairment and increased...
risk of neurodegenerative disease. There is evidence of a link between moderate-severe TBI in young adults and Alzheimer’s disease and other dementias later in life. Gavett et al suggest the possibility that repetitive mTBI resulting in axonal injury can result in Alzheimer’s disease, frontotemporal dementia or chronic traumatic encephalopathy in later life.

To protect the brain health of athletes at risk of mTBI, it is important that the risks of concussion are carefully considered and that danger to the athlete should be reduced whenever possible. Demands to ban sports considered and that danger to the athlete should be reduced whenever possible. Gavett et al suggest the possibility that repetitive mTBI resulting in axonal injury can result in Alzheimer’s disease, frontotemporal dementia or chronic traumatic encephalopathy in later life.

This study uses single molecule array (Simoa) technology, which is a supersensitive immunoassay technology that allows us to measure proteins that give information about neuronal health using serum or plasma as the biofluid. We measured neurofilament light (NFL), a biomarker of large-calibre myelinated axon damage, glial fibrillary acidic protein (GFAP), which is a biomarker of astroglia cell damage, and tau, which is a biomarker of thin non-myelinated axon damage. Amyloid beta 1-40 (Aβ40) and amyloid beta 1-42 (Aβ42) are markers of amyloidogenic amyloid precursor protein processing, which is upregulated on axonal injury and can result in the formation of diffuse amyloid plaques that may be related to onset of amyloid aggregation typical of Alzheimer’s disease.

Most studies investigating blood biomarkers after concussion collect samples within a short time period (days to months) after injury. No study to our knowledge has looked at this combination of blood plasma biomarkers after a period of years in retired athletes participating in various sports with a risk of concussion. However, Di Battista et al used a similar approach by grouping athletes who competed in collision sports, but only assessed tau concentrations. It is hypothesised that this type of athletic history used in this study would cause an increased prevalence of neurodegenerative disease, as detected by biomarkers for neurodegenerative disease processes, compared with a control group.

**Aim**

To investigate NFL, tau, GFAP and Aβ40 and Aβ42 fluid biomarker concentrations in plasma of retired athletes who have competed in sports with a risk of concussion in comparison to a control group with no reported concussions.

**METHODOLOGY**

**Participants**

Participants were initially sought through a widely advertised study and invited to complete an online screening process. Participants responded to a detailed online questionnaire regarding self-reported concussion history, mood, sleep and physical and mental health status (online supplemental file 1). From the database of completed questionnaires, participants with a history of concussion were matched to control participants with no history of concussion of the same age and sex. All the participants in the concussion group participated at a ‘professional or semi-professional’ level in their primary adult sport. The control group were active and played recreational sports with no self-reported history of concussion. Volunteers were all functioning normally in the community with no clinical evidence of neurodegenerative disease and were of a sound mind capable of leading an independent life. Participants with a history of concussion and their age-matched and sex-matched controls were then randomly selected for more detailed screening, including neuropsychological assessment and neuroimaging in London, UK. All the volunteers were interviewed to ensure their concussion history was recorded correctly.

Recruitment was via publicity in sports-related media with 1200 volunteers enquiring to enrol into the study. Questionnaires were sent with 787 completed and included in the final cohort database. The physical screening on volunteers was initially focused on residents in England, Scotland or Wales and who were over the age of 55 (a total of 189 volunteers). To obtain statistical significance, it was estimated that a target total of 250 screened subjects was needed, so the invitation was extended to those aged 50–54 (an additional 129 volunteers). All 318 volunteers were invited to attend a screening day in London of which 32 declined. Of the remaining cohort, 166 were finally screened before COVID-19 prevented travel and screening. After this process, 159 samples were obtained for blood plasma biomarker concentration analysis.

Inclusion criteria: Participants were eligible to participate if they (1) participated but were then retired from their primary sport; (2) were able to complete the online screening assessment; (3) could understand and participate in the testing procedures; and (4) were able to provide informed consent for their participation.

Exclusion criteria: Participants were ineligible if they were aged <18 years; had a history of severe TBI; were currently taking sedative or psychotropic medication; or a pre-existing medically diagnosed neurological disorder (eg, Alzheimer’s dementia, Parkinson’s disease, multiple sclerosis, motor neuron disease).

