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Repetitive head impacts in football

Quantifying exposure and assessing outcomes

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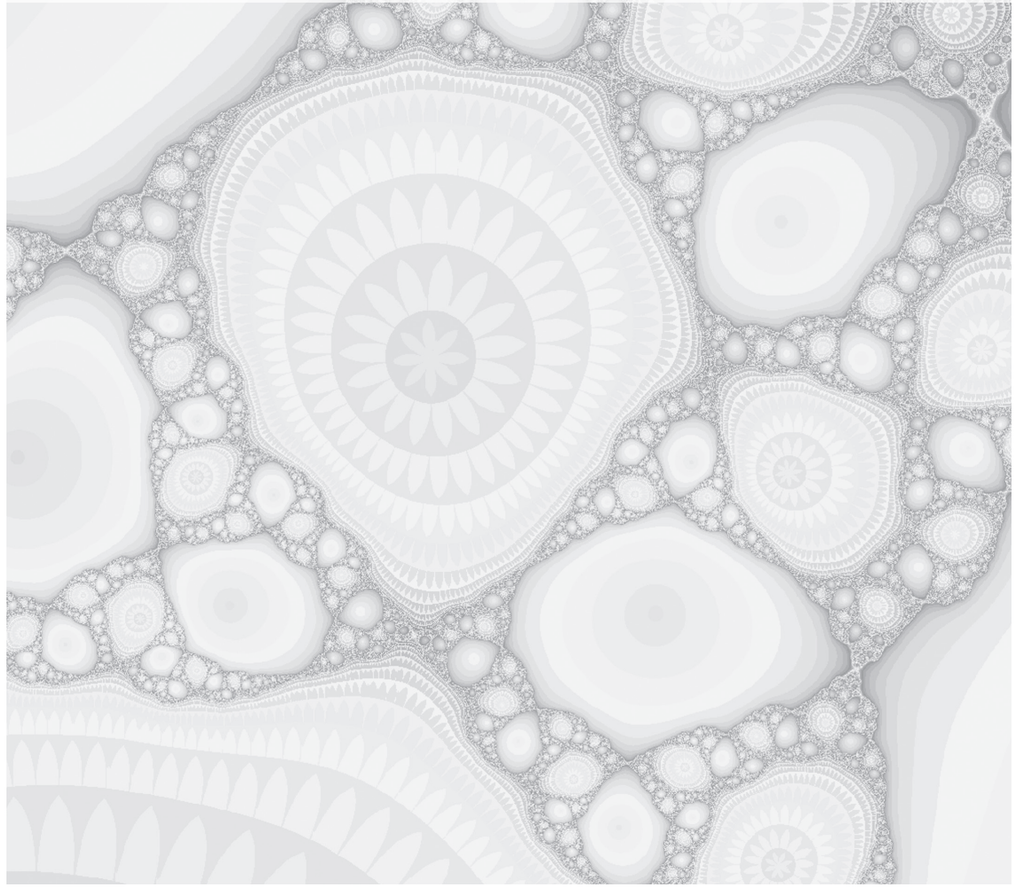

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PhD thesis

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Oslo Sports Trauma
RESEARCH CENTER

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Oslo, April 2020

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List of papers

This thesis is based on the following original research papers, which are referred to in the text by their Roman numerals:

I. Sandmo SB, Andersen TE, Koerte IK, Bahr R. Head impact exposure in youth football – Are current interventions hitting the target? *Scand J Med Sci Sports.* 2020 Jan;30(1):193-198.

II. Sandmo SB, McIntosh AS, Andersen TE, Koerte IK, Bahr R. Evaluation of an in-ear sensor for quantifying head impacts in youth soccer. *Am J Sports Med.* 2019 Mar; 47(4):974-981.

III. Sandmo SB, Goiijers J, Seer C, Kaufmann D, Bahr R, Pasternak O, Lipton ML, Tripodis Y, Koerte IK. Evaluating the validity of self-report as a method for quantifying heading exposure in male youth soccer. Submitted to *Res Sports Med* 23 Feb 2020.

IV. Sandmo SB, Filipcik P, Cente M, Hanes J, Andersen TE, Straume-Naesheim TM, Bahr R. Neurofilament light and tau in serum after head-impact exposure in soccer. *Brain Inj.* 2020 Feb 25:1-8. [Epub ahead of print]

Abbreviations

ANOVA: Analysis of variance

AUC: Area under the curve

CI: Confidence interval

CTE: Chronic traumatic encephalopathy

DTI: Diffusion tensor imaging

GCS: Glasgow Coma Scale

ICC: Intraclass correlation coefficient

MRI: Magnetic resonance imaging

NfL: Neurofilament light chain

PCR: Polymerase chain reaction

PET: Positron emission tomography

PLA: Peak linear acceleration

PRA: Peak rotational acceleration

PRV: Peak rotational velocity

RNA: Ribonucleic acid

ROC: Receiver operating characteristic

SCAT: Sport concussion assessment tool

SD: Standard deviation

TBI: Traumatic brain injury

Summary

In football, intentional heading is an inherent part of the game. Moreover, the game carries a risk of head injuries, including concussions. Playing football can therefore expose players to repetitive head impacts over time. Prospective studies are needed to elucidate whether such exposure can lead to adverse neurological consequences. However, these studies encounter several methodological challenges, relating to exposure quantification as well as outcome assessment.

The general aim of this thesis was to further our understanding of the link between repetitive head impacts in football and potential neurological consequences.

Providing accurate data on heading exposure is key to assess risk and to inform injury prevention measures. Therefore, in Paper I, we aimed to quantify exposure to repetitive head impacts in youth football, assessing the effects of sex and age. For this, we observed football matches (n=267) played during an international youth football tournament, without heading restrictions. Here, we found that boys headed the ball more often than girls (2.7 vs 1.8 headers per hour), and that heading rates increased with age for both sexes. There was substantial variation between and within teams for both sexes in all age groups. The youngest age groups, girls younger than 12 years in particular, rarely headed the ball. In conclusion, we demonstrated that heading rates in football were influenced by sex and age. Importantly, heading was a rare event in the age groups currently targeted by interventions.

In Paper II, the aim was to test the validity of using in-ear sensors for quantifying repetitive head impacts in male youth football. This was first done in a laboratory setting, followed by on-field testing. In the laboratory, we found substantial random *and* systematic error as compared with a reference system. For the on-field testing, six youth football players were instrumented with custom-molded in-ear sensors. First, they completed a structured training protocol consisting of heading and non-heading exercises. Second, they completed two regular training sessions with their team. As recorded by the sensors, on average, heading events resulted in greater accelerative forces than non-heading events in both settings. The on-field accuracy for the sensor to discriminate heading from non-heading events was excellent, and we identified an optimal cut-off value of 9 *g* to do so. However, while this cut-off yielded a positive predictive value of 100% for headers in the structured training protocol, this decreased to 65% in regular training sessions. Consequently, secondary verification (using e.g. video analysis) of head impacts in real-life settings was still necessary, making the use of such sensors highly labor intensive.

In Paper III, we tested the validity of using a self-report questionnaire for quantifying heading exposure in a similar cohort. For this, male youth football players (n=34) from three European countries completed the questionnaire after having been observed while playing with their team for a two-week period. Self-reported numbers were compared to observation (considered reference). Players systematically overestimated their heading exposures with a substantial random error. Therefore, self-report was not considered an adequate measure for quantifying individual heading exposures. However, using rank orders, self-reported numbers had a moderate to strong correlation with observed numbers. Self-reported numbers could also identify players belonging to high and low-exposure groups. Thus, in conclusion, self-report could serve as a tool for ranking or grouping players with respect to heading exposure, supporting its potential use in prospective studies.

In Paper IV, we explored if repetitive headers or accidental head impacts in football cause structural damage to the brain, detected as an increase in serum levels of NfL or tau proteins, controlling for the effects of exercise alone. This was based on a previous prospective cohort study of male professional football players from the Norwegian premier league over two consecutive seasons. First, blood samples were drawn in pre-season. Then, repeat blood samples were drawn 1 and 12 h after the following short-term exposures: (1) high-intensity exercise, (2) repetitive headers, and (3) accidental head impacts in a match. Accidental head impacts were subcategorized as concussive or non-concussive based on reported symptoms. By analyzing a total of 354 blood samples from the original study, we observed no short-term effects on NfL after exposure from any of the three conditions. Tau levels rose from baseline to 1 h after high-intensity exercise and repetitive headers, but not after accidental head impacts in a match. The highest absolute values were seen 1 h after high-intensity exercise. We also evaluated the effect of long-term head impact exposure by comparing two groups with relative differences in previous concussions and headers at baseline (low vs. high levels). We did not detect any group differences. In conclusion, we found no evidence of short- or long-term structural brain injury, as detected by serum NfL and tau. Importantly, however, tau levels increased in response to high-intensity exercise, highlighting an important limitation for using it as a biomarker in sports.

Introduction

Head impacts in contact sports

Traumatic brain injuries (TBI) represent a leading cause of mortality and morbidity worldwide.[1] The association between single high-energy injuries and acute neurological consequences can be readily explored, as there is an obvious causal relationship. In contrast, the effects of repetitive head impacts in the milder range are difficult to investigate, as their consequences are typically more subtle and might take time to establish. A common arena for such repetitive head impacts is contact sports – including boxing, American football, ice hockey and football. The medical community has explored the link between head-impact exposure in sports and neurological outcomes for almost a century, going back to the description of "punch drunk boxers" by Dr. Harrison Martland in 1928.[2] However, despite significant efforts, our understanding of this link is still limited.

Types and terminology

This thesis sets out to explore the effects of repetitive head impacts in football. Initially, it is necessary to clarify (1) the different types of head impacts and (2) the terminology to be used. The spectrum of TBI is typically depicted using the Glasgow Coma Scale (GCS). Assessing three different domains – verbal response, motor response and eye opening – this scale was introduced by Teasdale and Jennett in 1974.[3] Originally, it was employed as a practical tool for assessing the depth and duration of impaired consciousness, regardless of the cause. Since then, it has also been widely used as a way of categorizing the severity of head injuries. Figure 1 shows how GCS scores translate to mild, moderate and severe brain injuries.

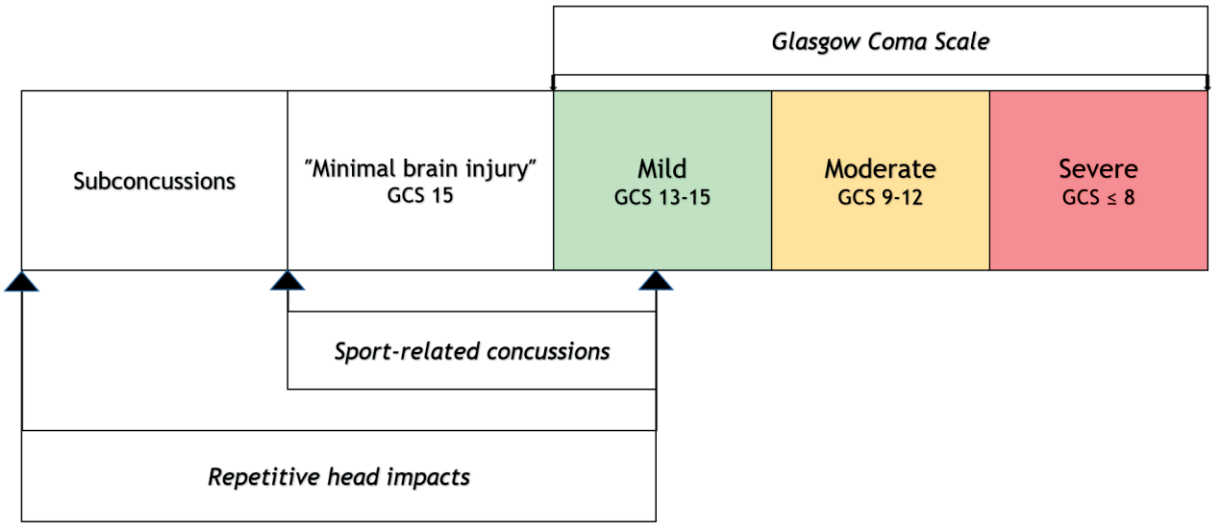

Figure 1. *The Glasgow Coma Scale is used to categorize traumatic brain injuries as mild, moderate or severe.[3] Sport-related concussions are described as belonging to the mildest end of this spectrum.[4] Subconcussions are defined as impacts not causing acute symptoms, and thereby fall outside the range of the classification. Adapted from and reproduced with the permission of Dr. Paul McCrory.*

Concussion is often used synonymously with *mild traumatic brain injury* (mTBI).[5] Others argue that sport-related concussions should be considered a subtype of mTBI, belonging to the mildest end of the spectrum.[4] Regardless, a concussion is a symptomatic head impact affecting neuronal integrity, and is typically defined as the onset of short-lived neurological impairment due to a biomechanical force to the head.[4] Such impairments include a wide range of acute clinical signs and symptoms, e.g. headache and dizziness,[6] which are thought to arise from complex pathophysiological processes in the brain. A concussion is mainly considered to cause transient electrophysiological changes in the neurons. As it lacks a well-defined structural basis, it is often described as a predominantly functional disturbance of the brain.[7,8]

Subconcussive head impacts, on the other hand, is a relatively new term.[9] Such impacts are typically of lower magnitude[10] and do *not* result in immediate symptoms. However, they might still negatively affect neuronal integrity.[11] This is thought to be particularly relevant when they occur repetitively over time, such as in contact sports.[9,11,12] *Repetitive head impacts* can be considered to represent cumulative head-impact exposure, encompassing both *concussive* and *subconcussive* head impacts.[13] Of note, head impacts in the subconcussive range represent the vast majority of head impacts in sports. In this thesis, concussions and subconcussions will be discussed separately where appropriate, while repetitive head impacts will refer to cumulative head-impact exposure.

Neurological consequences

A historical perspective

Repetitive head impacts have long been considered a potential risk factor for adverse neurological outcomes in contact sports. Throughout the 20th century, several landmark papers have laid the foundations for our current understanding of the topic. When the term 'punch drunk' was first introduced,[2] this was a clinical description of an already established observation in boxers by the lay community.[14] Boxers would sometimes display gait abnormalities as well as neuropsychiatric symptoms. At the time, Martland[2] launched his theory that such symptoms were the consequence of 'multiple concussion hemorrhages', but this was eventually discredited.[15]

Nine years later, in 1937, Millspaugh[16] coined the term *dementia pugilistica* (latin for 'boxer's dementia'), based on similar clinical observations as those by Martland. Eventually, more researchers came to the scene, and already in the following decade we saw the advent of the currently used term 'chronic traumatic encephalopathy' (CTE).[17,18] The first case series of neuropathological features in former boxers was then published by Corsellis et al. in 1973.[19] In 2005, Omalu et al.[20] described similar findings in a former American football player, demonstrating that this was not a condition unique to boxers. Bearing in mind marked heterogeneity of the first cases described, it seems plausible that all of these terms have aimed to describe many of the same neurodegenerative processes. Today, the neuropathological basis of CTE has been described in detail,[21] although the underlying mechanisms and clinical features of the condition are poorly understood.[22]

Clinical concepts

From a contemporary clinical perspective, there is a variety of potential neurological consequences due to head injuries in sports. Somewhat simplified, these can be divided into *acute (i.e. short-term)* and *chronic (i.e. long-term) clinical consequences*, as summarized in table 1.

Table 1. *An overview of possible neurological consequences due to head injuries in sports. Adapted from Ling et al.[23]*

Acute consequences	**Chronic consequences**
Concussion	Postconcussive syndrome
Catastrophic brain injuries	Neurodegenerative disorders
Second impact syndrome	*Subclinical findings*
Subclinical findings	

Concussion has already been defined, including where it belongs on the Glasgow Coma Scale. In sports medicine, this has long been recognized as a common injury, with well-known clinical features.[6,8,24] Symptoms are often divided into three domains: somatic (e.g. headache and dizziness), cognitive (e.g. confusion or feeling slowed down), and emotional (e.g. irritability and sadness).[6] Physical signs such as amnesia and loss of consciousness might also be present, but are not mandatory for the diagnosis.[6] The majority of concussive symptoms either resolve or improve substantially within two weeks in adults, and within four weeks in children.[8,25] Greater severity of initial symptoms, previous migraine headaches, and pre-existing mental health problems are all likely predictors of slower recovery (see review by Iverson et al.[25]).

Figure 2 conceptualizes different trajectories in time. *Postconcussive syndrome* denotes the clinical condition where concussive symptoms remain present, or evolve, beyond a time frame of 3 months.[5,23] In some unfortunate cases this might also take on a chronic trajectory, where symptoms persist for more than a year.[5]

Neurodegeneration is another potential consequence. Note that pre-existing chronic symptoms is not a mandatory precondition for its onset (figure 2). Neurodegeneration can be regarded the pathophysiological term referring to progressive atrophy and loss of function of neurons.[26] Different neurodegenerative processes can potentially establish as distinct neurodegenerative disorders, such as Alzheimer disease, Parkinson disease, frontotemporal dementia, amyotrophic lateral sclerosis and CTE.[27] From a broader clinical perspective, the link between TBI and neurodegeneration is becoming increasingly understood.[27] Still, our insight is limited as to how such findings relate to outcomes of repetitive head impacts in contact sports.[28]

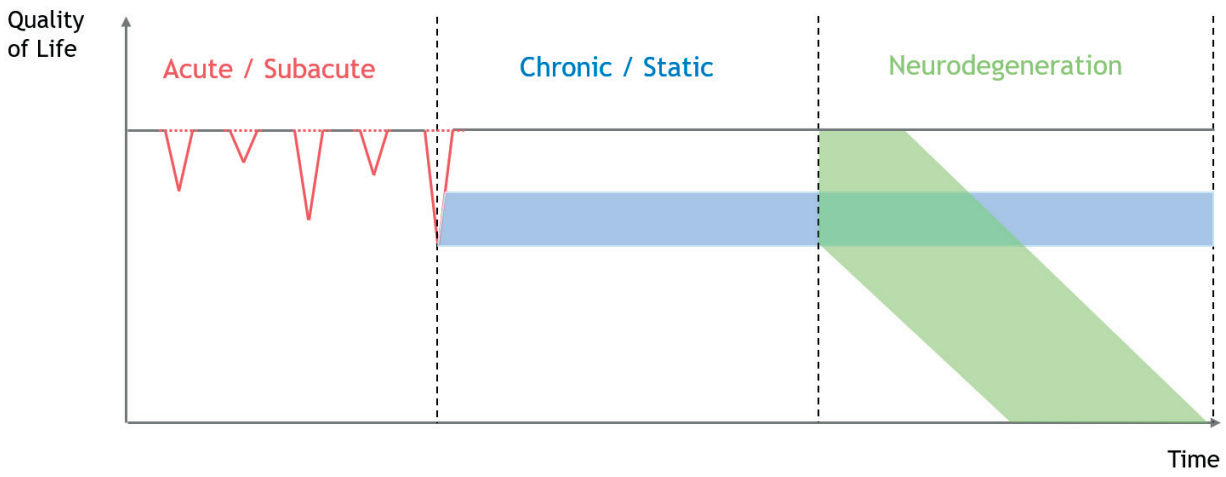

Figure 2. *A model by Koerte et al.,[29] conceptualizing different clinical trajectories after repetitive head impcacts. Quality of life reflects symptom burden in the respective stages, expressed as a function of time. Reproduced with the permission of* Brain Pathology.

As the focus of this thesis is on repetitive head impacts, acute complications in the form of *catastrophic brain injuries* (i.e. moderate to severe TBI involving acute hemorrhages, fractures etc.) will not be discussed further. Neither will the *second impact syndrome*, a contested condition where diffuse cerebral swelling is thought to arise from a subsequent head impact shortly after e.g. a concussion.[8]

Subclinical findings

In addition to the recognized clinical entities listed above, there are also potentially relevant subclinical findings (table 1). These include, but are not limited to, subtle neurocognitive deficits, abnormalities on neuroimaging, and changes in fluid biomarkers. Such findings can provide higher-resolution information on brain health, relating to acute as well as chronic neurological consequences. Note that many of the clinical diagnoses described above are based on either coarse clinical criteria or post-mortem assessments. Importantly, the currently available technologies (e.g. advanced neuroimaging) have limited clinical use in the context of repetitive head impacts. Rather, they are considered important research tools, with an ongoing search for objective biomarkers *in vivo*.[30]

Last, not only can neurological consequences be conceptualized as *acute*, *chronic* and *subclinical*. Brain alterations are also often described as *functional* or *structural*. This is perhaps best illustrated using an example. Clinically, a concussion is considered an *acute* neurological consequence of a head impact. The current paradigm refers to concussion as a complex pathophysiological process in the brain causing transient *functional* alterations, without consistent *structural* abnormalities.[8] Conversely, a neurodegenerative disorder such as Alzheimer disease is defined by its *structural* characteristics on histopathology.[31] Admittedly, such distinctions are arbitrary and will often overlap, but they can facilitate our understanding when we will later explore neurological outcomes.

Repetitive head impacts in football

Role in the game

The rules of modern football were developed in 1863, when rugby and football branched off on different trajectories.[32] While heading the ball in football was initially considered 'ludicrous',[33] it has since become an integral part in many aspects of the game. Heading is a somewhat unique activity compared to other contact sports, as it requires the intentional use of an unprotected head.

Based on our previous definitions, as headers typically are asymptomatic, they can be considered *subconcussive* head impacts. At the same time, heading duels and other parts of the game involve an inherent risk of accidental head injuries, including *concussions*.[34] Thus, football can expose individual players to *repetitive head impacts* over time (figure 1). Football is today considered to be the world's most popular sport, with hundreds of millions of active players. Any neurological risk from such exposure could therefore have a substantial public health impact.

Understanding the magnitude of exposure is key to assess risk. Therefore, before we explore the potential neurological consequences of repetitive head impacts in football, we need to answer the question: How common are (1) concussions and (2) subconcussions (i.e. heading) in football? We will deal with these head impact types separately.

Concussion rates

Concussions are estimated to account for 2-22% of all football injuries.[35] In 2014, Maher et al.[36] reviewed the literature on concussion in football. Based on 13 different studies, they concluded that females typically have higher concussion rates than males. In one of the studies included, Delaney et al.[37] evaluated the incidence and characteristics of concussions in Canadian university players. They found that 62.7% of the players reported at least one event of concussive symptoms during the previous year of play, but only 12.4% of the players recognized this as a concussion. The two most important factors associated with greater risk for concussions were (1) having experienced a previous football-related concussion (odds ratio=3.15) and (2) female sex (odds ratio=2.60).

In their review, Maher et al.[36] also highlighted how concussion rates seem to vary between training and match play. In one study, Marar et al.[38] compared rates and patterns of concussions in a large cohort of high school athletes. For male football players, the overall rate was 0.19 concussions per 1 000 athletic exposures (AE), 0.53 in matches vs. 0.04 during training. For females, the overall concussion rate was 0.34 (almost twice that for males); the rate was 0.92 in matches vs. 0.08 during training. Interestingly, Marar et al.[38] also compared concussion rates between sports. Comparing male athletes only, concussion rates were significantly lower in football (0.19) than in American football (0.64), ice hockey (0.54) and lacrosse (0.40). The authors noted that these numbers were not necessarily generalizable, and that concussions were likely to be underreported. Nevertheless, the study provided valuable insight into the effects of sport, session type, and sex.

Last, Maher et al.[36] noted how age and level of play were likely to play a role. As an example, a study by Gessel et al.[39] compared concussion rates in high school and collegiate football players. For boys, the overall rate (i.e. match and training) increased from 0.22 (per 1000 AEs) in high school athletes to 0.49 in collegiate athletes; for girls, the rate increased from 0.36 to 0.63. Since then, Faude et al.[40] have evaluated the youngest age groups (7-12 yrs, 96% males) in Europe. They concluded that the overall incidence and severity of head injuries were low. Specifically, they found a concussion incidence of 0.02 concussions per 1 000 exposure hours.

In summary, concussion is recognized as an issue in football, but is likely to be underreported. Concussion rates seem to depend on sex, age, level of play and session type. The reasons behind such variations are largely unknown, but playing style and intensity,[41] neck strength[42] and visual awareness[43] are all thought to be involved.

Head injury mechanisms

It is also important to describe head injury mechanisms and playing situations with high injury propensity. Not only is such information relevant when evaluating the risk for adverse outcomes, but also when considering preventive measures such as rule changes.[44]

Andersen et al.[34] used video analysis to investigate mechanisms of head injuries in male elite football in Norway. They found that the most frequent injury mechanism was elbow-to-head and head-to-head contact; the most common playing situation leading to head injuries was engaging in a heading duel (58%). Beaudouin et al.[45] later confirmed this at the elite level in Germany, reporting similar descriptions of injury mechanisms and match play situations.

Other studies have explored injury mechanisms and playing situations in younger cohorts. O'Kane et al.[46] registered concussions in female youth players (11-14 yrs) through weekly online questionnaires. Events leading to concussive symptoms were followed up by retrospective interviews of players and parents. Based on this, they reported that 30.5% of concussions were related to heading activities, while the most common injury mechanism was non-specified player-to-player contact (54.3%). Similarly, Comstock et al.[47] used an online injury surveillance system to evaluate concussions in male and female high school football (14-18 yrs). Heading was the most common sport-specific activity leading to concussions in both boys (30.6%) and girls (25.3%). The remaining incidents were seen during other parts of normal match play. Contact with another player was described as the most common concussion mechanism (68.8% in boys vs. 51.3% in girls).

Preventive measures

Andersen et al.[34] used their findings at the male elite level in Norway to suggest stricter rule enforcement or rule changes concerning elbow use to prevent head injuries. Such a measure was later introduced in the form of a red card (i.e. a match suspension) for intentional high elbow use in duels. Bjørneboe et al.[48] then conducted a preintervention/postintervention study in a similar cohort using video analysis, and demonstrated a decreased rate of situations with a high risk of head injury. Beaudouin et al.[49] have since characterized head injury rates during consecutive seasons of the German male Bundesliga.[49] After the rule change for high elbow use was introduced, they found a 29% reduction in head injuries, including concussions.[49]

In youth football, Comstock et al.[47] suggested a reduction of athlete-to-athlete contact across all parts of play, not focusing specifically on heading, to be the most promising preventive measure. Nevertheless, in 2016, the US Soccer Federation issued a statement announcing that heading was to be banned for players younger than 10 years, with subsequent restrictions in practice from 11 to 13 years.[50] At the time, the initiative was based on a law-suit settlement, and inspired by effective measures in reducing concussion rates in e.g. youth ice hockey.[51] The aim was primarily to reduce concussion incidence, but also to limit cumulative exposure to repetitive head impacts. The effects of this intervention have not been evaluated. In 2020, the Irish, Scottish and English football associations are set to become the first European countries to implement similar restrictions on heading.[52,53] There, guidelines have been developed to gradually introduce heading in training from the age of 11, without restrictions in matches.[53]

Heading exposure

Heading exposure has not been characterized systematically in the same manner as concussions. To obtain relevant information on this topic, a literature search was performed using the following search strategy in PubMed:

1) (heading OR headers OR repetitive head impact* or repetitive impact*) AND (football OR soccer) AND (hasabstract[text] AND English[lang]) AND (epidemiology OR incidence OR rate)

Abstracts of all identified articles were screened as to whether they specifically aimed to evaluate heading exposure. Candidate articles were then reviewed in full text, only to be included if the study provided objective information on heading exposures. Reference lists of the included articles

were screened to identify other potentially relevant studies. Figure 3 provides an overview of the literature selection process.

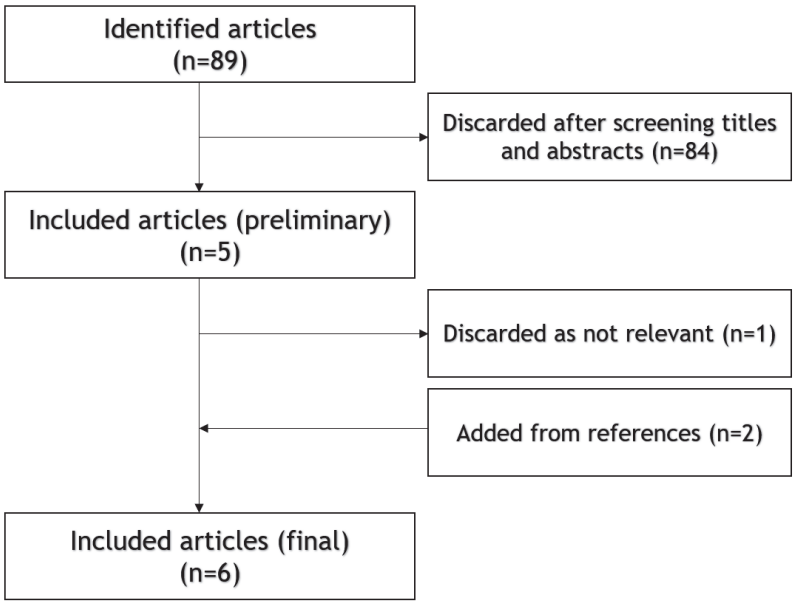

Figure 3. *Flow chart summarizing the identified articles describing heading rates in football.*

In total, four original studies and one systematic review were included after screening titles and abstracts; the systematic review[36] was subsequently discarded, as it did not report numbers on heading exposure. Two more articles were included after checking the reference lists for potentially relevant studies. Table 2 summarizes the papers that were considered relevant, providing objective information on heading rates.

Table 2. *Heading exposure in football.*

				Heading rates	
Study	Sample characteristics	Year	Method	Match	Training
Rahnama et al.[54]	Male elite players from the English Premier League	2002	Video analysis of 10 games	4.6 headers per player hour	*Not reported*
Kaminski et al.[55]	Female high school players (n=26) and collegiate players (n=21)	2007	Direct observation by athletic trainers; 22 match exposures for high school players, 25 for collegiate players	0.8 headers per player per game for high school players; 2.7 headers per player per game for collegiate players	*Not reported*
Chrisman et al.[56]	Male (n=10) and female (n=7) youth players (11-14 yrs)	2016	Skin-patch accelerometers/ direct observation of 72 match exposures	0.93 headers per player per game	*Not reported*
Chrisman et al.[57]	Male (n=21) and female (n=25) youth players (11-14 yrs)	2017	Skin patch accelerometry/ direct observation of 189 match exposures	1.83 headers per player per game	*Not reported*
Press and Rowson[58]	Female collegiate players (n=26; 18-22 yrs)	2017	Skin patch accelerometers/ direct observation of 26 practices and 20 matches	2.16 *impacts* per player per game (90% headers)	1.69 *impacts* per player per practice
Harriss et al.[59]	Female youth players from three teams (12-14 yrs)	2018	Video analysis of 20 matches per team	0.07 headers per player hour	*Not reported*

The study by Rahnama et al.[54] reported the only data on heading exposure at the male elite level, part of a project evaluating injury risks in football in general. They defined heading the ball as an action carrying a significant injury risk. Based on video analysis, they registered a total of 1 723 headers over the course of 10 matches (i.e. an average of 4.6 headers per player per hour).

Two studies evaluated heading exposure in female high school or collegiate athletes. In the study by Kaminski et al.,[55] this was part of evaluating the effects of heading on neuropsychological tests and balance in a group of 26 collegiate players and 21 high school players. They estimated heading exposure in matches over the course of one season, using direct observation by athletic trainers. Collegiate players headed the ball approximately three times more often per game than high school players (2.7 vs. 0.8 headers per player per match). Press and Rowson[58] also reported on heading exposure in collegiate players. Specifically, they followed a group of 26 players over the course of 26 practices and 20 matches. To measure exposure, they used skin patch accelerometers with video confirmation of each impact. They reported an average of 2.16 impacts per player per match, out of which 90% were headers. The remaining events were caused by head-to-head, head-to-ground or unintentional ball contact. Interestingly, this was the only study to also report on heading frequency during training, which was found to be somewhat lower than in matches (1.69 impacts per player per training). Notably, both studies reported large variations within teams.[55,58] The study by Press and Rowson[58] also reported differences between player positions; midfielders headed the ball most often, followed by defenders, forwards and goalkeepers.

The three remaining studies evaluated heading exposure at the youth level. Chrisman et al.[56] followed 17 players (10 boys and 7 girls, 11-14 yrs) during a weekend tournament. They quantified exposure using skin patch accelerometers, and confirmed all impacts with direct observation. Overall, they found an average of 0.93 headers per player per game. They noted that some of the girls played multiple matches without heading the ball once, but emphasized that they were unable to draw any conclusions on the influence of sex due to the small sample size. In a later study, Chrisman et al.[57] followed a similar cohort of 46 players, measuring exposure during one month of match play. Here, they found an average of 1.83 headers per player per game, but noted substantial variation in exposure that seemed to be influenced by sex and age. Last, Harriss et al.[59] followed three female youth teams (12-14 yrs), using video recordings to register headers during one season of match play. Overall, they described a frequency of 0.07 headers per player hour. They concluded that heading frequency increased with age, but that there were no differences between player positions.

Having reviewed this literature, it seems that: (1) there is limited data on heading exposure across different cohorts, and (2) current hypotheses and conclusions are based on small samples with low generalizability. Factors such as age, sex, player position and level of play have been suggested to influence heading exposure. However, no study has examined these factors systematically in larger, representative populations of football players. Existing injury prevention measures targeting heading may therefore be ill-informed. In Paper I, we addressed the influence of sex and age on heading exposure in youth football.

Effects on the brain

We will now turn the attention to what *effects* repetitive head impacts in football might have on the brain. Of note, three different reviews[60-62] recently summarized the available evidence, providing a foundation for our current understanding of the topic.

First, Rodrigues et al.[60] completed a systematic review in 2016, where they evaluated the effects of heading on brain structure and function. Based on 11 studies, they concluded that there was preliminary evidence for an association between heading and abnormal brain structure. One of the highlighted studies came from Lipton et al.[63] Using advanced neuroimaging in male and female amateur football players (n=37), they described an association between self-reported heading during the last 12 months and white matter alterations in the brain. Interestingly, this association was independent of previous concussions, suggesting a role of subconcussive head impacts. Nevertheless, the cross-sectional design meant they could not infer causation. Summarizing 15 studies on the effects of heading on cognitive function, Rodrigues et al.[60] found the evidence to be inconclusive. While six studies detected impairment on one or more neurocognitive tests, nine studies found no such associations.

Second, in 2017, Kontos et al.[61] conducted a meta-analysis on the effects of heading on brain function. Including 28 studies, focusing specifically on neurocognitive performance and concussive symptoms, they found no overall effect of heading. They did, however, observe that age trended towards having a negative influence on outcomes. The authors suggested that any effects may be limited to professional players with substantial exposures over the course of several years. As a final remark, they emphasized the need for caution when interpreting findings from single studies.

Third, in 2017, Tarnutzer et al.[62] reviewed the literature on chronic effects on brain structure and function from playing football. Based on a total of 30 studies, they concluded that there is limited evidence for football-related head impacts to cause persistent functional or structural changes in

the brain. However, they did describe a possible link between multiple previous concussions and neurocognitive abnormalities. Tarnutzer et al.[62] stressed how they were unable to draw any firm conclusions due to methodological shortcomings. Most importantly, there was an overall low quality of exposure quantification in previous studies. The authors considered this a key issue to be solved going forward. All three studies summarized above[60-62] emphasized the need for large-scale prospective studies to clarify what effects repetitive head impacts in football might have on the brain. Ideally, this would include a combination of advanced neuroimaging and neurocognitive tests, allowing for a combined assessment of brain structure and function.

Since then, emerging evidence has suggested an association between playing football and adverse neurological outcomes. In a prospective study from 2017, Koerte et al.[64] demonstrated poorer cognitive performance in a group of 16 male youth football players compared to 14 age-matched controls, suggesting an association with repetitive head impacts. The same year, Stewart et al.[65] described how heading and unintentional head impacts were independently associated with neurological symptoms (e.g. pain or dizziness) in a group of adult amateur football players (78% male). In a similar group, Stewart et al.[66] also found that heading was associated with poorer performance on neurocognitive tests, but that unintentional head impacts were not. The same research group recently published findings on an association between heading and poorer memory performance on computerized testing; in this study, they also demonstrated that genetic factors may be relevant.[67]

In 2019, Mackay et al.[68] published the first large-scale evaluation on neurodegenerative disease mortality in former professional Scottish football players. Compared to the general population, their main findings included a lower all-cause mortality in the football group. Worryingly, however, was that football players had higher mortality from neurodegenerative disease (1.7% vs 0.5%; hazard ratio 3.45). The study was not able to account for the reasons behind the observed difference, as they did not quantify exposure to potential risk factors, such as heading exposure, previous concussions or lifestyle-related factors (e.g. substance abuse).

