Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

FEATURED ARTICLE

Concussion and long-term cognitive function among rugby players—The BRAIN Study

Valentina Gallo[1,2,3,4] 🄳 | **Damien M. McElvenny**[2,5,6] | **Giulia Seghezzo**[1] | **Simon Kemp**[2,7] | **Elizabeth Williamson**[2] | **Kirsty Lu**[8] | **Saba Mian**[2] | **Laura James**[1] | **Catherine Hobbs**[2,9] | **Donna Davoren**[2] | **Nigel Arden**[10] | **Madeline Davies**[9,10] | **Andrea Malaspina**[11] | **Michael Loosemore**[12] | **Keith Stokes**[7,9] | **Matthew Cross**[9,13] | **Sebastian Crutch**[8] | **Henrik Zetterberg**[14,15,16,17] | **Neil Pearce**[2]

[1] Centre for Primary Care and Public Health, Queen Mary, University of London, London, UK

[2] Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, UK

[3] School of Public Health, Imperial College London, London, UK

[4] Campus Fryslân, University of Groningen, Leeuwarden, the Netherlands

[5] Research Group, Institute of Occupational Medicine, Edinburgh, UK

[6] Centre for Occupational and Environmental Health, University of Manchester, Manchester, UK

[7] Rugby Football Union, London, UK

[8] Dementia Research Centre, UCL Queen Square Institute of Neurology, London, UK

[9] Department of Health for Keith Stokes and Madeleine Davies, Department of Psychology for Catherine Hobbs, University of Bath, Bath, UK

[10] Centre for Sport, Exercise & Osteoarthritis Research Versus Arthritis, University of Oxford, Oxford, UK

[11] Blizard Institute, Queen Mary University of London, London, UK

[12] Institute of Sport Exercise and Health, University College London, London, UK

[13] Premiership Rugby, London, UK

[14] UK Dementia Research Institute, UCL Queen Square Institute of Neurology, London, UK

[15] UK Dementia Research Institute, University College London, London, UK

[16] Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden

[17] Clinical Neurochemistry Laboratory, Sahlgrenska University Hospital, Mölndal, Sweden

Correspondence
Prof Valentina Gallo, Campus Fryslân, University of Groningen, Wirdumerdijk 34, 8911 CE Leeuwarden, Netherlands.
E-mail: v.gallo@rug.nl

Abstract

Objective: The BRAIN Study was established to assess the associations between self-reported concussions and cognitive function among retired rugby players.

Methods: Former elite-level male rugby union players (50+ years) in England were recruited. Exposure to rugby-related concussion was collected using the BRAIN-Q tool. The primary outcome measure was the Preclinical Alzheimer Cognitive Composite (PACC). Linear regressions were conducted for the association between concussion and PACC score, adjusting for confounders.

Results: A total of 146 participants were recruited. The mean (standard deviation) length of playing career was 15.8 (5.4) years. A total of 79.5% reported rugby-related

concussion(s). No association was found between concussion and PACC (β −0.03 [95% confidence interval (CI): −1.31, 0.26]). However, participants aged 80+ years reporting 3+ concussions had worse cognitive function than those without concussion (β −1.04 [95% CI: −1.62, −0.47]).

Conclusions: Overall there was no association between concussion and cognitive function; however, a significant interaction with age revealed an association in older participants.

KEYWORDS
cognitive function, occupational epidemiology, rugby, sports-related concussion

1 | INTRODUCTION

Since chronic traumatic encephalopathy (CTE) was first described as a nosological entity,[1,2] scientific attention has focused on the long-term sequelae of sports-related mild traumatic brain injury, or concussion.[3] Neuropathological changes suggestive of CTE have been reported in boxers,[4] American football players,[5] ice hockey players,[6] football (soccer) players,[7,8] and rugby players.[8,9] However, these reports are mostly based on case series, with limited sample sizes. The findings among American footballers showed also that length of career was associated with more severe neuropathology,[10–12] suggesting a possible role of subconcussive head impacts. Reviews of current epidemiological evidence suggest an increased risk of lower cognitive function in previously concussed athletes, but the findings are inconsistent.[13] Conversely, the health benefits of physical activity and participation in sports, including a protective effect against cognitive decline, are well established.[14] What is currently unclear is to what extent the sports benefits outweigh any potentially harmful effects of concussion, and whether such hazards are sport-specific.

In rugby union players, little evidence is currently available on the long-term cognitive consequences of concussion. One study found an association between concussion and lower cognitive function, but the effect size was small and there were multiple comparisons.[15] Conversely, the same association was not found in another study, possibly due to lack of power to detect small effects.[16] A third study found no association, although mild cognitive disorders were found to be more common in the rugby players compared to other non-contact athletes.[17]

The aim of the Brain Health and Healthy Ageing in Retired Rugby Union Players (BRAIN) Study was therefore to assess the long-term association between concussions and cognitive function among retired elite rugby players.

2 | METHODS

The design of the BRAIN Study has been described in detail previously.[18] Briefly, this is a cross-sectional study recruiting former elite male rugby union players aged 50+ years from two sources: former Oxford/Cambridge University players previously recruited in a study conducted in the Centre for Sport, Exercise and Osteoarthritis Research Versus Arthritis at the University of Oxford, who had consented to be re-contacted;[19] and all individuals listed on the England Rugby Internationals Club (ERIC) database—an organization of current and former England international players. We estimated that by recruiting 150 former players, considering that the standard deviations (SDs) of the psychometric tests are in the range of 8% to 15% of the absolute value, the study would have more than 95% power to detect a 10% difference, and 80% power to detect a 7% difference in psychometric test scores between exposed (to concussion) and non-exposed participants.[18]

Those invited were given the choice to be assessed in a clinic (London, Manchester, or Bristol), or at home. The assessment included questions on rugby playing career, occupation, lifestyle factors, cognitive ability, and self-reported history of concussion.[18] Participants who could not attend an assessment completed a postal questionnaire; those cognitively impaired were included in the study and assessed in person with the assistance of a close family member. All participants signed an informed consent. The study was approved by the Ethical Committee of the London School of Hygiene and Tropical Medicine (EC/11634) and further approved by the other participating institutions' ethical committees. A meeting was held with the representatives of participants to discuss how to increase response rates and how to communicate results to participants and the general public.

2.1 | Exposure assessment

Information on concussions was collected at the end of the assessment to avoid observer bias, using the BRAIN-Q tool.[20] This tool was developed to overcome some of the limitations of existing tools, which are not designed specifically for sports-related concussions, and do not always provide a clear-cut definition of concussion (which is particularly relevant for people who have been exposed to concussion in a context of changing definitions, such as the sports arena). In addition, the BRAIN-Q was designed to maximize recall in different stages of the playing career. Participants were asked to report the number of concussions they suffered after being given the following definition of concussion:[3,18]

"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 (e.g., blurriness, double vision); co-ordination 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."

