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Prospective cohort study of long-term neurological outcomes in retired elite athletes: the Advanced BiomaRker, Advanced Imaging and Neurocognitive (BRAIN) Health Study protocol

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ABSTRACT

Introduction Although limited, recent research suggests that contact sport participation might have an adverse long-term effect on brain health. Further work is required to determine whether this includes an increased risk of neurodegenerative disease and/or subsequent changes in cognition and behaviour. The Advanced BiomaRker, Advanced Imaging and Neurocognitive Health Study will prospectively examine the neurological, psychiatric, psychological and general health of retired elite-level rugby union and association football/soccer players.

Methods and analysis 400 retired athletes will be recruited (200 rugby union and 200 association football players, male and female). Athletes will undergo a detailed clinical assessment, advanced neuroimaging, blood testing for a range of brain health outcomes and neuropsychological assessment longitudinally. Follow-up assessments will be completed at 2 and 4 years after baseline visit. 60 healthy volunteers will be recruited and undergo an aligned assessment protocol including advanced neuroimaging, blood testing and neuropsychological assessment. We will describe the previous exposure to head injuries across the cohort and investigate relationships between biomarkers of brain injury and clinical outcomes including cognitive performance, clinical diagnoses and psychiatric symptom burden.

Ethics and dissemination Relevant ethical approvals have been granted by the Camberwell St Giles Research Ethics Committee (Ref: 17/LO/2066). The study findings will be disseminated through manuscripts in clinical/academic journals, presentations at professional conferences and through participant and stakeholder communications.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The longitudinal nature, unique population and large sample size provide ability to test the relationship between head impact exposure in professional sport, biomarkers of brain health and long-term clinical outcomes.
⇒ Detailed fluid and neuroimaging biomarkers of brain structure and function will be collected and allow for the assessment of the relationship between head impact exposure and brain health/neurodegenerative risk in detail.
⇒ The results will define the range of neurological, psychological and psychiatric problems experienced by retired elite rugby and footballers and inform the causation of these problems assisting in managing elite sportsmen and women in retirement and inform prevention interventions.
⇒ We rely in part on retrospective self-reported assessment of head impacts and concussion which may be inaccurate, although a range of measures of exposure will be collected, including total years of elite play.
⇒ There may be a bias in recruitment due to the nature of referral into the study, and several populations may be over-represented which may limit the interpretability of study findings in the context of the wider retired player population, although this does not limit our ability to pursue our stated research questions and hypotheses.

INTRODUCTION

There is growing concern regarding the consequences for long-term brain health associated with participation in contact sports such as association football (soccer) and rugby, where head impacts are common aspects of the sport.[1 2] Previous studies of retired rugby players have shown higher reported rates of depression and mild cognitive disorders,[3] poorer overall mental health and more prevalent sleep disruption.[4] In older players, cognitive performance was worse in players

with a concussion history and longer career,[5] while active players showed evidence of changes to brain structure.[6] In retired footballers, there are reports of higher rates of sleep problems and negative mood, although without higher incidences of depression or anxiety.[7 8] These outcomes may be attributed to a number of risk factors that might contribute to poorer brain health of retired elite athletes including chronic pain,[9] comorbid mood disorders,[10] difficulty transitioning following retirement from elite career,[11] a lack of social support,[12] socioeconomic status,[13] cardiovascular and metabolic health[14 15] and possibly head impact exposure. The multifaceted nature of brain health outcomes following exposure to repeated neurotrauma is presently underexplored and forms the basis of the study.

Contact sports carry an intrinsic risk of head impacts that can produce a range of symptoms (the presence of which are described as a concussion). These symptoms may be present immediately or evolve over time following a biomechanically plausible injury.[16] They will often resolve within hours or days but can persist for months or even years after apparently trivial injuries.[17–19] Some of these head impacts may cause a traumatic brain injury (TBI), which can produce these symptoms, but symptoms associated with concussion may also result from other types of injuries.[18] TBI is a risk factor for neurodegeneration[20 21] and poorer brain health outcomes. It is associated with an increased risk of mortality[22] and all-subtype dementia.[23] TBI can cause progressive brain volume loss,[24] which is associated worse clinical outcomes.[25–28]

Head impacts that do not produce acute symptoms are also of concern. Described as 'sub-concussive head impacts', the total number of head impacts an individual has been exposed to over their career and their likely biomechanical severity appears to be an important consideration of brain health outcomes based on the emerging literature. Repeated exposure to head impacts has been associated with increased neurodegenerative risk,[20 29 30] and recent studies of deceased Scottish association football and rugby union players have shown higher risk of mortality and neurodegenerative disease when compared with age, gender and postcode-matched controls.[31 32] Participation in professional contact sports with repetitive head impacts has also been reported to increase the risk of developing motor neuron disease.[33] The degree of exposure to repeated head impacts can be estimated by assessing the playing history of a player, including years of play and playing position, as well as the number of concussions reported or identified,[34–36] or via the development of an exposure matrix based on measurements from instrumented mouthguards.[37 38]

Chronic traumatic encephalopathy (CTE) is a progressive neurodegenerative disorder associated with repeated head impact exposures.[30 39–41] It has been reported following a range of sporting exposures, including rugby and football.[42–44] The diagnosis of CTE can currently only be made definitively at postmortem.[45 46] Recent consensus research diagnostic criteria for traumatic encephalopathy syndrome (TES), the clinical syndrome associated with CTE, provide a potential framework for patient assessment in the absence of pathological information.[47] These criteria have been applied to ex-American football players[48] and professional fighters.[49] However, the prevalence of TES in ex-rugby and association football players is unknown and it is uncertain what contribution other conditions make to the symptoms used to define TES.

