Is there a link between alcohol use and long-term neurocognitive or neurodegenerative outcomes in athletes with a history of Traumatic Brain Injury? A systematic review

Tara Munro

A dissertation submitted to Auckland University of Technology in partial fulfilment of the requirements for the degree of Bachelor of Health Science Honours in Psychology

November 23rd 2021

Faculty of Health and Environmental Sciences

Primary supervisor – Professor Alice Theadom

Co-supervisor – Professor Patria A. Hume

Advisors: Dr Stephen Casper, Dr Doug King, Dr James Webb

ATTESTATION OF AUTHORSHIP

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person (except where explicitly defined in the acknowledgements) nor material which to a substantial extent has been accepted for the award of any other degree or diploma of a university or other institution of higher learning.

Tara Munro

23rd Nov 2021

ACKNOWLEDGEMENTS

I would like to acknowledge and express gratitude for the amazing support and knowledge shared throughout the year by my supervisors and advisors. Firstly, my supervisor Alice Theadom, for introducing me to this research topic and helping generate my interest in the area, providing support and valuable feedback along the way. Co-supervisor Patria Hume, for her support, keen help and commitment, advisor Doug King for his insight, knowledge and constructive feedback around systematic reviews and my research topic, advisor Stephen Casper for his thought-provoking insight and sharing of expertise, and advisor James Webb for his support and feedback for my dissertation. I am very lucky to have had such a great and committed team around me, and I have gained invaluable writing, research and thinking skills through their feedback and edits on my work.

I thank my lecturers at AUT, whose enthusiasm and knowledge have strengthened my passion and knowledge for psychology, writing, and research.

I am thankful for my friend and classmate Indi during the year, who has made my year at AUT through her support.

I am also grateful for the support of my family, friends and partner throughout my studies.

Contents

LISTS

List of figures

List of tables

List of abbreviations

mTBI	mild traumatic brain injury
HI	head injury
CTE	chronic traumatic encephalopathy
SRC	sport-related concussion
SR-mTBI	sport-related mild traumatic brain injury
SSS	symptom severity score
TBI	traumatic brain injury

DEFINITIONS

Mild traumatic brain injury (mTBI)

The term mTBI within this dissertation is defined by the World Health Organisation Collaborating Centre for Neurotrauma Task Force on mTBI[1] as "an acute brain injury resulting from mechanical energy to the head from external physical forces. Operational criteria for clinical identification include: (i) 1 or more of the following: confusion or disorientation, loss of consciousness for 30 minutes or less, post-traumatic amnesia for less than 24 hours, and/or other transient neurological abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery; (ii) Glasgow Coma Scale score of 13–15 after 30 minutes post-injury or later upon presentation for healthcare. These manifestations of mTBI must not be due to drugs, alcohol, medications, caused by other injuries or treatment for other injuries (e.g., systemic injuries, facial injuries or intubation), caused by other problems (e.g., psychological trauma, language barrier or coexisting medical conditions) or caused by penetrating craniocerebral injury." (p. 140)[1] The term sport mTBI will be used throughout this paper as reference to hit(s) to the head or concussion sustained through participation in sport.

Neurocognition

The use of the term neurocognition throughout this dissertation follows the American Psychological Association's Dictionary of Psychology definition:[2] "Cognitive processes or functioning understood in relation to the specific neural mechanisms by which they occur in the brain and any impairment of these mechanisms."

Neurodegeneration

The use of the term neurodegeneration and neurodegenerative disease throughout this dissertation follows the American Psychological Association's Dictionary of Psychology definition:[3] "Any disease characterised by progressive nervous system dysfunction and loss of neural tissue. Alzheimer's disease, amyotropic lateral sclerosis, and Parkinson's disease are all examples of neurodegenerative diseases. Also called *neurodegenerative disorder*."

Alcohol abuse

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defined 'alcohol abuse' symptoms and characteristics as drinking more than intended, not being able to cut down when wanting to, or being sick from aftereffects of drinking.[4] 'Alcohol dependence' criteria included having drinking interfere with daily life, engaging in risky behaviours from drinking, having to drink more than usual to feel the effects of alcohol, and having withdrawal symptoms.[4]

Heavy drinking & Heavy alcohol use

'Heavy alcohol use' is defined by the Substance Abuse and Mental Health Services Administration (SAMHSA) as "Binge drinking on 5 or more days in the past month".

‘Heavy drinking’ is defined by the NIAA as “For men, consuming more than 4 drinks on any day or more than 14 drinks per week. For women, consuming more than 3 drinks on any day or more than 7 drinks per week”.

ABSTRACT

Background: It is often argued that the long-term effects observed in athletes who have experienced multiple mild traumatic brain injuries (mTBI) are due to alcohol rather than the mTBI(s). This systematic review aims to identify and critique the literature to explore whether alcohol use is a modifier in the clinical presentation of chronic traumatic encephalopathy (CTE) and cognitive functioning of athletes with a history of mTBI.

Objectives: This systematic review aimed to investigate the evidence surrounding the potential role of alcohol use on long-term cognitive functioning, neurodegenerative outcomes, and possible increased likelihood of the post-mortem diagnosis of CTE for athletes with a history of TBI. The review intended to create a greater understanding of this evidence through the synthesis and quality appraisal of existing knowledge in literature.

Methods: Systematic searches of CINAHL Complete, MEDLINE and SPORTDiscus, Scopus, Web of Science and PsycINFO databases using keywords related to contact sports, athletes, traumatic brain injury/concussion, neurodegenerative diseases, and alcohol. The database searches were conducted within the months of June to 11th November 2021. The databases searched included literature from the 1970s' until July 2021. To be included in the review, studies needed to present data on: 1) Sportspeople engaged in at least one competitive season of sport; 2) Alcohol use 3) Include participants with a history of mild traumatic brain injury or repeated head impact sustained from sports participation; and 4) Include at least one neurocognitive or neuropathological outcome. The included studies were appraised using the British Medical Journal Appraisal Tool for Cross-Sectional Studies; containing 20 items surrounding study design, reporting quality, ethical quality and potential conflicts of interest - the latter of which was highlighted for its importance in the review due to its socio-political context.

Results: Five articles (Bieniek et al., 2020;[5] Gardner et al., 2017;[6] Hume et al., 2016;[7] Jordan et al., 1996[8] and Mathias et al., 2014[9]) met the inclusion criteria. All five studies had no strong evidence for the role of alcohol as a modifier for long-term cognitive difficulties or the likelihood of the post-mortem diagnosis of CTE. One study[5] showed higher rates of antemortem alcohol use in cases with CTE.

Discussion: Although numerous articles suggested alcohol use as a modifier, a lack of literature in which alcohol use data were linked with neurocognitive and neurodegenerative outcomes for athletes with a history of TBI was identified. Interpretations of such data were seldom reported. Of the five included articles, authors found no differences in measures of depression, anxiety, or cognitive functioning. There was no evidence of alcohol use as a modifier for tauopathy or increased likelihood of CTE for athlete cases, although one study[5] found higher rates of antemortem alcohol use in CTE cases.

Conclusion: There was no conclusive evidence from the literature for the potential role of alcohol use in long-term cognitive functioning, neurodegenerative outcomes, or possible increased likelihood of the post-mortem diagnosis of CTE for athletes with a history of TBI.

PROSPERO registration number: CRD42021250409 (last updated on 21st May 2021).

INTRODUCTION AND RATIONALISATION

"Playing through the pain" of injury is often seen as a sign of strength and commitment in athletes.[10, 11] This is also influenced by socio-cultural norms and the values of sport.[10, 11] Mild traumatic brain injury (mTBI) in sports has long been recognised as a major concern in sports medicine and public health as greater attention and understanding of its impacts on sports players is researched and reported.[10] Athletes involved in contact sports, such as American football, soccer, rugby, boxing, wrestling, and hockey, are prone to experiencing multiple mTBI over their career.[12] mTBI are defined as a pathophysiological process in which an impact or force to the head or body transmitted to the head disrupts brain function.[8, 10] A mTBI involves temporary neurological impairments and symptoms impacting cognitive, behavioural and physical function.[8] As contact sports have demonstrated a high risk of mTBI in players, research into the long-term effects of these events on participants' cognitive functioning[2] and brain health, and modifiers of those resulting health outcomes, is important.[13, 14] Being informed about the potential risks for cognitive, neuropsychological, and neuropathological outcomes that implicate on wellbeing and quality of life post TBI and repeated concussion are integral to enabling athletes in their decision making. The range of effects of repeated mTBI on mood, mental and emotional wellbeing, cognitive impairment and brain health can be severe.[15]

Cognitive functioning has been defined as "*the performance of the mental processes of perception, learning memory, understanding, awareness, reasoning, judgment, intuition, and language*".[2] While deficits in post-exposure cognitive functioning after mTBI are well known, researchers have found evidence for, and against, the long-term impairment of cognitive functioning.[8, 13, 16, 17] Cunningham et al.'s[13] review on neurocognitive and neuropsychological outcomes for retired athletes identified evidence of decreased cognitive performance from various tests in observed participant groups, when compared with controls. Tests of cognitive functioning covered aspects of visual and verbal memory, attention, information processing and motor speed.[18] However, conclusions around findings were limited due to possible methodological biases, issues with self-reporting in participants, lack of control for certain confounding variables (such as musculoskeletal injury). There were no meaningful observed difference between athletes and population norms.[13]

Over time, research on the impacts of repetitive mTBI such as those sustained through boxing and American football have demonstrated the potential for a progressive neurodegenerative disease termed chronic traumatic encephalopathy (CTE).[19] CTE was first termed 'punch drunk' by Martland[20] in 1928 and described as a condition seen in boxers hypothesized to result from repeated punctate, traumatic cerebral hemorrhages due to a single mTBI or repeated blows to the head. Gurdjian and Voris[21] defined 'punch-drunk' as a neuropsychological disorder presumed to be caused by repeated head injury and noted to be often associated with chronic alcohol use disorder. Affected boxers were seen to demonstrate episodes of confusion, hand tremors, unsteadiness, and staggering gait.[20] The severity of these symptoms were like those observed in Parkinson's disease, referred to by the author as parkinsonian syndrome.[20] Observations of the steady advancement, progressive nature and irreversibility of the condition were undertaken and investigations into the pathology of the brain in those people

affected eventuated in terms ‘dementia pugilistica’ and ‘chronic traumatic encephalopathy’ or CTE[22, 23] The observed relationship between concussion, CTE and contact sports has since remained controversial.[13, 14]

CTE is characterised by a range of pathological, neurocognitive, neuropsychiatric (i.e., mood decline and motor function), impaired cognitive function (i.e., thinking and problem-solving), and behaviour (i.e., aggression and suicidality) presentations.[14, 19, 24, 25] Like many other neurodegenerative diseases, CTE can only be diagnostically confirmed post-mortem through pathological examination of the brain.[14, 26] CTE has been identified in athletes, military personnel and patients with histories of interpersonal or intimate partner violence.[14, 26] CTE manifests as a tauopathy of the brain and may include cerebral atrophy, fenestration of the septum pellucidum, tau and neurofibrillary inclusion, depigmented substantial nigra and locus caeruleus, in addition to enlarged ventricles.[27]

How recurring head impact trauma mechanistically results in the tauopathy and its associated clinical symptomology continues to be investigated. Identification of modifying factors in the disease’s natural history is a particularly salient area of research.[18] Such investigation could well reveal ways that the condition is worsened or reveal predispositions that could put contact sports player at a higher risk.[18] Limitations in the current knowledge of CTE, and the long-term effects of mTBI have also been suggested by some researchers.[5, 18, 28] Understanding the risk and modifying factors for CTE, and broader neurocognitive outcomes that may be potentially influenced by environmental and behavioural factors, are important in creating a more comprehensive and complete picture of the condition.[29, 30]

The long-standing question of whether alcohol use is a modifier in the clinical presentation of CTE and broader cognitive functioning of athletes with a history of mTBI has been pondered by numerous authors[12, 18, 28, 30-32] While highlighted as either a potential confounder, or a factor of interest by these researchers, alcohol use and alcohol use disorder data in empirical studies have been rarely included as a measure.[12] There have been no shortage of editorials and reviews that have pondered the role alcohol may play in the development of CTE. For this reason, the paucity of evidence surrounding it is surprising.