They were then invited to complete a "life timeline" with the most significant milestones of their youth and professional career, and to review their recalled concussions in each of the periods, confirming the information given. For each concussion, additional details were collected, for example, hospitalization.[20] Two variables were then derived: the total number of rugby-related concussions, categorized into "no concussion," "low concussion (1 or 2)," and "high concussion (3+)"; and the rugby-related concussion density defined as the total number of concussions divided by the time interval in years (participants with 2+ concussions only). Given the accumulation of new evidence since the analysis plan for the BRAIN Study was finalized, length of rugby career was added to the analysis as an independent exposure, in addition to number of concussions.

2.2 | Assessment of cognitive function

The primary outcome measure was an adapted version of the Alzheimer's Disease Cooperative Study–Preclinical Alzheimer Cognitive Composite (ADCS-PACC).[21] The PACC includes: (1) The Total Recall score from the Free and Cued Selective Reminding Test (FCSRT; 0–48 words);[22] (2) The Delayed Recall score on the Logical Memory-II subtest from the Wechsler Memory Scale (0–25 story units);[21] (3) The Digit Symbol Substitution Test score from the Wechsler Adult Intelligence Scale–Revised (0–93 symbols);[21] (4) The Mini-Mental State Examination (MMSE; 0–30 points).[21] The FCSRT was replaced with the total score of the 12-item Face–Name Associative Memory Exam (FNAME-12), 0 to 96 points,[23] which is similar in terms of testing immediate and delayed recall,[24] as it showed evidence of convergent validity with the established paired associative memory task, FCSRT (Pearson r 0.32, $P < 0.05$).[23] All tests were administered and scored according to the standard procedures. The test scores of the four components of the PACC were standardized to create z-scores based on the overall BRAIN Study sample and averaged. At least three tests had to be completed to create a PACC score, one of them being the MMSE.[21]

2.3 | Covariates and potential confounders

Potential confounding variables and their categorization were pre-specified in the analysis plan. Age in years was recorded at the time of the assessment. Highest educational qualification was classified into: A-level or below; university degree; post-graduate degree. Occupational history was categorized according to the International Stan-

RESEARCH IN CONTEXT

1. **Systematic review**: Reviewing the literature, three types of comparisons were identified: internal comparisons (comparing cognitive function among sportspeople exposed to different levels of concussion within the same sport), between-sports comparisons (comparison among different categories of sportspeople), and external comparisons (comparison between sportspeople and the general population). The results on rugby players overall suggest a possible association between concussion and long-term memory impairment.

2. **Interpretation**: The present findings, based on an internal comparison involving former elite rugby players, suggest that neither self-reported concussion nor length of career are associated with lower cognitive function among former rugby union players, overall. However, among older adults (aged 75+ years) having suffered three or more concussions (compared to those with no reported concussions) was associated to worse cognitive function. In the same age group, length of career was also associated with worse logical memory.

3. **Future directions**: These findings have implications for the clinical management of older ex-rugby players, and possibly ex-players of other contact sports who may be at increased risk of impaired cognitive function and various sequelae. They also further support the need for avoidance, or minimization, of concussion in rugby and other contact sports. More research on the association between contact sports and cognitive function among older adults is required, including the underlying mechanisms, and whether chronic traumatic encephalopathy plays a role.

dard Classification of Occupations (ISCO)-88[25], using the job held with the longest duration, into "legislators, managers and senior officials," "professionals," and "other" (including both skilled and unskilled manual labor). Tobacco smoking and alcohol drinking were classified as current/former/never. Diagnoses of hypertension and diabetes were recorded. Height and fully dressed body weight were recorded during the assessment for calculating the body mass index (BMI). Length of rugby career and predominant position played were recorded and classified as back (back 3, midfield, scrum half) or forward (back row, second row, front row). Early-life intelligence was assessed using the National Adult Reading Test (NART), 0 to 50 points.[25]

2.4 | Statistical analysis

The potential for selection bias was explored in the sample recruited through the University of Oxford by comparing the basic information

of those who agreed and those who declined to take part in the study.

Scores of cognitive tests were coded as zero if the participant did not undertake them because he was cognitively unable to do so. Missing values for cognitive tests (except the MMSE), exposure variables, and covariates were imputed using multiple imputation by chained equations (MICE), that is, fully conditional specification,[26] creating 10 imputed datasets.[27] Individual imputation models used logistic regression for binary variables, ordinal logistic regression for ordered categorical variables, and multinomial regression for unordered categorical variables. For continuous variables with missing values, predictive mean matching was used, with five nearest neighbors, to address potential issues with non-normality.[27]

Linear regression models were conducted for the PACC score, with the cumulative number of concussions (ordinal categorical) as the main exposure variable; concussion density, and length of career were also analyzed as independent exposure variables. The analyses were adjusted for prespecified potential confounders: age (continuous), education, occupation, smoking, alcohol, BMI (continuous), medical history, rugby position, NART, and study assessor. An interaction between concussion history and age in 10-year age bands was sought. The analyses were repeated modeling age using restricted cubic splines, and results were displayed graphically.

To compare the cognitive function of the study participants with a convenience sample of cognitively normal individuals, a predicted score was estimated for each participant for the main cognitive tests and compared to those obtained by each BRAIN participant, and displayed graphically. These predicted values were generated using the National Alzheimer's Coordinating Center Uniform Data Set (UDS) normative calculator, which is based on data from 3268 clinically cognitively normal older subjects,[28] by inputting age, years of education, and sex of each BRAIN participant (all were male) into the model.

The following equations were used:[28]

$$Predicted\ MMSE = 28.41 + (-0.48 * Sex) + (0.14 * Education) + (-0.02 * Age)$$

$$Predicted\ LMDR = 9.13 + (-1.39 * Sex) + (0.41 * Education) + (-0.026 * Age)$$

$$Predicted\ DigitSubstitution = 71.23 + (-3.15 * Sex) + (1.12 * Education) + (-0.56 * Age)$$

The predicted scores of the FNAME test were taken from a model derived from a study of 216 cognitively normal Greek individuals. These predicted scores were derived from inputting age of each BRAIN participant; however, this model was limited to only those between the ages of 60 and 85 with at least 6 years of education,[29] thus not entirely comparable with the BRAIN sample. The following equation was used to calculate predicted FNAME scores:[29]

$$Predicted\ FNAME = 70.30 + (-0.23 * Age)$$

The predicted scores were then compared to the scores obtained by each BRAIN participant, and displayed using box and whisker plots.