Summary of research gaps

The current state of the research suggests that there may be an association between playing football and adverse neurological outcomes. However, the specific role of repetitive head impacts remains poorly understood due to small sample sizes, cross-sectional study designs and methodological shortcomings. Thus, there is an established need for high-quality *prospective* studies in different cohorts, including male and female players in different age groups at various levels of play. Such

studies need to include (1) high-quality quantification of exposure to repetitive head impacts and (2) a detailed assessment of neurological outcomes.

RepImpact – a prospective cohort study

RepImpact is an ongoing multidisciplinary, prospective cohort study including male youth football players aged 14 to 16 yrs.[69] The aims of RepImpact are: (1) to evaluate the effects of repetitive head impacts in football on brain structure, function and connectivity; (2) to characterize potential clinical or behavioral consequences; (3) to develop diagnostic biomarkers; and (4) to accurately quantify exposure to repetitive head impacts and identify the role of other risk factors. RepImpact represents the foundation for this thesis; all the papers included relate to the third and fourth aims.

The design of RepImpact includes an observation period of 12 months, enrolling participants in Norway, Belgium and Germany. During this period, the participants are examined at three separate time points: At pre-season (0 months), after a season of play (10 months) and then again after a period of relative rest (12 months). At each time point, a battery of examinations is completed: Advanced magnetic resonance imaging (MRI), computerized neurocognitive tests, balance tests, fluid biomarkers and structured interviews on sport participation and other risk factors. An age-matched group of athletes from non-contact sports (e.g. swimming, cross-country skiing and tennis) is also included, undergoing the same examinations. This design allows for comparing brain development over time between two groups of otherwise healthy youth athletes. The crucial difference between the groups is that the football players are exposed to repetitive head impacts, while the reference group is not. The question of how to quantify this exposure in RepImpact was addressed in Papers II and III.

Quantifying exposure and assessing outcomes – exploring the link

The remainder of the introduction will explore central methodological aspects relevant to the link between repetitive head impacts in football and neurological outcomes. Specifically, this will entail a more elaborate description of (1) *how* to quantify exposure accurately in future studies and (2) *how* to evaluate neurological outcomes in detail. Figure 4 provides a theoretical framework. On each side of this equation, the different elements represent currently available methods to examine the link. Note that this is not an exhaustive list. Rather, it represents and overview of the most informative and promising alternatives to date. Where available, the focus will be on knowledge

from studies in football; if not, the discussion will be based on findings from other contact sports, illustrating potentially relevant findings.

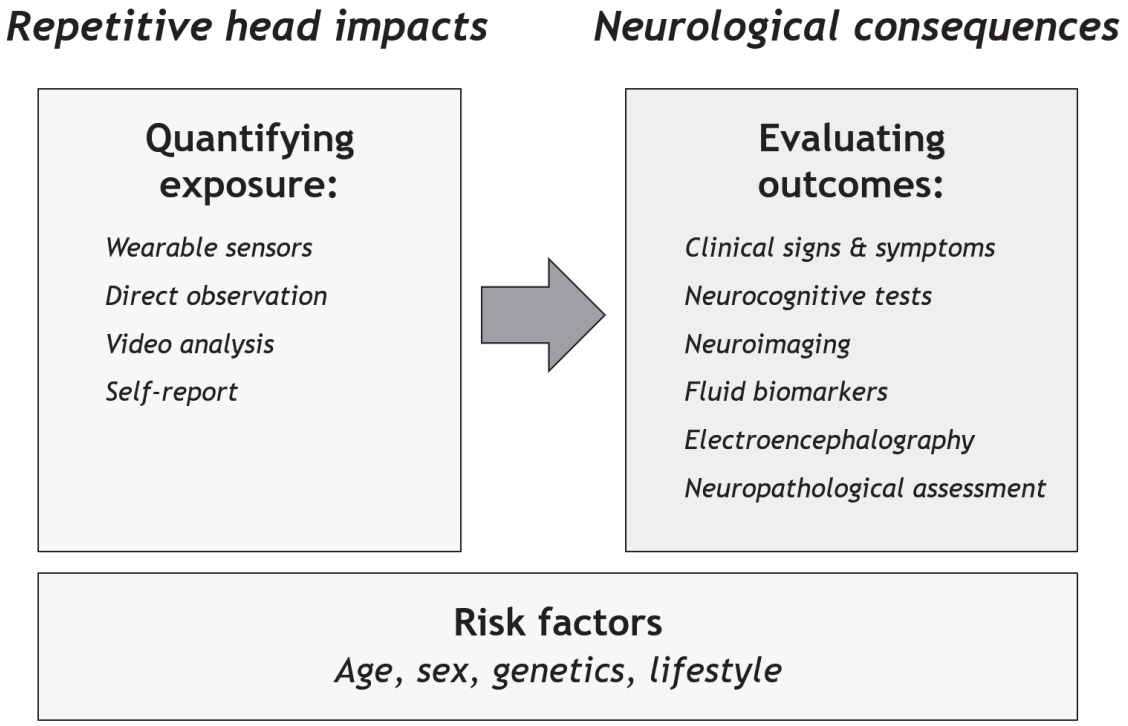

Figure 4. *Exploring the link between repetitive head impacts in football and their potential neurological consequences requires a detailed understanding of exposure and outcomes. Several methods exist to gain insight on both sides of the link. Importantly, this link exists in the presence of several potentially relevant risk factors.*

Quantifying exposure

From a biomechanical perspective, any head impact can potentially cause shearing and tearing of neuronal tissue. With this in mind, a concussion can be regarded the term reserved for when such forces lead to observable signs or symptoms.[70] Importantly, there are no established biomechanical thresholds for categorizing head-impact severities in sports, and accelerative forces correlate poorly with clinical features.[71] (This is a highly complex issue,[10,70] going well beyond the scope of this thesis.) Biomechanical studies suggest several factors to influence head accelerative forces in football.[42] These include heading technique,[42] head and neck mass,[72] sex,[73] ball mass,[74] and the type of header.[75] Regardless, when we aim to quantify repetitive head impacts in sports, there are two main variables of interest: (1) the *number* of impacts over time and (2) the biomechanical *magnitude* of each individual impact (e.g. peak linear acceleration). In addition, timing between impacts[10] and

impact location[76] are believed to affect outcomes. Such knowledge enables a critical evaluation of the methods available for quantifying exposure, as shown in table 3.

Table 3. *The methods available for quantifying repetitive head impacts in football, and their ability to provide objective information on numbers and magnitudes of impacts.*

Method	Number/frequency	Magnitude
Video analysis	Yes	No*
Direct observation	Yes	No
Wearable sensors	Yes	Yes
Self-report	Yes	No

*Combining high-speed video analysis with information on other biomechanical factors (e.g. ball mass) can potentially derive magnitudes.

Video analysis

Video analysis is an established method to study exposures[77] and injury mechanisms[34,78] in sports medicine. It mainly provides an objective means of quantifying the *number* of head impacts. As structured video analysis allows for repeat assessments of individual events, it can be considered the gold standard for doing so. However, it is highly resource-demanding for use over longer time periods. Not only does it require repeat set-up of equipment and presence of research personnel, but also a subsequent analysis of the recordings. Standard video recordings also fail to inform on objective impact magnitudes, i.e. the accelerative forces involved. Sophisticated video analysis with detailed information on ball velocities, ball mass etc., from multiple angles, could account for this.[79,80] Nevertheless, this is currently not feasible for use in prospective studies.

Direct observation

Direct observation can also quantify the number of head impacts during play. Using one or two dedicated observers for registering headers in matches has been shown to be a reliable method compared to structured video analysis.[81] Some studies have used athletic trainers or parents as observers;[82] this approach has not been critically evaluated. Moreover, the validity of direct observation in training sessions has not been characterized in detail. Such sessions can include several balls in play at the same time, and it is likely that additional observers must account for this. Direct observation inevitably depends on the physical presence of dedicated personnel, making it a labor-intensive method not well-suited for longer observation periods in prospective

studies. Similar to video analysis, it also fails to provide an objective account of impact magnitudes. Any pragmatic attempt to account for this is subjective, such as categorizing headers as 'mild vs. hard' or 'short vs. long'.

Wearable sensors

Wearable sensors, such as accelerometers, is the only method that specifically aims to account for the number *and* the magnitude of head impacts (table 3). This allows for characterizing biomechanical features, such as linear and rotational accelerations of one or multiple head impacts.[71] From a theoretical perspective, it is therefore the preferred choice. Multiple options exist, including instrumented helmets alongside non-helmeted alternatives such as headbands, mouthguards, skin patches and in-ear sensors.[83]

Even though accelerometers were introduced in helmets for use in American football as early as 1962,[84] they are still riddled with multiple methodological limitations.[83] First, from a technical perspective, they do not always measure what they are meant to. In short, helmeted[85] and non-helmeted[86] sensor systems have shown large measurement errors compared to a gold standard in laboratory settings. Second, additional challenges arise when used *in vivo*.[87] Note how the goal for a sensor ultimately is to provide information on what is happening *inside* the skull. Factors such as poor coupling to the head makes it hard to discriminate head impacts from noise (e.g. touching the sensor) and other accelerative events (e.g. jumping and running).[58,88] Press and Rowson[58] recently quantified head-impact exposures using skin patches in female collegiate football players, and found a high rate of false-positive events. Similar findings were demonstrated by Cortes et al.[88] Both studies therefore concluded that there is a need for video analysis or direct observation to verify any accelerative event recorded by such devices. This makes their use in prospective studies highly labor-intensive. Last, sensors need to be user-friendly in real life, for the researchers as well as the players.

In summary, wearable sensors are promising tools for quantifying repetitive head impacts in football, but require secondary verification of recorded events. Any method requires careful evaluation before being used, accounting for its specific limitations in representative settings. The utility of in-ear sensors in youth football, designed to improve head coupling, was evaluated in Paper II.

Self-report

As all methods described above have central limitations for large-scale use, self-report has been targeted as the most viable option for use in prospective studies.[81] The advantages of self-report include low cost and allowing for easy administration over time, making it suitable for long-term observation at a population level. Disadvantages include an inherent risk of recall bias, measurement errors, and a failure to account for impact magnitudes. Catenaccio et al.[81] have demonstrated the utility of using a questionnaire to retrospectively quantify repetitive head impacts over a two-week period in adult amateur football. Despite inaccuracies in absolute numbers, the questionnaire retained the capacity for ranking players with respect to heading exposures. Interestingly, they also observed sex differences, in that male players slightly underestimated and females overestimated exposure by a factor of five.[81] Studies from American football have also shown self-report to be useful for quantifying repetitive head impacts.[89,90] As an example, Montenigro et al.[90] developed the 'cumulative head impact index' based on previously published data from instrumented helmets combined with self-reported athletic history (years of play, position etc.).

In conclusion, self-report questionnaires are regarded as the most feasible option for quantifying repetitive head impacts in populations over time, in football as well as in other contact sports. However, the extent to which their accuracy is influenced by sex, age and the duration of recall periods is poorly understood. The validity of using self-report in youth football was assessed in Paper III.

Assessing outcomes

No single examination can fully account for what is happening in the brain in response to repetitive head impacts. Consequently, there is a need to combine methods that collectively assess different aspects of brain structure *and* function. Tarnutzer et al.[62] targeted advanced neuroimaging and neurocognitive tests as an appropriate strategy to do so. However, as shown in figure 4, other methods are also available. Below follows an overview of each method's utility in providing information on acute and/or chronic neurological consequences.

Clinical signs and symptoms

Clinically, subconcussive head impacts are regarded as impacts *without* acute signs and symptoms.[9] Conversely, a thorough clinical evaluation is the mainstay in concussion diagnostics.[6,8] To make the diagnosis in sports, the 'Sport Concussion Assessment Tool 5 (SCAT5)' has been developed –

assessing symptom burden, cognitive status, balance and gross neurological function.[91] Due to a relatively high occurrence of vestibular and ocular manifestations, emerging evidence also suggest a role for specific diagnostic tests targeting these motor systems.[8] As an example, the King-Devick test evaluates eye movements and attention by having the athlete quickly read numbers from three test cards.[92]

Repetitive head impacts have been shown to correlate with acute symptoms in adult amateur players. Stewart et al.[65] found that both headers and accidental head impacts were associated with episodes of neurological symptoms (e.g. dizziness) over a two-week period. Interestingly, these assocations were independent, and stronger for unintentional head impacts. Nevertheless, exposure and outcome were based on self-report, and such isolated findings are difficult to interpret in the absence of more objective measures. Nowak et al.[93] recently reported findings from a randomized clinical trial in male and female adult football players. They evaluated the effects of headers (n=10) on the ocular system by comparing one group heading the ball to another group kicking. As measured by the King-Devick test, they found that the heading group displayed poorer performance. The authors suggested that heading causes short-term neurophysiological changes in the brain, and that these changes manifest as functional impairments in the ocular system.

Regarding signs and symptoms potentially related to chronic neurological outcomes (e.g. cognitive impairment or chronic postconcussive symptoms), the data are scarce in former football players. A few studies, however, have explored the link between repetitive head impacts and chronic symptoms in American football players. Montenigro et al.[90] used the cumulative head impact index to demonstrate that exposure to repetitive head impacts predicted a higher risk of later-life cognitive, mood and behavioral symptoms. However, they emphasized that this study did not evaluate neurodegenerative disorders.[90] In two previous studies, however, the same group aimed to characterize the clinical presentation of CTE in former American football players and boxers.[94,95] In one study, they reviewed the literature on confirmed neuropathological cases.[95] As a result, they proposed clinical research criteria for CTE, coined *traumatic encephalopathy syndrome*. In another study, they combined neuropathological assessment with retrospective interviews (e.g. from family members) in a case series.[94] Here, they described two major clinical manifestations of CTE. One variant was characterized by behavior- and mood-related symptoms with earlier onset, while the other was dominated by cognitive impairment later in life.[94] Note that both of these studies were retrospective and based on neuropathological findings, and that neither included football players. As such clinical descriptions have not been validated in prospective studies, they should be regarded preliminary. Importantly, how they relate to neuropathology is therefore not clear.[22]

Neurocognitive tests

From a clinical point of view, structured neurocognitive testing – assessing memory, reaction time, executive function etc. – is a recognized tool for evaluating both acute and chronic neurological consequences. First, when recovering from concussion, subtle cognitive deficits might remain despite the resolution of clinical signs and symptoms; a detailed neurocognitive assessment can therefore help guide return-to-play decisions.[6] Neurocognitive testing is also established as one of the mainstays in diagnosing neurodegenerative disorders.[96]

Providing high-resolution information on different aspects of brain function, neurocognitive testing has been widely adopted as a research tool, often as computerized test batteries. Since the review by Tarnutzer et al.[62] in 2017, Levitch et al.[97] suggested that different heading exposures can affect different neurocognitive domains in adult amateur players. Specifically, they found that long-term exposures were linked to poorer verbal memory performance, while short-term exposures had a negative influence on psychomotor speed. The link between long-term exposure and poorer verbal memory has later been reproduced.[67] This was described as a 'subclinical cognitive impairment' by the authors, as the absolute values fell within what was considered normal range. In light of such findings, neurocognitive testing is considered one of the most informative and sensitive methods for evaluating functional neurological outcomes.

Neuroimaging

Neuroimaging has a limited role in the acute clinical evaluation of head impacts in the milder end of the exposure spectrum.[30] For concussion, standard anatomical sequences on computed tomography (CT) and magnetic resonance imaging (MRI) are primarily useful to *exclude* severe intracranial complications. In the longer term, MRI has an established role in evaluating neurodegenerative disorders such as Alzheimer disease,[96] e.g. by monitoring brain atrophy over time.[27]

In research settings, advanced neuroimaging is considered the most promising method to evaluate both acute and chronic effects of repetitive head impacts (see review by Koerte et al.[29]). One of the central aims in this research field is to develop objective biomarkers for functional or structural brain alterations.[13,29] Some of the relevant imaging modalities include high-resolution structural imaging, diffusion tensor imaging (DTI), MR spectroscopy, functional MRI and positron emission tomography (PET) imaging.

High-resolution structural imaging allows for objective quantification of volumes and shapes of different brain structures. Koerte et al.[98] used this to demonstrate cortical thinning in a small sample of former football players. These findings were also associated with poorer cognitive performance. The authors suggested that repetitive head impacts in football may cause accelerated age-related cortical atrophy, leading to cognitive decline.[98] In addition to cortical atrophy, other neuroimaging biomarkers have been proposed for evaluating long-term outcomes. As an example, proposed markers of a neurodegenerative disorder such as CTE include a cavum septum pellucidum and decreased volumes of brain structures such as the hippocampus.[13,29]

DTI is a method highly sensitive to water diffusion. This enables the evaluation of microstructural integrity of white matter in relation to both short- and long-term exposure to repetitive head impacts (see review by Schneider et al.[99]). Cross-sectional studies by Lipton et al.[63] and Koerte et al.[100] have shown an association between long-term exposure to repetitive head impacts in football and white matter microstructural abnormalities, independent of previous concussion history. DTI is considered the most promising tool for investigating longitudinal microstructural changes in the brain.[13,99]

MR spectroscopy measures the concentration of neuronal metabolites. Neurochemical signatures in select brain regions may reflect different functional alterations.[29] Koerte et al.[101] have used MR spectroscopy on former professional football players. Comparing them to control athletes, they described neurochemical alterations suggestive of neuroinflammation. As these findings were not associated with neurocognitive performance, the authors suggested that neuroinflammation might precede cognitive decline. MR spectroscopy may eventually also generate objective biomarkers to evaluate neurodegenerative changes.[13]

Functional MRI provides an indirect measure of cerebral blood flow, and is thereby assumed to reflect neuronal activity. To date, few studies have used this to study the effects of repetitive head impacts in contact sports, but it is considered an informative research tool.[13,29]

PET imaging detects gamma rays emitted from radionucleotide tracers injected into the body. PET tracers that bind to different neurodegenerative proteins (e.g. tau and amyloid; see section on neuropathology below) have been used to evaluate neurodegenerative changes after traumatic brain injuries.[27] Stern et al.[102] recently used PET imaging in former American football players. Compared to controls, they found higher tau levels in brain regions implicated in CTE. The authors highlighted several limitations to the method, including suboptimal specificity and only allowing for assessments on a group level.[102] However, by overcoming such challenges, selective tau tracers could eventually provide *in vivo* biomarkers of CTE.[13]

Fluid biomarkers

When the brain is exposed to head impacts, accelerative forces might cause neuronal tissue injury. This, again, can lead to the release of structural proteins into different body fluids, such as the cerebrospinal fluid, saliva or blood.[103] Release of certain proteins can also result from neurodegenerative processes.[27] Consequently, many candidate fluid biomarkers have been proposed over the last decades (figure 5).

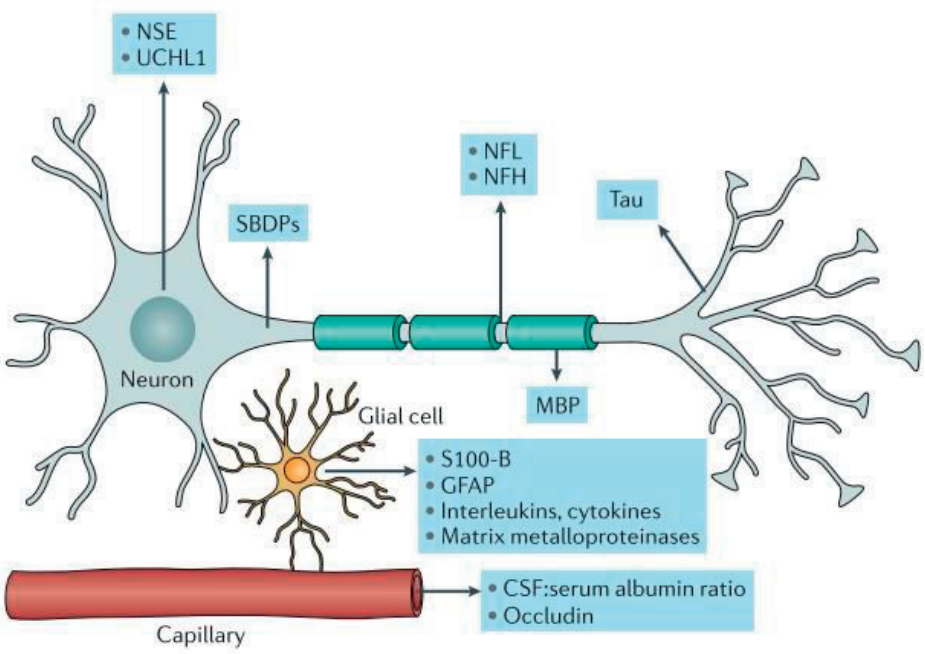

Figure 5. *As shown by Zetterberg et al.,[103] several structural neuronal and glial proteins have been targeted as candidate fluid biomarkers to reflect the severity of traumatic brain injuries. Of these, tau proteins and neurofilament light chains (NfL) have shown particular promise for use in sports medicine. Reproduced with the permission of* Nature Reviews Neurology.

Protein S100B, GFAP and UCHL-1 in blood have already been approved for clinical use.[104,105] However, this is currently limited to guide the need for neuroimaging in the acute setting following TBI, utilizing the high negative predictive value of these biomarkers for detecting intracranial complications.

For evaluating the effects of repetitive head impacts, fluid biomarkers are mainly considered important research tools.[30] Challenges include poor sensitivity and specificity, which make their diagnostic or prognostic value in sports medicine limited. As an example, Straume-Næsheim et al.[106] demonstrated how exercise alone caused an increase in protein S100B, rendering it a

suboptimal biomarker for assessing head impacts in football. For each candidate biomarker, such factors must be accounted for in representative sport-specific settings.

Neurofilament light chain (NfL) and tau in blood reflect axonal injury, i.e. structural neuronal tissue injury (figure 5). Both of these proteins have been targeted as promising candidates for use in sports medicine.[107] As an example, Shahim et al.[108] recently found elevated NfL levels to be a highly sensitive marker for concussion in boxers as well as a predictor of prolonged postconcussive symptoms. Furthermore, NfL levels have been associated with frequency and magnitude of head impacts in collegiate American football players.[109] Tau and NfL levels in blood have also been linked to neurodegenerative changes.[110,111]

MicroRNAs are short, non-coding nucleotide sequences involved in regulating gene expression. In addition to the structural proteins mentioned above, several microRNAs have recently been proposed as potential TBI biomarkers.[112] Not only can microRNAs be released into the blood stream as a result of structural tissue damage. They can also be up- or downregulated in response to different physiological and pathological processes in the brain,[113] possibly providing insight into functional alterations. To date, the data on microRNAs and head impacts in sports remain scarce. Preliminary studies in mixed martial arts and rugby, however, suggest that microRNAs in blood and saliva can be informative.[114,115]

In summary, fluid biomarkers can be used in research settings to evaluate the acute and chronic effects of repetitive head impacts, but their clinical use is limited.[8] In the future, fluid biomarkers might ultimately provide objective diagnostic or prognostic information. Blood is considered a promising biofluid, despite several technical and biological issues (e.g. passing the blood-brain barrier).[103] In Paper IV, we explored the effects of repetitive head impacts in football on serum tau and NfL, controlling for the effects of exercise alone.

Electroencephalography

Electroencephalography (EEG) is a method used for recording electrical activity in the brain, thereby providing information on neurophysiological processes *in vivo*. Tysvaer et al.[116,117] published some of the first studies on the effects of repetitive head impacts in football, reporting abnormal EEG findings in former and active football players compared to controls. These findings have not been replicated in larger samples or in prospective studies. Because of methodological issues, Tarnutzer et al.[62] summarized the evidence on EEG abnormalities due to football participation as inconclusive. In short, EEG is a resource-intensive method and has not been widely adopted for assessing outcomes in contact sports.

Neuropathological assessment

Post-mortem neuropathological assessment of brain tissue is the only way of providing a definite diagnosis of neurodegenerative disorders, including CTE.[118] CTE is considered a distinct condition characterized by its pathognomonic feature: aggregates of hyperphosphorylated tau proteins at the depth of the cortical sulci (see review and staging criteria by McKee et al.[21]). Based on neuropathological studies and retrospective interviews, exposure to repetitive head impacts is considered the greatest risk factor for triggering its onset.[12,119] Also, cumulative exposure to repetitive subconcussive head impacts, even in the absence of concussions, is suggested to play an independent role in its pathogenesis.[13] However, our current understanding of the disease is limited,[22] primarily due to the lack of objective biomarkers and clinical criteria to make the diagnosis *in vivo*.

Most of the available data on CTE originates from former American football players with relatively long careers at a high level.[119] A recent report from Mez et al.[12] described how the risk of developing CTE increased with the number of years played, suggesting a dose-response relationship. The prevalence of the disease in the general population is unknown. However, Bieniek et al.[120,121] have demonstrated that CTE was more strongly associated with former participation in American football compared to other sports. A complicating matter is that CTE is well-known to be comorbid alongside other neurodegenerative disorders, including Alzheimer disease and frontotemporal dementia.[21] Also, disease progression and the role of other risk factors (e.g. substance abuse) are still poorly understood.[13,122]

Data on neurodegenerative changes in football players are limited. Two case series have documented neuropathologic findings consistent with CTE in players who developed dementia in later life.[123,124] In many of these cases, CTE was described as a comorbid condition accompanying a primary dementia, such as Alzheimer disease. One study suggested their findings to be related to repetitive head impacts,[124] while the other emphasized an uncertain clinical significance.[123] Last, as mentioned previously, Mackay et al.[68] have reported increased mortality from neurodegenerative diseases in former professional football players, based on death certificates as a proxy for neuropathological assessment. Even though they were unable to account for exposure to repetitive head impacts or other risk factors, this is the most informative epidemiologic study on long-term neurological outcomes in football players to date.

Risk factors

Until now, we have focused on elements targeting the direct link between repetitive head impact exposure and neurological outcomes. Figure 4 shows how this link exists in the presence of risk factors that are potentially relevant for developing adverse neurological outcomes. Such factors should therefore ideally be controlled for in prospective studies.

Age and sex

Age needs consideration for several reasons. First, age is suspected to affect outcomes after concussion. In 2017, Iverson et al.[25] reviewed the literature on predictors of clinical recovery, and suggested that the teenage years might be a particularly vulnerable period for developing postconcussive symptoms. Second, evidence from American football suggests that age of first exposure to repetitive head impacts might be linked to long-term cognitive, neurological and neuropsychiatric disturbances (see review by Alosco et al.[125]). Taken together, the underlying causes and mechanisms for such findings are unknown. However, increased vulnerability of a rapidly developing and maturing brain in youth has been suggested.[125,126] Last, aging itself is independently linked to neurodevelopment[125] and neurodegeneration.[21]

Regarding sex, Iverson et al.[25] also pointed out that girls might be at greater risk than boys for prolonged recovery from concussion. Interestingly, recent neuroimaging studies have shown sex to influence white matter abnormalities after concussive[127] and subconcussive head impacts.[128] Of particular interest, Rubin et al.[128] used DTI to examine white matter changes in adult male and female football players with similar heading exposure during the previous 12 months. They found women to demonstrate more widespread changes compared to males, and the authors therefore suggested sex-dependent variations in the brain's response to trauma.[128] Nevertheless, as they quantified heading exposure using self-report, they were unable to account for how biomechanical impact magnitudes potentially contributed to their findings. As sex also seem to influence head accelerations when heading the ball, with greater impact forces in females,[73] this provides an alternative explanation for such findings.

Genetics and lifestyle factors

Genes are known to affect outcomes after TBI.[27] Specific *apolipoprotein (APOE)* genotypes are acknowledged risk factors for e.g. Alzheimer disease,[129] and have also been linked to chronic neurological deficits in boxers[130] and poorer cognitive performance in American football players.[131] Interestingly, Hunter et al.[67] recently examined the association between self-reported heading

exposure and verbal memory performance in adult football players. When comparing two groups with high exposure levels over the last 12 months, they found that having a high-risk *APOE* genotype was assoicated with poorer performance on the test. They regarded their findings as preliminary evidence for considering genetic factors when making future safe-play recommendations.

Last, lifestyle factors such as physical activity, sleep, substance abuse (e.g. alcohol) and nutrition can all influence a wide range of acute and chronic neurological outcomes. Importantly, they can be overrepresented in at-risk populations, thereby introducing confounding.[22] How such factors relate to e.g. neurodegenerative conditions such as CTE is still largely unknown.[13,22]

Aims of the thesis

The general aim of this thesis was to further our understanding of the link between repetitive head impacts in football and potential neurological consequences.

Specific aims relating to the different papers were:

I. To quantify exposure to repetitive head impacts in youth football, assessing the effects of sex and age (Paper I).

II. To test the validity of using in-ear sensors for quantifying repetitive head impacts in male youth football (Paper II).

III. To test the validity of a questionnaire for quantifying heading exposure in male youth football players over a two-week period (Paper III).

IV. To explore if repetitive headers or accidental head impacts in football cause short-term structural damage to the brain, detected as an increase in serum levels of NfL or tau, controlling for the effects of exercise alone (Paper IV).

V. To explore potential long-term effects on the brain by evaluating the influence of previous exposure to repetitive head impacts in football on resting serum levels of NfL and tau (Paper IV).

Methods

This thesis is based on four studies, each study corresponding to an original research paper. Paper I focus on quantifying exposure to repetitive head impacts in youth football. Papers II and III evaluate methods for quantifying exposure to repetitive head impacts in RepImpact. Paper IV evaluate potential blood biomarkers for assessing outcomes after head impacts in professional football.

Study designs and populations

Paper I

In Paper I, male and female players participating in Norway Cup in 2018 were included. Norway Cup is one of the world's largest international football tournaments, including thousands of male and female players from different age groups (11 to 19 yrs). At the time, the tournament had no restrictions on heading. Based on a convenience sample of tournament matches, we registered repetitive head impacts using direct observation by trained research assistants. For each match, one observer was present. All headers were assigned to individual players, and were classified as 'short' or 'long' based on the observer's subjective impression of the impact magnitude. Moreover, headers were classified as to where on the pitch they occurred, used as a proxy for player position. For each sex and age group, we calculated heading rates. Matches from the senior elite level in Norway were included as reference; for these, we used structured video analysis of commercially available TV video recordings.

Moreover, any events thought to involve a high risk of head injury were registered. All such *head impact incidents* were defined according to previously used criteria by Andersen et al.[34] Specifically, events were included if all the following criteria were fulfilled: (1) a player appeared to be hit in the head, face or neck; (2) the match was interrupted by the referee; and (3) the player remained lying on the ground for 15 s or more.

Paper II

In Paper II, we conducted a stepwise evaluation (i.e. laboratory and on-field) of an in-ear sensor. The sensor has been designed to optimize head coupling and thereby obtain more accurate

readings (figure 6). For any head accelerative event above 3 *g*, the sensor records peak linear acceleration (PLA), peak rotational acceleration (PRA) and peak rotational velocity (PRV).

Figure 6. *In the first step, the in-ear sensor was mounted to a reference system (Hybrid III) in a laboratory setting (left). The reference system was impacted with a linear impactor, recording measured accelerations from both systems (middle). Then, the sensor was tested* in vivo *(right).*

As a first step, we validated the in-ear sensor in a laboratory setting by comparing its outputs to a headform reference system (Hybrid III). A range of different impact severities, types and locations were included, focusing on impact magnitudes typical for football. For the main analyses, we tested a custom-made sensor with a flat configuration to optimize coupling to the Hybrid III. We also repeated a subset of the impacts twice to evaluate how variations in head coupling would affect the outputs of a sensor with a regular (i.e. in-ear) configuration. First, we carved out an artificial ear canal in the Hybrid III rubber surface, allowing for tight coupling when impacted. Second, we expanded the same ear canal, allowing for loose coupling, repeating the same impact conditions. All tests were cross-referenced with high-speed video analysis of each individual impact.

We then included six male elite youth football players (14-16 yrs) from Norway, instrumenting them with custom-molded in-ear sensors (figure 6). We first conducted on-field testing in a controlled setting. For this, the players completed a structured training protocol with drills typical for football; the protocol consisted of five heading exercises and six non-heading exercises. Then, the players completed two regular training sessions with their team. For each nominal head impact event recorded, we obtained PLA, PRA and PRV values from the sensors. The events were classified by comparing them with structured video analysis. For the two on-field settings, we

evaluated the sensor's ability to discriminate between head impacts and other accelerative events. This was done to identify optimal cut-off values.

Paper III

In Paper III, we evaluated the use of a self-report questionnaire in male youth football players. For this, we included a total of 34 players from Norway (n=12), Belgium (n=8) and Germany (n=14). The same questionnaire has previously been used in adult amateur football to retrospectively quantify two weeks of exposure to repetitive head impacts in football.[81] Briefly, the players were asked how many matches and training sessions they had participated in during the last two weeks, and how many times they had headed the ball on average for each session type. The validity of self-reported numbers was assessed by comparing them to numbers obtained from direct observation or video analysis. Direct observation was used in Belgium and Germany; in Norway, direct observation was used for matches, while structured video analysis was used for training sessions.

Paper IV

Paper IV was based on a prospective study by Straume-Næsheim et al.,[106] and included male professional football players from two consecutive seasons (2004 and 2005) of the Norwegian premier league. The original study was designed to detect if minor head impacts in football could cause neuronal tissue injury[106] or cognitive impairment[132]; for this, they collected blood samples and performed neurocognitive tests. The blood samples have since been stored (-80°C) for later analyses. A subset of the blood samples (n=354) were reanalyzed for Paper IV. This was done to explore the effects of repetitive head impacts in football on serum tau and NfL concentrations, measured using an ultrasensitive assay.

Short-term effects

To evaluate short-term effects, blood samples were first drawn at pre-season (baseline), and then 1 and 12 h after the following exposures: (1) a high-intensity training session without heading; (2) a training session with repetitive headers and otherwise low exercise intensity; and (3) accidental head impacts in a match.

Three teams completed the two training sessions. Both sessions were designed to closely mimic regular exposure to football, and were completed on separate days. *High-intensity exercise* served as a reference condition; here, heading was not allowed in order to isolate the effects of vigorous

physical activity. The session with *repetitive headers* included multiple heading drills with impact magnitudes typical for professional football; here, the exercise intensity was kept low in order to isolate the effects of subconcussive head impacts. Heading exposure was quantified based on structured video analysis of a subset of the players. The average number of headers per player was estimated to 18.9, ranging from 7 to 33.[106]

Head impact incidents in regular league matches were identified from direct sideline observation by medical or research personnel; these incidents were defined according to the same criteria described above for Paper I. The subcategorization of head impact incidents as either *concussive* or *non-concussive* was based on symptoms reported by the players. At the time, *concussion* was defined according to the Vienna consensus statement in 2001.[133]

Long-term effects

Long-term effects of previous head-impact exposure on baseline tau and NfL levels were also evaluated. This was done by comparing two groups with high vs. low exposure to previous concussions and headers, estimated using self-report questionnaires completed by the players at baseline. For the purposes of the questionnaire, a concussion was defined as having experienced loss of consciousness and/or amnesia after a head impact. Low-risk players were defined as those reporting no previous concussions *and* an average of five or fewer headers per match; high-risk players were defined by one or more previous concussions *and* more than 10 headers per match.

Statistical analyses

In Paper I, heading rates were expressed as the average number of headers per player per hour. Independent t-tests were used to assess the effects of sex, and ANOVA to assess the effects of age. The sensitivity of direct observation as a method was validated compared to structured video analysis of a subset of matches from Norway Cup that were commercially broadcast. For these matches, we also had two independent observers present; inter-rater reliability of direct observation was expressed by the intraclass correlation coefficient (ICC).

In Paper II, the validity of the in-ear sensor in the laboratory setting was evaluated by calculating its systematic and random error.[134] Systematic error reflect accuracy, while random error reflect precision; both were expressed as a percentage compared to reference. For the on-field evaluation, we calculated mean values ± SD for all (1) heading and (2) non-heading events. Receiver operating characteristic (ROC) curves were constructed to determine the discriminatory capacity of the

sensor, expressed as the area under the curve (AUC). For different cut-off values identified on the ROC curve, we then calculated sensitivity and positive predictive value to investigate how the sensor would perform without secondary verification of events.

