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The International Concussion and Head Injury Research Foundation Brain Health in Retired Athletes Study of Ageing and Impact Related Neurodegenerative Disease (ICHIRF-BRAIN Study)

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Abstract

Introduction and aims: Traumatic brain injury (TBI) is a leading cause of death and disability worldwide. Large registry studies have demonstrated a dose response relationship between TBI and neurodegenerative disease; however, disentangling the direct effects of TBI from ageing and/or a progressive neurodegenerative process is problematic. This study is a prospective long term cohort study to examine a population of retired elite athletes at high risk of concussion and mTBI during their sporting careers compared to age and sex matched controls with no history of TBI. The aim is to determine the incidence and risk factors for neurodegenerative disease and/or age related effects on brain health in this population.

Methods and analysis: A population of retired male and female elite athletes and controls aged 40-85 years, will be assessed at baseline and serial time points over 10 years during life using a multi-dimensional assessment including: Questionnaire; SCAT3/5; Neurological and physical examination; Instrumented balance assessment; Computerised neurocognitive screen; Neuropsychological assessment; Advanced MR brain neuroimaging; Visual saccades; Blood workup; Fluid biomarkers; Gut metabolomics; Salivary MicroRNA analysis; Genetic analysis; and where available Brain banking and neuropathology

Ethics and dissemination: Ethics approval was granted by St Mary's University SMEC as well as at the various satellite trial sites. The trial is registered with ISRCTN (BioMed Central) with ID number: 11312093. In addition to the usual dissemination process, this phenotypically well characterised dataset will reside in a publicly accessible infrastructure of integrated databases, imaging repositories, and biosample repositories and de-identified data will be made available to collaborating researchers.

Keywords: Dementia • Chronic traumatic encephalopathy • Neurodegenerative disease • Ageing • Brain health • Traumatic brain Injury

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Introduction

Background and rationale

Traumatic brain injury (TBI) is a leading cause of death and disability worldwide [1]. A recent review has highlighted population based epidemiological evidence linking head injury with dementia [2]. Large registry studies have demonstrated a dose response relationship between TBI and neurodegenerative disease with a doubling of the risk of dementia following severe injuries, but also a 1.6x increase after mild TBI (mTBI) [3-6]. Disentangling the direct effects of TBI from ageing and/or a progressive neurodegenerative process is problematic.

When examining the long term effects of repeated concussion or repetitive head impacts, there is evidence that some former athletes in contact, collision, and combat sports suffer from depression, cognitive deficits, or mild cognitive impairment later in life [7-9]. Neuroimaging studies show evidence of macrostructural, microstructural, functional, and neurochemical changes in some athletes [10-19].

Some studies have found an association between these deficits and a history of multiple concussions [7] whereas other studies have not found any relationship [20]. Former high school American football players do not appear to be at increased risk for later life neurodegenerative diseases according to two studies [21,22] however, an increased risk for neurodegenerative diseases in retired American football [23] and UK professional soccer players [24] is suggested in studies examining death certificates. It is important to appreciate, however, that survey studies of former collegiate [25-27] and professional [28] athletes indicate that the majority of people rate their functioning as normal and consistent with the general population. To date, a cause and effect relationship between CTE and concussions or age of exposure to contact sports has not been established [29-32].

The extent to which repetitive neurotrauma causes static or progressive changes in brain microstructure and physiology and contributes to later life mental health and cognitive problems, is poorly understood, and requires further study.

Trail design

This study is a prospective long term cohort study to examine a population of retired elite athletes at high risk of concussion and mTBI during their sporting careers compared to age and sex matched controls with no history of TBI.

Trial aims and objectives: To determine the incidence of and risk factors for neurodegenerative disease in this population; To determine the incidence of age related cognitive change in this population; To develop early predictors for neurodegenerative disease in this population.

Methods

Study setting

Volunteers will be recruited by the International Concussion and Head Injury Research Foundation (ICHIRF).