Retired athletes may experience a range of problems in addition to neurodegeneration. Psychiatric problems such as depression are common in retired athletes,[3 4 10] and this is often associated with cognitive problems,[50] increased levels of anxiety and stress.[16] Chronic pain is also common in retired athletes[51 52] and can itself disrupt cognitive function,[53] and cause depression and anxiety.[54] For example, retired National Football League (NFL) players with a combination of chronic pain and depression were 32 times more likely to report difficulty with sleeping,[9] which is also common in retired athletes.[4 7 8] In particular, obstructive sleep apnoea is more prevalent in contact sport athletes than the general population.[55] Sleep issues are associated with psychiatric issues, particularly depression, and cognitive issues.[56–59] Long-term sleep disturbance is also implicated in dementia pathology[60] and is associated with increased risk of neurodegenerative disorders.[61]

Cardiovascular and metabolic health are also of key importance for long-term brain health.[14 15] These are linked to physical activity level,[62] which can vary markedly after retirement in elite athletes. Lifestyle changes following an elite sporting career may further modulate this relationship. Physical inactivity and poor cardiovascular health are associated with several comorbidities including neurodegeneration[63] and cognitive decline.[64] To our knowledge, there are no studies that have investigated the combination effect of modifiable risk factors (physical activity, cardiovascular health) and repeated head injury exposure on neurodegenerative disease risk.

More objective ways of identifying brain pathologies in vivo are needed in retired contact sport athletes, given the complexity of inter-related symptoms. A range of promising biomarkers are now available, which will be evaluated in this study. Advanced neuroimaging and fluid biomarker detection can provide a method of sensitively assessing patients for the presence of TBI-related neuropathology such as diffuse axonal injury,[65] which causes many of the long-term effects of TBI,[66 67] or neurodegenerative diseases, including in the presymptomatic period.[68] Diffusion tensor imaging (DTI) is sensitive to white matter damage,[69] predicts long-term clinical outcomes[66 70] and can be applied at the individual level.[71] This can be complemented by longitudinal imaging, such as serial structural imaging, which can be used to generate metrics of brain atrophy[21 72] that are associated with poorer clinical outcomes[26 27] and provide a method of sensitively assessing whether neurodegeneration is taking place and mapping its spatial pattern.[73] These have been previously used in a study of active elite rugby

players, showing abnormalities in white matter structure using DTI and evidence of irregular white matter volume changes.[6] Employing these imaging biomarkers in retired players will help clarify whether these abnormalities are related to poorer brain health outcomes following elite rugby participation.

There are also a range of fluid biomarkers that are potentially useful. Axonal marker neurofilament light (NfL) is sensitive to axonal damage and progressive degeneration,[65] and the astroglial marker glial fibrillar acidic protein (GFAP) has been shown to reflect neurodegenerative disease pathology presymptomatically.[74] Both NfL and GFAP are elevated acutely after mild TBI[75] and remain chronically elevated after more severe TBI.[76] In cases of exposure to repetitive head impacts, boxers exposed to impacts through bouts showed higher NfL levels acutely that remained elevated at 3 months after bouts, with higher concentrations present in those with more severe head impacts.[77] NfL concentrations are elevated in recently active American footballers out of season when compared with controls.[78] In active elite rugby players, the concentration of GFAP was associated with abnormal cortical thickness following injury.[79] The combination of imaging and fluid biomarkers may therefore be useful in understanding the pathophysiological relationship between exposure to head impacts and brain health. Salivary non-coding RNAs also show promise in detecting acute concussion but have not been tested in retired athletes and warrant further investigation.[80]

In summary, the Advanced BiomaRker, Advanced Imaging and Neurocognitive (BRAIN) Health Study will investigate the associations between prior participation in elite rugby and association football and long-term brain health outcomes. Athletes will undergo a standardised assessment in a brain health clinic with an aligned research programme for those consenting. Participants will be followed up longitudinally over a period of 4 years and undergo assessment of physical, cognitive and psychiatric well-being, and fluid and imaging biomarkers of axonal injury and neurodegeneration. This study will be the first to comprehensively study a young mid-life cohort of elite athletes with detailed biomarker assessments. The study aims to identify modifiable risk factors for brain health in mid-life, such as post-career physical activity and cardiovascular profile, provide insights into disease mechanisms, improve prognostication and clinical care for retired athletes and explore the prevalence of a range of medical conditions, including neurodegeneration, following a period of repeated head impact exposure.

Research questions and hypotheses of the Advanced BRAIN Health Study

The following research questions will be pursued:

1. What is the prevalence of head impact exposure (years of play and playing position), concussion (self-report) and TBI in retired contact sport athletes (rugby and association football)?
2. How does head injury history and cumulative exposure relate to evidence of progressive neurodegeneration, measured with neuroimaging and fluid biomarkers?
3. How does head injury history and cumulative exposure to head impacts relate to physical, cognitive and psychiatric well-being?
4. How do biomarkers of neurodegeneration and TBI relate to physical, cognitive and psychiatric well-being?
5. Is TES (as defined using consensus criteria) associated with abnormalities in biomarkers of neurodegeneration and TBI?
6. Do modifiable risk factors for neurodegeneration, such as cardiovascular health status (as measured by exercise testing and wearables) or sleep quality (as measured by sleep tracking devices), modulate the relationship between head impact exposure/TBI and outcome?
7. What measures best inform the development of triage tool to identify people at risk of long-term problems and in need of investigations?