Sensitivity analyses were carried out after excluding participants with MICE imputed values, excluding cognitively impaired participants (MMSE < 25/30), and excluding adjustment for the study assessor from the multivariable model.

3 | RESULTS

Of the 205 invitations sent by the University of Oxford, 190 were valid, from which 113 participants were recruited (response rate: 59.5%). Of the 104 invitations sent to the ERIC participants (103 valid), 33 participants were recruited (response rate: 32.0%). The overall response rate was 49.8% (Figure S1 in supporting information). An analysis of non-respondents comparing the 77 participants invited by the University of Oxford but not recruited in the BRAIN Study with the 113 recruited from the same source showed no systematic differences between the two groups except that 62% of those recruited reported a concussion in the original study versus 51% of those not recruited ($P = 0.04$; Table S1 in supporting information). The difference in response rate might be because participants recruited through the University of Oxford were already engaged in rugby-related research, and there was updated contact information available.

The main analyses were based on 143 participants, excluding those assessed remotely. MICE imputations were performed on the missing data ($N = 7$). The demographic and playing characteristics of the sample are shown in Table 1. The median age (p25–p75) of the sample was 70 years (61–77). The sample was highly educated. The mean (SD) length of playing career was 15.8 (5.4) years; the position played by the participants was grouped into backs (55%) and forwards (45%).

A total of 116 (80%) respondents reported at least one rugby-related concussion. Among the concussed, the number of rugby-related concussions varied between 1 and 25, with a median (p25–p75) of 2 (1–4). The number of rugby-related concussions was not associated with position played ($P = 0.75$; Figure S2 in supporting information), or with length of career (Figure 1). Considering total concussion, only 27 participants (18%) reported none.

The findings for the individual tests of the PACC are reported in Table 2. PACC scores by age groups are shown in Figure 2. Age (Pearson $r = 0.58$, $P < 0.001$) and NART score (Pearson $r = 0.34$, $P < 0.001$) were found to be positively correlated with PACC. Predicted test scores were displayed in Table S2 in supporting information, and shown in Figure S3 in supporting information: former rugby players scored lower than predicted for logical memory but better than predicted for immediate and delayed recall. Interestingly, this advantage seems to be lost with age, as in both cases those in the older age group scored lower than the predicted scores.

An interaction between the effects of concussion history and age was evident ($P = 0.003$); therefore, the analyses were also repeated by age group (Table 3). Overall, there was no association between concussion and cognitive function measured by the PACC (β-coefficient for high vs. no concussion −0.03 [95% confidence interval (CI): −0.31,

TABLE 1 Characteristics of study participants by rugby-related concussion category

	No concussion[a] N = 30	Low concussion[a] (1–2) N = 52	High concussion[a] (3+) N = 64	All N = 146
Number of concussions, median (p25, p75)	0	2 (1, 2)	4 (3, 6)	2 (1, 4)
Concussion density, median (p25, p75)[b]	0	0.40 (0.29, 1)	0.46 (0.33, 1)	0.45 (0.31,1)
Age (years), median (p25, p75)	76 (65, 82)	71 (61.5, 76.5)	67.5 (60, 74)	70 (61, 77)
Education, N (%)[c]				
A-level or below	7 (23.3)	16 (30.7)	15 (23.4)	38 (26)
University degree	14 (46.7)	21 (40.4)	27 (42.2)	62 (42.5)
Post-graduate degree	9 (30)	15 (28.8)	22 (34.4)	46 (31.5)
Occupation, N (%)				
Legislators, senior officials, managers	16 (53.3)	19 (36.5)	25 (39)	60 (41.1)
Professionals	8 (26.7)	17(32.7)	23(35.9)	48 (32.9)
Other	6 (20)	16 (30.8)	16 (25)	38 (26)
Smoking, N (%)[d]				
Never smoker	25 (83.3)	39 (75)	42 (65.6)	106 (72.6)
Former smoker	5 (16.7)	13 (25)	20 (31.3)	38 (26)
Current smoker	0	0	2 (100)	2 (1.4)
Alcohol, N (%)[d]				
Never drinker	3 (10)	6 (11.5)	15 (23.4)	24 (16.4)
Former drinker	0	0	1 (1.6)	1 (0.7)
Current drinker	27 (90)	46 (88.5)	48 (75)	121 (82.9)
BMI (kg/m^2), mean (SD)[e]	27.9 (4.5)	27.9 (4.2)	29.5 (4.02)	28.6 (4.2)
Hypertension, N (%)				
Yes	9 (30)	17 (32.7)	20 (31.3)	46 (31.5)
No	21(70)	35 (67.3)	44 (68.8)	100 (68.5)
Diabetes, N (%)				
Yes	1 (3.3)	3 (5.8)	2 (3.1)	6 (4.1)
No	29 (96.7)	49 (94.2)	62 (96.9)	140 (95.9)
Position played, N (%)[f]				
Backs	**15 (51.7)**	**31 (60.8)**	**31 (50.8)**	**77 (54.6)**
Back 3[g]	4 (13.8)	15 (24.2)	30 (37.5)	30 (37.5)
Midfield[h]	10 (34.4)	14 (22.6)	39 (48.8)	39 (48.8)
Scrum half	1 (3.4)	3 (4.8)	11(13.8)	11(13.8)
Forward	**14 (48.3)**	**20 (39.2)**	**30 (49.2)**	**64 (45.4)**
Back row[i]	3 (10.3)	13 (21)	24 (37.5)	24 (37.5)
2nd row	5 (17.2)	9 (14.5)	19 (29.7)	19 (29.7)
Front row[j]	6 (20.7)	8 (12.9)	21 (32.8)	21 (32.8)
Length of career (years), mean (SD)[k]	15.2 (6.2)	16.02 (6.0)	15.9 (4.6)	15.8 (5.4)
MMSE score below 25, N (%)[l]	0	1 (1.9)	4 (6.3)	5 (3.5)
NART score, median (p25, p75)[l]	41.5 (39.5, 45)	42 (37.5, 45)	42 (38, 45)	42 (38, 45)

(Continues)

TABLE 1 (Continued)

	No concussion[a] N = 30	Low concussion[a] (1–2) N = 52	High concussion[a] (3+) N = 64	All N = 146
Study center, N (%)				
London	11 (36.7)	24 (46.2)	31 (48.4)	66 (45.2)
Manchester	3 (10)	0	4 (6.3)	7 (4.8)
Bristol	0	2 (3.8)	5 (7.8)	7 (4.8)
Home	14 (46.7)	26 (50)	23 (35.9)	63 (43.2)
Remote	2 (6.7)	0	1 (1.6)	3 (2.1)

[a]Rugby-related;

[b]estimated as total concussions divided by time in years between first and last on a total of 92 participants with 2 or more concussions occurring at least 1 year apart;

[c]one missing value;

[d]smoking and alcohol categorized into ever/never in the multivariable model;

[e]three missing values;

[f]five missing values;

[g]back 3 include wings and full back positions;

[h]midfield include center and fly half positions;

[i]back rows include number 8 and flanker positions;

[j]front row include props and hookers;

[k]18 missing values

[l]three missing values (remote participants).

