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Brain health in retired athletes

Submission date
11/08/2020

Recruitment status
No longer recruiting

Registration date
12/08/2020

Overall study status
Ongoing

Last Edited
10/12/2025

Condition category
Nervous System Diseases

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Mild head injury is also often referred to as concussion, minor head injury or mild traumatic brain injury (mTBI). Regardless of the terminology used, the occurrence of a head injury in these cases causes the brain to shake back and forth inside the skull, causing mild damage.
Mild head injury is commonly caused by falls, road crashes, assaults and sports accidents. While most mild head injuries result in no long-term damage to the brain, it can cause temporary disruption to brain function that can last for at least a number of weeks.
This study is a long-term study to look at retired elite men and women athletes (who had a high risk of concussion during their sporting careers) and compare them to similarly aged controls with no history of TBI. The overall aim is to see whether a history of head injury makes individuals more at risk of Alzheimer's disease, Parkinson's disease, motor neuron disease or other brain problems.

Who can participate?
Anyone who is a retired former elite sports man or woman aged 40-85 years and can understand and participate in the testing procedures. Controls are drawn from individuals with no previous head injuries and do not have to be former elite athletes. There is an online screening questionnaire to check eligibility.

What does the study involve?
This study involves an initial online screening questionnaire. If accepted into the study, the subject will be invited to attend one of the test centres (London, Dublin) for an initial baseline assessment. This will involve a physical examination, doing a detailed questionnaire, having a blood test, a MRI brain scan, a cognitive (memory) test with a neuropsychologist, an eye test and providing saliva, blood and urine samples. The testing will take most of a day to complete and subjects are reimbursed for their travel expenses (including the expenses fora partner or carer to attend). Results will be made available to the individual and their usual general practitioner. Subjects may be invited for retesting after a gap of no less than 5 years with the same testing process.

What are the possible benefits and risks of participating?
There are no anticipated risks with the testing and no medical interventions or treatments are given with this study. Blood testing will be performed by professional phlebotomists. All data obtained is coded and de-identified and confidentiality is maintained throughout the study. At

the conclusion of the study, deidentified data will be made available for researchers to understand the effects of aging and head injuries.

The tangible benefits are of a comprehensive assessment of physical and brain health at each assessment time point and this information will be provided to the subject and a copy to their usual GP to follow up on any issues of note. The intangible benefit is an altruistic one of participating in an important study that will help understand the link between head trauma, ageing and long-term brain disease.

Where is the study run from?
The International Concussion and Head Injury Research Foundation (ICHIRF) in association with St Mary's University, London (UK)

When is the study starting and how long is it expected to run for?
June 2014 to December 2026 (taking into account a period of suspended testing during COVID)

Who is funding the study?
The funding of the project is as follows:
1. Injured Jockeys Fund
2. Godolphin Racing
3. British Association of Sport and Exercise Medicine
4. Irish Injured Jockeys
5. The Players Foundation
6. National Football League
7. The Racing Foundation
8. MARKER AG
9. Private donations

Who is the main contact?
Dr Michael Turner, michael@ichirf.org

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
216703

Study information

Scientific Title
Brain health in retired athletes - ageing and impact related neurodegenerative disease

Acronym
ICHIRF-BRAIN Study

Study objectives
1. To determine the incidence of and risk factors for neurodegenerative disease in this population
2. To determine the incidence of age-related cognitive change in this population
3. To develop early predictors for neurodegenerative disease in this population

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 01/06/2015 St Mary's University SMEC (Waldegrave Road, Twickenham, London TW1 4SX, UK; no telephone number provided; no email provided), ref: n/a
Amendments:
Screening protocol - approved 27/10/2015, ref: SMEC-2015-16-53
Brain donation - approved 12/06/2017, ref: SMEC-2016-17-115
PET Scanning - approved 26/01/2018, ref: SMEC-2017-18-051
2. Approved 22/09/2017, University of Birmingham (Edgbaston, Birmingham, B15 2TT, UK; no telephone number provided; no email provided), ref: 17/EE/0275
3. Approved 10/10/2019, Beacon Hospital REC (Sandyford, Dublin, Ireland; +353 12936600; ethics@beaconhospital.ie), ref: BEA0130