The core hypotheses include:

1. Retired contact sport athletes with greater head impact exposure and more history of concussions will show: (a) more evidence of cognitive and psychiatric impairment; (b) more evidence of white matter abnormalities as measured by DTI; (c) more brain atrophy as measured serial volumetric structural T1 MRI; and (d) increased concentrations of plasma biomarkers of trauma in blood including NfL and tau protein.
2. TES (as defined using consensus criteria) is associated with: (a) evidence of neurodegeneration (excessive brain atrophy as measured serial volumetric structural T1 MRI) and brain injury in regions that show more CTE pathology (eg, the base of sulci); and (b) will show increased concentrations of plasma biomarkers of trauma in blood including NfL and tau protein.
3. Modifiable risk factors for neurodegeneration will modulate the relationship between head injury history and head impact exposure and biomarkers of neurodegeneration.

METHODS AND ANALYSIS

Overall design

The Advanced BRAIN Health Study is a prospective longitudinal cohort study of retired elite rugby and association football players. Participants will be recruited from the Advanced BRAIN Health Clinic, which provides a structured clinical assessment of brain health. Participants will complete questionnaires on psychiatric outcomes. We will ascertain the clinical profile of participants via a semistructured interview including current symptoms, concerns and medical history, along with a history of sporting career and head injury exposure. We will perform advanced MRI, neuropsychological tests and advanced fluid biomarker analyses to investigate how exposure to head injuries and head impacts relates to signs of TBI and cognitive performance. Assessments will be repeated

longitudinally at 2 and 4 years after the baseline visit to determine how individual's injury history relates to long-term progression of cognitive and functional outcomes, neuroimaging and fluid biomarker profiles. Healthy volunteers without a history of TBI or repetitive head impacts will be recruited and undergo an aligned assessment protocol including advanced neuroimaging, blood testing and neuropsychological assessment as a comparison group.

Funding for the study and role of the funders

Funding for the clinic assessment of brain health is provided by the Rugby Football Union, Premiership Rugby and the Football Association. Additional funding to support an aligned research programme linked to the clinic assessment is provided by the funders. Regular updates on the operation of the clinic and research study will be provided to the funding bodies but raw data and identifiable clinical information on participants will not be provided. The funders' role was limited to the set-up of the clinic and study, including study timelines, but funding body representatives will not be a part of the study team and all research and analysis will be conducted independently of the funders with no restriction on analysis. Funders will be provided with notice in advance of manuscripts and dissemination materials but there will be no restriction on the publication of study findings. Funders will not be coauthors on scientific outputs of the study. An independent Scientific Advisory Board has been set up with biyearly discussions to monitor procedures and results and assist in study-related decisions.

Participating centres and recruitment progress

Study visits are conducted at the Institute of Sport Exercise and Health (ISEH). All patients who attend the Advanced BRAIN Health Clinic are offered to join the Advanced BRAIN Health Study, which incorporates additional neuroimaging (inclusion of DTI and functional MRI (fMRI)), additional blood collection (30 mL) and additional neuropsychological assessments. The study aims to recruit at least 200 retired elite rugby and 200 retired elite association football players in total. In addition to retired players, the study will aim to recruit 30 non-sporting controls and 30 sporting non-contact controls who have participated to an elite level in their sport and have had no prior exposure to repetitive head impacts or history of head injury. The Advanced BRAIN Health Study began recruiting retired rugby players in November 2021, and retired association footballers in August 2022. As of November 2023, a total of 268 retired athletes and 33 controls have been recruited into the study (figure 1). Study recruitment is planned to complete end of 2024, and all follow-ups completed end of 2028.

Entry into the study

Retired elite rugby and football players (male and female) who are eligible (see table 1 for inclusion and exclusion criteria) will be admitted through self-referral to the Advanced BRAIN Health Clinic at the ISEH. Research staff will discuss details of the study with clinic participants. Individuals will be given the opportunity to ask questions and if a potential participant is suitable for the study, they will be invited to provide informed consent.

The consent procedure will be carried out in strict compliance with UK legislation and, where applicable, General Data Protection Regulation (GDPR). The right of the participant to refuse consent without giving reasons will be respected, with clear indication that refusal of consent does not influence clinical care. Individuals will also be free to withdraw, or be withdrawn by their legal representative if appropriate, at any point in the study, and they need not state any reason. A copy of the consent will be given to the participant.

Controls (male and female) will also be recruited. Controls will be age and sex matched to the participant group. Healthy controls will be assessed using the same exclusion criteria but will additionally be screened and excluded if there is evidence of history of head trauma or previous concussion according to the BRAIN Study Concussion Questionnaire (BRAIN-Q) concussion definitions[34] (table 2A). We will additionally exclude healthy

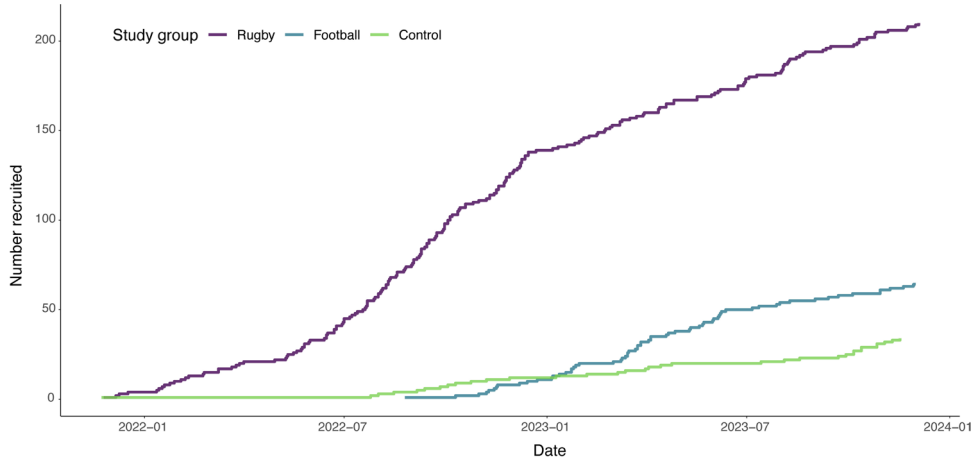

Figure 1 Recruitment progress as of November 2023.