Phase 1: After online registration of interest at http://www.ichirf.org participants will complete a detailed online questionnaire regarding concussion history, mood, sleep and physical and mental health status. From the database of completed questionnaires, participants will be allocated to groups on the basis of their history of sports related concussion, age and gender. Participants in the concussion group will be matched to control subjects of the same age and gender. A balanced number of female participants to male participants in both concussion/control and age groups will be included in the study.

Phase 2: Selected participants and controls will undergo an identical screening protocol at the ICHIRF offices in London, UK or at one of the satellite testing centres in Manchester and Dublin, Ireland. The initial cohort screening will commence with those aged >50 years followed by younger aged groups. The details of the screening program are outlined in the methods section below. Following the completion of all screening elements, the results of the assessment and any findings and/or recommendations will be discussed with the participant and copies of the test results will be made available to them and their general practitioner.

Phase 3: All participants (including controls) will be serially reassessed at suitable intervals (provisionally every 5 years) using the same multidimensional assessment platform at the ICHIRF offices in London, UK or at one of the satellite testing centres in Manchester and Dublin, Ireland.

Eligibilty criteria

Inclusion criteria: Participants will be eligible to participate if they have completed the online screening assessment; have participated in elite sport; can understand and participate in the testing procedures and are able to provide informed consent for participation.

Exclusion criteria: Participants will be ineligible if: For the questionnaire study if they are aged <18 years; Have a history of previous severe traumatic brain injury; Are on current psychotropic medication; They have a pre-existing medically diagnosed neurological disorder (e.g., Alzheimer's dementia, Parkinson's disease, Multiple Sclerosis, Motor Neuron Disease); The participant is currently enrolled in a disease modifying therapeutic (drug or interventional) trial; 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.

Funding

The ICHIRF-BRAIN project is funded through a combination of Competitive grant funding EU Erasmus in collaboration with the Galway-Mayo Institute of Technology SCAT Project. Commercial partnerships MARKER AG (MicroRNA study). Philanthropic support including Godolphin Racing; the Injured Jockeys Fund; British Association of Sport and Exercise Medicine; the Irish Injured Jockeys; the Professional Footballers Association; the National Football League (US); the Racing Foundation; and private donors. Charitable fund raising Individual contributions from volunteers taking part in the national or local fund raising initiatives (e.g., The Virgin London Marathon, Vitality 10,000 London Run, Prudential Ride London-Surrey.

Outcomes

Primary outcome: 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 [33-41]. Neurodegenerative diseases of specific interest include Alzheimer's disease, Amyotrophic Lateral Sclerosis, Frontotemporal Dementia, Parkinson's disease, Lewy Body Dementia, Stroke and Chronic Traumatic Encephalopathy.

Secondary outcomes: 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 [41-43]. Predictors will be based on the study measures listed below.

Sample size

The aim is to recruit a combined number of 250 participants (concussed and controls), with full phenotypic and investigational workup over a 5 year period, from within the UK, Ireland, and Australia. Incidence of neurodegenerative disease following sport related TBI unknown but in NFL football has been estimated up to 4% of US Professional football participants (McKee et al 2013). The main recruitment group in this study is retired professional jockeys which have a 100x greater risk of concussion/head injury that NFL players based on published study data (Turner et al 2001). Thus 125 retired athlete's vs 125 controls with a 50/50 male female mix should have sufficient power (0.8) to detect a 0.05 alpha difference between groups.

Recruitment and allocation

Volunteers will be recruited by the International Concussion and Head Injury Research Foundation (ICHIRF). After online registration of interest at http://www.ichirf.org participants will complete a detailed online questionnaire regarding concussion history, mood, sleep, and physical and mental health status.

From the database of completed questionnaires, participants will be allocated to groups on the basis of their history of sports related concussion, age, and gender.

