Concussion History Among Icelandic Female Athletes: Mental Health, Cognition and Possible Concussion Biomarkers

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Abstract

Concussion symptoms are complex. They are non-specific to a concussion, and there is no gold standard for diagnosis and evaluation. For most, symptoms will resolve in days or weeks following a concussion. However, symptoms can become more serious, lasting for months or even years, considerably affecting quality of life. Long-lasting concussion symptoms can include worse mental health and cognitive function, impaired sleep, and ocular and vestibular problems. Sports are a significant risk factor for concussions. Previous concussions, medical history and background, age and gender are also factors influencing the prevalence and the sequela of concussion and progression of symptoms. Despite being underrepresented in the concussion literature, many studies have found that women are more at risk of sustaining a concussion and have more severe symptoms.

All of the participants in this study were Icelandic female athletes, retired and still active. All had been playing at the highest level in their sport in Iceland. The aims of this Thesis were to 1) examine the usefulness of self-report of concussion history and test if different methods of obtaining self-report would affect the report given and the relationship with an outcome variable; 2) examine concussion history and symptoms among retired and still active female athletes and the relationship with mental health and cognitive abilities; 3) validate self-reported concussion history and symptoms by assessing phycological responses and physical markers in a virtual reality environment.

Self-reported history varied according to the method used to elicit concussion history. This change indicates a lack of concussion knowledge and that detailed questioning might be preferable when asking for a self-report of concussion history. This change and how groups were formed depending on concussion count affected the relationship with current symptoms. History of concussion was connected to poorer impulse control, more current post-concussion symptoms and more problems with sleep, as well as more anxiety and depression symptoms. Retired athletes with a concussion history tended to have a worse outcome. When evaluating concussion symptoms and responses in a virtual reality environment, biological signals showed discriminative powers when comparing those with and without a concussion history. This supports their use as possible

biomarkers for concussion. The Random forest algorithm predicted concussion history with over 90% accuracy.

Overall, the findings support the use of self-report while assessing concussion history and symptoms among female athletes with the appropriate framework. However, the limitations of self-report and how they can affect results are also recognised. In addition, results suggest that concussion history is connected to worse mental health and poorer impulse control. The findings also highlight the use of a multimodal approach to concussion assessment and support the use of several biological measures as possible biomarkers for concussion. Results also underline the importance of including technology from different fields in concussion assessment.

Útdráttur

Einkenni sem hafa verið kennd við heilahristing eru flókin, þau eru ekki sértæk fyrir heilahristing og það er engin ein algild leið til þess að greina og meta heilahristing. Flestir jafna sig á einkennum á nokkrum dögum eða vikum. Hins vegar, geta einkenni orðið mjög slæm, varað í nokkra mánuði eða ár og haft mikil áhrif á lífsgæði. Langtímaafleiðingar eftir heilahristing geta verið verri líðan og hugræn geta, verri svefn og vandi með augnhreyfingar og jafnvægi. Íþróttir eru einn þeirra áhættuþátta sem hefur mikið vægi þegar kemur að heilahristing, þó ekki fylgi öllum íþróttum jafn mikil áhætta. Fyrri heilahristingssaga, heilsa og bakgrunnur hafa jafnframt áhrif, en einnig aldur og kyn. Allt eru þetta þættir sem hafa áhrif á algengi og afleiðingar heilahristings. Þrátt fyrir að konur eru ekki eins mikið rannsakaðar og karlar gefa margar rannsóknir til kynna að konur séu í meiri hættu á því að fá heilahristing og glími við alvarlegri einkenni.

Allir þátttakendur í þessari rannsókn voru íslenskar íþróttakonur sem annað hvort voru enn að æfa og keppa í efstu deildum í sinni íþrótt, eða voru hættar. Markmið þessa verkefnis voru að 1) skoða gagnsemi þess að fá þátttakendur sjálfa til að greina frá heilahristingssögu sinni ásamt því að meta hvort mismunandi aðferðir við að fá fram heilahristingssögu hafi áhrif á það sem er uppgefið og tengsl við fylgibreytur; 2) skoða heilahristingssögu og einkenni meðal íþróttakvenna, sem eru hættar og þeirra sem eru enn virkar, og meta samband við líðan og hugræna getu; 3) staðfesta mat á eigin heilahristingssögu og einkennum með því að skoða svörun og líffræðileg merki sem safnað var í sýndarveruleika.

Mat á heilahristingssögu breyttist á milli aðstæðna og var háð því hvaða upplýsingar voru gefnar og hvernig þáttakandi var beðinn um að rifja upp. Þessi breyting bendir til þekkingarleysis á heilahristing og að nákvæmari spurningar um heilahristingssögu séu mikilvægur hluti af gagnasöfnun þegar nota á sjálfsmat. Þessi breyting og það hvernig hópar voru myndaðir út frá fjölda heilahristinga hafði áhrif þegar tengslin við fylgibreytu voru metin. Tengsl voru á milli heilahristingssögu og stýrifærni, núverandi heilahristingseinkenna, meiri svefnvanda, og kvíða-og þunglyndiseinkenna. Þeim íþróttakonum sem áttu sögu um heilahristing og voru hættar keppni gekk í mörgum

tilvikum verr en öðrum hópum. Merki frá nemum sem mældu líffræðilega svörun við áreiti í sýndarveruleika gáfu ennfremur til kynna að hægt var að greina á milli þeirra sem greindu frá sögu um heilahristing og þeirra sem ekki greindu frá heilahristingssögu. Niðurstöður stiðja því að hægt sé nota þessi merki sem viðmið við mat á heilahristingseinkennum. Með notkun Random forest reikniritsins var hægt að spá fyrir um heilahristingssögu með yfir 90% nákvæmni.

Þegar á heildina er litið gefa niðurstöður þessa verkefnis til kynna að hægt sé að styðjast við sjálfsmat á einkennum og heilahristingssögu. Þó er mikilvægt að vera meðvitaður um þær takmarkanir sem kunna að fylgja þessari aðferð og áhrifum á niðurstöður. Að auki benda niðurstöður til þess að tengsl séu á milli heilahristingssögu og verri andlegrar heilsu og að hluta til stýrifærni. Niðurstöður undirstrika einnig mikilvægi þessa að notast við fleiri en eina mælingu við mat á einkennum og mikilvægi þess að nýta aðferðir sem koma úr ólíkum áttum við mat á heilahristing. Með því opnast fleiri möguleikar á mögulegum greiningarviðmiðum fyrir heilahristing.

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List of Studies

This Thesis is based on the following original studies, which are referred to in the text by their Roman numerals (I-III)

I. Unnsteinsdottir Kristensen, I. S., Kristjansdottir, H., Sigurvinsdóttir, R., Sigurjonsdottir, H. A., Eggertsdottir Claessen, L. Ó., & Jónsdóttir, M. K. (n.d.). Methodology matters: Self-reported concussion assessed by recollecting specific events. Under review.

II. Unnsteinsdottir Kristensen, I. S., Jónsdóttir, M. K., Lund S. H., Sigurjonsdottir, H. A., Eggertsdottir Claessen, L. Ó., & Kristjansdottir, H. (n.d.). Concussion history, cognition and mental health among retired and still active female athletes. Under review.

III. Jacob, D.[1], Unnsteinsdottir Kristensen, I. [1], Aubonnet, R., Recenti, M., Donisi, L., Ricciardi, C., Svansson, H., Agnarsdóttir, S., Jónsdóttir, M. K., Kristjansdottir, H., Sigurjonsdottir, H. A., Cesarelli, M., Eggertsdottir Claessen, L. Ó., Hassan, M., Petersen, H., & Gargiulo, P. (2022). Towards defining biomarkers to evaluate concussion using virtual reality and a moving platform (BioVRSea). Nature Scientific Reports: https://doi.org/10.1038/s41598-022-12822-0

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Declaration of Contribution

The doctoral candidate, Ingunn S. Unnsteinsdóttir Kristensen (ISUK), wrote this doctoral Thesis under the guidance of María Kristín Jónsdóttir (MKJ), and Hafrún Kristjánsdóttir (HK), supervisors, and the Thesis committee, Helga Ágústa Sigurjónsdóttir (HÁS) and Sigrún Helga Lund (SHL). Further collaborators on the manuscripts were Lára Ósk Eggertsdóttir Claessen (LÓEK), Rannveig Sigurvinsdóttir (RS), Deborah Jacobs (DJ), Romain Aubonnet (RA), Marco Recenti (MR), Leandro Donisi (LD), Carlo Ricciardi (CR), Halldór Svansson (HS), Sólveig Agnarsdóttir (SA), Andrea Cesarelli (MC), Mahmoud Hassan (MH), Hannes Petersen (HP) and Paolo Gargiulo (PG). Grant applications were written by ISUK with guidance from MKJ. The contribution to each study was as follows:

I. ISUK was responsible for data analysis, interpreting results, and drafting the manuscript. MKJ and HK made several revisions and suggestions. RS made suggestions regarding data analysis. All co-authors (MKJ, HK, HÁS, RS, LÓEK) made critical revisions to the article for relevant scientific and intellectual content.

II. ISUK was responsible for data analysis interpreting results and drafting the manuscript. MKJ and HK made several revisions and suggestions. SHL made suggestions regarding data analysis. All co-authors (MKJ, HK, HÁS, SHL, LÓEK) made critical revisions to the article for relevant scientific and intellectual content

III. ISUK and DJ drafted the main manuscript text and contributed equally as the first authors. MKJ, HK, ISUK, PG, DJ and RA equally contributed to the design of the study. RA performed EEG analysis, prepared figures related to the EEG analysis and contributed text for the EEG results. ISUK performed SCAT5 analysis and prepared figures and tables related to the SCAT5 analysis. DJ performed EMG area analysis, HR analysis, prepared figures and tables related to EMG and HR analysis, and prepared supplementary information. LD performed spectral analysis of EMG data and contributed text relating to EMG parameters. AC performed CoP analysis and contributed text related to this. MR and CR performed machine learning analysis. MR prepared figures and tables related to machine learning and contributed text for the machine learning results and discussion. All co-authors (MKJ, HK, HÁS, LÓEK, RA, MR, LD, CR, HS, SA, MC, MH, HP, PG) took part in interpreting the results and made critical revisions to the article for relevant scientific and intellectual content.

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List of Abbreviations

ACTH = Adrenocorticotropin

ADA-B = Ada-Boosting

ADH = Antidiuretic Hormone

ADHD = Attention Deficit and Hyperactivity Disorder

AI = Artificial Intelligence

ANS = The Autonomic Nervous Systems

BCE = Before common era

BESS = The Balance Error Scoring System

BBT = The Buffalo Treadmill Test

BP = Balance problems

BPM = Beats per minute

CoP= Centre of Pressure

CT = Computer tomography

EEG = Electroencephalography

EMG = Electromyographic

EOG = Electrooculogram

FSH = Follicular-stimulating hormone

GAD-7 = General Anxiety Disorder Questionnaire 7

GH = Growth hormone

GPA = Grade point average

GB = Gradient boosting

HOC = History of concussions

HP = Hypopituitarism

HR = Heart rate

HRV = Heart rate variability

ImPACT = The Immediate Post-Concussion Assessment Cognition Test

IPV = Intimate parter violence

ISI = The Insomnia severity index

KD = The King Devick

LH = Luteinizing hormone

LOC = Loss of consciousness

ML = Machine learning

MLP = Multilayer perceptron

MRI = Magnetic resonance imaging

NOC = No history of concussions

PHQ-9 = The Patient Health Questionnaire 9

POST = The beginning of the VR acquisition of the Hands-off condition

PRE = The hands-off condition at the end of the experiment

PRL = Prolactin

PSC = Post concussive syndrome

PSS4 = The Perceived Stress Scale 4

PTM = Post-traumatic migraine

QOL = Quality of life

QOLS = The Quality of Life Scale

RF = Random Forest

SART = The Sustained Attention to Response Task

SARTes = Sart error score

SARTrt = Sart response time

SCAT = Sport Concussion Assessment Tool

SRC = Sport related concussion

SSVEP = Steady-state visual-evoked potential

SVM = Support Vector Machine

TBI = Traumatic brain injury

TI = Tibialis anterior

TMT = The Trail Making Test

TSH = Thyroid-stimulating hormone

VOMS = Vestibular/oculmotor motor screening

VOR = Vestibular-ocular reflex

VR = Virtual reality

WAIS = Wechsler Adult Intelligence Scale

WASI = Wechsler Abbreviated Scale of Intelligence Test

1 Introduction

Traumatic brain injury (TBI) is defined as a change in brain function or physiology because of an external force (Ponsford et al., 2013). A concussion is a form of traumatic brain injury graded as mild (mTBI) (McCrory, Meeuwisse, et al., 2017; Ponsford et al., 2013). The definition of concussion has been debated, and as of now, there is no gold standard in concussion diagnosis (Chancellor et al., 2019; McCrory, Meeuwisse, et al., 2017; Moody et al., 2019). Nevertheless, a panel of concussion specialists has reached a consensus on how to understand concussions in sports, what symptoms one should look for, and guidelines for managing recovery after concussive incidents (McCrory, Meeuwisse, et al., 2017). The possible long-term consequences of concussions can be severe, affecting quality of life to a great degree (King & Kirwilliam, 2011; Manley et al., 2017; H. J. McCrea et al., 2013; M. McCrea et al., 2013). Because of this, there has been a heightened focus on concussions and concussion symptoms over the past years.

Sports are among the biggest risk factors for concussions (H. J. McCrea et al., 2013; Noble & Hesdorffer, 2013), with some sports, such as football and ice hockey, carrying more risk than others (Chun et al., 2021; Clay et al., 2013). Therefore, and because of the high likelihood of underreporting (Dams-O'Connor et al., 2014; Pennock et al., 2020; Mooney et al., 2020), a common understanding is essential in the case of sport-related concussions.

For most, concussion symptoms resolve in a matter of days or weeks (Iverson et al., 2017). For those who develop more persistent symptoms, symptoms can include cognitive and mental health problems (Iverson et al., 2017; King & Kirwilliam, 2011; Manley et al., 2017). Vestibular and ocular problems can also follow a concussion, including problems with balance and postural control (Chen et al., 2014; Kontos et al., 2017; Mucha et al., 2018).

The role of sex and gender in concussion studies is still in their infancy and should be considered to a greater extent moving forward (Mollayeva, El-Khechen-Richandi, et al., 2018). When it comes to sex and gender differences, some studies show mixed results, showing men being more at risk than women (Black et al., 2017; Kontos, Eagle, et al., 2020; Mollayeva, El-Khechen-Richandi, et al., 2018). However, most studies, at least those focusing on sports-related concussions, show that women are more at risk and perform worse on neuropsychological tests, have greater overall symptoms, and take longer to recover (Clay et al., 2013; Covassin et al., 2018; Daneshvar et al., 2011; Dave et al., 2020; Iverson et al., 2017; N. S. King, 2014; Koerte et al., 2020; McGroarty et al., 2020; Merritt et al., 2019; Mooney et al., 2020). Studies that do not show gender or sex-related differences have been criticized for their methodology (Koerte et al., 2020). For instance, many studies that do not show sex-related differences have used subjective assessment tools and have not included more than one method of evaluating symptoms (Koerte et al., 2020). The reasons behind gender- or sex-related differences could be several, from biological to social differences, and are not fully understood (Koerte et al., 2020; Mollayeva, El-Khechen-Richandi, et al., 2018). Because of the serious implication for women, the underrepresentation of women in concussion studies is a problem and can even be harmful (Colantonio, 2016), possibly affecting successful rehabilitation after a concussion and prevention strategies.

Because of the complexity of concussion symptoms and the multitude of factors that increase the risk of complicated recovery (DeRight, 2022; Gunn et al., 2019; Iverson, 2005; Iverson et al., 2017; King & Kirwilliam, 2011; Manley et al., 2017; McInnes et al., 2017), a multi-modal approach has been recommended when evaluating and treating concussions (Broglio & Puetz, 2008; Collins et al., 2016; Register-Mihalik & Kay, 2017). The use of a multi-modal approach highlights the importance of evaluating symptoms arising from the many different systems that might be affected after a concussion (Register-Mihalik & Kay, 2017). Moreover, with fast-moving technological advances come new opportunities to assess and treat symptoms. It will become important to implement these advances in concussion research and clinical management (Snyder & Giza, 2019).

1.1 Concussions: A brief historical overview

A total of 1.853 results are obtained when the word concussion is typed in the PubMed search engine for 2000-2010. When looking at 2011-2021, this number goes up to 10.416 results. Despite the recent surge in interest, the topic of concussions is far from new. In their article, Masferrer et al. (2000) give a historical account of concussions and how knowledge has changed over the years. In the biblical story of David and Goliath, the giant loses the battle when he loses consciousness after a hit to the head. Skulls from indigenous pre-Columbian warring societies indicate that repetitive head injuries might have been common in that era. The first known medical writings about head injuries and possible concussions are from 2.000 before common era (BCE) and are found in the Corpus Hippocraticum, a collection of ancient Greek medical texts. The Corpus Hippocraticum mentions a condition of the brain caused by a blow, affecting the ability to see, hear and speak (Masferrer et al., 2000). The end of the first millennium marks the time when the term concussion was used in a modern context when the Persian physician Razes used the term to describe an abnormal physiological state of the brain (Sharp & Jenkins, 2015). At the end of the 10th century, concussions were first clearly described, and concussion definitions continued to change throughout the next hundreds of years (McCrory & Berkovic, 2001). In the 13th century, a distinction was made between two types of head injuries (Sharp & Jenkins, 2015). One referred to disruption of cerebral function because of shaking of the brain and the other to structural brain damage because of bruising. This distinction can be seen in a concussion definition from 1966, where concussions are defined by immediate and short-lived impairment of neural function (Sharp & Jenkins, 2015).