**Sample collection and measurements**

Five millilitres of blood was collected from each participant in plasma EDTA tubes. Samples were centrifuged at 2000g and plasma aliquoted and stored at −80°C until assay. NFL, tau, GFAP and Aβ40 and Aβ42 were measured on the Simoa HD-X platform (Quanterix, Billerica, Massachusetts) according to the manufacturer’s instructions. Briefly, plasma samples were diluted fourfold and then incubated with paramagnetic beads coated with anti-Aβ40, anti-Aβ42, anti-GFAP, anti-NFL or...
anti-tau antibodies and biotinylated detector antibodies. Beads were washed and combined with a conjugate of streptavidin-b-galactosidase. This enzyme binds to biotinylated antibodies; bound enzyme is hydrolysed by resorufin-b-D-galactopyranoside producing a fluorescent signal that is read by the analyser. Calibrators run on the same assay produce a standard curve, enabling quantification of samples. All samples were analysed on one occasion using one batch of reagents; intra-assay coefficients of variation were below 10%. The number of results for each biomarker differs as a number of measurements can be lost due to technical issues or sample quality. In the control group, the number of measurable samples was tau (n=37), GFAP (n=38), NfL (n=38), Aβ40 (n=38) and Aβ42 (n=37). In the concussion group: tau (n=121), GFAP (n=119), NfL (n=119), Aβ40 (n=119) and Aβ42 (n=117).

Data analysis

The data were uploaded to Microsoft Excel and GraphPad Prism V.9.0 (GraphPad) for analysis. A Shapiro-Wilk test was used to assess the normality of the data. Post hoc analysis using a Mann-Whitney U test was used to compare biomarker concentrations between the concussion group and the controls. An unpaired t-test was used for the comparisons of the demographics between groups. The Pearson correlation coefficient was used for analyses of correlation between various biomarker concentrations and variables (the number of concussions reported and age). An analysis of variance test was used to test the significance of correlations. Significance was set at p<0.05.

Patient and public involvement

Participants and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

RESULTS

From this process, one hundred and fifty-nine participants were recruited (90 males, 69 females). This included 121 retired athletes who had experienced at least one concussion (basketball, boxing, cricket, cycling, equestrian, football, horse racing, motor sports, martial arts, rugby league, rugby union, sailing, shooting, skiing, trapeze). Thirty-eight age-matched and sex-matched controls, who did not report having had any concussions, were also screened. All the controls came from the same online registry. See table 1.

No significant differences were found in fluid biomarker concentrations between the control group and the retired athletes with a history of self-reported concussion (table 2). No association was found between each of the biomarkers and the number of concussions in the concussion group, tau r (0.04), GFAP r (-0.01), NfL r (-0.11), Aβ40 r (0.01) and Aβ42 r (-0.03) (figure 1). However, we found a moderate correlation between age and NfL concentration (r=0.44, p<0.001) and a weak correlation for GFAP (r=0.36, p<0.001) (figure 2). No associations were found between age and tau, Aβ40 or Aβ42 concentrations (p>0.05). The sex differences were also analysed between the controls and the participants with one or more self-reported concussion. No significant differences were found in males or females (table 3).

DISCUSSION

Main findings

This study found that retired athletes with a history of self-reported concussion (mean±SD 10.7±11.5) did not have a significant increase in biomarkers for neurodegeneration (NfL and tau), astrocytic activation (GFAP) or amyloid aggregation (plasma Aβ42/Aβ40) compared with a control group without reported concussions. The participants were retired from sport but functioning normally in the community without clinical evidence of neurodegenerative disease.

Neurofilament light

Several previous studies have shown that NfL can be regarded as a global marker of neurodegeneration due to elevated concentrations being present in frontotemporal dementia, Alzheimer’s disease, Huntington’s disease and other neurodegenerative disease. It has also been reported that serum NfL was elevated in amateur boxers 3 months after a bout of boxing in comparison to the control group. Similarly, NfL blood concentration has been shown to increase during the season in American football players. This implies that NfL could potentially be used as a marker of ongoing neuroaxonal injury secondary to repeated concuss.