The first study[33] reporting alcohol use in participants concerning encephalopathy was on boxers. Johnson[33] reported that of 17 participants (including four ‘heavy drinkers’ and two ‘compulsive drinkers’), one participant was observed to have alcohol use as a major etiological factor in the psychosyndrome. There was no evidence that alcohol was a notable modifier in participant outcomes.[33] More recent studies have similarly touched upon alcohol use as a potential confounder. Riley et al.[28] acknowledged that greater recognition of the confounding factors for outcomes in brain injury and CTE were needed. This included control for alcohol misuse in relevant studies.[28] Grashow et al.[30] illustrated potential modifying factors and outcomes encompassing pre-professional factors, exposures during their career and post-retirement (long-term) outcomes. Pre-professional factors included socio-demographic indices, mental health history, initial exposures (e.g., age at playing, sustaining concussion), game-related exposure during a career in sport (e.g., seasons played, number of concussions and injuries), and

post-retirement outcomes (e.g., impairment in cognitive functioning and mood, neurodegenerative disease among others).[30] Underlying mid-and long-range outcomes were behavioural modifying factors including socio-economic status, stress levels, exercise, alcohol, and tobacco use.[30]

The rationale for the interest in alcohol use as a modifier could be explained broadly by several factors. These factors include: (1) The high rates of reported alcohol use in athletes; (2) The effects of alcohol on the brain and neurocognitive functioning; and (3) The question of who and why individuals develop CTE, while others do not.[29, 34] Alcohol use has been associated with numerous neurocognitive impacts, depression of the central nervous system, dysfunction of the blood-brain barrier and central nervous system depression.[29] Heavy alcohol use has also been associated with difficulties in problem-solving, attention and working memory, potentially attributable to altered regional brain activation and decreased grey/white matter volumes.[29] Cognitive impairment following mTBI may also be exacerbated by heavy alcohol use.[29]

McKee et al.[12] suggested several factors that could influence either the development or acceleration of tau pathology in CTE, such as physiological stress, age at first 'exposure' or mTBI, gender and environmental influences (including alcohol use, opiates or performance-enhancing drugs).[29] This highlights the need to further understand the risk factors that can elevate characteristics of, or the development of, CTE.[12, 29] These risk factors and other biopsychosocial factors may be potentially important in the development of CTE. These factors include aspects such as the effects of demographic and developmental context, ageing, retirement adjustment, surgeries, anesthesia, difficulties with sleep, neurodevelopment disorders and drug and alcohol use disorders.[29] Alcohol abuse, as well as prescription medications and steroids, were also described as potentially having negative effects on the neurobehavioral profile of athletes over time and with age.[29] An obvious consequence of heavy drinking could be also mean further head injury exposure (i.e. falls, accidents, and interpersonal violence).

Post-injury alcohol use as a means of self-medicating to deal with symptoms of brain injury is also of additional importance to consider for the study population.[35] Alcohol use and TBI are described[35] as being comorbid with symptoms of negative affectivity (i.e. mood and emotions) and cognitive dysfunction possibly contributing to use of alcohol and substances post-TBI. Self-medicating through these methods can present the risk of exacerbating symptoms and hindering recovery post TBI.[35] Of additional importance is further head injury exposure because of heavy drinking (I.e., falls, accidents or interpersonal violence)[36] as occurring in a dose-response manner.

1.1 Literature review

This review evaluates and synthesizes the existing evidence on the impacts of alcohol use for both long-term cognitive functioning and neurodegenerative outcomes following mTBI sustained in athletes involved in contact sports. The effects of alcohol-related neurodegeneration and its links with CTE symptomatology/presentation will be explored. The development of CTE, its relationship to both outcome measures and possible links to alcohol will also be discussed. Further, the socio-political background of sport

mTBI and CTE with its relevance to context in New Zealand are described. Information has been sourced through online database searches for published articles on the research area for this literature review.

1.1.1 Alcohol and cognition

High alcohol use can negatively impact cognitive and psychomotor functioning, and it is a known contributor to both neurological and organic brain damage.[37, 38] Neurocognitive health consequences of alcohol are both acute and long-term, including central nervous system (CNS) depression, dysfunction of the blood-brain barrier, as well as reduction of cerebral blood flow.[29] Cognitive effects are associated with impaired working memory, attention and problem solving, with impacts exacerbated following a traumatic brain injury.[29] Heavy alcohol use is associated with numerous effects on neurocognitive health and functioning both acutely and in the long term.[29] This includes impairment in working memory, attention and deficits in problem-solving abilities.[29] Symptoms of cognitive impairment following alcohol misuse have been attributed to altered regional brain activation and decreased grey/white matter volumes.[29] Impairment in cognitive functioning in older age may also be related to heavy alcohol use, with a potentially higher risk of developing dementia.[29]

1.1.2 Alcohol and neurodegenerative outcomes

It has been suggested[12] that several factors could influence either the development, or the acceleration of tau pathology in CTE. These factors include physiological stress, age at first 'exposure' or mTBI, gender and environmental influences (including alcohol use, opiates or performance-enhancing drugs).[29] This highlights the need to further understand the risk factors that can elevate characteristics of, or the development of, CTE.[12, 29] "Risk factors" and "biopsychosocial factors" potentially important in the development of CTE are reviewed by the authors through the effects of demographic and developmental context, ageing, retirement adjustment, surgeries, anesthesia, difficulties with sleep, neurodevelopment disorders and drug and alcohol use disorders.[29] Alcohol abuse, as well as prescription medications and steroids, were also described as potentially having negative effects on the neurobehavioral profile of athletes over time and with age.[29]

A severe consequence of alcohol abuse, a condition presenting with similar characteristics to dementia, is Wernicke-Korsakoff syndrome.[39] Although Wernicke-Korsakoff syndrome is very rare, it could be presented as a potential confound in the participant population as the condition produces CTE-like memory deficits.[39] Wernicke-Korsakoff syndrome was recognised individually by Carl Wernicke and S.S. Korsakoff in the late 1800's as an illness occurring in individuals with a history of severe alcohol misuse; typically characterised by impaired mental ability, confusion, memory and ataxia of gait.[39] People presenting with the condition were impacted by cognitive impairment including a permanent memory gap and reduced short-term memory, although preserved immediate memory.[39] Neuropsychological decline in the syndrome has been attributed to thiamine deficiency, 'alcoholic neurotoxicity' and individual susceptibility.[39] The combination of the name is derived from Wernicke's encephalopathy (resulting from vitamin B1/thiamine deficiency) and Korsakoff syndrome; including neuropsychiatric symptoms of memory, emotion and executive functioning impairment.[40]

Corsellis et al.'s[41] study with autopsy examination of 15 retired boxers revealed interesting findings surrounding alcohol use in their participant group. The cases were established to have neurofibrillary degeneration, septal changes, cerebellar scars and degeneration of the substantial nigra.[41, 42] Of the fifteen cases, six had a history of heavy alcohol use and the study[42] described how the atrophy of mammillary and hypothalamus bodies raised interest in the discussion of thiamine deficiency and the possible presence of Wernicke-Korsakoff syndrome.

A correlation between CTE and Wernicke-Korsakoff syndrome has been reported.[43] In a case study of a retired boxer the cognitive decline was potentially attributed to Wernicke-Korsakoff syndrome along with cerebral infarcts.[43] In their analysis of the case through an autopsy, the authors concluded that dementia in retired boxers could be influenced by or ascribed to as cerebral infarcts and Wernicke-Korsakoff syndrome. This meant that similar cases of dementia in boxers could be either caused, or exacerbated, by additional etiological factors than dementia pugilistica (or CTE) such as alcoholic neurotoxicity in Wernicke-Korsakoff syndrome. Comprehensively examining cases for any neuropathological changes that could contribute to both cognitive deficits and behavioural changes was described as crucial.[43]

A historical case of an achondroplastic dwarf who presented with alcohol use disorder and dementia pugilistica is an additional case of interest.[44] This case concurrently demonstrated the development of potential Wernicke Korsakoff syndrome and CTE.[44] The man was described as having cerebellar damage typically seen in CTE, but in this case, resulted from alcohol-induced superior vernal folial atrophy.[44] Symptomatology, in this case, was typical of that often seen in CTE and Wernicke-Korsakoff syndrome, with poor concentration and aggressive behaviour.[44] The presentation of neuropathology in this case resulted from both behavioural and physical trauma-related mTBI and brain neurodegeneration with concurrent alcohol misuse and repeated concussion as a result of experiencing impacts during dwarf throwing competitions.

1.1.3 Socio-political background and relevance to a New Zealand context

In conducting research for this literature review, numerous media articles and opinion pieces that mentioned the use of alcohol as either a confound or impactful for CTE in athletes were apparent.[45, 46] Kitson's[45] article published in *The Guardian* presented the idea that head impacts may not be the sole cause of neurodegeneration and dementia for contact sports players. Behavioural and environmental factors including excessive alcohol use, depression and unhealthy diet could also contribute to deteriorating brain health for athletes showing symptoms of early-onset dementia'.[45] This proposition was described as being controversial in comparison to the opinions of those who believed repeated head impact/mTBI in sport to be a main cause of CTE and dementia-like symptoms.

New Zealand has a high number of people participating in sports, particularly in contact sport such as rugby.[47] Rugby players are at high risk for concussions, and this is a particular concern for the sport.[48] Non-professional players make up the majority of the population playing rugby, albeit there is a paucity of research

conducted involving this population.[48] The impacts of CTE and early-onset dementia symptomatology is relevant for contact sports players in New Zealand. Carl Hayman, a retired All Blacks rugby player, was diagnosed with CTE at age 41.[49] Hayman was described as experiencing mental confusion and constant headaches, which led to developing alcohol use disorder, erratic behaviour, and suicidality.[49]

The risks of concussion are becoming more well-known as media as journal articles have described the prevalence and impacts of sport mTBI, with the mental/emotional and social benefits of sports, particularly in youth also having been considered.[25, 29, 50] Cunningham et al.[51] described the consequences of the knowledge and acceptance of the risks of sport mTBI for youth. Some individuals were described as advocating for the banning of contact sports in children and young teenagers.[51] Conversely, the idea was presented that banning sport was counteractive to health promotion due to the presence of largely 'inactive' or sedentary societies.[51]

1.2 Aim of study

This systematic review aimed to investigate the evidence surrounding the potential role of alcohol use in long-term cognitive functioning, neurodegenerative outcomes, and likelihood or diagnosis of post-mortem diagnosis of CTE for athletes with a history of TBI. The review intended to create a greater understanding of this evidence through the synthesis and quality appraisal of existing knowledge in literature.

1.3 Impact of study

The impact that this study has achieved means that we know what evidence exists surrounding the role of alcohol as a modifier for outcomes; the information provides a rationale for the significance of understanding the role of alcohol; and the gaps in the literature have been highlighted. We have provided recommendations for further research based on the comprehensive view of alcohol as an aetiological factor for cognitive and neurodegenerative outcomes in the athlete population.

2.0 METHODS

2.1 Research design

For this study, a quantitative systematic review was chosen as the most suitable approach to address the research question as it provides a robust method to identify and critique existing knowledge.[52] This method was chosen as there is a body of research conducted internationally that is publicly available online. Although numerous articles presented with reported alcohol use in participants relevant to the topic area, it appeared that there had not yet been a systematic review synthesising and discussing the research evidence. The systematic review thus aims to provide a comprehensive view on the area of interest, while generating new insight surrounding the evidence and the analysis of the quality of this evidence. Systematic reviews are a rigorous and reliable method through their transparency, empirical basis, and minimisation of bias by the researcher.[53] Therefore, this method was chosen from other research designs as it provides an unbiased and thorough view of the evidence.[53] Numeric referencing with superscript numbers is used in this dissertation along with APA 7th edition in the reference list.

2.2 Methodology

Systematic reviews draw on the scientific and objective values underlying a positivist research paradigm.[54] The positivist approach is based on the theory that psychosocial phenomenon can be accurately measured and links between psychosocial phenomena can be identified.[55] Indeed, a primary goal of positivist inquiry is to test hypotheses and identify explanatory associations as was the aim in this systematic review.[55]

2.3 PROSPERO application

The systematic review was approved by the International Prospective Register of Systematic Reviews (PROSPERO) on 21/5/2021 (ID: CRD42021250409). The application for PROSPERO involved presenting an overview of study information (timelines, review stages, team members involved, conflicts of interest and searches conducted) as demonstrated in Appendix A. In addition to information around the study population, intervention/exposure, comparator, context, outcome(s), extraction of data, quality assessment and data synthesis. The review was appraised by reviewers and amended according to feedback received (e.g., providing clarity on aspects of the proposed review process). Prospectively registering the review was considered to be an important part of the research process to ensure transparency of research methods, reduce the risk of bias and to avoid potential duplication of reviews.

2.4 Ethical approval

The study did not require ethical approval as it aimed to review empirical data that was published in the public domain.[56] Guidelines for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [57] were followed. The PRISMA guideline contain checklists that were utilised for conducting and reviewing the included studies. As part of the systematic review process, the quality of the empirical research included was reviewed.[56] This included identifying potential conflicts of interest, reflecting on context, and positioning of authors. The overall quality of evidence and its interpretation were examined. Whether ethical approval had been obtained for each study was reviewed.[56] In the quality appraisal that was conducted via the BMJ AXIS (British Medical Journal Appraisal Tool for Cross-Sectional Studies),[58] of significance were items 19: (funding sources and conflicts of interest potentially affecting interpretation of findings) and 20: (ethical approval and consent from participants involved in studies).[58] To ensure objective interpretation of the findings of the review, the results and interpretations were discussed with the supervision team and via personal reflexivity when analysing evidence and discussing findings in this systematic review.

2.5 Inclusion criteria

To be included in the review, studies must have met the following inclusion criteria:

1. Published in the English language
2. Recruited human participants
3. Full text available
4. Studies also needed to present data on:

a. Sportspeople engaged in at least one competitive season of sport; and
b. Alcohol use; and
c. Traumatic brain injury history or repeated head impact sustained from sports participation for participants; and
d. Include at least one neurocognitive or neuropathological outcome including CTE. Neurocognitive outcomes could be assessed via neuropsychological assessment, computerised tests of cognition or self-reported cognitive functioning.

Exclusion criteria were also established. Studies were excluded if:

1. Not published in English; and/or
2. Full text unavailable; and/or
3. Did not study athletes or retired athletes; and/or
4. Did not report on head injury, TBI, sport-related concussion or CTE; and/or
5. Did not include a cognitive, neuropathological or neurodegenerative outcome; and/or
6. Did not include alcohol data; and/or
7. Did not link alcohol data with cognitive, neuropathological or neurodegenerative measures.