Study design
Prospective long-term non-interventional longitudinal study

Primary study design
Observational

Study type(s)
Screening

Health condition(s) or problem(s) studied
Neurodegenerative disease

Interventions

Current interventions as of 24/01/2025:
The examination will consist of the following:

Questionnaire - Participants will complete a questionnaire which includes questions on past medical history, injury history, concussion history, playing history, sleep, mood. Additional history and information will be sought from the participant's partner or spouse. Patient reported outcome measures (PROMs) will include DQOL, PDQ, PIMS and MCQ (https://safetyandquality.govcms.gov.au/condition-specific-proms)

Sports Concussion Assessment Tool 3/5 (SCAT3/5) Participants will complete the SCAT3 or the latest iteration of the same tool - currently SCAT5. The SCAT3/5 includes the following assessments: Glasgow Coma Scale, Maddock's questions, Standardized Assessment of Concussion, a modified version of the Balance Error Scoring System (mBESS consisting of 3 stances performed on a hard surface), cervical spine examination and modified neurological examination. There are published normative data on this test.

Physical and Neurological examination - The neurological examination will be performed by a consultant neurologist following a standardized exam protocol. Physical examination will include visual acuity and colour vision using Isihara plates, urinalysis and University of Pennsylvania - Brief Smell Identification Test.

Balance Assessment -In addition to the clinical mBESS assessment (see above), each subject will perform a balance test using the SWAY iPhone app. Sway is a FDA-approved balance test that uses the inbuilt accelerometers in a smart phone or iPad device and objectively measures balance and reaction time

Computerized Neurocognitive Screen - Participants will complete the CogState Brief Battery, a validated computerized cognitive assessment, which includes four separate tasks: Processing Speed (simple reaction time), Attention (choice reaction time), Learning (visual recognition memory) and One Back (Working Memory test). Participants will perform the test in a quiet room under the supervision of a study investigator. As per test protocol, participants will complete a practice trial for each task before completing the scored test. The primary outcome measure is the speed and accuracy of responses relative to normative data for that age-group.

Neuropsychological assessment - Neuropsychological tests for the current study will be selected on the basis of a study into neuropsychological function following repeat concussion in active jockeys. The total administration time for the neuropsychological battery will be approximately 60 minutes and will be performed by a consultant clinical neuropsychologist. All neuropsychological tests will be administered and scored according to standardised instructions. The following neuropsychological domains assessed: premorbid function (Test of Premorbid Function); vocabulary and verbal ability (Vocabulary subtest from Wechsler Adult Intelligence Scale- Fourth UK Edition WAIS-IV); auditory verbal short term and working memory (Digit Span subtest from the WAIS-IV; processing speed (Symbol Digit Modalities Test); and the Speed of Comprehension Test; verbal learning and memory (California Verbal Learning Test II); response inhibition (Stroop), visual scanning and response alternation (Colour Trails Test); and fluency across both semantic and letter conditions. Administration of the digit span subtest from the WAIS-IV will allow the use of an embedded measure (Reliable Digit Span) sensitive to the application of cognitive effort. Preliminary analysis will compare performance on neuropsychological composites, the number of abnormal scores and performance on individual tests between concussion and control groups. Future analyses will investigate the relationship between neuropsychological test performance and co-morbid factors such as mood, a history of learning difficulties and/or attention deficit hyperactivity disorder, substance use, and pain; and

between neuropsychological test performance and sports related factors such as number of concussions, age at first concussion, and type of sport. Finally, relationships between neuropsychological test performance and imaging, neurology, balance and eye movements will also be explored