In our study, we did not find any difference in plasma

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Values are means±SD</th>
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<tbody>
<tr>
<td>Criteria</td>
<td>Study group</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
</tr>
<tr>
<td>Number of participants</td>
<td>38</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>55.3%/44.7%</td>
</tr>
<tr>
<td>Age</td>
<td>62.1±6.8</td>
</tr>
<tr>
<td>Number of concussions</td>
<td>0±0</td>
</tr>
</tbody>
</table>

An unpaired t-test was used to calculate significance. Age was not significantly different between groups.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Values are median and IQR</th>
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</thead>
<tbody>
<tr>
<td>Biomarker</td>
<td>Study group (median (IQR))</td>
</tr>
<tr>
<td></td>
<td>Controls</td>
</tr>
<tr>
<td>Tau (n=158)</td>
<td>1.1±1.2</td>
</tr>
<tr>
<td>GFAP (n=157)</td>
<td>105.1±81.5</td>
</tr>
<tr>
<td>NfL (n=157)</td>
<td>16.1±9.6</td>
</tr>
<tr>
<td>Aβ40 (n=157)</td>
<td>60.0±64.1</td>
</tr>
<tr>
<td>Aβ42 (n=154)</td>
<td>4.2±3.9</td>
</tr>
</tbody>
</table>

The Mann-Whitney U test was used to calculate significance. No significant findings were found.

GFAP, glial fibrillar acidic protein.
NfL concentration between the two study groups. This may suggest that retired athletes with a history of concussions did not have a higher prevalence of neurodegenerative disease, as measured by plasma NfL or that increases in NfL related to acute brain injury may not be persistent in plasma over time.

**Tau**

Elevated blood plasma tau concentrations have been previously shown to be linked with neurological conditions including Alzheimer’s disease. Furthermore, exosomal tau has shown the potential to be a chronic traumatic encephalopathy biomarker in retired NFL players. When tau concentrations are raised, it suggests that axonal injury has occurred and can be seen in peripheral blood of professional boxers and ice hockey players within a short period after the event. However, the half life of tau in blood is short (around 10 hours), and Neselius et al. did find that after 14 days plasma tau concentrations were no longer significantly different from the controls. Nevertheless, in a study involving retired American football athletes it has been shown that greater exposure to repetitive head impacts correlated with elevated later life plasma total tau concentrations. Similarly, Di Battista et al. found in male university-level athletes that plasma tau concentrations were significantly higher in collision sport athletes in comparison to non-collision sport athletes with samples collected at the start of the competitive season, although this was not seen in females. Also, when plasma tau concentrations were evaluated in combination with collision sport involvement, biomarker variability was not impacted by the athletes’ concussion history and found to be a non-significant influence. Therefore, Di Battista et al. suggested that a larger biological response may be evoked from frequent subconcussive hits due to collision sport involvement than reported concussion. Kenney et al. found higher plasma tau concentration in military personnel with a history of TBI. This was shown particularly in military personnel who have reported more than three TBIs throughout their deployment or with a medical diagnosis of TBI. Kenney et al.’s study was also similar to our study, limited due to the self-reporting of the TBIs. Olivera et al. also conducted a study testing retired military personnel many years after injury. Furthermore, it was found that total tau concentration was found to be elevated in the military personnel which reported multiple TBIs. Similarly, Olivera et al. and our present study are both limited due to the highly variable time from testing to the time of the study.
occurrence of the last TBI/mTBI. Although, this present study disagrees with these findings, this could be due to mTBI/concussions experienced in our study which are not as damaging as TBIs used in Kenney et al. and Olivera et al.’s studies of military personnel.

Glia fibrillar acidic protein
Blood GFAP concentrations have been shown to be greater in participants with Alzheimer’s disease, Parkinson’s disease dementia and dementia with Lewy bodies in comparison to controls. Only a few studies have researched GFAP concentrations in blood plasma in regard to assessing neurodegenerative diseases; therefore, more investigation is needed for complete clarity. Bogoslovsky et al. found that in a cohort predominately with mTBI, they were able to differentiate plasma GFAP levels from uninjured controls. Furthermore, it was found that although GFAP levels declined over the first few weeks following injury, they stayed increased for up to 3 months in a subgroup of patients when compared with undamaged controls. However, little research has been done long term. No studies, to our knowledge, have assessed blood plasma concentration of GFAP many years after injury, which this study accomplishes.

Amyloid markers: Aβ40 and Aβ42
Elevated blood plasma Aβ42 concentrations have been linked to long-term neurodegenerative conditions, including Alzheimer’s disease. Kenney et al. compared participants with ≥3 mTBIs to participants with one to two mTBIs and the TBI-negative controls and found no significant differences between groups for Aβ40 and Aβ42. This is reflected in the present study, the results of which speak against a higher prevalence of Aβ pathology in the brains of the exposed subjects.