Intervention studies such as randomised controlled trials were excluded as the aim of the review was to explore naturally occurring associations, rather than identifying treatments to improve outcome. Additional study designs excluded were reviews, editorial or opinion pieces.

Neurocognitive functioning and its impacts could entail memory loss/deficits, mood behaviours such as aggression and neuropsychological outcomes including presence/history of mental disorders such as depression.[14] For neuropathological outcomes, the clinical diagnosis of Alzheimer's disease, dementia, mild cognitive impairment, or chronic traumatic encephalopathy were included. A range of study designs were included; retrospective or prospective cohort design, case studies; case series; and cross-sectional studies.

To ensure a comprehensive view of the evidence of the effects of alcohol use on neurocognitive and neurodegenerative outcomes for athletes with a history of TBI, all forms of alcohol use in participants were included were considered in this review. Due to the heterogeneity in terms used by authors, this included 'alcohol use' 'alcohol abuse' and 'alcohol use disorder' as examples. In encompassing all these terms, 'alcohol use' is used primarily throughout the literature review and discussion. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defined 'alcohol abuse' symptoms and characteristics as drinking more than intended, not being able to cut down when wanting to, or being sick from aftereffects of drinking.[4] 'Alcohol dependence' criteria included having drinking interfere with daily life, engaging in risky behaviours from drinking, having to drink more than usual to feel the effects of alcohol, and having withdrawal symptoms.[4]

2.6 Search strategy

The review search strategy involved entering selected key search terms in the following online search databases: CINAHL Complete, MEDLINE and SPORTDiscus, Scopus, Web of Science and PsycINFO. The database searches were conducted within the months of June to August 2021. Study dates searched within ranged from the 1970s' (found to have the first studies on alcohol use and boxing) until July 2021.

The search strategy was developed to include a range of terms relevant to the population, variables, and outcomes of interest. A multiple-stage process was undertaken to ensure search terms were comprehensive in encompassing all relevant outcomes and potential wording differentiations with advice from the supervisory team. Terms were added that included additional sports terms, a range of keywords surrounding tau pathology in the neurological search term group, and a range of neurocognitive/neuropsychological terms that additionally included terms such as 'dementia' and 'Alzheimer'. This maximized the heterogeneity of outcomes and measures surrounding brain injury/impacts were defined and reported by studies as well as the range of contact sports in which were studied.

Grouped terms were entered into separate fields in database search bars or combined with 'AND between each group. The finalised search terms were:

- Term 1 (selected as searched through abstract/title): sport* OR athlet* OR play* OR "sports person" OR sportswom* OR contact sport* OR box* OR football OR rugby
- Term 2 (selected as searched through abstract/title): concuss* OR traumatic brain inj* OR head impact* OR brain inj* OR Head inj* OR TBI OR "skull fracture" OR mTBI
- Term 3 (selected as searched through abstract/title): Alzheimer OR dementia OR "mild cognitive impairment" OR CTE OR neurodegenerative OR "tau pathology" OR "dementia pugilisitica" OR "punch drunk" OR "traumatic encephalopathy" OR tau* OR "major neurocognitive disorder" OR "neurofibrillary tangles" OR "serum tau" OR "senile plaques" OR presenile OR pre-senile OR cogniti*
- Term 4 (searched through whole text): alcohol* OR drink* OR etoh (where etoh is ethanol)

In summary the key words related to contact sports, athletes, traumatic brain injury/concussion, neurodegenerative diseases, and alcohol.

Search terms were made according to guidelines for each database's search specifications. For example, the use of apostrophes for grouped terms "sports person" capitalisation of conjunctions 'AND' and 'OR'. This was researched before conducting searches for each database. Identified citations were downloaded into Endnote. Duplicates were then removed. The remaining citations were then copied into an Excel spreadsheet to record reasons for exclusion against the inclusion criteria. The following data were extracted from the identified citations: 'Authors', 'Title', 'Year', 'Journal', 'Volume', 'Issue', 'Document type', 'DOI', 'Contact address', 'Link', 'Full text available' (Y/N), 'Inclusion criteria', 'Exclusion reason', 'Exclusion based on abstract/title', and 'Included in literature review' (Y/N).

Following review of each abstract against the inclusion/exclusion any reasons for exclusion were recorded. Abstracts were reviewed by the student and one supervisor independently. Any disagreements were resolved through discussion and consensus. A third reviewer was available and assisted with the decision-making of the inclusion of one article. If it remained unclear if the article met the inclusion/exclusion criteria the abstract was retained in the review.

Following initial review of the identified abstracts, the full text articles were obtained for all abstracts that appeared to meet the inclusion criteria. As this stage the identified studies were compared against the inclusion for alcohol use (for which the term was searched in the whole article text) rather than just the abstract. This was conducted as often alcohol was not the primary research question of the study. Studies that recorded and described alcohol use data for participants were initially selected and subsequently screened to identify articles that linked this data with neurocognitive functioning or neurodegenerative outcomes. Two reviewers reviewed (TM, AT) the full text articles against the inclusion/exclusion criteria independently. Decisions were compared between the two reviewers and any disagreements were resolved through discussion. A third reviewer (DK) was required to check an article and it was rejected after the discussion. The identification of studies through the online database searches is shown in Figure 1.

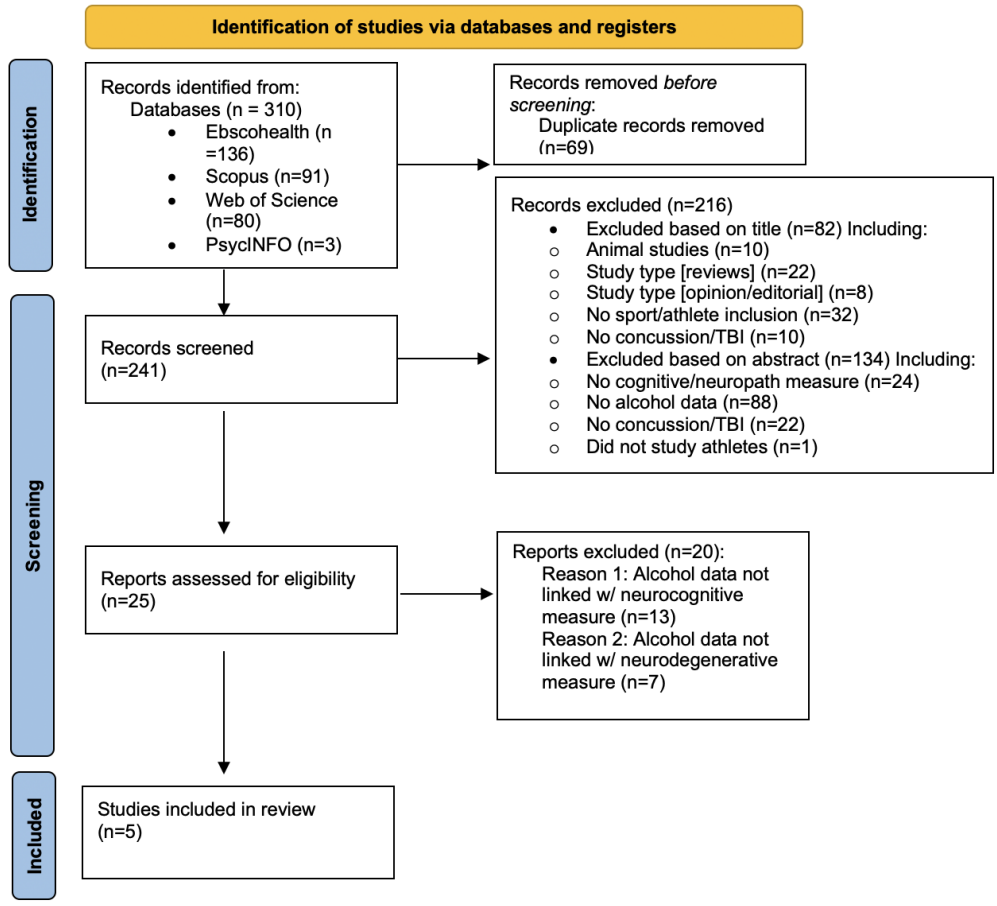

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) flow diagram for the identification, screening, eligibility, and inclusion of studies in the systematic review. N=number.

2.7 Data extraction

To ensure consistency of data extraction, a new excel spreadsheet was set up including the following column headings. Relevant data were extracted for each heading with one row per article. The following data collection headings were used to guide the data extraction process: 'Lead author surname', 'Year (published)', 'Sport(s) included', 'Cases', 'Controls', 'Number of participants', 'Gender of participants', 'Age range of participants', 'Alcohol assessment', 'Cognitive outcome assessment', 'Concussion history assessment', 'Key findings', 'Country (research was conducted)', 'Funder of research', 'Cognitive/neurodegenerative outcomes linked with alcohol data' (Y/N).

2.8 Assessment of article quality via critical appraisal

After identifying the final number of articles that met inclusion criteria, the quality of the individual studies was appraised using the British Medical Journal Appraisal Tool for Cross-Sectional Studies (BMJ AXIS).[58] Developed as a systematic method of assessing cross-sectional studies in terms of their reliability, value, relevancy, and risk of bias,[59, 60] the BMJ AXIS contains 20 items surrounding study design, reporting quality, ethical quality, and potential conflicts of interest - the latter item of which was highlighted for its importance in the review due to its political and societal context.[60, 61] To be rated as being of quality through this tool, studies must have met most of the questions with a 'yes' response. The lack of a quantifiable rating scale to determine study quality has been identified as a limitation of the tool by Downes et al.[59] The findings from the review were synthesised using narrative analysis.

3.0 RESULTS

3.1 Search results

Upon searching the databases, a total of 310 results were retrieved over the databases: 136 results in EBSCO Health databases (CINAHL, MEDLINE and SPORTDiscus); 91 results in Scopus, 80 results in Web of Science and 3 results PsycINFO. During the selection process, 69 articles were identified as duplicates, bringing the number of total findings from the database search to 241. Figure 1 shows the flow of the selection of studies based on the initial search of the databases and then the exclusion based on criteria.

3.2 Selection of studies

A total of 82 articles were excluded based on title, including 10 animal studies, 30 by study type (22 reviews and 8 editorial/opinion pieces), 10 with no concussion/TBI and 32 by no sport/athlete inclusion. A further 134 articles were excluded based on the abstract (including 22 by no concussion/TBI measure, 24 by no cognitive/neurodegenerative measure, 88 with no alcohol data and one that did not recruit athletes). Twenty-five articles met initial inclusion criteria (n=25) underwent full-text screening. On reviewing the full-text articles it became evident that some articles included assessments of alcohol use and cognition and neurodegenerative outcomes, but the data was not linked. As a result, these articles were excluded during this second stage. Five

articles[5-9] ultimately met the inclusion criteria and linked alcohol and neurocognitive and neurodegenerative outcomes (see Figure 1).

3.3 Study range and characteristics

Of the five articles that met inclusion criteria, four were of a cross-sectional design[6-9] and one was a retrospective cohort study[5] that involved post-mortem examinations. The studies largely involved male participants (with the inclusion of female participants in two studies), a range of ages (18 to 68 years old) and encompassed both current professional athletes and retired athletes. Studies covered a broad range of contact sports including rugby, soccer, American football, baseball, basketball, boxing, hockey, and wrestling. All studies had a control group with matched participants who were either not involved in contact sports or had a history of repeated head traumas.

Over the five studies, a range of assessments were conducted that measured numerous aspects of cognitive and psychological functioning, mental wellbeing, mood, and emotional wellbeing. In the cross-sectional studies the CNS Vital Signs neuropsychological test,[7] the Depression, Anxiety, Stress (DASS-21) 21 item scale, in addition to learning, attention, processing speed, memory and fluid executive function tests,[6] memory, problem-solving and abstract reasoning tests[9] were included. In terms of the neurocognitive/neuropathology grouping, Bieniek et al.[5] involved post-mortem examination of participants, and the outcome measures utilised medical record queries encompassing mental health disorder history, 'alcoholism' and 'drug abuse'[5]. Jordan et al.[8] utilised magnetic resonance imaging scores and screening for past neurological illness.

Concussion histories were determined through questionnaire/interviewing. For example, Hume et al.,[7] recorded the number of times participants self-reported that they had experienced a concussion during sport and symptoms experienced, or who had received a medical evaluation from a physician for concussion. Jordan et al.,[8] utilised a scale of 'potential heading' sustained through a participant's sports career through a grading system. Mathias et al.,[9] utilised a grading scale for TBI severity based on the Glasgow Coma Scale (GCS), loss of consciousness and post-traumatic amnesia. Gardner et al.,[6] utilised the 'Rivermead Post Concussion Symptoms Questionnaire' to determine experience of concussion symptoms in their participant group. Bieniek et al.,[5] used medical record query and assessment of sports participation to determine the severity of concussion in addition to the presence of tau pathology or chronic traumatic encephalopathy.

Alcohol use assessment in participants was determined through medical record query for the retrospective and prospective cohort autopsy studies. For the cross-sectional studies, alcohol abuse history was screened through use of the Alcohol Use Disorders Identification Test (AUDIT)[62] by Hume et al.,[7] Mathias et al.,[9] and Gardner et al.,[6] while Jordan et al.,[8] utilised the CAGE questionnaire for determining alcohol dependency.