For years, experts have debated how to define concussions, and a definition that is uniformly and universally accepted by all has not been agreed upon (Chancellor et al., 2019). A good definition is a basis for a solid diagnosis and treatment. A shared understanding would also have minimized the confusion around concussions over the years (Sharp & Jenkins, 2015). The term concussion has been used throughout history to describe a clinical state resulting from a strain or stress with an absence of any neurological change in the brain (i.e., following symptoms) (McCrory & Berkovic, 2001). It has also been used to describe what brings about the clinical state, that is (i.e., structural or neurological damage or changes in the brain) (McCrory & Berkovic, 2001), the symptoms. This distinction often leads to confusion about what exactly is being referred to when discussing concussions (McCrory & Berkovic, 2001). In addition, the terms concussion and mTBI are sometimes used interchangeably, and it is not always clear how or if researchers distinguish between the terms (Anderson et al., 2006). Anderson et al. (2006) stated that the difference between the term concussion and mTBI is that while mTBI refers to changes due to the pathophysiological impact on the brain because of changes in brain structure or neuronal movement, the term concussion refers to the functional status that results from the trauma. Concussion symptoms, therefore, reflect a disturbance in function and not structure (Bergfeld et al, 2011). This distinction is similar to the one from the 13th century in that the concussion is seen as a disturbance in function (Sharp & Jenkins, 2015). Although this distinction has not always been clear, the view that the resulting symptoms define concussions is widely used today (Kazl & Torres, 2019).

1.2 Definition and immediate symptoms of concussion

Concussion definitions are guided by how concussions can be assessed, and it is possible they do not always reflect the complexity of what happens in the brain and the long-term effects (Slobounov et al., 2014). A common understanding of concussions is essential in regard to sport-related concussions (SRCs), as sports carry a high concussion risk (Noble & Hesdorffer, 2013). In addition, rehabilitation for athletes can be long and complicated (Khurana & Kaye, 2012; Marshall, 2012; McKeithan et al., 2019; Musumeci et al., 2019). Today there are some aspects of the concussion definition that researchers do agree on (Bergfeld et al., 2011; Daneshvar et al., 2011; McCrory, Meeuwisse, et al., 2017). The 2017 consensus statement on concussions in sports was built around an expert-based approach reflecting the current state of knowledge in the field (McCrory, Meeuwisse, et al., 2017). According to the statement, an SRC can be identified by several features:

- *SRC may be caused either by a direct blow to the head, face, neck or elsewhere on the body with an impulsive force transmitted to the head.*

- *SRC typically results in the rapid onset of short-lived impairment of neurological function that resolves spontaneously. However, in some cases, signs and symptoms evolve over a number of minutes to hours.*

- *SRC may result in neuropathological changes, but the acute clinical signs and symptoms largely reflect a functional disturbance rather than a structural injury and, as such, no abnormality is seen on standard structural neuroimaging studies.* (McCrory, Meeuwisse, et al., 2017, p. 839).

Symptoms following a concussive incident can be physical, cognitive and emotional (H. J. McCrea et al., 2013). They can include disorientation, amnesia, nausea, confusion, sleep/wake disturbance, visual disturbance, troubles with balance and gait, irritability, loss of consciousness, amnesia, confusion, slowed reaction time and headache, indicating a neurological dysfunction (King et al., 2014; McCrory, Meeuwisse, et al., 2017; Moser, 2007). In most cases, symptoms of concussion resolve after a week or two. Nonetheless, it is suggested that 10-20% will continue to have symptoms for a more extended period, with certain groups having a higher risk of prolonged symptoms than others (H. J. McCrea et al., 2013). It has been argued that 10-20% is not an accurate estimate due to research limitations, like non-representative samples and a too-broad definition of a concussion (Iverson, 2005). The variability in numbers between studies might also indicate a lack of knowledge about concussions or unwillingness to report them (McCrory, Feddermann-Demont, et al., 2017; Sharp & Jenkins, 2015).

Loss of consciousness (LOC) was traditionally a significant factor when diagnosing concussions, even serving as a grading scale for the seriousness of the traumatic brain injury (Ghajar, 2000). However, it is currently not a deciding factor and is not necessary for a diagnosis (Gardner, 2017; McCrory, Feddermann-Demont, et al., 2017). In fact, some studies have shown that less than 10% of those sustaining a concussion in sports experience LOC (Lovell et al., 1999). Some studies show as high as 20-30%, but this could depend on the sport, with ice hockey and rugby showing more LOC incidents than other sports (Gardner et al., 2015; Marshall et al., 2015; Peltonen et al., 2020).

The constant debate about defining a concussion is partly due to the non-specificity of concussion symptoms (McCrory, Meeuwisse, et al., 2017) and how difficult it is to confirm a concussion with valid measures. It can be challenging to determine whether symptoms are the direct results of the concussion or the results of other factors that follow the injury or even a preexisting condition. Because of the non-specificity of post-concussive symptoms, concussion-like symptoms can be seen in patients with no history of brain injury (Iverson, 2005). For instance, headaches, the most common concussion symptoms (Tator & Davis, 2014), are the most common reason for general neurological consultation and can be classified into multiple subgroups depending on their aetiology (Lipton et al., 2004). There is also a significant overlap in symptoms between those suffering after a concussion and those suffering from whiplash injuries (Gil & Decq, 2021). Concussion-like symptoms can also be found among those who are depressed, have anxiety disorders and sleep disorders, and suffer from non-neurological chronic illnesses. Thus, according to some researchers, concussions should be classified according to symptoms and severity as the term concussion on its own is confusing and vague and not comprehensive enough (Sharp & Jenkins, 2015).

There have been attempts to classify concussions depending on the symptoms that follow. In 2015, an expert panel aimed to describe the current landscape of concussion treatment and provide an agreement on how to treat concussions (Collins et al., 2016). The panel highlighted, among other things, that concussions should be characterized by symptom patterns and how symptoms persist (Collins et al., 2016). According to this, concussions could be classified into six clinical profiles, requiring different clinical approaches. The six types were 1) anxiety/mood profile, 2) vestibular profile, 3) ocular-motor profile, 4) cognitive/fatigue profile, 5) post-traumatic migraine profile, and 6) cervical profile (Collins et al., 2016; Sandel et al., 2017). Symptoms profiles have also been described by clusters (Johnson et al., 2011). These clusters are defined by different symptoms and include a physical/somatic cluster, cognitive, emotional and one defined by sleep-related difficulties (Johnson et al., 2011). It is important to acknowledge that despite using different profiles and approaches when treating concussions, one profile does not exclude another, and prominent symptoms characterized under one profile could relate to prominent symptoms in another profile. For instance, dizziness could be a part of both ocular and cognitive profiles (Kontos et al., 2019), and anxiety could be linked to symptoms included in most profiles. Kontos et al. (2019) recommend prioritizing clinical profiles when identifying more than one profile, which is common among athletes, into primary, secondary and tertiary. However, because of possible overlap between different profiles, prioritizing profiles is potentially very complicated (Kontos et al., 2019), further highlighting the complexity of concussion symptoms and diagnosis.

1.3 The leading risk factor for concussions: Sports.

The leading risk factor for concussion is sport participation (Noble & Hesdorffer, 2013). In North America, American football has been associated with the greatest number of traumatic brain injuries (Daneshvar et al., 2011). However, it also has the largest number of participants, and it is hard to distinguish between more severe head injuries and concussions (Daneshvar et al., 2011). Because of this, it is difficult to determine how common concussions are and compare incident rates between different sports. This is also true for combat sports, where there is limited data specific to concussions (Neidecker et al., 2019).

Concussions in the athletic community are an important topic. Sports introduce a heightened risk of multiple concussions, and recurrent concussions can lead to complicated recovery (Clay et al., 2013). Therefore, the need for more quality studies that include different types of sports, considering the impact of gender, sex and age, and social factors specific to athletes, is very high. With high-quality studies comes the opportunity to make appropriate return-to-play guidelines specific to different groups, beneficial for athletes, sports organisations, and teams.

1.3.1 Incidence, prevalence and sport-specific concussion risk

Over the last two decades, the general population has seen an upward trend in concussion diagnosis (Reid et al., 2020). In a study where 1.2% of the general population of Ontario was included, the average annual incidence of diagnosed concussions between 2008 and 2016 was 1153 per 100.000 residents (Langer et al., 2020). In an earlier nationwide Canadian study (Gordon et al., 2006), it was estimated that the annual prevalence of concussions in the preceding 12 months was 110 per 100.000 individuals. However, in this earlier study, only incidents when the concussion was listed as the most serious injury, enough to limit normal activities, were included. Nevertheless, more than 54% of all concussions in this earlier study were sport-related (Gordon et al., 2006).

A large percentage of the population participates in sports, and millions of SRCs are thought to happen every year (Mullally, 2017). Most sports seem to carry at least some risk of concussion. However, the risk varies between sports. For instance, soccer-related concussions are thought to represent a significant proportion of worldwide SRCs, with concussions accounting for between 4-22% of overall injuries (Mooney et al., 2020). Even so, the incidents rate in football is likely higher than in soccer, and it is even higher in hockey (Clay et al., 2013). Concussion prevalence for high school football players has been reported to be between 20-63% (Moser, 2007). Concussions among hockey players have been found to account for 6.3% of all injuries during practice and 10.3% of injuries during games (Daneshvar et al., 2011). Mechanism of injury could also be different between sports. Studies show that up to 70% of concussion incidents in soccer were due to collisions, and contact with another player while heading the ball rarely results in a concussion (Mooney et al., 2020). In volleyball, incidents related to player-to-player contact were less prevalent (20%), with 57.1% of concussion incidents related to ball contact (Meeuwisse et al., 2017). In basketball, most concussions happen because of rebounding and defence/loose ball, e.g. player-to-player contact (Zuckerman et al., 2016). Incidence also depends on the athlete’s professional status. Professional players seem to be more likely to have a higher injury rate than amateur players (Yeomans et al., 2018). This is perhaps because of a more intense way of playing and training at a professional level or even better physical shape (Yeomans et al., 2018). The athletes are faster and stronger, which might increase the force during a collision (Yeomans et al., 2018). The intense playing might also explain why more concussions happen during a game when more is at stake than during practice (Daneshvar et al., 2011).

There is no a priori reason to assume that characteristics of concussive incidents in the Icelandic athletic population are different from what has been seen in other countries. However, there is no information available on the incidence rate among Icelandic athletes. When Icelandic female athletes, retired and still active, were asked if they had at some point received a concussion after being provided with a concussion definition, 63% reported a concussion history (Kristjánsdóttir et al., 2020). When dived by sport, 68.3% of soccer players, 68.4% of handball players and 53.6% of basketball players reported a concussion history (Kristjánsdóttir et al., 2020). A prior study, including both women and men competitors in handball, football and basketball, showed that 40% of the athletes had a history of concussions (Hermannsson et al., 2014). Although in this study, the term concussion was not clearly defined, and the author states that many participants did not know how many injuries they had received (Hermannsson et al., 2014). Another Icelandic study focusing on overall injuries among boxers listed concussions as the second most common injury (29,2%) after spraining (Ragnarsdóttir, 2019). However, injuries were only accounted for if there was a complaint of a physical injury serious enough for the boxer to terminate training or competition or if they had to take a break for over 24 hours after the injury (Ragnarsdóttir, 2019). Additionally, a concussion definition was not included, and the trainer and the boxer had to determine if the injury was serious enough. Only three studies with a focus on head injury incidents

(Gísladóttir et al., 2014; Halldórsson, 2013; Jonsdottir et al., 2017) have been done in an Icelandic population where mTBIs were included. None of them focused primarily on concussions or athletes. Halldórsson (2013) assessed emergency unit visits following TBI in a paediatric and adolescent population (age 0-19). Results showed that 72.5% were also diagnosed with a mTBI. In Gísladóttir et al. (2014) the mean age was 26 years. The study included emergency unit visits because of head injuries. Results showed that 14% of visits were because of intracranial- and cranial nerve injuries. Of the 14%, 96% were also diagnosed with a concussion (Gísladóttir et al., 2014). Jonsdottir et al. (2017) also conducted an incidence study, including emergency unit visits because of bain injury. In the study, the mean age was 41. A total of 39% of patients were diagnosed with mTBI, with car accidents being the most common cause of the injury (Jonsdottir et al., 2017). Results could possibly indicate underreporting as the average age was high, and sports only accounted for 7.2% of overall TBI incidents (Jonsdottir et al., 2017). Studies on concussions, and in particular on SRC, are lacking in Iceland, possibly affecting overall policy decisions regarding at-risk groups and return-to-play guidance.

1.3.2 Why there is a heightened focus on SRCs

The rise in concussion incidence has been related to an increase in sport-related events (Zhang et al., 2016). More media coverage and more interest in the medical literature (Upshaw et al., 2012) are also likely to influence concussion reports. Nonetheless, the media's lack of consistency in reporting is thought to impact and limit the correct information transmitted to the public (Ahmed & Hall, 2017). This misinformation is likely to influence whether incidents are reported. Studies have shown that as many as 44-59% of athletes do not report concussion symptoms and might continue to play following a concussion (Mooney et al., 2020). Even though multiple studies have shown that over half of the athletes do not report concussions, the reason why is not always examined (Pennock et al., 2020) and is likely to be multi-faceted. Lack of knowledge, wanting to continue the game, and not letting the team down are among the barriers that have been described as influencing the report of concussions (Pennock et al., 2020).

The increased focus on SRCs in recent years is reflected in a PubMed search for the years 2000-2010 and 2011-2021. Results obtained when SRC is typed in the search window result in 340 and 2.955 hits, respectively. The heightened focus on concussions and on concussion management and return-to-play (RTP) protocols, i.e. guidelines to a safe return to physical (and mental) activity, is likely due to the possible long-term consequences and how common concussions are among athletes (Khurana & Kaye, 2012; Marshall, 2012; McKeithan et al., 2019; Musumeci et al., 2019).

Long-term effects of concussions among athletes have been shown across different studies, with recurrent concussions resulting in worse long-term outcomes, including depression and cognitive problems (Manley et al., 2017; Montenigro et al., 2017). One study (Tator & Davis, 2014) showed that the median duration for concussion symptoms among athletes was six months, with symptoms duration ranging from one year to 14 years (Tator & Davis, 2014). Football players with three or more concussions were three times more likely to be diagnosed with depression than players with no concussion history (Guskiewicz et al., 2007). Those with a history of one or two concussions were 1.5 times more likely than players without concussion history to be diagnosed with depression (Guskiewicz et al., 2007). However, in a systematic review by Mannes et al. (2019), some results suggest that mental health among retired athletes is no worse than that of the general population. Several health problems are common in the athletic community, including chronic pain, substance abuse, and sleep problems (Mannes et al., 2019), and it is possible that if preexisting, they could be affecting the outcome of concussion studies. Supporting this are the recent findings that physical health problems and emotional symptoms among older men in the general population were a stronger predictor of memory problems than concussion history (Patten and Iverson; 2021). Therefore more high-quality studies addressing this issue are critical.

1.4 Possible long-term consequences following a concussion

Concussions pose an important societal health concern because of how common they are and how severe symptoms can be in the long term. Because of this and the fact that concussion symptoms are not always evident straight away or to the untrained eye, concussions are sometimes referred to as a *silent epidemic* (Buck, 2011).

Despite symptoms having to be immediate for a concussion diagnosis, they can worsen the day after, and for some, they can last for a more extended period (Anderson et al., 2006; Stein et al., 2016). Several factors can affect recovery after a concussion, including age, gender and sex, and prior concussion history (Chancellor et al., 2019;

Iverson et al., 2017) and, in general, sports (Clay et al., 2013; Daneshvar et al., 2011; Moser et al., 2005; Mullally, 2017). Low pre-morbid psychological resilience, or difficulty adapting in the face of adversity, has also been linked to a longer recovery time (Ernst et al., 2020).

There are some who suggest that persisting problems and symptoms are because of expectancy or pre-existing disorders and argue that long-term symptoms after a concussion correlate with the severity of the injury (Iverson, 2005). In this regard, those with a history of attention deficit and hyperactivity disorder (ADHD) and learning difficulties seem to be more susceptible to having concussions (Gunn et al., 2019). However, ADHD does not seem to be linked to a longer recovery time (Cook et al., 2021; Iverson et al., 2017).

Results from studies regarding symptom resolution and recovery time are mixed, and more comparative studies are needed (Cook et al., 2020). Methodologies between studies also vary, which makes comparing different studies complex (Iverson et al., 2017). Even though results from studies vary, long-term consequences after a concussion can be very severe and long-lasting (Iverson et al., 2017), possibly resulting in later-life cognitive and mental health problems (Iverson et al., 2017; King & Kirwilliam, 2011; Manley et al., 2017). Moreover, for some, symptoms will be psychological, and for others, they will be more physical (King, 2003). When individuals report physical, cognitive, emotional and behavioural problems persisting for over one to three months, their collective symptoms are sometimes referred to as post-concussive syndrome (PCS) (DeRight, 2022; Ryan & Warden, 2003). However, PCS is highly controversial, dividing clinicians, methodologists, and healthcare experts (Iverson & Lange, 2011; Polinder et al., 2018). The controversy around PCS is mainly due to whether symptoms represent specific, cohesive and predictable symptoms (Iverson & Lange, 2011). The same symptoms can also be seen in healthy individuals and those with a history of whiplash injuries (Polinder et al., 2018). The symptoms could also be connected to other injuries or factors unrelated to mTBI (Iverson & Lange, 2011). For instance, chronic pain, headaches, depression, and anxiety could cause a report of PCS symptoms (Iverson & Lange, 2011). PCS is a controversial diagnosis, and if studies will continue to show little or no consensus when it comes to possible biomarkers or means of assessment (Begaz et al., 2006; Gumus et al., 2021; Khong et al., 2016; Mercier et al., 2018), PCS will remain controversial.

The complexity of concussion symptoms and their relationship to different factors affecting recovery complicates concussion assessment. Not only is it important to know how symptoms emerge and progress, but as important is the individuals' background and concussion history. Medical background and symptom history are important as they relate to whether symptoms could be the result of the concussive incident or not and if the individual is likely to develop long-term symptoms.