Blinding

Outcome assessors (imaging, fluid biomarkers, genetics, microRNA, gut metabolomics, visual saccades) will be blinded as to the allocation groups for their assessment and analysis. Emergency unblinding where abnormal results are noted e.g., on blood tests. The PI will unblind the allocation and notify the participants usual GP re follow up of the abnormal test result. No treatment will be provided.

Participant timeline

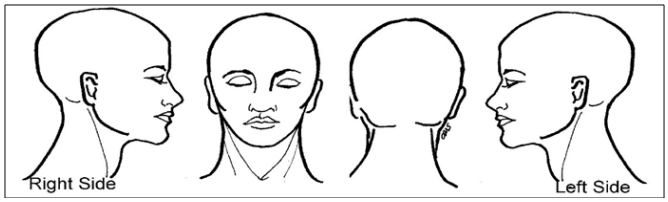

Figure 1. Tenderness/pain/allodynia (mark anatomical site on figures)

Data collection

During life, a baseline and serial multidimensional assessment on subjects and controls will be done including: Questionnaire, SCAT3/5, neurological and physical examination, instrumented balance assessment, computerised neurocognitive screen, neuropsychological assessment, advanced MR brain neuroimaging, visual saccades, blood workup, fluid biomarkers, salivary microRNA analysis, genetic analysis, brain banking and neuropathology.

At baseline and at each assessment visit, participants will complete the following outcome measures:

Questionnaire: Participants will complete a questionnaire (**Appendix 1**) which includes questions on past medical history, injury history, concussion history, playing history, sleep and 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).

Verification: On arrival at the screening centre, volunteers will undergo a face to face discussion to review the answers provided in the questionnaire (e.g., the number of concussions reported). This data will also be verified by the Consultant Neurologist during screening (see below).

Spouse/partner questionnaire: In addition, a partner/spouse questionnaire will be provided on arrival at the screening centre and the answers will be recorded in a face to face interview with a member of the ICHIRF Staff.

Sports concussion assessment tool 3/5 (SCAT3/5): Participants will complete the SCAT3 or SCAT5 [44,45]. The SCAT3/5 includes the following assessments: Glasgow Coma Scale [46], Maddock's questions [47,48], Standardized Assessment of Concussion [49,50], a modified version of the Balance Error Scoring System (mBESS consisting of 3 stances performed on a hard surface) [51], cervical spine examination and modified neurological examination. There are published normative data on this test [52-55].

Physical and neurological examination: The neurological examination will be performed by a consultant neurologist following a standardized exam protocol. (**Appendix 2**) Physical examination will include visual acuity and colour vision using Isihara plates, urinalysis and University of Pennsylvania Brief Smell Identification Test.

Appendix 1. Questionnaire.

Stage	Time point	Enrolment	Allocation	Initial screen	Year 3	Year 5	TBA/	Close out
Enrolment		Online						
Assessments	Eligibility screen	X						
	Informed consent	X						
	Allocation		X					
	Questionnaire			X	X	X	X	X
	Clinical & neuro exam			X	X	X	X	X
	Neuropsychological testing			X	X	X	X	X
	Balance Testing			X	X	X	X	X
	Advanced MR imaging			X	X	X	X	X
	Visual saccades			X	X	X	X	X
	Blood and fluid biomarkers			X	X	X	X	X
	Gut metabolomics			X	X	X	X	X
	MicroRNA			X	X	X	X	X
	Genetics			X	X	X	X	X
	Neuropathological exam			X	X	X	X	X

Appendix 2. Neurological examination.

