Mild traumatic brain injury in female athletes —possible pituitary dysfunction and effect on psychological and neuropsychological function

Lára Ósk Eggertsdóttir Claessen

Thesis for the degree of Philosophiae Doctor

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Afleiðing heilahristings hjá íþróttakonum – möguleg vanstarfsemi í heiladingli og áhrif á andlega líðan og taugasálfræðilega virkni

Lára Ósk Eggertsdóttir Claessen

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Ágrip

Inngangur

Heilahristingur getur leitt til vanstarfsemi í heiladingli (VH) með áætlað algengi 13 – 48%. Þar sem einkenni VH geta líkst einkennum heilahristings og hægt er að meðhöndla með lyfjum gæti VH endurspeglað meðhöndlanlega orsök fyrir einkennum eftir heilahristing. Íþróttakonur hafa verið minna rannsakaðar en karlar með tilliti til VH eftir heilahristing þrátt fyrir að nýgengi heilahristings sé hærra hjá konum en körlum og bataferlið sé lengra. Því er brýnt að rannsaka áhrif heilahristings á íþróttakonur meðal annars með tilliti til VH.

Markmið þessa doktorsverkefnis var að meta algengi VH eftir heilahristing hjá íþróttakonum, að finna mögulega forspárþætti fyrir VH eftir heilahristing, þar með talið sálfræðilega og taugasálfræðilega forspárþætti, og meta andlega líðan, taugasálfræðileg frammistöðu og lífsgæði hjá íþróttakonum eftir heilahristing með VH samanborið við íþróttakonur með eðlilega starfsemi á heiladingli. Samkvæmt okkar bestu vitund er rannsóknin sú fyrsta sem fjallar um algengi VH eftir heilahristing í þýði íþróttakvenna sem og taugasálfræðilega frammistöðu, andlega líðan og lífsgæði.

Aðferðir

Íþróttakonur (n = 508) á Íslandi tóku þátt í rannsókninni með því að svara rafrænum spurningalista um heilahristings sögu og andlega líðan. Af þessum konum höfðu 308 konur fengið einn eða fleiri heilahristing og samþykktu 166 (53,8%) þeirra frekari þátttöku í taugasálfræðilegum prófum. Af þeim tóku síðan 151 (90,9%) kona þátt í viðtali og skoðun hjá lækni. Eftir viðtalið voru blóðrannsóknir til skimunar fyrir mögulegri VH gerðar hjá 133 (88,1%) konum klukkan átta að morgni þar sem allir hormónaöxlar heiladingluls voru metnir. Konum sem höfðu niðurstöður blóðrannsókna endurtekið utan viðmiðunarmarka var vísað í frekari uppvinnslu vegna mögulegrar VH eins og við átti.

Niðurstöður

Niðurstöður blóðrannsókna voru utan viðmiðunarmarka hjá 88 konum (66,2%, n = 133) og reyndist líklegra að skimunar blóðprufur væru utan viðmiðunarmarka hjá yngri konum og þeim sem höfðu fleiri einkenni heilahristings.

Eftir frekari uppvinnslu reyndust 16 íþróttakonur (12,2%, n = 131) vera með truflun á heiladingulshormónum eftir heilahristing, sex (4,6%) konur voru með VH (vanstarfsemi á skjaldkirtilshormóna öxli n = 4; 3,1% og vaxtarhormónskortur n = 2; 1,5%) og tíu (7,6%) konur voru með hækkað prólaktín. Fjórar (3,0%, n = 131) af þeim tíu konum sem voru með

hækkun á prólaktín greindust með hefðbundið prólaktínóma og sex (4,6%, n = 131) konur voru ekki með prólaktínóma. Lyfjameðferð var hafin hjá 13 konum (9,9%, n = 131). Ekki fundust marktækir forspárþættir varðandi truflun á heiladinglushormónum eftir heilahristing við samanburð á milli kvenna með og án truflunar á starfsemi heiladinguls.

Konur með truflun á heiladingulshormónum voru með hærri stigafjölda á *Sustained Attention to Response Task error score* (SARTes) en konur með eðlilega starfsemi heiladinguls (16,7 stig miðað við 12,8 stig; p = 0,004). Ekki var annar marktækur munur á taugasálfræðilegri frammistöðu, andlegri líðan, eða lífsgæðum á milli kvenna með truflun á heiladingulshormónum og kvenna með eðlilega starfsemi heiladinguls.

Ályktanir

Meirihluti þýðisins (66,2%, n = 133) þurfti frekari uppvinnslu vegna mögulegrar VH. Lægri aldur og aukinn fjöldi heilahristingseinkenna auka þörf á skimun fyrir mögulegri VH eftir heilahristing. Eftir frekari uppvinnslu var VH greind hjá umtalsverðum fjölda íþróttakvenna með sögu um heilahristing (12,2%). Konur með truflun á heiladingulshormónum höfðu aukinn stigafjölda á SARTes sem bendir til áhrifa á getu til að viðhalda athygli eða á hömlur.

Þar sem truflun á heiladingulshormónum var hjá 12,2% íþróttakvennanna er það mikilvægur hluti af mati eftir heilahristing. Þörf er á frekari uppvinnslu vegna mögulegrar VH eftir heilahristing hjá yngri konum, ef aukinn fjöldi heilahristingseinkenna er til staðar eða hjá konum með háan stigafjölda á SARTes eftir heilahristing.

Lykilorð:

Heilahristingur, íþróttakonur, vanstarfsemi í heiladingli, taugasálfræðileg próf, andleg líðan

Abstract

Introduction

Hypopituitarism (HP) can occur following mild traumatic brain injury (mTBI) with an estimated a prevalence of 13 – 48%. As HP can be treated with hormonal replacement therapy and symptoms of HP may overlap with symptoms of mTBI, HP represents a potentially treatable cause of mTBI symptoms. Women remain an understudied population with regards to HP following mTBI even though the incidence of mTBI appears to be greater and recovery time longer in women compared to men. Thus, studies on the effects of mTBI in female samples are highly needed.

The aim of this thesis was to identify female athletes needing further endocrinological evaluation for possible pituitary dysfunction (PD), including both HP and hyperprolactinemia (HPRL), following mTBI, find the prevalence of PD following mTBI in female athletes, identify possible predictive factors for PD after mTBI, including psychological and neuropsychological predictive factors, and evaluate psychological and neuropsychological outcome as well as quality of life in women with PD following mTBI compared to women with normal pituitary function (nPF). To the best of our knowledge, this study is the first to report the prevalence of PD after mTBI and the effect of PD on psychological and neuropsychological function in an all-female population.

Methods

Female athletes (n = 508) in Iceland participated by answering online questionnaires regarding mTBI history and mental health. One or more mTBI was reported by 308 women and 166 (53.8%) of them accepted further participation which included neuropsychological tests. Of these 166 women, 151 (90.9%) participated in a medical interview. Following the medical interview, screening blood tests (SBT) for each pituitary axis were performed in 133 (88.1%) at 8 A.M. When SBT were repeatedly outside the reference value (O-RV), a detailed endocrinological evaluation was performed including further endocrinological testing when indicated.

Results

Repeated hormonal SBT were O-RV in 88 women (66.2%, n = 133). Lower age and increased number of mTBI symptoms were associated with increased risk of SBT O-RV.