Strengths and limitations
The major strength of this study is that a large range of participants was used from many sporting backgrounds, including many female participants. Also, the concussion group included a high mean total of concussions in comparison to similar studies assessing sport concussion/mTBI. The validity of the participants’ concussion history is limited due to it being self-reported. However, it was not possible to gather the participants’ clinically diagnosed concussion history due to fragmented documentation. Another limitation of the study was that although the control group was recreationally active, they were not retired athletes. Also, these concussions occurred prior to current concussion guidelines. This study is also limited due to the highly variable time between participants from the last concussion received and the time of sample collection. This data is not available to publish. It is also possible that the age range analysed may be a time window prior to any clinical deterioration; therefore, a follow-up study looking at this cohort at multiple time points in their life is critical.

CONCLUSION
This study found no difference in blood concentrations of the neurodegeneration markers NfL and tau, as well as the astrocytic activation GFAP and biomarkers for amyloid plaque formation (plasma Aβ42/Aβ40 ratio), in athletes with a history of multiple concussions in comparison to controls. No correlation was found between the number of concussions experienced and any of the measured biomarkers.

Table 3 Values are median and IQR

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Study group (median (IQR))</th>
<th>Controls</th>
<th>Concussion group</th>
<th>P value</th>
<th>Females</th>
<th>Controls</th>
<th>Concussion group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tau</td>
<td>Males</td>
<td>0.9±1.5</td>
<td>0.9±1.4</td>
<td>0.83366</td>
<td>1.1±1.0</td>
<td>0.7±1.0</td>
<td>0.42372</td>
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<tr>
<td>GFAP</td>
<td>Males</td>
<td>103.1±61.6</td>
<td>97.0±73.8</td>
<td>0.97606</td>
<td>134.0±124.4</td>
<td>99.9±71.2</td>
<td>0.65272</td>
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</tr>
<tr>
<td>NfL</td>
<td>Males</td>
<td>17.0±7.7</td>
<td>15.5±11.0</td>
<td>0.42952</td>
<td>14.3±10.8</td>
<td>14.6±9.6</td>
<td>0.61006</td>
<td></td>
</tr>
<tr>
<td>Aβ40</td>
<td>Males</td>
<td>63.5±56.7</td>
<td>45.3±76.8</td>
<td>0.65994</td>
<td>40.4±55.4</td>
<td>35.9±58.1</td>
<td>0.95216</td>
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</tr>
<tr>
<td>Aβ42</td>
<td>Males</td>
<td>4.4±4.0</td>
<td>3.0±4.5</td>
<td>0.37346</td>
<td>2.8±3.6</td>
<td>2.6±3.8</td>
<td>0.93624</td>
<td></td>
</tr>
</tbody>
</table>

The Mann-Whitney U test was used to calculate significance. No significant findings were found in the male or female group.

GFAP, glial fibrillar acidic protein.

Acknowledgements
The ICHIRF project is currently philanthropically funded by Godolphin Racing, the Injured Jockeys Fund (UK), the Irish Injured Jockeys Fund, the Professional Footballers Association (UK), the NFL (USA), the Concussion Foundation, the Racing Foundation, the British Association of Sport and Exercise Medicine as well as private donations. The ICHIRF-BRAIN Study would not be possible without the input of the ICHIRF project manager, Pippa Theo.

Contributors
The conception and design of the project originated from MT and HZ. MT/International Concussion and Head Injury Research Foundation (ICHIRF) provided the demographic data and the blood samples. Acquisition, analysis and interpretation of data were completed by AH, OJS and HZ. OJS drafted the manuscript. HZ, MT, AH and OJS critically reviewed and revised the manuscript for publication.

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intellectual content. HZ, MT, AH and OJS approved and agree to be accountable for the final version of the manuscript. HZ was the guarantor of this study.

Funding This study was funded by UK Dementia Research Institute (UKDRI-1003).