In Paper III, the accuracy of self-report was expressed as a factor based on the observed numbers. Random error was used to express precision.[134] Spearman's rank correlation coefficient was used to evaluate the association between self-reported and observed heading exposure. Furthermore, ROC curves were used to determine the ability of self-report to accurately identify players belonging to different exposure groups (i.e. high vs. low levels of exposure). For this, the data were randomly split into a training set (n=17 players) and validation set (n=17 players). The exposure groups were arbitrarily defined and identified based on observed numbers in the training dataset, using either (1) median or (2) tertile values.

For Paper IV, we used repeated measures ANOVA to identify any between-group or within-group differences in protein biomarker levels, correcting for multiple comparisons. Any differences were further explored using independent t-tests.

For all papers, SPSS (IBM SPSS Statistics, IBM Corporation, Chicago, IL) or SAS (SAS Institute Inc., Charlotte, NC) were used for statistical analyses. Unless otherwise specified, tests were two-sided using an α-level of <0.05 to denote statistical significance.

Ethical considerations

All four studies were approved by the relevant ethics committees and institutions (Appendix I). Specifically, Papers I and II were approved by the Ethics Committee at the Norwegian School of Sport Sciences. Paper III was approved by the Regional Committee for Medical and Research Ethics South East in Norway (as part of RepImpact), the Ethics Committee of the Medical Faculty at the University of Munich in Germany, and the local Ethics Committee of UZ/KU Leuven in Belgium. Paper IV was approved by the Regional Committee for Medical and Health Research Ethics South East. The original study by Straume-Næsheim et al.[106] was approved by the Regional Committee for Medical and Health Research Ethics South and the Data Inspectorate in Norway, allowing for storage and later analyzes of blood samples. For Paper I, informed consent was not deemed necessary as no sensitive personal information was registered. In Papers II, III and IV, voluntary participation was emphasized. Written informed consent was obtained from the players, as well as from their legal guardians when appropriate (Appendix II). None of the studies involved experimental procedures on humans.

Results and discussion

Repetitive head impacts in youth football (Paper I)

In Paper I, we evaluated exposure to repetitive head impacts in youth football, assessing the influence of sex and age. For this, we observed a total of 267 matches, corresponding to 4 011 player hours.

Heading exposure

In total, we registered 9 049 headers. Boys headed the ball more frequently than girls (t-test, $p<0.001$), and heading rates increased with age (ANOVA, $p<0.001$). Table 4 shows heading rates according to different age and sex groups.

Table 4. *Heading rates (with 95% CI) by age and sex. Rates are expressed as the average number of headers per player per hour.*

	Boys			Girls		
Level	Short headers	Long headers	Total headers	Short headers	Long headers	Total headers
U-12	1.0 (0.7-1.2)	0.3 (0.2-0.4)	1.2 (0.9-1.6)	0.5 (0.4-0.7)	0.1 (0.0-0.2)	0.6 (0.4-0.8)
U-13	1.3 (1.1-1.5)	0.6 (0.4-0.7)	1.8 (1.6-2.1)	0.8 (0.6-0.9)	0.1 (0.0-0.2)	0.9 (0.7-1.1)
U-14	1.5 (0.8-2.8)	0.8 (0.6-1.0)	2.2 (1.9-2.6)	0.5 (0.3-0.7)	0.2 (0.0-0.3)	0.6 (0.3-0.9)
U-15	1.6 (1.3-1.9)	0.7 (0.5-0.9)	2.3 (2.0-2.5)	1.1 (0.8-1.3)	0.4 (0.2-0.6)	1.4 (1.1-1.7)
U-16	1.7 (1.3-2.2)	0.6 (0.3-1.0)	2.4 (1.8-3.0)	1.5 (1.2-1.7)	0.4 (0.2-0.7)	1.9 (1.5-2.3)
U-17	2.1 (1.6-2.6)	1.2 (0.9-1.4)	3.3 (2.7-3.9)	1.7 (1.3-2.0)	0.6 (0.4-0.8)	2.3 (1.8-2.7)
U-18	1.7 (0.9-2.4)	1.4 (1.1-1.7)	3.1 (2.2-4.0)	1.3 (0.9-1.6)	0.6 (0.4-0.8)	1.9 (1.4-2.3)
U-20	1.9 (1.4-2.3)	1.4 (1.0-1.7)	3.2 (2.8-3.7)	1.7 (1.1-2.2)	0.8 (0.5-1.1)	2.4 (1.7-3.2)
Senior*	0.9 (0.7-1.1)	2.5 (2.1-3.0)	3.4 (2.8-4.0)	0.8 (0.6-0.9)	1.9 (1.7-2.2)	2.7 (2.4-3.0)

*Senior level was observed from TV video recordings from the Norwegian premier leagues (Toppserien and Eliteserien), and included for comparison.

Figure 7 displays absolute heading exposure per match. We observed substantial variation between and within teams for both sexes in all age groups. There was a general trend for a few players on each team to do most of the heading. For the youngest age groups, especially girls, heading the

ball was a rare phenomenon. Evaluating pitch distribution, the most common location for headers to occur was the central midfield (40%).

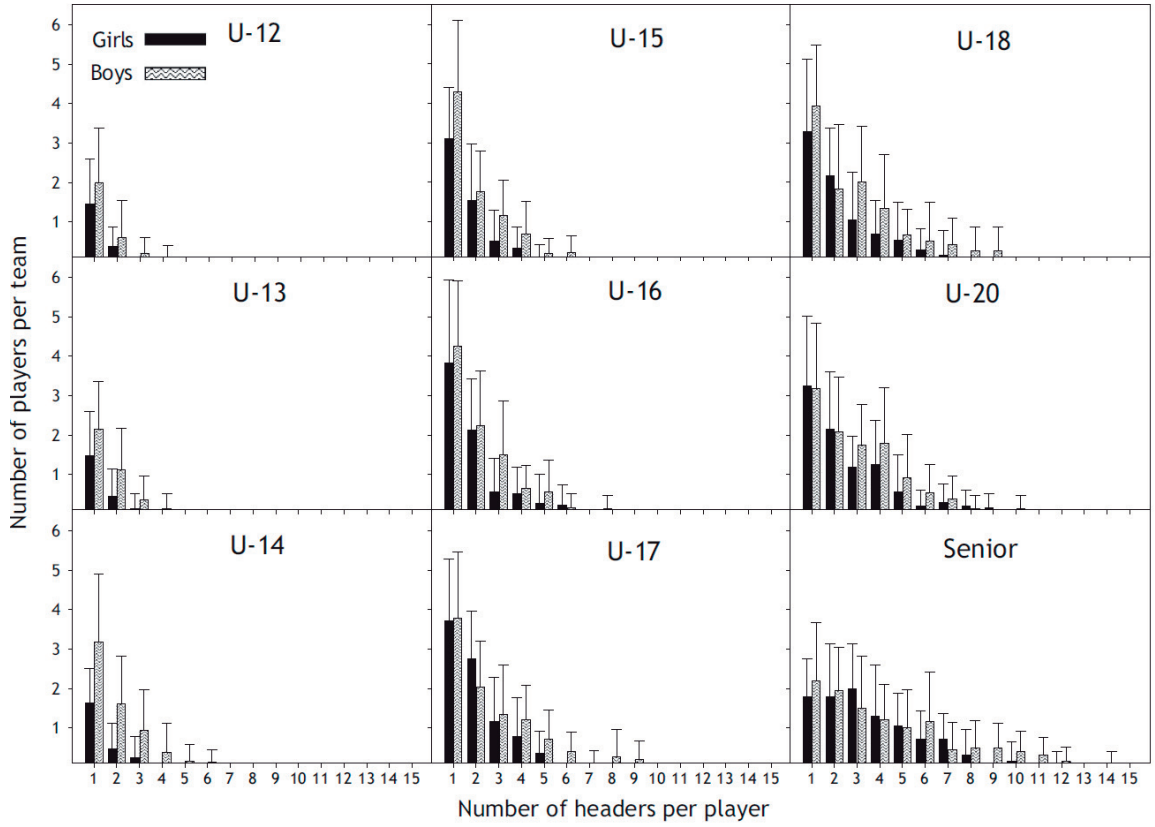

Figure 7. *Distribution of absolute heading exposure per match in the different sex and age groups. Numbers are presented as the average number (±SD) of headers per player per team.*

Comparing our results to the limited data available is difficult due to differences in methods. Most of the previous studies reported rates per athletic exposures, not hours. However, Harriss et al.[59] used video analysis in female youth soccer (U-13, 14 and 15), and found a rate of 0.07 headers per hour. Interestingly, this is 10-20 times lower than in the same age segment in our study (table 4, 0.6-1.4 headers per hour). Furthermore, Rahnama et al.[54] used video analysis to report heading rates at the male elite level in England and found a rate of 4.6 headers per hour. This is slightly higher, but in the same range as what we observed in our reference group at the male elite level in Norway (3.4 headers per hour).

Taken together, our findings on heading exposure in youth football provide several insights. First, note that the existing injury prevention measure in the US have banned heading in matches for players 10 years or younger, indiscriminately for boys and girls. Although we included mostly Norwegian teams, our findings suggest that the youngest age groups rarely head the ball. Such an

intervention would therefore target a close to non-existing exposure. Adding to this, boys seemingly introduce heading as an inherent part of the game at a younger age than girls. It therefore seems warranted also to take sex into consideration. Second, there is considerable variation *between* teams. As previous studies on heading exposure have included small sample sizes, restricted to a few teams, any conclusions have likely been of low external validity. Indeed, this could contribute to the discrepancies between our numbers and those of others. Factors such as playing style and intensity are likely to also have an influence. Third, variation *within* teams suggest that any risk from heading the ball is relevant mainly for a subset of the players. The differences in pitch distribution of headers suggest that players in central positions are more likely to be exposed. In summary, these findings underpin the importance of a data-driven approach to guide injury prevention measures.

Head injuries

Throughout the youth tournament, we observed a total of 15 head impact incidents, corresponding to a rate of 4.5 (95% CI 2.6-7.2) incidents per 1 000 player hours. These were included to represent events with a greater risk of head injury, and were primarily registered to evaluate their relative frequency compared to headers. Such events were rare compared to headers (2 incidents per 1 000 headers), and absent in the youngest age group (U-12).

Comparing these results to those of others is challenging, as we did not collect data on clinical outcomes. Nevertheless, Faude et al.[40] have previously concluded that the overall rate and severity of head injuries in children's football (boys and girls, 7-12 yrs) was low, using an online registry. As part of their study, they specifically analyzed head and neck injuries in matches. They reported an overall rate of 0.25 injuries per 1 000 player hours, out of which 27.5% were concussions. Their rate was considerably lower than ours (0.25 vs. 4.5), but was based on a younger cohort. However, most events in our study appeared to be of minor severity and the players typically returned to play after a short assessment. It seems likely that many of these incidents would not have been registered as injuries in a similar database as that used by Faude et al.[40] Last, there was a trend for head impact incidents to increase with age for both sexes, being more common at the senior elite level. As for headers, this suggests a role of playing styles and intensity. However, we were unable to statistically evaluate this due to the limited absolute number of events.

In-ear sensors for quantifying repetitive head impacts in youth football (Paper II)

In Paper II, we evaluated the validity of an in-ear sensor for quantifying repetitive head impacts in youth football. This was first done in a laboratory setting, followed by an on-field assessment.

Laboratory evaluation

For the main analyses, we included 112 impacts. For all impacts combined, the systematic error was 11% for PLA, 20% for PRA and 5% for PRV; the random error was 11% for PLA, 19% for PRA and 5% for PRV. Both the systematic and random error varied with impact type, location and severity. Figure 8 demonstrates the systematic error and variations in random error for PLA.

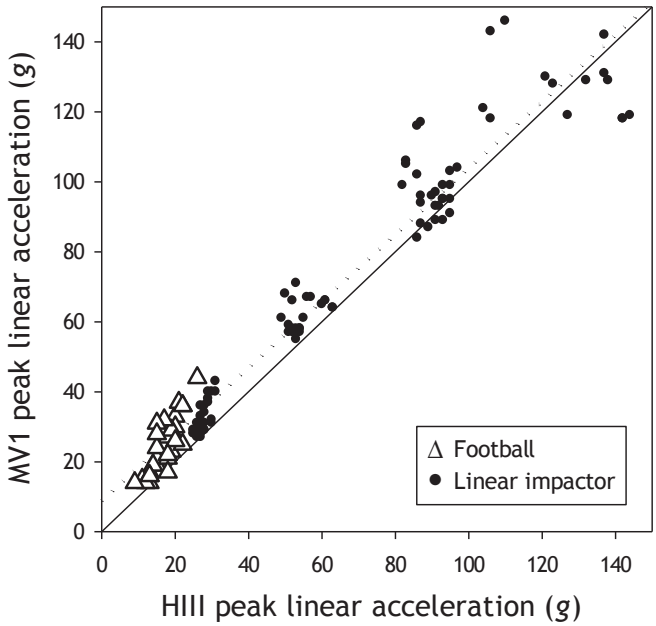

Figure 8. *Peak linear acceleration from the in-ear sensor plotted against the Hybrid III (reference). Reference line (solid) and line of best fit (dotted) are for all impacts combined.*

We repeated eight impacts (7 right frontal, one frontal; range 29-122 *g*) twice, in order to evaluate the effects of variations in head coupling. Going from tight to loose coupling, the systematic error increased from 17% to 33% for PLA, 19% to 202% for PRA and 13% to 32% for PRV. Random error increased from 10% to 14%, for PLA, 10% to 55% for PRA and 13% to 32% for PRV.

Our results align with previous studies. In his review, Patton[83] described how discrepancy between sensor and Hybrid III measurements was a recurrent issue for helmeted as well as non-helmeted

systems. Specifically, he mentioned culprits such as imperfect head coupling and suboptimal algorithms for transforming data to the center of gravity of the head. Tyson et al.[86] have since reported on large measurement errors for both skin patches and headbands. Even though we used a custom-made sensor designed specifically to achieve optimal head coupling, we also observed substantial random and systematic error. We further demonstrated how such errors varied in different settings, and were exacerbated by loose coupling. This suggests that absolute values measured *in vivo* should be interpreted with great caution, especially since this involves adding elements of noise like sweating and user errors.

On-field evaluation

All six players completed the structured training protocol. In total, we included 1 181 accelerative events. Heading events (n=431) resulted in higher average values than non-heading events (n=750) for all three variables (PLA: 15.6±11.8 vs. 4.6±1.2 *g*; PRA: 10543±10854 vs. 1095±823 *rad/s²*; PRV: 35.1±18.3 vs. 9.8±4.6 rad/s). Figure 9 shows PLA values for the different exercises.

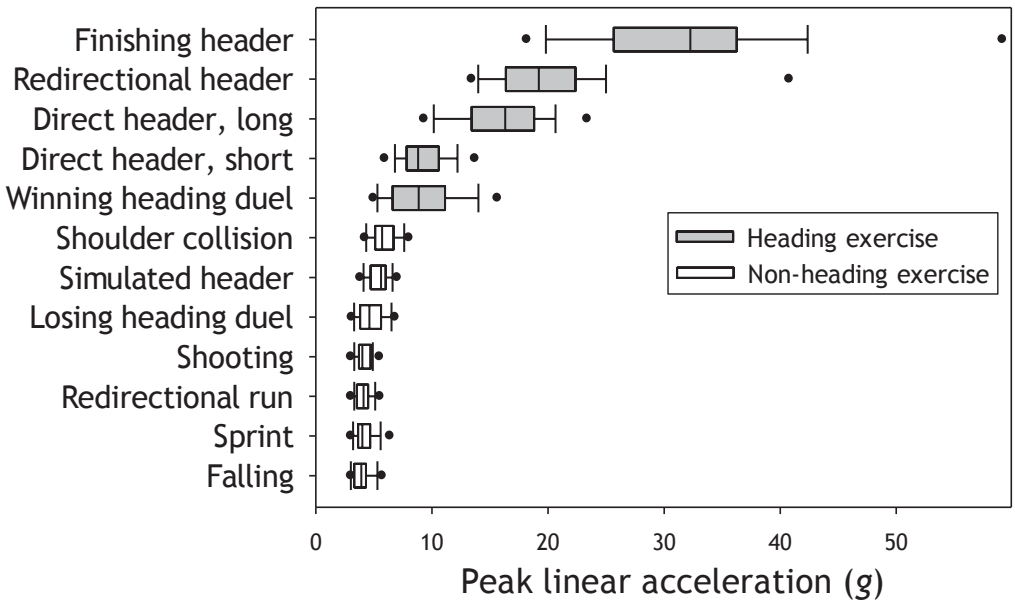

Figure 9. *Peak linear acceleration recorded by the in-ear sensors for each exercise. Box plots show median values and interquartile ranges, while the left and right markers display 5th and 95th percentile, respectively.*

Determining the sensor's ability to discriminate between heading and non-heading events, ROC analyses resulted in an AUC of 0.98 for PLA, 0.99 for PRA and 0.97 for PRV. An optimal cut-off value of 9 *g* was identified based on the ROC curve; while yielding a sensitivity of 73%, this was the lowest cut-off to achieve a positive predictive value of 100%.

Five of the players also completed one or two regular training sessions. In total, the in-ear sensors registered 2 039 nominal head impact events. Of these, 15 were heading events (PLA: 20.7±10.6 *g*; PRA: 14 541±7 994 *rad/s²*; PRV: 43.5±16.4 *rad/s*), while the remaining events were triggered by tackling, jumping, running, touching the sensor etc. (PLA: 4.0±3.1 *g*; PRA: 835±2541 *rad/s²*; PRV: 7.4±4.9 *rad/s*). ROC analyses resulted in an AUC of >0.99 for PLA, PRA and PRV. Using a cut-off value of value of 9 *g* in this setting yielded a sensitivity of 87% and a positive predictive value of 65%.

As interpreted by the AUC values, both steps of the on-field evaluation demonstrated an excellent ability for the in-ear sensors to discriminate between headers and other types of accelerative events. However, the positive predictive value using a 9 *g* cut-off in regular training sessions was lower than for the controlled setting (100% vs. 65%). Raising the cut-off value could potentially compensate for this. However, we observed that going from 9 to 10 *g* in the controlled setting led to a decline in sensitivity from 73% to 65%. Simultaneously, the positive predictive value in regular training sessions remained the same. Raising the threshold further would exclude a substantial amount of headers. Importantly, during regular training sessions, players were observed e.g. dropping the sensor to the ground. Such events were registered spuriously as head impacts by the sensors, with values as high as 124 *g*, i.e. considerably greater magnitudes than for any event recorded in the structured training protocol (figure 9). Consequently, we demonstrated a need for secondary verification of events, in order to filter out such spurious events in a real-life setting.

Our on-field findings thereby align with previous studies using skin patches to record head impacts in football. Cortes et al.[88] and Press and Rowson[58] both described the need for video analysis to filter out false-positive events.[58,88] We demonstrated how this challenge also extends to in-ear sensors, thereby making their use highly resource demanding over time. Furthermore, it is interesting to compare the absolute values recorded in the on-field settings to previous data evaluating impact magnitudes. As an example, a meta-analysis by Brennan et al.[71] estimated the mean PRA of concussive events to be in the range of 4500 to 7000 *rad/s²*. For many of the heading events in our study, the in-ear sensors recorded PRA values twice as high, while the players did not report any symptoms. This disagreement likely reflects large *in vivo* measurement errors. Our laboratory evaluation demonstrated a plausible explanation for this: inherent measurement error exacerbated by poor head coupling.

Combined, our findings demonstrated that the in-ear sensors were not feasible for use in prospective studies in youth football. Future methods should aim to improve sensor accuracy and head coupling, as well as to develop data algorithms better able to filter out spurious head impact

events. Moreover, such improvements should be made while allowing for user-friendliness. Before taken into use, any novel method should undergo a systematic evaluation in both a laboratory and an on-field setting, to properly account for its limitations.

Self-report for quantifying heading exposure in youth football (Paper III)

In Paper III, we evaluated the validity of a self-report questionnaire to retrospectively quantify heading exposure in youth football. All 34 participants completed the questionnaire at the end of the two-week observation period. In total, the players participated in 64 matches and 157 training sessions. We observed 1 051 headers, out of which 88% occurred in training sessions. Overall, players systematically overestimated their heading exposures by a factor of 3.0 and with a 46% random error. The overestimation was by a factor of 0.5 for matches and 3.7 for training sessions; random error was 44% for training sessions and 49% for matches. Figure 10 displays self-reported vs. observed numbers.

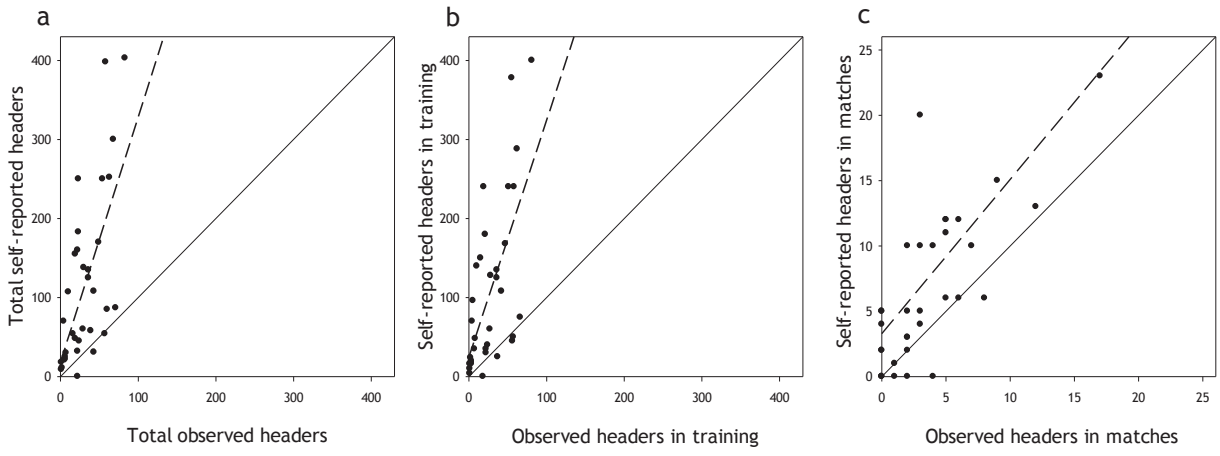

Figure 10. *Self-reported numbers over a two-week period plotted against observed numbers (reference). Reference line (solid) and line of best fit (dotted) are for all players combined.*

Measurement errors when using self-report have been described previously. Catenaccio et al.[81] described the validity of the same questionnaire as we used, but in a cohort of adult amateur players. They found that females overestimated heading exposure by a factor of 5, while males reported a slight underestimation. Consequently, they proposed calibrating the questionnaire in females. Harris et al.[135] evaluated the validity of self-report in a cohort of female youth players (13 yrs). Based on a recall period of an entire season, players overestimated their heading exposure by 51% compared to video analysis. However, both studies evaluated match exposure only. We

demonstrated a tendency for male youth players to systematically overestimate their heading exposure, and how this applied to matches *and* training sessions. Our numbers suggest a difference between sessions (factor of 0.5 in match vs. 3.7 in training), but we were unable to statistically evaluate any effect of session type. Furthermore, due to the random error of self-reported numbers, we were not able to adjust for the systematic overestimation. The exact reasons for such measurement errors are unknown, but it seems to be a recurrent challenge. Nevertheless, the self-report questionnaire could therefore not be regarded an adequate tool for quantifying heading exposure for individual players.

The Spearman's correlation coefficient for self-reported and observed numbers was 0.68 ($p<0.001$) for all sessions combined. This is in the same range as that described in adult amateur players by Catenaccio et al.[81] Thus, also in our cohort of youth players, self-report retained a moderate-to-strong ability to *rank* heading exposures appropriately across the sample. However, note how this method disregards absolute numbers. Consequently, although self-report often correctly identified which of two players headed the ball more often than the other, it lost higher-resolution information on *how much* their heading exposures differed.

Based on the median value from observed numbers (n=36 headers), we defined four players belonging to a high-exposure group and 13 belonging to a low-exposure group. Using self-reported numbers, the AUC was 0.87 (95% CI 0.67-1) for correctly identifying players in the two groups. Based on tertiles (low<22, high>54), we identified three players in the high-exposure group and nine in the low-exposure group. The AUC then increased to 0.96 (95% CI 0.86-1). This shows that self-reported numbers could also *group* players with respect to exposure levels. It also implies that those with medium levels of exposure introduced much of the noise in the sample, while players at the more extreme ends of the exposure spectrum more accurately identified themselves in their respective group.

Taken together, we demonstrated that self-report was ill-suited to quantify heading exposure for youth football players at the individual level. However, self-reported numbers could still serve as a tool for ranking or grouping players with respect to heading exposure. Importantly, these findings provide insights for using the questionnaire in a prospective study like RepImpact; while absolute numbers should be disregarded, self-reported heading exposures can allow for crude *within-group* evaluations of neurological outcomes among the football players.

Tau and NfL after head impacts in professional football (Paper IV)

In Paper IV, we evaluated whether head-impact exposure in professional football causes structural brain injury, detected as an increase in serum tau or NfL. For this, we analyzed a total of 354 blood samples.

Short-term effects

We observed no short-term effects on NfL (ANOVA, p=0.69). However, as shown in figure 11, we observed several within-group differences in tau levels (ANOVA, p<0.001). Specifically, we detected an increase 1 h after high-intensity exercise (Δ 0.50 pg/mL, 95% CI 0.19-0.81, p<0.01) and 1 h after repetitive headers (Δ 0.29 pg/mL, 95% CI 0.10-0.48, p<0.01). Both exposures displayed a subsequent decrease back to baseline values after 12 h. Accidental head impacts displayed no within-group differences. For tau proteins, we also observed between-group differences (ANOVA, p<0.01). Specifically, compared to high-intensity exercise (reference), accidental head impacts displayed lower values at baseline (p<0.001) and 1 h after exposure (p<0.001) (figure 11).

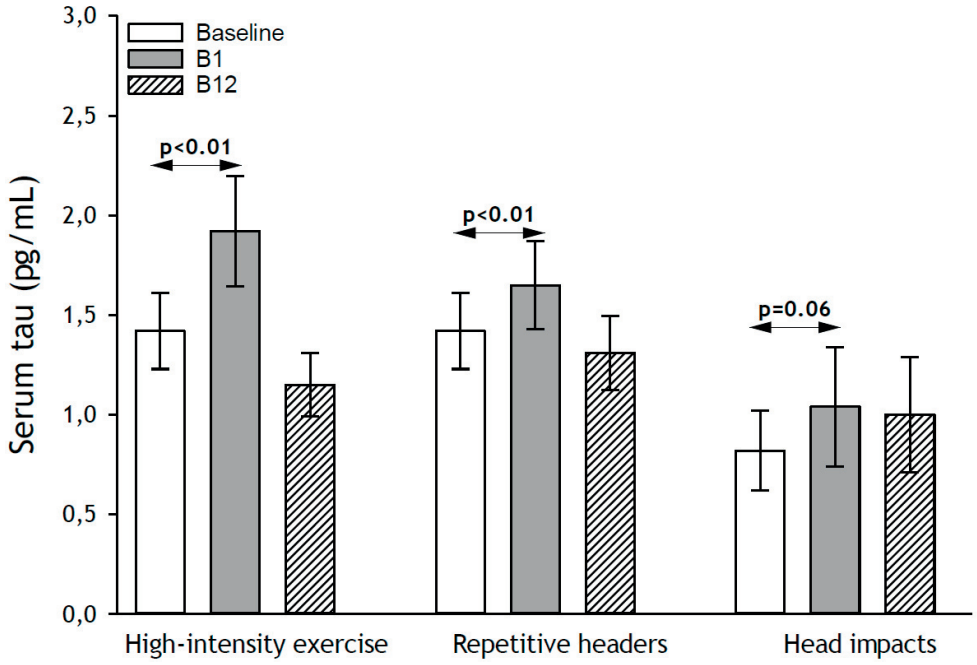

Figure 11. *Serum tau levels in response to high-intensity exercise, repetitive headers and accidental head impacts in a match. B1 and B12 are 1 and 12 h after exposure, respectively. Values are presented as means with error bars representing the 95% CIs.*

It is interesting to compare the absence of any short-term effects on NfL levels to previous studies. Shahim et al.[108] examined amateur boxers, and found serum NfL to be increased 12 h after a bout. The highest levels were seen 144 h after exposure, suggesting a gradual, delayed release. Shahim et al.[107] also examined the effects on NfL from concussions in professional ice hockey players. There, they found NfL levels to increase after 1 h, drop at 12 h, then to increase steadily until 10 d after injury. In another study, Wallace et al. [136] examined the short-term effects of repetitive headers on serum NfL and concussive symptoms (using the SCAT3) in a group of male collegiate football players. Specifically, they evaluated the effects of 40 headers, compared to a sham condition consisting of controlling the ball 40 times with other parts of the body. Both conditions led to an increase in serum NfL levels 1 h after exposure, but the percent change was greater after heading. Repetitive headers also led to an increase in concussive symptoms, while the sham condition did not. Based on these findings, the authors suggested that repetitive headers may lead to axonal damage.[136] We did not observe such changes. How these discrepancies relate to differences in exposure, timing of samples, collection procedures and laboratory methods is unknown.

Neselius et al.[137] have demonstrated an association between boxing and elevations in plasma tau one to six days after a bout. They suggested that axonal injury may ensue after concussive as well as subconcussive head impacts. In our study, we also observed short-term elevations in tau levels. However, these were primarily consistent with an acute exercise effect, returning rapidly to baseline. Specifically, even though all three conditions displayed similar dynamic changes, the most prominent increase was seen in the condition consisting *solely* of high-intensity exercise. This aligns with similar results by Kawata et al.[138] They examined the association between mouthguard-registered repetitive head impacts and serum tau levels in collegiate American football players. Evaluating changes from pre- to post-practice, they observed an increase in tau levels. This increase was independent of head impacts, leading the authors to suggest exercise as a cause. Gill et al.[139] made similar observations when examining serum tau levels in a heterogeneous group of collegiate athletes from different sports. Regular sport participation led to an increase in tau levels after 6 h, and athletes also displayed higher baseline values compared to controls. However, they also found that elevated tau levels 6 h after concussion were associated with prolonged return to play (>10 days). The authors went on to suggest that tau levels may increase in response to exercise *and* brain injury.[139] Together, these studies indicate that tau is a non-specific, suboptimal biomarker for evaluating head impacts in sports.

Long-term effects

Comparing groups with previously high and low levels of exposure to repetitive head impacts, we found no differences in tau or NfL levels (figure 12).

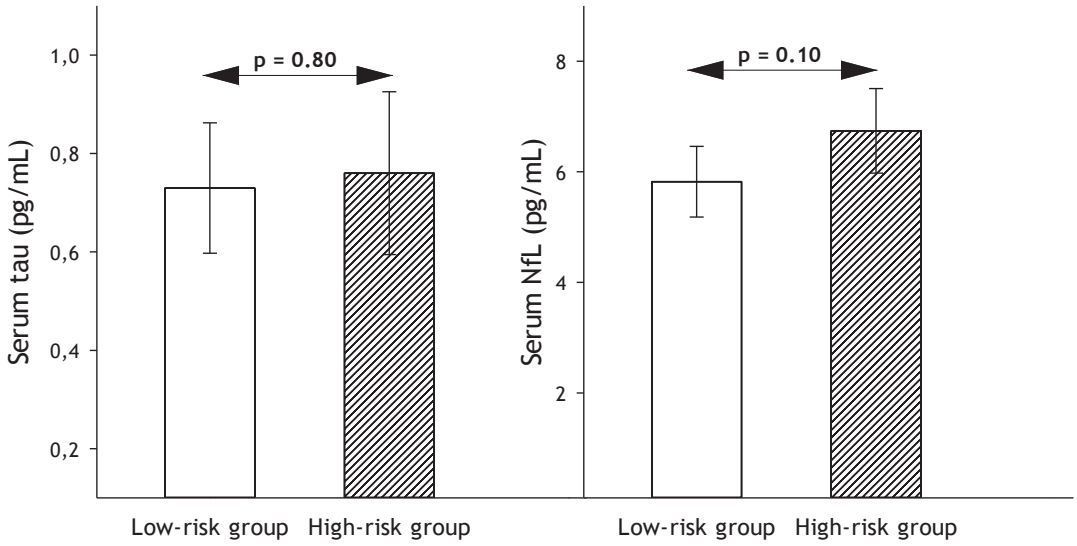

Figure 12. *Evaluating the long-term effects of repetitive head impacts by comparing baseline levels in two groups with different levels of previous exposure to heading and concussion. Values are presented as means with error bars representing the 95% CIs.*

Our current understanding of neurodegenerative disorders involves a role of several structural proteins, including accumulations of hyperphosphorylated tau tangles in CTE[21] and neuritic amyloid β plaques in Alzheimer disease.[96] Preische et al[110] have shown that dynamics in serum NfL may predict neurodegeneration and cognitive changes in those at risk for Alzheimer disease, almost two decades before onset. In a recent review, Graham et al.[27] highlighted the potential role of blood biomarkers to investigate neurodegenerative changes in response to TBI. Interestingly, Pattinson et al.[111] have evaluated the effects of previous TBI on tau and NfL levels in military personnel. For those with a history of TBI, tau levels were associated with a greater burden of postconcussive symptoms. Moreover, those with a history of *repetitive* TBI displayed elevated levels of NfL. The authors were unable to link such findings to neurodegenerative processes, but they suggested a role of tau and NfL in maintaining neurological and behavioral symptoms after TBI.[111] In our cohort of professional football players, we found no evidence for previous exposure to repetitive head impacts to cause sustained elevations of tau or NfL.

Methodological considerations

Study designs and participants (Papers I-IV)

The main strength of Paper I was including a large, heterogeneous sample while collecting the data over a limited time period. Although most players were Norwegian, we included teams from all over the world. Our findings can therefore be considered robust and of high external validity. A limitation was that match durations in Norway Cup were shorter than for regular league matches. This likely led to low estimates of absolute exposures. However, as durations were adjusted specifically for each age group, the relative differences between groups remain representative. Note that heading rates were calculated per hour, and were therefore not affected by this. Last, although not a limitation of the study *per se*, we did not assess the influence of age and sex on heading exposure during training. How our findings translate to such settings is therefore unknown.

For Paper II, the main strength was using a stepwise approach in a sport-specific setting. This allowed us to interpret the on-field evaluation in light of lessons learned in the laboratory setting. The main limitation was only including six players for the on-field evaluation, as well as including a limited number of regular training sessions. Compensating for this, we recorded a high number of accelerative events.

In Paper III, we were only able to compare self-reported and observed heading exposure from the players' primary team. This could be a source of bias, as some of the players would have to disregard heading exposure related to participation in football academies etc. Our findings were also limited to a small sample (n=34). We compensated for this by including players from teams in different countries, making the sample more representative.

The main strength of Paper IV was the study design, which allowed for the comparison of the different short-term exposures in a homogeneous, representative cohort, controlling for the effects of exercise alone. However, note how the long-term effects were evaluated using a cross-sectional design. We used highly sensitive methods for quantifying serum levels of total tau and NfL. That said, Rubenstein et al.[140] have recently demonstrated how a novel assay, targeting subtypes of tau specific for the central nervous system, outperformed measures of total tau. Future studies should strive to incorporate the most promising assays available, potentially bypassing some of the issues we encountered.

Paper IV was exploratory of nature. This should be considered when interpreting the results and conclusions. Also, we were not able to account for how long-term storage might have affected sample integrity.

Exposure quantification (Papers I-IV)

In Paper I, we quantified exposure using direct observation. Here, we demonstrated how using one observer was a valid method compared to video analysis (sensitivity of 91%). Moreover, the inter-rater reliability was excellent (ICC=0.99, 95% CI 0.98- 1). Although we also subcategorized headers as 'long' or 'short', these were arbitrary distinctions. We observed a higher proportion of 'long headers' with greater age, but this might be misleading with respect to impact magnitudes. It is conceivable that a 'long header' for a player with good technique involves lower accelerations than a 'short header' for an inexperienced player. These numbers should therefore be interpreted with caution.