Advanced MR brain imaging - Anatomical and functional magnetic resonance imaging (MRI) will be acquired for all subjects. MRI studies will be performed using a 3.0 Tesla Siemens scanner using a 32-channel head coil and will require a minimum of 45 minutes to complete (normally around 60 minutes). The image sequences will include:
Structural scans, consisting of 3D T1-weighted (T1w) high-resolution sequences and fluid-attenuated inversion recovery (FLAIR) sequences with whole brain coverage. The T1w and FLAIR sequences will permit detection of any underlying structural lesion. Volumetric analysis will be performed using the 3D T1-weighted high-resolution sequences Magnetisation Prepared Rapid Gradient Echo (MPRAGE) sequence. Data measurement and analysis will be as per Guo et al. (66). Analysis of structural brain imaging will be undertaken to detect subtle changes in brain morphology and morphometry related to mild TBI, such as by voxel-based morphometry for whole-brain analysis, and FSL-FIRST for analysis of the subcortex.
Diffusion weighted imaging (DWI) (B3000), which will allow for mapping of white matter tracts in the brain. Analysis will be undertaken for both tract based spatial statistics and tractography, such as with constrained spherical deconvolution (CSD), a method robust to crossing fibres.
T2-relaxometry and susceptibility weighted imaging sequences, which allows detection of regional grey and white matter changes that may reflect long-term changes in the brain following mild TBI.
Resting-state functional MRI (rs-fMRI), acquired by blood oxygenation level dependent (BOLD), will be acquired to assess both resting state functional activity and functional connectivity, and its relationship to mild TBI.
Analysis of the scans will be performed using standard statistical techniques, such as by non-parametric randomised permutation testing with appropriate statistical correction for multiple comparisons.

Visual Saccadic testing - Saccadic latencies (reaction times) will be recorded using a portable, microminiaturised head-mounted saccadometer, in accordance with a standard published methodology.Three lasers projected high-contrast red targets in a horizontal line at -10°, 0° and +10° on a wall in front of the seated participant. Each trial begins with the central target illuminated. After a random delay of 0.5–1.5s, this jumps 10° to the left or right randomly. Participants are instructed to follow the target with their gaze and 200 saccades will be recorded, taking around 7 minutes. The device records saccadic latency using scleral infrared oculometry, with automatic deletion of blinks, movements in the wrong direction and those with an abnormal velocity profile. Each participant's saccadic latency distribution will be analysed using custom-built software, which calculates best-fit parameters using an established model of saccadic latency, as previously described.

Blood testing - Participants in this study will have blood drawn and labelled at baseline and each assessment time point. Samples will be anonymised prior to analysis. All blood will be drawn by professional phlebotomists. Routine blood workup will be analysed under the supervision of The Doctors Laboratory Ltd, 60 Whitfield Street, London, W1T 4EU, UK. The blood screen includes: Full blood count + 5-part differential; erythrocyte sedimentation rate; c-reactive protein; sodium; potassium; chloride; bicarbonate; urea; creatinine; bilirubin; alkaline phosphatase; aspartate transaminase; alkaline transaminase; creatine kinase; lactate dehydrogenase; gamma glutamyl transferase; total protein; albumin; globulin; calcium; phosphate; uric acid; random blood glucose; cholesterol; high density lipoprotein; low density lipoprotein; triglycerides; serum iron; total iron binding capacity; ferritin; vitamin D; blood group; free thyroxine (T4); thyroid

stimulating hormone; growth hormone; cortisol; prolactin; coeliac disease profile (tissue transglutaminase (IgA), HLA DQ2/DQ8, total immunoglobulin A). In females only, luteinizing hormone and follicle stimulating hormone. In males only, prostate profile - total prostate specific antibody, free prostate specific antibody, calculated ratio.

Fluid Biomarkers studies - Participants in this study will have 5ml Serum and 5ml plasma drawn, labelled, stored in cryovials of 0.5ml and frozen at -80°C in liquid nitrogen at baseline and at each assessment time point. Samples will be anonymised prior to analysis. All blood will be drawn by professional phlebotomists. Samples will be batch-tested using ultrasensitive single molecule array (Simoa) methods (Quanterix, Billerica, MA) (69, 70) for the following biomarkers: neurofilament light polypeptide (NFL), tau, ubiquitin carboxylterminal hydrolase isoenzyme L1 (UCH-L1), glial fibrillary acidic protein (GFAP), Aβ40 and Aβ42. Genotyping the apolipoprotein E (APOE) ε4 allele will also be performed . Neuron-specific enolase (NSE) and S100B will be measured using immunoassays with electrochemiluminescence detection.