Table 1 Inclusion and exclusion criteria for retired contact sport athletes

Inclusion criteria	Exclusion criteria
30–60 years	Inability or unwillingness to participate in the study
Retired professional rugby player*	Contraindication to MRI
Retired association football player†	

*Defined as either Retired England Men/Women, Retired England 7s Men/Women, Retired Premiership players, Retired AP15s players or Retired Championship players. The latter three player types need to have been contracted for at least one full season (leagues represent the highest level of domestic men and women's leagues, and the second highest men's league in England).
†Defined having held a full-time professional contract for three or more years; for female football if they played in the current FA Women's Super League or Championship, or the previous Women's Premier League in either Premier, North or South Division.

volunteers with a history of exposure to repetitive head impacts as defined by the CTE/TES criteria[47] (table 2B) or history of early-onset dementia in a first-degree relative (diagnosed before age 65) or family history of genetic dementia (eg, Huntington's disease). Sporting non-contact controls will be recruited using the same exclusion criteria and will consist of retired elite athletes from sports without exposure to repetitive head impacts. Elite will be defined by previous representation of their nation internationally and/or participation at the highest domestic level of competition for at three full seasons.

Structure of assessments

Retired players will complete the following assessments at baseline and during follow-up visits in 2 and 4 years' time. Controls will follow the same protocol as retired players but will be asked to return for just one follow-up visit in 2 years' time. All players will undergo a clinical assessment as part of the clinic visit, and if consent is obtained for the Advanced BRAIN Health Study, information collected within their clinical appointment will be saved for research purposes.

Clinical assessment

A semistructured interview will be conducted to collect information on medical history, family history and current symptoms. This includes assessment of smoking status, diabetes status, medical history, previous orthopaedic surgeries and current medications. Family history of heart disease, stroke, high blood pressure, diabetes, mental health issues, arthritis, cancer and neurological disease will be recorded. Retired players' current brain health concerns and issues will be recorded. Heart rate, blood pressure, height and weight will be measured, allowing for calculation of a 10-year cardiovascular risk using the Q-RISK calculator.[81] Body fat percentage and muscle mass will be collected using a TANITA MC-980 body composition scale. After an initial assessment by research staff, players will be assessed during a second visit by a clinical neurologist to corroborate information on medical history and player's professional history and perform a detailed clinical investigation. The clinical team will meet to agree on players' diagnoses and TES criteria classification.

Head injury and exposure history

To acquire detailed history of head trauma, the BRAIN-Q[34] and the Ohio State University (OSU) TBI Identification Method (OSU TBI-ID) Interview Form[82] will be completed. The BRAIN-Q assessment involves reading aloud the definition of concussion (as defined in table 2); participants will then be asked to confirm whether they understand this definition, before being asked to self-report the following: (1) how many times have you been concussed while playing or training for rugby/football, and (2) how many times have you been concussed when you have not been playing or training for rugby/football.

Table 2 Head trauma assessment criteria

A. BRAIN-Q definition of concussion[34]	B. CTE/TES criteria[47]
Concussion is defined as an alteration in brain function caused by an external force. Symptoms include: ► A decreased level/loss of consciousness. ► Memory loss (before or after the injury). ► Weakness /temporary paralysis. ► Loss of balance. ► Change in vision (eg, blurriness, double vision). ► Coordination difficulties. ► Numbness. ► Decreased sense of smell. ► Difficulty understanding what others are saying. ► Difficulty communicating with others. ► Confusion, disorientation or slowed thinking. Loss of consciousness is not required for a concussion to be diagnosed.	The definition for substantial exposure to repetitive head impacts falls under: ► More than 5 years of play, with minimum including 2 years aged 16+, in contact sports involving repetitive head injuries (examples include boxing, American football, ice hockey, soccer, rugby, professional wrestling, mixed martial arts (MMA), motocross). ► Military service involving repetitive head injuries. ► Other sources involving multiple head contacts including but not limited to domestic violence.

BRAIN-Q, BRAIN Study Concussion Questionnaire; CTE, chronic traumatic encephalopathy; TES, traumatic encephalopathy syndrome.

For each episode of concussion identified, the following details will be ascertained: age when acquired, whether there was a fracture of the skull or any other head bone, whether they were seen in accident and emergency department, whether they were admitted to hospital, the duration of any admission, whether they experienced a temporary loss of consciousness and the mechanism of injury.

The OSU TBI-ID Interview Form[82] involves asking the participants about whether they have experienced injuries to the head or neck. Details collected include whether they were admitted to hospital or an emergency room; the cause (vehicle crash, playing sports, fight or military); whether there was loss of conciousness (LOC) and, if so, its duration; whether they experienced a post-trauma daze or memory gap; and the age at the time of head injury. Participants will additionally be asked to list periods in which there were multiple, repeated impacts to the head, and if so, what were the usual effects (LOC/post-traumatic amnesia), what was the most severe effect from one of these impacts and age when the repeated injuries began and ended.