Handedness		Right	Left	Ambidextrous
Lying and standing BP/HR Lying ..... Standing				
Gait and Balance				
Gait		Normal	Abnormal	Not done
Tandem gait forward		Normal	Abnormal	Not done
Rombergs		Normal	Abnormal	Not done
Rombergs + neck extension		Normal	Abnormal	Not done
Modified BESS		Error score	Double leg stance..... of 10	
			Single leg stance..... of 10	
			Tandem stance..... of 10	
			Total errors..... of 30	
Timed up and go (3 m)..... secs				
Cervical spine				
C spine ROM/pain		Normal	Abnormal	Not done
TMJ tenderness		Yes	No	Not done
Cranial nerves				
Smell - BSIT		Normal	Abnormal	Not done
Score /12				
Ocular				
Visual Acuity		Right	Left	(glasses or contacts Y/N)
Colour vision		Normal	Abnormal	Not done
PERL		Normal	Abnormal	Not done
Fundi		Normal	Abnormal	Not done
Smooth pursuit		Normal	Abnormal	Not done
Saccades – horizontal		Normal	Abnormal	Not done
Saccades – vertical		Normal	Abnormal	Not done
Near point convergence ..... cm				
Vestibular				
Weber		Normal	Abnormal	Not done
Rinne		Normal	Abnormal	Not done
Dix-Hallpike (if indicated)		Normal	Abnormal	Not done
VOR		Normal	Abnormal	Not done
Head shake		Normal	Abnormal	Not done
Head Thrust		Normal	Abnormal	Not done
CN 5-12		Normal	Abnormal	Not done
Other neuro				
Long Tracts	UL	Normal	Abnormal	Not done
	LL	Normal	Abnormal	Not done
Coordination		Normal	Abnormal	Not done
Cerebellar		Normal	Abnormal	Not done
Clinical RT (Best of 3) Right ..... cm, Left ..... cm				
Extrapyramidal signs		Normal	Abnormal	Not done
Postural reflexes		Normal	Abnormal	Not done
Primitive reflexes		Normal	Abnormal	Not done
Luria 3 step hand gesture				
Right		Normal	Abnormal	Not done
Left		Normal	Abnormal	Not done

Balance assessment: In addition to the clinical mBESS assessment (see above), each subject will perform a balance test using the SWAY iPhone app [56]. 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 [57], 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 [58]. 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) [59]; vocabulary and verbal ability (Vocabulary subtest from Wechsler Adult Intelligence Scale Fourth UK Edition WAIS-IV) [60]; auditory verbal short term and working memory (Digit Span subtest from the WAIS-IV) [60]; processing speed (Symbol Digit Modalities Test) [61]; and the Speed of Comprehension Test) [62]; verbal learning and memory (California Verbal Learning Test II) [63]; response inhibition (Stroop) [64], visual scanning and response alternation (Colour Trails Test) [65]; 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.

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. (1). Analysis of T1w MRI shall 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, volumetric changes with Geodesic Information Flows and FSL-FIRST for analysis of the subcortex. We shall also ascertain the predicted brain age of all participants using BrainAgeR. Utilising both the T1w and FLAIR sequences shall also permit detection of white matter hyperintensities across the cohort.

- Diffusion weighted imaging (DWI) (B3000), which will allow for mapping of white matter tracts in the brain. Analysis will be undertaken for both tracts 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, including the presence of haemosiderin staining and microhaemorrhage.

- 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. This shall include investigating for brain connectivity network differences between the cohort, its relationship to other collected patient parameters including biomarkers. Graph theory metrics of this shall also be collected, including node centrality measures.

- Analysis of the scans will be performed using standard and well validated statistical techniques, including by non-parametric randomised permutation testing with appropriate statistical correction for multiple comparisons, and Bayesian regression models.

Visual saccadic testing: Saccadic latencies (reaction times) will be recorded using a portable, microminiaturised head mounted saccadometer, in accordance with a standard published methodology [66]. 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 [67,68].

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. Professional phlebotomists will draw all blood. 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 5 ml Serum and 5 ml plasma drawn, labelled, stored in cryovials of 0.5 ml and frozen at -80˚C in liquid nitrogen at basely.ne and at each assessment time point. Samples will be anonymised prior to analysis. Professional phlebotomists will draw all blood. 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 carboxyl-terminal 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 [71]. 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 150 bp. 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.