1.4.1 Mental health and cognitive function

Concussion history has been linked to sleep problems (Bramley et al., 2017; Jaffee et al., 2015), worse mental health (Gouttebarge et al., 2019; Hoge & Engel, 2008; Jónsdóttir et al., 2021; Knell et al., 2020; Kontos, Pan, et al., 2020; Stein et al., 2016), including depression, anxiety, substance abuse and behavioural problems (Finkbeiner et al., 2016), with depression being the most commonly studied mental health problem (Manley et al., 2017; Rice et al., 2018). Moreover, an anxiety/mood profile has been suggested as one of the subtypes of concussion (Kontos, et al., 2020; Sandel et al., 2017). A linear relationship has even been found between concussion incidents and depressive symptoms (Guskiewicz et al., 2007). In the systematic review by Rice (2018), which included 27 studies with retired and still active athletes, depression was the most commonly studied mental health symptom and found to be connected to concussion exposure. In a meta-analysis including ten cohort studies on participants with (n=713.706) and without a concussion (n=6.236.010), five cross-sectional studies (n=4.420 with concussion /n=11.125 without a concussion), and two case-control studies (n=446 with concussion /n=8.267 without a concussion), concussion history was connected to a higher risk of suicide attempt and suicidal thoughts (Fralick et al., 2018).

When post-concussion symptoms persist, they can become very severe. In one study in a non-athletic sample, concussive symptom score post-injury was found to be high even seven years post-injury (King & Kirwilliam, 2011). Symptoms assessed were cognitive problems, measured by eleven cognitive tests, anxiety, depression and post-injury unemployment (King & Kirwilliam, 2011). This study included only 24 participants, 50% of whom were women, but it is the first study to investigate individuals with long-term post-concussive symptoms systematically. The unemployment rate in King and

Kirwillian´s (2011) study went from 91.7% pre-concussion to 50.0% post-concussion. A more recent study looked at this issue in a larger group (N = 55.424) and also found concussion history to be connected to unemployment and income (Fallesen & Campos, 2020). In particular among those in the age range 30-39 and those with less than a high-school education. Those with less than a high school education and those between 30 and 39 in age had the most income decrease (Fallesen & Campos, 2020).

Although psychological factors have been connected to concussion history and prognosis after a concussion (Bloom et al., 2020), little focus has been on how these factors could affect RTP and rehabilitation (Bloom et al., 2020). More research is needed, but some guidelines have been suggested. This includes assessing psychological factors with multi-modal approaches, thus evaluating psychological readiness to return when doing RTP assessments (Bloom et al., 2020). More studies are also needed where mental health prior to concussion is evaluated in relation to recovery and how this risk factor is represented in the concussion population (Iverson et al., 2020). Because pre-existing mental health problems have been connected to worse outcomes after a concussion, including prolonged recovery time (Iverson et al., 2020), it could be essential to include them in multimodal assessments.

Poor sleep is common among athletes (Jaffee et al., 2015), and the number of concussions has been found to predict worse sleep among college athletes (Duffield et al., 2021). Athletes with a shorter sleep duration after a concussion have been found to report more severe symptoms (Hoffman et al., 2020). However, reduced sleep was not connected to prolonged symptom recovery, although an increase in symptom severity was evident up to 4 days after the concussion. Concussed athletes with less sleep showed a reduced processing speed, but it is difficult to determine if that was connected to the concussion or just worse sleep (Hoffman et al., 2020). It has been reported that up to 34% of concussed patients experience a disturbance in sleep (Bramley et al., 2017). In addition, a connection between mood and vestibular dysfunction and sleep problems following a concussion has been found (Brustman et al., 2020), highlighting how different types of concussion symptoms could interact and influence cognitive efficiency and everyday life.

Executive dysfunction and troubles with memory and concentration are possible later life problems related to concussion history (Haddanni & Efrati, 2016; Manley et al., 2017; Montenigro et al., 2017). Because of the possible long-term effects on cognitive function, neuropsychological testing is recommended after a concussion (Jennings et al., 2021; McAllister & McCrea, 2017). However, neuropsychological testing is not without their limitation, as discussed in chapter 6. Cognitive testing recommended after a concussion includes tests assessing memory, reaction time, attention and processing speed (Jennings et al., 2021; Johnson et al., 2011; Kontos et al., 2016; McInnes et al., 2017; Sicard et al., 2018). Late-life cognitive problems, like troubles with memory and concentration, are also risk factors for late-life cognitive impairment (Haddanni & Efrati, 2016; Manley et al., 2017; Montenigro et al., 2017). Repeated head trauma has even been connected to late-life neurodegenerative diseases, like an elevated risk for Alzheimer's disease (AD) (McAllister & McCrea, 2017). Over the years, many studies have focused on cognitive symptoms following a concussion. This is reflected in more studies using neuropsychological assessment (Comper et al., 2010).

Cognitive problems connected to concussion history include poorer performance in verbal memory, reaction times, and attention (Beaulieu et al., 2019; Cunningham et al., 2020) and less awareness of errors when completing attention-related tasks (McAvinue et al., 2005), Concussion history has even been linked to a decline in verbal memory, recall and attention among professional athletes up to ten years post-concussion (Zhang et al., 2019). Even 30 years after their last concussion, athletes with a history of concussion have been found to show more abnormalities in cognitive and motor function than athletes with no concussion history (De Beaumont et al., 2009). One study showed that the ability to perform well on a challenging cognitive test battery, evaluating executive function, was worse for those with a history of concussion (Sicard et al., 2018). Again here, as with other aspects of concussion, women may be more vulnerable, as they were found to perform worse than men (Sicard et al., 2018). Additionally, even after a single concussion, results show that many individuals continue to have measurable impairment in various cognitive domains, both children and adults (McInnes et al., 2017).

1.4.2 Vestibular and oculomotor dysfunction

Disruption of the vestibular and oculomotor systems is common following a concussion (Kontos et al., 2017). The vestibular system helps regulate postural stability and integrate vision and movement of the head. The oculomotor system helps stabilize the gaze and hold an image steady (Kontos et al., 2017). Disruption can result in stabilization and vision problems, and dizziness (Kontos et al., 2017; Strupp & Brandt, 2009). Vision problems following a concussion have been associated with neurocognitive impairment, e.g. worse verbal memory, reaction time and visual-motor speed (Pearce et al., 2015). Because of this, oculomotor and vestibular screening are recommended after a concussion (McCrory, Meeuwisse, et al., 2017). Results from one study, claiming to be the first to document prospective changes in vestibular and ocular symptoms in high school athletes pre- and post-SRC, showed impairment 1-7 days post-injury (Elbin et al., 2018). Impairment of the vestibular oculomotor reflex, which stabilizes gaze during head movement, and vestibular motor sensitivity (sensitivity to change in the movement of the head) was also documented 8-14 days post-injury (Elbin et al., 2018).

Impairment in both the vestibular and oculomotor systems has been connected to motion sickness (Fife & Kalra, 2015; Mucha et al., 2018; Sufrinko et al., 2019). Motion sickness could therefore affect concussion assessment and post-injury management (Elbin et al., 2019). Typical signs of motion sickness include eye strain, headache, nausea, dizziness, and general discomfort (Golding, 2016), all of which are symptoms that can occur after a concussion both immediately and in the long term (McCrory, Meeuwisse, et al., 2017). In the study by Sufrinko et al. (2019), all participants reported vestibular dysfunction 9-10 days after a concussion. Those who reported a history of motion sickness had more symptoms after a concussion and worse vestibular dysfunction than those with no concussion history. This connection between motion sickness and vestibular dysfunction after a concussion was only found 11-20 days after the concussion, not earlier, indicating a later onset of symptoms and a longer recovery time among those with a history of motion sickness (Sufrinko et al., 2019). Sufrinko's results support the idea that motion sensitivity could be a risk factor for prolonged symptoms after a concussion.

Postural control represents an interaction between the environment and a task and how the individual controls stability with his environment (Samuel et al., 2015). Postural control depends on inputs from the visual and vestibular systems and the somatosensory system (Samuel et al., 2015). Because these systems can be affected by a concussion, it is reasonable to suggest that there is a connection between impaired postural control and concussion, although more research is needed (Alkathiry et al., 2019; Buckley et al., 2016; Doherty et al., 2017; Purkayastha et al., 2019; Quatman-Yates et al., 2015). A connection between suggestibility to motion sickness and body sway, and cognitive performance has been seen in female boxers post-fight (Chen et al., 2014). This supports the possibility of using motion sickness, postural control and cognitive performance to track symptom resolution and recovery after a concussion (Mucha et al., 2018). As of now, there is no gold-standard method for doing balance assessment after a concussion. Although, few tests have shown to be consistent across different studies, mainly VOR, assessing vestibular-ocular reflex, and VOMS, assessing vestibular/oculomotor motor screening (Quintana et al., 2021). Furthermore, vestibular- and oculomotor screening has become more common after a concussion and is thought to have high importance (Quintana et al., 2021).

1.4.3 Additional long-term effects of concussion – Hormonal imbalance

The pituitary gland is responsible for producing and secreting multiple hormones that help the body function normally (Melmed, 2010). Dysfunction in the pituitary gland can result in hormonal changes, especially growth hormones and sex hormones, but other hormones may also be affected (Jónasdóttir, 2014). When the pituitary gland fails to produce hormones in adequate amounts, it is referred to as hypopituitarism (HP) (Aimaretti & Ghigo, 2005). HP can affect all hormonal axes of the pituitary, i.e. production of growth hormone (GH), thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicular-stimulating hormone (FSH), adrenocorticotropin (ACTH), prolactin (PRL), antidiuretic hormone (ADH)/vasopressin and oxytocin (Gounden & Jialal, 2019). HP due to injuries sustained after a concussion is referred to as secondary hypopituitarism (Aimaretti et al., 2005b; Aimaretti & Ghigo, 2005; Jónasdóttir, 2014; Kim, 2015; Li & Sirko, 2018; Molaie & Maguire, 2018). Even mild concussions can lead to HP (Jónasdóttir, 2014). Because of the nature of post-concussive symptoms, the connections between head trauma and pituitary deficits have been studied, supporting that post-concussive symptoms could, in some cases, be explained by pituitary disruption (Aimaretti & Ghigo, 2005; Gilis-Januszewska et al., 2020; Jónasdóttir, 2014; Li & Sirko, 2018; Molaie & Maguire, 2018). Furthermore, a total of 15-27%, or even higher, of patients that suffer from traumatic brain injury are thought to develop pituitary deficit (Schneider et al., 2007; Tanriverdi & Kelestimur, 2015).

HP due to head trauma has also been connected to mental distress and worse outcomes on neuropsychological tests, including vocabulary tests, speed tests, spatial learning tests, and reaction time tests (Popovic et al., 2005). Poor quality of life, abnormal body composition and body mass index, hypertension, fatigue, anorexia, sexual dysfunction, tiredness, and headaches are also among the symptoms linked to HP due to head trauma (Caputo et al., 2019). More and more evidence shows that dysfunction in the pituitary gland can result in post-concussive symptoms and can affect the quality of life a great deal (Molaie & Maguire, 2018). In line with this, there are reports of cases where hormonal replacement therapy improved concussion symptoms (Aimaretti & Ghigo, 2005; Masel, 2004). HP treatment could, therefore, in certain cases, help facilitate recovery after a concussion (Popovic et al., 2005). An HP diagnosis after head trauma is important as clinical experience suggests a worse outcome for untreated HP patients post-concussion (Caputo et al., 2019). Although males are more commonly studied, female athletes with a concussion history have also been shown to have a higher prevalence of HP than the general population (Aimaretti & Ghigo, 2005; Regal et al., 2001). Despite the seriousness of HP, it is most likely highly underdiagnosed (Kim, 2015; Tanriverdi & Kelestimur, 2015).

1.5 Women and concussions – Gender and sex considerations

Sex and gender studies on traumatic brain injury could be considered to be still in their infancy (Merritt et al., 2019). Furthermore, sex differences have not been consistently found across studies (Colantonio, 2022). In one study, female athletes with multiple concussions seemed to do better than males with multiple concussions on tasks measuring reaction time and motor processing speed (Covassin et al., 2010). Another study did not show a gender difference among athletes other than that women were more often concussed (Black et al., 2017). A recent study (Kontos et al., 2020) found that more boys than girls had concussions from a heading among youth football players. In spite of that, more girls sought medical treatment following the concussion. Even though results are mixed, most studies conclude that women are at a greater risk of sustaining a concussion than men, have more persistent symptoms and take longer to recover (Biegon, 2021; Clay et al., 2013; Covassin et al., 2018; Daneshvar et al., 2011; Iverson et al., 2017; King, 2014; Koerte et al., 2020; McGroarty et al., 2020; Mooney et al., 2020). In a pediatric population (age 5-18), with most concussions stemming from sports or recreation, boys were shown to be more likely to have improved symptoms the first week after an incident, and girls were more likely to show symptoms as stable or worsening (Rosenbaum et al., 2020). Girls also recovered slower than the boys, which could be seen in the persistence of symptoms in the following weeks (Rosenbaum et al., 2020). A longer recovery time among young female athletes was also highlighted in the study by Valera et al. (2021). This supports the gender differences seen in concussion studies among adults (Valera et al., 2021) and highlights the importance of appropriate treatment and concussion education early on. Valera et al. (2021) also address the need for more long-term follow-up data, a broader age range in studies, and the importance of including both males and females. Over a five-year period, one study showed that female athletes had an overall higher incidence rate of concussions than males (Covassin et al., 2016). The study included several sports, 903 female athletes and 779 males. In Sicard et al. (2018), medical staff diagnosed SRC in males and females (N=49/N=49) within 24 hours. They claim that they are the first to show that women perform worse on cognitive tasks than men, not only in acute phases of trauma but also in chronic phases (Sicard et al., 2018). The first study on the potential long-term consequences of SRC in women is from 2020 (Prien et al., 2020). The study assessed concussion history retrospectively with self-reports gathered through a semi-structured interview. Participants were all retired athletes with a history of either playing football or a non-contact sport. The main finding suggested that athletes from non-contact sports and athletes from football performed similarly on neurocognitive tests. This was the case for all tests except that former football players performed worse on verbal memory and verbal fluency tests (Prien et al., 2020).

There is reason to believe that the mechanism behind a concussion, the "why they occur", might be different between the sexes (Varriano et al., 2018), whether it is biological or social (Colantonio, 2016, 2022; Mollayeva et al., 2021; Mollayeva, Mollayeva, et al., 2018). Sex-related differences have been found not only in regard to individual biological and behavioural characteristics (e.g. medical disorders) and in regard to how the concussion happens (e.g. falls, sports injuries) but also in relation to the social and physical environment (e.g. where the individual lives or where the concussion took place) (Mollayeva et al., 2022). Several biological factors have been suggested in order to explain sex-related differences in concussion outcome (Colantonio, 2022). Results from one study showed that women were more likely than men to have more physical symptoms and cognitive impairment after a concussion (Hutchison et al., 2017). Supporting this is that women have been shown to be more likely to sustain neck injuries in conjunction with the concussion (Sutton et al., 2018). One meta-analysis found that female soccer players were more likely than males to get a concussion while heading, and female goalkeepers received more concussions than males (Dave et al., 2020), possibly supporting the idea that biological structure is linked to sex differences. Less neck stability, for instance, might make women more vulnerable to getting a concussion than men (Mollayeva, El-Khechen-Richandi, et al., 2018). Female athletes might also have a lower biomechanical threshold than males, making their biological structure, as a whole, more at risk for injuries (Mollayeva, El-Khechen-Richandi, et al., 2018). Females have also been found to have a higher prevalence of preexisting mental health conditions both pre-and post-injury (Colantonio, 2022). Hormonal changes affecting recovery can also be different between the sexes, as hormones affected after a concussion can be specific to women (Mollayeva, El-Khechen-Richandi, et al., 2018). Few studies have been done to assess the connection between sexual functioning and concussion history (Anto-Ocrah et al., 2020). Results suggest that women that have sustained a concussion report more sexual dysfunction than men (Anto-Ocrah et al., 2020). Mortality connected to post-concussion HP is also higher for women (Jasim et al., 2017).

It is important to not only include physiological factors when considering sex and gender differences. Behaviour guided by gender norms could also be an influence. "Doing gender", for example, a behaviour guided by gender norms can cause distress and expectations about self-care, affecting recovery after traumatic brain injury (Fabricius et al., 2020). In addition to the difference in coping strategies, gender-guided behaviour can also include an overall difference between the genders in risk-seeking behaviour and stress (Mollayeva, El-Khechen-Richandi, et al., 2018). It has also been suggested that women tend to report more symptoms at baseline (Brown et al., 2015), which might explain gender differences.

Despite the fact that women are thought to do worse after a concussion, male participants have been more prominent in concussion research. This can lead to an incomplete understanding of concussions in women, which can even be harmful

(Colantonio, 2016; Valera et al., 2021). This incomplete understanding is especially important to consider in regard to how it might affect proper guidance after a concussive incident. Clinical guidelines after a concussion, for instance, do not consider how sex and gender could influence symptoms and their progression (Colantonio, 2022). Moreover, there are no guidelines specific to older adults. This could have severe implications for women, especially as the highest concussion rate among older individuals is thought to be among older women (Colantonio, 2022). This incomplete understanding, noticeable in concussion guidelines, highlights the significance of sex- and gender-driven studies in concussion research.

Colantonio (2016) notes that it is important to use appropriate assessment tools when considering gender. For example, it is important not to assume that the construct is binary as it could give a skewed result and limit how the participant wants to answer (Colantonio, 2016). This could especially be important when assessing younger populations, as a growing number of adolescents are now using non-binary pronouns to describe their gender (Bower-Brown et al., 2021). Sports are, however, still binary, with females and males competing separately according to their sex at birth. Nevertheless, it is important not to limit the study when it comes to gender-specific roles, even if the targeted population is athletes, especially if one of the aims is to assess a gender difference and include non-binary participants.