MicroRNA Study – Saliva samples will be obtained from participants and subject to Next Generation Sequencing (NGS) analysis for the identified miRNAs. NGS sequencing libraries will be prepared, quantified and sequenced for all samples. The collected reads will be subjected to quality control, unique molecular index-based correction (to remove PCR replicates), alignment and downstream analysis. Identified miRNA's will be validated by qPCR, in situ hybridization or miRNA inhibition.

Genetics - The advantages of using saliva for whole genome sequencing (WGS) include - the ease in obtaining samples non-invasively from participants, the convenience in mailing saliva collection kits and the long-term stability of saliva samples at room temperature. However, as saliva samples have substantially lower DNA yield than blood, and are prone to microbial contamination, a carefully standardised saliva collection protocol is essential for saliva DNA to meet the stringent QC metrics needed to generated good quality WGS data.

Saliva samples will therefore be collected from participants using the Oragene DNA Self-Collection kit (tube format OG-500; DNA Genotek Inc., Kanata, Ontario, Canada) and used for DNA extraction. Each sample will be bar-coded, temporarily stored at room temperature and subsequently transferred to a central laboratory for DNA extraction, biobanking and subsequent analysis. DNA will be extracted from a 500 µl aliquot from the Oragene DNA/saliva Self-Collection kits in accordance with the manufacturer's instructions. Extracted samples will be stored at –20°C prior to NGS. WGS will be performed using DNBSEQ-G400RS (BGI, Shenzhen, China) to a target average coverage depth of 30x and a read length of 150bp. WGS will be used to determine and compare common and rare single nucleotide variants (SNV) and copy number variants (CNV) between cases and controls.

Neuropathological brain examination - Participants and control subjects will be given the opportunity to enrol in the brain bank program, which requires specific informed consent through University College London. If willing to participate, the names and contact details will be forwarded to the Queen Square Brain Bank (QSBB) for neurological disorders coordinator who will make contact and provide additional information as required. All further dialogue with the volunteer will be coordinated by the QSBB who will enrol the participant in the brain bank program. In the event of the participant dying, the QSBB coordinator will make the necessary logistical arrangements with the family, hospital, or funeral director for harvesting brain tissue for detailed neuropathological analysis and tissue preservation for future research. All material stored at the QSBB is under HTA licence and any tissue used for research will have ethical

approval obtained from the National Research Ethics Service Committee London. The neuropathological assessment, including staining methods, anatomical sampling sites and diagnostic criteria will be in accordance with a recent NIH consensus conference.

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Fluid Biomarkers studies - Participants in this study will have 5ml Serum and 5ml plasma drawn, labelled, stored in cryovials of 0.5ml and frozen at -80°C in liquid nitrogen at baseline and at each assessment time point. Samples will be anonymised prior to analysis. All blood will be drawn by professional phlebotomists. Future consideration to performing fluid biomarkers on CSF will be undertaken. Samples will be batch-tested using ultrasensitive single molecule array (Simoa) methods (Quanterix, Billerica, MA) (69, 70) for the following biomarkers: neurofilament light polypeptide (NFL), tau, ubiquitin carboxylterminal hydrolase isoenzyme L1 (UCH-L1), glial fibrillary acidic protein (GFAP), Aβ40 and Aβ42. Genotyping the apolipoprotein E (APOE) ε4 allele will also be performed . Neuron-specific enolase (NSE) and S100B will be measured using immunoassays with electrochemiluminescence detection.

Gut Metabolomic study – Participants will be given a faecal sample collection kit, with instructions regarding collection, storage and transport. Faecal samples will be processed, and DNA extracted and subjected to next generation sequencing to determine the composition and potential function of the gut microbiota. Follow-up work will focus on metabolically active microbes and for this faecal samples will be stored at -80°C for the analysis of microbial metabolites such as short-chain fatty acids and for follow-up work which may focus on metabolically active microbes. Microbes present in faecal samples will also be assessed through culture based (agar) assays to assess their ability to produce antimicrobial peptides. A urine sample may also be collected and stored at -80°C for metabolite analysis at a future date.