Due to the heterogeneity of how the variables were assessed between studies, and participant characteristics, the ability to make inter-study comparisons through statistical analysis was restricted. Data were consequently synthesized using a narrative approach.

3.4 AXIS rating summary

The included articles were assessed independently by two evaluators (TM, AT) through the BMJ AXIS tool (British Medical Journal Appraisal Tool for Cross-Sectional Studies).[58] The five studies were rated as being of moderately good quality (75-80% met criteria with 'yes' responses) with scores ranging from 14/20 to 16/20 as illustrated in Table 1. The highest scores were for the studies by Hume et al.,[7] 16/20, Bieniek et al.,[5] 15/20, Gardner et al.,[6] 15/20, followed by the studies by Jordan et al.,[8] 14/20 and Mathias et al.,[9] 14/20.

All the studies stated clear objectives and had appropriate study designs for their aims. For the methods section, all studies except Mathias et al.,[9] sufficiently described their methods in a way that would enable them to be repeatable (item 11). All studies met the criteria for item 5; noting that sample frames were taken from population bases that represented their target audience (athletes). Results were justified in all discussion and conclusion sections (item 17). All studies were identified to have used piloted or published measures for variables/outcomes (item 9). Basic data were described sufficiently in all studies (item 12) and results were shown for all analyses in the results section (item 16).

The most common item the studies lacked overall were a lack of sample size justification (item 3), largely due to small size participant groups, including Gardner et al.[6] and Jordan et al.[8] All studies were identified to have some possible selection bias in their participant group as their methods selected participants that were representative of the population (item 6). Item 13 surrounding concern about non-response bias was least relevant to the five studies. Bieniek et al.,[5] Gardner et al.,[6] and Hume et al.,[7] did not have a response rate that raised concern around non-response bias, while it was unclear if this applied to the studies of Jordan et al.,[8] and Mathias et al.[9] Two studies had a potential conflict of interest in the author/funding source (item 19); Hume et al.,[7] through its funding (World Rugby & New Zealand Rugby) and an author (Quarrie; employed by New Zealand Rugby). The study by Jordan et al.,[8] noted a possible conflict of interest in their funding for statistical support by the United States Soccer Federation.

Table 1: British Medical Journal Appraisal Tool (BMJ-AXIS) analysis of the studies included in this systematic review.

	British Medical Journal Appraisal Tool (BMJ-AXIS) item																				
Lead Author Surname, Year (score/20)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**Additional comments**
Hume, 2016[7] (16)	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	NA	NA	Y	Y	Y	Y	Y	Possible conflicts of interest.
Bieniek, 2020[5] (15)	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	N	NA	NA	Y	Y	Y	N	Y	CTE measure piloted. Alcohol measure not.
Gardner, 2017[6] (15)	Y	Y		Y	Y	Y	NA	Y	Y	Y	Y	Y	N	NA	Y	Y	Y	Y	N	Y	Small sample size (16). Only this limitation discussed.
Jordan, 1996[8] (14)	Y	Y	N	Y	Y	Y	NA	Y	Y	Y	Y	Y	U	N	NA	Y	Y	N	Y	Y	Small sample size, possible conflict of interest.
Mathias, 2014[9] (14)	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	U	N	NS	Y	Y	Y	N	Y	Not all methods explicitly described

Y=Yes; No=N; U=Unclear; NA=Not Applicable; NS=Not stated.

3.5 Finding's summary

Four of five studies that met inclusion criteria showed no compelling evidence for the role of alcohol as a modifier for long-term cognitive difficulties or the likelihood of the post-mortem diagnosis of CTE in athletes (see Table 2).

Table 2: Characteristics of the included studies reporting on alcohol and the long-term neurocognitive or neurodegenerative outcomes.

Study; Design; Funding	**Country; Sport; Cases; Controls; Participant characteristics (sex, age)**	**Assessments: 1) Alcohol; 2) Cognitive/neuropathological; 3) Concussion History**	**Key Findings**
Hume et al., 2016[7] Cross-sectional; World Rugby, AUT & NZ Rugby.	NZ; Rugby: 103 Elite-rugby group; 198 community-rugby group, 65 Non-contact-sport	1) Alcohol Use Disorders Identification Test (AUDIT); 2) CNS Vital Signs neuropsychological test battery; 3) Questionnaire: concussion frequency, evaluation for	More hazardous alcohol use was found in the rugby players compared with the non-contact players.

	group; male; mean 43.3 yr.	concussion, loss of consciousness or other symptoms, reporting concussion.	
Jordan et al., 1996[8] Cross-sectional; United States Soccer Federation.	USA; Soccer: 20 Soccer Team training camp members; 20 Age-matched elite track athletes; male; mean 24.9 yr.	1) CAGE questionnaire; 2) MRI scan & head injury symptom index; 3) Scale of soccer participation: length of season, frequency of heading.	Alcohol in CAGE test eliminated as confounding variable.
Mathias et al., 2014[9] Cross-sectional; National Health and Medical Research Foundation of Australia.	Australia; Sports: 27 Physical assault TBI patients & 26 sporting/athlete TBI patients; 36 Orthopaedic control group (OC); male & female; Sport 28.5 yr, assault 34.3 yr, OC control 34.4 yr.	1) Alcohol Use Disorders Identification Test (AUDIT); 2) Psychosocial & emotional: post-concussion symptoms, injury-related stress, depression & Cognitive: memory, abstract reasoning, problem solving, and verbal fluency; 3) TBI severity score.	Time since injury & alcohol correlated w/ long to medium-immediate recall w/ no group difference. Time since injury & alcohol unlikely to affect outcomes of all groups.
Gardner et al., 2017[6] Cross-sectional; New South Wales Sporting Injuries Committee – Sports Research & Injury Prevention Scheme Grant, & Brain Foundation, Australia – Brain Injury Award.	Australia; Rugby: 16 Retired professional rugby league players; 16 Age and education-matched controls w/ no participation in contact sports neurotrauma history; male; 30-45 yr.	1) Alcohol Use Disorders Identification Test (AUDIT); 2) Psychological & cognitive testing: (DASS-21 scale), Cognitive: attention, processing speed, learning, memory, & fluid executive function; 3) Rivermead Post Concussion Symptoms Questionnaire.	Retired athletes had greater alcohol use, worse manual dexterity w/ non-dominant hand. Alcohol use was possibly associated w/ MRS findings in both groups.
Bieniek et al., 2020[5] Retrospective cohort study (autopsy); Florida Department of Health Ed and Ethel Moore Alzheimer's Disease Research Program, Mayo Clinic Younkin Scholars Program on Synaptic Biology and Memory, Mayo Clinic Alzheimer's Disease Research Center Pilot Project Grant and	USA; Contact sports: Donated brains - Autopsy sample population; 300 athletes, 450 Non-athletes; male & female; mean age at death athletes 68 yr, non-athletes 64 yr.	1) Alcoholism Diagnostic codes - The Rochester Epidemiology Project; 2) Medical record query: Anxiety, bipolar, dementia, depression, drug abuse, head injury, movement disorder, psychosis, PTSD, schizophrenia, suicide, tobacco abuse; 3) Medical record query, sports participation assessment & presence of tau pathology/CTE.	Cases w/ CTE had higher frequencies of antemortem dementia, psychosis, movement disorder & alcohol abuse compared to cases w/o CTE.

National Institutes on Aging.			

Bieniek et al.'s[5] study found higher rates of alcohol use in cases with CTE, although we discuss this finding further in light of methodological quality. The study assessed retrospective sport participation with historical data and medical record queries. The authors found that of their participant groups comprising of 300 athletes and 450 controls, 42 presented with CTE pathology (27 athletes and 15 controls). Of these, 16% of athletes and 20% of non-athletes had 'alcoholism' as a clinical information feature, likely reflecting the way the brain bank acquired brains and from whom. Of note, cases with CTE had higher antemortem features of alcohol abuse (in addition to dementia, movement disorders and psychosis) in comparison to participants without CTE pathology.[5]

Gardner et al.'s[6] study examined neurometabolic concentrations, psychological and cognitive functioning in 16 retired rugby players and 16 age- and education-matched control participants. The authors found no differences in measures of depression, anxiety, or cognitive functioning across groups. Athletes had a significantly higher rate of alcohol use. The control group had significant correlations between AUDIT scores (The Alcohol Use Disorders Identification Test) and neurometabolites.[6] The same findings were not seen in the athlete participants. Based on the authors' review of the literature, it was found that there were no significant findings associated with magnetic resonance spectroscopy (MRS) and alcohol use.[6]

Hume et al.'s[7] study assessed differences in cognitive functioning for 301 former rugby players (elite and community players) and 65 non-contact sport retired players (field hockey). CNS Vital Signs test, AUDIT scores and self-reported concussion history were evaluated. 'High' levels of current alcohol use were reported in 33% of elite rugby players, 32.8% of community rugby players and 20% of non-contact sports players. No significant correlations were reported between demographics, age, ethnicity, education level, level of sport played or alcohol use with the neuropsychological outcome measures.

Jordan et al.'s[8] 1996 study investigated the presence of CTE pathology in 20 elite soccer players due to repeated heading of the ball with comparison to 20 age-matched track athletes. Magnetic resonance imaging (MRI), a query into the history of head traumas and alcohol use (identified through the CAGE alcohol tool) were utilised. The questionnaire and MRI showed no statistical differences between the groups. There were no

differences in alcohol use between the two groups and no correlation between MRI findings and alcohol use. The CAGE tool eliminated alcohol as a compounding variable. Overall findings demonstrated that evidence of encephalopathy may be more related to acute head injuries rather than the repetitive heading of the ball.

Mathias et al.'s[9] 2014 study aimed to determine whether the cause of injury (sporting or assault) affected outcomes on samples that contained mixed injuries. Tests of psychological and cognition measures (including psychosocial and emotional tests, memory, problem-solving, verbal, and visual abstract reasoning) were used to assess differences.[9] The traumatic brain injury (TBI) assault group showed poorer psychosocial and emotional outcomes than the other two groups, and there were no differences in cognitive or functional outcomes between the three groups. AUDIT scores showed no significant differences in alcohol use, although the TBI sport group had lower scores than others. The AUDIT findings were associated with immediate memory. It was considered not necessary to control for alcohol as a variable statistically when analysing group outcomes.[9] The findings of the study demonstrated that the cause of TBI may explain outcome differences for comparable injuries.

4.0 DISCUSSION

This systematic review aimed to identify and critique the literature to explore whether alcohol use was a modifier in the clinical presentation of neuropathology and cognitive functioning of athletes with a history of mTBI. It is often argued that the long-term effects observed in athletes who have experienced multiple mild traumatic brain injuries (mTBI) are due to alcohol rather than the mTBI(s). The main findings of this review were that: 1) there was limited evidence exploring the role of alcohol in specifically in athletes; with a history of mTBI and 2) there was no conclusive evidence in the current literature for the potential role of alcohol use as a modifier in long-term cognitive functioning, neurodegenerative outcomes, or possible increased likelihood of the post-mortem diagnosis of CTE for athletes with a history of TBI.

Study critiques of the five inclusion articles, including sample size, participant groups, and outcome measures, data interpretation of the studies, and discussion of alcohol use as a modifier for outcomes are explored. The limitations of this dissertation, its relevance and contribution to the literature, as well as recommendations for further research and implications, will be also discussed.

4.1 Sample size

Researchers often have difficulties collecting enough data to enable the testing of the hypothesis.[63] This may occur when the target group is small, there is a sparsity of data, participants are hard to access, data collection entails prohibitive costs or participants come from a population base prone to drop-out. [63] The majority of studies included in this review reported small participant groups ranging from six retired athletes and 16 age- and education-matched controls[6] to 26 athletes, 27 physical assault patients and 36 orthopaedic controls.[9]

The small sample sizes raised questions of validity and reliability of outcomes in the studies as well as the potential of generalisability to larger populations if larger participant groups were included. Small sample size

has been previously reported[64] that the number of participants needs to be considered carefully. For moderate-to-strong associations, between 20 to 50 cases are needed to identify these associations. For small-to-moderate associations that may enable generalisability, the sample size would need to be 200 participants.[64] Based on this information, the data reported in these studies would only be able to report if there were moderate-to-strong associations between alcohol consumption and the development of CTE.

The small number of participants reported in the studies included in this systematic review may have resulted in any chance of discovering small-to-moderate true effects are limited.[65] In addition, for studies with a small sample size, any observed effect that reaches a nominally statistically significance (i.e., $p<0.05$), there is a lower probability that is passes the required threshold and this is likely to exaggerated (Button, et al., 2013). Other aspects that may be associated with small participant numbers and result in low reliability of the evidence provided are: (1) Studies are likely to provide a 'vibration of effects' (wide range of estimates); (2) Publication bias, selective data analysis and selective reporting of outcomes may occur; and (3) There may be lower quality in other aspects of the study design.[65]

4.2 Data interpretation

Through this review, it was apparent that interpretations of such data relating to measures of cognitive functioning, neuropathology, or presence of CTE pathology were less reported. There were a high number of opinion/article pieces, articles mentioning alcohol & suggesting it as a confound but not measuring it.