Following a detailed endocrinological evaluation, 16 (12.2%, n = 131) women were diagnosed with PD after mTBI, six (4.6%) with HP (central hypothyroidism n = 4, 3.1% and

growth hormone deficiency n = 2, 1.5%) and ten (7.6%) with HPRL. Of the ten women who had HPRL, four (3.0%, n = 131) had a prolactinoma and six (4.6%, n =131) did not. Medical treatment was required in 13 women (9.9%, n = 131). Significant prognostic factors for PD following mTBI were not found.

Women with PD had a significantly higher mean Sustained Attention to Response Task error score (SARTes) than women with nPF (16.7 and 12.8 respectively; p = 0.04). There were no other significant differences between women with PD and women with nPF with regards to psychological symptoms, neuropsychological symptoms or quality of life.

Conclusions

Following pituitary hormone SBT, further endocrinological evaluation was indicated in a large majority (66.2%, n = 133) of the population. Lower age and increased number of symptoms of mTBI indicates that screening for HP following mTBI is required. Following further endocrinological evaluation a substantial proportion of female athletes (12.2%) were diagnosed with PD after mTBI. Women with PD following mTBI had a higher mean SARTes indicating decreased sustained attention or inhibitory performance.

As 12.2% of the female athletes were diagnosed with PD, it is an important concern after mTBI. Thus, endocrinological evaluation for possible PD following mTBI is indicated in women of a younger age, if prominent symptoms of mTBI are present, or in women who have higher SARTes and a history of mTBI.

Keywords:

Mild traumatic brain injury, female athletes, pituitary dysfunction, neuropsychological tests, mental health

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Contents

List of Abbreviations

ACTH = Adrenocorticotropic hormone

BMI = Body mass index

CH = Central hypothyroidism

CoD = Corticotropin deficiency

CVD = Cardiovascular disease

FSH = Follicle stimulating hormone

GAD-7 = General Anxiety Disorder Questionnaire 7

GD = Gonadotropin deficiency

GH = Growth hormone

GHD = Growth hormone deficiency

GHRH = Growth hormone-releasing hormone

GHRH-arg = Growth hormone releasing hormone and arginine

HoC = Hormonal contraception

HP = Hypopituitarism

HPRL = Hyperprolactinemia

IGF-1 = Insulin like growth factor 1

ISI = Insomnia Severity Index

ITT = Insulin tolerance test

LH = Luteinising hormone

MRI = Magnetic resonance imaging

mTBI = Mild traumatic brain injury

nPF = Normal pituitary function

O-RV = Outside the reference value

PCS = Post-concussion syndrome

PD = Pituitary dysfunction

PHQ-9 = Patient Health Questionnaire 9

PRL = Prolactin

PSS4 = Perceived Stress Scale 4

QOL = Quality of life

RV = Refence value

s-anti-TPO = Serum anti-thyroid peroxidase antibodies

SART = Sustained Attention to Response Task

SARTes = SART error score

SARTrt = SART response time

SBT = Screening blood tests

SCAT-5 = Sport Concussion Assessment Tool 5

s-cortisol = Serum cortisol

SCWT = Stroop Colour- and Word Test

s-FSH = Serum FSH

s-fT_4 = Serum free thyroxine

s-GH = Serum growth hormone

s-IGF-1 = Serum insulin-like growth factor 1

s-LH = Serum LH

s-oestrogen = Serum oestrogen

s-progesterone = Serum progesterone

s-PRL = Serum prolactin

SRC = Sport-related concussion

s-TSH = Serum thyroid stimulating hormone

TBI = Traumatic brain injury of all severity, mild, moderate and severe.

TMT = Trail Making Test

TSH = Thyroid stimulating hormone

WAIS-III = Wechsler Adult Intelligence Scale-III

WASI-IS = Wechsler Abbreviated Scale of Intelligence, Icelandic version (IS)

List of Figures

List of Tables

List of Original Papers

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals (paper I, paper II, and paper III):

I. Eggertsdóttir Claessen LÓ, Kristjánsdóttir H, Jónsdóttir MK, Lund SH, Unnsteinsdottir Kristensen IS, Sigurjónsdóttir HÁ. Screening for possible hypopituitarism following mild traumatic brain injury: The first all-female study. Who do we need to evaluate further? NeuroRehabilitation. 2023;52(2):259-271. Erratum in: NeuroRehabilitation. 2023;53(3):419.

II. Eggertsdóttir Claessen LÓ, Kristjánsdóttir H, Jónsdóttir MK, Lund SH, Unnsteinsdóttir Kristensen I, Sigurjónsdóttir HÁ. Pituitary dysfunction following mild traumatic brain injury in female athletes. Endocrine Connections. 2024 Jan 16;13(2):e230363.

III. Eggertsdóttir Claessen LÓ, Jónsdóttir MK, Kristjánsdóttir H, Lund SH, Unnsteinsdóttir Kristensen I, Sigurjónsdóttir HÁ. Pituitary dysfunction following mild traumatic brain injury in female athletes: neuropsychological and psychological findings. Submitted for publication.

Declaration of Contribution

The doctoral candidate, **Lára Ósk Eggertsdóttir Claessen (LÓEC)** contributed to the data collection for the current study, analysis and interpretation of the data, and wrote the manuscripts of the original papers in collaboration with and under the supervision of:

- **Professor Helga Ágústa Sigurjónsdóttir (HÁS), MD, PhD, specialist in internal medicine and endocrinology**, my main supervisor, who was responsible for the endocrinological part of the study (part III) which is the focus of the current thesis.
- **Professor María Kristín Jónsdóttir (MKJ), PhD, neuropsychologist**, who was responsible for the psychological and neuropsychological evaluation in part I and II of the study.
- **Professor Hafrún Kristjánsdóttir (HK), PhD, psychologist**, who was responsible for the psychological and neuropsychological evaluation in part I and II of the study.
- **Professor Sigrún Helga Lund (SHL), PhD, statistician,** who oversaw the statistical analysis of the entire study (part I, II, and III) and advised and supervised the statistical analysis used in the current study, performed by LÓEC.

The data collection involved a medical interview, and a physical and neurological examination of all participants performed by LÓEC. Hormonal screening blood test were performed to screen for possible hypopituitarism (HP) following mild traumatic brain injury (mTBI). LÓEC contributed to the interpretation of the hormonal screening blood tests under the supervision of HÁS. When indicated, a detailed endocrinological evaluation was performed including endocrinological tests for further evaluation of pituitary dysfunction (PD) following mTBI. All endocrinological tests were performed by LÓEC and HÁS and the interpretation of the results of the endocrinological tests was overseen by HÁS**.**

Ingunn Unnsteinsdóttir Kristensen, PhD contributed to the data collection in part I and II of the study under the supervision of MKJ, HK, and HÁS. Further analysis and interpretation of this data with regards to pituitary function was performed by LÓEC in collaboration with MKJ, HK, IUK, SHL, and HÁS and under the supervision of MKJ, HK, SHL, and HÁS.

1 Introduction

1.1 Mild traumatic brain injury

Traumatic brain injury (TBI) is classified into mild traumatic brain injury (mTBI), also referred to as concussion, moderate traumatic brain injury, and severe traumatic brain injury (Figure 1) (Brasure et al., 2012; Kazl and Torres, 2019; Lefevre-Dognin et al., 2021; Silverberg et al., 2023). The focus of this thesis is on mTBI which results from a direct blow to the head, neck or body, acceleration – deceleration movements or forces from a blast injury transmitting mechanical force to the brain (Patricios et al., 2023; Silverberg et al., 2023).