In Paper II, we used a widely recognized reference system (Hybrid III) for the laboratory part. Nevertheless, any such system will also have its own imperfections. As an example, we had to exclude some of the tests because the impact kinematics from the HIII were not considered representative for real-life head impacts. For the on-field evaluation, we used structured video analysis to confirm head impacts. We therefore lacked objective data on impact magnitudes, and had to extrapolate our conclusions regarding absolute values based on the laboratory evaluation.

In Paper III, we used direct observation to quantify heading exposure in matches, similar to the method validated in Paper I. Training sessions, however, were quantified using either direct observation or structured video analysis. We were not able to validate direct observation in this setting. Importantly, training drills can be more chaotic by e.g. having several balls in play at the same time. This could have negatively affected the sensitivity in some scenarios, and thereby contributed to a spurious overestimation of self-reported numbers.

In Paper IV, for the short-term exposures, we quantified head impacts with direct observation and video analysis. Even though this involved a lack of objective impact magnitudes, the head impacts were regarded highly representative due to the study design. The session with repetitive headers was designed together with coaching staff, and involved typical heading drills with multiple headers per player. The accidental head impacts occurred at the professional level in real-life match scenarios. For the long-term exposure, we used a self-report questionnaire to quantify previous exposure to headers and concussions. The exposure groups (high vs. low) were defined based on arbitrary thresholds, and reported numbers were inevitably subject to recall bias. Thus, inherent

measurement error could result in considerable overlap between the groups, introducing a risk for type I error.

Outcome assessment (Paper IV)

Blood biomarkers represent only a small piece of a large puzzle when assessing neurological outcomes. Thus, Paper IV should be interpreted as such. However, note that Straume-Næsheim et al.[106,132,141] not only evaluated the effects on serum levels of S100B,[106] but also on neurocognitive tests[132,141] in the same cohort. They revealed poorer neuropsychological performance the day after an accidental head impact,[141] but found no effects of long-term exposure.[132]

A recurrent limitation when evaluating dynamic changes in biomarkers is only being able to assess specific time points – inevitably a challenge in such studies as continuous monitoring is unfeasible. Biomarkers have specific temporal profiles in biofluids,[142] and we were unable to account for what was happening at other time points. As an example, NfL levels after concussion have been described to rise several days after exposure.[108]

Last, accidental head impacts were defined as concussive using the consensus definition at the time.[133] For the purposes of the self-report questionnaire, the definition of concussion was based on loss of consciousness and/or amnesia. Both definitions used were thereby stricter than the one currently used in sports.[4] When evaluating long-term effects, this might have led to an underestimation of previous concussions from some of the players. Consequently, they could potentially have been incorrectly categorized in the low-risk group, thereby masking actual group differences.

Conclusions

Based on the results from the papers presented in this thesis, the conclusions are as follows:

I. Heading rates in youth football were influenced by sex and age; males were more frequently exposed than females and heading rates increased with age. Importantly, heading was a rare event in the age groups currently targeted by interventions.

II. In-ear sensors displayed substantial systematic and random error. Despite excellent on-field accuracy for discriminating heading from non-heading events in youth football, secondary verification of head impacts in real-life settings was necessary.

III. Self-report was not an adequate measure for quantifying individual heading exposures in youth football due to measurement errors. However, it could still serve as a tool for ranking or grouping players, supporting its potential use in prospective studies.

IV. There was no evidence of structural brain injury by repetitive headers or accidental head impacts in football, as detected by serum tau and NfL.

V. Tau levels increased in response to high-intensity exercise, highlighting an important limitation for using it as a biomarker in sports.

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ORIGINAL ARTICLE

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Head impact exposure in youth football—Are current interventions hitting the target?

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Restrictions on heading in youth football have been implemented in some countries to limit head impact exposure. However, current interventions remain poorly guided by evidence. Our objective was to quantify heading exposure in youth football, assessing the effects of sex and age. Football matches played during an international youth football tournament with no heading restrictions were directly observed, including players from both sexes (11-19 years). The elite senior level was included for comparison, using video analysis. All heading events were registered, classified, and assigned to individual players. Heading rates were calculated for each sex and age group. We observed a total of 267 matches, corresponding to 4011 player hours (1927 player hours for females, 2083 player hours for males). Males headed more frequently than females (2.7 vs 1.8 headers/player hour; $P < .001$). Heading rates increased with age (ANOVA, $P < .001$), approaching the elite senior level for players 16 years and older. There was substantial variation within teams for all age and sex groups, with the widest range (1-18 headers) observed for girls aged 19. Girls younger than 12 years had the lowest exposure, with an average of <2 players per team heading the ball, each with 1-2 headers. In conclusion, age and sex influence head impact exposure in youth football, and warrants careful consideration when introducing injury prevention measures. Males are more frequently exposed than females, heading rates increase with age, and there is substantial variation between players. Heading is a rare event in the youngest age groups, especially among females.

KEYWORDS
concussion, epidemiology, repetitive, soccer, subconcussive, TBI

1 | INTRODUCTION

Repetitive head impacts are common in football due to the sport's unique feature of purposeful heading of the ball with the unprotected head. This element of the game remains controversial, as the potential associations with long-term neurological consequences are still unsettled.[1,2] Nevertheless, even though heading is normally asymptomatic and rarely causes concussion,[3-6] there is evidence to suggest that cumulative heading exposure may lead to brain alterations in adults[7-10] and affect cognitive function in adolescents.[11,12] As a result, rule changes have been implemented by US Soccer to restrict heading behavior in youth football, aiming for primary prevention of head injuries. More specifically, heading the ball is banned for players until the age of 11, while limiting the number of headers until the age of 13.[13] However, although well intended, such initiatives are poorly supported by evidence.

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Importantly, little is known about which factors influence head impact exposure in youth football. Based on a study on female youth players, Harriss et al[14] found that the number of purposeful headers increased with age. Chrisman et al[15] suggested that also sex may play a significant role. Both studies, however, were careful to emphasize the limited generalizability of their conclusions, mainly due to small sample sizes and homogenous populations.[14,15] In addition, these studies were conducted in North America, and potential differences in playing styles between countries might further limit the external validity of their findings. Providing more accurate data on heading exposure, and how this may be influenced by age and sex, is key to assess risk. Furthermore, such data will help guide much-needed prospective studies on the effects of repetitive head impacts in youth football.

Norway Cup is the world's largest international youth football tournament,[16] currently played with no heading restrictions. Including thousands of players, from teams of both sexes and across several age groups, the setting is ideal to assess differences in heading exposure. Thus, the primary aim of this study was to quantify heading exposure in youth football, assessing the effects of sex and age. As a secondary aim, we wanted to assess the incidence of head impact incidents carrying a high risk of acute head injury, and compare it to the elite senior level.

2 | METHODS

2.1 | Study design and participants

This study was based on direct observation of football matches played during an international football tournament, during the summer of 2018 in Oslo, Norway. Norway Cup is the world's largest football tournament for children and adolescents aged 10 to 19 years old, with nearly 30 000 players participating over the course of 7 days.[16] Out of nearly 2000 teams, most are from Norway, but teams from all over the world are participating. There are separate classes for male and female players, as well as for different age groups, including under-12 (U-12), U-13, U-14, U-15, U-16, U-17, U-18, and U-20. Standard match durations differ between age groups: U-12 and U-13 play 2 × 15 minutes, U-14 and U-15 play 2 × 20 minutes, U-16 and U-17 play 2 × 25 minutes, and U-18 and U-20 play 2 × 30 minutes. There are seven players per team for U-12 and U-13, nine players per team for U-14, and eleven players per team for U-15 and older. A convenience sample of matches from every age group from both sexes was included (Table 1).

In addition, the study included video observation of a random selection of 10 matches each from the female and male Norwegian premier leagues (Toppserien and Eliteserien) during the 2018 season; matches at this level have a standard duration of 2 × 45 minutes. These were added to include a professional/semi-professional senior level for comparison, observed from TV video recordings.

The Ethics committee at the Norwegian School of Sport Sciences approved the study. The study was observational and did not involve registering any sensitive personal information. Furthermore, as registered head impact exposure was not linked to any other personally identifiable information, player consent was not deemed necessary.

2.2 | Registration of head impact exposure

A group of trained research assistants observed the matches, with one observer present per match. Before the match started, the sex, age group, and nationalities of the teams were noted. All heading events in each match were then registered and classified as short or long headers. This was done based on the observer's subjective interpretation of the impact forces involved for the player. Short headers were defined as

TABLE 1 Number of observed matches, player hours, heading events, and head impact incidents according to age and sex during an international youth football tournament in Norway

	Boys				Girls			
Level	Matches (n)	Player hours	Headers (n)	Incidents (n)	Matches (n)	Player hours	Headers (n)	Incidents (n)
U-12	16	112	138	0	12	84	53	0
U-13	33	231	423	2	28	196	178	0
U-14	21	252	562	0	12	144	77	1
U-15	17	249	565	0	14	205	293	0
U-16	10	183	432	1	12	220	411	1
U-17	18	330	1079	3	12	220	495	0
U-18	6	132	405	0	14	308	536	1
U-20	12	264	855	4	10	220	534	2
Senior*	10	330	1127	9	10	330	886	6

*Senior level was observed from TV video recordings from the Norwegian premier leagues (Toppserien and Eliteserien), and included for comparison.

lower-grade impacts based on the distance of the incoming ball and a seemingly low force when heading; long headers were defined as higher-grade impacts based on a combination of a relatively longer distance and higher force when heading. Each event was assigned to an individual player by the number and color of his or her jersey. Headers were also classified based on the player's position on the pitch when the event occurred (defense, midfield, or attack) and according to the player's position in the center or in one of the side corridors (right or left), thereby dividing the pitch into nine equal zones.

In addition to purposeful headers, incidents thought to carry a high risk of head injury were registered, based on the following criteria: (a) the player appeared to be hit in the head, neck or face, (b) the match was interrupted by the referee, and (c) the player remained lying down on the pitch for more than 15 seconds. The same definition of head impact incidents was used by Andersen et al[17,18] and Straume-Næsheim et al[19,20] in previous studies.

To validate direct observation as a method, we included a subset of 24 Norway Cup matches that were broadcast on commercial television. For these matches, there were two independent observers present, in addition to one observer registering events through systematic video analysis (used as reference). This was done in order to assess: (a) the inter-rater reliability and (b) the sensitivity of direct observation for identifying heading events.

2.3 | Statistical analyses

For each sex and age group, the total number of observed player hours was calculated as the number of observed matches multiplied by the standard number of players on the pitch multiplied by the standard match duration. Heading rates (short, long and total) were calculated for each sex and age group as the average number of headers per player hour. To evaluate the distribution of heading exposure between players within teams, we also calculated the number of events per player for each match. Intraclass correlation coefficients (one-way random effects) were calculated to express inter-rater reliability. SPSS version 24 (IBM SPSS Statistics, IBM Corporation) was used for statistical analyses.

3 | RESULTS

We observed a total of 267 matches, corresponding to 4011 player hours, 124 matches for females (1927 player hours) and 143 matches for males (2083 player hours). In total, we registered 9049 headers, 3463 for females and 5586 for males. Table 1 shows an overview of the number of matches, player hours and heading events for the different age groups. Overall, males headed more frequently than females, with 2.7 headers per player hour for males and 1.8 for females (independent samples t test, $P < .001$). As shown in Table 2, heading rates also differed between age groups (ANOVA, $P < .001$). Of the 247 tournament matches observed, 84% were played by Norwegian teams only, while 16% involved at least one team from another country.

Heading exposure for each player differed substantially within and between teams, with shifting distributions by age for both sexes (Figure 1). The most common location for heading events on the pitch was the central corridor, especially the central midfield (Figure 2), with the same pattern observed across all age groups for both sexes.

Throughout the youth football tournament, we observed a total of 15 head impact incidents, corresponding to an incidence of 4.5 (95% CI 2.6-7.2) incidents per 1000 player hours. For the matches on the elite senior level, the incidence was 22.7 (95% CI 13.2-36.7) events per 1000 player hours. Table 1 shows the number of incidents for each sex and age group.

Based on the 24 broadcast matches observed by two independent observers, the intraclass correlation coefficient was 0.99 (95% CI 0.98-1) for the total number of headers, 0.89 (95% CI 0.76-0.95) for short headers, and 0.85 (95% CI 0.67-0.94) for long headers. Compared to systematic video analysis, direct observation had a sensitivity of 91% for identifying heading events.

4 | DISCUSSION

This is the first study to investigate heading behavior in youth football in a large, heterogeneous cohort. Our results showed that male players consistently headed the ball more frequently than female players, and that heading rates increased gradually with age for both sexes. Importantly, as current restrictions target players 12 years old or younger, we document that heading the ball was a rare phenomenon in the youngest age groups, especially among girls. Not until teams started playing on full-sized pitches (U-15 and older) did we observe any notable increase in total heading exposure, gradually approaching the elite senior level (Figure 1). Furthermore, there was substantial variation in heading rates between players; some players hardly ever headed the ball, while a minority headed more frequently.

4.1 | Heading exposure in youth football

Our finding that heading rate increased with age is in line with that of Harriss et al.[14] In their study on three female teams from three age levels (U-13 to U-15), they found that age had a significant effect on heading behavior. We show how that this also applies to males, as well as over a wider range of age. However, our rate of 1006 headers per 1000 player hours in the same age group as that studied by Harriss et al[14] was more than 10-fold higher than theirs (74 per 1000 player hours). Lynall et al[21] investigated head impact biomechanics in 19-year-old female collegiate players, and reported 7.16

TABLE 2 Heading rates (with 95% CI) by age and sex during an international youth football tournament in Norway. Rates are expressed as the average number of headers per player per hour

	Boys			Girls		
Level	**Short headers**	**Long headers**	**Total headers**	**Short headers**	**Long headers**	**Total headers**
U-12	1.0 (0.7-1.2)	0.3 (0.2-0.4)	1.2 (0.9-1.6)	0.5 (0.4-0.7)	0.1 (0.0-0.2)	0.6 (0.4-0.8)
U-13	1.3 (1.1-1.5)	0.6 (0.4-0.7)	1.8 (1.6-2.1)	0.8 (0.6-0.9)	0.1 (0.0-0.2)	0.9 (0.7-1.1)
U-14	1.5 (0.8-2.8)	0.8 (0.6-1.0)	2.2 (1.9-2.6)	0.5 (0.3-0.7)	0.2 (0.0-0.3)	0.6 (0.3-0.9)
U-15	1.6 (1.3-1.9)	0.7 (0.5-0.9)	2.3 (2.0-2.5)	1.1 (0.8-1.3)	0.4 (0.2-0.6)	1.4 (1.1-1.7)
U-16	1.7 (1.3-2.2)	0.6 (0.3-1.0)	2.4 (1.8-3.0)	1.5 (1.2-1.7)	0.4 (0.2-0.7)	1.9 (1.5-2.3)
U-17	2.1 (1.6-2.6)	1.2 (0.9-1.4)	3.3 (2.7-3.9)	1.7 (1.3-2.0)	0.6 (0.4-0.8)	2.3 (1.8-2.7)
U-18	1.7 (0.9-2.4)	1.4 (1.1-1.7)	3.1 (2.2-4.0)	1.3 (0.9-1.6)	0.6 (0.4-0.8)	1.9 (1.4-2.3)
U-20	1.9 (1.4-2.3)	1.4 (1.0-1.7)	3.2 (2.8-3.7)	1.7 (1.1-2.2)	0.8 (0.5-1.1)	2.4 (1.7-3.2)
Senior*	0.9 (0.7-1.1)	2.5 (2.1-3.0)	3.4 (2.8-4.0)	0.8 (0.6-0.9)	1.9 (1.7-2.2)	2.7 (2.4-3.0)

*Senior level was observed from TV video recordings from the Norwegian premier leagues (Toppserien and Eliteserien), and included for comparison.

head impacts per 90 minutes played (approx. 4800 per 1000 player hours), close to double the rate observed in our study (2427 per 1000 player hours). A key difference, however, is that they used skin-patch accelerometers to count the number of impacts. Employing a 10 g threshold, they classified anything above as a head impact, without secondary verification of events. As wearable sensor systems have several limitations,[22] false-positive events in particular,[23] it is difficult to compare these numbers directly to ours. Chrisman et al[15] used accelerometers, combined with visual verification, on a sample of 46 male and female youth players (11-14 years), and concluded that both age and sex seemed to have a significant influence on the variations they observed in head impact exposure; our data confirm this finding.

In addition to inherent differences between methods and low sample sizes, selection bias related to teams and playing styles are likely to have played a role in the above-mentioned studies; this is supported by our data showing substantial variation between matches within each age group (Figure 1). Previous studies have also shown that exposure varies between player positions.[6,21] Based on our findings, we are not able to confirm this directly, as we did not collect data on player position, but only on pitch area. These showed that most heading events occurred in the central corridor (Figure 2), consistently across sex and age groups, suggesting that players in central positions are more exposed than players on the flanks.

4.2 | Head impact incidents

Regarding the head impact incidents, we remain careful to interpret these data, due to the low absolute number in the different sex and age groups (Table 1). Also, although such events are believed to carry a high risk for acute head injury, we did not gather any information on clinical outcomes. However, we do note that such incidents were relatively rare compared to the number of headers seen during regular game play (approx. 2 incidents per 1000 headers). Furthermore, head impact incidents were fivefold more frequent at the elite senior level than at the youth level. The incidence we observed at the elite senior level was comparable to previously reported data from Andersen et al,[18] using the same definition of head impact incidents. Analyzing the mechanisms of head injuries in youth football, as well as their clinical outcome, should be the subject of future studies.

4.3 | Methodological considerations

The main strength of our study is its large sample size, including both sexes over a wide range of age groups. Additionally, collecting the data during a limited time period in the same tournament setting ensures that the data can be directly compared between the different groups. Furthermore, as the tournament includes a diverse group of teams from different areas and nations, this increases the external validity of our findings. Lastly, as demonstrated through video validation, direct observation proved well suited to detect heading events.

We acknowledge several study limitations. First, using direct observation we were unable to obtain kinetic measures of individual impacts. To compensate, we classified heading events into “long headers” and “short headers” based on the observer's subjective interpretation. Despite acceptable inter-rater reliability, how this classification translates into actual accelerative forces is unknown. Second, we only included matches. Variations in head impact exposure during practices should also be explored. Third, other factors might have influenced our results, such as field conditions and style, level and intensity of play. As an example, most of the matches observed during Norway Cup were played on natural grass, some on relatively hard turfs; this was further exacerbated by a hot and dry summer in 2018. Whether this could interfere with more technical play on the ground, leading to more physical or aerial play, is unknown. For comparison,

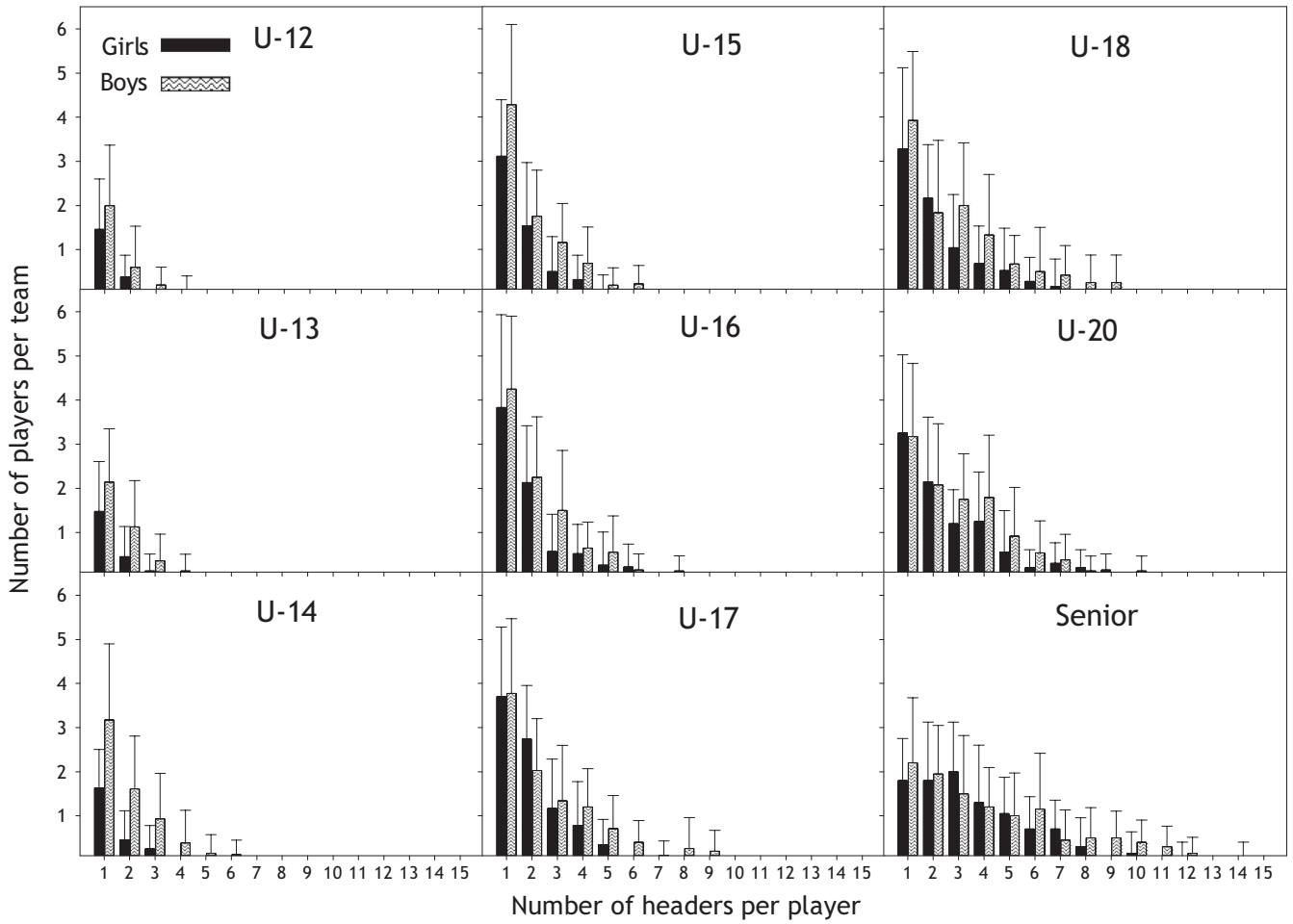

FIGURE 1 Distribution of headers within teams by sex and age groups during an international youth football tournament in Norway. Numbers are presented on a match basis as the average number of headers (± SD) per player per team. The elite senior level is included for comparison, based on numbers from the Norwegian premier leagues for men and women. Values exceeding 15 headers per player are excluded, comprising five players from the senior level and one player from girls U-18

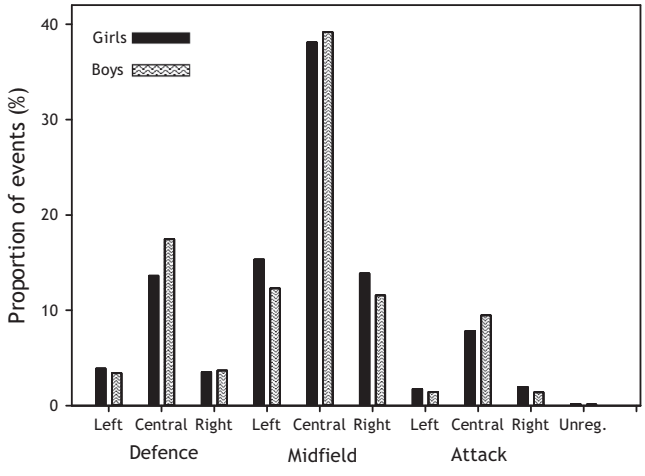

FIGURE 2 Pitch location of heading events during an international youth football tournament in Norway

we included the elite senior level from the Norwegian premier leagues, which is mostly played on artificial turf. We observed that their total heading rates were slightly higher than for the U-20 level, but noted a higher proportion of long headers. We do not know if this is related to any of the above-mentioned factors. Lastly, sometimes younger players (and, on rare occasions, entire teams) play with an older age group, usually if they are particularly skilled. This happens relatively infrequently, but we were unable to account for it. In summary, however, it seems unlikely that any of these limitations undermine our main conclusions.

5 | PERSPECTIVE

This study demonstrates large variations in head impact exposure in youth football, demonstrating how age and sex are significant influencing factors. Our findings have several theoretical and practical implications. As previous biomechanical studies have also shown sex differences in head impact acceleration when heading the ball, attributed to, for example, neck strength and head-neck segment mass,[24,25] the risk profiles between sexes may indeed be inherently

different. Thus, factors such as sex and age warrant careful consideration when planning and conducting studies on the link between repetitive head impacts in football and their potential neurological consequences. To prevent head injuries, it seems unlikely that a one-size-fits-all approach is satisfactory, and current interventions seem to target age groups where heading the ball is a rare phenomenon. Heading restrictions might miss the target, and future initiatives should be informed by scientific evidence—not by public opinion.

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II

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Evaluation of an In-Ear Sensor for Quantifying Head Impacts in Youth Soccer

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Background: Wearable sensor systems have the potential to quantify head kinematic responses of head impacts in soccer. However, on-field use of sensors (eg, accelerometers) remains challenging, owing to poor coupling to the head and difficulties discriminating low-severity direct head impacts from inertial loading of the head from human movements, such as jumping and landing.

Purpose: To test the validity of an in-ear sensor for quantifying head impacts in youth soccer.

Study Design: Descriptive laboratory study.

Methods: First, the sensor was mounted to a Hybrid III headform and impacted with a linear impactor or a soccer ball. Peak linear acceleration (PLA), peak rotational acceleration (PRA), and peak rotational velocity (PRV) were obtained from both systems; random and systematic errors were calculated with Hybrid III as reference. Then, 6 youth soccer players wore sensors and performed a structured training protocol, including heading and nonheading exercises; they also completed 2 regular soccer sessions. For each accelerative event recorded, PLA, PRA, and PRV outputs were compared with video recordings. Receiver operating characteristic curves were used to determine the sensor's discriminatory capacity in both on-field settings, establishing cutoff values for predicting outcomes.

Results: For the laboratory tests, the random error was 11% for PLA, 20% for PRA, and 5% for PRV; the systematic error was 11%, 19%, and 5%, respectively. For the structured training protocol, heading events resulted in higher absolute values (PLA = 15.6*g* ± 11.8*g*) than nonheading events (PLA = 4.6*g* ± 1.2*g*); the area under the curve was 0.98 for PLA. In regular training sessions, the area under the curve was >0.99 for PLA. A 9*g* cutoff value yielded a positive predictive value of 100% in the structured training protocol versus 65% in the regular soccer sessions.

Conclusion: The in-ear sensor displayed considerable random error and substantially overestimated head impact exposure. Despite the sensor's excellent on-field accuracy for discriminating headings from other accelerative events in youth soccer, absolute values must be interpreted with caution, and there is a need for secondary means of verification (eg, video analysis) in real-life settings.

Clinical Relevance: Wearable sensor systems can potentially provide valuable insights into head impact exposures in contact sports, but their limitations require careful consideration.

Keywords: TBI; repetitive; soccer; subconcussive; wearable; accelerometer

Repetitive head impacts in the "subconcussive" range (ie, head impacts without immediate symptoms) are common in soccer, where purposeful and unprotected heading of the ball is an integral part of the game. There is evidence of long-term structural and functional brain alterations among soccer players.[4-6,9] Moreover, recent studies suggested a potential effect on cognitive function among children and adolescents during a vulnerable period of brain maturation.[7,22] However, the link between exposure to repetitive head impacts and brain alterations is still controversial and remains to be elucidated. In this context, accurate measurement of head impact exposure in soccer is a key challenge when investigating the effect of head impact exposure on brain health.

Wearable sensor systems, such as accelerometers/gyroscopes, can potentially provide valuable insights into the dynamics of single and repetitive head impacts. However, several issues have made quantifying head impact exposure challenging, despite the multiple systems currently available.[12,13] A central issue has been poor sensor

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coupling with the head; methods such as skin patches and skull caps are subject to relative motion between the device and the skull and are therefore not able to accurately measure head impact exposure in vivo.[20] This issue extends beyond erroneous outputs for direct head impacts: failure to discriminate these from non–head impact accelerative events typically seen during game play (running, jumping, tackling, etc) also leads to high false-positive rates.[2,14] Thus, previous studies concluded that secondary means of verification, such as video analysis, are needed to verify whether the events recorded actually represent head impacts.[2,8,14] This makes surveillance of exposure in large-scale cohort studies considerably more demanding.

In-ear sensor systems have recently become commercially available, aiming to improve skull coupling by custom-molded placement in the bony portion of the external ear canal. However, before usage in prospective cohort studies, it is necessary to evaluate their performance in both a laboratory setting and an on-field setting. The aim of this study was to test the validity of a new in-ear sensor for quantifying head impacts in youth soccer.

METHODS

Study Design and Participants

This study was conducted in 3 phases: (1) validation of the in-ear sensor in a controlled laboratory setting, (2) controlled on-field evaluation of its ability to differentiate headings from other accelerative events typically seen in soccer, and (3) on-field evaluation in regular soccer training sessions. In phases 2 and 3, 6 male youth soccer players participated (mean ± SD age, 15.3 ± 0.3 years; height, 170.3 ± 5.0 cm; mass, 54.8 ± 6.1 kg), with all playing at the regional elite youth level in Norway during the 2017 season. The ethics committee at the Norwegian School of Sport Sciences approved the study, and written informed consent was obtained from the participants and their legal guardians.

In-Ear Sensor

MV1 (MVTrak) is a sensor system designed for custom-molded placement in the left external ear canal to optimize coupling to the head. A small lumen runs through the sensor to allow air conduction, limiting hearing loss to approximately 3 dB. The sensor samples linear acceleration and rotational velocity data at 1000 Hz, filtering the data with a phaseless 300-Hz 8-pole low-pass Butterworth filter to remove noise; rotational acceleration is calculated by differentiating these filtered rotational velocity data. The sensor then provides a time-stamped output of peak linear acceleration (PLA), peak rotational velocity (PRV), and peak rotational acceleration (PRA) for all accelerative events exceeding 3*g* (ie, nominal head impacts), followed by a 250-millisecond latency period before another impact can be registered. The sensor stores event-specific data on a microchip and connects via USB to a computer for download. Raw data are uploaded to the MVTrak server before being processed by the producer's algorithm. These data can then be downloaded for each player (ie, sensor) as time-stamped and event-specific summaries in Excel charts, including PLA, PRV, PRA, and the individual kinematic components of each accelerative event.

Experimental Procedures

Phase 1: Laboratory Validation. The MV1 sensor was mounted at the ear region of an in-calibration Hybrid III (HIII) head and neck assembly (Humanetics). Three mounting configurations were assessed: (1) a custom-made flat MV1 sensor (MV1 flat) attached with double-sided tape and reinforced with external taping to minimize relative motion between the HIII headform and the sensor and to optimize the coupling conditions for assessment as an alternative to in-ear mounting; (2) a regular in-ear MV1 (MV1 in-ear) firmly placed in a tight canal on the HIII headform, representing an artificial ear canal; and (3) a regular in-ear MV1 (MV1 loose) loosely placed by expanding the same canal (Figure 1). We created the canal by carving out a piece of the artificial skin covering the HIII headform. The tight canal's diameter was slightly smaller than the sensor's, only enough to allow the compliant properties of the rubber to expand and create a snug fit, mimicking real-life custom-molded placement; the expanded canal's diameter was slightly larger (2-3 mm) than the sensor's, allowing slight relative motion for the sensor. The HIII head was instrumented at its center of

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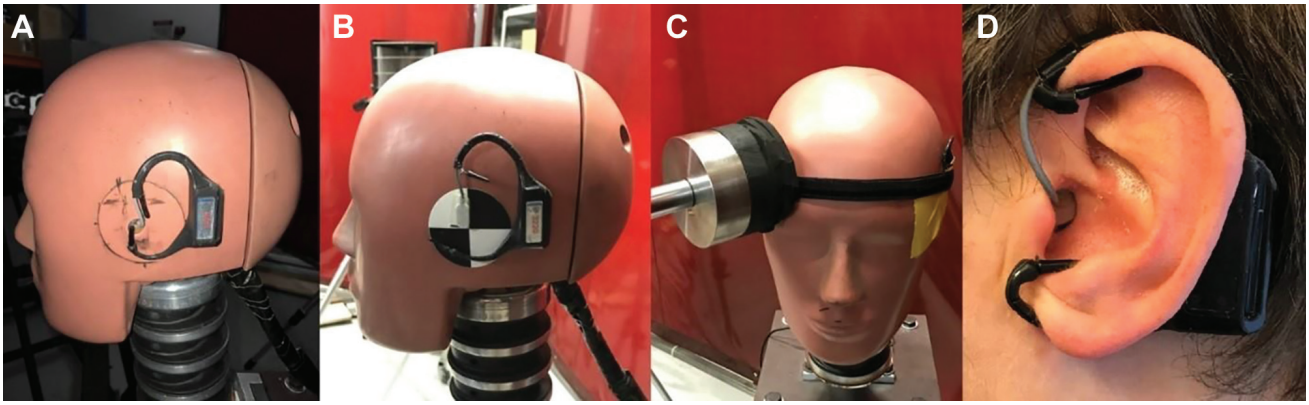

Figure 1. (A) Mounting of the MV1 in-ear and (B) MV1 flat on the Hybrid III headform. (C) A sample setup for right frontal impacts with the padded impactor striking from a 45° angle. (D) MV1 in a real-life setup.

mass with an in-calibration triaxial linear accelerometer (Endevco; Meggitt Sensing Systems) and triaxial angular velocity sensor array (Diversified Technical Systems), sampling at a rate of 20 kHz. Linear acceleration and angular velocity data were filtered with a SAE CC1000 filter and a SAE CC180 filter[15] (DIAdem 2011; National Instruments), respectively, before computing a preliminary set of PLA and PRV values for each impact. PRA values were calculated by differentiating the filtered angular velocity data. HIII-measured impact characteristics were considered reference values for MV1 flat; for evaluating between-sensor agreement, MV1 flat was considered reference for MV1 in-ear. The HIII was impacted at selected locations over a range of magnitudes with a linear impactor with a stiff interface, a linear impactor with a compliant interface, or a FIFA-approved soccer ball inflated to 11 psi (Table 1). Each test was videoed with a GoPro HERO5 Black camera, recording at 240 Hz.

Phase 2: Controlled On-Field Evaluation. The 6 participants were invited to complete a structured training protocol in a controlled setting twice while wearing a custom-molded MV1 in the left ear canal. The protocol was designed and supervised by research staff with long-standing experience in soccer (S.B.S. and T.E.A.) and consisted of 5 heading and 6 nonheading exercise drills typical for soccer. Heading exercises included finishing headers, redirectional headers, long direct headers, short direct headers, and headers from in-air duels. Nonheading exercises included shoulder-to-shoulder collisions, forceful shooting, redirectional running with maximal intensity, short straight sprinting with maximal intensity, falling abruptly forward on the ground and landing on out-stretched arms, and in-air duels without ball contact (losing the duel).

Phase 3: In-Training On-Field Evaluation. The participants wore the sensors for 2 regular training sessions with their team. The sessions were instructed by their regular coaching staff and included warm-up, passing and playing drills, and regular play in teams.

Phases 2 and 3 were performed on artificial turf in an outdoor setting. Video recordings were obtained with 2 digital video cameras (1080p, 50 fps), placed to capture all movements on the pitch to subsequently verify and classify events.

Data Analyses

For the laboratory validation, the HIII kinematic time histories (eg, linear acceleration) were reviewed for comparison with the high-speed video of each test. The aim was to review the preliminary PLA, PRA, and PRV values for each test and to identify the peak values directly related to the initial interaction between the impactor/soccer ball and the HIII headform. After review by S.B.S. and A.S.M., a final set of HIII PLA, PRV, and PRA values was determined.

To estimate the accuracy of the MV1 sensor for different impact types, locations, and mounting configurations, we calculated its random and systematic error. The random error was calculated by first dividing the SD of the mean difference between the MV1 and the reference (HIII) by the square root of the number of measurements (n = 2); this value was then divided by the mean of the combined measurements, expressing the random error as a percentage.[16] The systematic error was calculated as the mean difference between the sensor and the reference, divided by the mean reference value. Expressed as percentages, positive and negative results indicate systematic overestimation and underestimation by the MV1, respectively. For the soccer ball impacts, MV1 flat and MV1 in-ear were mounted to the HIII simultaneously; agreement between the sensors was expressed with the same formulas, with MV1 flat as the reference.