Cognitive and functional outcome assessment

Participants will be asked to complete self-report questionnaires prior to visits that encompass a broad range of domains such as mood, symptoms, sleep and quality of life (table 3), along with informant/caregiver questionnaires. Additionally, on each visit, participants will complete a battery of neuropsychological assessments and computerised tests to assess cognitive function (table 3). Five computerised tasks were selected among a large set of tasks available on the Cognitron platform.[83 84] Tasks were selected to measure different types of cognitive abilities which have previously been associated with CTE.[85] These tasks were also shown to be able to detect a number of cognitive impairments associated with moderate-severe TBI with comparable sensitivity to standard neuropsychological tests.[84] The National Opinion Research Centre Diagnostic Screen for Gambling Disorders – Preoccupation, Escape, Chasing and Risked Relationships (NODS-PERC)[86] screening questionnaire will be used to screen for pathological and problem gambling. Participants will be asked if they are involved in any medicolegal claims, but this will not impact their participation in this study.

MRI assessment

Participants will undergo an MRI scan to assess brain structure and function. A Siemens Skyra 3T scanner, equipped with Syngo MR E11 software, and a head coil with 20 receiver coil channels will be used. The scanning protocol (table 4) will include a set of structural MRI scans including a T1 (for high-resolution structural detail), susceptibility-weighted imaging (SWI; for detecting microhaemorrhages), T2 fluid-attenuated inversion recovery (for detecting other abnormalities) and diffusion MRI (for investigation of white matter abnormalities). Resting-state functional MRI (rs-fMRI) will be used to measure regional brain activity over time. Participants will lie at rest in the scanner, with the instruction to keep eyes open during the rs-fMRI. These different types of MRI will provide complementary information about the location and incidence of brain injuries. Repeated MRI assessments will allow for the investigation of within-subject changes that are necessary to detect how damage may progress over time. All MRI scans will be reported by a consultant neuroradiologist and abnormal findings followed up clinically. Neuroimaging reports will be coded into the database following the International Initiative for Traumatic Brain Injury Research Imaging common data elements.

Fluid biomarkers

Venous blood (≈30 mL on each occasion) will be drawn and comprise 4× K3 EDTA (5 mL, for plasma biomarkers and whole bloods) and 2× serum z-clot activator (5 mL, for serum biomarkers). Samples will be taken at each study visit. Sample processing involves centrifugation at 2500g for 10 min, before being stored at −80°C. Blood samples will be labelled with pseudonymised participant codes. We will process, store and dispose of all tissue in accordance with all applicable legal and regulatory requirements. All blood samples will be processed within 30 min of collection. Samples will be kept in a secure biobank and will be stored for up to 15 years from the end of the study. Participants can withdraw their consent for their samples to be stored or used at any point. If they choose to do so, and notify us, their samples will not be used for any further research and will be destroyed in accordance with all applicable legal and regulatory requirements. Salivary and cerebral spinal fluid assays are not currently part of the testing protocol but may be explored at follow-up visits 2 and 3.

Clinical follow-up

Participants will attend a clinical follow-up appointment around 2 months after the initial visit to receive feedback on clinical findings. During the clinical follow-up, participants will be asked to confirm head injury and impact exposure history, along with medical history and current concerns. A clinical review will follow, with recommendations for patient care made, along with confirmation of research diagnoses and classification of TES/CTE criteria based on the 2021 National Institute of Neurological Disorders and Stroke (NINDS) diagnostic criteria.[47]

Additional measures at follow-up visits 2 and 3

When participants return in 2 years (visit 2) and 4 years (visit 3) after baseline, they will be asked to assess their sleep quality and risk of sleep disorders such as obstructive sleep apnoea and rapid eye movement (REM) sleep behaviour disorder using self-report questionnaires.[87 88] Participants will also be asked to wear an accelerometer on their wrist and given an under-mattress sleep tracker[89] to be placed under their bed mattress for around 2 months. The Withings Sleep Analyser (WSA) will be used to derive

Table 3 Neuropsychology questionnaires and assessments

Neuropsychology assessment/questionnaire	Outcome measure
Self-report questionnaires	
Alcohol Use Disorders ID Test (AUDIT)[110]	Alcohol harm screening
Drug Use Disorders ID Test (DUDIT)[111]	Drug use
Becks Depression Inventory (BDI)[112]	Depression rating
Generalized Anxiety Disorder 7 (GAD-7)[113]	Anxiety rating
Insomnia Severity Index (ISI)[114]	Sleep quality
Pittsburgh Sleep Quality Index (PSQI)[106]	Sleep quality
modified Rivermead Post-concussion Symptoms Questionnaire (mRPQ)[115]	Post-concussion symptoms
EuroQol 5 Dimensions 5-level (EQ-5D-5L)[116]	Quality of life
Behavior Rating Inventory of Executive Function-Adult version (BRIEF-A)[117]	Inhibit, self-monitor, plan/organise, shift, initiate, task monitor, emotional control, working memory and organisation of materials
Informant questionnaires	
Neuropsychiatric Inventory (NPI)[118]	Neuropsychiatric disturbances
Informant BRIEF-A[117]	Inhibit, self-monitor, plan/organise, shift, initiate, task monitor, emotional control, working memory and organisation of materials
Neuropsychology assessments	
Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[119]	Immediate memory, visuospatial/constructional, language, attention, delayed memory
Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV)[120]	Working memory, processing speed
Wechsler Memory Scale-Fourth Edition (WMS-IV)[121]	Auditory memory
Trail Making Tests A and B[122]	Executive function
Delis-Kaplan Executive Function System (D-KEFS) Color Word Interference Test[123]	Executive function
Dot Counting Test[124 125]	Performance validity
Test of Premorbid Function (TOPF)[126]	Premorbid function
Computerised tests[83 84]	
Object memory	Immediate object memory
Stop reaction time (SRT) task	Processing speed
Choice reaction time (CRT) task	Processing speed
Tower of London	Planning\executive functions
2D manipulations	Visuospatial ability
Object memory delayed recall	Delayed object memory