Data management

Each individual will be given a unique data identification number of Individuals will not be identifiable from the data. Data will be double entered, and range checked into the relevant database spread sheet and further checked by the PI and study statistician for completeness.

Statistical methods

The main aim is to examine the characteristics of concussed and control subjects. Initially, descriptive data for each variable was calculated. The descriptors will vary depending upon the data type. For continuous variables mean (and SD) will be computed. If the variables are categorical, medians will be calculated for ordinal variables, and proportions for nominal variables. Significance will be set a priori at $P<0.05$. All estimates will be accompanied by a 95% confidence interval. All computations will be conducted using R statistics for computing. In addition to the base package, the MASS, Robustbase, EpiR, Psych, Effsize, lsr, desctools, and corrplot packages will be employed.

Primary outcome analysis: As the study is observational, volunteers being either a case of concussion or a control, regressions will be used for analysis. The outcome variable will determine the specific regression; binary variables, logistic regression; continuous variables, linear regression; ordered logistic regression ordinal variables. For some variables robust regressions will be needed to account for and reduce the weight (influence) of outlying observations. Robust regression will use MM estimators to decrease inefficiency that leads to loss of power [72]. Regardless of the type of regression, Age and gender will be included in the analyses, as the two potential confounders [73].

Additional analyses: To address potential underlying factors, the neuropsychological measures and the biomarkers data sets will be examined using exploratory factor analyses (EFA). The technique is designed to reveal any underlying relationships between measured variables. The resulting EFA composite scores from the regression function will be entered into any subsequent regression analysis. For neuropsychological analysis three factors were established: Combined Cognition index (CCI), Cognition Memory Index (C-MI) and Cognition Executive/Speed Index (C-ESI). For biomarkers factors were identified including Tau, Abeta40, Abeta42, NFL, GFAP and UCH-L1.

Treatment of missing data: The treatment of missing data values depended upon the type of data. For continuous variables, volunteers were assigned the mean value score for that variable. For categorical variables, the median was applied.

Data monitoring

No formal Data Monitoring Committee is required as this is an observational study.

Interim analysis

An interim analysis of the result is planned at the conclusion of Phase 1 (screening of initial cohort) to determine the usefulness of the outcome measures and whether additional outcome measures need to be considered. As this is not an interventional study, the study will not be 'terminated' on the basis of an interim analysis.

Saftety/harms

There are no anticipated major adverse risks with the testing. If the participants become upset about the questioning or the procedures the testing will stop. Professional phlebotomists will draw all blood samples. The questionnaires being used have been used in research previously. They are valid and dependable, and it is not anticipated that adverse reactions will take place. Each volunteer will get an individual report within 30 days outlining the results of their screening and making recommendations about any further action that is required.

Results and Discussion

Recent studies have suggested an association between contact sport participation and an increased risk of late neurodegenerative disease but separating the effects of brain trauma from ageing, unrelated mental health or neurodegenerative disease, is problematic. To assess the hypothesis that contact sport participation is linked to an increased incidence of dementia, prospective longitudinal studies such as the ICHIRF-BRAIN study are critical.

Conclusion

The trial is registered with the ISRCTN (BioMed Central) Registry with ID number: 11312093.

Acknowledgements

The ICHIRF-BRAIN Study would not be possible without the input of the ICHIRF Project Manager, Pippa Theo, and the Queen Square Brain Bank Coordinator, Karen Shaw.

Auditing

The PI will audit the various components of the trial conduct and will conduct regular site visits to all test sites and analysis laboratories to check compliance with study protocols.

Research Ethics Approval

All participants will provide written informed consent as well as written informed consent from their next of kin where appropriate. Ethical approval for the study was obtained as follows (including protocol amendments):

Staged ethical approval was obtained from St Mary's University, Twickenham, Waldgrave Road, London TW1 4SX, UK initially on 1st June 2015 (no reference number was provided by St Mary's Ethics Committee SMEC). Study approved.