For the structured training protocol (phase 2), the individual events of each exercise drill were used as reference and compared with the time-stamped outputs from the sensors. If an event failed to exceed the sensor's 3*g* threshold and was therefore not recorded, kinematic values were set as follows to be included in later analyses: PLA = 3.0*g*, PRV = 3.0 rad/s, and PRA = 200 rad/s^2. These values were set arbitrarily, under the assumption that these events involved slightly lower values than the lowest-magnitude events recorded from the sensor; this was done to include them in the receiver operating characteristic (ROC) analyses. For the regular training sessions (phase 3), all head impacts were first identified on video to be included in the analyses; they were then compared with their potential

TABLE 1
Hybrid III Headform (Reference) vs MV1 Flat With Random and Systematic Errors of PLA, PRA, and PRV Values by Impact Type and Location[a]

Impact Type: Location	Impacts, n	Range			PLA, %		PRA, %		PRV, %	
		PLA, *g*	PRA, rad/s^2	PRV, rad/s	Random Error	Systematic Error	Random Error	Systematic Error	Random Error	Systematic Error
Linear impactor										
Frontal	37	26-132	1121-6901	12-23	3	4	14	13	1	1
Right frontal	21	27-110	1755-8030	12-20	9	28	18	21	6	9
Right zygomatic	12	27-138	1835-5087	16-26	5	6	11	45	1	5
Right temple	13	25-144	1668-11,537	11-20	12	–4	13	–6	7	8
Total	83	25-144	1121-11,537	11-26	10	8	18	15	5	4
Soccer ball										
Frontal	9	9-20	997-2203	5-11	17	33	30	54	2	–1
Right frontal	7	13-22	958-4638	7-13	16	67	29	40	11	16
Frontal/crown	10[b]	13-26	1362-3343	7-14	17	39	38	39	10	6
Face	3	11-19	722-3352	6-10	15	40	18	6	10	11
Total	29[b]	9-26	722-4638	5-14	18	45	33	39	10	7

[a]PLA, peak linear acceleration; PRA, peak rotational acceleration; PRV, peak rotational velocity.
[b]PRA and PRV values were excluded for 1 impact.

time-stamped sensor outputs. All other nominal head impact events recorded by the sensors (ie, either non–head impact accelerative events or spurious events) were then classified according to the video.

SPSS (v 24; IBM) was used for all statistical analyses.

RESULTS

Phase 1: Laboratory Validation

For MV1 flat, 112 impacts were included for final analyses (Table 1). When reviewing HIII outputs, we excluded angular kinematic data (ie, PRA and PRV) from 1 of the 112 impacts, since we were unable to identify the appropriate initial peak values. Furthermore, for 1 series of consecutive impacts (n = 12)—all within the same period with identical setup on the same afternoon—angular kinematic values (PRA and PRV) from MV1 flat were recognized as severe outliers (with values ranging from 4 to 13 times higher than the reference). Upon our request, the MV1 producer reviewed the data for these specific impacts and suspected that vibrations between the MV1 flat and the HIII were the cause. We replaced these data points with outputs from MV1 in-ear from the same impacts.

As shown in Figure 2, PLA values showed the strongest correlation, followed by PRV and PRA. The random error for all impacts was 11% for PLA, 20% for PRA, and 5% for PRV. The systematic error was 11% for PLA, 19% for PRA, and 5% for PRV. The random error varied with impact type and location, consistently overestimating PLA, PRA, and PRV values (Table 1). When agreement was tested between MV1 flat and MV1 in-ear for the soccer ball impacts (n = 29 for PLA, n = 28 for PRA and PRV), with MV1 flat as reference, the random error was 6% for PLA, 20% for PRA, and 6% for PRV; the systematic error was –5% for PLA, –23% for PRA, and –3% for PRV.

For MV1 loose, we replicated 7 right frontal impacts and 1 frontal impact (HIII PLA range, 29*g*-122*g*) also used for mounting configuration 2 (ie, MV1 in-ear). As compared with MV1 in-ear, the loose coupling in mounting configuration 3 led to an increase in the random error from 10% to 14% for PLA, 10% to 55% for PRA, and 7% to 20% for PRV. Systematic error increased from 17% to 33% for PLA, 19% to 202% for PRA, and 13% to 32% for PRV.

Phase 2: Controlled On-Field Evaluation

All 6 participants completed each exercise drill at least once, with the number of events obtained per drill ranging from 44 to 180. Heading events (n = 431) resulted in higher average values for all 3 variables (PLA = 15.6*g* ± 11.8*g*, $P < .001$; PRA = 10,543 ± 10,854 rad/s^2, $P < .001$; PRV = 35.1 ± 18.3 rad/s, $P < .001$) as compared with nonheading events (n = 750, PLA = 4.6*g* ± 1.2*g*, PRA = 1095 ± 823 rad/s^2, PRV = 9.8 ± 4.6 rad/s). ROC curve analyses revealed an area under the curve (AUC) of 0.98 (95% CI, 0.98-0.99; $P < .001$) for PLA, 0.99 (95% CI, 0.99-1.00; $P < .001$) for PRA, and 0.97 (95% CI, 0.96-0.98; $P < .001$) for PRV. Figure 3 shows the distribution of peak values for each specific exercise.

Phase 3: In-Training On-Field Evaluation

Five participants completed one or both of the regular training sessions, and from the resulting 8 sessions, the MV1 sensors recorded 2039 nominal head impact events. Of these, 15 events were confirmed on video analysis to be direct head impacts (PLA = 20.7*g* ± 10.6*g*, $P < .001$; PRA = 14,541 ± 7994 rad/s^2, $P < .001$; PRV = 43.5 ± 16.4 rad/s, $P < .001$), all of them attributed to purposeful heading of the ball. No other head impacts were identified on video. The remaining 2024 events were triggered by

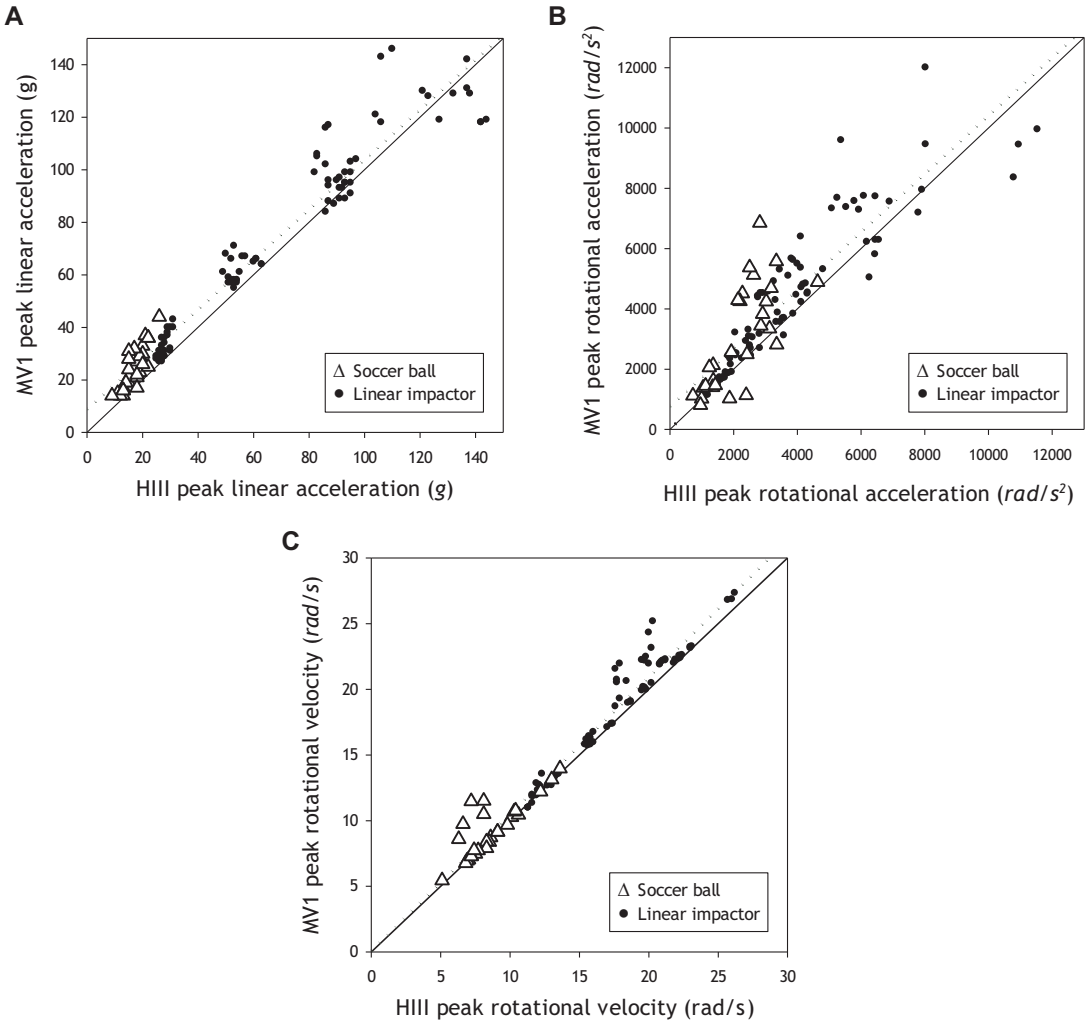

Figure 2. (A) Peak linear acceleration, (B) peak rotational acceleration, and (C) peak rotational velocity from MV1 flat, plotted against the reference (Hybrid III headform). Linear regression lines (dotted) with reference lines (solid) are for all head impacts combined (ie, with linear impactor and soccer ball).

non–head impact events, such as jumping, tackling, running with change of direction, and touching or losing the sensor (PLA = 4.0g ± 3.1g, PRA = 835 ± 2541 rad/s^2, PRV = 7.4 ± 4.9 rad/s), resulting in an AUC >0.99 (95% CI, 0.99-1.00; $P < .001$) for PLA, PRA, and PRV. Tables 2 and 3 show the sensitivity and positive predictive value of different cutoff values for PLA and PRV for the structured training protocol and the regular training sessions.

DISCUSSION

In this study, we found that the in-ear sensor systematically overestimated head kinematic parameters and with a considerable random error (phase 1). Still, the accuracy for discriminating headers from non–head impact accelerative events in a controlled on-field setting was excellent (phase 2). However, as the proportion of head impacts (ie, headers) was relatively low as compared with non–head impact events, false-positive results nevertheless remained a challenge in the real-life setting (phase 3).

Obtaining accurate results from compact wearable sensor systems is difficult, as shown by Cummiskey et al[3] and others.[11,18,19] In a recent review, Patton[13] described multiple examples of large discrepancies even in controlled laboratory settings. In the laboratory validation (phase 1), we therefore aimed to test the technical performance of the in-ear sensor, optimizing all factors, including coupling to the head. We found a consistent systematic overestimation for all peak values (PLA, PRA, and PRV) and with a considerable random error, varying with impact type and location. Even though the exact reasons are uncertain, several previously recognized technical limitations, such as low sampling rate (1 kHz for the in-ear sensor vs 20 kHz for the reference system), might account for some of the discrepancy. The observation that the PRA component generally performed poorer than PLA and PRV simply reflects that it is derived from PRV, rendering it more susceptible to

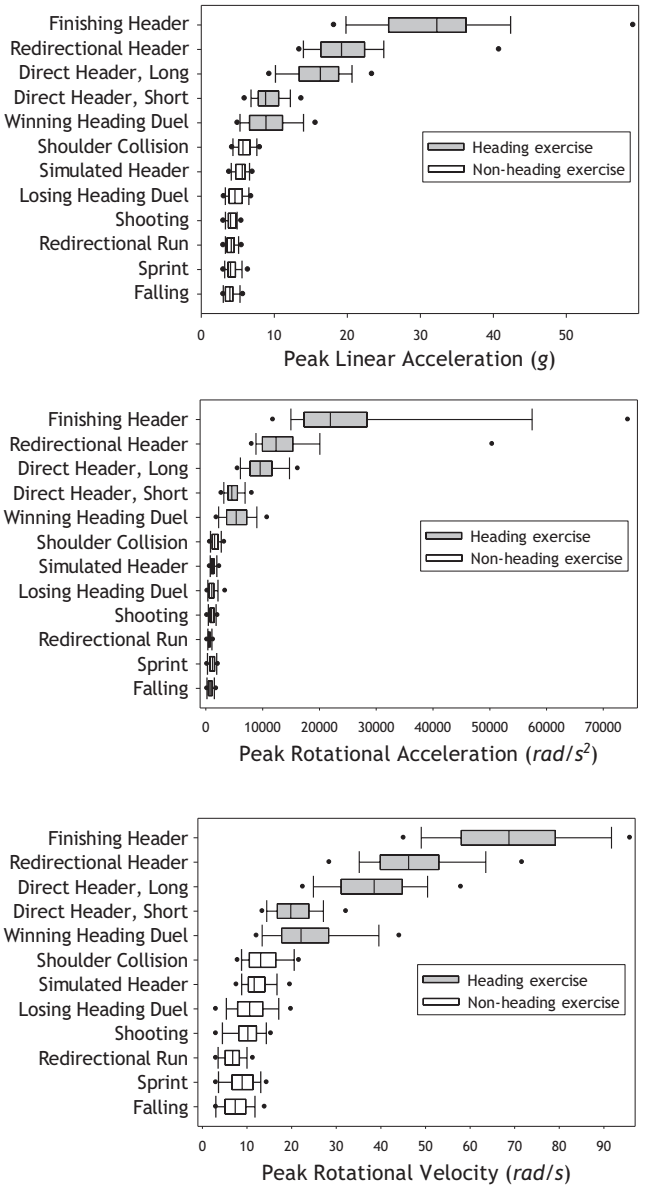

Figure 3. Box plots showing median value and interquartile range of peak linear acceleration, peak rotational acceleration, and peak rotational velocity from MV1 for the exercises from the structured training protocol. The left and right black dots represent the 5th and 95th percentiles, respectively.

noise and to the relatively low sample rate. This is consistent with the finding that PRA values also displayed considerably poorer agreement between sensors (approximately 80%) as compared with both PLA and PRV (approximately 95%). As an additional barrier, algorithms of any externally mounted system need to correct for its relative position on the head to measure what is happening at the center of mass.

As we were interested in how on-field conditions could affect sensor performance in phases 2 and 3, we included a loose mounting configuration in phase 1. The idea was to test how poor coupling could affect the inherent issues

TABLE 2
MV1 Sensitivity and Positive Predictive Value for Classifying Accelerative Events as Head Impacts (Headers) or Non–head Impacts for Different Peak Linear Acceleration Cutoff Values

	Sensitivity, %		Positive Predictive Value, %	
Cutoff Value, *g*	Training Protocol	Regular Training	Training Protocol	Regular Training
>6	96	100	82	22
>7	90	93	93	37
>8	83	87	98	50
>9	73	87	100	65
>10	65	87	100	68

TABLE 3
MV1 Sensitivity and Positive Predictive Value for Classifying Events as Head Impacts (Headers) or Non–head Impacts for Different Peak Rotational Velocity Cutoff Values

	Sensitivity, %		Positive Predictive Value, %	
Cutoff Value, rad/s	Training Protocol	Regular Training	Exercise Protocol	Regular Training
>10	99	100	57	4
>15	92	100	82	18
>20	75	93	94	52
>25	61	93	100	78
>30	52	80	100	75

described here. With an unfavorable effect on both systematic and random errors for all variables, we observed a 10-fold increase in the systematic error for PRA. We believe that this effectively illustrates why one should interpret absolute kinematic values from sensor systems in contact sports with caution. We suspect that the main explanation for some of the very high on-field values observed (Figure 3) is a combination of inherent systematic overestimation and poor head coupling. Arguably, a mean value of well over 20,000 rad/s^2 for finishing headers almost certainly represents a gross overestimation, based on previous biomechanical studies from heading in soccer and mild traumatic brain injuries[1,10,17,21]; the players considered the exercise to be in the upper but normal heading severity range.

Press and Rowson[14] recently quantified head impact exposure in collegiate women's soccer using a skin patch placed behind the ear. They observed that the recorded number of head impacts vastly exceeded those confirmed on video, concluding that data from head impact sensors warrant careful interpretation when used in automated settings. Cortes et al[2] drew similar conclusions when measuring head impact exposure in lacrosse—with both studies highlighting the need to classify accelerative events

with, for example, video analysis. Thus, the main objective of the structured training protocol (phase 2) was to evaluate the in-ear sensor's capacity to discriminate head impacts from non–head impact accelerative events. By classifying all recorded accelerative events into these 2 main categories—in both the structured training protocol and the regular training sessions—our results showed that the sensor displayed an excellent discriminatory capacity. However, despite the ability to maintain high sensitivity and specificity, there is a crucial difference between the on-field settings, with real-life implications. In the structured training protocol, it was possible to use a cutoff value (eg, 9*g*) (see Table 2) yielding 100% positive predictive value while maintaining sensitivity >70%. Although such a scenario misses many head impacts in the lowest range, one can safely conclude that any event above this threshold is actually caused by a direct impact to the head, obviating secondary means of verification (eg, video). We were unable to replicate this finding in the regular training sessions (phase 3) owing to spurious non–head impact events, such as touching the sensor or dropping it on the ground, recording values as high as 65*g* and 124*g*. Tables 2 and 3 illustrate the difficulties of identifying a PLA or PRV cutoff value in a real-life setting and how it is not possible to maximize the positive predictive value in a similar manner to the structured training protocol. Thus, there is still a need to confirm what actually caused any event above a given threshold. During the regular training sessions that we observed, headers were relatively infrequent. But even if a greater proportion of headers would most likely yield higher positive predictive values, there would still be a need for video confirmation, for example.

As the main aim of this study was to evaluate the sensor's potential for usage in large-scale data collection in youth soccer, practical considerations on feasibility and user-friendliness need to be addressed. We encountered several software problems during the course of the study, such as having to retrieve apparently missing data from one of the on-field sessions. Furthermore, players differed in their opinions regarding whether they would accept wearing the sensors over longer periods throughout the season, including matches. Despite being designed with a lumen to minimize any hearing impairment, this seemed to be one of the main criticisms. We also observed that some of the sensors were partially obstructed with cerumen after the sessions. Such concerns are likely to limit the utility of such devices; they not only render the data potentially unreliable but might also negatively affect compliance.

We acknowledge several study limitations. First, a laboratory validation needs to rely on a reference system, with its own imperfections. We chose a well-recognized method (HIII) to make our results comparable with the work of others, as well as easy to replicate. Initially, we performed a thorough assessment of frontal impacts (considered most relevant for soccer) and then proceeded to address the issues of impact location and severity. This explains the discrepant number of impacts across conditions. We chose to exclude and replace data from a series of severe outliers. We did this because we consider the suspected cause plausible: a specific mechanical response of the HIII head and neck during a sequence of impacts gave rise to an artifact in the MV1 sensor. Such an artifact may reflect specific technical sensor characteristics, including sample rate and sensor resonant frequency response or bandwidth. Including these data would potentially disguise our main findings, as this particular issue does not reflect a challenge related to the real-life human scenarios that we ultimately evaluated. Second, we recognize that only 6 players took part in this study and that only 2 regular training sessions were included, potentially limiting the external validity to other playing levels, sex, and styles of play. Compensating for this, we have a data set composed of several hundreds of events. Last, for logistical reasons, we attached the sensors ourselves for the on-field parts of the study, without an on-site demonstration recommended by the producer. Even though this might be a source of systematic error, we did our best to comply with the instructions. In summary, however, it seems unlikely that these limitations invalidate our main findings.

The main strength of this study lies in its stepwise approach, allowing us to translate our findings from the laboratory into a real-life setting. As a result, we believe that our findings have illustrated several challenges that need to be taken into account when considering the use of such sensor systems for quantifying head impact exposures in any collision or contact sport. We suggest that new methods be evaluated carefully before being taken into use, including not only a laboratory validation but also an on-field evaluation. Future sensor systems should seek to improve technical specifications (eg, sampling rate), create algorithms better capable of filtering out spurious non–head impact events, and optimize head coupling. Until then, it is important to remain critical when interpreting data acquired from such systems and to confirm all events with secondary means of verification.

CONCLUSION

This study highlights several previously recognized challenges when attempting to quantify head impacts in contact sports with sensor systems. It also demonstrates the need for careful and systematic evaluation before being used in real-life and research settings. In-ear sensors represent a novel method for quantifying head impact characteristics in youth soccer. However, the device tested in this study displayed considerable random error and overestimated head impact exposures substantially, depending on the severity and type of impact. Despite showing excellent on-field accuracy for discriminating headings from other accelerative events in youth soccer, absolute values should be interpreted with caution, and there is a need for secondary means of verification (eg, video analysis) in real-life settings.

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III

Evaluating the validity of self-report as a method for quantifying heading exposure in male youth soccer

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Evaluating the validity of self-report as a method for quantifying heading exposure in male youth soccer

Participation in soccer has been associated with brain alterations. The association with heading the ball is poorly understood. In adults, questionnaires have been proposed to assess heading exposure. However, the validity of self-report in adolescents remains to be elucidated. Male youth soccer players (n=34) completed a questionnaire on heading exposure after a two-week period, which included matches and training sessions. Self-reported numbers were compared to observation (considered reference). In total, we observed 157 training sessions and 64 matches. Self-reported heading exposure correlated with observed heading exposure (Spearman's rho 0.68; $p<0.001$). Players systematically overestimated their heading exposure by a factor of 3 with random error of 46%. Area under the curve was 0.87 (95% CI 0.67-1) utilizing self-report for identifying players from high and low-exposure groups. In conclusion, self-reported data could be used to group youth players into high and low heading exposure groups, but not to quantify individual heading exposure.

Keywords: subconcussion, TBI, neurodegeneration, football, soccer heading

Word count: 3 333

Introduction

Recent studies suggest an association between head impact exposure in contact sports and neurological consequences (Asken, Sullan, DeKosky, Jaffee, & Bauer, 2017; Mez et al., 2019; Mez et al., 2017). In soccer, even though an increased risk of neurodegenerative disorders in later life has been found (Mackay et al., 2019), it has not yet been established whether or not heading the ball is the cause of harm to the brain (Kontos et al., 2017; Tarnutzer, Straumann, Brugger, & Feddermann-Demont, 2017). However, preliminary studies using advanced neuroimaging techniques have implied that heading the ball may cause structural alterations in the brain (Koerte, Ertl-Wagner, Reiser, Zafonte, & Shenton, 2012; Koerte et al., 2015; Koerte et al., 2016; Lipton et al., 2013). Moreover, recent evidence also suggests that heading may impair cognitive function in both adults (Lipton, et al., 2013; Stewart et al., 2018) and adolescents (Koerte et al., 2017; Zhang, Red, Lin, Patel, & Sereno, 2013). With hundreds of millions of active players worldwide, any short- or long-term neurological consequences could have considerable public health impact.

A recurrent methodological issue in previous studies has been inadequate quantification of head-impact exposure (Tarnutzer, et al., 2017); this relates to single sessions as well as longer periods. Ideally, data are needed not only on the number of headers for each player, but also on the biomechanical characteristics of each impact (Broglio, Lapointe, O'Connor, & McCrea, 2017). In theory, wearable sensor systems have the potential to achieve this (Brennan et al., 2017; O'Connor, Rowson, Duma, & Broglio, 2017; Patton, 2016). However, previous studies have demonstrated that sensors are impractical for large-scale studies (Press and Rowson, 2017; Sandmo, McIntosh, Andersen, Koerte, & Bahr, 2019). Specifically, inaccurate sensor outputs and failure to adequately filter out false-positive events constitute central impediments (Cortes et al., 2017; Press and Rowson, 2017; Sandmo, McIntosh, et al., 2019). Alternative methods, such as direct observation or video analysis, can provide objective information on the number of head impacts, but not readily on their magnitudes. Regardless, such methods are resource intensive as they require the presence of research personnel to observe each player during each session.

Self-report allows for low-cost and easy administration, and therefore remains a favorable alternative for quantifying head-impact exposure in large-scale cohort studies. Importantly, self-reported heading exposure has been associated with structural brain alterations (Koerte, et al., 2015; Koerte, et al., 2016; Lipton, et al., 2013) as well as neurological symptoms (Stewart et al., 2017) and cognitive performance (Lipton, et al., 2013;

Stewart, et al., 2018). Previous studies have described how self-reported head-impact exposure can be used in adult populations (Catenaccio et al., 2016; Lipton et al., 2017; Montenigro et al., 2017). Specifically, Catenaccio et al. (2016) described the external validation of a two-week recall questionnaire in adult soccer. However, it is unknown how reliable this approach is among youth players. Thus, the aim of this study was to test the validity of a questionnaire (Catenaccio, et al., 2016) for quantifying heading exposure in male youth soccer players over a two-week period.

Methods

Study design and participants

Male elite youth soccer players from Norway, Germany and Belgium were invited to participate in the study during the 2018 season. Players from Norway were part of the study RepImpact (www.repimpact.org); RepImpact is a multidisciplinary, longitudinal study evaluating the effects of repetitive head impacts on brain structure, function and connectivity. Players from Germany and Belgium were recruited solely for the purposes of the current study. Recruitment was done through coaches and supporting staff of local teams that invited their respective team members to participate voluntarily. Table 1 shows the characteristics of the participants.

The study was approved by the Regional Committee for Medical and Health Research Ethics South East, Norway; the Ethics Committee of the Medical Faculty at the University of Munich, Germany; and the local Ethics Committee of UZ/KU Leuven, Belgium. Written informed consent was obtained from the participants and their legal guardians.

[Table 1 near here]

Observed heading exposure

For two weeks, trained research personnel attended all training sessions and matches of the participating teams. During this period, all heading exposure for each player in each session was registered, using either (1) direct observation or (2) video recordings. Specifically, direct observation was used for both training sessions and matches in Germany and Belgium. For each training session, two to eight observers were present; each observer was assigned to

specific players, with a maximum of seven players per observer. For each match, one to four observers were present; each observer was instructed to follow the ball, and any discrepancies were resolved by consensus. In Norway, direct observation was used for matches, while video recordings with subsequent structured video analysis was used for training sessions. Video recordings were obtained with three digital video cameras (1080p, 50 fps), placed to capture all players for the entirety of the training sessions.

Any observed heading event, regardless of the perceived magnitude, was registered and assigned to each individual player as one header. Observed heading exposure was subsequently used as reference.

Self-reported heading exposure

On the last day of the observation period, all 34 participants completed a questionnaire in their native language, retrospectively quantifying their heading and playing exposure during the study period. Participants in Norway completed the questionnaire digitally, receiving a link to the form via SMS; participants in Germany and Belgium used pen and paper.

The questionnaire was based on a previously validated method for adult populations (Catenaccio, et al., 2016; Lipton, et al., 2017); a detailed account of its contents has been published elsewhere (Catenaccio, et al., 2016; Lipton, et al., 2013). In short, the respondents were asked to quantify their absolute number of training sessions and matches at the end of a two-week period, as well as the average number of headings for each of these two session types (see supplemental material for a full copy of the questionnaire that was used).

The participants were not blinded to the aims or outcome measures of the study, as prior consent was needed. Furthermore, when completing the questionnaire, they were specifically instructed to only include heading exposure during organized training sessions and matches with their primary team (i.e. the team that was observed in the study); thus, they were told to disregard sessions with e.g. soccer academies and regional/national teams.

Data analyses

Self-reported heading exposure for each participant over the two-week period was calculated by (1) multiplying the reported average number of headers in training with the reported number of training sessions, and (2) multiplying the reported average number of headers in matches with the reported number of matches. These were summed to represent total heading exposure.

As the heading exposure scores were non-normally distributed, Spearman's rank correlation coefficient was used to evaluate the association between self-reported and observed heading exposure (i.e. the reference). This was done separately for training sessions and matches, as well as for all sessions combined. In the same way, we also explored associations between other self-reported and observed exposure variables (e.g. the number of matches). To estimate the accuracy and precision of self-reported heading exposure, we calculated its systematic and random error. Systematic error was calculated as the difference between median self-reported and observed heading exposure. This difference was expressed as a factor based on observed heading exposure, with corresponding interquartile ranges (IQR); positive (negative) results indicate overestimation (underestimation) of self-reported heading exposure, and factors are directly translatable to percentages. Random error was expressed as the coefficient of variation (CV), and was calculated in two steps: First, the method error (ME) was calculated by dividing the standard deviation (SD) of the mean difference between self-reported and observed heading exposure by the square root of the number of measurements:

$$ME = SD_{mean\ difference} / \sqrt{2}$$

Second, the method error was divided by the mean of the combined measurements:

$$CV = ME / (mean_{self\ report} + mean_{observed} / 2)$$

Random error is expressed as a percentage; greater values represent more variation and thereby poorer precision (Sale, 1991).

We also conducted receiver operating characteristic (ROC) analyses to evaluate the ability of self-reported data to identify players belonging to high and low exposure groups. For defining the exposure groups, we randomly and equally split our dataset into two groups: a training (n=17) and a validation dataset (n=17). Then, based on either (1) the median or (2) the tertiles of the observed heading exposure in the training dataset, we categorized players in the validation dataset into groups of high and low levels of exposure. The ROC analyses were performed on the validation dataset, using the self-reported scores.

All statistical analyses were performed using SAS (version 9.4; SAS Institute Inc., North Carolina, USA), and an alpha level of 0.05 was used to denote statistical significance.

Results

For all 34 participants combined, we observed a total of 157 training sessions and 64 matches during the two-week study period. In total, we observed 1 051 headers; 928 headers (88%) occurred during training, and 123 headers (12%) occurred during matches. Table 2 shows how training sessions, matches and heading exposure were distributed for players from different countries.

As shown in table 2, players tended to overestimate their heading exposure compared to the numbers observed. Evaluating the systematic error, the players overestimated total heading exposure by a factor of 3.0 (IQR = 4.8); the corresponding random error was 46%. In training sessions, the overestimation was by a factor of 3.7 (IQR = 6.3), with a random error of 49%. In matches, the overestimation was by a factor of 0.5 (IQR = 1.4), with a random error of 44%.

[Table 2 near here]

For self-reported and observed total heading exposure during the study period, the Spearman's rank correlation coefficient was 0.68 ($p<0.001$) (figure 1a). For training sessions, the correlation was 0.67 ($p < 0.001$) (figure 1b); for matches, the correlation was 0.73 ($p < 0.001$) (figure 1c).

[Figure 1 near here]

For the ROC-analyses, the median observed exposure in the training dataset was 36; using this cut-off in the validation dataset, 4 players belonged to the high-exposure group and 13 players to the low-exposure group. The area under the curve (AUC) was 0.87 (95% CI 0.67-1) for using the self-reported scores to identify the two groups. Based on the tertiles (low<22, high>54), the validation dataset had 3 players in the high-exposure group and 9 players in the low-exposure group, for which the AUC for using the self-reported scores increased to 0.96 (95% CI 0.86-1).

When exploring correlations between other self-reported and observed exposures, we detected several significant associations (table 3). Exempting total headers in matches, the

greatest numerical correlation was seen between self-reported and observed number of matches (0.70; $p<0.001$).

[Table 3 near here]

Discussion

This study evaluated the validity of using a questionnaire to assess heading exposure over a two-week period in male youth soccer players. Self-reported data displayed a marked systematic overestimation of heading exposure in combination with considerable random error (figure 1), suggesting low accuracy and precision. Nevertheless, there was a 0.68 correlation coefficient (Spearman's rho) between self-reported and observed heading exposure, indicating a moderate to strong ability of self-report to capture the rank order of heading exposure between players. Moreover, the accuracy of self-report to categorize players into groups of different exposure levels (e.g. high vs. low) was high, suggesting that self-reported heading exposure could be used for such purposes.

With ongoing studies evaluating the potential effects of heading in youth soccer, developing adequate measures for quantifying exposure is key to assess outcomes (Tarnutzer, et al., 2017). We therefore set out to assess the utility of self-reported heading exposure in youth players, using a previously validated method (Catenaccio, et al., 2016). Catenaccio et al. (2016) evaluated the ability of a two-week recall questionnaire to measure match-related heading exposure in male and female collegiate soccer players. Based on their findings, they concluded that self-report is a valid and reliable instrument for tracking heading exposure in population studies, but noted that it might have to be calibrated in women. Specifically, they described a slight underestimation in men (requiring little to no adjustment) and a marked overestimation in women (factor of 5). Comparing our match-related results to those of male senior players from Catenaccio et al. (2016), both studies found a similar positive correlation between self-reported and observed heading exposure in matches (Spearman's rho of 0.73 in our study vs. a range of 0.75-0.95 in theirs, looking at multiple two-week periods). Nevertheless, we found that youth players systematically overestimated their exposure (factor of 0.5 in matches); in contrast, Catenaccio et al. (2016) found that male collegiate players systematically underestimated theirs, but only slightly.

We note that our observation of a systematic overestimation in youth players is in accordance with a recent study by Harris et al. (2018). They evaluated the ability of female

youth players (age 13 yrs) to recall their match-related heading exposure over an entire season, and found that the players overestimated heading frequency by 51% compared to video observation; this is comparable to our reported systematic overestimation in matches by a factor of 0.5. As they evaluated a cohort of female players, this suggests that youth players tend to overestimate regardless of sex. Harris et al. (2018) went on to emphasize the need to take recall bias into account when using self-report. Their conclusion, however, was based on a considerably longer recall period (i.e. a whole season) compared to our capturing a two-week interval. In summary, based on these two studies (Catenaccio, et al., 2016; Harriss, et al., 2018) and ours, age and sex warrant careful consideration when using self-report to estimate heading exposure.

Ideally, one could adjust for a systematic overestimation. However, there was also substantial random error (46% overall) in our data, indicating poor precision. Thus, combining the systematic and random error, the value of using self-report to measure absolute number of headers for an individual player becomes limited. Furthermore, systematic and random error might vary between session types. Of note, previous studies (Catenaccio, et al., 2016; Harriss, et al., 2018) were solely based on match exposure. In our data, we observed that the total self-reported systematic overestimation was mainly driven by poor accuracy in training-related exposure (factor of 3.7 versus 0.5 in matches).

We can only speculate as to why self-report in adolescents is inaccurate to such an extent. A previous study by Rutherford and Fernie (2005) pointed out that heading the ball can be regarded an everyday event for active soccer players. They hypothesized that self-reported estimates of such daily events are likely to be governed by specific psychological mechanisms, such as rule-based estimation strategies; such strategies typically lead to overestimations (Thompson and Mingay, 1991). As shown in table 3, we also explored relationships between other self-reported and observed variables. This allowed us to obtain a broader view of the general validity of self-report in a youth population. Interestingly, many of the participants not only overestimated their average heading exposure per session, but also reported inaccurate numbers for matches and training sessions. Previous research on self-reported physical activity has pointed out the limited ability for children to perform abstract reasoning and detailed recalls (Sallis, 1991). Based on our experience, we also find it reasonable to suspect that it can vary how interested and devoted adolescents are when completing any such questionnaire. Furthermore, it remains unknown how variation in factors such as observation periods, session types, playing styles and impact characteristics might affect the ability to accurately recall heading exposure in youth soccer players.

Despite the challenges concerning systematic and random error, our results indicate that self-report might still be an appropriate method for quantifying heading exposure in youth soccer. First, the method seems to retain an acceptable ability to rank players with respect to exposure levels, as illustrated by the correlation coefficient (0.68 across all sessions). We interpret this as being facilitated by Spearman's rho as a statistical method; specifically, as the numbers are converted to rank orders across the sample, it remains unaffected by extreme values. Second, as demonstrated by the ROC-analyses, self-reported heading exposures displayed the ability to correctly categorize players into different exposure groups (e.g. high and low). In other words, players with relatively higher levels of heading exposure tended to report numbers that would classify them correctly as belonging to a high-exposure group. As expected, this finding was more accurate when comparing more extreme ends of the high vs. low exposure spectrum. This is demonstrated by the AUC increase from 0.87 to 0.96 when applying it to smaller groups. Summarizing these findings, self-reported data may serve as a tool for ranking or grouping players with respect to heading exposure levels.