Competing interests MT is employed as CEO and Medical Director of the International Concussion and Head Injury Research Foundation (ICHIRF) and was formerly employed as the Chief Medical Adviser to the British Horseracing Authority (BHA) and the Lawn Tennis Association (LTA). He is an Honorary Medical Adviser to the Professional Jockeys Insurance Scheme (PRIS) for which he receives a discretionary honorarium. ICHIRF is a not-for-profit organisation. He undertakes no clinical duties but has been reimbursed for travel and accommodation at conferences, symposia and scientific meetings by the organisers. He does not hold any shares in any company related to concussion or brain injury assessment or technology. HZ has served at scientific advisory boards and/or as a consultant for AbbVie, Alector, Annexon, Artery Therapeutics, AZTherapeutics, CogRx, Denali, Elisa, Nervgen, Pintecne Therapeutics, Red Abbey Labs, Passage Bio, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics and Wave; has given lectures in symposia sponsored by Cellectriion, Fujirebio, Alzecure, Biogen and Roche; and is a co-founder of Brain Biomarker Solutions (BBS) in Gothenburg, which is a part of the GV Ventures Incubator Program (outside submitted work). HZ is a Wallenberg Scholar supported by grants from the Swedish Research Council (2018-02532), the European Research Council (681712), Swedish State Support for Clinical Research (ALFGBG-720931), the Alzheimer Drug Discovery Foundation (ADDF), USA (201809-2016862), the AD Strategic Fund and the Alzheimer’s Association (ADSF-21-831376-C, ADSF-21-831381-C and ADSF-21-831377-C), the Olav Thon Foundation, the Erling-Persson Family Foundation, Stiftelsen für Gamla Tjänarinnor, Hjärnfonden, Sweden (F2019-0228), the European Union’s Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement number 860197 (MIRIADE), European Union Joint Program for Neurodegenerative Disorders (JPND2021-00694) and the UK Dementia Research Institute at UCL.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Ethical approval was obtained from St Mary’s University, Twickenham, London, UK on 1 June 2015, SMEC_2015-16_53, SMEC_2016-17_115 and SMEC_2017-18_051.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Not applicable.

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REFERENCES
ICHIRF v1 Questionnaire

Please ensure you have read data privacy notice and signed consent before proceeding

A. Part A

1. Enter your ID number

   (this will be issued once completed Questionnaire is returned)

2. Your Year of Birth - e.g. 1980

   Year of Birth

3. What is your nationality?

4. What is your gender?
   - Male
   - Female

5. Current relationship status
   - Single
   - Married / civil partnership
   - Living with partner (not married)
   - Separated / divorced
   - Widowed

6. What is the highest degree or level of schooling you have completed?
   - Primary or middle school (under or up to age 16 years)
   - High school / secondary school / upper school (to year 12, secondary 5 or higher or to age 18 years)
   - University / College degree
   - Other postgraduate qualification e.g. diploma, etc.
   - Trade qualification
   - Other qualification
7. Has your doctor or other medical professional ever diagnosed you with any of the following conditions that may have affected your school, sport or work performance?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Yes</th>
<th>No</th>
<th>Not Sure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention deficit disorder (ADHD)</td>
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<tr>
<td>Learning disorder e.g. dyslexia</td>
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<tr>
<td>Hearing or Auditory processing problem</td>
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<td>Migraine or chronic headaches</td>
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<tr>
<td>Depression, anxiety or other mental health problem</td>
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<tr>
<td>Epilepsy or seizures</td>
<td></td>
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<td>Memory problems</td>
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<tr>
<td>Alzheimer’s disease or other dementia</td>
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<tr>
<td>Permanent brain injury/damage from sport</td>
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</tr>
</tbody>
</table>

8. Are you currently employed?
- Yes
- No

If yes, what is your main occupation, or if at school, what year/grade level?

9. Are you currently receiving welfare, disability or injury insurance benefits from any source?
- Yes
- No
- No, but have applied/planning to apply
C. Not applicable

10. What is your CURRENT weight? (select 1 only)
   - Pounds Weight in pounds
   - Kilograms Weight in kilos

11. If you have retired from sport, what was your approximate weight during your LAST YEAR of competition? (select 1 only)
   - Pounds Weight in pounds
   - Kilograms Weight in kilos
   - Not retired
   - Not a sportsman or sportswoman

12. What is your CURRENT height (without shoes)? (select 1 only)
   - Inches Height in inches
   - Centimetres Height in centimetres

13. With regard to sports activity, what is your dominant / preferred arm and leg?

   Arm
   - Right
   - Left

   Leg
   - Right
   - Left

B. Part B

1. What is your current level of physical activity?
   - Participate in organised or school sport
   - General physical activity on more than 3 days or more than 150 minutes per week (e.g. walking, jogging, gym, etc.)