In the review by Colantonio (2016), which is a result of the work of the Girls and Women with ABI Task Force of the American Congress of Rehabilitation Medicine (ARMC), Colantonio focuses on research in brain injury among women and the importance of advancing research focusing on sex (biological/physiological factors) as well as gender (social factors). Colantonio (2016) offers two strategies to be implemented to counter this lack of sex/gender considerations in concussion research. Number one, appropriate research, and professional training material that focuses on consideration of sex/gender, and number two, encouragement to peer-reviewed journals to adopt a requirement to report especially on gender and sex.

1.6 Concussion assessment and approaches

As previously stated, there is no exact universal way to define a concussion (Chancellor et al., 2019; Heinmiller & Gunton, 2016). Nor are there medical tests to administer or blood tests or imaging techniques available for routine clinical assessment or diagnosis. Thus, there is no concrete way to physically confirm a concussion, and no single method has been proven to be adequate to stand alone as a diagnostic tool (Dessy et al., 2017). The lack of proper diagnostic tools is partly because concussion symptoms are not visibly structural but rather functional (Anderson et al., 2006; McCrory & Berkovic, 2001; Register-Mihalik & Kay, 2017). Because there is no standard test to confirm a concussion, medical professionals must rely on clinical assessment. Those who treat concussed patients must be well informed and adequately trained, and symptoms should be approached with a multi-modal assessment (Register-Mihalik & Kay, 2017).

1.6.1 Concussion assessment: The initial assessment

Concussion assessment is complicated. This is partly due to the complexity of symptoms and the fact that symptoms are nonspecific (McCrory, Meeuwisse, et al., 2017), how they can manifest differently from one individual to another (Comper et al., 2012; Dessy et al., 2017; D. King et al., 2014) and how preexisting conditions will affect diagnosis (Iverson, 2005). Symptoms could therefore relate to other illnesses or characteristics.

Concussion assessment should be carried out following a potential concussion incident or soon after. However, some symptoms are not always visible straight away or to the physical eye. A cut to the head is visible, but concussion symptoms are not as apparent, and some are dependent on a subjective report from the concussed individual. Because there is no concussion diagnosis criterion available (Feddermann-Demont et al., 2017), a clinical assessment is necessary to confirm a possible concussion (Register-Mihalik & Kay, 2017). This assessment depends on knowing what happened during the incident, what symptoms emerged soon after, and if they were there before the incident.

When concussion assessment is done on-site, as often is the case with SRCs, an assessment of neurological changes and symptoms needs to be well structured and, in many cases, fast. Under some circumstances, the assessment is done by a non-medical professional. Sideline evaluations are usually brief and used to rule out a more severe injury but should not replace a more comprehensive evaluation (N. S. King, 2014). Moreover, this assessment is not a concussion diagnosis and should only be the first step toward a more comprehensive diagnosis with a multi-modal approach.

Concussion assessments are usually done by questionnaires built around the most recent and most agreed-on definition and concussion symptoms. Through the years, there have been many SRC symptom scales available. Some are more sensitive to the more severe injuries, and some focus more on symptoms that could reflect neurological damage (Johnston et al., 2001). Others are very sport-specific, and some focus on performance or mobility (Johnston et al., 2001). Today, several sideline evaluation tools are available to provide a quick assessment using methods to capture a range of post-concussive symptoms (Yue et al., 2020). The Sport Concussion Assessment Tool or the SCAT has been found very useful in determining the likelihood of concussions immediately after an injury. The SCAT, which is the current gold standard for sideline evaluation (Yue et al., 2020), is used as an on-site assessment tool and is on its fifth iteration ("Sport Concussion Assessment Tool - 5th Edition," 2017). The symptom checklist that is a part of the SCAT is useful following the injury and in tracking recovery (Gardner, 2017). This checklist assesses head and neck pain, vision and balance problems, memory and concentration problems, emotional problems, and sleep problems. It includes symptoms like disorientation, memory loss, nausea, visual disturbances, and headaches ("Sport Concussion Assessment Tool - 5th Edition," 2017). The Berlin Consensus Statement recognises the SCAT5 as a useful tool when making an initial evaluation (McCrory, Meeuwisse, et al., 2017), and it has been shown to have high reliability across various samples (Robinson, 2019) and adequate validity (Asken et al., 2020). However, the scale should not be used on its own as a concussion diagnostic tool (Robinson, 2019). In a review of current management and concussion diagnosis practices, Heinmeller and Gunton (2016) noted that there is a focus on straightforward and easily administered tests. In this respect, they mention the SCAT, the King Devik (KD), The Balance Error Scoring System (BESS), and the Immediate Post-concussion Assessment Cognition Test (ImPACT). All tests are easy to use. It is important to recognize that they all have their disadvantages, and no method can identify all concussion cases, mainly because concussion symptoms are complex and can appear differently between individuals (Heinmiller & Gunton, 2016). Vestibular assessment is also something that should be considered when making an initial assessment (Heinmiller & Gunton, 2016; Russell-Giller et al., 2018).

There are several individual factors that should guide concussion assessment and RTP guidelines. Neurocognitive factors are prominent among those (Lovell, 2009). Assessment of cognitive symptoms following a concussion is important as these symptoms are among those that could manifest and reflect more long-lasting functional changes (Goldberg & Madathil, 2015). Symptoms like memory and attention decline and altered processing speed are usually assessed by self-report and performance on cognitive tests (Goldberg & Madathil, 2015). Neuropsychological testing seems to be more sensitive to recovery than symptom reporting and has been found to be both reliable and valid when identifying concussed individuals (Johnson et al., 2011).

1.6.2 Methodological problems in concussion research

Methodology in concussion studies has been criticised because of flaws and inconsistencies, and many studies on the sequelae of concussion and multiple concussions are inconclusive (Bonke et al., 2021; Carroll et al., 2014; Comper et al., 2010; Yumul & McKinlay, 2016). Cancelliere et al. (2014) highlighted several limitations affecting the quality of concussion studies, making it more challenging to compare studies and draw conclusions about results. They mention the lack of high-quality studies and that methodological quality is highly variable in concussion studies. Examples are small sample sizes, unknown response rates, and variability in concussion definitions across studies (Cancelliere et al., 2014). Suppose an unclear definition is used. Participants might therefore not understand, or understand differently, what is meant by a concussion. Problems with definition could result in unclear or unreliable results because of misclassification and a lack of understanding of how concussion recurrence relates to symptoms.

When different studies are compared, variability in prevalence can be seen between studies (D. King et al., 2014; McCrory, Feddermann-Demont, et al., 2017). This could be due to inconsistent use of concussion definitions used for diagnosis (D. King et al., 2014; McCrory, Feddermann-Demont, et al., 2017). Lack of concussion knowledge among athletes could be another cause of variability in concussion studies. There has been a heightened focus on concussions in the public media over the past years. Yet, the correct information is not always being portrayed (Ahmed & Hall, 2017). Less than optimal concussion knowledge can be reflected in a concussion count change after participants are provided with a concussion definition (Kristjánsdóttir et al., 2020;

Robbins et al., 2014; Alosco et al., 2017; Unnsteinsdottir Kristensen et al., 2021). In Kristjánsdóttir et al. (2020), self-reporting of concussions among Icelandic female athletes increased from 39.8% to 63.0% after they were given a concussion definition. This change in concussion reports highlights the importance of providing participants in concussion studies with a definition and not assuming they have adequate knowledge when asked about concussion history. This change in self-report also highlights the importance of a reliable, objective concussion assessment tool that can be used across studies. Educating athletes may not be enough to increase the reliability of self-report. When assessing underreporting among athletes, Pennock et al. (2020) concluded that concussion education alone does not seem to improve reporting. Other factors like sports culture and attitude regarding concussions might affect reporting and should be considered in future studies (Pennock et al., 2020).

Medical records and self-reports are commonly used to obtain information about past concussions (Gardner, 2017). Medical records are, in many cases, thought of as a gold standard when it comes to concussion assessment in research settings (Broglio & Puetz, 2008). Nevertheless, by using only clinical records, a certain loss in accuracy is to be expected, even when studying high-risk populations, as many who suffer from a concussion do not seek medical assistance (Dams-O'Connor et al., 2014). Around 30% (McCrea et al., 2004; Meehan et al., 2013) and as high as 73% (Leahy et al., 2020) of athletes have reported undiagnosed concussions when asked. Additionally, medical records cannot be relied on as the gold standard unless all suspected concussion cases get evaluated by physicians. Therefore, it could be argued that self-report is a useful way to obtain information about past concussions (Dams-O'Connor et al., 2014; Kerr et al., 2012). Self-report is commonly used in health sciences and has been shown to be reliable, even in concussion studies (Kerr et al., 2012). Limitations of self-report include problems regarding how well the self-report captures the construct and whether participants understand what is being asked (Chan, 2009). Self-report also introduces problems regarding confirmation bias and memory, especially in retrospective studies, and if there is a lack of concussion knowledge. In the absence of another gold-standard method to assess concussions, self-report will likely be a part of concussion assessment in the research environment. A challenge for researchers is to design a framework that minimises possible recall and reporting biases.

Although neuropsychological testing is recommended after a concussion, it is not without its problems. Neuropsychological testing has been shown to lack sensitivity both when the reported concussion symptoms seem to be resolved (Randolph et al., 2005) and to lack sensitivity when predicting RTP (Darling et al., 2014). Traditional neuropsychological tests are also not designed to mimic real-world settings (Sbordone, 2001). How they reflect everyday dysfunctions is thus not clear. However, more novel approaches may hold promise (Teel et al., 2016). It is also important to consider symptoms like fatigue and anxiety that could influence the outcome of neuropsychological testing (Combs et al., 2019; Dorenkamp & Vik, 2018). Even when there is no overall difference between concussed and healthy groups, there is evidence that fatigue could cause subtle differences in scores (Bens et al., 2018). Social and cultural factors are also something that should be considered, possibly affecting the outcome of tests (Casaletto & Heaton, 2017). Although they are an important part of overall concussion surveillance, meaning both at baseline and after an injury, neuropsychological tests should always be used as a part of a more comprehensive battery (Comper et al., 2012).

In a review from 2010, in which the methodology of neuropsychologically focused concussion studies is addressed, several recommendations are given to future researchers in order to improve the quality of concussion studies (Comper et al., 2010). Recommendations are to include various sports and different levels, explore sex differences and describe demographic variables comprehensively. It is also recommended to use an agreed-upon definition and report on the percentage of participants that agreed to partake in the study. Inclusion of healthy controls and groups with orthopaedic or musculoskeletal injuries is also recommended to rule out that the symptoms are because of issues related to other factors than concussions. A proper description of test measures is important as well but is often lacking (Comper et al., 2010). Moreover, there is a significant need for a 'gold-standard' tool to be used in assessment across clinical settings and research (Moody et al., 2019), and, as has previously been stressed, a multi-modal evaluation is recommended (Broglio & Puetz, 2008).

1.6.3 A multi-modal approach

The current consensus is that concussion assessment should be done using multi-faceted assessment batteries to evaluate the various aspects of concussion symptoms (Collins et al., 2014; Johnston et al., 2017). This includes a clinical interview, assessment of concussion symptoms, mental health and cognitive factors, and motor and physiological assessment. A multi-modal approach allows evaluating the complex nature of concussion symptoms and how different types of symptoms are related to each other.

A battery of self-reports of symptoms, postural control, and neurocognitive functioning has been shown to be sensitive in concussion assessment in up to 89-96% of cases, measured as a deviation from a baseline (Broglio et al., 2007). A multi-modal evaluation was the most robust assessment in another study when predicting concussions among athletes, classifying 64.6% of the overall sample (Sherry et al., 2019). The multi-modal approach could also be important in showing different recovery times for different problems. One study, for example, assessed neurocognitive performance, post-concussion symptoms, and vestibular and ocular dysfunction (Henry et al., 2016). This multi-modal approach to symptoms resulted in a documented recovery time of 3-4 weeks after the concussion instead of the commonly reported one to two weeks. Neurocognitive problems took the longest to resolve entirely or up to 28 days after the incident (Henry et al., 2016).

1.6.4 Functional neuroimaging and other biological measures

For some patients, changes in brain function captured by neuroimaging contribute to symptoms prolonging (Biagianti et al., 2020). Nonetheless, it is unclear exactly how these changes relate to persistent post-concussive psychological/mood changes (Biagianti et al., 2020). By assessing biological signals come the opportunities to add to concussion batteries, already including neuropsychological testing and mental health assessment. There is evidence of neurological changes after a concussion and an increase in neurodegenerative diseases among those at risk for head trauma (Manley et al., 2017). Because of this, the use of functional and structural neuroimaging techniques could be helpful when studying the mechanics behind a concussion (Biagianti et al., 2020) and the connection to mental health and cognitive symptoms.

Different types of neuroimaging have been used in concussion studies for years. In a review from 2001, the authors mention different types of neuroimaging methods that have shown potential in concussion studies. They conclude that findings are inconsistent and unclear (Johnston et al., 2001). However, newer neuroimaging technics offer the opportunity to improve understanding of concussions and what underlying factors could relate to apparent symptoms (Honce et al., 2016). The use of structural neuroimaging, like computer tomography (CT) and structural magnetic resonance imaging (MRI), has not been found useful in terms of identifying possible causes of post-concussion symptoms. However, they are helpful in ruling out bleeding or swelling (Gardner, 2017). In his review, Gardner (2017) points out that the reliable use of structural neuroimaging in clinical settings is low because of the limitations of studies. Nevertheless, it is not possible to rule out their use in determining the physiological effect of concussions (Gardner, 2017). In recent years, more studies have focused on the role of neuroimaging (Chancellor et al., 2019). Results show promise as functional neuroimaging has been found useful when documenting abnormalities in the brain after a concussion (Chancellor et al., 2019).

Electroencephalography (EEG) records spontaneous rhythmic electrical activity in the brain (Shaw, 2002), potentially providing important information when studying concussion and its pathophysiology (Shaw, 2002). EEG can quickly capture neurophysiological changes and can be easily utilised in clinical settings (Conley et al., 2018; Ianof & Anghinah, 2017; Munia et al., 2017; Simmons & Kerasidis, 2020). EEG is also more easily manageable and relatively inexpensive compared to other brain imaging methods (Kam & Todd, 2015), making EEG affordable and more accessible for researchers and clinicians.

The probability of disturbance to brain function, reflected by an EEG outcome, has been connected to the severity of concussion symptoms in male athletes (Prichep et al., 2013). Furthermore, this disturbance may extend beyond the usual 7-10 day recovery time (Prichep et al., 2013), possibly indicating that subjective recovery, and thus assessment with self-report symptom scales, is not a reliable indicator of brain recovery. In a new study, the first known to assess steady-state visual-evoked potential (SSVEP) in concussed athletes, the SSVEP differentiated between athletes with a concussion history and those who did not report concussions (Fong et al., 2020). Another study found that deficits could be present months after the injury when EEG was paired with a postural task (Thompson et al., 2005). A change in EEG measures, more precisely a change on the P300 wave, has even been found 30 years after a concussion (De Beaumont et al., 2009). Concussion history has also been connected to a lower theta (Thompson et al.,

2005) and changes in alpha activity (Guay et al., 2018). In one study, the EEG outcome showed a disturbance (a reduced beta, theta and alpha activity during ImPACT testing and increased activity during a task set in virtual reality) compared to a non-concussed group. (Teel et al., 2014). In a review by Koohestani et al. (2019), the authors mention that a change in theta and delta waves has been connected to motion sickness, with different waves connected to motion-sickness-inducing circumstances in real-life settings. Motion sickness is connected to problems in vestibular and oculomotor systems (Fife & Kalra, 2015; Mucha et al., 2018; Sufrinko et al., 2019) that are common after a concussion, as previously discussed. EEG measurements show potential (Donati et al., 2003; Gardner, 2017; Ianof & Anghinah, 2017; Prichep et al., 2013; Shaw, 2002). Nevertheless, the methodology between studies varies, and EEG markers as guides for RTP remain to be defined (Conley et al., 2018; Poltavski et al., 2019).

Electromyographic (EMG) is not commonly used to assess the sequelae of a concussion (Mittenberg et al., 2001). However, EMG recordings have been suggested in RTP guidelines (Nguyen et al., 2013). EMG recordings give signals representing neuromuscular activity (Reaz et al., 2006), and EMG has been used to assess postural stability (Paillard & Noé, 2015). Given the connection between postural control and concussion (Guskiewicz, 2001), EMG signals could give important information about how, or if, neuromuscular activity in relation to postural control is affected in concussed athletes. This is supported by the finding that abnormalities in EMG recordings correlate with injury severity among concussed athletes (Nguyen et al., 2013).

Another biological measure that could be used as a part of a concussion assessment battery is heart rate (HR). Early exercise is thought to be important in concussion treatment and connected to recovery time (Leddy et al., 2016; Leddy et al., 2018; Thomas et al., 2015). HR, as a guide towards RTP, has been used in conjunction with the Buffalo treadmill test (BTT). The BBT has been shown to be useful in identifying exercise tolerance levels in concussed athletes and uses the HR as a threshold marker while assessing if the individual becomes symptomatic (Darling et al., 2014; Leddy et al., 2016; Leddy et al., 2018). In addition, a lower HR threshold when an individual becomes symptomatic, i.e., a greater level of exercise intolerance, relates to a longer recovery time (Leddy et al., 2018). The difference in HR threshold and resting HR has also been used to predict recovery time (Haider et al., 2019). Results showed that when the HR difference was less than 50 beats per minute, it predicted a prolonged recovery time in concussed individuals with 73% sensitivity and 78% specificity (Haider et al., 2019). Heart rate variability (HRV) has also been used in concussion studies with the aim of indexing autonomic nervous system (ANS) function in reaction to a concussion (Bishop et al., 2018). HRV is the measure of the heart rate fluctuation around the mean heart rate (Van Ravenswaaij-Arts et al., 1993). A systematic review from 2018 (Pertab et al., 2018) indicates that concussion history could be connected to ANS dysfunction, possibly explaining concussion symptoms. HRV during physical exertion has been shown to be affected weeks or months after a concussion (Abaji et al., 2016), supporting the use of HRV in RTP guidance. In the first know study to assess HRV in conjunction with psychological factors over multiple time points, results supported the use of HRV as a marker for recovery after a concussion (Hutchison et al., 2017). Despite an improvement in psychological measures, the HRV remained reduced across time points, indicating a change in the physiological state beyond self-reported symptoms (Hutchison et al., 2017). In a study published in 2021 (Memmini et al., 2021), the objective was to assess the effect of concussion history on HRV. Results suggested a decreased HRV in athletes with a history of concussions (Memmini et al., 2021). In addition, they took a longer time to return to baseline after exercise compared to athletes without a concussion history. Recovery to baseline was also connected to a history of repeated concussions (Memmini et al., 2021). In another study, HRV was connected to clinical symptoms and worse neurobehavioral function three to fifteen days following a concussion (Coffman et al., 2019).