27th October 2015 as above Reference SMEC_2015-16_53. Approved

12th June 2017 as above Reference SMEC_2016-17_115. Approved

26th January 2018 as above Reference SMEC_2017-18_051. Approved

Ethical approval for the saliva collection was obtained by Professor Antonio Belli from The East of England Essex Research Ethics Committee, The Old Chapel, Royal Standard Place, Nottingham NG1 6FS on 22nd September 2017. An investigation into Repetitive Concussion in Sport (RECOS). REC Reference 17/EE/0275. IRAS Project ID 216703. Protocol number ERN.11.0429AP28. Approved.

In preparation for BREXIT, and prior to screening in Dublin, the whole study was re-submitted for ethical approval to the Beacon Hospital Research Ethics Committee (BHREC), The Beacon Hospital, Sandyford, Dublin D18 AK68, Ireland, and approved on 10th October 2019. Reference BEA0130. An International, multicentre study into the long term effects of concussion. The International Concussion and Head Injury Research Foundation (ICHIRF) Study. Fully Approved.

Clinical Trial Registry

The trial is registered with ISRCTN (BioMed Central) with ID number: 11312093

Informed Consent Process

All participants will provide written informed consent as well as written informed consent from their next of kin where appropriate as per the Ethic Committee approvals.

Confidentiality

Each individual will be given a unique data identification number of Individuals will not be identifiable from the data. The data will only be accessed by principal investigators and data will be stored in hard copy and electronically at the offices of ICHIRF in UCL London, at the Beacon Hospital, Dublin and backed up at the University of Melbourne.

Declaration of Interests

All contributors will be required to provide a written competing interest declaration using the standard ICMJE form.

Open Access to Data

One of the fundamental aims of the ICHIRF project is to enable data sharing, prevent duplication of efforts and foster collaboration among research teams in order to accelerate research in TBI. This phenotypically well-characterised dataset will reside in a publicly accessible infrastructure of integrated databases, imaging repositories, and biosample repositories. We believe that such datasets only serve their intended purposes with a robust, transparent, and open-access data sharing plan.

Approximately 12 months after the end of the initial phase of the project, de identified data will be made available to collaborating researchers involved in the project. Twelve months after publication of the results, data will be open to all qualified and approved researchers. We will develop policies and procedures to allow us to collaborate and share data throughout the study to advance knowledge in TBI.

Ancillary and Post Trial Care

As this is an observational study, no harms are expected for the trial subjects. In all cases, a copy of the results is given to the subject and, with their permission, their usual GP

Dissemination Policy

Participants

All volunteers will receive a detailed report, including the results of any tests conducted, within 30 days of the screening. This will include recommendations regarding any further action that may be required as a result of any abnormal findings (e.g., in the event of a raised cholesterol, the volunteer would be advised to consult his/her GP and recommended to have the test repeated).

Publication

De-identified trial data will be presented at conferences, seminars and published in the medical literature.

Open access

At the end of the initial phase of the project, de-identified data will be made available to collaborating researchers involved in the project. After publication of the results, data will be open to all qualified and approved researchers.

Authorship

Authorship will be open to all contributors involved in the study who fulfil the ICMJE 2018 authorship requirements namely: substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; and drafting the work or revising it critically for important intellectual content; and final approval of the version to be published; and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Reproducibility of Results

As discussed above, following the conclusion of the trial and publication of the results, data will be open to all qualified and approved researchers.

Expected Outcomes

Provide detailed information on the prevalence of mental health issues, cognitive impairment, and/or neurodegenerative disease in a cohort of retired professional athletes vs. control subjects; Identify risk factors in this cohort that may lead to or predict the severity of mental health issues, cognitive impairment, and/or neurodegenerative disease in this population; Identify the health and personal impact of TBI-related sequelae; Establish the role of advanced multimodal assessments in this setting; Improve TBI-related sequelae taxonomy for future targeted clinical treatment trials; Identify new diagnostic and prognostic markers and refine outcome assessments for this population; Create an open access database enabling research collaboration and data sharing capability; Disseminate the research data to community athletes

Competing Interests

Michael Turner

Is employed by ICHIRF as CEO and Medical Director. He has been reimbursed by universities, scientific bodies, and commercial organizations for travel and accommodation related to presenting research relating to concussion at meetings, scientific conferences, and symposiums. He did not receive any form of financial support related to this manuscript.