   What is your main type of exercise or physical activity?
   - Not physically active (exercise less than 3 days or less than 150 minutes total per week)

2. What is your current sporting status?
   - Current student athlete
- Current amateur athlete
- Current professional athlete
- Retired amateur athlete
- Retired professional athlete

If retired from sport, main reason for retirement:

- Not a sportsman or sportswoman - If not a sportsman or sportswoman, skip the next questions and go to question C1

3. What is your main sport played?

- Australian Football
- Boxing
- Equestrian (show jumping, eventing, etc.)
- Football (soccer)
- GAA sports
- Horseracing (professional / amateur)
- Martial Arts
- Motor sports
- NFL and American Football
- Rugby Union
- Rugby League
- Snow & Alpine sports
- Wrestling
- Other sports

4. For your main sport, at what age did you start taking part in regular or organised competition?

5. For your main sport, what was/is your position on the field (e.g. hooker, full back, etc.) or sub-category within sport (e.g. jump jockey, 60kg boxer, F1 driver, slalom skier, etc.)
6. For your main sport only, in your sporting career approximately how many rides, games, bouts, matches or events did you participate in?

School, age grade or under age sport
Local club, community, under 21 senior club, amateur or point to point jockey, amateur boxing, club level motor and alpine sport
Professional sport, including rugby provincial level, super rugby, county level competitions, professional jockey, professional boxing, national level motor and alpine sports
International or Olympic representative competitions, international level motor and alpine sport (or inter county competitions where no international competition exists e.g. GAA)

C. Part C

The following questions deal specifically with any concussions or head injuries that you may have had during your life and any risk factors for these injuries. If you cannot remember the exact number make an estimate or guess.

1. Have you had any concussions or head injuries during your life NOT from sport (e.g. car accidents, falls, assaults etc.)?

   ○ Yes
   Approximate number of times [ ]
   Approximate date of most recent injury [ ]

   ○ No

2. Have you had any severe facial or dental injuries (e.g. facial fractures requiring surgery or specialist treatment, lost or permanently damaged teeth)?

   ○ Yes
   Number of times [ ]

   ○ No

3. Has anyone in your family been diagnosed with dementia or Alzheimer’s Disease?

   ○ Yes
   Please give details (i.e. which relative - mother, grandfather, etc.) [ ]

   ○ No

4. Have you ever had a concussion from playing sport?

   ○ Yes

   ○ No - If no, skip the next questions and go to question D1
5. How worried are you about the possible effect of concussion(s) or head injuries sustained during your career on your memory or thinking skills, as you get older?

(select one only)

<table>
<thead>
<tr>
<th>Not worried</th>
<th>Moderately worried</th>
<th>Very worried</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>☐ 4</td>
<td>☐ 5</td>
<td>☐ 6</td>
</tr>
<tr>
<td>☐ 7</td>
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</tbody>
</table>

6. We are trying to determine the total number of concussions (mild and severe) that you may have experienced in your career. The most obvious concussions are where you are knocked out cold or are unconscious. You may also have experienced milder concussions where you were briefly dazed or stunned after a collision or where you have some dizziness, confusion, balance problems, blurred vision, slowed reactions, nausea, difficulty concentrating or headache after a collision or impact.

Please enter the details in the table below.

<table>
<thead>
<tr>
<th>Estimated number of severe concussions where you were knocked out or unconscious</th>
</tr>
</thead>
<tbody>
<tr>
<td>School; age grade or underage sport (please specify)</td>
</tr>
<tr>
<td>Local club, community, under 21</td>
</tr>
<tr>
<td>senior club, amateur or point to point jockey, amateur boxing, club level</td>
</tr>
<tr>
<td>motor and alpine sport</td>
</tr>
<tr>
<td>Professional sport, including rugby provincial level, super rugby, county</td>
</tr>
<tr>
<td>level competitions, professional jockey, professional boxing, national level</td>
</tr>
<tr>
<td>motor and alpine sports</td>
</tr>
<tr>
<td>International or Olympic representative competitions, international level</td>
</tr>
<tr>
<td>motor and alpine sport (or inter county competitions where no international</td>
</tr>
<tr>
<td>exists, e.g. GAA)</td>
</tr>
<tr>
<td>Estimated number of times you had a mild concussion where you were dazed or</td>
</tr>
<tr>
<td>stunned or had other symptoms (as above) but were NOT knocked out</td>
</tr>
</tbody>
</table>

7. From the concussions listed in the table above, approximately how many times did you return to the sport on the same day as the concussion occurred?