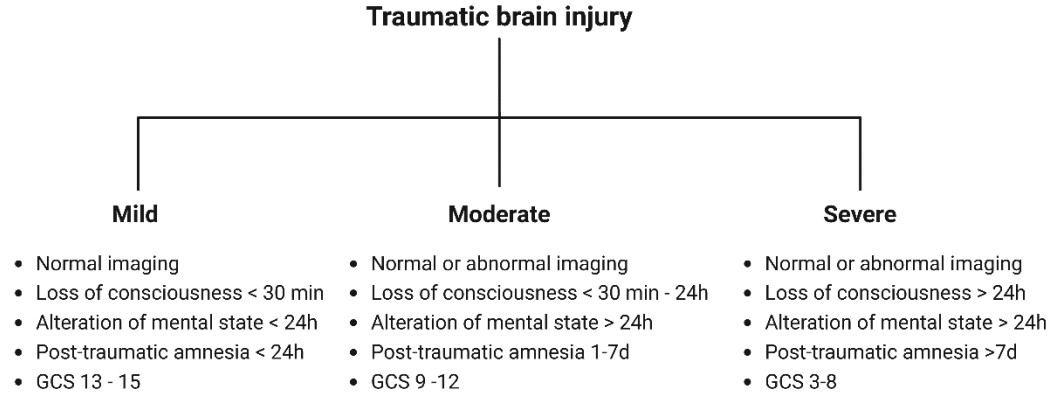

Figure 1 Classification of TBI
The classification of TBI according to acute injury characteristics. The GCS score represents the best score within 24 hours of the injury.
d = days, GCS = Glasgow Coma Scale, h = hours, min = minutes, TBI = traumatic brain injury
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1.1.1 Epidemiology of mild traumatic brain injury

The global incidence rate of TBI is estimated as 69 million cases annually (Dewan et al., 2018) with mTBI representing 70 – 95% of all TBI cases (Capizzi et al., 2020; Cassidy et al., 2004; Feigin et al., 2013). The incidence rate of mTBI has been reported as 749 per 100,000 person-years in New Zealand (Feigin et al., 2013) and 1153 per 100,000 person-years in Canada (Langer et al., 2020). However, as up to at least 30% of individuals do not seek medical attention following mTBI, the incidence of mTBI is likely underestimated (Whiteneck et al., 2016). In recent years, the incidence of mTBI appears to be rising as a

three-fold increase has been reported over a period of 23 years. Whether this represents a true rise in the incidence of mTBI or increased awareness regarding mTBI remains unclear (Reid et al., 2020).

Common mechanisms of injury for mTBI includes falls, transport accidents, assaults, and sports (Feigin et al., 2013; Voss et al., 2015). A mTBI occurring during sports, sport-related concussion (SRC), represents 5 – 6.2% of all sport-related injuries in the USA (Daneshvar et al., 2011; Zuckerman et al., 2015) and most commonly affects individuals at the age of 10 – 35 years (Theadom et al., 2014). An estimated 1.6 to 3.8 million SRCs occur annually in the USA (Langlois et al., 2006) which is likely underestimated as diagnosis relies partly on self-reported symptoms that in many cases may be absent or go unrecognised immediately after the injury (Harmon et al., 2019; Silverberg et al., 2023).

1.1.2 Pathophysiology of mild traumatic brain injury

In mTBI, mechanical force transmitted to the brain initiates a complex pathophysiological process of axonal injury, neurotransmitter release, and metabolic disturbances disrupting brain function (Barkhoudarian et al., 2011). Research on the underlying pathophysiology of mTBI is ongoing although important advances have been made. Possible pathophysiological mechanisms of mTBI are presented in Figure 2.

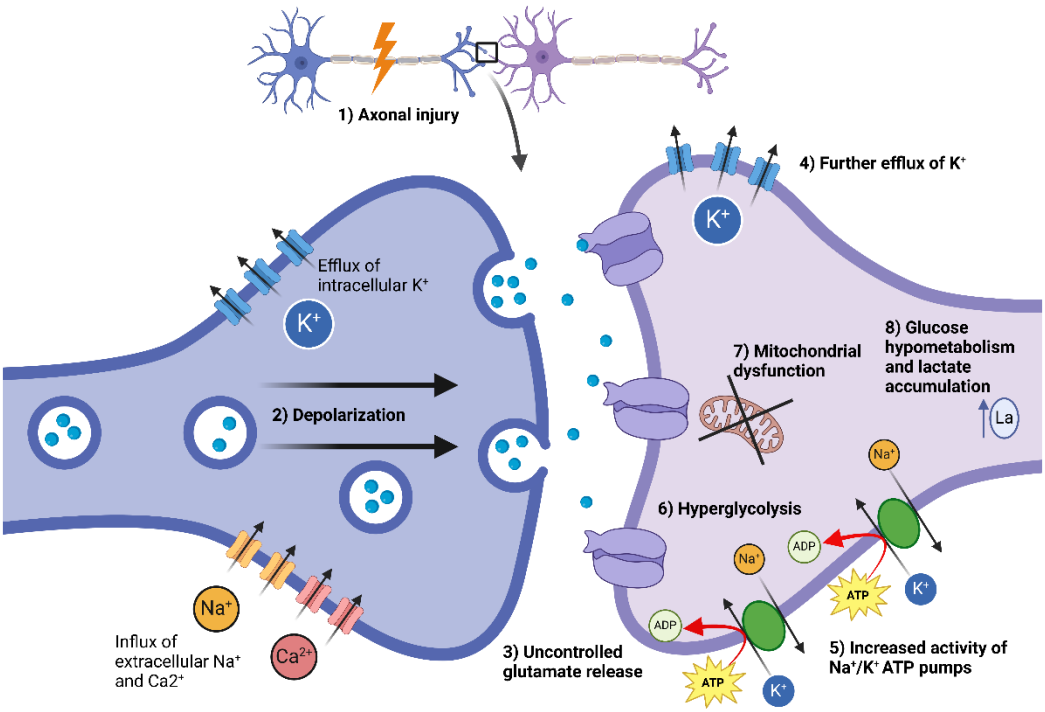

Figure 2 The pathophysiology of mTBI
An overview of the acute phase metabolic and neurotransmitter release cascade that occurs following mTBI.
ADP = adenosine diphosphate, ATP = adenosine triphosphate, Ca^{2+} = calcium, Glu = Glutamate, K^+ = potassium, La = Lactate, mTBI = mild traumatic brain injury, Na^+ = sodium.
Created with BioRender.com

1.1.2.1 Neurotransmitter release and metabolic disturbances

Mechanical force causes neuronal cell axonal injury affecting cell membrane permeability resulting in diffuse neuronal depolarization and disrupted flux of ions across the neuronal cell membrane (Figure 2) (Farkas et al., 2006; Katayama et al., 1990; Yuen et al., 2009). This flux of ions causes uncontrolled glutamate release, promoting further potassium efflux (Figure 2) (Katayama et al., 1990; Vespa et al., 1998).

To restore the ionic homeostasis the sodium/potassium adenosine triphosphate pumps work at maximum capacity resulting in a state of hyperglycolysis depleting intracellular energy reserves (Figure 2) (Kawamata et al., 1992; Yoshino et al., 1991).

The increased levels of intracellular calcium and hyperglycolytic state eventually causes mitochondrial dysfunction (Xiong et al., 1997). This leads to a period of lactate accumulation and glucose hypometabolism which can last for up to one month following TBI (Bergsneider et al., 2000; Bergsneider et al., 2001).