Abbreviations: BMI, body mass index; MMSE, Mini-Mental State Examination; NART, National Adult Reading Test; PACC, Preclinical Alzheimer Cognitive Composite; SD, standard deviation.
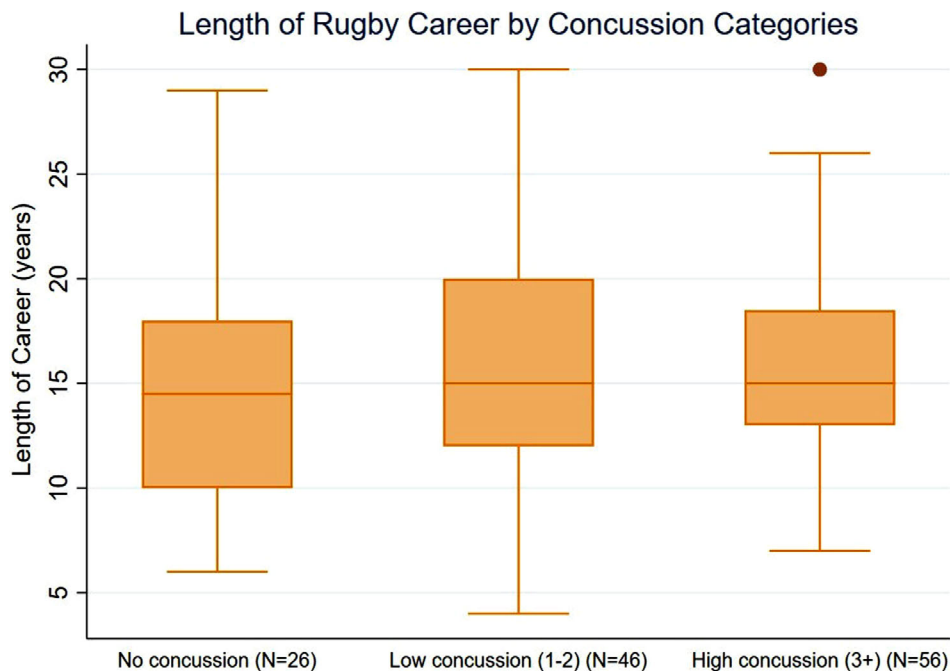
FIGURE 1 Categories of concussions by length of career in the BRAIN Study (N = 143)

0.26]). However, the β-coefficients for the high concussion category compared to no concussion decreased with increasing age. In the 80+ age group, having had three or more concussions was associated with a decreased cognitive function of about one SD below the mean PACC score (β –1.04 [95% CI: –1.62, –0.47]). β-coefficients were plotted against age using restricted cubic splines (Figure 3): the association of high concussion and PACC over age showed a steep decline starting from about age 75 years. Length of career was not associated

TABLE 2 Median (p25, p75) scores for the individual cognitive function tests, by concussion and age categories

	N	PACC score, median (p25, p75)	MMSE,median (p25, p75)	FNAME score, median (p25, p75)	Logical-Memory Delayed Recall, median (p25, p75)	Digit-Symbol Substitution,median (p25, p75)
All ages						
No concussion	27	0.04 (−0.32, 0.34)	29 (28, 30)	66 (45, 74)*	9 (6, 13)*	41 (37, 49)
Low concussion	52	−0.04 (−0.62, 0.43)	29 (28,30)	53.5 (34.5, 78)	9 (5.5, 11.5)	46 (40, 53.5)
High concussion	63	0.31 (0.004, 0.70)	29 (28, 30)	74 (56, 82)	10 (8, 13)	52.5 (40, 62)*
Age 50–59 (N = 28)						
No concussion	5	0.47 (0.20, 0.64)	30 (30, 30)	72 (69, 74)	10 (9, 13)	61 (48, 63)
Low concussion	8	0.68 (−0.10, 0.93)	30 (30, 30)	73 (49.5, 87)	11.5 (8, 15)	52.5 (44, 61)
High concussion	15	0.74 (0.46, 0.91)	30 (39, 30)	79 (74, 89)	11 (8, 14)	63 (54, 67)
Age 60–69 (N = 43)						
No concussion	5	0.18 (0.07, 0.78)	29 (29, 29)	79 (52, 82)	8 (6, 14)	49 (49, 65)
Low concussion	13	0.33 (−0.05, 0.55)	30 (28, 30)	68 (49,79)	9 (6, 11)	51 (45, 55)
High concussion	25	0.40 (−0.13, 0.65)	30 (29, 30)	75 (64, 82)	11 (9, 13)	55.5 (47, 62)
Age 70–79 (N = 47)						
No concussion	8	−0.04 (−0.32, 0.20)	29 (28, 29)	67 (45, 75)	12 (9, 13)	42 (38, 46)
Low concussion	22	−0.08 (−0.60, 0.21)	29 (28, 30)	51.5 (41, 69)	8.5 (5, 11)	45.5 (42, 49)
High concussion	17	0.01 (−0.31, 0.27)	29 (28, 30)	58 (41, 79)	10 (8, 11)	42 (37, 53)
Age 80–89 (N = 25)						
No concussion	10	−0.44 (−0.88, −0.10)	28.5 (28, 29)	50 (34, 65)	8.5 (4, 10)	35 (29, 40)
Low concussion	9	−0.75 (−1.15, −0.27)	29 (28, 30)	33 (13, 34)	8 (3, 10)	28 (28, 38)
High concussion	6	−2.33 (−2.94, −0.51)	23 (20, 28)	5.5 (0, 27)	1 (0, 7)	32 (14, 36)

*One missing value.