4.3 Participants

The studies largely involved male participants, with the inclusion of female participants in only two studies: six in Mathias et al.'s[9] study and 273 in Bieniek et al.'[5] study. Across the 1277 participants in the five studies (cases and controls), this meant 279 or 21.84% were female. The studies had a range of ages (18 to 68 years old) and encompassed both current professional athletes and retired athletes. Participants were either from the professional level of participation, community level of participation and were current or retired athletes. Hume et al.[7] and Bieniek et al.[5] were the only two studies that recorded ethnicity or race of participants. Bieniek et al.[5] measured this demographic information solely as 'Race (white)', while Hume et al.[7] recorded ethnicity demographics as 'European', 'Other' and 'Unknown/missing'. Studies were also based in New Zealand, Australia, and the United States of America.

Asken et al.[29] discussed the effects of developmental and environmental variables on cognition, emotional and behavioural changes for contact-sports athletes with a history of repeated mTBI; including socio-cultural factors, ethnicity, and socio-economic status. Professional sports athletes are described by the authors as being diverse overall, yet having demographic biases in their population.[29] Demographic characteristics are described in how they are potentially associated with cognitive, emotional and mood symptoms involved in CTE.[29] In addition to biological factors, these environmental/developmental variables are recognised as contributing to our knowledge of the aetiology of CTE in the understanding of who develops clinicopathological changes following

repeated head injury in sport and while others do not.[29] Pre-professional demographics of race and socio-economic status (SES) and behavioural health modifying factors (including SES) have been further highlighted by Grashow et al.[30] The post-retirement or long-term outcomes following exposure in sports participation included neurodegenerative disease, CTE and symptoms of its clinicopathology; impairment in cognition, mood, and social, mental and physical measures of life quality.[30]

The relationship between SES and developmental factors with psychological and emotional wellbeing is complex. Individuals with lower or disadvantaged SES may have a higher susceptibility to depression, aggressive behaviour or poor conduct as a maladaptive reaction to adverse early life experiences and familial stressors [29, 66] SES can also impact cognitive functioning and development, including verbal fluency, processing speed and memory.[67] The implications of these observations for the present study are undetermined. Although environmental and developmental variables that can influence a range of factors (cognitive ability, literacy, psychological health, mood, and behaviour) are likely impactful on participant outcomes in the inclusion articles, the extent of such additional modifiers is also unknown. Concerning alcohol as a modifier for neurocognitive outcomes, the impacts of heavy alcohol use, or alcohol abuse over time would exacerbate deficiencies or impairments in cognitive functioning.[38]

An additional factor to consider when discussing participant groups for the inclusion articles was bias in autopsy selection and any possible limitations that may have arisen. McKee et al.[68] described this as ascertainment bias in autopsy-based studies, with brain donation being influenced by the health of the individual. Those whose family member was demonstrating impairments in behavioural mood or cognition may be more likely to participate in brain donation than those who were presenting as more 'functioning' or healthy.[68]

Bieniek et al.'s[5] retrospective cohort study with postmortem examination of donated brains is relevant for this discussion. The study was noted to have possible selection bias in item 6 of the BMJ AXIS appraisal. Bieniek et al.[5] retrospectively assessed outcome measures with historical data through the use of medical record queries including the Rochester Epidemiology Project (REP). In presenting alcohol use data, it was reported that 16% of athletes and 20% of non-athletes were reported to have 'alcoholism' as a feature of clinical information.[5] Both statistics, at 16% and 20.4% were judged as a high percentage of alcoholism in the athlete and non-athlete control group. Questions arose surrounding who the controls in this study were, and why this statistic was high. In comparing these statistics to the larger U.S. population according to the 2019 National Survey on Drug Use and Health (NSDUH) Annual National Report, 5.3% of people aged 12 and over had an alcohol use disorder.[69]

In researching the REP, it was additionally found that through the years 1966 to 2008, the project excluded individuals who were physically or mentally disabled, were in assisted living, or were incarcerated.[70] Therefore, there may have been a possibility that people with alcohol use disorder were overrepresented, or individuals with dementia or other neurodegenerative disorders that were sports players were excluded in Bieniek et al.'s[5] findings.

Issues with reporting levels of alcohol use, alcohol use disorder, and how these terms are defined and interpreted are further discussed in section 4.3 Outcome measures.

4.4 Alcohol use

Kirkendall & Garrett[38] provided a rationale for exploring alcohol use in the athlete population for both impairments in cognitive functioning and neurodegeneration. Alcohol abuse was described by the authors as being known to lead to cognitive deficits in addition to organic and neurological brain damage.[38] Of relevance is the point communicated by the authors that simply mentioning 'alcohol intake' was not a valid means to assessing and determining alcohol intake or alcohol abuse in participants.[38] Jordan et al.[8] further strengthened the importance of validity of this measure by identifying past studies that had failed to include valid screening tools for alcohol use. Considering the five inclusion studies of this systematic review, four of five had reported the use of validated measures for assessing alcohol use in their participant groups.[6-9]

Three of five inclusion articles (Hume et al., 2016; Mathias et al., 2014; and Gardner et al., 2017) used the Alcohol Use Disorders Identification Test (AUDIT) a validated and published tool developed in 1989. The AUDIT screens for alcohol intake, the potential of alcohol dependency, and the level of alcohol-related harm experienced.[71] The AUDIT screening tool was developed by the World Health Organisation.[72] The AUDIT has been validated by numerous authors, in different countries since its development and has been regarded as the 'gold standard' tool for assessing alcohol use behaviours.[72-75]

Bieniek et al.[5] had assessed alcohol history retrospectively through a medical record query of the Rochester Epidemiology Project (REP). The latter method could have implications in that alcohol use history was determined based on the full lifetime of participants, and the validity of this clinical information (i.e., what tool was used to assess alcohol use disorder) is not immediately known. Kremers et al.[76] described that history of alcohol use was extracted through the medical record of patients for the REP.

Jordan et al.[8] used the CAGE alcohol tool to assess current and past alcohol use and dependency in their participant group. The CAGE tool is an acronym for 1) Have you ever felt you should *cut* down on your drinking?, 2) Have people *annoyed* you by criticising your drinking?, 3) Have you ever felt bad or *guilty* about your drinking?, and 4) Have you ever had a drink first things in the morning to steady your nerves or to get rid of a hangover (i.e., an '*eye-opener*')?[8] (p. 206). The CAGE tool has demonstrated high validity and test-retest reliability in past studies.[77] However, a limitation of the CAGE is that it is less suitable for individuals with low alcohol intake or a moderate form of 'problem drinking'.[77, 78] This is pertinent in analysing alcohol data for Jordan et al.'s[8] study as participants who were 'heavy' drinkers who had less impact on their interpersonal relationships and mental/emotional health (such as feeling guilty because of drinking) reported a less valid response to the tool. Individuals who never drank alcohol for example, as compared to a person with moderate levels of weekly alcohol use may, therefore, be difficult to differentiate using the CAGE tool. A study by McCusker et al.[79] examined differences in the administration of the AUDIT and CAGE screening tools. The authors found through comparison of the two tools

that the CAGE was most effective in determining lifetime prevalence of alcohol use disorder, and the AUDIT was advantageous in identifying 'hazardous' drinkers who have not reached a severe level of harm by their alcohol use.[79] Bradley et al.[80] conversely held a stronger view in the comparison of the tools, having described that the AUDIT was superior to the CAGE in identifying patients with heavy drinking behaviours and alcohol dependence.

In thinking about assessing the long-term effects of alcohol use for athletes for cognitive functioning and brain health, there are further considerations with the use of tools such as the AUDIT and the CAGE for participants. The CAGE and AUDIT tools have presented with possible limitations as identified by numerous authors. Steinbauer et al.[81] reported that the CAGE tool presented inconsistencies when administered to a male and female participant group of different ethnic backgrounds, suggesting that the tool may be affected by ethnicity and sex bias. The authors reported that the AUDIT tool was not affected by the same biases in their participant group.[81] Additionally, although the AUDIT and CAGE can illustrate present and past issues through self-reporting of participants, they evidently cannot screen for lifetime use with young participant groups such as in Jordan et al.'s (1996) study with a mean age of 24.9. A further potential limitation to consider with tools such as the AUDIT include reluctance to self-report honestly due to social stigma with alcohol use disorder.[82]

In comparing the use of the AUDIT, CAGE, and medical record query methods of assessing alcohol use in participant groups, recommendations for valid use of these measures can be made. Current & past, standard weekly, received medical help from a professional, history of diagnosis, impacts on daily life and relationships, risk/experience of harm. Initially, this could mean ensuring that knowledge of what constitutes a 'standard drink' is shared between the interviewer and participant and is relevant or adapted for the country/location in which the test is taken. Structuring interview questions in a neutral way that does not influence answers or introduce bias into the response is also recommended. In accounting for limitations presented by the AUDIT and CAGE tools, enhancing the validity of the measure of alcohol use and dependency would mean accuracy in its application to individuals with any level of drinking history, past and current.

The discussion around CTE has raised popularity in recent years due to increased media coverage and literature surrounding its prevalence and impacts on athletes, largely in the United States of America.[29] McKee et al.[12] described the political and societal implications for the increased recognition of the impacts of sport mTBI and CTE. The authors discussed the great financial repercussions of accepting head trauma as the primary causal factor for CTE, with implications in major changes for sports play and its management.[12] As an example for recommendations based on research findings in this area, Brand and Finkel[61] described the implications of CTE as an accepted result of repeated head impact/mTBI in sport. This included improved protective equipment, changes in professional (American) football rules, tackling and blocking to reduce blows to the head.[61] If alcohol were proved to be a modifier for outcomes in the neuropathology of CTE, recommendations could also be made to reduce its potentially harmful impact. While this dissertation has clearly shown that there is no evidence supporting alcohol abuse as productive of tau pathology in athletes (current, retired or deceased), it may remain a

serious co-morbid condition that requires clinical intervention. Clear messaging in places where head impacts occur are recommended, in addition to the avoidance of alcohol in cases with suspected CTE.

Two notable researchers, and authors, in the field of sports concussion and chronic traumatic encephalopathy (CTE); Dr. Anne McKee and Dr. Chris Nowinski, were contacted toward the end of the dissertation to invite any advice or reflections on alcohol use with CTE. Anne McKee's research coordinator, Madeline Uretsky responded on her behalf. Madeline advised that although they had not yet completed analyses on the topic (of the impact of alcohol on CTE), it was in progress. It was recommended that reading and citing papers on alcohol use with dementia (including Wernicke Korsakoff syndrome) and understanding this literature would provide additional background for this research area.

Dr. Chris Nowinski acknowledged that there was no evidence currently of alcohol use as a modifier for CTE or neurodegenerative outcomes. However, Dr. Nowinski advised that although alcohol use disorder would, in theory, impact the ability to measure cognition, it hadn't yet been formally studied. He noted that alcohol use was included in questionnaires for studies for both living and deceased subjects, although had not yet revealed any meaningful findings. Dr. Nowinski also shared a study by Kovacs et al. (2015) on the impact of heroin abuse on the age-related deposition of hyperphosphorylated tau and p62-positive inclusions. Kovacs et al.'s (2015) paper raised opioids as a confound but established that tau pathology from opioids was dissimilar to that presented in CTE.

4.5 Measurements

Analysis of the five inclusion studies centered around four outcome measures. These were: (1) mTBI, concussion or repetitive head injury in sport; (2) Cognitive functioning; (3) Neurodegenerative outcomes; and (4) Alcohol use. How outcome measures were defined, reported, and interpreted, in addition to the overall findings across studies, were described. The cross-sectional studies had questionnaires for alcohol and concussion/TBI history, a range of cognitive testing measures, and medical imagining techniques including magnetic resonance imaging (MRI)[8] and magnetic resonance spectroscopy (MRS).[6 6, 8]

4.5.1 Concussion/TBI measures

Across the five studies, a range of measures were reported to determine the participants TBI history. Three studies utilised self-reporting measures with questionnaires to measure concussion or TBI history. Similarities between measures across the studies are raised, as well as reflections based on definitions of concussion and potential issues with self-reporting measures.

Gardner et al.'s[6] study, utilised magnetic resonance spectroscopy to examine neurodegenerative pathologies, in addition to utilising a clinical interview to report medical and concussion history. The Rivermead Post Concussion Symptoms Questionnaire[83] covers severity of symptoms pre- and post-injury, including physical symptoms of fatigue, dizziness, headache, nausea, and vision problems. The questionnaire also can identify

cognitive impairments such as forgetfulness and poor concentration. Psychological symptoms of feelings of irritability, depression and frustration are also included in the test.[83]

Hume et al.[7] determined past concussion history though a self-report general health questionnaire administered to participants. The questionnaire was developed specifically for the study. Questions included reporting the number of times participants had sustained a concussion during sport. The participants may have been evaluated by a doctor or other health professional for the concussion, had sustained symptoms or may not have reported a concussion.[7] A definition of concussion and its symptoms were provided for the participants. The strengths of this questionnaire were that it provided a clear time frame from pre- to post-injury. When compared with the study by Gardner et al.,[6] the use of the Rivermead Questionnaire covers symptoms 'now' compared to 'before the accident'. This is seen as a limitation to this study as there is an unclear time frame to when the injury occurred and the number of concussions/TBI sustained over one's career.[83] Hume et al.'s[7] questionnaire included the number of times participants had received, or not received, medical attention for a head injury and had lost consciousness from a head injury.