1.1.2.2 Inflammation

Neuroinflammation may also have a role in mTBI as elevated levels of interleukin 6, interleukin 1 receptor antagonist, interleukin 1β, and chemokine ligand 2 have been reported within six hours from mTBI (Meier et al., 2020; Nitta et al., 2019; Sun et al., 2019).

1.1.3 Clinical presentation

Various physical, psychological, and neuropsychological symptoms can occur immediately after mTBI or have a delayed onset presenting within a few hours (Figure 3). Among the most reported symptoms of mTBI and SRC are headaches, confusion, dizziness, nausea, and fatigue (Benson et al., 2011; Guskiewicz et al., 2003; Makdissi et al., 2010). As shown in Figure 3, acute symptoms of mTBI can be divided into five subtypes and two mTBI associated conditions possibly providing useful treatment targets following mTBI (Langdon et al., 2020; Lumba-Brown et al., 2020).

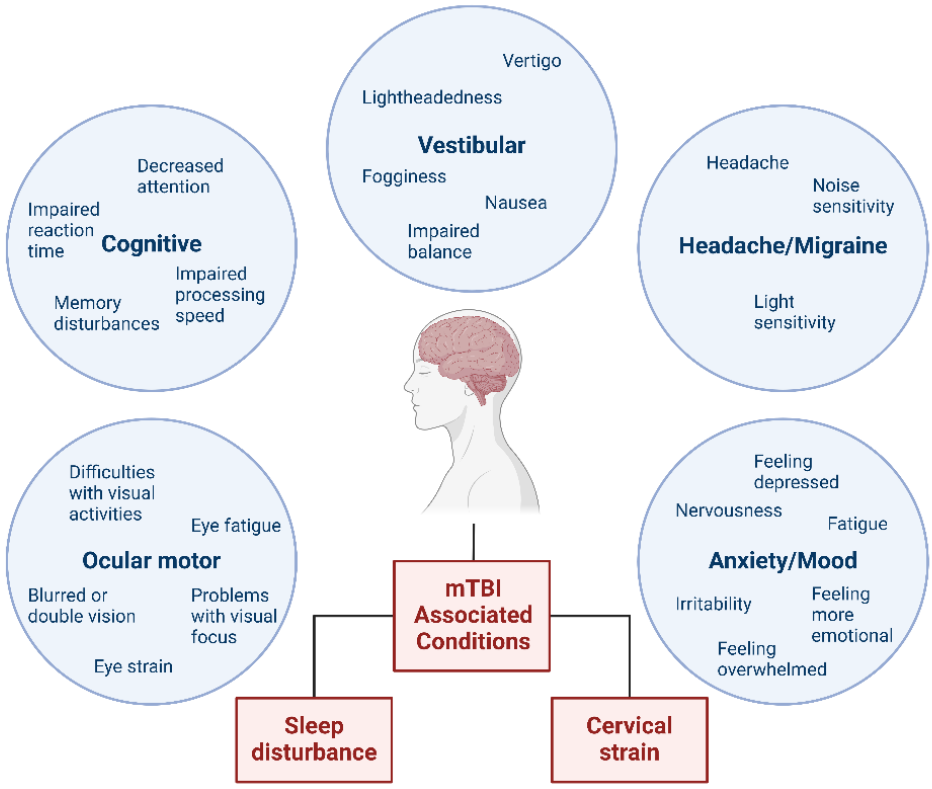

Figure 3 Symptom subtypes of mTBI and associated conditions
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Psychological symptoms can occur following mTBI and SRC with one study reporting a 32.5% prevalence of anxiety-related disorders in the first year following mTBI which was 2.5 times higher than in a general population (Lamontagne et al., 2022). Higher prevalence of moderate and severe depression (19.1%) has also been reported in male retired players in American football (Kerr et al., 2018) compared to a general male population (5.9%) (Kocalevent et al., 2013) with a possible dose-response relationship between the number of SRCs and clinical depression (Didehbani et al., 2013; Guskiewicz et al., 2007; Kerr et al., 2012; Kerr et al., 2018). A possible dose-response relationship between mTBI and psychological symptoms was also reported in earlier phases of the current study. Symptoms above the clinical cut-off for depression were 3.5 times more likely in women reporting 2 – 3 mTBI and 4.9 times more likely in women reporting ≥ 4 mTBI compared to women who did not report a mTBI. Symptoms above the clinical cut-off for anxiety were also 3.5 times more likely in women reporting 2 – 3 mTBI and 3.4 times more in women reporting ≥ 4 mTBI compared to those who did not report a mTBI (Jónsdóttir et al., 2021). Increased risk of suicide has also been reported following mTBI (Fralick et al., 2016).

Sleep disturbances can also occur following mTBI and SRC and appears to be more common in female athletes (42.0%) than male athletes (29.3%) (Davis-Hayes et al., 2017). Studies have also reported that the presence of sleep disturbances following mTBI can prolong mTBI symptom recovery (Bramley et al., 2017).

Various neuropsychological symptoms of mTBI have been reported affecting different neuropsychological domains such as executive functioning, attention, memory, processing speed, and reaction time (Belanger and Vanderploeg, 2005; Collins et al., 1999; Henry et al., 2016; Makdissi et al., 2010; McCrea et al., 2003). These symptoms appear to resolve within five to ten days (Belanger and Vanderploeg, 2005; Iverson et al., 2006; Karr et al., 2014; McCrea et al., 2003) although they may take longer to resolve (Cunningham et al., 2020; Henry et al., 2016; Zhang et al., 2019).

1.1.4 Post-concussion syndrome

Although the majority (80 – 90%) of those who sustain a mTBI recover within 7 – 10 days (Benson et al., 2011; Carney et al., 2014; Guskiewicz et al., 2003; Makdissi et al., 2010; McCrea et al., 2003; Nelson et al., 2013; Ponsford et al., 2011; Silverberg et al., 2023), persistent symptoms can occur and are referred to as post-concussion syndrome (PCS). The definition of PCS remains debated although PCS is commonly defined as having persistent symptoms of mTBI beyond four weeks after injury (Henry et al., 2016; McKeithan et al., 2019; Patricios et al., 2023; Savola and Hillbom, 2003) or three months after injury (Lagacé-Legendre et al., 2021). Of those who sustain a mTBI, 22 – 36% still experience symptoms of mTBI after four weeks (Savola and Hillbom, 2003) and 10 – 22% are still symptomatic after three months (Hou et al., 2012; Ponsford et al., 2011). The recovery time

of PCS remains unclear although one study reported only 27% of PCS patients recover within three years (Hiploylee et al., 2017).

1.1.4.1 Symptoms of post-concussion syndrome

Symptom clusters similar to those proposed for acute symptoms of mTBI have been proposed for PCS although further research is needed (Figure 3) (Langdon et al., 2023). Headaches, memory deficits, concentration difficulties, imbalance, and dizziness are most commonly reported (Tator et al., 2016).

Psychological symptoms of PCS are an important consideration as symptoms of depression, anxiety, or both have been reported in 35.2% of patients with PCS and are associated with diminished quality of life (QOL) (Doroszkiewicz et al., 2021; Popov et al., 2022). A bidirectional relationship appears to exist between PCS and psychological symptoms as a positive association has been reported between PCS and depressive symptoms (Jónsdóttir et al., 2021; Lambert et al., 2022) and premorbid psychological symptoms appear to predict the development of PCS (Ponsford et al., 2019).