Abbreviations: FNAME, Face–Name Associative Memory Exam; MMSE, Mini-Mental State Examination; PACC, Preclinical Alzheimer Cognitive Composite.
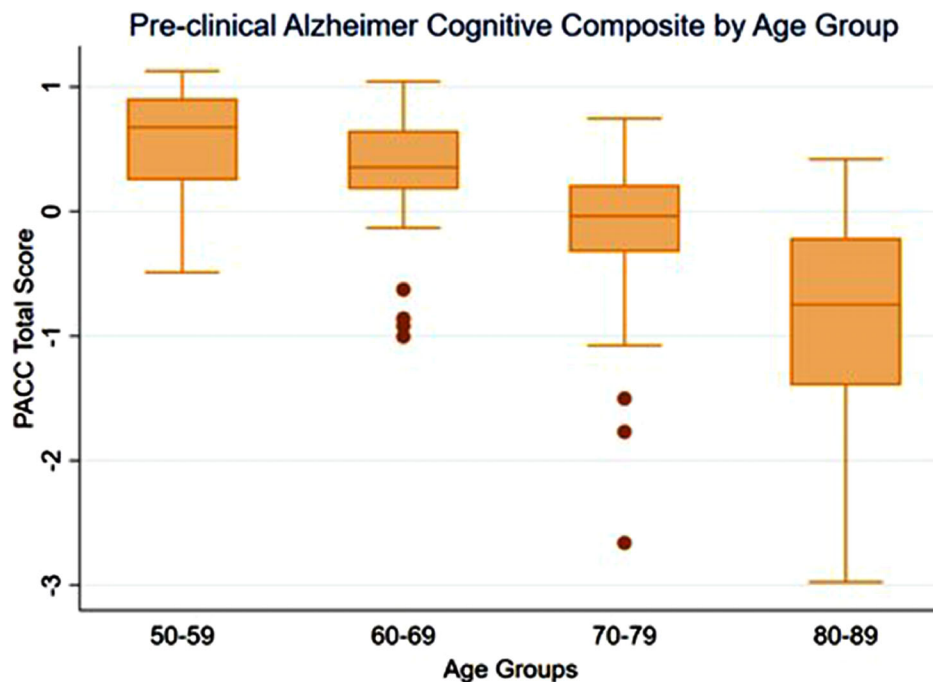
FIGURE 2 Preclinical Alzheimer Cognitive Composite (PACC) score distribution by age group in the BRAIN Study (N = 143)

TABLE 3 Linear regression coefficient for the associations between rugby-related concussions and length of playing career and PACC scores, adjusted for potential confounders

	N	Age-adjusted coefficient (95% CI)[a]	Fully adjusted coefficient (95% CI)[a,b]
No concussion	27	Reference	Reference
Low concussion (1-2)	52	−0.18 (−0.48, 0.12)	−0.09 (−0.37, 0.19)
High concussion (3+)	63	−0.08 (−0.38, 0.22)	−0.03 (−0.31, 0.26)
Total concussions		−0.01 (−0.04, 0.03)	−0.0002 (−0.03, 0.03)
Concussion density[c]		0.01 (−0.17, 0.19)	−0.03 (−0.22, 0.16)
Length of career, years[d]		−0.01 (−0.03, 0.01)	0.001 (−0.02, 0.02)
Age 50–59 (N = 28)			
No concussion	5	Reference	Reference
Low concussion (1-2)	8	0.03 (−0.64, 0.70)	0.19 (−0.44, 0.81)
High concussion (3+)	15	0.20 (−0.41, 0.81)	0.47 (−0.11, 1.04)
Total concussions		−0.01 (−0.10, 0.09)	0.04 (−0.06, 0.13)
Concussion density		0.06 (−0.59, 0.72)	−0.08 (−0.75, 0.60)
Length of career, years		−0.01 (−0.08, 0.07)	0.04 (−0.03, 0.11)
Age 60–69 (N = 43)			
No concussion	5	Reference	Reference
Low concussion (1-2)	13	−0.12 (−0.74, 0.50)	−0.37 (−0.94, 0.21)
High concussion (3+)	25	0.22 (−0.36, 0.79)	−0.004 (−0.54, 0.53)
Total concussions		0.01 (−0.04, 0.05)	0.003 (−0.035, 0.04)
Concussion density		0.03 (−0.19, 0.25)	−0.01 (−0.22, 0.21)
Length of career, years		−0.02 (−0.05, 0.01)	0.0 (−0.03, 0.03)
Age 70–79 (N = 47)			
No concussion	8	Reference	Reference
Low concussion (1-2)	22	−0.26 (−0.76, 0.23)	0.01 (−0.46, 0.47)
High concussion (3+)	17	−0.07 (−0.58, 0.44)	−0.11 (−0.58, 0.36)
Total concussions		0.002 (−0.05, 0.06)	0.002 (−0.05, 0.05)
Concussion density		−0.20 (−0.58, 0.18)	−0.30 (−0.71, 0.10)
Length of career, years		0.01 (−0.04, 0.03)	−0.001 (−0.03, 0.03)
Age 80–89 (N = 25)			
No concussion	10	Reference	Reference
Low concussion (1-2)	9	−0.23 (−0.77, 0.31)	−0.15 -(−0.66, 0.35)
High concussion (3+)	6	−1.42 (−2.02, −0.81)	−1.04 (−1.62, −0.47)
Total Concussions		−0.32 (−0.47, −0.18)	−0.24 (−0.38, −0.09)
Concussion Density		−0.02 (−0.48, 0.44)	0.002 (−0.45, 0.46)
Length of career, years		−0.04 (−0.10, 0.01)	−0.04 (−0.09, 0.01)
		Test for interaction with age groups	
Concussion groups (shown above)			P = 0.003
Total concussions			P = 0.011
Concussion density			P = 0.590
Length of career, years			P = 0.220