As an interesting additional finding in our study, based on our observed data, we describe how total heading exposure in this cohort mainly originated from training sessions (88%). Importantly, while match-related heading exposure was recently characterized in detail (Sandmo, Andersen, Koerte, & Bahr, 2019), such objective data on training-related exposure have been scarce. However, we note that this difference seemed to be greater in Germany and Norway than in Belgium (table 2). Despite low sample sizes when comparing between sites, this suggests that factors such as playing styles and coaching philosophies have an influence. Such factors should be explored in future studies.

We recognize several methodological considerations. First, using direct observation as reference has its own limitations. A recent study demonstrated that having one sideline observer in matches yielded a sensitivity of 91% for identifying headers, with close-to-perfect inter-rater reliability (Sandmo, Andersen, et al., 2019). However, whether this translates to training sessions is not known. Of note, training sessions are highly variable with respect to drills and exercises and may therefore become more chaotic than matches (e.g. by having more than one ball in play at the same time). We therefore strived to have one observer per player during training sessions, which, however, was not possible for all sessions. With one observer sometimes having to account for more than one player at a time (maximum of seven), this might have negatively affected the sensitivity of a subset of the observations. Second, both observed and self-reported heading exposure quantify the number of impacts only. Consequently, it was not possible to account for variations in impact magnitudes (i.e.

linear and rotational accelerations); this has previously been shown to vary according to factors such as head and neck size (Caccese et al., 2017), as well as session and heading types (Caccese, Lamond, Buckley, & Kaminski, 2016; Sandmo, McIntosh, et al., 2019). As an example, we note that some participants would sometimes juggle the ball on their head during training, which could lead to a high number of what is likely to be low-magnitude impacts. Third, our findings relate to a limited sample, potentially compromising the external validity of our findings. Fourth, for logistical reasons, we were able to observe players on their primary team only. As a result, the observed heading exposure is almost certainly an underestimation of the total two-week exposure for some of the participants. Playing on a high level, some players had other sessions as part of soccer academies and regional/national teams. While we specifically instructed players to only include exposure related to their primary team, this could have been confusing and consequently a source of bias; importantly, this might have contributed to the overestimation when completing the questionnaire. Last, the participants knew they were being observed throughout the study period. We do not know if this may have led to changes in behavior or to more accurate reports than would otherwise be expected. In summary, however, it is unlikely that these limitations undermine our main findings. Instead, they highlight important aspects that make head-impact quantification in contact sports challenging.

In conclusion, this study demonstrates the need for careful interpretation when using self-reported data to quantify heading exposure in male youth soccer. Due to substantial systematic and random error, self-report should not be used for determining individual absolute heading exposures. It may, however, serve as a potential tool to rank or group players with respect to heading exposure in adequately sized populations.

Table 1. Descriptive characteristics of the participants.

Characteristic	Belgium	Germany	Norway	Total
N	8	14	12	34
Age (mean ± SD)	14.2 ± 0.3	14.3 ± 0.4	15.4 ± 0.6	14.7 ± 0.7
Playing positions (N)				
Goalkeeper	0	2	0	2 (6%)
Central defender	1	3	3	7 (21%)
Fullback/wingback	1	3	2	6 (18%)
Central/inside midfielder	3	1	2	6 (18%)
Wing/offensive midfielder	3	1	4	8 (23%)
Striker	0	4	1	5 (15%)

Table 2. Observed vs. self-reported heading exposure for youth soccer players during a two-week period.

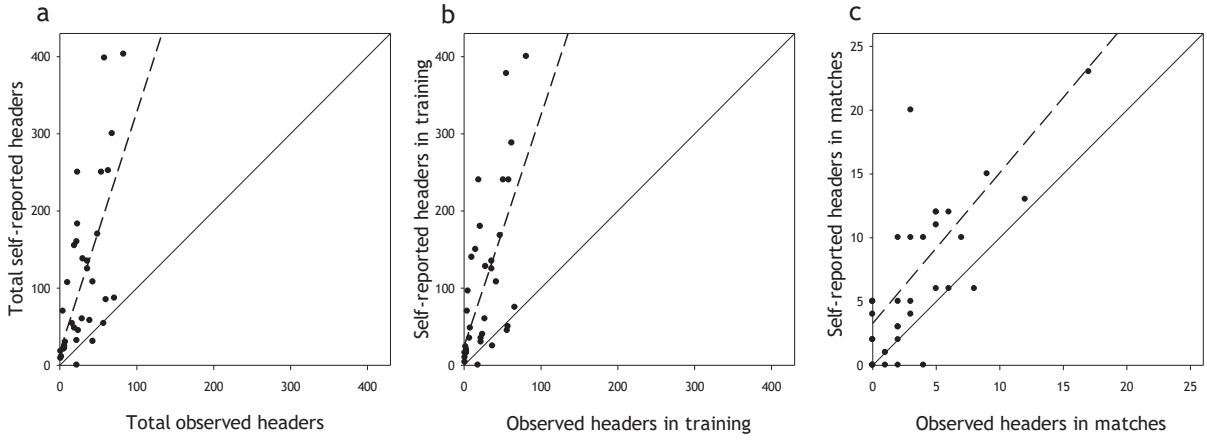
	Belgium		Germany		Norway		All sites combined	
	Observed	Self-reported	Observed	Self-reported	Observed	Self-reported	Observed	Self-reported
Total headers in matches	3.0 (6.5)	5.5 (4.8)	2.0 (2.0)	2.5 (10.0)	4.5 (3.0)	8.3 (9.5)	3.0 (4.0)	5.0 (8.5)
Total headers in training sessions	3.5 (6.0)	29.5 (43.0)	36.0 (27.0)	131.5 (180.0)	22.0 (49.0)	47.5 (90.6)	22.0 (42.0)	65.0 (125.0)
Number of matches	2.0 (1.0)	1.5 (2.0)	2.5 (2.0)	2.0 (1.0)	2.0 (1.0)	1.5 (2.0)	2.0 (2.0)	2.0 (2.0)
Number of training sessions	6.5 (3.0)	8.0 (0.5)	4.5 (2.0)	5.0 (2.0)	4.5 (1.5)	5.0 (2.3)	5.0 (1.0)	5.8 (2.0)
Headers per match	2.0 (3.3)	4.0 (3.3)	1.0 (1.5)	2.5 (3.0)	2.0 (2.9)	3.0 (4.0)	1.6 (1.8)	3.0 (3.0)
Headers per training session	0.7 (0.7)	4.0 (3.5)	9.0 (3.8)	27.5 (30.0)	7.4 (9.3)	13.8 (11.3)	7.3 (9.2)	13.8 (25.0)

Numbers are presented as median (interquartile range).

Table 3. Correlations between self-reported and observed exposures from two weeks of participation in youth soccer. Top numbers display the Spearman's rank correlation coefficient, and lower numbers denote the corresponding p-value.

		Observed					
		Total headers in matches	Total headers in training sessions	Headers per match	Headers per training session	Number of matches	Number of training sessions
Self-reported	Total headers in matches	0.73 <.0001					
	Total headers in training sessions		0.67 <.0001				
	Headers per match			0.52 <.01			
	Headers per training session				0.61 <.001		
	Number of matches					0.70 <.0001	
	Number of training sessions						0.63 <.0001

Figure 1. Self-reported heading exposure from (a) all sessions combined, (b) training sessions only and (c) matches only, over a two-week period, plotted against observed exposure. Solid lines are for reference, dashed lines indicate the line of best fit.



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HeadCount questionnaire 2 weeks

The following questions ask about various aspects of organized competitive soccer in which you have participated over the past 2 weeks. Please note that the various sections and questions ask separately about competitive soccer GAMES versus soccer PRACTICE and about INDOOR versus OUTDOOR play. For this reason, it may seem that same questions are asked more than once. This is not an error, but is because we want to learn about aspects of your soccer play in different contexts. Please pay careful attention to the instructions in order to be sure you are answering the specific question that is asked.
For GAMES, consider competitive games between your team and another team.
For PRACTICE, consider any sessions of organized team practice, including practice games (e.g., scrimmages).

1. Have you played any soccer over the past 2 weeks?
   ☐ Yes ☐ no → *skip to Q48*

2. Did past 2 weeks coincide with the active season of your soccer team/club/group?
   ☐ yes ☐ no

<u>OUTDOOR GAMES</u>

3. Did you play any GAMES OUTDOORS over the past 2 weeks? (For OUTDOOR GAMES, consider any competitive games between your team and another team played outdoors)
   ☐ yes ☐ no → *skip to Q12*
4. How many GAMES did you play OUTDOORS during the past 2 weeks? _____
5. During OUTDOOR GAMES, what was your MAIN POSITION, i.e. the position you played most often in the past 2 weeks?
   ☐ Goalkeeper ☐ Center back ☐ Wing back
   ☐ Forward ☐ Midfield defensive ☐ Midfield offensive / Winger
6. When you were not playing in your MAIN POSITION, what ALTERNATE POSITION did you play most often in the past 2 weeks in OUTDOOR GAMES? (Select "none" if you did not play in an alternate position)
   ☐ Goalkeeper ☐ Center back ☐ Wing back
   ☐ Forward ☐ Midfield defensive ☐ Midfield offensive / Winger
   ☐ none
7. On average, how many times did you head the ball per OUTDOOR GAME played in the past 2 weeks?
   _____

Usually heading is unremarkable. Sometimes, though, heading is not quite right and may cause dizziness, confusion or other feelings. Referring to the scale and examples below, please indicate how often you experience different severities of heading.

Best Heading > > > > > > > > > > > > > Worst Heading				
Very Low Impact	**Mild Impact**	**Moderate Impact**	**Severe Impact**	**Very Severe Impact**
Did not notice **No pain** **Headed it just right**	**Noticed it** **Slight pain** **Did not head it quite right**	**Stopped playing a few seconds** **Moderate pain / some dizziness** **Definitely headed it wrong**	**Needed medical attention** **Stopped playing** **Felt dazed or injured**	**Knocked out unconscious**

8. How often did MILD IMPACT happen in the past 2 weeks during OUTDOOR GAMES?
   ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐5+
9. How often did MODERATE IMPACT happen in the past 2 weeks during OUTDOOR GAMES?
   ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐5+
10. How often did SEVERE IMPACT happen in the past 2 weeks during OUTDOOR GAMES?
    ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐5+
11. How often did VERY SEVERE IMPACT happen in the past 2 weeks during OUTDOOR GAMES?
    ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐5+

OUTDOOR PRACTICE

Comment: In the following, a "set" is representing a series of headings during heading drills, e.g. ball thrown multiple times by hand. The number of headings per set is defined as "reps", i.e. number of thrown balls for heading. Example: "3 sets with 10 reps each".

12. Did you PRACTICE OUTDOORS over the past 2 weeks?

    ☐ yes ☐ no → *skip to Q22*

13. How many days did you PRACTICE OUTDOORS over the past 2 weeks? _____

14. On average, how many sets of heading drills did you do per OUTDOOR PRACTICE during the past 2 weeks?

    ☐ 0 → *skip to Q16* ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐5+

15. On average, how many times did you head the ball ("reps") in each "set" during OUTDOOR PRACTICE over the past 2 weeks?

    ☐ < 10 ☐ 10-19 ☐ 20-29 ☐ 30-39 ☐ 40+

16. On average, how many times did you head the ball during OUTDOOR PRACTICE over the past 2 weeks (in total, including drills)? _____

17. Did you experience any symptoms (headache, nausea, confusion, dizziness) related to heading drills during OUTDOOR PRACTICE over the past 2 weeks?

    ☐ yes ☐ no

Usually heading is unremarkable. Sometimes, though, heading is not quite right and may cause dizziness, confusion or other feelings. Referring to the scale and examples below, please indicate how often you experience different severities of heading.

Best Heading > > > > > > > > > > > > > Worst Heading				
Very Low Impact	**Mild Impact**	**Moderate Impact**	**Severe Impact**	**Very Severe Impact**
Did not notice **No pain** **Headed it just right**	**Noticed it** **Slight pain** **Did not head it quite right**	**Stopped playing a few seconds** **Moderate pain / some dizziness** **Definitely headed it wrong**	**Needed medical attention** **Stopped playing** **Felt dazed or injured**	**Knocked out unconscious**

18. How often did MILD IMPACT happen in the past 2 weeks during OUTDOOR PRACTICE?

    ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐5+

19. How often did MODERATE IMPACT happen in the past 2 weeks during OUTDOOR PRACTICE?

    ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐5+

20. How often did SEVERE IMPACT happen in the past 2 weeks during OUTDOOR PRACTICE?

    ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐5+

21. How often did VERY SEVERE IMPACT happen in the past 2 weeks during OUTDOOR PRACTICE?

    ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐5+

INDOOR GAMES

22. Did you play any GAMES INDOORS over the past 2 weeks? (For INDOOR GAMES, consider any competitive games between your team and another team played indoors)

    ☐ yes ☐ no → *skip to Q31*

23. How many GAMES did you play INDOORS during the past 2 weeks? _____

24. During INDOOR GAMES, what was your MAIN POSITION, i.e. the position you played most often in the past 2 weeks?

    ☐ Goalkeeper ☐ Defense ☐ Midfield ☐ Forward

25. When you were not playing in your MAIN POSITION, what ALTERNATE POSITION did you play most often in the past 2 weeks in INDOOR GAMES? (Select "none" if you did not play in an alternate position)

    ☐ None ☐ Goalkeeper ☐ Defense ☐ Midfield ☐ Forward

26. On average, how many times did you head the ball per INDOOR GAME played in the past 2 weeks?

    _____

Usually heading is unremarkable. Sometimes, though, heading is not quite right and may cause dizziness, confusion or other feelings. Referring to the scale and examples below, please indicate how often you experience different severities of heading.

Best Heading > > > > > > > > > > > > > Worst Heading				
Very Low Impact	**Mild Impact**	**Moderate Impact**	**Severe Impact**	**Very Severe Impact**
Did not notice **No pain** **Headed it just right**	**Noticed it** **Slight pain** **Did not head it quite right**	**Stopped playing a few seconds** **Moderate pain / some dizziness** **Definitely headed it wrong**	**Needed medical attention** **Stopped playing** **Felt dazed or injured**	**Knocked out unconscious**

27. How often did MILD IMPACT happen in the past 2 weeks during INDOOR GAMES?

    ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐5+

28. How often did MODERATE IMPACT happen in the past 2 weeks during INDOOR GAMES?

    ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐5+

29. How often did SEVERE IMPACT happen in the past 2 weeks during INDOOR GAMES?

    ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐5+

30. How often did VERY SEVERE IMPACT happen in the past 2 weeks during INDOOR GAMES?

    ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐5+

INDOOR PRACTICE

Comment: In the following, a "set" is representing a series of headings during heading drills, e.g. ball thrown multiple times by hand. The number of headings per set is defined as "reps", i.e. number of thrown balls for heading. Example: "3 sets with 10 reps each".

31. Did you PRACTICE INDOORS over the past 2 weeks?

    ☐ yes ☐ no → *skip to Q41*

32. How many days did you PRACTICE INDOORS over the past 2 weeks? _____

33. On average, how many sets of heading drills did you do per INDOOR PRACTICE during the past 2 weeks?

    ☐ 0 → *skip to Q35* ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐5+

34. On average, how many times did you head the ball ("reps") in each "set" during INDOOR PRACTICE over the past 2 weeks?

    ☐ < 10 ☐ 10-19 ☐ 20-29 ☐ 30-39 ☐ 40+

35. On average, how many times did you head the ball during INDOOR PRACTICE over the past 2 weeks?

    _____

36. Did you experience any symptoms (headache, nausea, confusion, dizziness) related to heading drills during INDOOR PRACTICE over the past 2 weeks?

    ☐ yes ☐ no

Usually heading is unremarkable. Sometimes, though, heading is not quite right and may cause dizziness, confusion or other feelings. Referring to the scale and examples below, please indicate how often you experience different severities of heading.

Best Heading > > > > > > > > > > > > > Worst Heading				
Very Low Impact	**Mild Impact**	**Moderate Impact**	**Severe Impact**	**Very Severe Impact**
Did not notice **No pain** **Headed it just right**	**Noticed it** **Slight pain** **Did not head it quite right**	**Stopped playing a few seconds** **Moderate pain / some dizziness** **Definitely headed it wrong**	**Needed medical attention** **Stopped playing** **Felt dazed or injured**	**Knocked out unconscious**

37. How often did MILD IMPACT happen in the past 2 weeks during INDOOR PRACTICE?

    ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐5+

38. How often did MODERATE IMPACT happen in the past 2 weeks during INDOOR PRACTICE?

    ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐5+

39. How often did SEVERE IMPACT happen in the past 2 weeks during INDOOR PRACTICE?

    ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐5+

40. How often did VERY SEVERE IMPACT happen in the past 2 weeks during INDOOR PRACTICE?

    ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐5+

Finally, please answer the following questions regardless indoor, outdoor, game or practice:

41. How many times in the past 2 weeks did you: Get hit in the back of the head by a ball?

    □ 0 □ 1 □ 2+

42. How many times in the past 2 weeks did you: Hit your head against a goalpost?

    □ 0 □ 1 □ 2+

43. How many times in the past 2 weeks did you: Hit your head against another player´s head?

    □ 0 □ 1 □ 2+

44. How many times in the past 2 weeks did you: Fall and hit your head on the ground?

    □ 0 □ 1 □ 2+

45. How many times in the past 2 weeks did you: Hit your head against a player´s elbow, knew, fist, etc.?

    □ 0 □ 1 □ 2+

46. How many times in the past 2 weeks did you: Have your head stepped on or kicked by another player?

    □ 0 □ 1 □ 2+

47. Other than from soccer, were you dazed or knocked unconscious from a head injury in the past 2 weeks?

    □ yes □ no → *skip to end of questionnaire*

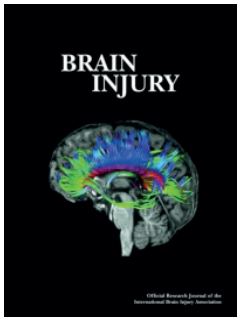
48. What was the cause of the injury?

    □ other sports
    □ car/traffic accident
    □ fall
    □ assault
    □ other _____

49. Check the one that best describes what happened:

    □ I was dazed but not unconscious
    □ I was knocked out for less than 1 minute
    □ I was knocked out for 1 to 5 minutes
    □ I was knocked out for more than 5 minutes
    □ I was hospitalized
    □ I don´t remember

IV



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Neurofilament light and tau in serum after head-impact exposure in soccer

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ABSTRACT

Introduction: Blood-based biomarkers can provide valuable information on the effects of repetitive head impacts in sports. This study investigated if repetitive headers or accidental head impacts in soccer could cause structural brain injury, detected as an increase in serum neurofilament light (NfL) or tau.

Methods: NfL and tau were measured in professional soccer players in pre-season. Then, the effect of three short-term exposures on biomarker levels was assessed: (1) high-intensity exercise, (2) repetitive headers, and (3) head impacts in a match.

Results: We analyzed 354 samples and observed no effects on NfL from any of the three short-term exposures. Tau levels rose significantly from baseline to 1 h after (1) high-intensity exercise (Δ0.50 pg/mL, 95% CI 0.19–0.81, $p < .01$); the same was observed after (2) repetitive headers (Δ0.29 pg/mL, 95% CI 0.10–0.48, $p < .01$), but not after (3) accidental head-impact incidents (Δ0.36 pg/mL, 95% CI −0.02–0.74, $p = .06$). The highest absolute values were seen 1 h after high-intensity exercise (mean±SD, 1.92 ± 0.83 pg/mL).

Conclusion: NfL and tau in serum were unaffected by head impacts in soccer. Importantly, tau levels seem to rise in response to exercise, emphasizing the need for control groups. Our findings highlight important characteristics and limitations when using these biomarkers in sports.

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Subconcussive; TBI; chronic traumatic encephalopathy; football; repetitive head impacts

Introduction

Head-impact exposure in contact sports remains a controversial issue because of the potential association with long-term neurological sequelae (1–3). Soccer is unique in that voluntary and unprotected use of the head, in the form of heading the ball, is an integral part of the game. This exposes players not only to repetitive head impacts in the relatively lower and typically asymptomatic range (4–6), but also to situations which may cause accidental and injurious head impacts of greater magnitudes (7). However, research on whether head-impact exposure in soccer is harmful for the brain has been inconclusive, as several key questions remain unanswered (8–10).

In order to further the understanding of different types of head-impact exposures and their potential consequences, it is central to develop objective diagnostic and prognostic tools (11). When the brain is exposed to accelerative forces, shearing of the white matter tracts accompanied by axonal injury might ensue (12,13). This, again, can result in the release of structural neuronal proteins into the bloodstream. Consequently, several candidate blood-based biomarkers have been explored for use in traumatic brain injury (TBI) (14,15), and some have been approved for clinical purposes (16,17). However, previous studies have demonstrated the need for caution when using biomarkers in contact sports (18), as the confounding effects of e.g. exercise might limit their utility (19).

Two of the currently most promising blood biomarkers for use in contact sports are neurofilament light (NfL) and tau proteins, as recently demonstrated by Shahim et al. (20) using an ultrasensitive assay. Therefore, the main aim of this study was to explore if repetitive headers or accidental head impacts in soccer could cause short-term structural damage to the brain, detected as an increase in serum NfL or tau. In addition, as these two biomarkers have been shown also to reflect neurodegenerative processes (21,22), we wanted to assess potential long-term effects on the brain by exploring the influence of previous head-impact exposure on pre-season resting NfL and tau serum concentration.

Methods

Study design

This study is based on a prospective cohort study designed to detect if minor head impacts in soccer could cause injury to the nervous tissue (19) or lead to measurable impairment in brain function (23,24). During two consecutive seasons of the male Norwegian premier league, a total of 289 players in 2004 and 332 players in 2005 participated in the study, covering a total of 621 player seasons. To assess potential injury to the nervous tissue, blood samples were collected throughout the study period; data on changes in serum S100B have been

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published previously, where the effects of different conditions involving head impacts and/or exercise were assessed (19).

A subset of the blood samples were re-analyzed for the current study (Table 1). This was done in order to assess acute changes in serum NfL and tau concentrations as a result of three different short-term exposures: (1) high-intensity exercise with no head-impact exposure, (2) low-intensity exercise with high head-impact exposure in the form of repetitive headers, and (3) head-impact incidents during a regular league match. All three conditions included blood samples before (baseline), 1 h after (B1), and 12 h after (B12) exposure. Furthermore, to assess changes in serum NfL and tau in relation to long-term effects, baseline samples from a subset of players from groups considered to be at low and high risk for cumulative head-impact exposure were re-analyzed.

The original study was approved by the Regional Committee for Medical and Health Research Ethics South (2004/14054) and the Data Inspectorate, and written informed consent was obtained from all participants. The approval and informed consent included the possibility of storing blood samples for later analyses, and the data have since been anonymized. For the purposes of this study, the Regional Committee for Medical and Health Research Ethics South East approved the analyses of the stored blood samples (2017/1104).

Short-term exposure: (1) high-intensity exercise and (2) repetitive headers

Players from three teams were invited to participate in two separate exercise sessions during the 2006 season. Blood samples were drawn once before the first session (baseline), and then within 1 h (B1) and the morning after (B12) both sessions. No other exercise was allowed between collection of the B1 and B12 samples. The sessions lasted 90 min each, were led by the team's regular coaching staff, and were completed on separate days. Both sessions were designed to closely mimic regular match situations, but with different characteristics related to head-impact exposure. Specifically, the high-intensity exercise session included regular soccer play, but with no heading of the ball. The repetitive headers session included multiple match-related drills where repetitive headers are commonly observed (e.g. corner kicks), but otherwise with low exercise intensity throughout the session. Importantly, the heading drills were specifically designed to reflect typical head impact magnitudes. On average, each player headed the ball 18.9 times (range 7.0–33.0) during the session. This average was approximately twice as high as the average number of headers per player in a regular league match (8.5, range 0–26), based on a manual count of 18 players during the 2004 season (19).

Table 1. Overview of the number of samples analyzed from the different groups at each time point.

	Short-term exposure			Long-term exposure	
	High-intensity exercise	Repetitive headers	Head impacts	High-risk group*	Low-risk group*
Baseline samples, BL (n)	47	47	35	23	57
1h post-expoure, B1 (n)	37	38	35	*N/A*	*N/A*
*Concussions*** (n)*	*N/A*	*N/A*	*14*		
Non-concussions (n)	*N/A*	*N/A*	*21*		
12 h post-exposure, B12 (n)	33	30	19	*N/A*	*N/A*
*Concussions*** (n)*	*N/A*	*N/A*	*8*		
Non-concussions (n)	*N/A*	*N/A*	*11*		

*Risk groups related to long-term exposure were based on self-reported previous head-impact exposure, including average headers per match and concussion history.

**For the head-impact group, concussions were classified according to the presence of symptoms, based on the Vienna concussion definition (2001). Two of the 14 cases were reported as time-loss injuries.

Short-term exposure (3): head-impact incidents

Blood samples were drawn from the participants before the start of the 2004 and 2005 season (baseline). Head impacts during regular league matches were then recorded by the team doctors or dedicated research personnel attending every match. Specifically, a *head-impact incident* was defined as and included if it fulfilled all three of the following criteria: (1) the player appeared to be hit in the head, neck or face, (2) the match was interrupted by the referee, and (3) the player remained lying down on the pitch for more than 15 s (7,25). After a head-impact incident, our research personnel were instructed to draw a blood sample within 1 h (B1) and within 12 h after (i.e. the next morning, B12) the match.

All head-impact incidents were classified as concussions or non-concussions based on the symptoms reported by the players themselves. Concussion was characterized as any short-lived impairment of neurological function after head trauma, as defined by the Concussion in Sports Group in Vienna 2001 (26). The concussion data were further cross-referenced with the reports from the team doctors to the league's injury surveillance system, which at the time included all time-loss injuries (27).

Long-term effects: previous head-impact exposure

Players from the 2005 season (n = 280) were trichotomized into a low-risk, medium-risk and high-risk group. This was done using a questionnaire completed by the players (24), where they self-reported their previous head-impact exposure, including (1) the typical number of headers per match (never, 1–5 times, 6–10 times, 11–20 times, and >20 times per match) and (2) the number of previous concussions. Previous concussions included both soccer and non-soccer related incidents, and, for the purposes of the questionnaire, a concussion was defined as having experienced loss of consciousness and/or amnesia after a head injury. The *low-risk group* was defined as those with no previous concussions and 0–5 headers per match; the *high-risk group* was defined as those with one or more previous concussions and ≥11 headers per match. The remaining players were

defined as a medium-risk group. Only samples from the low-risk and high-risk groups were analyzed.

Blood samples and biochemical measurements

All blood samples were collected from an antecubital vein, drawn into a standard gel 7 mL tube (BD Vacutainer blood collection tube, Becton Dickinson, Franklin Lakes, NJ, USA), before allowed to clot for 30 min. They were then centrifuged (3000 *g* for 10 min) before the serum was divided between two 1.5 mL Eppendorf tubes (Eppendorf, Hamburg, Germany). The samples were then frozen within 2 h, after which one batch was used for the analyses in the original study (19) and the other batch was stored at −80°C for later analyses.

During the summer of 2018, the samples were thawed to 20°C and centrifuged (20 000 *g* for 10 min). Serum NfL and serum tau concentrations were then measured using ultrasensitive single molecule array technology (SIMOA-HD1, Quanterix Corporation, Lexington, MA, USA). Simoa™ NF-Light Advantage Kit and Simoa™ Tau Advantage Kit (Quanterix Corporation, Lexington, MA, USA) were used for NfL and tau protein quantification, respectively. Each measurement was done in duplicate, with a limit of detection of 38 fg/mL for serum NfL and 20 fg/mL for serum tau.

All analyses were performed blinded at the Institute of Neuroimmunology, Slovak Academy of Sciences, Bratislava, Slovakia, and in accordance with the manufacturer's recommendations.

Statistical analyses

Parametric tests were deemed appropriate for all groups at all time points. First, we screened for between-group and/or within-group differences using repeated measures ANOVA with Bonferroni correction for multiple group comparisons. If any significant differences were found, we further explored the dataset to locate their origin. For this, independent sample t-tests were used to evaluate between-group differences, and paired sample t-tests to evaluate within-group differences. When assessing the effects of short-term exposure (high-intensity exercise, repetitive headers and head-impact incidents), high-intensity exercise was considered reference. ΔB1 and ΔB12 values were calculated as the change in serum concentration from baseline to B1 and B12, respectively. For the effects of long-term exposure (number of previous concussions and headers), the low-risk group was considered as reference. All tests were two-sided using an α-level of 0.05 for statistical significance. Multiple comparisons were not corrected for when using t-tests, as these analyses were considered exploratory. SPSS version 24 (IBM SPSS Statistics, IBM Corporation, Chicago, IL) was used for all statistical analyses.

Results

Sample characteristics

In total, we analyzed 354 samples for serum concentrations of NfL and tau proteins. Mean ± SD concentration of NfL was 6.8 ± 2.6 pg/mL; mean tau concentration was 1.2 ± 0.7 pg/mL. The number of samples from the respective groups are shown in Table 1. Baseline characteristics of the groups are described in detail in the original study (19).

Short-term effects on serum NfL

Evaluating short-term effects on serum NfL levels, there were no between-group differences (ANOVA, $p = .69$), nor any within-group differences (ANOVA, $p = .64$) (Figure 1). For the head-impact group, comparing non-concussive and concussive head-impact incidents as sub-groups, ΔB12 values were higher for the non-concussive head impacts (0.4, 95% CI −0.4 to 1.2, vs. −0.6, 95% CI −1.3 to 0.00, pg/mL; $p = .03$); there were no between-group differences for B1, B12 or ΔB1 values.

Short-term effects on serum tau

Evaluating short-term effects on serum tau, there were both between-group differences (ANOVA, $p < .01$) and within-group differences (ANOVA, $p < .001$). When further exploring within-group differences, high-intensity exercise and repetitive headers displayed an increase in serum tau levels from baseline to B1 ($p < .01$ for both); furthermore, both groups showed a subsequent decrease from B1 to B12 ($p < .001$ for high-intensity exercise and $p < .01$ for repetitive headers; Figure 2). For the head-impact incidents, there were no within-group differences between any time points (Figure 2). Compared to high-intensity exercise (reference), there were no between-group differences at any time point when evaluating the effects of repetitive headers; head-impact incidents displayed lower baseline and B1 values ($p < .001$ for both), but there were no differences for B12, ΔB1 and ΔB12 values (Figure 2). When comparing non-concussive and concussive head-impact incidents as sub-groups, there were no between-group differences for B1, B12, ΔB1 or ΔB12 values.

Long-term effects on serum NfL and serum tau

When comparing the low-risk and high-risk groups, we did not detect any long-term effects on serum NfL or tau concentrations (Figure 3).

Discussion

In this study, we investigated the potential short-term structural effects on the brain from head-impact exposure in elite soccer, using serum NfL and tau as biomarkers. Compared to high-intensity exercise as a reference, we found no evidence of acute axonal damage, neither from repetitive headers nor from head-impact incidents.

Furthermore, we assessed the potential long-term effects of previous, cumulative head-impact exposure. Comparing two groups with low vs. high exposure to previous concussions and headers, we found no evidence to indicate that previous head impacts initiate neurodegenerative processes or long-term changes, as detected by serum NfL and tau.

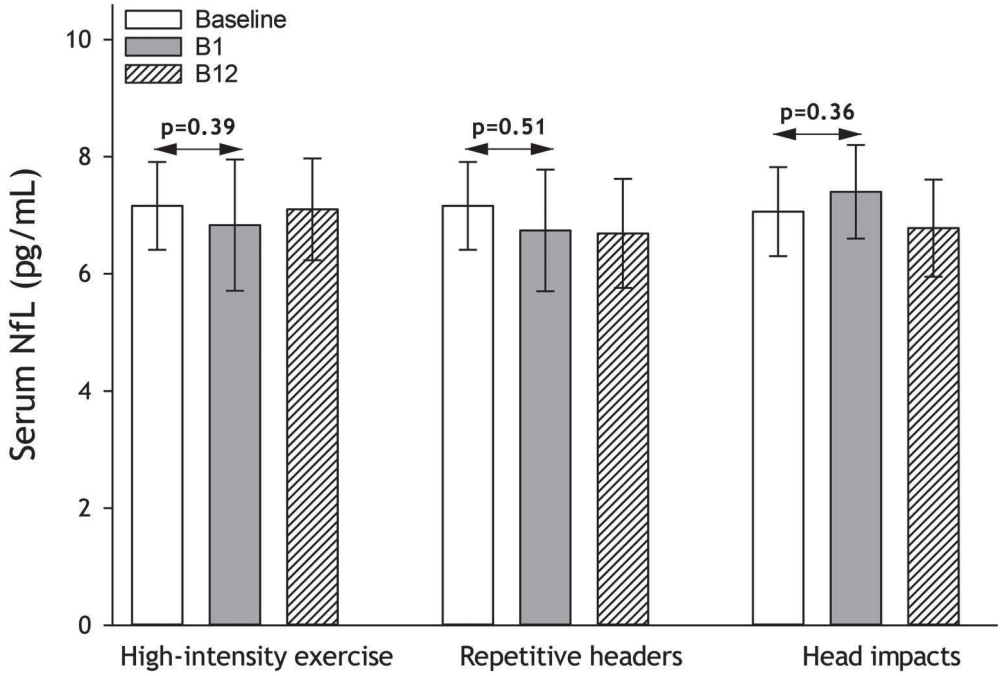

Figure 1. Serum NfL values at baseline, 1 hour (B1) and 12 hours (B12) after exposure to high-intensity exercise, repetitive headers and a head-impact incident in a match. Values are presented as means and error bars represent 95% confidence intervals.

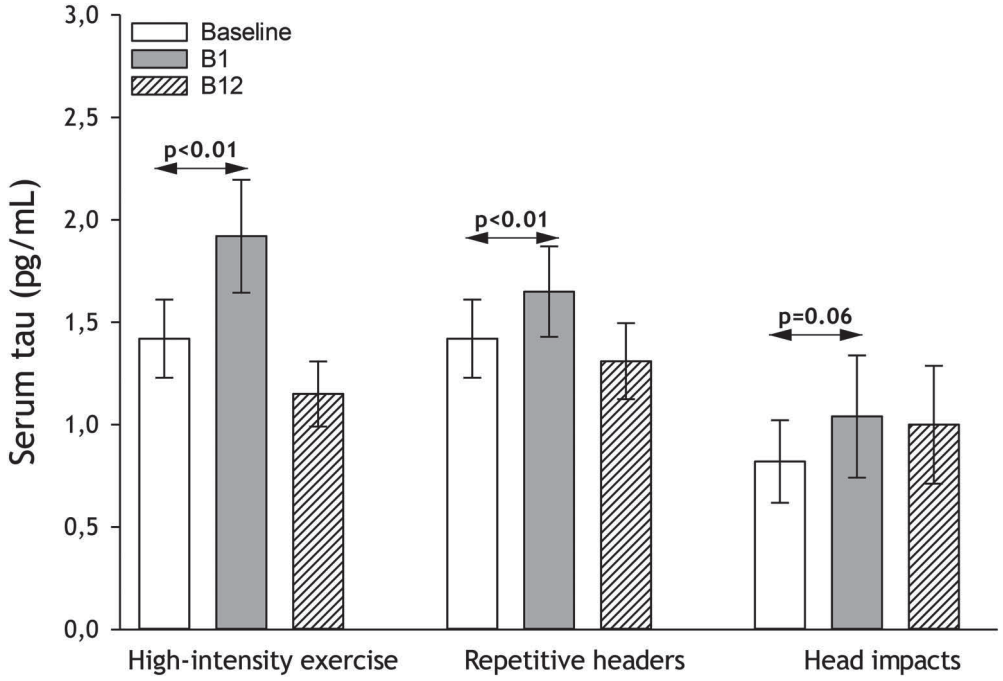

Figure 2. Serum tau values at baseline, 1 hour (B1) and 12 hours (B12) after exposure to high-intensity exercise, repetitive headers and a head-impact incident in a match. Values are presented as means and error bars represent 95% confidence intervals.

Short-term effects on serum NfL

In previous studies, NfL levels in blood have demonstrated diagnostic and prognostic utility in several scenarios related to head impacts in contact sports (20,28–30). As an example, Shahim et al. (28) demonstrated that NfL can serve as a sensitive and dynamic biomarker for axonal injury after concussive injuries in boxing and ice hockey. Furthermore, Rubin et al. (30) found that the frequency and magnitude of subconcussive head impacts in collegiate American football players were associated with changes in plasma NfL levels; this led the authors to speculate that NfL could be used to distinguish players sustaining more frequent and greater magnitude impacts from those with fewer and less severe impacts. Our results did not align with any of the findings described above. In fact, NfL levels seemed unaffected by all three conditions examined.