MicroRNA Study – Saliva samples will be obtained from participants and subject to Next Generation Sequencing (NGS) analysis for the identified miRNAs. NGS sequencing libraries will be prepared, quantified and sequenced for all samples. The collected reads will be subjected to quality control, unique molecular index-based correction (to remove PCR replicates), alignment and downstream analysis. Identified miRNA's will be validated by qPCR, in situ hybridization or miRNA inhibition.

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Intervention Type
Mixed

Primary outcome(s)
Neurodegenerative disease (e.g. Alzheimer's Disease) will be a clinical diagnosis supported by neuropsychological, radiological, pathological and/or fluid biomarker changes and in line with international diagnostic criteria measured as follows:
1. A questionnaire which includes questions on past medical history, injury history, concussion history, playing history, sleep, mood
2. Sports Concussion Assessment Tool 3/5
3. Physical and Neurological examination - The neurological examination will be performed by a consultant neurologist following a standardized exam protocol. Physical examination will include visual acuity and colour vision using Isihara plates, urinalysis and University of Pennsylvania - Brief Smell Identification Test
4. Balance Assessment: each subject will perform a balance test using the SWAY iPhone app
5. Computerized Neurocognitive Screen - Participants will complete the CogState Brief Battery, a validated computerized cognitive assessment, which includes four separate tasks: Processing Speed (simple reaction time), Attention (choice reaction time), Learning (visual recognition memory) and One Back (Working Memory test)
6. Neuropsychological assessment - Neuropsychological tests for the current study will be selected on the basis of a study into neuropsychological function following repeat concussion in active jockeys. The total administration time for the neuropsychological battery will be approximately 60 minutes and will be performed by a consultant clinical neuropsychologist.
7. Anatomical and functional magnetic resonance imaging (MRI) will be acquired for all subjects. MRI studies will be performed using a 3.0 Tesla Siemens scanner using a 32-channel head coil
8. Visual Saccadic testing - Saccadic latencies (reaction times) will be recorded using a portable, microminiaturised head-mounted saccadometer
9. Blood testing - Participants in this study will have blood drawn and labelled at baseline and each assessment time point. Blood will be tested for: Full blood count + 5-part differential; erythrocyte sedimentation rate; c-reactive protein; sodium; potassium; chloride; bicarbonate; urea; creatinine; bilirubin; alkaline phosphatase; aspartate transaminase; alkaline transaminase; creatine kinase; lactate dehydrogenase; gamma glutamyl transferase; total protein; albumin; globulin; calcium; phosphate; uric acid; random blood glucose; cholesterol; high density lipoprotein; low density lipoprotein; triglycerides; serum iron; total iron binding capacity; ferritin; vitamin D; blood group; free thyroxine (T4); thyroid stimulating hormone; growth hormone; cortisol; prolactin; coeliac disease profile (tissue transglutaminase (IgA), HLA DQ2/DQ8, total

immunoglobulin A). In females only, luteinizing hormone and follicle stimulating hormone. In males only, prostate profile - total prostate specific antibody, free prostate specific antibody, calculated ratio
10. Fluid Biomarkers studies - Participants in this study will have 5ml Serum and 5ml plasma drawn, labelled, stored in cryovials of 0.5ml and frozen at -80°C in liquid nitrogen at baseline and at each assessment time point. Samples will be batch-tested using ultrasensitive single molecule array (Simoa) methods (Quanterix, Billerica, MA) (69, 70) for the following biomarkers: neurofilament light polypeptide (NFL), tau, ubiquitin carboxylterminal hydrolase isoenzyme L1 (UCH-L1), glial fibrillary acidic protein (GFAP), Aβ40 and Aβ42. Genotyping the apolipoprotein E (APOE) ε4 allele will also be performed . Neuron-specific enolase (NSE) and S100B will be measured using immunoassays with electrochemiluminescence detection
11. MicroRNA Study – Saliva samples will be obtained from participants and subject to Next Generation Sequencing (NGS) analysis for the identified miRNAs
12. Neuropathological brain examination - Participants and control subjects will be given the opportunity to enrol in the brain bank program. In the event of the participant dying, the QSBB coordinator will make the necessary logistical arrangements with the family, hospital, or funeral director for harvesting brain tissue for detailed neuropathological analysis and tissue preservation for future research