[a]including imputed values, excluding remote participants, N = 143;
[b]adjusted for: age, highest educational qualification, smoking status, alcohol use, rugby position, NART test, BMI, occupation, medical history (high blood pressure, diabetes), and assessor;
[c]N = 92,
[d]N = 126.
Abbreviations: BMI, body mass index; CI, confidence interval; NART, National Adult Reading Test; PACC, Preclinical Alzheimer Cognitive Composite.
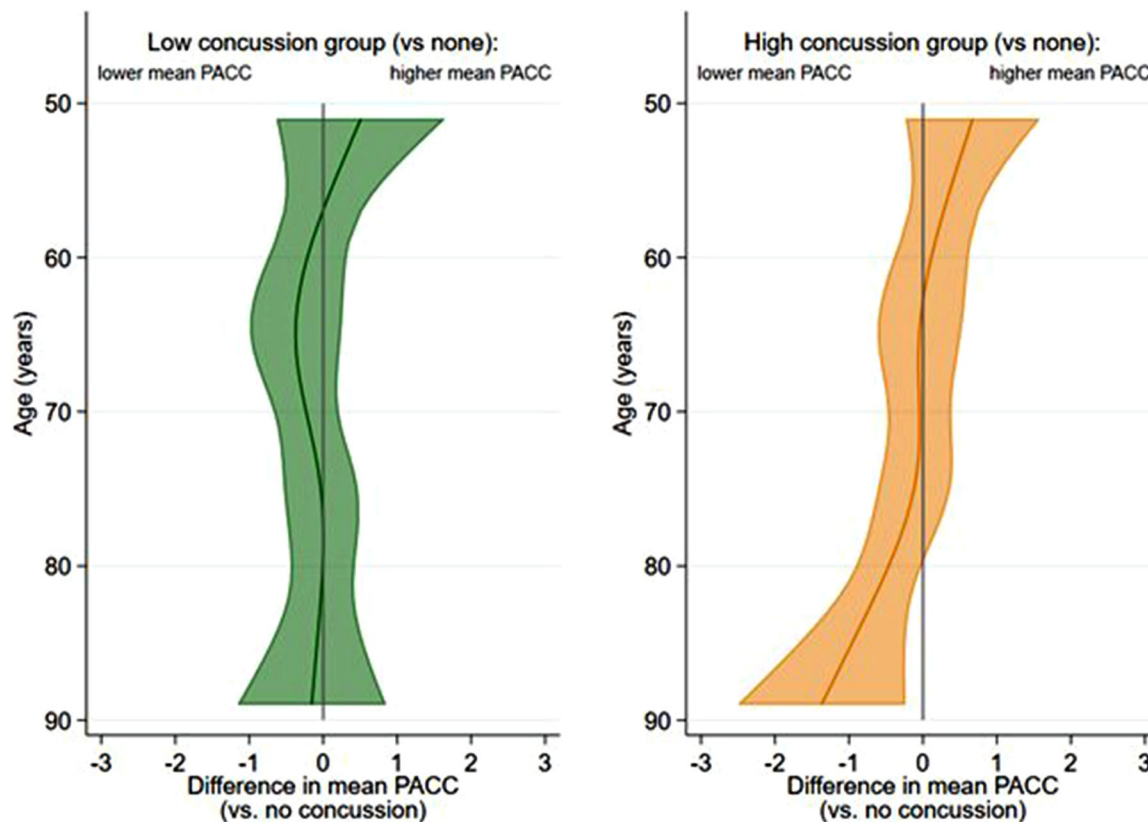
FIGURE 3 Restricted cubic spline analysis on the difference of mean Preclinical Alzheimer Cognitive Composite (PACC) score between moderate concussions and high concussions across age, with 95% confidence intervals

with measures of cognitive function, although an interaction with age was detected, and a borderline significant negative association was observed for participants aged 80+ years.

The analyses were repeated using the individual test results (Table S3 in supporting information). Among participants aged 80+ years, having had three or more concussions was associated with a worse performance on the MMSE and the FNAME test compared to participants of the same age who were not exposed to concussion. This association was strongest for the MMSE (β –2.18 [95% CI: –3.03, –1.34]). Conversely, in the same age group, length of rugby career was associated with worse delay recall at the logical memory (β –0.08 [95% CI: –0.16, –0.003]).

The findings for total concussion did not change substantially (Table S4 in supporting information); conversely, concussion density was found to be not associated with PACC in any of the analyses. Neither age at first concussion, nor at first rugby-related concussion, was associated with PACC scores (results not shown).

The sensitivity analysis conducted after removing imputed values (Table S5 in supporting information) and after removing study assessor from the model (results not shown) yielded virtually unchanged results. Conversely, removing the five cognitively impaired cases (MMSE < 25/30) yielded overall attenuated coefficients, and there was then no interaction with age ($P = 0.43$), resulting in a lack of association between concussion and PACC scores even among older participants (β 0.01 [95% CI: –0.69, 0.71]; Table S6 in supporting information).

4 | DISCUSSION

The findings of the BRAIN Study, conducted among former elite rugby players, suggest that having suffered rugby-related concussions during their playing career, or the length of the rugby career, are not associated with an overall worse long-term cognitive function. However, the relationship changed with age: among older former players (80+ years), having suffered more than three concussions is associated with a decrease in cognitive function of about 1 SD below the mean PACC score compared to former players of the same age who have suffered no concussion. The spline analysis suggested that this increased risk starts from about age 75 years. These findings are consistent with the comparison with non-impaired subjects: the study participants showed better mean scores than predicted in the younger age groups, and worse at older age. However, this effect in the older ages appeared to be driven by a small number of older participants in the high concussion group who were considered cognitively impaired according to their MMSE scores. In the same age group, a longer rugby career was associated with a worse delayed recall; however, its overall effect on PACC score was relatively weak. Further studies are therefore needed to confirm these findings among older individuals.

The main limitation of this study is the cross-sectional design, and potential susceptibility to recall bias. This was minimized by using the BRAIN-Q tool to assess history of concussion.[20] Unfortunately, further external validation using clinical records or video recording was

not possible. Recall bias, however, should not affect the analysis of length of rugby career. Selection bias may have arisen from a suboptimal response rate, and also because participants with more concussions appear to have been more likely to participate. However, this will not necessarily bias the main study analyses as they involve internal comparisons. Conversely, assuming that our sample may be also biased toward participants with better cognitive function, this may lead to an overestimation of any association between concussion and cognitive function, but any such bias is likely to be small, and unlikely to account entirely for the association found.

The cross-sectional cognitive assessment has known limitations due to increased potential for residual and unmeasured confounding by social engagement and pre-morbid intelligence.[30,31] We accounted for pre-morbid intelligence in the analyses. Nevertheless, a follow-up study with estimate of cognitive decline over time would be particularly informative in exploring these findings further. This may be particularly relevant for this highly educated population showing higher than predicted cognitive function at younger ages, reversing at older ages. Moreover, it is not possible to exclude that the PACC—despite its demonstrated ability to capture early changes in cognitive function[32]—was not sensitive enough to detect subtle cognitive changes in highly educated subjects engaged in mostly executive jobs. In addition, the PACC does not measure executive function, which was found to be compromised among concussed rugby and other sports players compared to non-concussed ones in one study,[15] but not in another.[16] It is also not possible to exclude from the present data that the association between concussion and cognitive function is modified by some genetic trait, for example, apolipoprotein E (APOE) genotype. Finally, no data on depression were collected.

A recent systematic review of the association between concussion and cognitive function in professional/elite sportspersons concluded that the current evidence suggests the presence of a negative association among rugby players, although it is not clear whether this is clinically relevant.[13] The evidence is derived from three studies: in one conducted in Scotland,[16] among 52 retired rugby players, with mean (SD; min, max) age of 53.5 (13.0; 26, 79), years, no association between concussion and cognitive function was found. However, the prevalence of cognitive decline was 17% among former players and 3% among population controls ($P = 0.087$).[16] A study in France on former players with a mean (p25, p75) age of 52 (49–56) years,[17] found no association between concussion and cognitive function; however, the prevalence of mild cognitive disorder was 57% among former rugby players and 40% among other athletes ($P = 0.005$). A New Zealand study[15] of former rugby players with mean (SD) age of 41.3 (7.5) found that individuals recalling one or more concussions had worse scores on cognitive flexibility, executive function, and complex attention than players without concussion. Moreover, the elite-rugby group performed worse on several cognitive tests than the non-contact sports group.[15] No previous study has reported the findings by age group, and no study has previously reported an association among the eldest age group (75+ years).