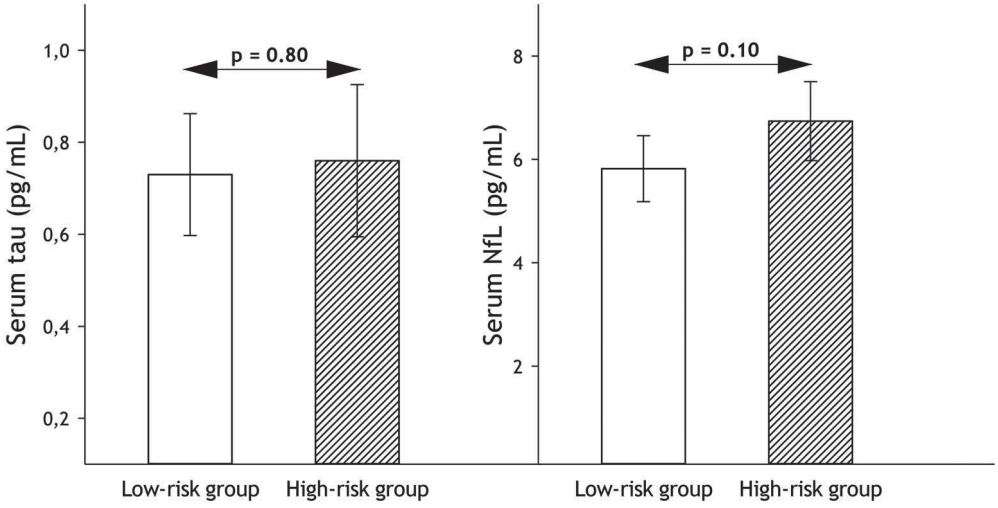

Figure 3. The long-term effects of previous head-impact exposure on serum tau and serum NfL in elite soccer players at pre-season. The two groups are categorized based on their previously low and high levels of exposure to concussions and soccer headers. Values are presented as means and error bars represent 95% confidence intervals.

We recognize several potential explanations for the apparent discrepancy. First, inherent differences in head-impact exposures between specific sports could mean that some impact types are more benign than others. Even though more than a third of the head-impact incidents in our study were classified as concussions, they were mostly in the milder end of the severity spectrum (19). Indeed, according to our injury-surveillance data, only two of the reported concussions were registered as time-loss injuries (Table 1). Second, variations in study designs, such as the timing of blood sampling in relation to the exposures, will inevitably obscure what happens at other time points. Notably, Shahim et al. observed elevated NfL levels at 144 h after concussion (28), while we had a follow-up of no more than 12 h. Therefore, our findings should be interpreted with caution. Nevertheless, even if future evidence should suggest that heading in soccer is harmful for the brain, our results document the limited utility of NfL as a biomarker for mild head impacts.

Short-term effects on serum tau

For serum tau, we observed dynamic short-term changes. However, these were only present for two of the conditions: repetitive headers and high-intensity exercise (Figure 2). Importantly, tau levels remained unaffected by the head-impact incidents during regular league matches, also for impacts considered to be in the concussive range. As the session with high-intensity exercise yielded the most pronounced finding in our study, this suggests that the increase observed for the session with repetitive headers may simply be an exercise effect. Even though this session was designed to contain repetitive headers with otherwise low-intensity exercise, a certain amount of movement during the drills was inevitable.

If exercise causes an increase in tau levels, this should also have been the case for the head-impact incidents, as the players had already warmed up and played parts of a match (the incidents occurred approx. 30 min into the match on average). Indeed, we did observe a trend toward an increase 1 h after exposure also in this group (Figure 2). One potential cause for a non-significant difference is that blood samples from this group were drawn later than for the reference, 77 min vs. 26 min (19). This time window could have allowed levels to fall.

Interestingly, we also observed some unexpected between-group differences, with head-impact incidents yielding lower absolute values compared to the reference at both baseline and B1. We can only speculate as to why this was the case. One possible explanation is that baseline tau levels fluctuate throughout the season. Specifically, the timing of the exercise sessions differed between the three teams, which might represent a critical source of heterogeneity; one team completed them during the middle of the pre-season, one team at the end of the pre-season, and one team right after the end of the season (all players had baseline sampling performed in the morning before the first of the two sessions). In contrast, the baseline samples for the head-impact incidents were all collected in the pre-season.

In summary, we found no evidence suggestive of structural neuronal damage, but revealed a substantial confounding effect from exercise. Indeed, this is in line with recent work by Kawata et al. (31). Examining collegiate American football players before and after a series of practices, they found that plasma tau levels increased after all the sessions; however, these changes were independent of subconcussive head impacts as measured by mouth-guard accelerometers.

Our study highlights several important limitations of measuring total tau as a biomarker for head injuries in the lower severity spectrum. Importantly, an appropriate control group should be included in similar studies in contact sports, as physical activity needs to be controlled for. This is also supported by findings of Gill et al. (32), describing elevated tau levels in response to exercise. What actually accounts for this remains unknown, but factors such as increased neuronal activity (33), clearance via the glymphatic system (34), and changes in the permeability of the blood-brain barrier (35,36) are thought to play a role. Furthermore, other sources of tau protein

release have been described, such as from the enteric nervous system (37). The ultrasensitive assay we used in this study does not distinguish between specific tau isoforms and their origins.

Long-term effects of previous head-impact exposure

NfL levels in blood have been linked to neurodegeneration, irrespective of the underlying cause (21), and elevated levels in e.g. Alzheimer's disease can appear years to decades before onset of neurological symptoms (22). Studies on military personnel have also demonstrated long-term elevations of circulating tau associated with multiple TBIs (38). Di Battista et al. (39) have demonstrated similar findings associated with participation in contact sports. It is important to point out, however, that other studies have failed to demonstrate any effects on NfL and tau levels from previous head-impact exposure and contact sport participation (30,31).

Therefore, as a secondary aim in our study, we wanted to explore the long-term effects of previous concussions and headers, by comparing two groups characterized by differences in cumulative exposure (low-risk vs. low-risk). We wanted to assess whether having a positive concussion history, in combination with a playing style with frequent heading behavior in matches, would lead to sustained elevations in serum levels of NfL and/or tau proteins. We did not observe such changes. Despite a trend toward higher NfL levels in the high-risk group (Figure 3), the effect size was negligible and we did not demonstrate any between-group differences.

We recognize at least three possible explanations for these findings. First, the previous head-impact exposure in the high-risk group was not deleterious to the brain, implying that reparative processes have been able to compensate and thereby 'keep up with' the forces exerted upon the nervous tissue over time. Second, and in contrast to the first, the biomarkers were not sufficiently sensitive to detect any deleterious effects of the previous exposure. Third, even though self-reported measures of head-impact exposure in contact sports have been shown to be useful (40), there is inevitably a high risk of bias (41). Also, in the questionnaire concussion was defined using the diagnostic criteria commonly used by medical personnel in Norway at the time (i.e. loss of consciousness/amnesia was required). Thereby using a stricter definition than the one currently used in sports (11), the low-risk group might also have sustained concussions that had not been recognized and therefore not reported. Consequently, and despite our best efforts to trichotomize the groups appropriately, there could be a considerable overlap between the high- and low-risk groups, which might conceal differences. Considering such limitations, these data should be interpreted with caution.

Methodological considerations

Relevant to all the investigations we conducted in this study, it should be noted that any one clinical biomarker reflects only a small piece of a complex pathophysiological puzzle. Notably, in the absence of other investigations such as neuroimaging, the limited sensitivity and specificity of serum NfL and tau to pick up neuronal damage might yield false negative findings. Therefore, it remains unknown to what extent the results are best explained by the exposure being benign or the biomarkers being inadequate. We used a highly sensitive and widely recognized method for both serum NfL and serum tau measurements. However, Rubenstein et al. (42) have already demonstrated how hyperphosporylated tau levels in blood outperforms total tau in both diagnosis and prognosis of TBI. In general, future studies should strive to utilize and advance the most sensitive and specific assays available.

Furthermore, the quantification of head impacts warrants careful consideration when exploring the effects of head-impact exposure in contact sports. In our study, the short-term exposures (i.e. repetitive headers and head-impact incidents) were only confirmed visually; therefore, we could not report on the objective impact forces involved (using e.g. accelerometers). This limitation also applies to the long-term exposure, which was quantified using self-report.

Regarding the absolute serum NfL and tau values, we hesitate in comparing our results directly to those of others. The main reason is that we do not know the impact of methodological differences between studies, such as the on-field blood sample collection procedures and subsequent management (e.g. duration of centrifugation). Concerning long-term storage of frozen blood samples, there are three main reasons why we deem our results to be valid: (1) previous research suggests that NfL and tau integrity is stable in relation to both long-term storage and multiple freeze-thaw cycles (43); (2) the serum concentrations were within the expected range when comparing with the data supplied by the producer of the kits; and (3) any degradation would affect the samples evenly between and within groups, thereby minimizing its impact on our results.

Lastly, as we did not correct for multiple testing when exploring specific within- and between-group differences, the results and conclusions from this part should be considered exploratory. We encourage others to further examine the time course of changes in the biomarkers and their relationship with head-impact characteristics.

Conclusion

This study demonstrates that serum NfL and tau were unaffected by head impacts in soccer. Furthermore, it shows how circulating tau levels rise immediately after exercise, with a rapid return to resting values, whereas NfL levels remain unchanged. Our findings highlight important characteristics and limitations when using NfL or tau as biomarkers in sports.

Acknowledgments

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Disclosure statement

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Medical Assessment and Research Center. The Oslo Sports Trauma Research Center has been established at the Norwegian School of Sport Sciences through generous grants from the Royal Norwegian Ministry of Culture, the South-Eastern Norway Regional Health Authority the International Olympic Committee, the Norwegian Olympic Committee and Confederation of Sport, and Norsk Tipping AS. No other competing financial interests exist.

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Appendix I

Ethics approval letters and permissions

Roald Bahr
Seksjon for idrettsmedisin

OSLO 20. juni 2018

Søknad 59 -190618 – Forekomst av nikking og hodeskader under Norway Cup 2018

Vi viser til søknad, prosjektbeskrivelse, informasjonsskriv og innsendt søknad til NSD.

I henhold til retningslinjer for behandling av søknad til etisk komite for idrettsvitenskapelig forskning på mennesker, ble det i komiteens møte av 19. juni 2018 konkludert med følgende:

Vedtak

På bakgrunn av forelagte dokumentasjon finner komiteen at prosjektet er forsvarlig.

Komiteen gjør oppmerksom på at vedtaket er avgrenset i tråd med fremlagte dokumentasjon. Dersom det gjøres vesentlige endringer i prosjektet som kan ha betydning for deltakernes helse og sikkerhet, skal dette legges fram for komiteen før eventuelle endringer kan iverksettes.

Med vennlig hilsen

På vegne av NIHs etiske komite
Professor Sigmund Loland
Leder, Etisk komite, Norges idrettshøgskole

Roald Bahr
Senter for idrettsskadeforskning

OSLO 28. august 2017

Søknad 16-220817 – Testing av måleinstrument av headinger og hodestøt i fotball

Vi viser til søknad, prosjektbeskrivelse, informasjonsskriv og innsendt søknad til NSD.

I henhold til retningslinjer for behandling av søknad til etisk komite for idrettsvitenskapelig forskning på mennesker, ble det i komiteens møte av 22. august 2017 konkludert med følgende:

Vedtak

På bakgrunn av forelagte dokumentasjon finner komiteen at prosjektet er forsvarlig og at det kan gjennomføres innenfor rammene av anerkjente etiske forskningsetiske normer nedfelt i NIHs retningslinjer. Til vedtaket har komiteen lagt følgende forutsetning til grunn:

- *At NSD godkjenner prosjektet og at eventuelle vilkår fra NSD følges*
- *At det etableres nødvendige avtaler med samarbeidende forskningsinstitusjoner.*

Ta kontakt med Avdeling for forskning og bibliotek for bistand med avtaler.

Komiteen vil bemerke at det er seksjonsleder som er forskningsansvarlig og ikke stipendiaten som oppgitt i søknaden. Komiteen gjør videre oppmerksom på at vedtaket er avgrenset i tråd med fremlagte dokumentasjon. Dersom det gjøres vesentlige endringer i prosjektet som kan ha betydning for deltakernes helse og sikkerhet, skal dette legges fram for komiteen før eventuelle endringer kan iverksettes.

Med vennlig hilsen
Professor Sigmund Loland
Leder, Etisk komite, Norges idrettshøgskole

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Stian Bahr Sandmo
Postboks 4014 Ullevål Stadion
0806 OSLO

Vår dato: 08.08.2017 Vår ref: 54952 / 3 / ASF Deres dato: Deres ref:

Tilbakemelding på melding om behandling av personopplysninger

Vi viser til melding om behandling av personopplysninger, mottatt 29.06.2017.
Meldingen gjelder prosjektet:

54952	*Validering av måleinstrument for måling av akselerasjonskrefter på fotballbanen*
Behandlingsansvarlig	*Norges idrettshøgskole, ved institusjonens øverste leder*
Daglig ansvarlig	*Stian Bahr Sandmo*

Personvernombudet har vurdert prosjektet og finner at behandlingen av personopplysninger er meldepliktig i henhold til personopplysningsloven § 31. Behandlingen tilfredsstiller kravene i personopplysningsloven.

Personvernombudets vurdering forutsetter at prosjektet gjennomføres i tråd med opplysningene gitt i meldeskjemaet, korrespondanse med ombudet, ombudets kommentarer samt personopplysningsloven og helseregisterloven med forskrifter. Behandlingen av personopplysninger kan settes i gang.

Det gjøres oppmerksom på at det skal gis ny melding dersom behandlingen endres i forhold til de opplysninger som ligger til grunn for personvernombudets vurdering. Endringsmeldinger gis via et eget skjema. Det skal også gis melding etter tre år dersom prosjektet fortsatt pågår. Meldinger skal skje skriftlig til ombudet

Personvernombudet har lagt ut opplysninger om prosjektet i en offentlig database.

Personvernombudet vil ved prosjektets avslutning, 15.08.2018, rette en henvendelse angående status for behandlingen av personopplysninger.

Dersom noe er uklart ta gjerne kontakt over telefon.

Vennlig hilsen

Dokumentet er elektronisk produsert og godkjent ved NSDs rutiner for elektronisk godkjenning.

Marianne Høgetveit Myhren

Amalie Statland Fantoft

Kontaktperson: Amalie Statland Fantoft tlf: 55 58 36 41 / amalie.fantoft@nsd.no
Vedlegg: Prosjektvurdering

Personvernombudet for forskning

Prosjektvurdering - Kommentar

Prosjektnr: 54952

PROSJEKT
Prosjektet skal teste hvorvidt måleinstrumenter kalt "akselerometere" kan benyttes på fotballbanen – bl.a. for å måle omfanget av gravitasjonskreftene som er i spill ved headinger, løping og hopping. Personvernombudet legger til grunn at forskerne innehar kompetansen som er nødvendig for å sikre forsvarlig gjennomføring av treningsopplegget og testene.

Prosjektet er godkjent av etisk komité ved Norges idrettshøgskole.

INFORMASJON OG SAMTYKKE
Utvalget informeres skriftlig og muntlig om prosjektet og samtykker til deltakelse. Informasjonsskrivet er godt utformet.

Merk at når barn skal delta aktivt, er deltagelsen alltid frivillig for barnet, selv om de foresatte samtykker. Barnet bør få alderstilpasset informasjon om prosjektet, og det må sørges for at de forstår at deltakelse er frivillig og at de når som helst kan trekke seg dersom de ønsker det.

INFORMASJONSSIKKERHET
Personvernombudet legger til grunn at forsker etterfølger Norges idrettshøgskole sine rutiner for datasikkerhet.

PROSJEKTSLUTT
Forventet prosjektslutt er 15.08.2018. Ifølge prosjektmeldingen skal innsamlede opplysninger da anonymiseres. Anonymisering innebærer å bearbeide datamaterialet slik at ingen enkeltpersoner kan gjenkjennes. Det gjøres ved å:
- slette direkte personopplysninger (som navn/koblingsnøkkel)
- slette/omskrive indirekte personopplysninger (identifiserende sammenstilling av bakgrunnsopplysninger som f.eks. bosted/arbeidssted, alder og kjønn)
- slette digitale videoopptak

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Hege Holde Andersson	22845511	02.02.2018	2017/2136 REK sør-øst B
			Deres dato:	Deres referanse:
			20.12.2017	

Vår referanse må oppgis ved alle henvendelser

Roald Bahr
Senter for idrettsskadeforskning

2017/2136 Nikking i fotball – Hjerneforandringer og kliniske konsekvenser som følge av gjentatte, lavgradige hodestøt (REPIMPACT)

Forskningsansvarlig: Senter for idrettsskadeforskning
Prosjektleder: Roald Bahr

Vi viser til tilbakemelding på ovennevnte forskningsprosjekt. Tilbakemeldingen ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK sør-øst) i møtet 17.01.2018. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10.

Prosjektleders prosjektbeskrivelse
«Prosjektet tar sikte på kartlegge potensielle skadevirkninger på hjernen som konsekvens av gjentatte lavgradige hodestøt – gjennom nikking av ballen – i fotball. Dette er et hittil uavklart spørsmål med behov for rask avklaring, i og med at over 250 millioner spiller aktivt på verdensbasis, og dermed potensielt blir utsatt for risiko. Studien er en prospektiv kohortstudie, hvor deltakerne følges over én sesong, og undersøkes til sammen tre ganger under forløpet: 1) før sesongstart 2018, 2) rundt sesongslutt 2018, og 3) før sesongoppstart 2019. Protokollen inneholder en serie med tester hver av de tre undersøkelsesdagene, som bl.a. MR, EEG, nevropsykologisk testing og blod-/spyttprøver. Vi vil rekruttere til sammen 35 fotballspillere, samt 35 idrettsutøvere som kontrollgruppe fra ikke-kontaktidretter (svømming, langrenn, etc.)»

Stein Andersson ble erklært inhabil og forlot møtet under komiteens behandling av søknaden.

Saksgang
Komiteen behandlet prosjektet i møtet 29.11.2017. I brev datert 19.12.2017 utsatte komiteen vedtak i saken. Komiteen skrev:
«Den foreliggende informasjonen er ikke tilstrekkelig til at komiteen kan fatte en avgjørelse.

Det søkes om å inkludere å rekruttere til sammen 35 fotballspillere og 35 kontroller fra ikke-kontaktidretter i alderen 14-15 år. I tillegg vil et tilsvarende antall deltakere bli inkludert ved ytterligere to datainnsamlingssteder, hhv. i Tyskland og Belgia. Studien er en prospektiv kohortstudie, hvor deltakerne følges over én sesong, og undersøkes til sammen tre ganger under forløpet: 1) før sesongstart 2018, 2) rundt sesongslutt 2018, og 3) før sesongoppstart 2019.

MR-undersøkelse
Deltagelse innebærer en rekke undersøkelser, herunder MR. Det opplyses i søknaden om at skulle det avdekkes uforutsette funn vil dette bli fulgt opp av prosjektleder, med henvisning til spesialist der dette måtte være aktuelt. Komiteen mener dette ikke er tilstrekkelig. Komiteen ber om en tilbakemelding på hvem som

skal gjennomføre MR-undersøkelsene, hvem som skal tolke data og hvem som håndterer eventuelle funn man gjør. Komiteen mener prosjektet bør forankres i et radiologisk miljø, slik at denne delen av studien kan gjennomføres på en forsvarlig måte.

Beredskap
Når man gjør denne type undersøkelser er det viktig at det er en god beredskap i prosjektet, som kan håndtere eventuelle uforutsette funn. Dette vil også gjelde i forkant av prosjektet. Det er viktig at deltagere og foresatte informeres på en måte som ikke skaper uro og bekymring. Komiteen ber derfor prosjektleder redegjøre nærmere for hvilken beredskap man har i prosjektet.

Biobank
Det søkes om å opprette biobank. Det tas blod- og spyttprøver tas for å måle forskjellige stoffer som kan avdekke endringer i hjernen. Komiteen mener dette er upresist, og ber om en nærmere bekrivelse av hvilke analyser som skal gjøres, og nytten av disse.

Samarbeid med utlandet
Studien er et samarbeid med Tyskland og Belgia, men det er uklart hvordan dette samarbeidet skal gjøres. Det opplyses også om at data skal overføres til USA og Israel. Komitéen ber om en nærmere redegjørelse for hvordan det internasjonale samarbeidet er organisert og hvordan data skal utveksles.

Informasjonsskriv og samtykkeerklæring
Det innsendte informasjonsskrivet må revideres. Det står i skrivet at Ingen av undersøkelsene vil være smertefulle eller ubehagelige! Komiteen ber om at denne setningen fjernes, særlig med tanke på at det tidligere i skrivet står at MR kan oppleves som ubehagelig. Det må tydelig fremkomme i informasjonsskrivet at MR og andre undersøkelser i prosjektet kan oppleves som ubehagelig og til dels smertefullt.

Det står i informasjonsskrivet at man når som helst kan trekke seg fra studien. Når man trekker seg fra en studie kan det kreves at innsamlede opplysninger slettes. Dette må fremkomme i informasjonsskrivet. I denne studien skal deltagerne filmes. Komiteen ber om en tilbakemelding på hvordan man vil håndtere filmopptakene, dersom noen av deltagerne trekker seg fra studien.

Komiteens beslutning
Vedtak i saken utsettes. Komiteen tar stilling til prosjektet ved mottatt svar.»

Prosjektleders tilbakemelding
Komiteen mottok prosjektleders tilbakemelding 20.12.2017. Prosjektleders tilbakemelding gjengis i sin helhet:

«1) MR-undersøkelse
Prosjektet har sterk forankring i et allerede veletablert nevroradiologisk miljø ved Ludwig-Maximilians universitetssykehus (Munchen, Tyskland), noe som dessverre ikke fremkom i den opprinnelige søknaden. Selve MR-undersøkelsene vil gjennomføres av opplært personell ved Intervensjonssenteret ved Oslo universitetssykehus, gjennom vårt samarbeid med professor Tor Endestad ved Psykologisk institutt, UiO og professor Atle Bjørnerud, UiO (Rikshospitalet). Samtlige MR-bilder vil gjennomgås fortløpende av radiolog i forskningsgruppen, og vi vil følge opp uforutsette funn umiddelbart. Deltaker m/forelder/foresatt vil i så fall bli invitert til en samtale med professor Roald Bahr, og som vil konferere med og ved behov henvise videre til overlege dr. med. Ingunn Rise Kirkeby, spesialist i nevrologi og nevrokirurgi, ved nevrokirurgisk avdeling, Oslo universitetsykehus (Rikshospitalet).

2) Beredskap
Se punktet ovenfor for MR-delen av prosjektet. Muntlig informasjon om prosjektet vil bli gitt i forkant av prosjektoppstart, i form av foreldre- og spillermøter. Deretter vil alle som melder seg som interesserte få en personlig, muntlig gjennomgang av av protokollen og samtlige elementer av denne. I denne samtalen vil prosedyren ved uforutsette funn bli gjennomgått spesielt. Dette gjøres som en personlig samtale sammen med foreldre/foresatte, før innhenting av samtykke. Ved andre uforutsette funn enn de som allerede er beskrevet, som f.eks. ved nevrologisk undersøkelse, vil tilsvarende tilnærming som skissert ovenfor benyttes.

3) Biobank
Det henvises til forskningsprotokollen fra opprinnelig søknad, som også vedlegges her, hvor det fremkommer at blod- og spyttprøver vil analyseres mhp. følgende biokjemiske markører: MicroRNA (plasma og spytt), tau proteiner (plasma), beta amyloid (plasma), og interleukiner (plasma). Prøvene vil bli tatt av trent laboratoriepersonell i Norge, og deretter fryses ned og videresendes til nevroimmunologisk institutt i Bratislava, Slovakia, for analysering. Begrunnelsen for å analysere prøvene mhp. de ovenfor nevnte biomarkørene, er basert på nyere forskning som har vist at man kan få nyttig informasjon om hjernens status gjennom disse, både mtp. truende/etablert vevsskade og inflammasjon i etterkant av traumatiske hodeskader. Dysregulerte microRNAer har også foreslått å ha potensiale til å fungere som en "dynamisk markør" over tid, muligens i større grad enn andre markører. Da gjentatte, lavgradige hodestøt – som ved nikking i fotball – ikke defineres som traumatisk hodeskade per se, men potensielt også gir økt risiko for skadelige senvirkninger, ønsker vi å undersøke hvorvidt disse aktuelle markørene for vevsskade på hjernen endres som følge av fotballspill.

4) Samarbeid med utlandet
Studien er en internasjonal multisenterstudie. Data vil også bli samlet inn i Tyskland og Belgia, ihht. samme forskningsprotokoll og med tilsvarende antall deltakere som her i Norge. Andre medlemmer av forskningsgruppen har for øvrig tilknytning til hhv. Tel Aviv University (Israel, nevroradiologi), University Medical Center Utrecht (Nederland, nevroradiologi), Bratislava Institute of Neuroimmunology (Slovakia, nevroimmunologi) og Harvard Medical School (USA, nevroradiologi), for å oppnå den interdispiplinære kompetansen som er ansett nødvendig for et prosjekt av en slik art. Fordelingen av arbeidsopgaver mellom gruppens medlemmer er for øvrig beskrevet i detalj i prosjektprotokollen. Det er opprettet en sikker, passordbeskyttet server for opplasting og nedlastning av avidentifiserte data, med tilgang kun for forskergruppens medlemmer, for sikker datalagring ihht. aktuelle direktiver, slik det fremkommer i den opprinnelige søknaden.

5) Informasjonsskriv og samtykkeerklæring
Se revidert og vedlagt versjon av info/samtykke. Den aktuelle setningen er fjernet og i stedet er følgende tatt inn under "Fordeler og ulemper": "MR-undersøkelsen kan for noen oppleves som ubehagelig, da man må ligge stille over lengre tid, og noen også har angst for små, lukkede rom. Vi avbryter undersøkelsen umiddelbart, hvis dette skulle bli et problem. Blodprøven tas med et stikk i armen, men vi vil legge en lokalbedøvende krem på huden i forkant for at det ikke skal gjøre vondt. Blodprøven tas av trent laboratoriepersonell." Innsamlede opplysninger vil slettes umiddelbart hvis en deltaker trekker seg. Når det gjelder videoopptak av treninger/kamper vil disse bli analysert fortløpende mhp. telling av headinger/hodestøt, like etter innsamling, for deretter å slettes. Dersom en deltaker skulle trekke seg, vil mao. videoopptakene være slettet.»

Komiteens vurdering
Komiteen mener prosjektleder har svart tilfredsstillende på de merknader komiteen hadde. Komiteen har imidlertid en merknad til det reviderte informasjonsskrivet. Det oppgis at det er mulig å trekke seg fra studien, når som helst, og uten begrunnelse, men står ikke eksplisitt at man kan kreve data slettet. Komiteen ber om at dette innarbeides i informasjonsskrivet.

Ut fra dette setter komiteen følgende vilkår for prosjektet:
- Informasjonsskrivet revideres i tråd med det ovennevnte og sendes komiteen til orientering.

Vedtak
Komiteen godkjenner prosjektet i henhold til helseforskningsloven § 9 og § 33 under forutsetning av at ovennevnte vilkår oppfylles.

I tillegg til ovennevnte vilkår, er godkjenningen gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden.

Komiteen godkjenner også oppførelsen av en spesifikk forskningsbiobank som beskrevet i søknaden.

Biobankregisteret blir underrettet ved kopi av dette brev.

Hvis forskningsbiobanken opphører, nedlegges eller overtas av andre, skal det søkes REK om tillatelse, jf. helseforskningsloven § 30.

Tillatelsen gjelder til 31.03.2027. Av dokumentasjonshensyn skal opplysningene likevel bevares inntil 31.03.2032. Opplysningene skal lagres avidentifisert, dvs. atskilt i en nøkkel- og en opplysningsfil. Opplysningene skal deretter slettes eller anonymiseres, senest innen et halvt år fra denne dato.

Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder "*Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse- og omsorgssektoren"*

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningslovens § 28 flg. Klagen sendes til REK sør-øst B. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK sør-øst B, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Komiteens avgjørelse var enstemmig.

Med vennlig hilsen

Ragnhild Emblem
professor, dr. med.
leder REK sør-øst B

Hege Holde Andersson
Komitésekretær

Kopi til:
- *Norges idrettshøgskole ved øverste administrative ledelse*
- *Biobankregisteret*

LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

ETHIKKOMMISSION BEI DER LMU MÜNCHEN

Ethikkommission · Pettenkoferstr. 8 · 80336 München

Prof. Dr. Inga Koerte
Klinikum der Universität München
Klinik f. Kinder- und Jugendpsychiatrie,
Psychosomatik und Psychotherapie
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80337 München

Vorsitzender:
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www.ethikkommission.med.uni-muenchen.de

Anschrift:
Pettenkoferstr. 8a
D-80336 München

03.07.2017 Hb /sc

Projekt Nr: **17-369** (bitte bei Schriftwechsel angeben)

Beratung nach Fakultätsrecht
Votum

Studientitel: RepImpact
Antragsteller: Prof. Dr. Inga Koerte, Klinikum der Universität München , Klinik f. Kinder- und Jugendpsychiatrie, Psychosomatik und Psychotherapie, Nußbaumstr. 5a, 80337 München

Dear Professor Koerte,

Thank you very much for your letter with responses to all our questions and requests, for outstanding or revised documents.

The Ethics Committee approves that there are no ethical - legal concerns for your study.

For reasons of precaution, I would like to draw your attention on the fact that – even if the Ethics Committee gives a positive approval regarding the project - the medical and legal responsibility for the project execution remains in yours and your study team's hands.

The Ethics Committee has to be informed

- in case of modifications and amendments of the protocol
- about the results after the study has been finished.

Wishing you a lot of success with the Study,

With best regards

Prof. Dr. W. Eisenmenger
Chair of the Ethics Committee

Mitglieder der Kommission:
Prof. Dr. W. Eisenmenger (Vorsitzender), Prof. Dr. E. Held (Vorsitzender), Prof. Dr. H. Angstwurm, Prof Dr. C. Bausewein, PD Dr. Th. Beinert, Prof. Dr. C. Belka, Prof. Dr. H. Dörfler, Prof. Dr. B. Emmerich, Prof. Dr. St. Endres, Prof. Dr. H. U. Gallwas, Prof. Dr. O. Genzel-Boroviczény, Prof. Dr. A. Gerbes, Prof. Dr. K. Hahn, Prof. Dr. N. Harbeck, Dr. B. Henrikus, Prof. Dr. Ch. Heumann, Prof. Dr. V. Klauss, Prof. Dr. G. Marckmann, Dr. V. Mönch, Prof. Dr. A. Nassehi, Prof. Dr. D. Nowak, Prof. Dr. R. Penning, Prof. Dr. J. Peters, Prof. Dr. K. Pfeifer, Dr. I. Saake, Prof. Dr. M. Schmauss, Prof. Dr. U. Schroth, Prof. Dr. A. Spickhoff, Prof. Dr. O. Steinlein, PD Dr. U. Wandl, Prof. Dr. C. Wendtner, Dr. A. Yassouridis, Dr. Ch. Zach

LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

ETHIKKOMMISSION BEI DER LMU MÜNCHEN

Ethikkommission · Pettenkoferstr. 8 · 80336 München

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Anschrift:
Pettenkoferstr. 8a
D-80336 München

11.07.2017 Hb sc

Projekt Nr: **17-369** (bitte bei Schriftwechsel angeben)

Nachträgliche Änderungen;

Studientitel: RepImpact
Antragsteller: Prof. Dr. Inga Koerte, Klinikum der Universität München, Klinik f. Kinder- und Jugendpsychiatrie, Psychosomatik und Psychotherapie, Nußbaumstr. 5a, 80337 München

Dear Professor Koerte

Thank you very much for your letter of July 5th, 2017, with an amendment to the above mentioned clinical trial. We read through the following documents:

- Screening questionnaire.

The Ethics Committee approves that, against the background of your letter, there are no ethical - legal concerns for this amended protocol.

Wishing you a lot of success with the ongoing study.

With best regards

Prof. Dr. W. Eisenmenger
Chair of the Ethics Committee

Mitglieder der Kommission:
Prof. Dr. W. Eisenmenger (Vorsitzender), Prof. Dr. E. Held (Vorsitzender), Prof. Dr. H. Angstwurm, Prof Dr. C. Bausewein, PD Dr. Th. Beinert, Prof. Dr. C. Belka, Prof. Dr. H. Dörfler, Prof. Dr. B. Emmerich, Prof. Dr. St. Endres, Prof. Dr. H. U. Gallwas, Prof. Dr. O. Genzel-Boroviczény, Prof. Dr. A. Gerbes, Prof. Dr. K. Hahn, Prof. Dr. N. Harbeck, Dr. B. Henrikus, Prof. Dr. Ch. Heumann, Prof. Dr. V. Klauss, Prof. Dr. G. Marckmann, Dr. V. Mönch, Prof. Dr. A. Nassehi, Prof. Dr. D. Nowak, Prof. Dr. R. Penning, Prof. Dr. J. Peters, Prof. Dr. K. Pfeifer, Dr. I. Saake, Prof. Dr. M. Schmauss, Prof. Dr. U. Schroth, Prof. Dr. A. Spickhoff, Prof. Dr. O. Steinlein, PD Dr. U. Wandl, Prof. Dr. C. Wendtner, Dr. A. Yassouridis, Dr. Ch. Zach

LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

ETHIKKOMMISSION BEI DER MED. FAKULTÄT DER LMU MÜNCHEN

Ethikkommission · Pettenkoferstr. 8 · 80336 München

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Anschrift:
Pettenkoferstr. 8a
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24.11.2017 Hb /om

Projekt Nr: **17-369** (bitte bei Schriftwechsel angeben)

Nachträgliche Änderungen;

Studientitel: RepImpact
Antragsteller: Prof. Dr. Inga Koerte, Klinikum der Universität München, Klinik f. Kinder- und Jugendpsychiatrie, Psychosomatik und Psychotherapie, Nußbaumstr. 5a, 80337 München

Sehr geehrte Frau Prof. Koerte,

die Ethikkommission hat Ihren Antrag vom 20.11.2017 auf der Basis der eingereichten Unterlagen geprüft.

Es bestehen keine Bedenken gegen die geplanten Änderungen.

Mit freundlichen Grüßen

i.V. E. Lud
Prof. Dr. W. Eisenmenger
Vorsitzender der Ethikkommission

Mitglieder der Kommission:
Prof. Dr. W. Eisenmenger (Vorsitzender), Prof. Dr. E. Held (Vorsitzender), Prof. Dr. H. Angstwurm, Prof Dr. C. Bausewein, PD Dr. Th. Beinert, Prof. Dr. C. Belka, Prof. Dr. B. Emmerich, Prof. Dr. St. Endres, Prof. Dr. H. U. Gallwas, Prof. Dr. O. Genzel- Boroviczény, Prof. Dr. A. Gerbes, Prof. Dr. K. Hahn, Prof. Dr. N. Harbeck, Dr. B. Henrikus, Prof. Dr. Ch. Heumann, Prof. Dr. V. Klauss, Prof. Dr. G. Marckmann, Dr. V. Mönch, Prof. Dr. A. Nassehi, Prof. Dr. D. Nowak, Prof. Dr. R. Penning, Prof. Dr. J. Peters, Prof. Dr. K. Pfeifer, Dr. I. Saake, Prof. Dr. M. Schmauss, Prof. Dr. U. Schroth, Prof. Dr. A. Spickhoff, Prof. Dr. O. Steinlein, PD Dr. U. Wandl, Prof. Dr. C. Wendtner, Dr. A. Yassouridis, Dr. Ch. Zach

Leuven, 27 april 2018

Ethische Commissie
Onderzoek UZ/KU Leuven
Herestraat 49
B 3000 Leuven (Belgium)
tel +32 16 34 86 00
website: www.uzleuven.be/ec/onderzoek
email: ec@uzleuven.be

prof. Stephan Swinnen

Ons kenmerk:	EudraCT-nr:	Belg. Regnr:
S61443		B322201836330

Registratie van aantal kopballen in jeugdvoetballers door middel van vragenlijsten en observatie.