8. If a doctor was on duty at the event or after, did you always tell them when you had a concussion or significant head knock?

☐ No
9. Answer as much as you can about the WORST CONCUSSION that you can remember as a result of your sport?

a. Year occurred

b. Approximately how many days did it take to recover?

c. Are you still affected by the concussion?

e. Approximately how many games or events did you miss as a result of the concussion?

10. Do you think the sports concussions have had a permanent or lasting effect on your memory or thinking skills?

☐ Yes

☐ No - If no, skip the next questions and go to question D1

☐ Unsure - If unsure, skip the next questions and go to question D1

1. If 'yes' then...

What age were you when you started having symptoms?

How many years between your retirement from professional sport and the development of these symptoms?

12. If yes, were these symptoms a continuation of the last concussion (i.e. never fully recovered) or were they 'new' symptoms that developed some time after your last concussion?

☐ Continuation of symptoms from last concussion

☐ New symptoms

☐ Unsure

13. What were the symptoms that alerted you to the problem?

(select all that apply)

☐ Memory problems

☐ Lack of Concentration/Attention

☐ Confusion

☐ Getting lost when driving/walking

☐ Personality change e.g. irritability, mood swings, explosive temper

☐ Loss of ability to do everyday tasks

☐ Other
14. If you have already retired from sport, do family members or friends seem to think your memory is getting worse over time?
- Yes
- No
- Not applicable

15. If you have already retired from sport, do your memory problems interfere with your normal daily activities?
- Yes
- No
- Not applicable

16. Over the past month, did you have trouble controlling your anger to the point where you threatened someone with physical violence or got into a fight?
- Yes
- No

D. Part D

1. Score yourself on the following symptoms, based on how you feel RIGHT NOW. (select one only from each row – all rows must be answered)

<table>
<thead>
<tr>
<th></th>
<th>none</th>
<th>mild</th>
<th>moderate</th>
<th>severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>“Pressure in head”</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck Pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Nausea or vomiting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
<td></td>
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<tr>
<td>Blurred vision</td>
<td></td>
<td></td>
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<tr>
<td>Balance problems</td>
<td></td>
<td></td>
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<tr>
<td>Sensitivity to light</td>
<td></td>
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<td></td>
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<tr>
<td>Sensitivity to noise</td>
<td></td>
<td></td>
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<tr>
<td>Feeling slowed down</td>
<td></td>
<td></td>
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<tr>
<td>Feeling like “in a fog”</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
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<tr>
<td>--------------------------</td>
<td>------</td>
<td>------</td>
<td>----------</td>
<td>--------</td>
</tr>
<tr>
<td>“Don’t feel right”</td>
<td></td>
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<td></td>
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<tr>
<td>Difficulty concentrating</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Difficulty remembering</td>
<td></td>
<td></td>
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<tr>
<td>Fatigue or low energy</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Confusion</td>
<td></td>
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<tr>
<td>Drowsiness</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Trouble falling asleep</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>More emotional</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritability</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sadness /Depressed</td>
<td></td>
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<td></td>
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<tr>
<td>Nervous or Anxious</td>
<td></td>
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<tr>
<td>Difficulty speaking</td>
<td></td>
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<tr>
<td>Explosive temper</td>
<td></td>
<td></td>
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<tr>
<td>Lack of interest in life</td>
<td></td>
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<tr>
<td>Difficulty with planning things</td>
<td></td>
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<td></td>
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</tbody>
</table>

2. Do any of these symptoms get worse with activity?

<table>
<thead>
<tr>
<th>Activity</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical activity</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Mental activity</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
E. Part E

1. During the past month, how would you rate your sleep quality overall? *(select 1 only)*
   - Fairly bad
   - Average
   - Fairly good

2. During the past month, have you needed to take any sleeping pills or other tablets (e.g. prescribed or 'over the counter') to help you sleep?
   - Yes
   - No

3. Have you ever been medically diagnosed with a sleep disorder (e.g. obstructive sleep apnoea, restless legs syndrome, etc.)
   - Yes
   - No

F. Part F

1. In general, would you say your health is ...
   *(select 1 only)*
   - Excellent
   - Very good
   - Good
   - Fair
   - Poor

2. During the past one month, to what extent has any EMOTIONAL PROBLEMS (e.g. depression or sadness etc.) interfered with your normal social activities with family, friends, neighbours or groups?
   - Not at all *(select 1 only)*
   - Slightly
   - Moderately
   - Quite a bit
   - Extremely

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3. During the past one month, how much did pain from previous sporting injuries interfere with your normal work (including both inside and outside the home)?