Although these measures, EEG, EMG, HR and HRV, show promise, more research is needed on how they can be used and in conjunction with which other measures. Anxiety, for example, has been connected to troubles with balance (Adkin & Carpenter, 2018; Serrano-Checa et al., 2020) and troubles with postural control (e.g. body sway) when visual input is present (eyes open) (Ohno et al., 2004). Therefore it should not be surprising that the coexistence of psychiatric problems and dizziness has been connected to the persistence of concussion symptoms (Karlinska, 2017). Vision and vestibular problems have also been found to predict prolonged recovery after a concussion, with a history of motion sickness possibly being connected to vestibular dysfunction (Master et al., 2018). Thus an assessment of vestibular dysfunction is important as it could reveal common concussion symptoms like dizziness, nausea and visual impairment (Mucha et al., 2018). Although postural control dysfunction has been related to concussion history, resolution time could be affected by how it is measured, with some assessment tools being more sensitive than others (Broglio & Puetz, 2008; Buckley et al., 2016). Reduced brain activity, measured by an EEG, has been connected to post-traumatic migraine (PTM) in concussion patients (Kontos et al., 2016). This possibly reflects symptom severity or persistency as PTM has been connected to worse impairment and prolonged recovery (Kontos et al., 2016). With the inclusion of physical and psychological measures, the multi-modal approach gives the opportunity to assess how symptoms interact and allows for the development of symptom profiles that may lead to a better understanding of how various symptoms are interrelated.

1.6.5 Technical advances

With an increased interest in developing a gold standard to manage and diagnose concussion, research into possible biomarkers, biological, physiological or functional, has expanded (Snyder & Giza, 2019). Thus, there is now a focus on neuroimaging, electrophysiology, fluid specimens, genetics and behavioural signatures (McKeithan et al., 2019; Snyder & Giza, 2019). For example, a blood-based biomarker could be used to assess concussion severity (Yue et al., 2020), and balancing boards that can assess the centre of pressure during stance (Johnson et al., 2011) could be used to evaluate postural control. Although routine blood biomarkers for concussion diagnosis have not yet been established, technical advances on other fronts are moving fast and are rapidly being introduced (Snyder & Giza, 2019).

Virtual reality (VR) technology has advanced fast in the last few years. With the use of a head-mounted display or a cave automatic virtual environment, the individual is provided with a first-person view of scenes or places (Vince, 2004). VR gives an option to study patients or participants in a controlled and safe environment, possibly manipulating the environment and simultaneously assessing symptoms or evoking them. There are several examples where VR has been successful both as a concussion assessment tool and as a therapeutic tool, detecting vestibular problems and problems regarding postural control (Zanier et al., 2018). Although more research is needed, virtual reality, in conjunction with EEG (Slobounov, 2011; Slobounov et al., 2006) and EMG, show promise for concussion evaluation (Sawires et al., 2018). Slobounov et al.

(2011) proposed that balance and visual dysfunction following a concussion could be detected with the use of VR technology incorporated with EEG measures. In their study, athletes with no history of concussions were compared to athletes with a history of concussions. The athletes were asked to stand on a force plate during different manipulations and were introduced to a moving room through the VR. There was a difference in the ability to preserve postural stability between the groups. There was also a difference in theta waves represented by an increased activity among the non-concussed athletes at the end of the task. Interestingly, none of the concussed athletes could preserve balance in the moving room on day three post-injury, which the author connected to possible disintegration in the visual processing system (Sloubounov et al. 2011).

Machine learning (ML) is a method that uses artificial intelligence (AI) to analyse data by allowing a system to analyse the data and become more accurate at predicting outcomes (Etham, 2020). ML models have become popular because they are accurate and easy to use once trained (Wickramaratne et al., 2020). By using ML methods, concussion researchers could approach concussion symptom analysis differently while still focusing on a multi-modal approach. Using a brain and computer interface makes it possible to take several physical measures and assess how they interact with one another in a specific environment (Ramadan & Vasilakos, 2017), possibly a controlled VR environment. Wickramaratne et al. (2020) propose that ML models can be used in concussion assessment. In their study, a 92.86% classification accuracy was obtained when identifying concussed individuals with the use of EEG measures (Wickramaratne et al., 2020). They concluded that the model could be improved by adding more demographic factors and descriptions connected to concussion symptoms (Wickramaratne et al., 2020).

The use of new techniques in concussion research is exciting, and future studies must be open to multi-modal approaches and interdisciplinary collaboration between different scientific fields.

2 Aims

2.1 Overall aim

The overall aim of the project *Concussion among Icelandic athletes – A multi-component study* of which this Thesis is a part, is to evaluate concussion history among Icelandic female athletes and assess the relationship between concussion history and cognitive abilities, mental health, neural integrity, hormonal changes, and cervical function. An additional aim is to conduct a two-year incidence study among female and male athletes in football, handball and basketball. The project laid the foundations for this Thesis which aimed to assess concussion history among Icelandic female athletes, symptoms, and possible biomarkers. This Thesis consists of three papers, each with its specific aims.

2.2 Aim of Paper I

In Paper I, the aim was to assess the usefulness of self-report in concussion studies and how it could be made more useful and hopefully more reliable. This was done by examining whether different methods of assessing self-reported concussion history influenced concussion report and the statistical relationship with current concussion symptoms. The aim was to add to results from our previous study where participants were provided with a concussion definition (Kristjánsdóttir et al., 2020) and evaluate if reports changed when asking participants to describe specific incidents instead of only giving an estimate of the number of incidents. The first paper laid the ground for Papers II and III.

2.3 Aim of Paper II

In Paper II, the aim was to examine retrospective self-reported concussion and symptoms history, as reported in the semi-structured interview (Paper I), and the connection between concussion history and cognition, insomnia and mental health among active and retired female athletes.

2.4 Aim of Paper III

In Paper III, the aim was to use a multimodal approach to validate concussion history and self-reported symptoms and quantitatively evaluate physiological responses during postural control tasks associated with concussion symptoms. The purpose was to assess possible biomarkers for concussion by using virtual reality to assess postural control response to BioVRSea setup. In addition, ML techniques were used to improve concussion assessment.

3 Methods

An overview of methods used in each of the three manuscripts represented in this Tesis can be seen in Table 1. The table provides an overview of participants, measures, procedures, and statistical analysis for each of the papers. All participants were at the highest level in their sport, active and retired and participated in earlier stages of the *Concussion among Icelandic athletes – A multi-component study* project.

Table 1
Overview of Papers I, II and III

	Study I	Study II	Study III
Participants	Athletes with a history of concussion N=143, Age: M=28 (SD=7.3)	Athletes with a history of concussion, N=166, Age: M = 28.4 (SD=7.4) Athletes with no history of concussions, N=43, Age: M=29.6 (SD=7.8)	Athletes with a history of concussion, N=26, Age: M=30.5 (SD=6.9) Athletes with no history of concussions, N=28, Age: M=29.8 (SD=8.2)
Measures Main variables	Self-reported history of concussion Concussion count, indicated by a number by the athlete (Condition 1-3), Description of specific incidents and then counted (Condition 4) Current concussion symptoms	Current concussion symptoms Concussion symptoms after the first incident and the most severe one Attention related error Automatic processing and speed Visual search and	Current concussion symptoms Postural stability Neural integrity (EEG) Muscle activity (EMG) Heart rate

		speed cognitive flexibility, divided attention and working memory intellectual abilities and processing speed Sleep troubles Depressive symptoms Anxiety symptoms Stress Quality of life	
Procedure	Concussion count was assessed during an online questionnaire and in an in-person interview (2018-2019).	Participants participated in an in-person interview, where they also completed tests (2018-2019).	Participants answered a concussion symptoms questionnaire before entering a VR environment where biological signals were acquired (2020).
Data analysis	Repeated ANOVA Independent T-test One-way ANOVA	Fisher exact test Independent T-test Pearson correlation One-way ANOVA	Independent T-tests Pearson correlation Wilcoxon significance test ML (The Knime Analytics Platform analysis)

3.1 Participants

3.1.1 Paper I

All participants participated in the first stage of the *Concussion among Icelandic – A multi-component study* project by completing an online questionnaire. All participants reported a concussion history after being provided with a concussion definition in the online questionnaire reported in a prior study (Kristjánsdóttir et al., 2020). One hundred sixty-six participants participated in the interview, with 143 being included in the study. Those who reported having had a concussion between completing the online questionnaire and participating in the interview were excluded from the analysis. All participants were Icelandic female athletes, both currently training and competing or retired in football, handball, basketball, ice hockey, and martial arts. The mean age of all the athletes was 28 years (SD=7.3). A total of 42.0% reported that they had never gone to the emergency room because of a concussion.

Results from Paper I were used as a basis for assigning participants to appropriate groups (concussion group vs. non-concussion group) for both Paper II and for Paper III.

3.1.2 Paper II

Participants were all female athletes, including 166 with a history of concussions (HOC) and 43 with no history of concussions (NHOC). The athletes were both retired and still active (Table 2).

Table 2
Demographic Information for HOC and NHOC Groups

	Athletes with a history of concussion (HOC)	**Athletes with no history of concussion (NHOC)**	**Results from significance tests***
Age mean (SD)	28.3 (7.4)	29.9 (8.1)	*t* = -1.22
Retired % (n)	51.8 (86)	41.9 (25)	
Age mean (SD)	30.2 (7.9)	32.8 (7.9)	*t* = -1.42
Active % (n)	48.2 (80)	58.1 (18)	Fisher exact test, p = 0.50
Age mean (SD)	26.4 (6.2)	26.1 (6.6)	*t* = 0.23

* All comparisons resulted in nonsignificant results $p>0.05$.

3.1.3 Paper III

All of those that had participated in the online study (Kristjánsdóttir et al, 2020) were eligible to participate. Participants had the opportunity to contact the researchers if they wanted to partake in this part of the project. The final sample consisted of 26 (48.1%) athletes with a history of concussion (HOC) and 28 (51.9%) with no history of concussion (NHOC) (Table 3).

Table 3
Demographic Information for Those With a HOC and Those With NHOC

	Athletes with a history of concussion (HOC)	Athletes with no history of concussion (NHOC)
Age mean (SD)	30.5 (6.9)	29.8 (8.2)
Retired %(n)	68.0 (17)	59.3 (16)
Active %(n)	32.0 (8)	40.7 (11)

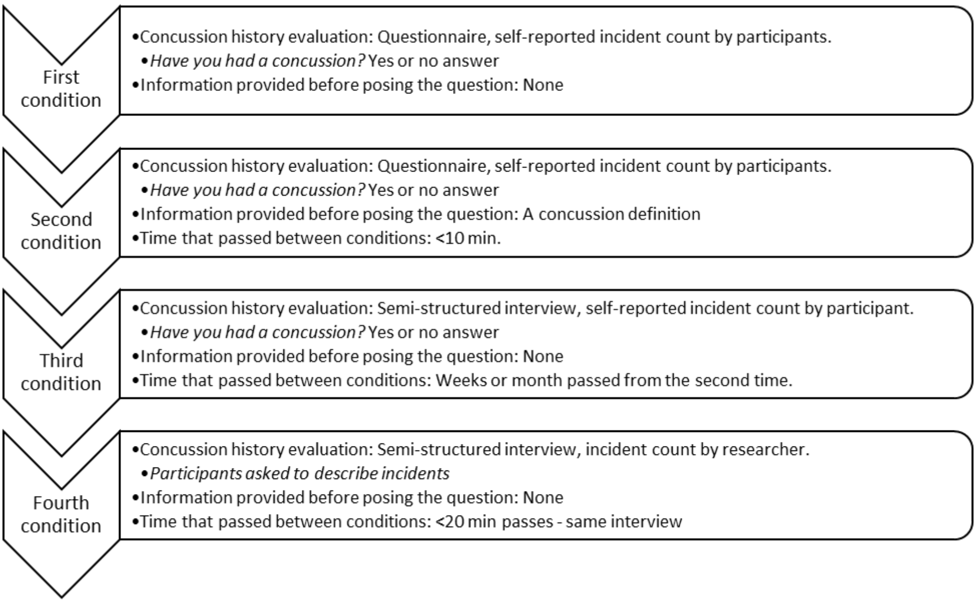
3.2 Procedure

3.2.1 Paper I

Participants answered questions about concussion history on two occasions, twice in the online study and twice in the semi-structured interview. A snowball sampling was used as the online questionnaire was distributed through sport-related social media pages. The online questionnaire was open from January 2018 until the end of April 2018. Participants that reported a concussion in the online study after having read a concussion definition (Kristjánsdóttir et al., 2020) were contacted by phone and invited to participate in the follow-up interview. The interview took about one and a half hours and included neuropsychological tests and questions about concussion history (reported in Paper II). During the interview, participants were also asked about current concussion symptoms. Interviewers had to follow a script and were trained by the study supervisors, including the author of this Thesis. Responses were recorded verbatim. The interviewing process took a year, from 2018 to 2019. The study design can be seen in Figure 1.

Figure 1

Study Design. Description of Conditions Where Participants Were Asked About Their Concussion History



3.2.2 Paper II

All participants that answered the online questionnaire in 2018 were eligible to participate in this study. Not all were in the final sample (See Figures 2 and 3). The interviewing procedure was the same as described in Paper I. In addition, participants answered questions about concussion history and mental health and completed neuropsychological tests. The interviewing process for those with a history of concussions took about a year (2018-2019). Those without a concussion history were interviewed in the summer of 2020.

Figure 2

A Flow Chart Representing the Inclusion-Exclusion Process for Those With a History of Concussion

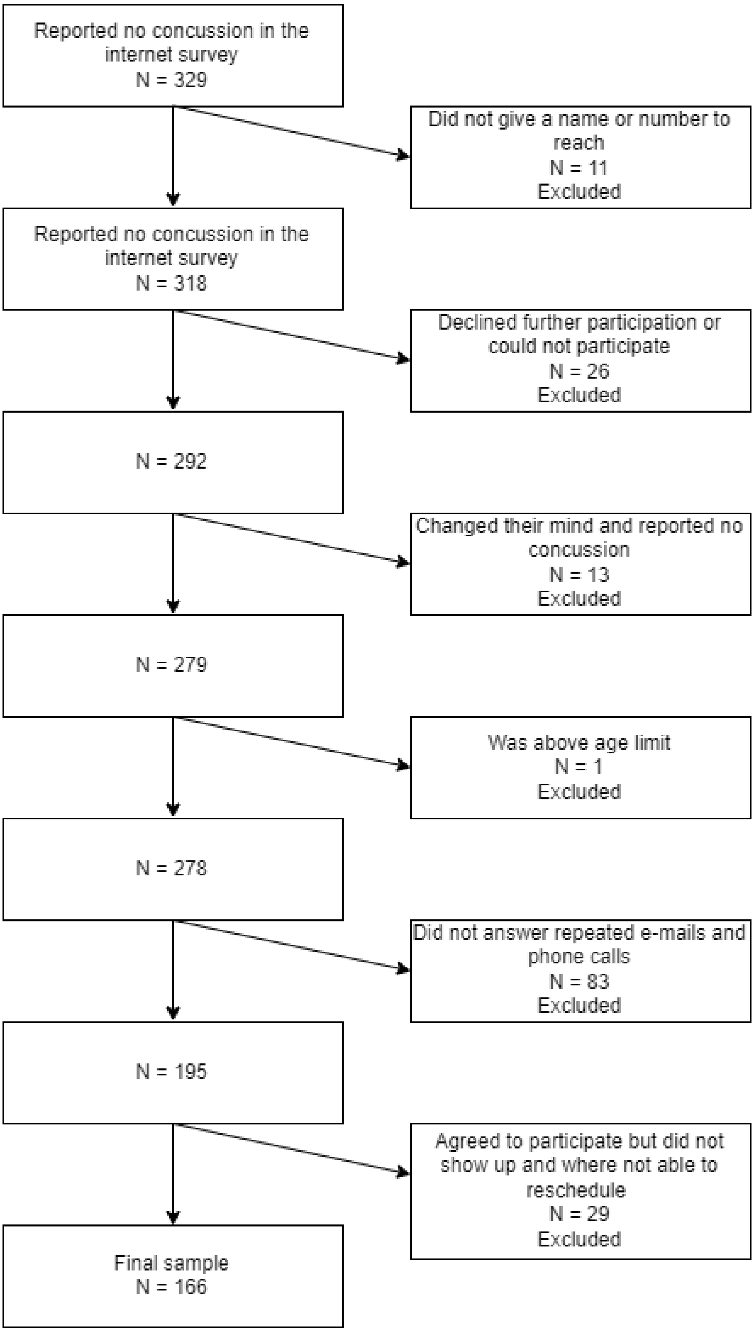
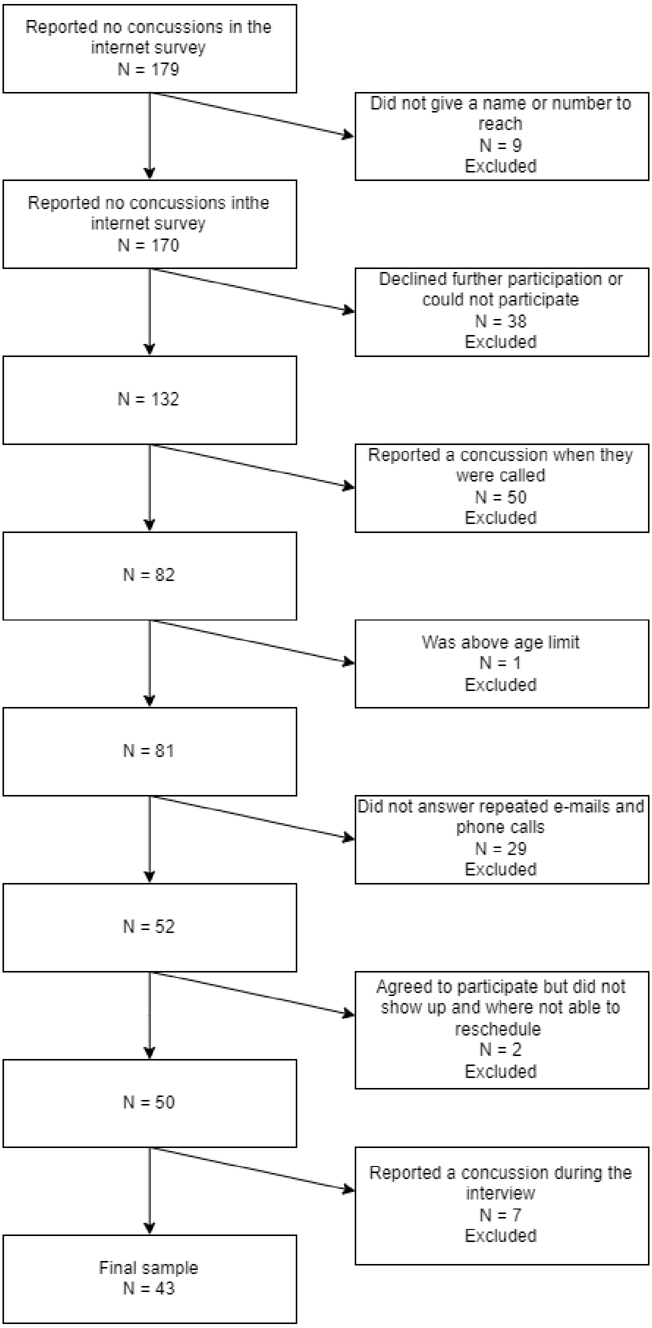