Similar to other studies[6, 7] included in this review, the study by Jordan et al.[8] utilised a participant survey to determine TBI history. The survey asked for the number of acute head injuries that resulted in post-concussion symptoms (dizziness, lightheadedness, forgetfulness) or loss of consciousness.[8] Through the description of the survey provided, the authors strengthen this measure through determining a more comprehensive view of concussion/TBI history. This included, for example, first age of head injury, number of head injuries reported, and not reported, or the severity of the reported head injuries. This may be particularly important as athletes, and other sportspeople, have shown non-reporting of concussion symptoms resulting in no medical attention for the head injuries sustained in sport.[84-86]

Fadnes et al.[87] described potential issues in self-reporting for epidemiological studies, including social desirability bias, selective recall, issues with question phrasing, and decreased accuracy over time in a 'recall period'. Question phrasing in surveys, and written questionnaires have the potential to alter the responses from participants.[87] Selective recall and issues with recall period may be particularly relevant when considering the reporting of head injury and TBI, and its impacts of cognitive functioning (including memory). The implications of memory recall issues may be further exacerbated by the effects of heavy alcohol use on cognition.[29] Additionally relevant is question phrasing in self-reported measures.[87] In determining participants' history of head injury sustained in sport, this could look like providing clear definitions of key terms, avoiding loaded questions, and considering possible bias through long recall periods or selected recall.

4.5.2 Cognitive functioning and psychological measures

Three cross-sectional studies[6, 7, 9] included in this review reported on cognitive functioning. These studies utilised a range of cognitive tests reporting on measures of working memory, processing speed, verbal fluency,

and fine motor functioning. The range of the cognitive tests utilised were similar across these studies, [6, 7, 9] and each study utilised previously piloted, published and validated tests.

Reporting on retired professional rugby league players, Gardner et al.[6] identified no meaningful differences between groups for cognitive functioning based on a composite score. This composite score was calculated using the mean of the scores for test measuring attention, processing speed, learning and memory, and fluid executive function. The most notable difference identified was the finding that retired players performed worse with fine-motor dexterity and speed using the non-dominant hand. This was discussed by the authors as possibly resulting from injuries sustained during the participants' sports careers.[6] This could be viewed as somewhat conflicting evidence of deficiencies, or decline, in cognitive functioning for athletes because of repeated mTBI in sport.[20] Although the importance of recording alcohol use in participants strengthen the relevance for the research area, a larger sample size may be needed. This would assist with the analysis of participants cognitive functioning to determine the impact of changes in fine motor functioning in this population. The findings of this study were like some of the included studies but conflicted with another study's[7] findings that demonstrated differences in cognitive impairment across participants.

Reporting on retired elite rugby union players, Hume et al.[7] assessed cognitive functioning utilising the CNS Vital Signs neuropsychological test battery. The findings demonstrated that the elite rugby group (103 players) had poorer performance on processing speed tests, complex attention, cognitive flexibility, and executive functioning.[7] The community rugby group (193 players) also had a poorer performance when compared with the non-contact sports group on tests of executive functioning and cognitive flexibility. Overall, the rugby player participants (who had a substantially higher rate of concussions sustained through sport than the non-contact sports group) showed impairments in cognitive functioning. The study[7] reported no meaningful correlation of the players' AUDIT scores and alcohol use in relation to these findings. As a result, alcohol use was not examined as a covariate in the analysis of the participants.[7] A strength of this study were the definitions given for cognitive measures (i.e., complex attention, executive function, cognitive flexibility), their functions and relevance for the participant population. Considering the research previously reported, Hume et al.'s[7] findings corroborate the evidence that points toward cognitive deficits because of repeated mTBI and the presentation of CTE.

The study by Mathias et al.[9] utilised verbal and visual memory, verbal fluency, abstract reasoning and problem solving in addition to psychosocial and emotional tests for depression and injury-related stress. The scores recorded for vocabulary, visual and verbal memory were average- to above-average for the three participant groups (physical assault TBI, sporting/athlete TBI, and orthopaedic control [OC] groups).[9] Performance of cognitive functioning throughout the three groups were generally good.[9] However, the TBI assault group had below average scores for the Logical Memory-Immediate test.[9] The TBI sport group had the lowest mean of the AUDIT scores in comparison to the TBI assault and OC group.[9] This demonstrated that alcohol use in the participant group did not show a meaningful correlation for cognitive functioning. The only test that did correlate with AUDIT scores was the immediate memory (Wechsler Memory Scale).[9] The finding that alcohol use did not

substantially affect outcomes was similar to Gardner et al.'s[6] study, although both had relatively small participant groups of sport participants at n=26 and n=16, respectively.

4.5.3 Medical imaging techniques

Two studies[6, 8] included in this review utilised medical imaging techniques to determine neuropathological and neurodegenerative outcomes. Both studies were heterogenous in their methodology and the findings are narratively synthesised to enable comparisons.

Reporting on 20 athletes (elite soccer players) and 20 age-matched track athletes, Jordan et al.'s[8] study investigated CTE clinicopathology to determine whether neurodegenerative outcomes occurred because of the repeated heading of the soccer ball. The authors utilised the CAGE alcohol use tool[88] to eliminate alcohol use as a confounding variable for outcomes. This was undertaken as it was reported that previous studies had methodologic problems with lack of valid screening for alcohol.[8] MRI changes were also described as being associated with alcohol use as a justification for this measure inclusion in the study.[8] The authors reported no statistical differences were identified for alcohol use between the soccer athlete group and track athlete control groups. No correlation was also found between measures of alcohol use and head injury symptoms or the MRI findings.[8]

The use of the CAGE alcohol use tool to score alcohol history in this study has been previously discussed (see 4.4 Alcohol use).As previously identified, there were no significant statistical differences identified between the study groups and the authors reported that the finding suggest that any evidence of encephalopathy was more related to acute head injuries playing soccer than from repetitive heading.[8] This was somewhat nuanced in the discussion, where Jordan et al.[8] (p. 209) raised the possibility that repeated heading of the ball may exacerbate the effects of acute head injuries. Of interest in this study was the finding (demonstrated in Table 3 of Jordan et al.'s 1996 study)[8] that three of the soccer players had cavum septum pellucidum. Cavum septum pellucidum is a commonly seen neuropathological characteristic of CTE. This is largely taken as strong evidence for the presence of CTE, as this pathology is rare in a normal, healthy population.[89] Participants in this study[8] were also young (soccer mean age 24.8 years old; track athletes mean age 26.4 years old) and were actively involved in sport. The authors acknowledged[8] that the possibility of delayed presentation of CTE clinicopathology could not be excluded due to this limitation. Of note the small sample size of the study possibly limits the generalizability of the findings to the larger population of athletes.

Although the study by Gardner et al.[6] had a similar sample size, the participants were older (38.3 ±4.6 yrs.[6] vs. 24.8 ±3.2 yrs.[8]). The study[6] enrolled 16 retired rugby players and included 16 age- and education-matched controls with no history of contact-sports participation and no history of TBI. The main findings of this study identified that although athletes had a significantly (p<0.01; Cohen's d=1.49) higher rate of alcohol use as demonstrated in their AUDIT scores, the control group showed significant correlations (r=0.52; p<0.05) between their AUDIT scores and the presence of neurometabolites.[6] This conflicted with the authors systematic review of

the literature where they reported no consistent findings on magnetic resonance spectroscopy (MRS) associated with the use of alcohol but modest evidence for reduced N-acetyl-aspartate (NAA) levels, reduced choline and increase of creatine as a result of 'chronic' alcohol use.[6]

The study[6] reported that it may be possible that alcohol use was associated with MRS outcomes in both groups. This may have conflicted with their findings for the athlete group. Neurometabolites have been demonstrated to show similar changes through MRS imaging to CTE pathology.[90] Alosco et al.[91] discussed that 'in vivo' presentation of CTE biomarkers could be identified through MRS measures. Limitations of this method surround the small sample sizes utilised in these studies and the inability to confirm the diagnosis of CTE.[90] It could be inferred through this study,[6] but similar to Jordan et al.'s[8] study, the limited sample size and age range limits generalizability of these findings. However, these studies provided a preliminary basis for further research to be conducted.

4.6 Limitations

Heterogeneity of the ways the variables were assessed between studies, and participant characteristics, meant the ability to make inter-study comparisons through statistical analysis was restricted. Data were consequently synthesized using a narrative approach. Limitations of this dissertation and its systematic review included potential issues with the search strategy and the lack of ability to make comparisons due to the heterogeneity of studies.

A limitation of this study may have been the restriction of search results or possibly restricting papers due to the search strategy. This could mean that relevant articles that used alternate terms which may have been useful for the review, or which met inclusion criteria were excluded. To mitigate this possibility, the keywords searched covered a broad range of search terms surrounding neurodegenerative outcomes, sports players, and cognitive functioning, as is described in section 2.6 Search strategy of the Methods. As there were only five articles that met inclusion criteria for the review the impact of excluding relevant studies may be significant, albeit all five articles generally showed no significant evidence of alcohol use as a modifier for outcomes. Further, potentially relevant articles published past the dates of the search strategy, and articles that were solely published in databases that this study did not include, would have been removed from consideration.

An additional limitation of this study is the restriction of the ability to make inter-study comparisons between the five articles, particularly with statistical data, due to the heterogeneity of outcome measures (i.e., how terms were defined, measured, and interpreted). This included three different forms of alcohol use measures (the AUDIT, CAGE and medical record query), different forms of concussion/TBI assessment across all studies, and some differing cognitive tests, although there were similarities across tests for this outcome measure. The restriction of inter-study comparisons may be due to the overall lack of research on the topic, particularly with the inclusion of alcohol use history in athlete participants and the linkage with this history with either cognitive or neurodegenerative outcomes in the same group. Through this dissertation, a gap in the literature surrounding its

research question has been highlighted. Having a higher number of articles that met inclusion criteria in this dissertation would enhance its ability to draw conclusions surrounding its research aim.

4.6 Recommendations

Recommendations for further research in this topic area and the political and societal implications for this research are discussed, in addition to correspondence with two leading authors/researchers in sports mTBI and CTE. The findings of this dissertation have contributed to the literature through its attempt to gather and synthesise the available evidence of alcohol use as a modifier for cognitive and neurodegenerative impacts on athletes with a history of TBI. Through the introduction and literature review it has become evident that:

- Heavy alcohol use is known to cause impairment in cognitive functioning for some individuals over time;[29]
- Alcohol misuse is a known contributor to both neurological and organic brain damage;[37, 38]
- In severe and rare cases, the impacts of alcohol use disorder can implicate in a condition similar to dementia, Wernicke Korsakoff syndrome;[39]
- There is a gap in the literature for studies that have empirically observed the impacts of alcohol use in the athlete population for their cognitive and neurological health.

The literature review of the five included studies has demonstrated that:

- Alcohol use has demonstrated to not be associated with impairment in different aspects of cognitive functioning for some athlete participant groups (Gardner et al., 2017;[6] Hume et al., 2016;[7] Mathias et al., 2014[9]);
- Alcohol use has not been seen to impact on MRI findings (Jordan et al.[8]);
- Alcohol abuse has been seen in higher frequencies in CTE cases (Bieniek et al.[5]).

The need to understand the risk factors and clinicopathological correlation of CTE is required and Schwab and Hazrati[25] have identified that prospective longitudinal studies were needed to understand this. As reported, due to the paucity of studies that met the inclusion criteria of this systematic review, and therefore only limited confidence that there is not currently any evidence that alcohol is a risk factor but there were limitations in the included studies that limit the ability to explore this fully. Therefore, further research is warranted to further explore if alcohol is a risk factor and clinicopathological correlation of CTE. In particular it is recommended that:

- A more standardised research approach be undertaken specifically looking at alcohol use and longitudinal changes post head injury; and
- An appropriate methodological approach be identified that accounts for all the limitations identified. Areas to be addressed should include:
    - Reliable and valid measure of alcohol use over time;
    - Larger sample sizes to enable moderate to strong correlations to be established;
    - Bias in participant groups (e.g., with autopsy studies); and
    - Accounting for additional external variables (other behavioural health modifying factors).

5.0 CONCLUSIONS

This systematic review aimed to identify and critique the literature to explore whether alcohol use was a modifier in the clinical presentation of neuropathology and cognitive functioning of athletes with a history of mTBI. The studies were rated as being of moderately good quality (75-80% met criteria with 'yes' responses) through the BMJ AXIS tool. The small sample sizes of participants, different alcohol assessment tools, concussion history assessment and various cognitive functioning and psychological measures utilised raised questions of the validity and reliability of the reported outcomes as well as the potential for generalizability to the larger population. Despite this, there was no conclusive evidence for the potential role of alcohol use as a modifier in long-term cognitive functioning, neurodegenerative outcomes, or the possible increased likelihood of the post-mortem diagnosis of CTE for athletes with a history of TBI. It is understood that, although it appears unlikely that heavy alcohol use produces a tau pathology that is CTE-like, alcohol may appear as a confounder for CTE for numerous reasons. People with a history of TBI may well use alcohol to self-medicate leaving individuals who have problems with alcohol misuse and play contact sports professionals at higher risk for further problems. Further, alcohol misuse is one of the strongest 'predictors' of TBI, potentially putting individuals at a risk of further head injury. Given the paucity of included studies that met the inclusion criteria, and therefore only limited confidence that there is no evidence of alcohol as a modifier, it is recommend a more standardised methodological approach to further research reporting on alcohol use and longitudinal changes post head injury is warranted.

6.0 REFERENCES

1. Holm L, David Cassidy J, Carroll L, et al. Summary of the WHO collaborating centre for neurotrauma task force on mild traumatic brain injury. *Journal of Rehabilitation Medicine* 2005; 37: 137-141.