Persistent neuropsychological symptoms three months after injury have been reported in 55% of individuals with even a single mTBI (McInnes et al., 2017). Long-term neuropsychological symptoms have also been reported 6 – 10 years after injury affecting executive function, learning, memory, attention, processing speed, and language (Cunningham et al., 2020; Konrad et al., 2011; Zhang et al., 2019).

1.1.4.2 Predictive factors for developing post-concussion syndrome

Numerous predictive factors for PCS have been suggested (Figure 4) with mental illness being most commonly reported including premorbid anxiety, depression (Hou et al., 2012; Ponsford et al., 2012; Wäljas et al., 2015), bipolar disorder, and personality disorders (Figure 4) (Langer et al., 2021). Lack of information regarding mTBI symptoms and coping strategies also appears to be a predictive factor for PCS as one study found that patients who sustained a mTBI and did not receive such information were more likely to develop PCS (Ponsford et al., 2002). Repeated mTBI or SRC also appear to be associated with the development of PCS (Benson et al., 2011; Covassin et al., 2013; Guskiewicz et al., 2003; Tator et al., 2016).

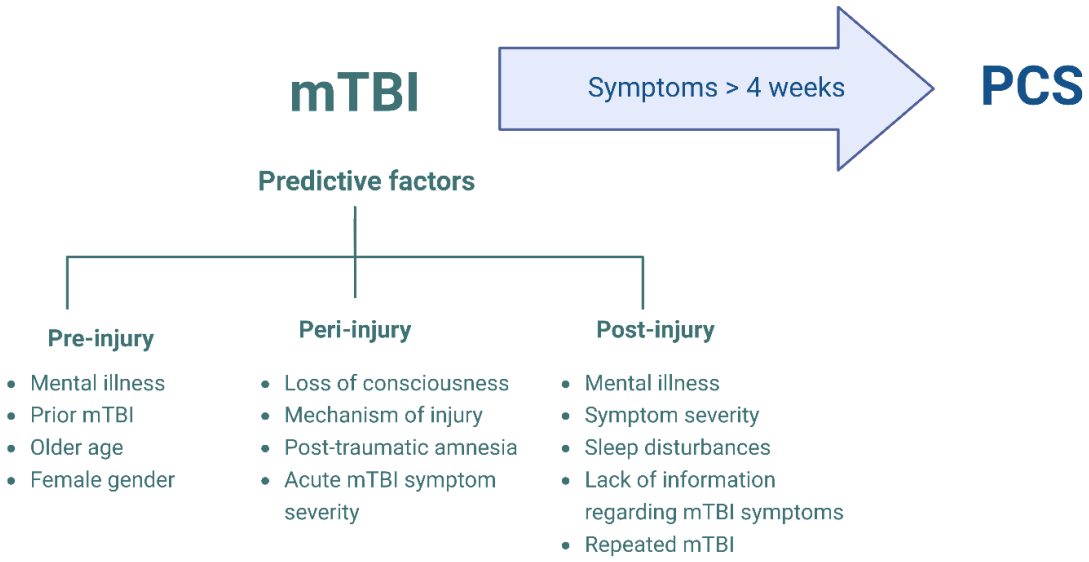

Figure 4 Predictive factors for developing PCS following mTBI
Pre-injury = factors that are present prior to mTBI, Peri-injury = factors that occur at the time of the mTBI, Post-injury = factors that are present following mTBI.
mTBI = mild traumatic brain injury, PCS = post-concussion syndrome.
(Bazarian et al., 2010; Ganti et al., 2014; Hinds et al., 2016; Iverson et al., 2017; Langer et al., 2021; McCrea et al., 2013; Ponsford et al., 2012; Ponsford et al., 2019; Ponsford et al., 2002; Preiss-Farzanegan et al., 2009; van der Naalt et al., 2017; Yue et al., 2019)

1.1.5 Neurodegenerative disorders and mild traumatic brain injury

Neurodegenerative disorders such as chronic traumatic encephalopathy (Gardner et al., 2014; Nowinski et al., 2022) have been associated with repeated mTBI as they are more common in athletes exposed to repetitive mTBI compared to general populations. Former players in American football are also five times more likely to develop Alzheimer's disease, four times more likely to develop motor neuron disease, and two times more likely to develop Parkinson's disease compared to a general population (Mackay et al., 2019). Moreover, former rugby players are 15 times more likely to develop MND and three times more likely to develop Parkinson's disease compared to controls (Russell et al., 2022)

1.1.6 Sex-based differences in mild traumatic brain injury

In recent years, women's sports have been gaining popularity. According to a global report from Fédération Internationale de Football Association (FIFA), 16.6 million women and girls participated in soccer in the year 2023 with 19,064 women playing professionally, which is a 24% increase from the year 2019 ("Women's Football: Member Associations Survey Report 2023," 2023). Despite increased female participation in sport, women remain an

understudied population with regards to SRC (D'Lauro et al., 2022). Thus, further research on sex-based differences in SRC incidence, symptom severity, and outcome is needed.

The incidence rate of SRC appears to be higher in female athletes than male athletes (Black et al., 2017; Dave et al., 2022; Davis-Hayes et al., 2017; Vedung et al., 2020). Women also experience more acute symptoms of SRC than men (Broshek et al., 2005; Colvin et al., 2009) and take longer to recover (Baker et al., 2016; Zuckerman et al., 2014). In a Swedish study, female soccer players had a higher number of symptoms within 48 hours after SRC compared to male soccer players and the median recovery time was 20 days in female athletes compared to 10 days in male athletes (Vedung et al., 2020).

Several physical, physiological, and behavioural explanations for these sex-based differences in SRC incidence and outcome have been proposed (Blyth et al., 2021). Women have less neck girth and strength, and less head mass than men resulting in increased head-neck accelerations after impact exposing female athletes to higher SRC rates (Bretzin et al., 2017; Tierney et al., 2005). Female athletes are also more likely to report symptoms of SRC than male athletes (McAllister-Deitrick et al., 2022; Sanderson et al., 2017). Sex-based hormonal differences and hormonal changes that occur across different phases of the menstrual cycle may also affect SRC outcome. Women who sustain a mTBI during the luteal phase of the menstrual cycle, when progesterone is high, reported more symptoms and had worse QOL one month after injury compared to women with lower progesterone levels, such as women who were injured during the follicular phase and women who were using hormonal contraception (HoC) when the mTBI occurred (Wunderle et al., 2014). These findings led to "the withdrawal hypothesis" stating that mTBI during the luteal phase causes a drop in progesterone intensifying mTBI symptoms. Conversely, sustaining a mTBI during the follicular phase of the menstrual cycle and while using HoC may have protective effects with regards to symptoms of mTBI as a significant drop in hormonal levels does not occur (Wunderle et al., 2014).

1.1.7 Diagnosis

Diagnosis of mTBI relies mostly on self-reported symptoms of mTBI or SRC (Figure 3) (Patricios et al., 2023; Silverberg et al., 2023). Although prompt diagnosis is essential, diagnostic delay can occur as symptoms can be subtle and unspecific and may not be recognized by patients or health care professionals (Delaney et al., 2002; Harmon et al., 2019; Powell et al., 2008). Symptoms of mTBI can also have a delayed onset affecting the sideline evaluation of athletes, exposing them to repeated SRC that may prolong recovery (Covassin et al., 2013; Harmon et al., 2019; Silverberg et al., 2023). Furthermore, it has been reported that 40 – 51% of athletes did not disclose symptoms of SRC for reasons such as not thinking that the injury was serious and not wanting to be withheld from competition

(Anderson et al., 2016; Asken et al., 2016; McCrea et al., 2004; Register-Mihalik et al., 2013).