sleep variables such as sleep duration, bed occupancy, night-time physiology (respiratory rate and heart rate) and apnoea. Participants will also be invited to undergo a cardiopulmonary exercise test (CPET) following a graded intensity protocol using continuous gas exchange at their first follow-up.[90] A Physical Activity Readiness Questionnaire[91] will be completed prior to testing and further evaluation of the resting ECG will be done before testing begins. Additional measures of physical activity will include the International Physical Activity Questionnaire,[92] and the wearing of an accelerometer wristwatch, to give insight into the intensity and duration of physical activity over a 7-day period. Behavioural Regulation in Exercise Questionnaire[93] will be filled out by participants, giving a self-reported measure of motivation to engage in exercise. Participants' cardiovascular function will be measured using a Vicorder, a clinically validated tool to measure arterial stiffness.[94] Waist circumference will be measured to complete the collection of the five criteria required to screen for metabolic syndrome (lipids, glycaemia, blood pressure).

Table 4 MRI parameters

Sequence	Voxel size (mm)	Function
T1 magnetisation-prepared rapid acquisition with gradient echo (MPRAGE)	1.0×1.0×1.0	Presence of lesions, assessment of volume and atrophy
T2 fluid-attenuated inversion recovery (FLAIR)	1.0×1.0×1.0	Assessment for traumatic damage, for example, contusions/gliosis
Susceptibility-weighted imaging	0.8×0.6×1.2	Assessment for microhaemorrhages and vascular injury
Diffusion-weighted MRI (64 directions, b value=1000)	2.0×2.0×2.0	Assessment of white matter microstructural integrity
Resting-state functional MRI	2.6×2.6×2.6	Assessment of brain network function and connectivity

Outcomes

Primary

- Lifetime head impact exposure, concussion rate and history of TBI.
- Ascertainment of diffuse axonal and diffuse vascular injury and contusions using DTI, SWI and clinical imaging.
- Assessment for neurodegeneration using annualised brain atrophy rate, determined by brain volume change on serial volumetric MRI.
- Fluid biomarker evidence of neurodegeneration and inflammation including NfL, total tau, 217-tau, GFAP and ubiquitin C-terminal hydrolase 1 (UCHL1).

Secondary

- Neuropsychological function (standard and computerised measures).
- Longitudinal assessment of fluid biomarkers of brain injury, inflammation and degeneration, including NfL, tau, 217/tau, GFAP and UCHL1.
- Subjective and objective measures of sleep and risk of sleep disorders using standardised questionnaires, sensors and wearables.
- Cardiovascular/metabolic profile and physical activity levels (cardiorespiratory fitness and duration/intensity tracking).
- Depression and anxiety symptoms (self-reported Becks Depression Inventory and Generalized Anxiety Disorder 7 questionnaires).
- Quality of life assessment (self-reported EuroQol 5 Dimensions questionnaires).
- Measures of social isolation, loneliness, financial hardship and psychosocial support.
- Self and collateral reported executive function (Behavior Rating Inventory of Executive Function–Adult version).
- TES/CTE diagnosis.[47]

Sample size

400 retired elite rugby and football players and 60 healthy volunteers will be assessed in the Advanced BRAIN Health Clinic. We will offer the Advanced BRAIN Health Study to all participants and anticipate an uptake in the region of 90%, resulting in 360 participants. As an exploratory study, it is unclear as to the effect sizes we can expect in across all our main outcome measures. However, we are well powered to detect effects of head impact exposure on our key neuroimaging outcome measures. We have previously studied MRI indicators of TBI in current elite rugby players.[6] Based on these results we will have >95% power to show if there are a higher proportion of abnormalities on individualised DTI MRI versus healthy age-matched controls (ϕ=0.23) with an alpha of 0.05. Our study design allows us to identify diffusion abnormalities on an individual level, provided we have a group of 30 controls available as a reference.[71] In addition, we will also be well powered to detect differences in brain atrophy rates. We have shown a moderate effect size comparing volumetric measures of brain structure white matter regions in elite rugby players to non-sporting controls (d=0.54).[6] The retired players in our study are older, so atrophy rates will potentially be more easily detected in this cohort. Assuming a similar effect size in retired players, with an alpha of 0.05 we will have >95% power to detect differences in atrophy rates, even accounting for loss to follow-up of 20%. The study will also be powered to detect clinically relevant differences in fluid biomarker concentrations of small effect size. Exposure to a single moderate/severe TBI has been shown to lead to elevated NfL and GFAP persisting 12 months after injury.[65] In boxers exposed to head injury during bouts, NfL remained elevated at 3 months after bouts, with higher concentrations present in those with more severe head impacts.[77] NfL concentrations have also been shown to be elevated in recently active American footballers when compared with controls while out of season (d=0.39).[78] While we would expect smaller effect sizes in retired athletes, we are still likely to be able to detect significant elevations in neurodegenerative markers, including NfL and phospho-tau species (217 and 181 tau) that show great promise as screening tools for Alzheimer's disease.[95]

Analysis plan

Head injury and impact exposure

Determining the numbers, type and severity of head injury is a key outcome of this study. The BRAIN-Q and Ohio State will provide a self-reported retrospective

assessment of TBI exposure. We predict this is likely to be highly variable.[10] There is also a clear need to consider repetitive impacts alongside symptomatic injuries. We will therefore also ascertain years of elite play, as classified by sport-specific bodies, and playing position, to have a surrogate measure for head impact exposure. We will test the relationship of both measures to other primary outcome measures while accounting for age with linear regression models. Investigations into head acceleration events using instrumented mouthguard will inform exposure estimates and will account for age group, position and sex.