2. American Psychological Association. Cognitive functioning. *American Psychological Association Dictionary of Psychology* 2020.

3. American Psychological Association. *American Psychological Association Dictionary of Psychology* 2020.

4. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (5th ed.)*. Arlington, VA. 2013.

5. Bieniek KF, Blessing MM, Heckman MG, et al. Association between contact sports participation and chronic traumatic encephalopathy: a retrospective cohort study. *Brain Pathology* 2020; 30: 63-74. Article. DOI: 10.1111/bpa.12757.

6. Gardner AJ, Iverson GL, Wojtowicz M, et al. MR Spectroscopy Findings in Retired Professional Rugby League Players. *International Journal of Sports Medicine* 2017; 38: 241-252. Article. DOI: 10.1055/s-0042-120843.

7. Hume P, Theadom A, Lewis G, 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 Medicine* 2017; 47: 1209-1220. DOI: 10.1007/s40279-016-0608-8.

8. Jordan SE, Green GA, Galanty HL, et al. Acute and chronic brain injury in United States National Team soccer players [corrected] [published erratum appears in AM J SPORTS MED 1996 Jul-Aug;24(4):563]. *American Journal of Sports Medicine* 1996; 24: 205-210. DOI: 10.1177/036354659602400216.

9. Mathias JL, Harman-Smith Y, Bowden SC, et al. Contribution of psychological trauma to outcomes after traumatic brain injury: assaults versus sporting injuries. *Journal of neurotrauma* 2014; 31: 658-669. DOI: 10.1089/neu.2013.3160.

10. Broglio SP, Eckner JT, Paulson HL, et al. Cognitive decline and aging: the role of concussive and subconcussive impacts. *Exercise and Sport Sciences Reviews* 2012; 40: 138.

11. Sanderson J, Weathers M, Snedaker K, et al. “I was able to still do my job on the field and keep playing”: An investigation of female and male athletes’ experiences with (not) reporting concussions. *Communication & Sport* 2017; 5: 267-287.

12. McKee AC, Daneshvar DH, Alvarez VE, et al. The neuropathology of sport. *Acta neuropathologica communications* 2014; 127: 29-51.

13. Cunningham J, Broglio S and Wilson F. Influence of playing rugby on long-term brain health following retirement: A systematic review and narrative synthesis. *BMJ Open Sport and Exercise Medicine* 2018; 4. Article. DOI: 10.1136/bmjsem-2018-000356.

14. McKee AC, Alosco ML and Huber BR. Repetitive head impacts and chronic traumatic encephalopathy. *Neurosurgery Clinics of North America* 2016; 27: 529-535.

15. Jordan BD. The clinical spectrum of sport-related traumatic brain injury. *Nature Reviews Neurology* 2013; 9: 222-230.

16. Collie A, McCrory P and Makdissi M. Does history of concussion affect current cognitive status? *British Journal of Sports Medicine* 2006; 40: 550-551. Article. DOI: 10.1136/bjsm.2005.019802.

17. Decq P, Gault N, Blandeau M, et al. Long-term consequences of recurrent sports concussion. *Acta neurochirurgica*, 2016; 158: 289-300.

18. Cunningham J, Broglio SP, O’Grady M, et al. History of sport-related concussion and long-term clinical cognitive health outcomes in retired athletes: A systematic review. *Journal of Athletic Training* 2020; 55: 132-158. Review. DOI: 10.4085/1062-6050-297-18.

19. Iverson GL and Gardner AJ. Risk of misdiagnosing chronic traumatic encephalopathy in men with depression. *The Journal of Neuropsychiatry and Clinical Neurosciences* 2020; 32: 139-146.

20. Martland HS. Punch drunk. *Journal of the American Medical Association* 1928; 91: 1103-1107.

21. Gurdjian ES and Voris HC. Report of ad hoc committee to study head injury nomenclature. *Neurosurgery* 1966; 12: 386-394.

22. Critchley M. Medical aspects of boxing, particularly from a neurological standpoint. *British Medical Journal* 1957; 1: 357.

23. Miller H. Mental Sequelæ of Head Injury: Mental After-Effects of Head Injury. *Section of Psychiatry* 1966; 59: 257-261.

24. Costanza A, Radomska M, Zenga F, et al. Severe suicidality in athletes with chronic traumatic encephalopathy: A case series and overview on putative ethiopathogenetic mechanisms. *International Journal of Environmental Research and Public Health* 2021; 18: 876.

25. Schwab N and Hazrati L. Assessing the limitations and biases in the current understanding of chronic traumatic encaphalopathy. *Journal of Alzheimer's Disease* 2018; 64: 1067-1076.

26. Symons GF, Clough M, Fielding J, et al. The Neurological Consequences of Engaging in Australian Collision Sports. *Journal of Neurotrauma* 2020; 37: 792-809. Article. DOI: 10.1089/neu.2019.6884.

27. McCrory P, Meeuwisse WH, Kutcher JS, et al. What is the evidence for chronic concussion-related changes in retired athletes: behavioural, pathological and clinical outcomes? *British Journal of Sports Medicine* 2013; 47: 327-330.

28. Riley DO, Robbins CA, Cantu RC, et al. Chronic traumatic encephalopathy: Contributions from the Boston university center for the study of traumatic encephalopathy. *Brain Injury* 2015; 29: 154-163. Review. DOI: 10.3109/02699052.2014.965215.

29. Asken BM, Sullan MJ, Snyder AR, et al. Factors Influencing Clinical Correlates of Chronic Traumatic Encephalopathy (CTE): a Review. *Neuropsychology Review* 2016; 26: 340-363. Review. DOI: 10.1007/s11065-016-9327-z.

30. Grashow RG, Roberts AL, Zafonte R, et al. Defining Exposures in Professional Football: Professional American-Style Football Players as an Occupational Cohort. *Orthopaedic Journal of Sports Medicine* 2019; 7. Review. DOI: 10.1177/2325967119829212.

31. Laker SR, Greiss C, Finnoff JT, et al. Football Participation and Chronic Traumatic Encephalopathy. *Pm&R* 2018; 10: 655-660. Editorial Material. DOI: 10.1016/j.pmrj.2018.05.001.

32. Rutherford A, Stephens R, Potter D, et al. Neuropsychological impairment as a consequence of football (soccer) play and football heading: preliminary analyses and report on university footballers. *Journal of Clinical and Experimental Neuropsychology* 2005; 27: 299-319.

33. Johnson J. Organic psychosyndromes due to boxing. *The British Journal of Psychiatry* 1969; 115: 45-53.

34. Nelson TF and Wechsler H. Alcohol and college athletes. *Medicine & Science in Sports & Exercise* 2001; 33: 43–47.

35. Jacotte-Simancas A, Fucich EA, Stielper ZF, et al. Traumatic brain injury and the misuse of alcohol, opioids, and cannabis. *International Review of Neurobiology* 2021; 157: 195-243.

36. Taylor B, Irving HM, Kanteres F, et al. The more you drink the harder you fall: a systematic review and meta-analysis of how acute alcohol consumption and injury or collision risk increase together. *Drug and Alcohol Dependence* 2010; 110: 108-116.

37. Brumback T, Cao D and King A. Effects of alcohol on psychomotor performance and perceived impairment in heavy binge social drinkers. *Drug and Alcohol Dependence* 2007; 91: 10-17.

38. Kirkendall DT and Garrett Jr WE. Heading in Soccer: Integral Skill or Grounds for Cognitive Dysfunction? *Journal of Athletic Training* 2001; 36: 328-333. Article.

39. Zubaran C, Fernandes JG and Rodnight R. Wernicke-Korsakoff syndrome. *Postgraduate Medical Journal* 1997; 73: 27-31.

40. Diekfuss JA, De Larwelle J and McFadden SH. Diagnosis makes a difference: Perceptions of older persons with dementia symptoms. *Experimental Aging Research* 2018; 44: 148-161. DOI: 10.1080/0361073X.2017.1422475.

41. Corsellis JAN, Bruton CJ and Freeman-Browne D. The aftermath of boxing. *Psychological Medicine* 1973; 3: 270-303.

42. Castellani RJ. Chronic traumatic encephalopathy: A paradigm in search of evidence? *Laboratory Investigation* 2015; 95: 576-584.

43. Nowak LA, Smith GG and Reyes PF. Dementia in a retired world boxing champion: case report and literature review. *Clinical Neuropathology* 2009; 28: 275-280.

44. Williams DJ and Tannenberg AE. Dementia pugilistica in an alcoholic achondroplastic dwarf. *Pathology* 1996; 28: 102-104.

45. Kitson R. Head collisions may not be the sole cause of dementia, World Rugby tells players. *The Guardian*, 17 November 2021.

46. Massie JB and Shumrick PL. Protecting the Head in Soccer. *Athletic Therapy Today* 2003; 8: 30-31.

47. Bird YN, Waller AE, Marshall SW, et al. The New Zealand Rugby injury and Performance Project: V. Epidemiology of a season of rugby injury. *British Journal of Sports Medicine* 1998; 32: 319-325.

48. Brown JC, Starling LT, Stokes K, et al. High concussion rate in student community rugby union players during the 2018 season: implications for future research directions. *Frontiers in Human Neuroscience* 2019; 13: 423.

49. NZ Herald. Rugby: Former All Black Carl Hayman diagnosed with early-onset dementia aged 41. *The New Zealand Herald*, November 3 2021.

50. McGlynn J, Boneau RD and Richardson BK. "It Might Also Be Good for Your Brain": Cognitive and Social Benefits That Motivate Parents to Permit Youth Tackle Football. *Journal of Sport and Social Issues* 2020; 44: 261-282. Article. DOI: 10.1177/0193723520903226.

51. Cunningham J, Broglio S and Wilson F. Influence of playing rugby on long-term brain health following retirement: a systematic review and narrative synthesis. *BMJ open sport & exercise medicine* 2018; 4: e000356. DOI: 10.1136/bmjsem-2018-000356.

52. Higgins JPT, López-López JA, Becker BJ, et al. Synthesising quantitative evidence in systematic reviews of complex health interventions. *BMJ Global Health* 2019. DOI: 4:e000858.

53. Mallett R, Hagen-Zanker J, Slater R, et al. The benefits and challenges of using systematic reviews in international development research. *Journal of Development Effectiveness* 2012; 4: 445-455.

54. Grant BM and Giddings LS. Making sense of methodologies: A paradigm framework for the novice researcher. *Contemporary Nurse* 2002; 13: 10-28.

55. Rahi S. Research design and methods: A systematic review of research paradigms, sampling issues and instruments development. *International Journal of Economics & Management Sciences* 2017; 6: 1-5.

56. Suri H. Ethical considerations of conducting systematic reviews in educational research. *Systematic Reviews in Educational Research* 2020: 41-54.

57. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *Journal Clinical Epidemiology* 2021; 134: 178-189.

58. BMJ. Appraisal tool for cross-sectional studies (AXIS). *British Medical Journal* 2016; https://www.google.com/search/q=bmj+axis&rlz=1C5CHFA_enNZ962NZ964&oq=BMJ+AXIS&aqs=chrome.0.69i59l3j69i60l3.1132j0j7&sourceid=chrome&ie=UTF-8#:~:text=Appraisal%20tool%20for%20Cross-Sectional,https%3A//assets.researchsquare.com%20%E2%80%BA%20files.

59. Downes MJ, Brennan ML and Williams HC. Development of a critical appraisal tool to assess the quality of cross-sectional studies (AXIS). *BMJ Open* 2016; 6:e011458. DOI: 10.1136/bmjopen-2016-011458.

60. Ma LL, Wang YY, Yang ZH, et al. Methodological quality (risk of bias) assessment tools for primary and secondary medical studies: what are they and which is better? *Military Medical Research* 2020; 7 29 Feb 2020.

61. Brand KP and Finkel AM. A decision-analytic approach to addressing the evidence about football and chronic traumatic encephalopathy. *Seminars in Neurology* 2019; Thieme Medical Publishers.

62. Bush K, Kivlahan DR, McDonell MB, et al. Ambulatory Care Quality Improvement Project (ACQUIP). The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. *Archives of Internal Medicine* 1998; 158: 1789-1795.

63. va de Schoot R and Miočević M. *Small sample size solutions: A guide for applied researchers and practitioners*. London: Routledge, 2020.

64. Bahr R and Holme IMK. Risk factors for sports injuries - A methodological approach. *British Journal of Sports Medicine* 2003; 37: 384-392.

65. Button KS, Loannidis JPA, Mokrysz C, et al. Power failure: Why small sample size underestimates the reliability of neuroscience. *Nature Reviews Neuroscience* 2013; 14: 365-376.

66. Amato PR and Zuo J. Rural poverty, urban poverty, and psychological well-being. *Sociological Quarterly* 1992; 33: 229–240.

67. Kaplan GA, Turrell G, Lynch JW, et al. Childhood socioeconomic position and cognitive function in adulthood. *International Journal of Epidemiology* 2001; 30: 256–263.

68. McKee AC, Stein TD, Nowinski CJ, et al. The spectrum of disease in chronic traumatic encephalopathy. *Brain* 2013; 136: 43-64.

69. Substance Abuse and Mental Health Services Administration [SAMHSA]. *Key substance use and mental health indicators in the United States: Results from the 2019 national survey on drug use and health*. 2020.

70. St. Sauver JL, Grossardt BR, Yawn BP, et al. Use of a medical records linkage system to enumerate a dynamic population over time: the Rochester epidemiology project. *American Journal of Epidemiology* 2011; 173: 1059-1068.