No previous study conducted on rugby players has assessed the association between length of career and cognitive function.[13,15–17]

Length of career may be a proxy measure for cumulative repetitive subconcussive head injury caused by the participation in contact sports, as suggested by the finding of higher level of serum biomarkers associated with oxidative stress and vascular damage among contact sportsmen.[33] Consistently, evidence from other sports strongly suggests an association of length of career with neuropathological findings compatible with CTE (including p-tau pathology, inflammation, and white matter rarefaction[33]), in American footballers,[10–12] or with the onset of clinical dementia, in soccer players.[34] Intriguingly, this last study also observed an increased risk of mortality from neurodegenerative diseases after the age of 80 years compared to population-based controls (after an initial decreased risk of mortality at younger ages).[34] Although these two studies are not directly comparable if the findings are both correct, then any effects of sports-related concussion and/or subconcussive repeated head injury on mortality from neurodegenerative disease is unlikely to be mediated through mechanisms that result in impaired cognitive function at earlier ages.

These findings are also consistent with a life-course approach to dementia:[35] our sample included highly educated and professionally engaged people; thus, it is plausible that their cognitive reserve[30] would compensate for cognitive function impairment until a higher-than-normal threshold is reached. Moreover, the higher-than-average social status and the overall healthy habits may confer an additional protective/delaying effect on the onset of the cognitive impairment,[35,36] which may manifest itself at a later-than-expected age. This may explain why these data are not directly consistent with findings from other sports, or from less selected populations.[13]

Some caution is needed before generalizing these results to other populations and time periods. A large part of the present sample included participants with a degree from Universities of Oxford/Cambridge, whereas rugby players may have different demographic profiles in other countries. Moreover, the game has changed considerably in the last 30 years[37] becoming faster with more contact events with a greater propensity to cause concussion, ball-in-play time has increased, and there have been increases in the weight of all players and the height of backs.[38,39] Over time, the identification and management of concussion will have also significantly improved.

5 | CONCLUSIONS

This study found no overall evidence of an association between rugby-related concussion and cognitive function, but there was an increased risk in older adults aged 75+ years who reported three or more concussions (compared to none).

CONFLICTS OF INTEREST

AUTHOR CONTRIBUTIONS

Study concept and design: V. Gallo, N. Pearce, D. McElvenny; analysis and interpretation of data: G. Seghezzo, E. Williamsons, V. Gallo, N. Pearce, K. Lu, D. McElvenny, S. Crutch, S. Kemp; drafting of the manuscript: V. Gallo; data collection: S. Mian, C. Hobbs, D. Davoren, L. James, M. Davies, K. Stokes, M. Cross; critical revision of the manuscript for important intellectual content: D. McElvenny, S. Kemp, E. Williamson, K. Lu, N. Arden, A. Malaspina, M. Loosemore, K. Stoke, M. Cross, S. Crutch, H. Zetterberg, N. Pearce.

DATA AVAILABILITY STATEMENT

ORCID

Valentina Gallo https://orcid.org/0000-0002-1268-8629

REFERENCES

1. McKee AC, Cantu RC, Nowinski CJ, et al. Chronic traumatic encephalopathy in athletes: progressive tauopathy after repetitive head injury. *J Neuropathol Exp Neurol*. 2009;68(7):709-735. https://doi.org/10.1097/NEN.0b013e3181a9d503.

2. McKee AC, Stern RA, Nowinski CJ, et al. The spectrum of disease in chronic traumatic encephalopathy. *Brain*. 2013;136:43-64. https://doi.org/10.1093/brain/aws307. Pt 1.

3. McCrory P, Meeuwisse W, Dvorak J, et al. Consensus statement on concussion in sport—the 5 th international conference on concussion in sport held in Berlin. *Br J Sports Med*. 2017;51(11):838-847. https://doi.org/10.1136/bjsports-2017-097699. Published online.

4. Bernick C, Banks S. What boxing tells us about repetitive head trauma and the brain. *Alzheimers Res Ther*. 2013;5(3):23. https://doi.org/10.1186/alzrt177.

5. Omalu BI, Hamilton RL, Kamboh MI, et al. Chronic traumatic encephalopathy (CTE) in a National Football League Player: case report and emerging medicolegal practice questions. *J Forensic Nurs*. 2010;6(1):40-46. https://doi.org/10.1111/j.1939-3938.2009.01064.x.

6. Mckee AC, Abdolmohammadi B, Stein TD. The neuropathology of chronic traumatic encephalopathy. *Handb Clin Neurol*. 2018;158:297-307. https://doi.org/10.1016/B978-0-444-63954-7.00028-8.

7. Ling H, Morris HR, Neal JW, et al. Mixed pathologies including chronic traumatic encephalopathy account for dementia in retired association football (soccer) players. *Acta Neuropathol*. 2017;133(3):337-352. https://doi.org/10.1007/s00401-017-1680-3.

8. Lee EB, Kinch K, Johnson VE, et al. Chronic traumatic encephalopathy is a common co-morbidity, but less frequent primary dementia in former soccer and rugby players. *Acta Neuropathol (Berl)*. 2019;138(3):389-399. https://doi.org/10.1007/s00401-019-02030-y.

9. Stewart W, McNamara PH, Lawlor B, Hutchinson S, Farrell M. Chronic traumatic encephalopathy: a potential late and under recognized consequence of rugby union? *QJM Mon J Assoc Physicians*. 2016;109(1):11-15. https://doi.org/10.1093/qjmed/hcv070.

10. Alosco ML, Stein TD, Tripodis Y, et al. Association of white matter rarefaction, arteriolosclerosis, and tau with dementia in chronic traumatic encephalopathy. *JAMA Neurol*. 2019;76(11):1298-1308. https://doi.org/10.1001/jamaneurol.2019.2244. Published online.

11. Mez J, Daneshvar DH, Kiernan PT, et al. Clinicopathological evaluation of chronic traumatic encephalopathy in players of American football. *Jama*. 2017;318(4):360-370. https://doi.org/10.1001/jama.2017.8334.

12. Mez J, Daneshvar DH, Abdolmohammadi B, et al. Duration of American football play and chronic traumatic encephalopathy. *Ann Neurol*. 2020;87(1):116-131. https://doi.org/10.1002/ana.25611.