Influence of sex

This study will recruit both male and female athletes. This offers potential for addressing important questions related to outcomes by sex. While we expect a majority male cohort, we will test the influence of sex on outcome measures and report these where appropriate.

Neuroimaging

Analyses of brain atrophy, diffusion and fMRI data will be performed along standard lines using software packages, including SPM and FSL. Primary outcome measures will include fractional anisotropy (FA) as measured by DTI, and longitudinal brain atrophy will be measured by the Jacobian determinant (JD) volume change rate.[6 21 65] Voxel-wise analyses will be performed according to standard approaches, including multiple comparison corrections.

1. DTI will enable analysis of white matter tract damage. Maps of FA will be created that can be compared both cross-sectionally and longitudinally. Tracts of interest will be explored, as well as global FA measures. We will use a standard DTI preprocessing and analysis pipeline.[71] Lesion masks, if required, will be created for each participant on each visit. This is to exclude any areas in a white matter tract that are not indicators of axonal injury, which could interfere with mean FA.
2. T1 structural imaging analysis: Cross-sectional individualised regional volumetric analyses will be conducted after segmentation of structural T1 images. Volumes will be normalised to total intracranial volume. Cortical thickness will be calculated using FreeSurfer[96] as a complementary approach to investigating volume differences. Longitudinal analysis will be conducted by producing individualised maps of volume changes over time (JD atrophy rate maps) from serial T1 images.[21] If required, lesion masks can be created for each participant on each visit to enable the segregation of JD values representing diffuse volume changes from those representing focal injury.
3. SWI provides information regarding the presence of diffuse vascular injury, an indicator of brain injury, which is not picked up in conventional imaging.
4. rs-fMRI: Blood oxygen-level dependent activity at rest will be measured to look at brain network function cross-sectionally and longitudinally. Functional connectivity will be calculated for specific regions of interest and also for brain networks commonly affected by TBI, including the default mode network, the salience network and the frontal parietal control network. Functional connectivity from subcortical regions, including the caudate/putamen and thalamus, to cortical regions and networks will be calculated. Standard approaches to the calculation of functional connectivity will be performed using FSL.[97 98] In addition, spectral dynamic causal modelling will be used to assess alterations in causal interactions between brain networks. Between and within-hub activation in resting state will be explored. We will evaluate the relationship between functional connectivity, brain structure (as defined above) and behavioural outcome measures.

Fluid biomarkers

Analysis of blood samples will allow circulating factors related to outcomes after TBI to be identified. These may include: NfL, tau, GFAP, UCHL1 and protein S100 (S100B). Fluid biomarker analyses will be performed using a digital ELISA technique, using a Quanterix Simoa analyser to provide ultrasensitive assessment of concentrations. More extensive proteomic assessment will be performed using either Olink, Somalogic or Alamar panels, depending on cost and technology developments. We will specifically investigate inflammatory markers to investigate whether prior exposure to head injuries is associated with elevated inflammatory state.

Whole blood samples will be collected to allow for assessment of known genetic factors and factors that will be eventually known in the future that may influence clinical outcome after TBI. DNA samples will be stored without any personally identifiable information for future analysis. Genetic analyses will include APOE genotype assessment and generation of an individualised polygenic risk score for Alzheimer's disease using a microarray targeting single nucleotide polymorphisms (SNPs) related to neurodegenerative disease.[99]

Blood biomarker trends will be compared between groups, as well as a longitudinal comparison within individuals. This will be achieved by first testing for normal distribution, followed by parametric/non-parametric tests as required for comparisons. For within-subject comparisons, paired tests for repeated measures will be used. The relationship between blood biomarkers and neuroimaging will be assessed as done previously.[100] To investigate the relationship between blood biomarkers and outcome measures, linear or logistic regression will be used, with multiple comparison corrections to adjust for number of biomarkers and time points of assessments.

Cognitive assessment

Standard neuropsychological assessments will be used to assess cognitive function across different time points. The tests will include assessment of premorbid cognitive functioning, memory, processing speed, language, visuospatial skills, working memory, attention and executive

functioning (table 3). Performance validity will be assessed in all assessments using specific tasks (dot counting task) but also intrinsic measures including the Wechsler Adult Intelligence Scale-Fourth Edition Digit Span. Test validity will be assessed in all cases by a clinical neuropsychologist. Cross-sectional analysis of neuropsychological tests will characterise cognitive function across the cohort in domains including executive function, working memory and processing speed. Additional measures of psychiatric health, quality of life and alcohol and drug use will be ascertained from questionnaires (table 3). Learning effects of repeated exposure to assessments are addressed using tests specific to repeated assessments (Repeatable Battery for the Assessment of Neuropsychological Status, Cognitron). Controls will also complete neuropsychological tests longitudinally to provide a comparison of longitudinal change in performance. Cognitive tests will be selected and tested per hypothesis and factor analysis employed where appropriate to improve statistical power. A mixed model multilevel approach will be explored when analysing performance longitudinally across all time points. The relationship between cognitive function and questionnaire measures will be determined. Neuroimaging analysis of DTI and rs-fMRI using predefined methods[6 97] will assess structural and functional connectivity; this will enable the relationship between network connectivity and behavioural outcome measures to be ascertained. During follow-up assessments we will add in additional measures to assess social isolation and loneliness,[101 102] financial hardship, psychosocial adjustment (including the Work and Social Adjustment Scale[103]) and episodic memory (the Subjective Cognitive Decline Questionnaire[104 105]). These will enable interactions between biopsychosocial factors to be explored in greater detail, particularly in relation to the transition period following retirement and how this connects to overall health, wellbeing and cognitive function.