71. Saunders JB, Aasland OG, Babor TF, et al. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption II. *Addiction* 1993; 88: 791-804.

72. Verhoog S, Dopmeijer JM, de Jonge JM, et al. The use of the alcohol use disorders identification test–Consumption as an indicator of hazardous alcohol use among university students. *European Addiction Research*, 2020; 26: 1-9.

73. Alvarado ME, Garmendia ML, Acuña G, et al. Assessment of the Alcohol Use Disorders Identification Test (AUDIT) to detect problem drinkers. *Revista Medica de Chile* 2009; 137: 1463-1468.

74. Bohn MJ, Babor TF and Kranzler HR. The Alcohol Use Disorders Identification Test (AUDIT): Validation of a screening instrument for use in medical settings. *Journal of Studies on Alcohol* 1995; 56: 423-432.

75. Fleming MF, Barry KL and MacDonald R. The Alcohol Use Disorders Identification Test (AUDIT) in a college sample. *International Journal of the Addictions* 1991; 26: 1173-1185.

76. Kremers HM, Myasoedova E, Crowson CS, et al. The Rochester Epidemiology Project: exploiting the capabilities for population-based research in rheumatic diseases. *Rheumatology* 2011; 50: 6-15.

77. Dhalla S and Kopec JA. The CAGE questionnaire for alcohol misuse: a review of reliability and validity studies. *Clinical and Investigative Medicine* 2007: 33-41.

78. Castells MA and Furlanetto LM. Validity of the CAGE questionnaire for screening alcohol-dependent inpatients on hospital wards. *Brazilian Journal of Psychiatry* 2005; 27: 54-57.

79. McCusker MT, Basquille J, Khwaja M, et al. Hazardous and harmful drinking: a comparison of the AUDIT and CAGE screening questionnaires. *QJM* 2002; 95: 591-595.

80. Bradley KA, Bush KR, McDonell MB, et al. Screening for problem drinking. *Journal of General Internal Medicine,* 1998; 13: 379-388.

81. Steinbauer JR, Cantor SB, Holzer III CE, et al. Ethnic and sex bias in primary care screening tests for alcohol use disorders. *Annals of Internal Medicine* 1998; 129: 353-362.

82. Dasgupta A. *Alcohol and its biomarkers: clinical aspects and laboratory determination*. Elsevier, 2015.

83. King NS, Crawford S, Wenden FJ, et al. The Rivermead Post Concussion Symptoms Questionnaire: A measure of symptoms commonly experienced after head injury and its reliability. *Journal of Neurology* 1995; 242: 587-592.

84. Ferdinand Pennock K, McKenzie B, McClemont Steacy L, et al. Under-reporting of sport-related concussions by adolescent athletes: a systematic review. *International Review of Sport and Exercise Psychology* 2020: 1-27.

85. Greenwald RM, Chu JJ, Beckwith JG, et al. A proposed method to reduce underreporting of brain injury in sports. 2012.

86. Meier TB, Brummel BJ, Singh R, et al. The underreporting of self-reported symptoms following sports-related concussion. *Journal of Science and Medicine in Sport* 2015; 18: 507-511.

87. Fadnes LT, Taube A and Tylleskär T. How to identify information bias due to self-reporting in epidemiological research. *The Internet Journal of Epidemiology* 2009; 7: 28-38.

88. Buchsbaum DG, Buchanan RG, Centor RM, et al. Screening for alcohol abuse using CAGE scores and likelihood ratios. *Annals of Internal Medicine* 1991; 115: 774-777.

89. Koerte IK, Hufschmidt J, Muehlmann M, et al. Cavum Septi Pellucidi in Symptomatic Former Professional Football Players. *Journal of Neurotrauma* 2016; 33: 346-353. Article. DOI: 10.1089/neu.2015.3880.

90. Tharmaratnam T, Iskandar MA, Tabobondung TC, et al. Chronic traumatic encephalopathy in professional American football players: where are we now? *Frontiers in Neurology* 2018; 9: 445.

91. Alosco ML, Jarnagin J, Rowland B, et al. Magnetic resonance spectroscopy as a biomarker for chronic traumatic encephalopathy. *Seminars in neurology* 2017; 37: 503-509.

APPENDICES

Appendix A – Prospero registration

PROSPERO
International prospective register of systematic reviews

NHS National Institute for Health Research

UNIVERSITY of York
Centre for Reviews and Dissemination

Systematic review

1. * Review title.

Give the title of the review in English

Is alcohol use linked to increased likelihood of post-mortem diagnosis of Chronic Traumatic Encephalopathy and long term cognitive difficulties in athletes with a history of TBI; A systematic review of retrospective and prospective observational studies.

2. Original language title.

For reviews in languages other than English, give the title in the original language. This will be displayed with the English language title.

3. * Anticipated or actual start date.

Give the date the systematic review started or is expected to start.

20/05/2021

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

05/11/2021

5. * Stage of review at time of this submission.

Tick the boxes to show which review tasks have been started and which have been completed. Update this field each time any amendments are made to a published record.

Reviews that have started data extraction (at the time of initial submission) are not eligible for inclusion in PROSPERO. If there is later evidence that incorrect status and/or completion date has been supplied, the published PROSPERO record will be marked as retracted.

This field uses answers to initial screening questions. It cannot be edited until after registration.

The review has not yet started: Yes

Review stage	Started	Completed
Preliminary searches	No	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.

6. * Named contact.

The named contact is the guarantor for the accuracy of the information in the register record. This may be any member of the review team.

Prof Alice Theadom

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Prof Theadom

7. * Named contact email.

Give the electronic email address of the named contact.

alice.theadom@aut.ac.nz

8. Named contact address

Give the full institutional/organisational postal address for the named contact.

Ar238, AUT North Campus, Auckland University of Technology (AUT)

Private Bag 92006

Auckland 1142 , New Zealand

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

+64 (0)21 2460728

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

Auckland University of Technology

Organisation web address:

https://www.aut.ac.nz/

11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country now MUST be entered for each person, unless you are amending a published record.**

Ms Tara Munro. AUT
Professor Patria Hume. AUT
Professor Alice Theadom. AUT
Dr Stephen Caspar. Clarkson University
Dr Doug King. AUT
Dr James Webb. AUT

12. * Funding sources/sponsors.

Details of the individuals, organizations, groups, companies or other legal entities who have funded or sponsored the review.

NA

Grant number(s)

State the funder, grant or award number and the date of award

13. * Conflicts of interest.

List actual or perceived conflicts of interest (financial or academic).

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country must be completed for each person, unless you are amending a published record.**

15. * Review question.

State the review question(s) clearly and precisely. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS or similar where relevant.

Is alcohol use linked to increased likelihood of post-mortem diagnosis of Chronic Traumatic Encephalopathy and long term cognitive difficulties in athletes with a history of TBI; A systematic review of retrospective and prospective observational studies.

16. * Searches.

State the sources that will be searched (e.g. Medline). Give the search dates, and any restrictions (e.g. language or publication date). Do NOT enter the full search strategy (it may be provided as a link or attachment below.)

MEDLINE, EMBASE, PsycINFO, Web of Science. From 1970s' (first studies on alcohol & boxing) until 30/04/2021

Studies published in the English language and have full text article available.

Have a retrospective, prospective cohort, case studies or case series design

Included professional or sports athletes involved in at one competitive season in any sport

Include the outcome of a clinical diagnosis of Alzheimer, dementia, mild cognitive impairment or chronic traumatic encepahlapoathy

17. URL to search strategy.

Upload a file with your search strategy, or an example of a search strategy for a specific database, (including the keywords) in pdf or word format. In doing so you are consenting to the file being made publicly accessible. Or provide a URL or link to the strategy. Do NOT provide links to your search **results**.

NA

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied in your systematic review.

Alcohol and links to Chronic traumatic encephalopathy in athletes

19. * Participants/population.

Specify the participants or populations being studied in the review. The preferred format includes details of both inclusion and exclusion criteria.

Adults diagnosed with CTE or cognitive functioning disorder

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the interventions or the exposures to be reviewed. The preferred format includes details of both inclusion and exclusion criteria.

Use of alcohol over the lifetime, including high (problematic) use, and no alcohol consumption

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the intervention/exposure will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

Control population in studies' participant groups

22. * Types of study to be included.

Give details of the study designs (e.g. RCT) that are eligible for inclusion in the review. The preferred format

includes both inclusion and exclusion criteria. If there are no restrictions on the types of study, this should be stated.

Retrospective or prospective observational studies, case studies and case series looking at influence of alcohol

23. Context.

Give summary details of the setting or other relevant characteristics, which help define the inclusion or exclusion criteria.

Studies in the community from any country will be included.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

Diagnosis of cte, cte like symptoms

Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

Alzheimer, Dementia, mild cognitive impairment

Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

Titles and abstracts of potentially eligible articles will be reviewed against the inclusion/exclusion criteria by one reviewer. Those where eligibility is unclear will be retained and the full article obtained. A second reviewer will check 10% to determine level of agreement against the criteria. Full articles will be obtained and reviewer against the criteria independently by two authors. Any disagreement will be resolved through discussion with a third team member until a consensus is reached. All decisions will be recorded in excel.

27. * Risk of bias (quality) assessment.

State which characteristics of the studies will be assessed and/or any formal risk of bias/quality assessment tools that will be used.

Quality of assessment will be undertaken using the ROBINS I Risk of Bias for non-randomized (observational) studies. One reviewer will assess the quality of included studies which will be checked="checked" value="1" by a second reviewer. Any disagreements will be resolved by a third reviewer.

28. * Strategy for data synthesis.

Describe the methods you plan to use to synthesise data. This **must not be generic text** but should be **specific to your review** and describe how the proposed approach will be applied to your data. If meta-analysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and software package to be used.

Narrative synthesis

29. * Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

No subgroups will be included

30. * Type and method of review.

Select the type of review, review method and health area from the lists below.

Type of review

Cost effectiveness
No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis
No

Intervention
No

Living systematic review
No

Meta-analysis
No

Methodology
No

Narrative synthesis
Yes

Network meta-analysis
No

Pre-clinical
No

Prevention
No

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
Yes

Blood and immune system
No

Cancer
No

Cardiovascular
No

Care of the elderly
No

Child health
No

Complementary therapies
No

COVID-19
No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions
No

Musculoskeletal
No

Neurological
Yes

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health)
No

Rehabilitation
No

Respiratory disorders
No

Service delivery
No

Skin disorders
No

Social care
No

Surgery
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

There is not an English language summary

32. * Country.

Select the country in which the review is being carried out. For multi-national collaborations select all the countries involved.

New Zealand

33. Other registration details.

Name any other organisation where the systematic review title or protocol is registered (e.g. Campbell, or The Joanna Briggs Institute) together with any unique identification number assigned by them. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

NA

34. Reference and/or URL for published protocol.

If the protocol for this review is published provide details (authors, title and journal details, preferably in Vancouver format)

NA

Add web link to the published protocol.

Or, upload your published protocol here in pdf format. Note that the upload will be publicly accessible.

No I do not make this file publicly available until the review is complete

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Do you intend to publish the review on completion?

Yes

Give brief details of plans for communicating review findings.?

A summary will be available on the TBI Network website TBIN.aut.ac.nz

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords help PROSPERO users find your review (keywords do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Systematic review, alcohol, CTE, sport, dementia

37. Details of any existing review of the same topic by the same authors.

If you are registering an update of an existing review give details of the earlier versions and include a full bibliographic reference, if available.

NA

38. * Current review status.

Update review status when the review is completed and when it is published.New registrations must be ongoing so this field is not editable for initial submission.
Please provide anticipated publication date

Review_Completed_published

39. Any additional information.

Provide any other information relevant to the registration of this review.

None

40. Details of final report/publication(s) or preprints if available.

Leave empty until publication details are available OR you have a link to a preprint (NOTE: this field is not editable for initial submission). List authors, title and journal details preferably in Vancouver format.

NA

Give the link to the published review or preprint.

Appendix B – British Medical Journal Appraisal Tool for Cross-Sectional Studies (BMJ AXIS)

Appraisal of Cross-sectional Studies

	Question	Yes	No	Don't know/
Introduction				
1	Were the aims/objectives of the study clear?			
Methods				
2	Was the study design appropriate for the stated aim(s)?			
3	Was the sample size justified?			
4	Was the target/reference population clearly defined? (Is it clear who the research was about?)			
5	Was the sample frame taken from an appropriate population base so that it closely represented the target/reference population			
6	Was the selection process likely to select subjects/participants that were representative of the target/reference population			
7	Were measures undertaken to address and categorise non-responders?			
8	Were the risk factor and outcome variables measured appropriate to the aims of the study?			
9	Were the risk factor and outcome variables measured correctly using instruments/measurements that had been			
10	Is it clear what was used to determined statistical significance and/or precision estimates? (e.g., p-values, confidence			
11	Were the methods (including statistical methods) sufficiently described to enable them to be repeated?			
Results				
12	Were the basic data adequately described?			
13	Does the response rate raise concerns about non-response bias?			
14	If appropriate, was information about non-responders described?			
15	Were the results internally consistent?			
16	Were the results presented for all the analyses described in the methods?			
Discussion				
17	Were the authors' discussions and conclusions justified by the results?			
18	Were the limitations of the study discussed?			
Other				
19	Were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results?			
20	Was ethical approval or consent of participants attained?			