- Not at all (select 1 only)
- Slightly
- Moderately
- Quite a bit
- Extremely

4. How stressful do you consider your life to be?

- Low (select 1 only)
- Moderate
- High

G. Part G

1. Do you take medications prescribed by a doctor?

- Yes (put medications here)
- No

2. Do you drink alcohol?

- Yes
- No - If no, skip the next questions and go to question G6

3. In the past month, on average how many days a week did/do you consume alcohol?

- None
- 1 - 2 days a week
- 3 - 4 days a week
- 5 - 7 days a week

4. In the past month, on average how many alcoholic drinks per week did/do you consume?

- None
- 1 - 2 drinks
- 3 - 5 drinks
- 6 - 7 drinks
- 8+ drinks
5. Has your drinking ever resulted in any legal problems, club disciplinary measures, relationship problems or have you ever needed counselling or rehabilitation due to a drinking problem?

- Yes
- No

6. How often do you use medications, alcohol, or other substances to help you relieve stress and relax?

(select 1 only)

- Frequently (several times a week)
- Occasionally (once or twice a week)
- Seldom (once or twice a month)
- Almost never
- Never

7. In the past 12 months, did you take any of the drugs listed below more than once, to get high, to feel elated, to get a buzz, or to change your mood?

Amphetamines speed, crystal meth Dexamphetamine, Ritalin, diet pills, rush THC, marijuana, cannabis, hashish, cocaine, crack steroids, GHB Valium, Xanax Ativan barbiturates, heroin morphine, methadone, opium, Demerol® codeine, Percodan, OxyContin, Vicodin, LSD, mescaline, PCP, angel dust, ecstasy MDA, MDMA ketamine, inhalants, glue, ether etc.

- Yes
- No
- Do not wish to reply

8. In the past 12 months, have you taken any performance enhancing drugs such as anabolic steroids?

- Yes
- No
- Do not wish to reply

H. Part H

1. How would you describe your smoking history?

- Current smoker
- Ex-smoker

- Never smoked - If never smoked, skip the next questions and go to question 11

2. Answer only if you are a current or ex-smoker
1. Part I

The following questions are related to your stress and mental well-being. Choose one response from the four given for each of the 7 questions. You should give an immediate response and do not try to think too long about the answers. You should answer how it CURRENTLY describes your feelings.

1. I feel tense or ‘wound up’?
   - Most of the time
   - A lot of the time
   - Occasionally
   - Not at all

2. I get a sort of frightened feeling as if something awful is about to happen?
   - Very definitely and quite badly
   - Yes, but not too badly
   - A little, but it doesn’t worry me
   - Not at all

3. Worrying thoughts go through my mind?
   - A great deal of the time
   - A lot of the time
   - From time to time, but not too often
   - Only occasionally

4. I can sit at ease and feel relaxed
   - Not at all
   - Not often
   - Usually
5. I get a sort of frightened feeling like butterflies in my stomach
   - Definitely
   - Very often
   - Quite often
   - Occasionally
   - Not at all

6. I feel restless and I have to be on the move
   - Very much indeed
   - Quite a lot
   - Not very much
   - Not at all

7. I get sudden feelings of panic
   - Very often indeed
   - Quite often
   - Not very often
   - Not at all

**J. Part J**

1. I still enjoy the things I used to enjoy
   - Hardly at all
   - Only a little
   - Not quite so much
   - Definitely as much

2. I can laugh and see the funny side of things
Not at all
Definitely not so much now
Not quite so much now
As much as I always could

3. I feel cheerful
Not at all
Not often
Sometimes
Most of the time

4. I feel as if I am slowed down
Nearly all the time
Very often
Sometimes
Not at all

5. I have lost interest in my appearance
Definitely
I don’t take as much care as I should
I may not take quite as much care
I take just as much care as ever

6. I look forward with enjoyment to things
Hardly at all
Definitely less than I used to
Rather less than I used to
As much as I ever did
7. I can enjoy a good book or radio or TV program

- Very seldom
- Not often
- Sometimes
- Often

Thank you for completing the paper format of the International Concussion and Head Injury Research Foundation Questionnaire. Please sign the Consent and return all paperwork in the envelope provided.