Computerised task scores of the cohort will be analysed in relation to a large-scale normative dataset (n=~400 000) collected via the Great British Intelligence Test.[83] Raw scores will be transformed into 'deviation from expected' scores which measure the difference between each participant's observed performance and the expected performance of a healthy individual with a similar demographic background, dividing this difference by the SD of the control population. The expected score is generated by using linear models trained to the normative dataset using a combination of demographic factors (age, age squared, gender, handedness, education, occupation status, ethnicity, residency and first language). Participants' cognitive performance will be studied in relation to structural imaging metrics to determine whether it can predict neuronal abnormalities associated with TES and their longitudinal progression.

Sleep

Sleep will be investigated using subjective and objective measures. Subjective sleep measures will include self-reported sleep quality score and Insomnia Severity Index score.[106 107] Objective sleep measures will include total sleep time, sleep-onset latency, wake after sleep onset and sleep efficiency as measured using the smart wristwatch. We will investigate whether changes in sleep relate to cognitive and psychiatric state. In addition, we will investigate whether sleep state modifies the relationship between head impact exposure and biomarkers of neurodegeneration. Obstructive sleep apnoea measures will include self-reported obstructive sleep apnoea risk score measured using the snoring, tiredness, observed apnoea, high BP, BMI, age, neck circumference and male gender (STOP-BANG) questionnaire and objectively measured apnoea-hypopnea index measured with the under-mattress sleep tracker. REM sleep behaviour disorder will include self-reported response to a screening question.

Cardiovascular and metabolic health

We will analyse the relationship between cardiorespiratory fitness levels and structural and functional measures of brain health, including volumetric (regional and global), white matter hyperintensities and cognitive/psychiatric measures (table 3). Intensity and duration of physical activity levels obtained from smartwatches will be analysed against brain volume and cognition scores. A profile of cardiovascular health will include measurements from the Vicorder (augmentation index), cholesterol levels and blood pressure. The metabolic profile will be characterised using the criteria for metabolic syndrome. CPET testing[90] will be conducted on an upright cycle ergometer to determine the maximum rate of oxygen consumption (VO^2 max), the gold standard measure of cardiorespiratory fitness. A multivariate analysis will be run to investigate if there is a relationship between previous head impact exposure, current cardiovascular/metabolic profile, physical activity levels and various brain health outcome measures (imaging, fluid biomarkers and neuropsychology scores).

Data management

All data and appropriate documentation will be stored for a minimum of 15 years after the last participant's final follow-up. This is to enable subsequent analyses with new techniques as they are developed. All data will be handled in accordance with current legislation, at present the GDPR 2018 and the Data Protection Act 2018. Physical data will be pseudoanonymised and stored, accessible only by the research team. Digital data will be secured using dedicated data management software Research Electronic Data Capture (REDCap)[108 109] hosted at Imperial College. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and interoperability with external sources. Fluid biomarker data will be stored at University College London and

Imperial College London, and neuroimaging data at Imperial College London.

Limitations

There may be a bias in recruitment due to the nature of referral into the study through the Advanced BRAIN Health Clinic. Several populations may be over-represented, such as symptomatic retired players with concerns about their brain health or players who are well enough to travel and present in person to a clinic; with players who have developed serious neurodegenerative or health conditions perhaps being less able to attend the clinic. This may limit the interpretability of study findings in the context of the wider retired player population, although this does not limit our ability to pursue our stated research questions[2–4] and hypotheses.[1–5]

As with all longitudinal studies there is a risk of participant dropout over the course of the study. We will test for the imbalances in the data at each time point due to loss to follow-up and may use statistical approaches such as weighted analyses to account for this if appropriate. Missing data will be handled by multiple imputation where appropriate. Where assumptions are violated, other missing data imputation methods will be considered. Where the number of missing data is small, complete case analysis will be used.

Ethics and dissemination

Ethical considerations

The relevant ethical approvals have been granted by the Camberwell St Giles Research Ethics Committee. The proposed investigation methods of patients with a suspected history of TBI are safe if normal safety precautions are taken in the case of MRI. The study will be performed in accordance with the recommendations guiding ethical research involving human subjects adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013.

Our study will involve negligible risk to the patient and will not significantly interfere with freedom of action or privacy or be unduly invasive or restrictive. The primary inconvenience to the participant is to cooperate with an MRI scan that can take up to 60 min and, for some participants, be noisy, uncomfortable and claustrophobic. There is a risk to patients if they have ferromagnetic metal on their person and all the usual MRI safety checks and procedures will be undertaken to minimise this risk.

Dissemination

The study findings will be disseminated to participants, healthcare professionals, academics, policymakers and other stakeholders including through presentation at conferences and peer-reviewed publications. Data will be shared with approved researchers to provide further insights for patient benefit and will integrate with the UK-TBI Repository and Data Portal Enabling Discovery platform.

Patient and public involvement

The study protocol and clinical programme was set up with consultation from the football and rugby bodies alongside recommendations from former players. A biyearly remote participant panel has been created to involve discussion of the proposed work and research findings from the Advanced BRAIN Health Study with study participants and stakeholders.

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