Symptom scales and screening tools have been developed to improve mTBI diagnosis. The Sport Concussion Assessment Tool is the most commonly used sideline screening tool for SRC (Echemendia et al., 2023; Patricios et al., 2023). It is regularly reviewed by an expert panel and is accepted by major sporting organisations such as the International Olympic Committee and FIFA.

Objective measurements have been suggested for mTBI diagnosis although further research is needed (McCrea et al., 2017). Electroencephalography may be able to measure increased cognitive effort to maintain postural control and balance during a virtual reality simulation in female athletes with a history of SRC compared to female athletes with no history of SRC (Jacob et al., 2022). Computerized tomography and magnetic resonance imaging (MRI) are normal in mTBI and thus not useful (Silverberg et al., 2023). However, advanced neuroimaging studies such as diffusion tensor imaging (Khong et al., 2016) and positron emission tomography scans (Allingham et al., 2023) may be useful as they can detect neurophysiological alterations and microscopic structural changes in the brain.

1.1.8 Treatment of mild traumatic brain injury

The initial step in the management of mTBI and SRC is preventing subsequent head injuries such as by removing athletes from their sport as repetitive SRC prolong recovery (Asken et al., 2018; Covassin et al., 2013; Eagle et al., 2022).

Although relative rest involving normal activities of daily living is advised for the first two days after mTBI and SRC (Figure 5), prolonged rest can lengthen recovery time (Thomas et al., 2015). Thus, return to light-intensity physical activity is advised within the first 24 – 48 hours where only mild exacerbation of symptoms should occur (Figure 5) (Leddy et al., 2023; Patricios et al., 2023). Progression into sub-symptom threshold aerobic exercise is recommended within 2 – 14 days from injury as it reduces the incidence of PCS (Figure 5) (Leddy et al., 2021). After that, exercise intensity and duration can be increased further depending on the symptom burden experienced during training (Leddy et al., 2023; Patricios et al., 2023).

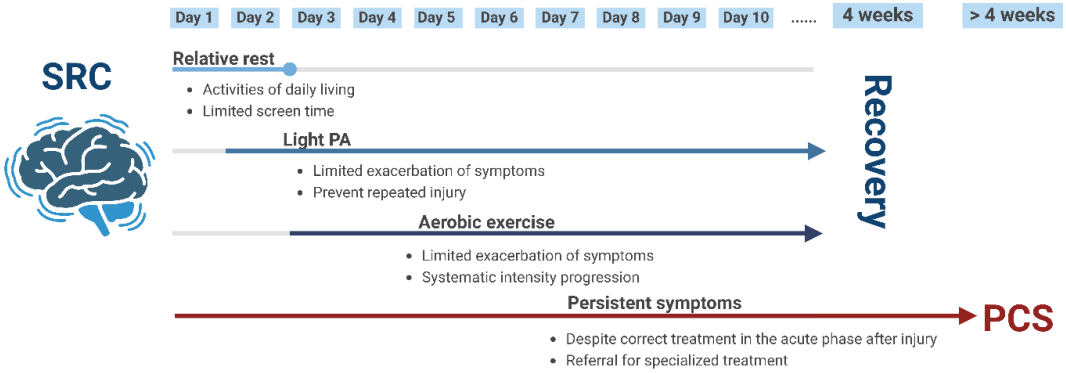

Figure 5 Treatment and recovery after SRC and mTBI
PA = physical activity, PCS = post-concussion syndrome, SRC = sport-related concussion.
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1.1.9 Treatment of post-concussion syndrome

When symptoms of mTBI or SRC are clinically severe or persist beyond 4 weeks despite appropriate treatment, referral for multimodal, specialized management of PCS is advised (Patricios et al., 2023). Management of PCS depends on the clinical symptoms that are present (Figure 3) and involves various non-pharmacological and pharmacological treatments. It also involves excluding underlying, reversible causes for PCS symptoms such as hypopituitarism (HP) (Marshall et al., 2018) as symptoms of PCS and HP can overlap and symptoms of HP may improve with hormonal replacement therapy where the insufficient hormone is replaced (Reed et al., 2013; Rosén et al., 1995).

1.2 Hormonal regulation

The hypothalamus and pituitary gland regulate hormonal homeostasis by producing hormones affecting target organs or glands as a response to environmental and physiological changes. Tight regulation is achieved through negative feedback (Figure 6). Releasing hormones from the hypothalamus and pituitary gland induce hormone production from target glands. When certain levels of target gland hormones are reached they provide negative feedback to the hypothalamus and pituitary gland preventing further releasing hormone production (Figure 6) (Hiller-Sturmhöfel and Bartke, 1998)

1.2.1 Hypothalamus

The hypothalamus is a small area in the brain connecting the central nervous system and endocrine system as it receives both hormonal and neuronal input (Hiller-Sturmhöfel and Bartke, 1998). Hypothalamic releasing hormones include growth hormone-releasing hormone (GHRH), corticotropin-releasing hormone, thyrotropin-releasing hormone, and gonadotropin-releasing hormone. These hormones are transported to the pituitary gland via hypothalamic-pituitary portal vessels in the pituitary stalk (Figure 7) where they stimulate the release of anterior pituitary gland hormones (Figure 8). The hypothalamus also produces the inhibiting hormones somatostatin and dopamine which inhibit the release of growth hormone (GH) and prolactin (PRL), respectively, from the anterior pituitary gland (Figure 8) (Ben-Shlomo and Melmed, 2022; Hiller-Sturmhöfel and Bartke, 1998; Lechan and Toni, 2000).

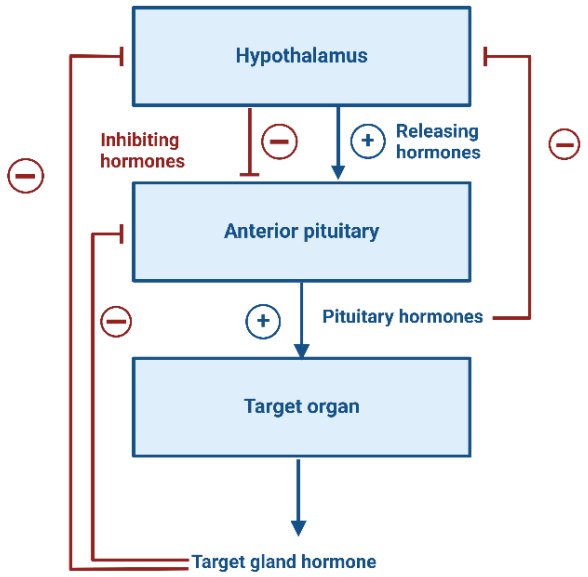

Figure 6 Hypothalamic-pituitary-target organ feedback mechanisms
+ = stimulating effects, – = inhibiting effects
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1.2.2 Pituitary gland

The pituitary gland has two lobes, the anterior and posterior lobe (Figure 7). The posterior pituitary lobe contains oxytocin and antidiuretic hormone produced in the hypothalamus and transported to the posterior lobe for storage and appropriate release. Six hormones are secreted by the anterior lobe: GH, adrenocorticotropic hormone (ACTH), thyroid stimulating hormone (TSH), PRL, luteinising hormone (LH), and follicle stimulating hormone (FSH). These hormones stimulate hormone production in target glands (ACTH, TSH, LH, FSH) or directly affect target organs (GH, PRL) (Figure 8) (Higham et al., 2016; Hiller-Sturmhöfel and Bartke, 1998).