Cliff Beirne

No conflicts declared.

Antonio Belli

Is founding member, consultant and shareholder of Marker Diagnostics, a spinout company of the University of Birmingham. He is a Director of ICHIRF.

Kaj Blennow

Is supported by the Swedish Research Council (#2017-00915), the Alzheimer Drug Discovery Foundation (ADDF), USA (#RDAPB-201809-2016615), the Swedish Alzheimer Foundation (#AF-742881), Hjärnfonden, Sweden (#FO2017-0243), the Swedish state under the agreement between the Swedish government and the County Councils, the ALF-agreement (#ALFGBG-715986), and European Union Joint Program for Neurodegenerative Disorders (JPND2019-466-236). KB has served as a consultant, at advisory boards, or at data monitoring committees for Abcam, Axon, Biogen, JOMDD/Shimadzu. Julius Clinical, Lilly, MagQu, Novartis, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program.

Bonnie Kate Dewar

Is employed by the International Concussion and Head Injury Research Foundation to provide screening and consultancy services. She has also received reimbursement for travel from ICHIRF.

Valentina di Pietro

Is founding member and shareholder of Marker Diagnostics, a spinout company of the University of Birmingham.

Conor Gissane

Is employed by the International Concussion and Head Injury Research Foundation to provide statistical analysis services. He has also received reimbursement for travel from ICHIRF.

Amanda Heslegrave

No conflicts declared.

Etienne Laverse

Is employed by the International Concussion and Head Injury Research Foundation to provide screening and consultancy services. He has also received reimbursement for travel from ICHIRF.

Victoria McEneaney

Has had travel and accommodation reimbursed by the International Concussion and Head Injury Research Foundation.

Adrian McGoldrick

No conflicts declared. He has received reimbursement for travel and accommodation from ICHIRF. He is a Trustee of the Concussion Foundation.

James Murray

Is employed by the International Concussion and Head Injury Research Foundation to provide consultancy services. He has also received reimbursement for travel from ICHIRF.

Patrick O'Halloran

Has received financial support from the Drake Foundation and University of Birmingham in support of research in sport concussion and has been reimbursed by scientific organisations for travel and accommodation to present concussion related research at scientific conferences. He does not hold any shares in or receive monies from any company related to brain injury assessment or technology.

Ben Pearson

Is employed by the International Concussion and Head Injury Research Foundation to provide screening and consultancy services. He has also received reimbursement for travel from ICHIRF.

Yannis Pitsiladis

No conflicts declared.

Marco Toffoli

No conflicts declared.

Huw Williams

Is a Director of ICHIRF.

Henrik Zetterberg

Has served at scientific advisory boards for Denali, Roche Diagnostics, Wave, Samumed, Siemens Healthineers, Pinteon Therapeutics and CogRx, has given lectures in symposia sponsored by Fujirebio, Alzecure and Biogen, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU 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), and the UK Dementia Research Institute at UCL.

Paul McCrory

Has been funded by the National Health and Medical Research Council of Australia. He has been reimbursed by the government, professional scientific bodies, and commercial organizations including ICHIRF for discussing or presenting research relating to MTBI and sport related concussion at meetings, scientific conferences, and symposiums. He does not hold any individual shares in or receive monies from any company related to concussion or brain injury assessment or technology. He acknowledges unrestricted philanthropic support from CogState Inc. (2001-16). He is Scientific Consultant to ICHIRF and the Sports Surgery Clinic in Dublin. Dr. McCrory did not receive any form of financial support related to this manuscript.

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