Figure 3

A Flow Chart Representing the Inclusion-Exclusion Process for Those Without a History of Concussion



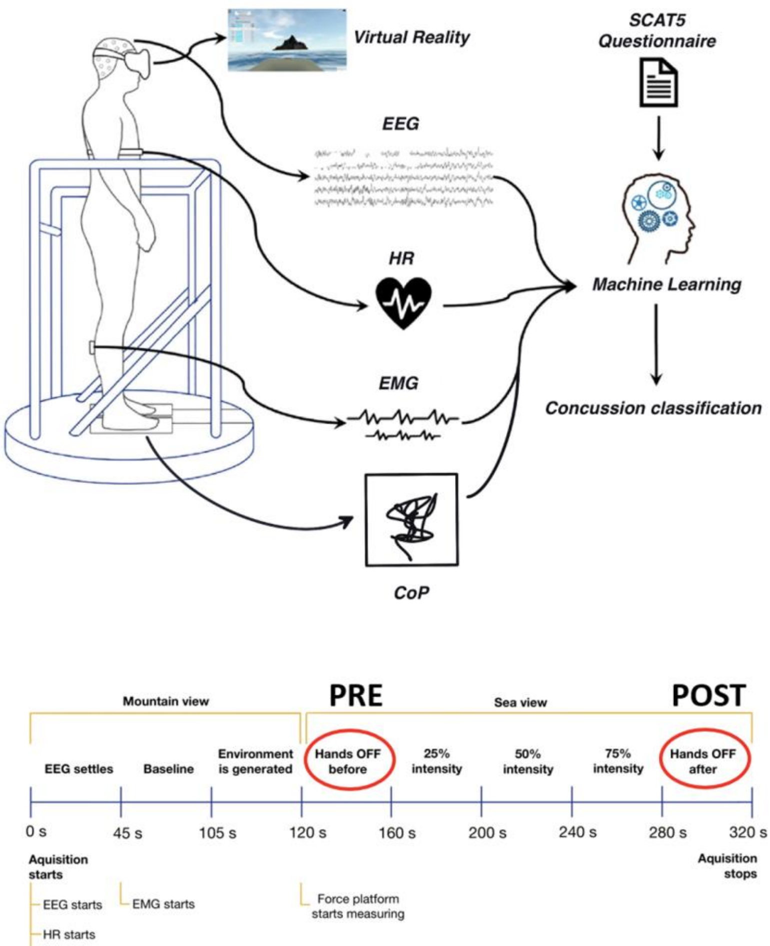
3.2.3 Paper III

Participants who had participated at earlier stages of the study (Paper II and Paper II) were contacted through the project´s Facebook page and other social media pages and invited to participate in the study presented in Paper III. Participants were told that the data acquisition was to be set in a virtual reality environment.

When participants were called to schedule the VR appointment, a concussion definition was read to them, and they asked if they had at any time sustained a concussion. This was done to make sure that they were assigned to the correct group (concussed or not concussed), as they could have sustained a concussion since their last report. Before entering the VR lab, all participants completed a concussion symptoms scale (SCAT5). Participants were then prepared for physiological measurements. In the measurement setup, called BioVRSea, virtual reality and a synchronized moving platform were used to trigger a postural control reaction while measuring physiological responses and CoP (Figure 4). This included a wet 64-electrode EEG cap, EMG sensors on the tibialis anterior, gastrocnemius lateral and soleus muscles of each leg, and a heart sensor strapped around the chest. Participants had to wear a backpack with the EEG amplifier connected to the cap and a tablet used for EEG signal acquisition. Before entering the VR environment, participants put on VR goggles and climbed on a platform equipped with a force plate.

Figure 4

Setup for Data Acquisition in The VR Environment and Mesurement Protocol (Jacob et al., 2022)



Data acquired in the experiment were processed using MATLAB, and a dedicated toolbox for EEG called Brainstorm.

3.3 Measures

3.3.1 Paper I

The concussion count used to evaluate concussion history was obtained with self-report four times in total (Figure 1). In the online study, participants were asked, "Have you had a concussion?" before and after being provided with a concussion definition. During the interview, participants were asked, "How many concussions have you had?". They were also asked to describe concussion incidents, which the interviewer then counted.

Current concussion symptoms were assessed with post-concussion symptoms checklist from the Concussion Assessment Tool, fifth edition (SCAT5). The checklist includes 22 items which were either present (1) or not (0). The SCAT5 has high reliability and adequate validity in research settings for the assessment of current symptoms (Asken et al., 2020; Lovell et al., 2006). However, here the symptom scale was used to assess and estimate symptoms retrospectively. The SCAT5 is recognized by the Berlin Consensus Statement on Concussion in Sport (McCrory, Meeuwisse, et al., 2017).

3.3.2 Paper II

Concussion symptoms, both past and current, were assessed with the SCAT5 as in Paper I. Past symptoms were assessed retrospectively. The retrospective assessment with the SCAT5 was used to evaluate different aspects of the athlete's reaction and if it supported recollection of concussion incidents. The interviewer counted concussions after participants had given a description of incidents. This number was used as an indicative measure of how many concussions participants had possibly sustained.

Cognition was assessed with several tests. The Sustained Attention to Response Task (SART) (Robertson et al., 1997) was used to assess attention-related errors. Performance on the SART has been correlated with everyday self-reported cognitive failure and validated against tests that measure attention and attention failures. Scores on the task have been found to be linked to brain damage severity as well as reports of everyday attention failures among normal controls (Robertson et al., 1997). In this study, the mean response time (SARTrt) and the error score (SARTes) were used to assess processing speed and error in attention (Carriere et al., 2010; Robertson et al., 1997).

The Stoop Colour-Word Test (Scarpina & Tagini, 2017) was used to assess automatic processing and attention. Response interference control is a form of cognitive inhibition (Dimoska-Di Marco et al., 2011). The interference score was used to assess automatic processing and attention (Davidson et al., 2003; Dulaney & Rogers, 1994) according to Icelandic norms (Magnusdottir et al., 2019).

The Trail Making Test (Scarpina & Tagini, 2017) was used to assess visual search and speed (TMT A), cognitive flexibility, divided attention and working memory (TMT B). The TMT difference (TMT B-TMT A) was used to obtain a derived score according to Icelandic norms (Magnusdottir et al., 2019).

Subtests from the Icelandic version of the Wechsler Abbreviated Scale of Intelligence (WASI-IS) (Wechsler, 2011; Guðmundsson, 2016) and the Wechsler Adult Intelligence Scale-III (Wechsler, 1997) (WAIS-III) were used to assess intellectual abilities, working memory and processing speed. The Vocabulary and Matrix Reasoning subtests from the WASI-IS, the Digit Span Test (digits forwards and reversed), the Letter-Number Sequencing Test, and the Coding and Symbol Search from the WAIS-III were used. The WASI-IS has been found to have good psychometric properties in the Icelandic population (Guðmundsson, 2016). The WAIS-III has been used in Iceland and has been found to be valid when tested against the WASI-IS (Jökulsdóttir & Guðmundsson, 2011). There are, however, no available norms for the WAIS-III in Iceland.

The Insomnia Severity Index (Morin et al., 2011) (ISI) was used to assess sleep problems. The ISI has been found to have good reliability and validity in English (Morin et al., 2011) and Icelandic samples (Sigurjónsdóttir, 2018). The severity of symptoms ranges from not being clinically significant insomnia (0-7), subthreshold insomnia (8–14), and clinically moderately severe (15–21) to clinically severe (22–28) (Morin et al., 2011). Cronbach's alpha for scores on the ISI for HOC was 0.86, and for NHOC was 0.82.

Symptoms of mental health problems were assessed with four scales. The General Anxiety Disorder Questionnaire 7 (GAD-7) (Spitzer et al., 2006) was used to assess anxiety symptoms. Psychometric properties of the English (Spitzer et al., 2006) and the Icelandic version of the GAD-7 have been found to be satisfactory with good reliability and validity (Ingólfsdóttir, 2014). The severity of symptoms ranges from mild (5-9) and moderate (10-14) to severe (15-21) (Spitzer et al., 2006).

The Perceived Stress Scale 4 (PSS4) (Cohen et al., 1983; Cohen & Williamson, 1988) was used to assess perceived stress. The psychometric properties of the scale have been found to be adequate (Cohen et al., 1983). Although the scale has been used in Iceland

(Jensdóttir, 2016), its psychometric properties in an Icelandic sample are unknown. Scores range from 0-16, with higher scores indicating more stress (Cohen et al., 1983).

The Patient Health Questionnaire 9 (PHQ-9) (Kroenke et al., 2001) was used to assess depression symptoms. The scale has been found to have good psychometric properties in English (Kroenke & Spitzer, 2002) and Icelandic samples (Ingólfsdóttir, 2014). The severity of symptoms ranges from mild (5-9), moderate (10-14) and moderately severe (15-19) to severe (20-27) (Kroenke et al., 2001).

The Quality of Life Scale (QOLS) was used as it has been found to be a valid measure of quality of life (Burckhardt & Anderson, 2003). The psychometric properties of the English (Burckhardt & Anderson, 2003) and the Icelandic version have been found to be good (Jónsdóttir & Sigurðardóttir, 2016). Scores range from 16 to 112 (Burckhardt & Anderson, 2003).

All tests and questionnaires were completed by athletes with a history of concussions and those without a history of concussions, with the exception of the mental health scales. Only the GAD-7 and PHQ-9 were completed by those without a history of concussion. Additionally, those without a concussion history only answered questions about current symptoms (SCAT5) and their background when participating in a shortened version of the semi-structured interview.

3.3.3 Paper III

The SCAT5 was used to assess current concussion symptoms. Participants completed the symptoms scale from SCAT5 (Echemendia et al., 2017) before the experiment evaluating the severity of each symptom on a scale of 0 to 6. The postural response was measured using VR software to mimic an open sea environment where participants had to stand on a boat. A platform simulating waves was set to disrupt stability, with the amplitude of the waves being between 0 to 2, set to a frequency between 0.5 Hz and 3 Hz (Friðriksdóttir et al., 2020).

An electroencephalogram (EEG) with a 64-electrode channel system was used to record neural activity. Electromyographic (EMG) signals were used to acquire muscle information about contraction in the legs and chest heart rate sensors to monitor participants' heart rate (beats per minutes=bpm). In addition, the centre of pressure (CoP) was assessed using signals from a force plate.

3.4 Statistical analyses

3.4.1 Paper I

A repeated measures ANOVA was used to examine if the reported number of concussions changed between conditions. Groups were formed by concussion count reported on each occasion. One-way ANOVA was used to make a comparison between multiple groups (0, 1, 2-3, 4-5, or 6 or more concussions). An independent t-test was also used to compare SCAT5 symptoms between two groups (1-2, 3 or more concussions). This division was done because of clinical guidelines recommending an athlete's removal from play if the number of concussions reaches three (Berry et al., 2019). Because of the online questionnaire's set-up and phrasing, this group division was only possible for reports obtained during the interview. The significance level was set at $\alpha = 0.05$ for statistical tests.

3.4.2 Paper II

In Paper II, descriptive statistics, means and standard deviations were calculated for the SCAT5, neuropsychological tests, sleep scale, and mental health scales. To further examine concussion history, a paired t-test and a Fisher exact test were used to examine the relationship between self-reported symptoms (SCAT5 score) and mental health history. An independent t-test was used to examine the relationship between repeated concussions and an outcome variable and to make comparisons to the control group. A further examination of recurrent concussions included a one-way ANOVA. An independent t-test was also used to compare scores on mental health scales and neuropsychological between athletes with and without a concussion history. In addition, Pearson correlation was used to assess the connection between measures of the SART. The significance level was set at $\alpha = 0.05$ for all statistical tests.

3.4.3 Paper III

Descriptive statistics were calculated for each group for the SCAT5 current concussion symptoms score representing symptom severity before the VR acquisition. An independent t-test was used to compare the means for each group.

Data for the EEG, EMG and CoP were analysed by calculating values from POST minus PRE data. PRE as at the beginning of the VR acquisition of the Hands-off condition and POST as the Hands-off condition at the end of the experiment (Figure 4). The athletes were compared according to concussion history. In addition, athletes with a concussion history were divided further into symptom-based subgroups.

Statistical significance for each EEG electrode was calculated with a one-tailed t-test. This was done for results representing the difference between PRE and POST for each frequency band and each group (concussed and non-concussed). Statistical significance was calculated using a two-tailed Wilcoxon test for the EMG area, heart rate and body sway data sets from data from signals (PRE and POST measures). A two-tailed Wilcoxon test was also used to assess the difference between PRE minus POST values, comparing frequency signals from the EMG between groups. The significance level was set at $\alpha = 0.05$ for all statistical tests.

The Knime Analytics Platform software was used to perform ML analysis with the aim of differentiating between the concussion group and the non-concussed. The analysis was made using 251 features extracted from the HR monitor, EEG and EMG data. Different algorithms, Random Forest (RF), Gradient Boosting (GB), Ada-Boosting (ADA-B), Support Vector Machine (SVM) and Multilayer Perceptron (MLP), were then used to combine the data, with the purpose of finding the one that had the best predictive capabilities for concussion history. Algorithms were assessed in regard to sensitivity (number of true positive assessments/number of all positive assessments), specificity (number of true negative assessments /number of all negative assessments) and accuracy (number of correct assessments/numbers of all assessments).

3.5 Ethical considerations

The National Bioethics Committee approved studies I and II (No: 17-183-S1) separately from study III. There was a delay in study II because it took longer than expected to have all the women come in for the interviews and for the hormonal testing to begin (not part of this Thesis). Because of this delay, athletes with a history of concussions had to answer mental health questionnaires again when they participated in the hormonal testing. This change was also approved by the National Bioethics Committee (No: 17-183-V1). In order to get a comparison with athletes without a concussion history, it was important to contact those who did not report a concussion history in the online study. This was an addition that the National Bioethics Committee approved (No: 17-183-V2). Study III was also approved by the National Bioethics Committee (No: VSN-19-213).

All participants gave their written informed consent after reading the study's aims and procedure, and all were informed that they could quit the study at any stage without any complications. No compensation was provided in any of the studies. The National Olympic and Sports Association of Iceland (ÍSÍ) was made aware of the study.

4 Results

Results from the three papers that this Thesis is based on are presented in this chapter. In Paper I, the focus was on estimating whether the method used to obtain self-reported concussion history affected the number of reported concussions. In Paper II, the focus was on the relationship between concussion history and several outcome variables among retired and still active female athletes. In Paper III, the aim was to assess concussion symptoms and possible biomarkers for concussion acquired from measures done in a VR environment.

4.1 Paper I

4.1.1 Concussion count throughout the study.

The self-reported concussions were estimated in four different conditions, detailed in the procedures (Figure 1). When comparing those who reported one concussion and those that reported two or more, there was a significant change in reported concussions across all conditions, $F(1.81) = 52.71$, $p < 0.001$. A planned comparison revealed that when compared to the condition where participants had to describe concussion incidents (the fourth condition), there was a significant difference in reported concussions. However, the difference was only significant when comparing the count reported when first asked during the online questionnaire (before participants were provided with a concussion definition) and when reporting at the beginning of the interview (the first and third conditions, respectively). More participants reported multiple concussions in the fourth condition on both occasions. When divided into four groups according to the number of concussions, there was a significant change in reported concussions across all conditions $F(2.40) = 8.99$, $p < 0.001$. Again, when comparing to the fourth condition, there was a significant increase in concussion reports when compared to condition one, but not to condition three. However, with this group division (four groups), there was also an increase in reported concussions when comparing condition four to condition two (Table 4).