13. Gallo V, Motley K, Kemp SPT, et al. Concussion and long-term cognitive impairment among professional or elite sport-persons: a systematic review. *J Neurol Neurosurg Psychiatry*. 2020;91(5):455-468. https://doi.org/10.1136/jnnp-2019-321170. Published online.

14. Rovio S, Kåreholt I, Helkala E-L, et al. Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. *Lancet Neurol*. 2005;4(11):705-711. https://doi.org/10.1016/S1474-4422(05)70198-8.

15. Hume PA, Theadom A, Lewis GN, et al. A Comparison of cognitive function in former rugby union players compared with former non-contact-sport players and the impact of concussion history. *Sports Med*. 2017;47(6):1209-1220. https://doi.org/10.1007/s40279-016-0608-8.

16. McMillan TM, McSkimming P, Wainman-Lefley J, et al. Long-term health outcomes after exposure to repeated concussion in elite level rugby union players. *Occup Environ Med*. 2017;74. In: Vol.

17. Decq P, Gault N, Blandeau M, et al. Long-term consequences of recurrent sports concussion. *Acta Neurochir Wien*. 2016;158(2):289-300. https://doi.org/10.1007/s00701-015-2681-4.

18. Gallo V, McElvenny D, Hobbs C, et al. BRain health and healthy AgeINg in retired rugby union players, the BRAIN Study: study protocol for an observational study in the UK. *BMJ Open*. 2017;7(12):e017990. https://doi.org/10.1136/bmjopen-2017-017990.

19. Davies MAM, DJ A, Delmestri A, et al. Health amongst former rugby union players: a cross-sectional study of morbidity and health-related quality of life. *Sci Rep*. 2017;7(1):11786. https://doi.org/10.1038/s41598-017-12130-y.

20. James L, Seghezzo G, Williamson E, et al. *The BRAIN-Q, a tool for assessing self-reported sport-related concussions for epidemiological studies*. Manuscr Prep.

21. Donohue MC, Sperling RA, Salmon DP, et al. The preclinical Alzheimer cognitive composite: measuring amyloid-related decline. *JAMA Neurol*. 2014;71(8):961-970. https://doi.org/10.1001/jamaneurol.2014.803.

22. Grober E, Hall CB, Lipton RB, Zonderman AB, Resnick SM, Kawas C. Memory impairment, executive dysfunction, and intellectual decline in preclinical Alzheimer's disease. *J Int Neuropsychol Soc*. 2008;14(2):266-278. https://doi.org/10.1017/S1355617708080302.

23. Papp KV, Amariglio RE, Dekhtyar M, et al. Development of a psychometrically equivalent short form of the Face-Name Associative Memory Exam for use along the early Alzheimer's disease trajectory. *Clin Neuropsychol*. 2014;28(5):771-785. https://doi.org/10.1080/13854046.2014.911351.

24. Lu K, Nicholas JM, Collins JD, et al. Cognition at age 70: life course predictors and associations with brain pathologies. *Neurology*. 2019;93(23):e2144-e2156. https://doi.org/10.1212/WNL.0000000000008534. Published online.

25. Nelson HE, Willison J. *The National Adult Reading Test (NART)*. https://www.academia.edu/2515150/National_Adult_Reading_Test_NART_test_manual_Part_1.

26. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med*. 2011;30(4):377-399. https://doi.org/10.1002/sim.4067.

27. Morris TP, White IR, Royston P. Tuning multiple imputation by predictive mean matching and local residual draws. *BMC Med Res Methodol*. 2014;14(1):75. https://doi.org/10.1186/1471-2288-14-75.

28. Shirk SD, Mitchell MB, Shaughnessy LW, et al. A web-based normative calculator for the uniform data set (UDS) neuropsychological test battery. *Alzheimers Res Ther*. 2011;3(6):32. https://doi.org/10.1186/alzrt94.

29. Kormas C, Megalokonomou A, Zalonis I, Evdokimidis I, Kapaki E, Potagas C. Development of the Greek version of the Face Name Associative Memory Exam (GR-FNAME12) in cognitively normal elderly individuals. *Clin Neuropsychol*. 2018;32(sup1):152-163. https://doi.org/10.1080/13854046.2018.1495270.

30. Stern Y. Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurol*. 2012;11(11):1006-1012. https://doi.org/10.1016/S1474-4422.

31. Chan D, Shafto M, Kievit R, et al. Lifestyle activities in mid-life contribute to cognitive reserve in late-life, independent of education, occupation, and late-life activities. *Neurobiol Aging*. 2018;70:180-183. https://doi.org/10.1016/j.neurobiolaging.2018.06.012.

32. Mormino EC, Papp KV, Rentz DM, et al. Early and late change on the preclinical Alzheimer's cognitive composite in clinically normal older individuals with elevated amyloid β. *Alzheimers Dement J Alzheimers Assoc*. 2017;13(9):1004-1012. https://doi.org/10.1016/j.jalz.2017.01.018.

33. Major BP, McDonald SJ, O'Brien WT, et al. Serum protein biomarker findings reflective of oxidative stress and vascular abnormalities in male, but not female, collision sport athletes. *Front Neurol*. 2020;11:549624. https://doi.org/10.3389/fneur.2020.549624.

34. Mackay DF, Russell ER, Stewart K, et al. Neurodegenerative disease mortality among former professional soccer players. *N Engl J Med*. 2019;381(19):1801-1808. https://doi.org/10.1056/NEJMoa1908483.

35. Whalley LJ, Dick FD, McNeill G. A life-course approach to the aetiology of late-onset dementias. *Lancet Neurol*. 2006;5(1):87-96. https://doi.org/10.1016/S1474-4422.

36. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet Lond Engl*. 2017;390(10113):2673-2734. https://doi.org/10.1016/S0140-6736.

37. Abazov VM, Abbott B, Abolins M, et al. Evidence for an anomalous like-sign dimuon charge asymmetry. *Phys Rev Lett*. 2010;105(8):081801.

38. Williams JJ. An investigation into why rule changes are introduced within sport and their intended and unintended effect on the game, with particular reference to rugby union. 2005. Published online. University of Cardiff Doctoral Dissertation.

39. Quarrie KL, Hopkins WG. Changes in player characteristics and match activities in Bledisloe Cup rugby union from 1972 to 2004. *J Sports Sci*. 2007;25(8):895-903. https://doi.org/10.1080/02640410600944659.

40. *International Standard classification of occupations: ISCO-88*. Published online 1990. https://www.ilo.org/public/english/bureau/stat/isco/

41. McKee AC. The neuropathology of chronic traumatic encephalopathy: the status of the literature. *Semin Neurol*. 2020;40(4):359-369. https://doi.org/10.1055/s-0040-1713632.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.