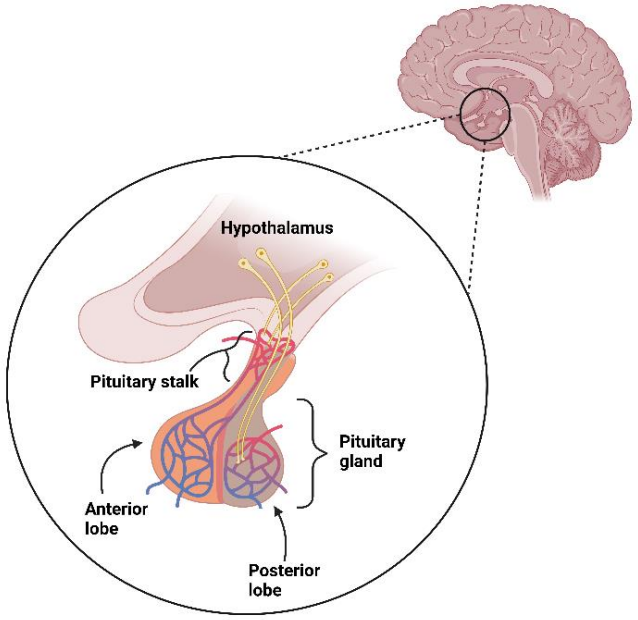

Figure 7 Hypothalamus and pituitary anatomy
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1.2.3 Target glands and organs

Somatotroph cells release GH in a pulsatile manner although deep sleep and physical stress, appears to increase GH release. The effects of GH include promoting growth by direct effect and induction of insulin-like growth factor 1 (IGF-1) production (Ranke and Wit, 2018). GH also affects various other organs, such as the central nervous system, liver, kidneys, bones, cartilage, muscles, adipose cells, and the immune system as well as inducing hyperglycaemia, lipolysis, and protein anabolism in the body (Hattori, 2009; Hiller-Sturmhöfel and Bartke, 1998; Rohrbasser et al., 2016; Wasinski et al., 2019).

ACTH stimulates cortisol production in the adrenal cortex. Cortisol is an important stress hormone during emotionally and physically stressful events such as trauma and severe infections (Papadimitriou and Priftis, 2009) and also has a role in carbohydrate, protein, and lipid metabolism (Hiller-Sturmhöfel and Bartke, 1998).

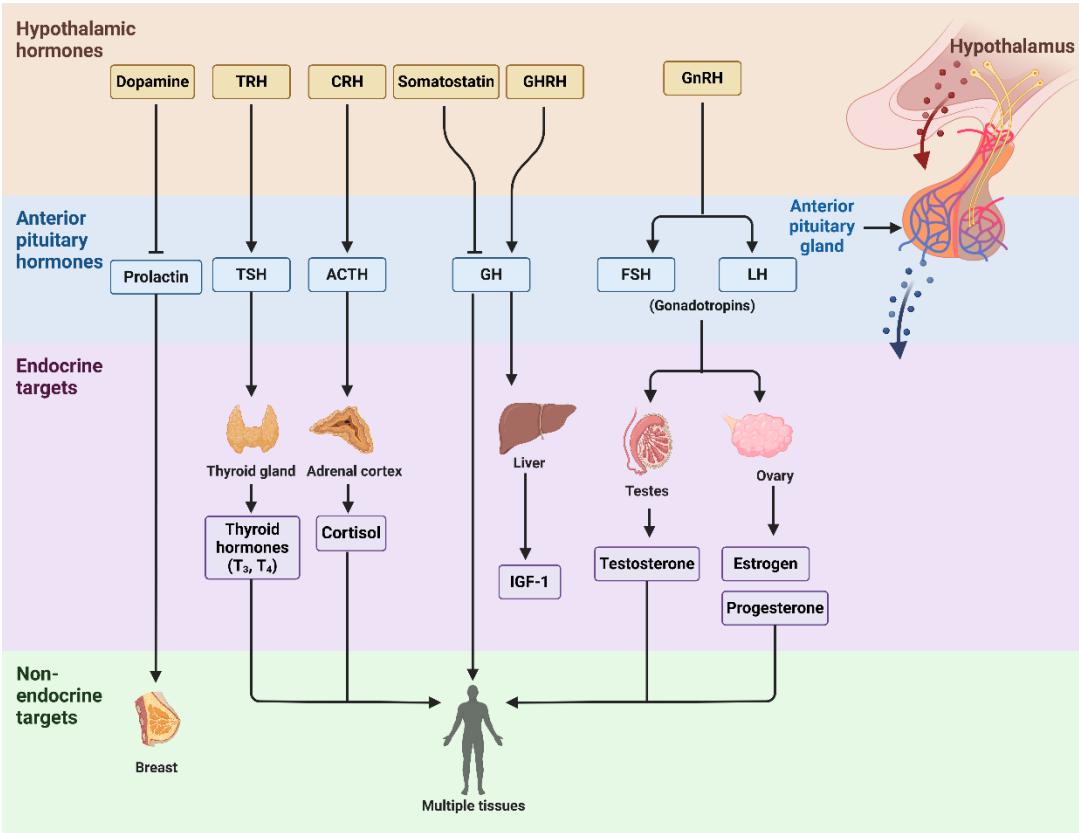

Figure 8 Hypothalamic-pituitary-target organ axes
An overview of the anterior pituitary hormonal axes.
ACTH = adrenocorticotropic hormone, CRH = corticotropin releasing hormone, FSH = follicular stimulating hormone, GH = growth hormone, GHRH = growth hormone releasing hormone, GnRH = gonadotropin releasing hormone, IGF-1 = insulin-like growth factor 1, LH = luteinising hormone, T_3 = triiodothyronine, T_4 = thyroxine, TRH = thyrotropin releasing hormone, TSH = thyroid stimulating hormone.
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The thyroid gland is stimulated by TSH to produce and release the thyroid hormones thyroxine and triiodothyronine increasing metabolism throughout the body (Rohrbasser et al., 2016).

The gonadotropins (FSH and LH) regulate oestrogen and progesterone production by the ovaries and testosterone production by the testes. Sex hormones are necessary for proper development and function of female and male reproductive organs and secondary sex characteristics (Hiller-Sturmhöfel and Bartke, 1998).

The lactotroph axis has a role in inducing and maintaining lactation and is the only anterior pituitary hormone axis regulated by hypothalamic inhibition rather than stimulation (Hiller-Sturmhöfel and Bartke, 1998; Phillipps et al., 2020; Rohrbasser et al., 2016).

1.2.4 Pituitary dysfunction

Pituitary dysfunction (PD) occurs when pituitary function is disrupted resulting in HP or hyperprolactinemia (HPRL) due to pituitary stalk dysfunction (Sav et al., 2019). Thus, PD in the thesis includes both HP and HPRL. When discussed separately, HP refers to pituitary hormone deficiency and HPRL to elevated levels of PRL.