Removed 24/01/2025:
Gut Metabolomic study – Participants will be given a faecal sample collection kit, with instructions regarding collection, storage and transport. Faecal samples will be processed, and DNA extracted and subjected to next generation sequencing to determine the composition and potential function of the gut microbiota

Key secondary outcome(s))
Age-related cognitive changes in this population will be a clinical diagnosis supported by neuropsychological, radiological, pathological and/or fluid biomarker changes and in line with international diagnostic criteria. Predictors will be based on the study measures listed in the primary outcomes.

Completion date
31/12/2026

Eligibility

Key inclusion criteria
Current inclusion criteria as of 24/01/2025:
1. Completed the online screening assessment
2. Participated in elite sport or amateur sport on a regular basis
3. Can understand and participate in the testing procedures
4. Are able to provide informed consent for participation
5. Are now retired from active participation in competitive sport

Previous inclusion criteria:
1. Completed the online screening assessment
2. Participated in elite sport
3. Can understand and participate in the testing procedures
4. Are able to provide informed consent for participation

Participant type(s)

Healthy volunteer

Healthy volunteers allowed
Yes

Age group
Mixed

Lower age limit
40 years

Upper age limit
85 years

Sex
All

Total final enrolment
200

Key exclusion criteria
1. For the questionnaire study if they are aged <18 years and ineligible for the phenotyping <50 years
2. Have a history of previous severe traumatic brain injury
3. Are on current psychotropic medication
4. They have a pre-existing medically-diagnosed neurological disorder (e.g. Alzheimer's dementia, Parkinson's disease, Multiple Sclerosis, Motor Neuron Disease)
5. The participant is currently enrolled in a disease modifying therapeutic (drug or interventional) trial
6. Presence of any of the following clinical conditions: Substance abuse within the past year; Unstable cardiac, pulmonary, renal, hepatic, endocrine, hematologic, or active malignancy or infectious disease; AIDS or AIDS-related complex; Unstable psychiatric illness defined as psychosis (hallucinations or delusions) or untreated major depression within 90 days of the screening visit

Date of first enrolment
01/06/2015

Date of final enrolment
01/12/2025

Locations

Countries of recruitment
United Kingdom

England

Ireland

Study participating centre
International Concussion and Head Injury Research Foundation (ICHIRF)
170 Tottenham Court Road
London
England
W1T 7HA

Study participating centre
Beacon Hospital Research Institute
Suite 13 Beacon Mall
Beacon Hospital
Dublin
Ireland
Dublin 18

Sponsor information

Organisation
The International Concussion and Head Injury Research Foundation (ICHIRF)

Funder(s)

Funder type
Charity

Funder Name
Injured Jockeys Fund

Funder Name
Godolphin Racing

Funder Name
British Association of Sport and Exercise Medicine

Funder Name

Irish Injured Jockeys

Funder Name
The Players Foundation

Funder Name
National Football League

Funder Name
The Racing Foundation

Funder Name
MARKER AG

Funder Name
Private donations

Results and Publications

Individual participant data (IPD) sharing plan
The data-sharing plans for this study are under review but will involve access on request via a non-publicly available repository

IPD sharing plan summary
Available on request, Stored in non-publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		01/09/2022	20/09/2022	Yes	No
Results article		16/07/2025	10/12/2025	Yes	No
Results article		19/03/2024	10/12/2025	Yes	No
HRA research summary			28/06/2023	No	No
Preprint results		05/11/2024	24/01/2025	No	No
Protocol (preprint)		27/05/2022	21/06/2022	No	No
Study website		11/11/2025	11/11/2025	No	Yes