Table 4
Concussion Count Among Female Athletes In The Internet Questionnaire (Before and After Definition) and In The Interview (At The Beginning and Counted by The Interviewer)

		Number of concussions (%)		
Conditions	N	Zero	One	Two or more
First condition.	140	42 (30)	39 (27)	59 (42)
Second condition.	137	0 (0)	34 (25)	103 (75)
Third condition.	141	0 (0)	47 (33)	94 (67)
Fourth condition.	143	0 (0)	33 (23)	110 (77)

Groups were also divided into two groups by concussion count, those that reported one to two concussions vs. three or more. The comparison was only made between conditions three and four (As explained in statical analyses). There was not a significant change in concussion reports between conditions when using this group division.

4.1.2 The relationship between reported concussions and current concussion symptoms

When comparing those who reported one concussion and those reporting two concussions or more, results showed a difference in SCAT5 scores in the first condition ($t(77.88) = -3.20$, $p = 0.002$) and the fourth ($t(57.53) = -2.87$, $p = 0.009$). A multi-group comparison resulted in the same results, a difference in scores on the SCAT5 between groups, only in the first condition ($F(4) = 6.99$, $p<0.001$) and the fourth ($F(3) = 2.77$, $p<0.044$). Post hoc test for the first condition showed a difference for those who reported no concussion, two to three ($p<0.001$), and one concussion and two to three ($p<0.001$). Post hoc for the fourth condition showed a difference on the SCAT5 between those who reported one concussion and those who reported four to five ($p<0.052$).

In addition, as in the concussion count comparison, participants were divided by concussion count into groups representing one to two concussions and three or more. Mean scores were higher for those who reported three or more concussions in both conditions, three (M=7.92 vs. M=6.81) and four (M=8.11 vs. 6.48), but the difference was not significant ($p>0.05$).

4.2 Paper II

4.2.1 History of concussions: Retrospective self-report of incidents

An overview of self-reported concussion history can be seen in Table 5.

Table 5

Self-reported Concussion History

Number of concussions M (SD)	2.8 (1.9)
Reported concussion count*	N (%)
1	33 (20.4)
2	49 (30.2)
3	40 (24.7)
4	20 (12.0)
5	13 (7.8)
6	4 (2.4)
7	1 (0.6)
8	1 (0.6)
20	1 (0.6)
	M (SD)
Age at first concussion	17.2 (6.0)
Age at most severe concussion	22.3 (5.89)
Years since first concussion	10.9 (8.4)
Years since most severe concussion	5.7 (6.8)
Years since most recent concussion	6.5 (6.5)

*Four athletes were not able to estimate a concussion count by describing incidents.

A total of 44% reported that their first concussion was also their most severe. In addition to current symptoms assessed with the SCAT5, participants also reported, retrospectively, symptoms they experienced after the first incident and the most severe one. Results can be seen in Table 6.

A further examination of concussion history included asking participants about memory loss and loss of consciousness after the first and most severe incidents and how long symptoms lasted (Table 6).

Table 6
Self-reported History of Concussion Symptoms

		After first incident	After most severe incident	Current symptoms
Symptom Count (SCAT5 score)	N	154	160	165
	Mean	10.6	12.9	7.5
	SD	5.1	5.3	5.0
	Min	0	0	0
	Max	22	22	19
Length of post-concussive symptoms	N	139	156	N/A*
<30 min	n (%)	14 (10.1)	7 (4.5)	N/A*
>30 min <7 days	n (%)	88 (63.3)	74 (47.4)	N/A*
≥7days	n (%)	37 (26.6)	75 (48.1)	N/A*
Reported loss of memory	N	148	159	N/A*
	n (%)	49 (33.1)	57 (35.8)	N/A*
Reported loss of consciousness	N	149	159	N/A*
	n (%)	36 (24.2)	39 (24.5)	N/A*

N/A*: Not applicable

4.2.2 Current status in relation to concussion history: Cognition, insomnia and mental health

All comparisons for neuropsychological tests between those with recurrent concussions and those with only one were non-significant ($p>0.05$). Those with a reported history of recurrent concussions had a higher SCAT5 score (M=8.0, SD=5.0) than those with a history of only one concussion (M=5.2, SD=4.5), $t(52.3) = -3.1$, $p=0.03$. They also reported worse insomnia ($t(57.84) = -3.02$, $p=0.04$) and had worse scores on the PHQ-9 ($t(45.79) = -2.33$, $p=0.02$)). When comparing multiple groups (one concussion, two to three, four to five and six or more), results from a one-way ANOVA were non-significant for all of the neuropsychological tests ($p>0.05$). Only when comparing scores for the insomnia scale ($F(3) = 3.08$, $p=0.03$) and current SCAT5 symptoms ($F(3) = 3.47$, $p=0.02$) were results significant. A post hoc test showed that in both cases, the difference in scores was only significant ($p < 0.05$) when comparing those with one concussion and those with four to five concussions.

Results from independent t-tests for neuropsychological tests, the SCAT5 current concussion symptoms scores, mental health scales, the insomnia scale and prior mental health diagnosis comparing the HOC and the NHOC groups can be seen in Table 7.

Table 7

Comparison of Outcomes on Neuropsychological Tests, Concussion Symptoms Scale, Insomnia Scale and Mental Health Scales for HOC and NHOC Groups

	History of concussion (HOC)			*No history of concussion (NHOC)*			*t-value*
	N	Mean	SD	N	Mean	SD	
SARTes	159	13.8	7.1	42	8.9	7.59	3.92*
SARTrt (ms)	159	357.3	84.9	42	399.5	102.7	-2.45*
*Stroop Interference***	157	50.9	7.8	43	51.5	8.3	-0.43
*TMT Difference****	158	50.0	7.3	43	50.1	7.3	-0.01
WASI Vocabulary	159	45.9	9.2	43	43.6	7.3	1.55
WASI Reasoning.	160	50.1	8.8	43	51.7	7.4	-1.24
WAIS Digit forward/							
WAIS Digit reversed	160	9.5	2.6	43	9.4	2.0	0.27
WAIS Letter-number	160	9.7	2.2	43	10.1	2.8	-1.15
WAIS Digit coding	161	11.6	2.6	43	12.3	2.2	-1.59
WAIS Symbol Search	160	12.2	2.8	43	12.8	2.2	-1.12
SCAT5 - Current concussion symptoms	165	7.5	5.0	43	4.2	3.9	4.01*
GAD-7	157	5.4	4.1	42	1.8	2.6	6.96*
PHQ-9	157	7.1	4.8	43	2.6	2.7	7.96*
Insomnia	166	8.5	6.0	42	3.3	3.5	5.34*
						Fisher exact (P-value)	
*Prior**** anxiety diagnosis % (n)*	15.7 (26)			9.5 (4)		*p* = 0.025*	
*Prior**** depression diagnosis %(n)*	32.0 (8)			9.5 (4)		*p* = 0.44	
*Prior**** ADHD diagnosis % (n)*	9.0 (15)			0 (0)		*p* = 0.044*	

*$p<0.05$. **Normal population: M=30.0 (M_{age} = 44.8) / M=27.3 (20-50 years old). ***Normal population: M=40.5 (M_{age}= 44.8)/ M=35.0 (20-50 years old) (data from Magnusdottir o.fl., 2019).**** *prior* here means prior to the interview, not necessarily prior to a concussive incident.

Retired and still active athletes were compared according to whether they reported a history of concussion. There was no difference on any of the cognitive tests except for the SART. Those in the HOC group had a higher error score and a faster response time. Results for the SART, mental health, insomnia and the SACT5 scales can be seen in Table 8.

Table 8

Comparison of Outcomes for The HOC Group and The NHOC Group Depending on Whether They Were Retired or Active

	History of concussion (HOC)			*No history of concussion (NHOC)*			*t-value*
	N	Mean	SD	N	Mean	SD	
Retired							
SARTes	78	13.4	7.0	24	7.9	7.0	3.3*
SARTrt (ms)	78	363.6	83.8	24	407.4	94.1	-2.2*
*SCAT5***	84	8.4	4.7	25	3.4	2.8	6.6*
GAD-7	74	5.5	4.1	23	1.9	2.8	4.8*
PHQ-9	76	7.4	5.2	23	2.5	2.6	6.1*
Insomnia	85	8.7	6.2	24	3.2	3.4	5.7*
Still active							
SARTes	159	14.1	7.2	42	10.1	8.4	2.0*
SARTrt (ms)	80	351.6	86.6	18	388.9	115.9	-2.45
*SCAT5***	80	6.4	5.1	18	5.3	4.8	4.01
GAD-7	69	5.5	4.1	17	1.9	2.6	3.5*
PHQ-9	68	7.0	4.2	18	3.1	2.9	3.7*
Insomnia	80	8.2	5.9	18	3.5	3.7	4.3*

*$p<0.05$, ** current concussion symptoms

4.3 Paper III

4.3.1 SCAT5 – Concussion symptoms scale

Results from an independent t-test can be seen in Table 9. Those with a history of concussion reported more severe concussion symptoms than those with no history of concussion.

Table 9

Severity Scores on The Concussion Scale (SCAT5) Before VR Acquisition (Jacob et al., 2022)

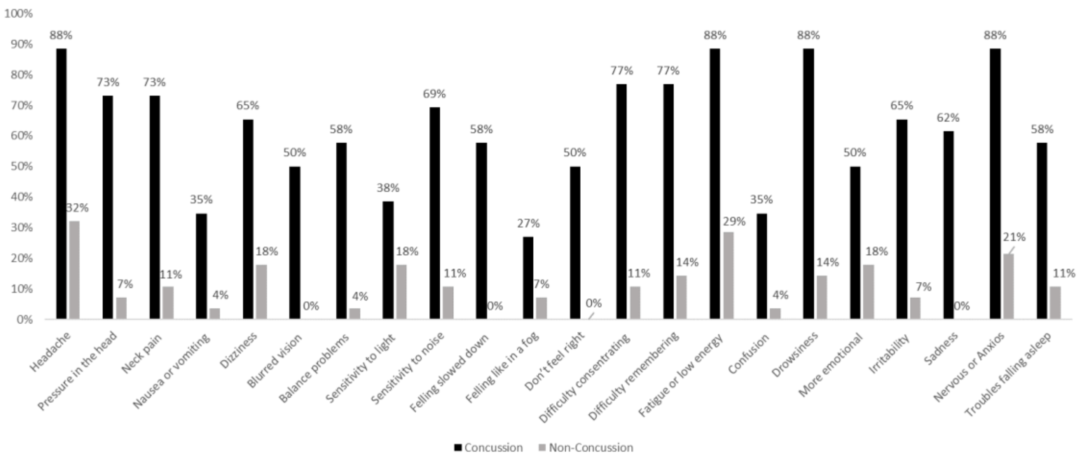
	Athletes with no history of concussion			Athletes with a history of concussion			
	N	M	SD	N	M	SD	t-value
SCAT5							
Before	28	3.71	4.50	26	36.47	23.71	-7.18*

*p<0.05

A closer look into concussion symptoms reported before the VR acquisition can be seen in Figure 5.

Figure 5

Symptoms (SCAT5) Reported by Participants Before The VR Acquisition (Jacob et al., 2022)



4.3.2 Summary of biological signals

4.3.2.1 CoP analysis

Several parameters were extracted from the stabilogram to evaluate the postural control response of the subjects before (PRE) and after (POST) the joined perturbation caused by the movement and the visual cues provided by the VR goggles. Six features from the displacement and velocity analysis showed significant differences ($p< 0.05$) between the PRE and the POST stages. The concussion group exhibited significantly larger changes from PRE to POST for all six features compared to the non-concussion group.

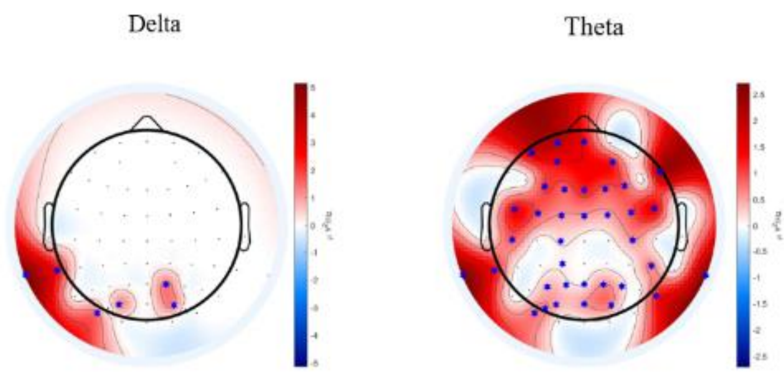
One feature in the spectral analysis, PSD_EXP_AP – Power Spectral Density (PSD) Power Law Exponent for the anterior posterior signal, reflecting the variability in signals from the muscles when moving front to back, showed statistical significance (p = 0.02) when comparing the concussion subgroup experiencing balance problems to the concussion subgroup not experiencing balance problems.

4.3.2.2 EEG analysis

Figure 6 shows the POST-PRE difference in the concussion group for the delta and theta bands, which were the only ones that showed significance. The difference was highlighted by an increase in power and a significant change in activity in the theta band and delta band (p = 0.038). The non-concussion group did not display any significant results in this experiment.

Figure 6

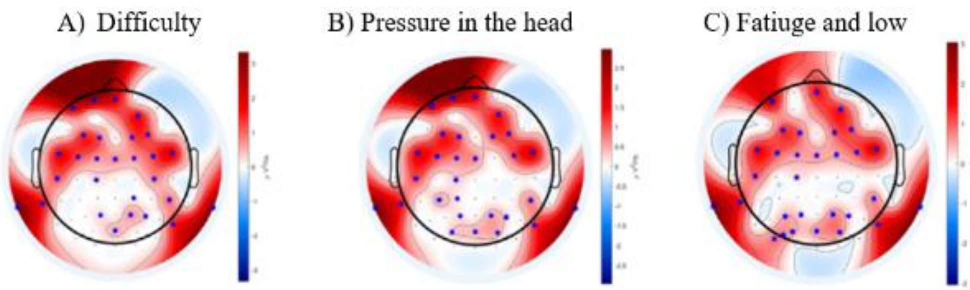
Topical Plot of Delta and Theta (Concussion Group) (Jacob et al., 2022)



The concussion group was divided into the following subgroups according to their SCAT5 symptoms: A) Difficulty to concentrate group (16 individuals), B) Pressure in the head group (17 individuals), and C) Fatigue and low energy group (19 individuals). POST-PRE comparison showed a significant difference in the theta band (Figure 8) ($0.008 \leq p \leq 0.049$), with increased activity in all subgroups (Figure 7).

Figure 7

Topical Plot of Theta for The Concussion Subgroups (Jacob et al., 2022)



4.3.2.3 EMG analysis

The muscle that discriminated the strongest between the concussed and then non-concussed athletes was the soleus muscle (muscle in the calf) for all features except median frequency. Median frequency has been a useful indicator of changes in EMG during fatigue (van Boxtel et al., 1983). When evaluating the following concussion subgroups: Those experiencing balance problems (BP) and those not experiencing balance problems (No BP), the median frequency for the right soleus of the BP group showed significantly more muscle contraction ($p=0.0075$) in the POST phase of the experiment when compared to the no BP group.

4.3.2.4 Heart rate analysis

Athletes without a concussion history experienced a minor change in heart rate, while athletes with a concussion history experienced a greater change in heart rate (bpm) from PRE to POST. However, this change PRE to POST was not significant for either group.

4.3.2.5 *Classification analysis*

Artificial neural network algorithms were used when assessing different algorithmic strategies for the classification of concussion history (concussed vs. non-concussed). The best results, the highest sensitivity and accuracy, were obtained by merging two feature sets, one including SCAT5 items and the other including nine principal analysis components features from brain, muscles, heart, and CoP signals (Figure 8). All the models exceeded 90 in accuracy except for one (GB).

Table 10

The 31 Combined Features of PCA and SCAT5 (Jacob et al., 2022)

PCA + SCAT5 Features (31)			
Algorithm	Accuracy	Sensitivity	Specificity
RF	90.9	89.5	92.0
SVM	95.5	94.7	96.0
ADA-B	93.2	94.7	92.0
MLP	90.9	96.0	86.0
GB	79.5	78.9	80.0

5 Discussion

The overall aim of this Thesis was to examine the concussion history of retired and still active female athletes in Iceland, using different methods to assess concussion history and its possible sequelae, and evaluate its connection to mental and physical markers and variables. All athletes had either previously or were currently training at the highest level in their sport. The examination included an assessment of self-report under different conditions, a detailed assessment of concussion history, and an assessment of mental health, neuropsychological functioning, insomnia, and current concussion symptoms. Possible concussion biomarkers were also evaluated in a controlled VR environment.

The results represented in this Thesis give an important insight into concussions among the female athletic population. This population is at high risk for concussions (Noble & Hesdorffer, 2013) and is likely not to report concussions and continue sport participation even though symptomatic (Mooney et al., 2020). The study is not a gender study, as males are not included. Nevertheless, the study, the first of its kind in Iceland, focuses on an underrepresented group in the concussion literature (Colantonio, 2016), and gives an insight into symptom history, concussion incident history and current status in relation to cognitive, mental and physical health. The results of this study could therefore be of great importance for those researchers interested in gender differences in concussions, as well as clinicians and practitioners involved in treatment and RTP guidance.

5.1 Assessment of self-report in a concussion study (Paper I)

The aim of Paper I was to assess the usefulness of self-report in concussion studies and how it could be made more useful and hopefully more reliable. Medical records are sometimes considered the gold standard when assessing concussion history (Broglio & Puetz, 2008). However, they do not necessarily give a good representation of past concussions. This is partly because of athletes' underreporting (Leahy et al., 2020; McCrea et al., 2004; Meehan et al., 2013). Self-report will therefore remain an important part of concussion studies, especially when doing retrospective studies. Studying how best to ask about past concussions in order to obtain a reliable concussion estimate is thus an important topic of research.

Providing a concussion definition in concussion studies is vital as results point to a lack of concussion knowledge, reflected in an increase in concussion count before and after being provided with a definition (Kristjánsdóttir et al., 2020). However, providing a concussion definition might not be enough, and more detailed questions could be necessary. Results from Paper I show that self-report of concussion (represented by concussion count) elicited under different conditions were affected by how information was obtained, affecting the relationship with current concussion symptoms (SCAT5). Results support that having participants describe incidents instead of only giving an estimate of the number of concussions they might have sustained further increases their concussion reports.