DEFINITIEF GUNSTIG ADVIES

Geachte Collega,

De Ethische Commissie Onderzoek UZ/KU Leuven heeft vermeld protocol onderzocht en besproken op haar vergadering van 23 april 2018.

Na inzage van de bijkomende informatie en/of aangepaste documenten met betrekking tot dit dossier is de EC van oordeel dat de voorgestelde studie, zoals beschreven in het protocol, wetenschappelijk relevant en ethisch verantwoord is. Ze verleent dan ook een gunstig advies over deze studie.

De EC wenst de hoofdonderzoeker/promotor van de studie te wijzen op zijn/haar verantwoordelijkheid betreft de privacy van de persoons-/patiëntgegevens bij contact met de patiënt en/of inzage in het elektronisch medisch dossier, inclusief de correcte implementatie hiervan door medewerkers en studenten. De EC verwijst naar de richtlijnen van ICH/GCP hierover op de website, en benadrukt dat een GCP-opleiding van elke hoofdonderzoeker verwacht wordt. De EC verwijst tevens naar de Belgische wetgeving (Wet van 8/12/1992 ter bescherming van de persoonlijke levenssfeer en Wet van 22/8/2002 betreffende de rechten van de patiënt).

Bij het beoordelen van dit dossier werd rekening gehouden met de documenten en informatie gerelateerd aan deze studie, ingediend op 9 april 2018 en 26 april 2018.

Dit gunstig advies betreft:

Protocol:
Versie 3 dd 25/04/2018
Informatie en toestemmingsformulier:
ICF ouders Versie 2 dd 25/04/2018 Nl

ICF proefpersoon Versie 2 dd 25/04/2018 Nl

Overige patiëntendocumenten:

Vragenlijst dagelijks versie ontvangen 09/04/2018 Nl

Vragenlijst 2 weken versie ontvangen 09/04/2018 Nl

De EC bevestigt dat ze werkt in overeenstemming met de ICH-GCP principes (International Conference on Harmonization Guidelines on Good Clinical Practice), met de meest recente versie van de Verklaring van Helsinki en met de van toepassing zijnde wetten en regelgeving.

De EC bevestigt dat in geval van belangenconflict, de betrokken leden niet deelnemen aan de besluitvorming omtrent de studie.

Een ledenlijst wordt bijgevoegd.

Aandachtspunten: (indien van toepassing)

De opdrachtgever is verantwoordelijk voor de conformiteit van de anderstalige documenten met de Nederlandstalige documenten.

*Indien er een **Clinical Trial Agreement** is, kan de studie in ons centrum pas aangevat worden wanneer dit Clinical Trial Agreement goedgekeurd en ondertekend is door de gedelegeerde bestuurder van UZ Leuven (en/of desgevallend door bevoegde vertegenwoordiger(s) van KU Leuven Research & Development).*

Studies met geneesmiddelen en sommige studies met "medische hulpmiddelen" dienen door de opdrachtgever aangemeld te worden bij het FAGG.
Studies met geneesmiddelen mogen slechts aanvangen op voorwaarde dat de minister (FAGG) geen bezwaren heeft kenbaar gemaakt binnen de wettelijke termijnen zoals beschreven in art.13 van de Belgische wet van 7/5/2004 inzake experimenten op de menselijke persoon.
Voor bepaalde studies met medische hulpmiddelen gelden eveneens wettelijke termijnen (zie KB van 17/3/2009). Voor meer informatie hieromtrent verwijzen we naar de website van het FAGG www.fagg-afmps.be.

Onderzoek op embryo's in vitro valt onder de wet van 11 mei 2003. Voor dergelijk onderzoek is er naast een positief advies van de EC ook een goedkeuring van de Federale Commissie voor medisch en wetenschappelijk onderzoek op embryo's in vitro noodzakelijk vooraleer dit onderzoeksproject kan doorgaan.

Gelieve ook rekening te houden met de regelgeving van het ziekenhuis betreffende weefselbeheer en met de beschikkingen van de wet van 19 december 2008.

Dit gunstig advies van de EC houdt niet in dat zij de verantwoordelijkheid voor de geplande studie op zich neemt. U blijft hiervoor dus zelf verantwoordelijk. Bovendien dient U, als betrokken hoofdonderzoeker, erover te waken dat de resultaten van dit onderzoek correct worden weergegeven in publicaties, rapporten voor de overheid enz..
U dient ongewenste voorvallen en ernstige bijwerkingen te rapporteren zoals aangegeven door de Belgische Wet aangaande Experimenten op de menselijke

persoon van 7 mei 2004 (Art 27 en 28) en de omzendbrief 586 van het FAGG.

Gelieve ons mee te delen indien een studie niet wordt aangevat of wanneer ze wordt afgesloten of vroegtijdig onderbroken (met opgave van reden).

*Indien de studie niet binnen het jaar beëindigd is, vereist de ICH-GCP dat een **jaarlijks vorderingsrapport** aan de EC wordt bezorgd.*

*Gelieve tenslotte het (vroegtijdige of geplande) stopzetten van een studie binnen de door de wet vastgestelde termijnen mee te delen en een **Clinical Study Report** aan de EC te bezorgen.*

Met vriendelijke groet,

Prof. Dr. Minne Casteels
Voorzitter
EC Onderzoek UZ/KU Leuven

Cc:
FAGG (Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten)

CTC (Clinical Trial Center UZ Leuven)

Ledenlijst/Samenstelling van de Ethische Commissie Onderzoek UZ/KU Leuven op 23 april 2018 (datum van de laatste bespreking van het dossier):

Voorzitter	prof. dr. Maria-Reinhilde Casteels	Clinical Pharmacology
Vice-voorzitter	prof. dr. Dominique Bullens	Paediatrics
	De heer Jean-Jacques Derèze	Medical Legislation
	De heer Kristof Muylaert	Nurse
	Mevr. Godelieve Goossens	Nurse
	Mevr. Hélène De Somer	Nurse
	apr. J.R. Thomas	Clinical Pharmacology
	apr. Stefanie Goris	Pharmacist
	dr. Anne Smits	Paediatrics
	dr. José Thomas	Medical Oncology
	dr. Lut De Groote	General Practitioner
	prof. Ben Van Calster	Statistics
	prof. dr. Gregor Verhoef	Haematology
	prof. dr. Jan Verhaegen	Laboratory Medicine
	prof. dr. Jan de Hoon	Clinical Pharmacology
	prof. dr. Maria Schetz	Intensive care
	prof. dr. Xavier Bossuyt	Immunology
	prof. dr. em. Raymond Verhaeghe	Cardiology

= 04/468 - 3

Regional komite for medisinsk forskningsetikk Sør-Norge (REK Sør)

Professor dr. med Roald Bahr
Senter for idrettsskadeforskning
Norges idrettshøgskole
Postboks 4014 Ullevål Stadion
0806 OSLO

Deres ref.: **Vår ref.:** S-04049 **Dato:** 16.06.04

Kan små hodetraumer i fotball føre til hjerneskade? - En prospektiv klinisk undersøkelse
Prosjektleder: Prosjektleder dr. med. Roald Bahr, Senter for idrettsskadeforskning, Norges idrettshøgskole

Svar på merknader. Revidert informasjonsskrivet. Søknad om opprettelse av forskningsbiobank

Vi takker for brev med vedlegg (udatert) fra Truls Martin Straume-Næsheim mottatt her 28.mai 2004.

Komiteen tar svar på merknad vedrørende rekruttering av kvinner til etterretning.

Komiteen finner søknad om opprettelse av forskningsbiobank tilfredsstillende.

Når det gjelder informasjonsskrivet må det opplyses om forskningsbiobanken, hvem som er ansvarshavende, og om mulighet til å trekke prøvene. Se også veiledning for utfylling av søknadsskjemaet for opprettelse av forskningsbiobank på internettsiden, http://www.etikkom.no/REK/skjemaer/veil_03, hvor det angis hvilke opplysninger som skal gis. (alle detaljer behøver ikke tas med).

Komiteen går ut i fra at merknaden ovenfor vedrørende informasjonsskrivet tas til følge, og tilrår at prosjektet gjennomføres. Opprettelse av forskningsbiobanken godkjennes. Prosjektleder sender selv søknad om opprettelse av forskningsbiobank til Helsedepartementet vedlagt komiteens standpunkt.

Vi ønsker lykke til med prosjektet.

På grunn av stor saksmengde har vi dessverre ikke kunnet svare så raskt som vi ønsker.

Med vennlig hilsen

Sigurd Nitter-Hauge (sign)
Professor dr.med.
Leder

Ola P. Hole
Avdelingsleder
Sekretær

6/7

DET KONGELIGE
HELSEDEPARTEMENT

2004/468 6 441
6/9
Straume Næsheim

Norges Idrettshøgskole
v/ Truls Martin Straume-Næsheim
Postboks 4014 Ullevål Stadion
0806 OSLO

Deres ref	Vår ref	Dato
	200403720-/ASD	30.8.2004

Melding om forskningsbiobank vedrørende prosjektet "Kan små hodetraumer i fotball føre til hjerneskade? - en prospektiv studie

Det vises til brev av 29. juli 2004 vedrørende ovennevnte, samt til departementets foreløpige svar av 11. august s.å.

Departementet har ingen innsigelser mot at biobanken opprettes i henhold til biobankloven. Departementet forutsetter at opprettelsen av den planlagte biobanken oppfyller nødvendige krav til godkjenning, konsesjon mv. i henhold til annet relevant regelverk, herunder bioteknologiloven og helseregisterloven.

I følge meldingen punkt 9 vil alle prøver være anonymiserte. Vi gjør oppmerksom på at dersom det indirekte er mulig å spore prøvene/opplysningene tilbake til avgiveren av materiale, for eksempel ved hjelp av et kodenummer, skal begrepet avidentifisert benyttes. Materiale er anonymisert dersom det ikke lenger kan knyttes til en enkeltperson, verken direkte eller indirekte.

Når det gjelder overføring av biobankmateriale til utlandet, er hovedregelen i biobankloven § 10 at det skal søkes Sosial- og helsedirektoratet om godkjenning før overføring finner sted. Unntak kan forekomme dersom overføringen dreier seg om helsehjelp til enkeltpersoner, jf. biobankloven § 10 annet ledd eller er ledd i alminnelig internasjonalt samarbeid, jf. forskrift 26. februar 2004 nr. 511 om overføring av biobankmateiale til utlandet. Nærmere regler om unntaket fra kravet om godkjenning følger av forskriftens kapittel 2. Utskriv av forskriften følger vedlagt. Dersom unntaksvilkårene ikke er oppfylt, må ansvarshavende selv sende søknad om overføring til utlandet til Sosial- og helsedirektoratet.

Postadresse	Kontoradresse	Telefon	Helserettsavdelingen	Saksbehandler
Postboks 8011 Dep	Einar Gerhardsens plass 3	22 24 90 90		Anne Sofie von Düring
0030 Oslo		Org no.	Telefaks	22 24 87 17
		983 887 406	22 24 27 69	

Meldingen om biobanken vil bli sendt til Nasjonalt folkehelseinstitutt, som har fått ansvaret for å føre et offentlig tilgjengelig register over landets biobanker, jf. biobankloven § 6.

Med vennlig hilsen

Roger Østbøl

Roger Østbøl e.f.
avdelingsdirektør

Anne Sofie von Düring

Anne Sofie von Düring
rådgiver

Vedlegg 1

Norsk samfunnsvitenskapelig datatjeneste AS
NORWEGIAN SOCIAL SCIENCE DATA SERVICES

Harald Hårfagres gate 29
N-5007 Bergen
Norway
Tel: +47-55 58 21 17
Fax: +47-55 58 96 50
nsd@nsd.uib.no
www.nsd.uib.no
Org.nr. 985 321 884

Truls Martin Straume-Næsheim
Senter for idrettsskadeforskning
Norges Idrettshøgskole
Postboks 4014 Ullevål stadion
0806 OSLO

Vår dato: 07.02.2006 Vår ref: 14054/GT Deres dato: Deres ref:

TILRÅDING AV BEHANDLING AV PERSONOPPLYSNINGER

Vi viser til melding om behandling av personopplysninger, mottatt 08.01.2006. Meldingen gjelder prosjektet:

14054	*Kan små hodeskader i fotball føre til hjerneskade? - En prospektiv klinisk undersøkelse*
Behandlingsansvarlig	*Norges idrettshøgskole, ved institusjonens øverste leder*
Daglig ansvarlig	*Truls Martin Straume-Næsheim*

Personvernombudet har vurdert prosjektet, og finner at behandlingen av personopplysninger vil være regulert av § 7-27 i personopplysningsforskriften. Personvernombudet tilrår at prosjektet gjennomføres.

Personvernombudets tilråding forutsetter at prosjektet gjennomføres i tråd med opplysningene gitt i meldeskjemaet, korrespondanse med ombudet, eventuelle kommentarer samt personopplysningsloven/-helseregisterloven med forskrifter. Behandlingen av personopplysninger kan settes i gang.

Det gjøres oppmerksom på at det skal gis ny melding dersom behandlingen endres i forhold til de opplysninger som ligger til grunn for personvernombudets vurdering. Endringsmeldinger gis via et eget skjema, http://www.nsd.uib.no/personvern/endringsskjema. Det skal også gis melding etter tre år dersom prosjektet fortsatt pågår. Meldinger skal skje skriftlig til ombudet.

Personvernombudet har lagt ut opplysninger om prosjektet i en offentlig database, http://www.nsd.uib.no/personvern/register/

Personvernombudet vil ved prosjektets avslutning, 31.03.2007 rette en henvendelse angående status for behandlingen av personopplysninger.

Vennlig hilsen

for
Bjørn Henrichsen

Geir Teigland

Kontaktperson: Geir Teigland tlf: 55 58 33 48

Vedlegg: Prosjektvurdering

Personvernombudet for forskning, NSD

Prosjektvurdering - Kommentar

14054

Personvernombudet beklager at prosjektet er igangsatt og datainnsamling gjennomført før prosjektet ble meldt til ombudet.

Informasjonsskrivet som i studien danner grunnlag for informantenes samtykke til deltakelse finnes å ha mangler. Ombudet forutsetter at det ved prosjektslutt for pågående prosjekt tas kontakt med utvalget, og at utvalget informeres om at data skal oppbevares i påvente av oppfølgingsstudie. Informantene skal gis mulighet for å reservere seg mot videre deltakelse i prosjektet.

Personvernombudet vil ved prosjektslutt 31.03.2007 rette en henvendelse til prosjektleder for å avklare forhold omkring informasjonen som skal gis supplerende til utvalget.

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Mariann Glenna Davidsen	22845526	15.06.2017	2017/1104/REK sør-øst B
			Deres dato:	**Deres referanse:**
			19.05.2017	

Vår referanse må oppgis ved alle henvendelser

Roald Bahr
Akershus universitetssykehus HF

2017/1104 Kan små hodetraumer i fotball føre til hjerneskade? - En prospektiv klinisk undersøkelse

Forskningsansvarlig: Akershus universitetssykehus HF
Prosjektleder: Roald Bahr

Vi viser til søknad om prosjektendring datert 19.05.2017 for ovennevnte forskningsprosjekt. Søknaden er behandlet av leder for REK sør-øst på fullmakt, med hjemmel i helseforskningsloven § 11.

De omsøkte endringene er beskrevet i skjema for prosjektendringer og gjengis her (uthevet i kursiv):

Analyser av tidligere innsamlete blodprøver med hensyn på nye og lovende biomarkører for milde traumatiske hodeskader. I prinsippet samme metode som tidligere, men denne gangen med mer sensitiv teknologi og basert på over ti år med ny forskning på området. Spesifikt ønsker vi å analysere prøvene mhp. micro RNA og tau-proteiner.

Endringene gjøres i lys av ovenfor nevnte redegjørelse, da nye biomarkører og ny teknologi nå tillater oss å utføre nye analyser på tidligere innsamlete blodprøver, som har potensiale til å utgjøre et viktig bidrag i forskning på hodeskader. Dersom disse biomarkørene er i stand til å skille mellom utøvere med og uten hjernerystelse (samt relevante kontrollprøver etter trening uten nikking av ball og intens nikking av ball), vil de kunne få stor betydning for diagnostikk av akutte, milde hodeskader.

Prosjektperioden avsluttes 31.12.2018.

Komiteens vurdering
Komiteen har ingen innvendinger til de omsøkte endringene. Komiteen har gjennomgått samtykket fra det opprinnelige prosjektet og finner det dekkende for dette formål.

Vedtak
Komiteen har vurdert endringsmeldingen og godkjenner prosjektet slik det nå foreligger med hjemmel i helseforskningsloven § 11.

Godkjenningen er gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i endringsmeldingen.

Komiteens vedtak kan påklages til Den nasjonale forskningsetiske komité for medisin og helsefag, jf. Forvaltningslovens § 28 flg. Eventuell klage sendes til REK Sør-øst. Klagefristen er tre uker fra mottak av dette brevet.

Vi ber om at alle henvendelser sendes inn via vår saksportal: http://helseforskning.etikkom.no eller på e-post til post@helseforskning.etikkom.no.

Vennligst oppgi vårt referansenummer i korrespondansen.

Med vennlig hilsen

Grete Dyb
professor, dr. med.
leder REK sør-øst B

Mariann Glenna Davidsen
rådgiver

Kopi til:
slurt@me.com
hilde.luras@ahus.no1

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Silje Hansen	22845514	23.11.2018	2017/1104 REK sør-øst B
			Deres dato:	**Deres referanse:**
			15.11.2018	

Vår referanse må oppgis ved alle henvendelser

Roald Bahr
Akershus universitetssykehus HF

2017/1104 Kan små hodetraumer i fotball føre til hjerneskade? - En prospektiv klinisk undersøkelse

Forskningsansvarlig: Akershus universitetssykehus HF
Prosjektleder: Roald Bahr

Vi viser til søknad om prosjektendring datert 15.11.2018 for ovennevnte forskningsprosjekt. Søknaden er behandlet av sekretariatet i REK sør-øst på delegert fullmakt fra REK sør-øst B, med hjemmel i helseforskningsloven § 11.

Prosjektleders prosjektbeskrivelse
Vi tar sikte på å gjøre oppdaterte analyser av blodprøver tatt ifm. prosjektet i 2004 og 2005, da ny teknologi nå har åpnet opp for muligheter hva angår forskning på biomarkører for hodeskader. Dette vil medføre transport av anonymiserte blodprøver til vår lab-partner i Bratislava, Slovakia, hvor de vil teste kvaliteten på prøvene og deretter analysere disse med nye metoder. Potensielt vil dette kunne være med på å utvikle en blodprøve som vil kunne avdekke alvorlighetsgraden av, og dermed også veilede behandlingen av hodeskader.

De omsøkte endringene er beskrevet i skjema for prosjektendringer og gjelder:
- Endring av sluttdato fra 31.12.2018 til 31.12.2020.

Prosjektleder begrunner endringen slik:
Den eneste aktuelle endringen, er utsettelse av tidspunkt for prosjektslutt. Dette er ønskelig fordi analysene har tatt noe lengre tid enn antatt, og vi derfor har behov for mer tid til gjennomgang og ferdigstilling av resultatene.

Komiteens vurdering
Komiteen har ingen innvendinger til de omsøkte endringene.

Vedtak
REK har gjort en forskningsetisk vurdering av endringene i prosjektet, og godkjenner prosjektet slik det nå foreligger, jf. helseforskningsloven § 11.

Vi gjør samtidig oppmerksom på at etter ny personopplysningslov må det også foreligge et behandlingsgrunnlag etter personvernforordningen. Det må forankres i egen institusjon.

Tillatelsen er gitt under forutsetning av at prosjektendringen gjennomføres slik det er beskrevet i prosjektendringsmeldingen og endringsprotokoll, og de bestemmelser som følger av helseforskningsloven med forskrifter.

Klageadgang
REKs vedtak kan påklages, jf. forvaltningslovens § 28 flg. Eventuell klage sendes til REK sør-øst B. Klagefristen er tre uker fra mottak av dette brevet. Dersom vedtaket opprettholdes av REK sør-øst B, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering, jf. forskningsetikkloven § 10 og helseforskningsloven § 10.

Vi ber om at alle henvendelser sendes inn med korrekt skjema via vår saksportal: http://helseforskning.etikkom.no. Dersom det ikke finnes passende skjema kan henvendelsen rettes på e-post til: post@helseforskning.etikkom.no.

Vennligst oppgi vårt referansenummer i korrespondansen.

Med vennlig hilsen

Knut W. Ruyter
avdelingsdirektør
REK sør-øst

Silje Hansen
førstekonsulent

Kopi til:
Truls Martin Straume-Næsheim: slurt@me.com
Akershus universitetssykehus HF ved øverste administrative ledelse: postmottak@ahus.no;

Appendix II

Information letters and consent forms

Forespørsel om deltakelse i forskningsprosjektet:

«Validering av måleinstrument for måling av akselerasjonskrefter på fotballbanen»

Bakgrunn og hensikt

Med bakgrunn i større og pågående internasjonale studier på hodeskader i fotball, tas det sikte på å teste hvorvidt måleinstrumenter kalt "akselerometre" kan benyttes på fotballbanen – bl.a. for å måle omfanget av gravitasjonskreftene som er i spill ved headinger, løping og hopping. Enkelt sagt vil dette gi muligheten til å måle hvorvidt et hodestøt er kraftig eller ei. Dette er også viktig i lys av at effekten av headinger, som en naturlig del av spillet i fotball, fortsatt er uavklart, og dermed er det behov for ytterligere forskning på området.

Følgende informasjonsskriv er derfor en forespørsel om å delta i en studie som tar sikte på å teste potensialet for slike måleinstrumenter hos fotballspillere i aldersgruppen 14-16 år. Selve måleinstrumentet er laget som en øreplugg, hvor måleren dermed plasseres i ørekanalen. Derfor vil det være nødvendig å ta avstøpninger av den ene ørekanalen til deltakerne før oppstart av studien, som gjøres hos autorisert audiograf. På denne måten får vi individuelt tilpassede målere til hver enkelt spiller.

Etter målerne er ferdigstilt, vil vi ved Senter for idrettsskadeforskning, Norges Idrettshøgskole (NIH), gjennomføre 1-3 arrangerte treningsøkter med deltakerne, som vil inneholde pasnings-, heading-, løpe- og hoppeøvelser. Deltakerne vil altså ha på seg ørepluggen under disse treningene, slik at vi kan teste hva de faktisk måler, og om de klarer å skille mellom de forskjellige bevegelsene på banen. Dette vil gi svar på hvorvidt det vil være mulig å benytte tilsvarende målere på banen i mer kaotiske kamp- og treningssituasjoner i fremtiden.

Fordeler og ulemper?

Det må påberegnes noe tid ifm. avstøpninger av ørekanalen hos audiograf, men prosedyren er rask (ca. 10 min) og ukomplisert. Det vil tas videoopptak av selve treningsøktene, for å kunne sammenligne registreringene til måleinstrumentene med de faktiske aktivitetene på banen. Det vil kun være autorisert forskningspersonell som har adgang til disse opptakene, og disse vil oppbevares i maksimalt 10 år. For øvrig vil det ikke samles inn personsensitive opplysninger, og det vil ikke være mulig å identifisere deltakerne i resultatene av studien når den publiseres. Da dette vil foregå på en organisert måte, anses det som ikke å være noen risiko forbundet med studien, utover det en ellers forventer fra normal deltakelse i fotball.

Frivillig deltakelse

Det er helt frivillig å delta i studien. Dersom deltaker og hans/hennes foresatte samtykker i deltakelse, undertegnes samtykkeerklæringen nedenfor. Deltaker/foresatte kan når som helst og uten å oppgi noen grunn avstå fra eller trekke seg fra videre deltakelse. Dette vil ikke ha noen negative konsekvenser. Prosjektet meldes til Norsk samfunnsvitenskapelig datatjeneste og lokal etisk komité på NIH for godkjenning, før treningsøktene og selve studien gjennomføres.

Dersom du ønsker å delta eller har spørsmål til studien, ta kontakt med Thor Einar Andersen (tlf. 901 53 928) eller Stian Bahr Sandmo (tlf. 476 66 497).

Samtykke til deltakelse i studien

Deltaker og deltakers foresatte er villige til å delta i studien «Validering av måleinstrument for måling av akselerasjonskrefter på fotballbanen».

Godkjenning til deltakelse for _____ av foreldre/foresatte:
(navn på deltaker)

(Signert av foresatte, dato)

Informasjon til foresatte i forskningsprosjektet:

«REPIMPACT: Kan nikking i fotball føre til endringer i hjernen?»

Bakgrunn og hensikt

Dette informasjonsskrivet er til foresatte for de som skal delta i vårt kommende forskningsprosjekt "**RepImpact**". Vi ønsker å undersøke om det å nikke i fotball kan føre til endringer i hjernen. Dette er også forsket på tidligere, men vi vet ikke om det faktisk er skadelig eller ikke.

Fotball er verdens mest populære idrett, med over 265 millioner spillere spredt over hele verden. Det unike med fotball er at man benytter hodet – uten beskyttelse – som en aktiv del av spillet. Med så mange spillere, og usikkerhet rundt om dette er trygt eller ikke, ser vi det som viktig å kartlegge om dette fører til økt risiko for hjernen.

Målet for prosjektet er derfor å undersøke om det skjer endringer i hjernen hos unge fotballspillere som skiller seg fra andre idrettsutøvere i vekst, fra f.eks. langrenn og svømming, hvor hodestøt ikke er en del av idretten. Dette planlegger vi å gjøre ved at deltakerne følges gjennom én sesong, hvor vi ønsker å undersøke barnet ditt tre ganger: 1) før sesongstart 2018 (januar), 2) mot slutten av sesongen 2018, og 3) en siste gang før sesongstart 2019 (januar). Undersøkelsene vil vare i til sammen 3-4 timer hver gang, og vil inneholde:

1. **MR-undersøkelse av hodet**

- Undersøkelse med såkalt magnetrøntgen, uten røntgenbestråling, hvor man ligger stille i en slags maskin i ca. 1 time. Denne undersøkelsen kan oppleves som litt ekkel for de som blir engstelige i små, lukkede rom (klaustrofobi). Selv om det går fint å avbryte underveis, så vil vi gjerne at dere sier ifra om dette på forhånd!

2. **Nevropsykologisk testing**

- Gjøres ved hjelp av et dataspill som tester reaksjonshastighet og andre evner til problemløsning, og tar ca. 30 min å gjennomføre.

3. **Balansetesting**

- Testing av balanse på et balansebrett med øynene lukket. Tar ca. 3-4 min å fullføre. Første testdag vil vi også gjøre en enkel legeundersøkelse av din sønn. Denne tar ca. 10 min.

4. **Blod- og spyttprøver**

- Blod- og spyttprøver tas for å måle forskjellige stoffer som kan avdekke endringer i hjernen. Blodprøvene tas i armen. Vi legger på en krem med lokalbedøvelse før vi tar prøven, slik at dette ikke skal gjøre vondt. Spyttprøvene tas ved at det tygges på en liten svamp i ca. 1 minutt, før vi tar vare på prøven.

5. **Spørreskjema**

- Utfylling av et spørreskjema som inkluderer spørsmål om tidligere sykdommer, hvor lenge og hvilke idretter sønnen din har holdt på med, skolehverdagen, osv.

I tillegg vil vi i løpet av sesongen filme/observere enkelte treninger og kamper, for å telle hvor ofte din sønn og de andre spillerne nikker. De vil også motta et spørreskjema enkelte ganger gjennom sesongen, hvor vi vil spørre om hvor ofte de selv tror at de nikker i treninger og kamper, samt om noen i mellomtiden har pådratt seg andre hodeskader, som for eksempel hjernerystelser.

Fordeler og ulemper?

Ulempen med å delta i studien er den tiden det tar å gjennomføre testene på de tre undersøkelsesdagene, samt tiden det tar å fylle ut spørreskjema i forkant av undersøkelsesdagene, og enkelte ganger gjennom sesongen. For øvrig vil din sønn holde på med idretten sin på samme måte som tidligere.

MR-undersøkelsen kan for noen oppleves som ubehagelig, da man må ligge stille over lengre tid, og noen også har angst for små, lukkede rom. Vi avbryter undersøkelsen umiddelbart, hvis dette skulle bli et problem. Blodprøven tas med et stikk i armen, men vi vil legge en lokalbedøvende krem på huden i forkant for at det ikke skal gjøre vondt. Blodprøven tas av trent laboratoriepersonell.

Skulle vi ved en tilfeldighet finne noe på undersøkelsene nevnt ovenfor, vil våre leger følge opp dette videre i form av innkalling til individuell samtale, og eventuelt henvise til spesialist dersom dette skulle være aktuelt.

Informasjon og opplysninger vi samler inn om din sønn

Alt av informasjon og andre opplysninger vi samler inn i løpet av studien vil det kun være oss i forskergruppen som har tilgang til, og det vil ikke være mulig å gjenkjenne hverken ditt barn eller andres når resultatene etterhvert presenteres. Vi ønsker å oppbevare informasjonen i maksimalt 10 år før den slettes/anonymiseres. Prosjektet er godkjent av Regional komité for medisinsk og helsefaglig forskningsetikk (REK).

For at vi skal kunne få best mulige resultater, så er det enkelte faktorer som gjør at din sønn kanskje ikke kan være med i studien:

1. **Kjent sykdom fra før**

- Kjent nevrologisk eller psykiatrisk diagnose, som f.eks. epilepsi eller dysleksi
- Annen kronisk sykdom som behandles med medisiner

2. **Grunner til at man ikke kan undersøkes med MR**

- Har sønnen din medisinsk utstyr og/eller implantater i kroppen påvirkes de av magnetfeltet i MR-maskinen, og dermed kan ikke undersøkelse med MR gjøres. Dette gjelder f.eks. pacemaker, nevrostimulator, insulinpumpe og metallspon i øyet.
- Har noen metall i området rundt hode og nakke vil dette forstyrre bildene, så hvis din sønn f.eks. har tannregulering i metall, eller planlegger å få det, kan han ikke delta.

Ta kontakt med oss dersom dere er usikre!

Frivillig deltakelse

Det er helt frivillig å delta i studien! Dersom det takkes ja til å bli med undertegnes samtykkeskjema på neste side, hvor det bekreftes at både du/dere og din/deres sønn er informert om prosjektet og hva deltakelse vil innebære. For deltakere som fyller 16 år i løpet av studien, vil vi for disse også samle inn skriftlig samtykke ved første kontakt etter fylte 16 år. Det er full mulighet for å trekke seg fra videre deltakelse, når som helst under forløpet og uten å oppgi noen grunn, og dette vil ikke medføre noen konsekvenser for hverken deltaker eller andre. Vi vil også slette resultatene fra undersøkelsene dersom det er ønskelig.

Ved spørsmål eller andre henvendelser, vennligst kontakt:

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Samtykke til deltakelse i studien

Deltaker og deltakers foresatte er villige til å delta i studien «**RepImpact**: Kan nikking i fotball føre til endringer i hjernen?».

Godkjenning til deltakelse av _____
Navn på spiller/prosjektdeltaker

(Signert av foresatte, dato)

(Signert av prosjektdeltaker (hvis over 16 år), dato)

http://www.repimpact.org/

Forespørsel om å delta i et forskingsprosjekt.

”Kan små hodetraumer i fotball føre til hjerneskade?”

De siste årene har det vært en økende bekymring for at fotballspillere kan utvikle kroniske hjerneskader i løpet av sin karriere. En har tidligere tenkt at dette hadde med heading å gjøre, og det er til og med foreslått å forby heading i fotball. Du har sikkert lagt merke til at enkelte spillere – særlig i amerikansk damefotball – har begynt å bruke hodebeskyttere. Senere forskning har dog mer eller mindre avist at heading er syndebukken. Dermed er fokus mer blitt rettet mot gjentatte hodeskader. Fotball er en kontaktidrett og fotballspillere er svært utsatt for hodetraumer—ikke bare i stadige hodedueller, men også i andre situasjoner på banen. Mange av disse traumene eller smellene mot hodet blir likevel ikke erkjent som hodeskader. En av grunnene til dette er at definisjonen på en hjernerystelse har vært streng—det har vært et krav at spilleren skal være bevisstløs eller i hvert fall desorientert for at diagnosen skal stilles. I løpet av senere år er det imidlertid blitt klart at hjernerystelser forekommer i mange andre tilfeller. Nyere forskning på fotballspillere har vist at hjernerystelser ikke blir erkjent i 4 av 5 tilfeller og utøveren fortsetter dermed å spille med påfølgende økt risiko for ny skade. Vi vil i dette prosjektet undersøke om slike små hodetraumer gir målbare effekter på hjernen—både i form av akutt forbigående skade og eventuelt i form av langtidsvirkninger etter at sesongen er over.

Vi vil undersøke dette ved hjelp av en databasert neuropsykologisk test (CogSport™), som kan avdekke endringer i bl.a. reaksjonstid, hukommelse, læring, etc. Testen er ikke en intelligenstest—resultatet er faktisk tilnærmet uavhengig av IQ. Testen er utviklet som et kortspill, og testingen vil ta om lag 30 minutter. I tillegg ønsker vi å ta en blodprøve for å lete etter en spesifikk markør på hjerneskade (et protein som kalles S-100b).

Gjennom sesongen vil begge testene bli gjentatt på spillere som pådrar seg en mulig hodeskade i en kamp. Testene vil da bli utført av lagets medisinske støtteapparat rett etter kampen, samt gjentatt en til to ganger de nærmeste dagene. Resultatene fra disse CogSport-testene vil umiddelbart bli gjort tilgjengelige for deg og lagets lege for å kunne hjelpe dere til å vurdere når det er forsvarlig å gjenoppta trening. Vi vil også følge alle kampene på video for å kunne analysere skademekanismene i hvert tilfelle.

Enkelte spillere/lag vil i tillegg bli bedt om å la seg teste på nytt etter en kamp i løpet av sesongen. Dette er for å få en relevant kontrollgruppe. Til slutt vil testene bli gjentatt for samtlige deltakere i studien på La Manga i 2005.

Resultatene fra studien vil kunne bekrefte, eller avkrefte, hvorvidt små hodetraumer gir hjerneskade. På basis av dette kan vi utvikle råd om forebygging av slike skader og bedre retningslinjer for når det er forsvarlig å gå tilbake til trening/kamp etter en slik hendelse.

Alle som deltar i forskningsprosjekter er dekket av en særskilt forsikring som gjelder for undersøkelsene som blir gjennomført på testdagen.

Det vil bli opprettet en forskningsbiobank for alle blodprøvene med undertegnede som ansvarshavende. Blodprøvene vil bli lagret etter analysene for S100B i påvente av nye markører, for lett hjerneskade, som er under utvikling.

Vi gjør oppmerksom på at all informasjon som gjelder deg vil bli behandlet konfidensielt, og undersøkerne har taushetsplikt. Ved din underskrift gir du samtykke til at du frivillig deltar i studien. Du kan når som helst trekke deg fra undersøkelsen, og du trenger ikke å oppgi noen grunn hvis du ønsker å trekke deg. Hvis du trekker deg vil alle innsamlede data bli anonymisert eller slettet, og blodprøvene destruert.

Prosjektet er meldt til Personvernombudet for forskning, Norsk samfunnsvitenskapelig datatjeneste AS. Studien er også vurdert av Regional komité for medisinsk forskningsetikk.

Prosjektet blir utført i regi av Senter for idrettsskadeforskning. Hovedfinansieringen av prosjektet vil være via det internasjonale fotballforbundets medisinske komite (FIFA-MARC). Prosjektet støttes i tillegg økonomisk fra Senter for Idrettsskadeforskning ved Norges idrettshøgskole, som er etablert gjennom økonomisk støtte fra Kulturdepartementet, Norges idrettsforbund og olympiske komite, Norsk Tipping AS og Pfizer AS.

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SENTER FOR Idrettsskadeforskning

Samtykkeerklæring

Jeg, _____,
samtykker i å delta i prosjektet "Kan gjentatte små hodetraumer gi hjerneskade?"
Jeg bekrefter at jeg har fått skriftlig og muntlig informasjon om studien.

_____ _____

Deltagerens signatur Dato (deltageren daterer selv)