5.2 Concussion history, cognition, and mental health among female athletes (Paper II)

In Paper II, the aim was to examine retrospective self-reported concussion and symptoms history and the connection between concussion history and cognition, insomnia and mental health among active and retired female athletes. In addition to asking about concussion history represented by concussion count after a description of incidents (Paper I), concussion history was also examined through reported symptoms after the first and most severe incidents. This is the first known study to assess retired and still active female athletes and include such a comprehensive assessment of concussion history and outcome variables. The only other known study known to include a comprehensive assessment of cognition and mental health among female athletes with a history of repeated head impacts is from 2020 (Prien et al., 2020). That study included only retired athletes, and results indicated that mental health and cognition were similar when they were compared to athletes from a non-contact sport. The study represented in this Thesis offers a deeper insight into this particular cohort, female athletes, by including a larger sample of athletes and both retired and still active athletes. In addition, the current study has a control group of similarly matched athletes with no concussion history.

The concussion count among the athletes was higher than what has been seen before in an all-female group (e.g., Prien et al., 2020), and the number of athletes reporting more than one concussion was higher than has previously been reported in mixed samples (Greco et al., 2019; Kerr et al., 2014; Veliz et al., 2019). Symptom count after the most severe incident was higher than for the first incident and more athletes reported a loss of consciousness and memory than after the most severe incident. All of this supports the athletes' recollection of incidents. This and the fact that many athletes did not seek out medical treatment after the concussion (Paper 1) highlights the importance of post-injury guidelines and guidance (Eagle et al., 2020; McCrea et al., 2020).

When compared against norms in an Icelandic population, participants with a history of concussion did worse on some of the neuropsychological tests, mainly tests indicating poorer cognitive inhibition and mental processes (TMT/Stroop) (Magnusdottir et al., 2019). Participants did, however, not deviate from normal means on the various subtest of intelligence tests (Guðmundsson, 2015; Wechsler, 1997). When examining mental health and sleep, participants with a history of concussion showed mild to moderate symptoms of anxiety and depression and over half reported troubles with sleep according to clinical cut-offs (Cohen et al., 1983; Kroenke et al., 2001; Spitzer et al., 2006). A history of recurrent concussions was connected to higher scores on a depression scale, more current concussion symptoms, troubles with sleep, and a worse self-assessment of quality of life (Burckhardt & Anderson, 2003).

When compared to female athletes with no history of concussion, the concussion group had poorer impulse control as measured by the SART, more current post-concussion symptoms, and more problems with sleep, anxiety and depression. Again, this highlights the importance of proper RTP guidance. Most of the cognitive tests did not show a difference between those with and without a concussion history. This is in accordance with finding from a recent study (Prien et al., 2020). However, more research is needed into this specific cohort. Elite athletes have trained to perfect specific skills and abilities which might affect performance on psycomotor tests (Prien et al., 2020).

Retired athletes with and without a concussion history were also compared as well as still active athletes from the same groups. This study goes further than what has been done previously (Prien et al., 2020) by including both active and retired athletes. Retired athletes in the HOC group made more errors and had a slower response time on the SART than the retired athletes in the NHOC group. The retired HOC athletes also reported more current concussion symptoms, more depression and anxiety symptoms, and worse insomnia. When comparing active athletes, the active athletes in the HOC group made only more errors on the SART compared to the active athletes in the NHOC group. They did report more depression and anxiety symptoms and worse insomnia. However, there was no difference in current symptom scores measured by the SCAT5. These results could have some significance for RTP guidelines and the role of SCAT5 in RTP, but more research is needed. It is not known why the athletes retired or whether concussion symptoms had a role in their decision. Results suggest there is a relationship between retirement and concussion symptoms, but this relationship needs further investigation.

5.3 Concussion symptoms and biomarkers predicting concussion history among female athletes (Paper III)

In Paper III, the aim was to assess possible biomarkers for concussion by using a multimodal approach to validate concussion history and self-reported symptoms and quantitatively evaluate physiological responses during postural control tasks associated with concussion symptoms. The assessment of possible biomarkers and the use of new technical advances have important implications both in clinical and research settings. By adding an evaluation of physical symptoms in conjunction with a list of symptoms known to follow a concussion (Echemendia et al., 2017; McCrory, Meeuwisse, et al., 2017) comes the opportunity to assess possible biomarkers for concussions.

The athletes with a history of concussions had a higher severity score on the SCAT5 than those without a concussion history. The most frequently reported symptoms among those with a concussion history were headaches, fatigue and low energy, drowsiness and nervousness. The symptom reported by the fewest was feeling like in a fog, reported by almost 30%. In the non-concussion group, the most frequently reported symptom was a headache. However, it was only reported by 32% and was the only symptom reported by more than 30%. Headache is the most commonly reported concussion symptom (Tator & Davis, 2014) and the most common reason for general neurological consultation (Lipton et al., 2004). Therefore, it was not surprising that it was the most reported symptom in both groups.

Theta band activity measured with an EEG showed that those with a history of concussion reacted differently than those without a history when they had to maintain postural control and balance. The increase in the theta band could be connected to the VR tasks being more demanding for those with a history of concussions. Theta activity has previously been shown to increase during cognitive tasks, indicating an active role in problem-solving (Ryu et al., 2016). Theta activity has also been linked to tasks that need more attention and cognitive demands (Wang et al., 2018). The increase in theta was also present in the concussion subgroups among athletes who reported having difficulty concentrating, feeling pressure in the head, and feeling fatigued and low energy, supporting their reports of concussion symptoms and possibly offering an objective way to assess post-concussive symptoms.

The EMG signals from the tibialis anterior (TI) showed a higher muscle activation in the concussion group and in the balance trouble subgroup, indicating more trouble with maintaining balance and postural control, supporting its involvement in maintaining upright balance (Di Giulio et al., 2009). The TI has previously been shown to be more active in an upright posture. Problems with postural control have been associated with concussion history (Buckley et al., 2016) and visual and vestibular problems (Echemendia et al., 2017; Samuel et al., 2015; Sandel et al., 2017). Because of the involvement of the TI in postural control, EMG measures from the TI could be an important indicator of postural balance problems after a concussion. When comparing within the concussion group, athletes who experienced balance problems versus those who did not experience balance problems significantly differed, demonstrating the discriminative power of the right soleus muscle. Heart rate was also higher among those with a history of concussions, supporting its use as a marker for concussion history, possibly indicating problems affecting RTP (Abaji et al., 2016; Leddy et al., 2016; Memmini et al., 2021; Pyndiura et al., 2020). Results from physiological measures support their use as possible biomarkers for concussion. Results support that neural activity (Ianof & Anghinah, 2017; Munia et al., 2017; Teel et al., 2014), muscle activity related to balance and stability (Guskiewicz, 2001; Nguyen et al., 2013; Reaz et al., 2006), and heart rate (Bishop et al., 2018; Leddy et al., 2016; Thomas et al., 2015) could be used to assess concussion, RTP and symptoms resolution, and possibility provides for a valid measure of concussions. However, more research into those symptoms and their relationship to psychological factors is needed.

With the use of a multi-faceted approach to concussion symptoms which is recommended (Broglio et al., 2007; Collins et al., 2014; Sherry et al., 2019), came the opportunity to use machine learning (ML) technology to predict concussion history. ML was able to predict concussion history with the Random Forest algorithm giving the best result.

5.4 General methodological limitations and strengths

The aim of the project was to assess concussion history and its connection to various mental and physical markers/variables among female athletes in Iceland. Females are underrepresented in the concussion literature. Therefore, this is a significant strength of the study.

One of the major limitations is how participants were recruited, affecting the generalizability of the results. All participants were first contacted through snowball sampling. Social media was used to contact athletes interested in participating in the study. This presents a selection bias possibility, as those interested in the project or who had a concussion experience could be more inclined to participate. After being presented with a concussion definition in the online study, which pre-dates the studies presented in this Thesis, about 40% reported no concussion (Kristjánsdóttir et al., 2020). In addition, there is a reason to believe that the Covid-19 pandemic did influence the recruitment of participants. Initially, the aim was to follow all participants through all stages represented in the three papers. Because of the Covid-19 pandemic and lack of funding, this was not possible, and researchers had a smaller window of time to collect data at later stages in the study. This resulted in a smaller sample of participants represented in the groups.

Another limitation is that when comparing concussed and non-concussed individuals, there are no participants representing a normal population. All of the participants had a history of playing at the highest level in their respective sport, all of whom could have experienced a sub-concussion without knowing. This homogeneity could, however, also be seen as a strength. The control group represent individuals that are very similarly matched to the concussion group, physically and regarding background. The main thing that distinguishes the groups is their self-reported concussion history.

Concussion history was measured by self-report. Self-report can present problems, including the possibility of the Hawthorne effect (Discussed in Paper I) and self-fulfilling biases (McCambridge et al., 2014). A confirmed concussion by a healthcare professional would have been preferred. However, this is rarely a realistic option when doing a retrospective study. Nor is it thought to give a good representation of concussion history because of underreporting among athletes (Leahy et al., 2020; McCrea et al., 2004; Meehan et al., 2013). A little under half of the participants sought medical assistance after a concussion (Paper I). Medical records would therefore not have fully represented the concussion group.

The multi-modal approach to concussion symptoms represented here is the study's major strength. It introduces the challenge of assessing all these different variables and how they are connected. With this approach also comes the opportunity for researchers from different fields to work together and use technological and methodological advances unique to their expertise. Limitations regarding the influence of a possible third variable are, however, recognized. Prior mental health (Iverson et al., 2020), whiplash injuries (Gil & Decq, 2021) and in general vestibular and ocular problems could all be influencing current symptoms and outcomes on tests and scales.

Although further research into this is needed, results are highly relevant, add significantly to the concussion literature, and have clinical value.

5.4.1 Paper I

In Paper I, methodological problems in concussion studies were explored. The Paper aimed to examine different ways of asking about concussion history and if more details affected recollection when using self-reported concussion assessment. Because of this, using self-report was not seen as a limitation. Self-reports may be limited by memory, inaccurate self-diagnosis, self-fulfilling biases like participants adjusting their answers to what they think are expected, and suggestibility (McCambridge et al., 2014; Rice et al., 2018). An attempt was made to minimize these limitations by having interviewers trained to follow a semi-structured interview format (Meier et al., 2015), and a detailed recollection of past events was possible. This method of a detailed description of past events has been used before to assess concussion history (Prien et al., 2020). This allowed for an evaluation of a self-report method that is rarely used in concussion studies, which serves as the study's major strength.

5.4.2 Paper II

Limitations regarding the report of concussion history are the same as listed in Paper I. The author recognizes problems regarding self-report and possible inaccuracy as participants had to rely on their own memory to recall events and symptoms (Chan, 2009; McCambridge et al., 2014; Rice et al., 2018). In some cases, incidents happened a long time ago, and participants were not sure if they had experienced a symptom or not. In those cases, participants had the option to skip an item on the symptom scales (SCAT5). The use of the SCAT5 to assess symptoms retrospectively is considered a limitation as the scale is not intended to be used this way. However, it was used as a structured tool to assess the recollection of participants, and it did differentiate between different concussive incidents.

Mental health scales were used to assess depression and anxiety symptoms. The scales used are not intended to serve as a proper diagnosis of mental health, only as an indication of a problem and were used to compare different groups. Therefore, results regarding mental health need to be interpreted accordingly. The potential overlap between the SCAT5 concussion symptom checklist and mental health scales also needs further investigation.

The control group sample was small and not comparable to the concussion group in size. Nevertheless, the control group represented athletes with similar backgrounds to those with concussion history, and the homogeneity is thought to serve as a strength of this study. However, it is not possible to rule out subconcussive events in the athletes. Subconcusive events have been linked to cognitive impairment (McCrory, Meeuwisse, et al., 2017; Rawlings et al., 2020), which could be affecting this population of athletes as a whole.

The major strength of this study is that it is the first done in a large sample of retired and still active female athletes with a concussion history, where reported concussion history included details about specific incidents and a neurocognitive test battery (Kontos et al., 2016; Lovell, 2009). It also included an assessment of mental health and offered a comparison of a group of non-concussed athletes. A multi-modal assessment of concussion symptoms which is preferred (Broglio et al., 2007; Sherry et al., 2019), is also one of the study's strengths.

5.4.3 Paper III

In Paper III, several limitations are recognised. Classification of groups based on concussion history was done based on the results in Paper I. Therefore, methodological problems introduced in Paper I regarding self-reports of concussion history also apply in Paper III. Although the concussion and control groups were similarly matched, the lack of third variable consideration could have affected the results. Participants were not asked about having balancing problems like inner ear problems or neck injuries, which are examples of a third variable which could have affected their performance in the VR environment. Another limitation is the number of participants divided between the groups. Results from the algorithm analysis could be affected by the number of participants as it limits its predictive capabilities.

Paper III aimed to assess possible biomarkers and if self-reported concussion history (concussion vs. non-concussed) was linked to biophysical measures. This is one of the studies' significant strengths as results support the use of EEG, EMG and HR as possible biomarkers for concussion and the use of ML algorithms to predict concussion history.

6 Conclusions and future directions

As of now, there is no concrete way to diagnose a concussion. This introduces several methodological problems when studying concussions (Bonke et al., 2021; Carroll et al., 2014; Comper et al., 2010; Yumul & McKinlay, 2016), especially when doing a retrospective study in a population where medical records are not readily available (Bonke et al., 2021; Carroll et al., 2014; Comper et al., 2010; Yumul & McKinlay, 2016). Results from papers included in this Thesis support the idea that self-report is an important aspect of concussion studies (Paper I), and despite methodological problems, it is possible to utilize self-report when participants are given an appropriate structure.

Results also support that prior concussion history is connected to worse mental health, sleep and cognition (Bramley et al., 2017; Dessy et al., 2017; Iverson, 2005; D. King et al., 2014; McCrory, Meeuwisse, et al., 2017) (Paper II), mainly worse cognitive inhibition. No connection was found to worse cognitive health in general when compared to a group of non-concussed athletes. It is important to recognize that possible symptoms after a concussion are many, ranging from being mostly physical to being mostly psychological (H. J. McCrea et al., 2013; McCrory, Meeuwisse, et al., 2017), appearing differently between different individuals (Dessy et al., 2017; D. King et al., 2014), possibly depending on their background and pre-existing conditions (Iverson, 2005). Symptom evaluation is therefore complex and third variable problems are potentially many. Therefore, it is essential to find a way to evaluate concussions more reliably. Results support the use of possible biomarkers for concussion diagnosis and symptoms assessment, namely EEG, EMG and HR signals, postural control analysis and technological advances like virtual reality and machine learning (Paper III).

The inclusion of a population that is poorly represented in the concussion literature is very important (Colantonio, 2016). Women seem to be at a greater risk of sustaining a concussion and have a more challenging time when recovering (Clay et al., 2013; Covassin et al., 2018; Daneshvar et al., 2011; Iverson et al., 2017; N. S. King, 2014; Koerte et al., 2020; McGroarty et al., 2020; Mooney et al., 2020). The lack of representation of women in concussion studies leads to an incomplete understanding of concussions in women (Valera et al., 2021). The clinical implications are, therefore, potentially great. Athletes are at a higher risk of sustaining a concussion (Noble & Hesdorffer, 2013) than the general population. Therefore, research done among female athletes is of great importance, as results will influence RTP guidelines and treatment.

This is the first Icelandic study to assess concussion history among female athletes. This is also the first known study to include a large sample of retired and still active female athletes where concussion history is evaluated in detail through a semi-structured interview, and mental health, cognition and physiological responses are also evaluated. Results from this Thesis have important implications, both for future researchers and clinical guidelines. In addition, this project represents the importance of a multi-facet approach and collaboration between different fields in concussion research and is something future researchers should continue to build on.

The project *Concussion among Icelandic athletes – A multi-component study* is only just beginning. The project is a part of a collaboration between Reykjavik University, the University of Iceland and Landspitali University Hospital. Several researchers and specialists have been involved in the project, as well as MSc- and Ph.D. students. The project resulted in a collaboration between different fields spanning psychology and medicine, statistical analysis, physiotherapy, and engineering. Papers including data from the earlier stages of the project have been published (Jónsdóttir et al., 2021; Kristjánsdóttir et al., 2020) but are not a part of this Thesis. The aim is to go further into concussion research among Icelandic athletes, including doing an incidence study and assessing cognition and mental health among male athletes and athletes participating in non-contact sports. The research group will continue to collaborate and work towards a better understanding of concussion symptoms and symptoms progression and their later life implications.

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Appendix: Studies I, II and III

I. Unnsteinsdottir Kristensen, I. S., Kristjansdottir, H., Sigurvinsdóttir, R., Sigurjonsdottir, H. A., Eggertsdottir Claessen, L. Ó., & Jónsdóttir, M. K. (n.d.). Methodology matters: Self-reported concussion assessed by recollecting specific events. *Under review*.

II. Unnsteinsdottir Kristensen, I. S., Jónsdóttir, M. K., Lund S. H., Sigurjonsdottir, H. A., Eggertsdottir Claessen, L. Ó., & Kristjansdottir, H. (n.d.). Concussion history, cognition and mental health among retired and still active female athletes. *Under review*.

III. Jacob, D.[1], Unnsteinsdottir Kristensen, I. [1], Aubonnet, R., Recenti, M., Donisi, L., Ricciardi, C., Svansson, H., Agnarsdóttir, S., Jónsdóttir, M. K., Kristjansdottir, H., Sigurjonsdottir, H. A., Cesarelli, M., Eggertsdottir Claessen, L. Ó., Hassan, M., Petersen, H., & Gargiulo, P. (2022). Towards defining biomarkers to evaluate concussion using virtual reality and a moving platform (BioVRSea). *Nature Scientific Reports*: https://doi.org/10.1038/s41598-022-12822-0

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Paper I

Paper II

Paper III