1.2.4.1 Hypopituitarism

Partial or complete loss of one or more anterior pituitary hormones due to hypothalamic or pituitary gland disease results in HP (Higham et al., 2016). Primary HP is caused by disorders of the pituitary gland that damage pituitary hormone-secreting cells, such as pituitary tumours, autoimmune disease, and Sheehan's syndrome. Secondary HP is caused by disorders of the hypothalamus or pituitary stalk that disrupt pituitary hormone secretion by interrupting the neuronal or vascular connections to the pituitary gland (Kim, 2015). Both primary and secondary HP can result from TBI (Gasco et al., 2021; Sav et al., 2019).

1.2.4.2 Hyperprolactinemia

The lactotroph axis is usually regulated by hypothalamic dopamine release inhibiting PRL production (Hiller-Sturmhöfel and Bartke, 1998; Phillipps et al., 2020; Rohrbasser et al., 2016). Thus, HPRL can occur due to PRL producing tumours, such as prolactinomas, or as a result of pharmacological or pathological disruption of the hypothalamic-pituitary dopaminergic pathways that suppress PRL production (Melmed et al., 2011).

1.3 Pituitary dysfunction following mild traumatic brain injury

In recent years, TBI has been recognized as a cause for PD. Traumatic cause for HP represents 2.2 – 5.4% of all HP cases (De Bellis et al., 2011; Doknić et al., 2017; Higham et al., 2016; Kim, 2015; Tanriverdi et al., 2014) and hypothalamic or pituitary stalk injury may impair dopaminergic inhibitory control of PRL release resulting in HPRL (Sav et al., 2019).

1.3.1 Epidemiology of traumatic hypopituitarism

The prevalence of HP following TBI ranges from 11 – 56% (Table 1 and 2) and from 18 – 48% following mTBI alone (Table 3). This wide prevalence range of HP after TBI and mTBI may be explained by variations in the endocrinological evaluation of HP between studies, differences in the definition of HP (Klose et al., 2014; Kokshoorn et al., 2010), and timing

of the endocrinological evaluation as the prevalence of HP after TBI appears to decrease with time although new cases may also occur (Aimaretti et al., 2005; Bavisetty et al., 2008; Klose et al., 2007a; Krahulik et al., 2010; Schneider et al., 2007b; Schneider et al., 2006b; Tanriverdi et al., 2013; Tanriverdi et al., 2006; Tanriverdi et al., 2008a).

Growth hormone deficiency (GHD) is most common following both TBI of all severity and mTBI. The estimated prevalence of GHD following TBI ranges from 10 – 37% (Table 1 and 2) and from 10 – 48% following mTBI (Table 3). The second most pituitary hormone deficiency after TBI of all severity is gonadotropin deficiency (GD) (Tables 1 – 2) although some studies have reported that GD is more common than GHD within the first 3 – 6 months after TBI with GHD becoming more common one year after injury (Agha et al., 2004a; Bavisetty et al., 2008; Klose et al., 2007a; Schneider et al., 2007b; Tanriverdi et al., 2006).

Posterior HP occurs mostly in the acute phase after TBI with a prevalence of 1.4 – 26% (Agha et al., 2004a; Agha et al., 2005; Aimaretti et al., 2004; Aimaretti et al., 2005; Bavisetty et al., 2008; Bondanelli et al., 2004; Klose et al., 2007a; Krahulik et al., 2010; Schneider et al., 2007b; Schneider et al., 2006b; Silva et al., 2015)

Identifying predictive factors for HP after mTBI is essential to facilitate efficient screening. Various predictive factors for HP after TBI have been suggested such as increased TBI severity (Table 1 and 2) (Bavisetty et al., 2008; Bondanelli et al., 2004; Kelly et al., 2000; Klose et al., 2007a; Klose et al., 2007b; Schneider et al., 2007b; You et al., 2019) although opposing results have also been reported (Agha et al., 2004b; Aimaretti et al., 2004; Aimaretti et al., 2005; Bensalah et al., 2020; Kozlowski Moreau et al., 2012; Schneider et al., 2006b). One study also reported that women appeared to be more likely to have HP after TBI than men (Klose et al., 2007a).

1.3.2 Epidemiology of traumatic hyperprolactinemia

The prevalence of HPRL after TBI ranges from 2 – 14 % although one study reported a prevalence of 39% in the acute phase after injury (Tables 1 and 2). Moreover, HPRL may be a marker of TBI severity as it correlates negatively with initial Glasgow Coma Scale following TBI (Agha et al., 2004a; Tanriverdi et al., 2006).

Author (year)	Sample	Type of TBI	Endocrinological evaluation	HP	Affected axes	Predictive factors for HP
Kelly (2000)	n = 22 18M, 4F	mTBI moTBI sTBI ¥	ITT, GHRH arg, TRH and GnRH.	36%	GD (22%), GHD (18%	Diffuse brain swelling, hypotensive and/or hypoxic insult. NA with TBI severity ǂ, raised ICP or decreased CPP.
Aimaretti (2004)	n = 100 69M, 31F	mTBI (55%) moTBI (24%) sTBI (21%)	SBT* and fT3 GHRH-arg	35%	GHD (21%), GD (17%), HPRL (10%)	NA with increased TBI severity ǂ
Bondanelli (2004)	n = 50 40M, 10F	mTBI (32%) moTBI (14%) sTBI (54%)	SBT*, ACTH, GHRH-arg	54%	GHD (28%), GD (14%) HPRL (8%)	TBI severity ǂ NA with type of injury, cranial or facial fractures, or time from TBI.
Aimaretti (2005)	n = 70 50M, 20F	mTBI (47%) moTBI (31%) sTBI (21%)	After 3m and 1y: SBT* and 24h urinary free cortisol, GHRH-arg	3m: 33% 1y: 22%	3m: sGHD (23%), GD (17%) HPRL (4%) 1y: sGHD (20%), GD (11%) HPRL (6%)	NA with increased TBI severity ǂ
Tanriverdi (2006) λ	n = 52 43M, 9F	mTBI (60%) moTBI (15%) sTBI (25%)	SBT*, fT3, ACTH, GH, SST, GHRH/GHRP-6	<24h: 57% 12m: 51%	<24h: GD (42%), GHD (20%), HPRL (8%) 12m: GHD (37%), CoD (25%), HPRL (12%)	— §
Klose (2007)	n = 104 78M, 26F	mTBI (42%) moTBI (19%) sTBI (38%)	SBT*, GH, IGFBP-3, ITT, GHRH-arg, SST	15%	GHD (15%), CoD (5%)	Female gender, increased TBI severity ǂ, increased ICP, longer duration of intubation, longer hospitalization.
Klose (2007)	n = 46 33M, 13F	mTBI (48%) moTBI (20%) sTBI (33%)	Tested within 0-12d, 3m,6m and 1y: SBT*, total T3, IGFBP-3, CBG. ITT or GHRH-arg (after 3m and 1y), SST	3m:13% 1y:11%	0-12d blood tests: GD (67%), HPRL (39%). 3m and 1y: GHD (11%), CoD (7%)	HP patients more frequently had sTBI than mTBI. NA with trauma cause pathological CT, intubation, and raised ICP.

Table 1 Studies on HP after TBI from 2000 – 2007
*IGF-1, cortisol, fT4, TSH, PRL, LH, FSH, oestradiol (F), testosterone (M).
ƛ These three studies (see also Table 3) are part of a prognostic follow up over a five year period.
§ No prognostic factors were reported.
¥ The proportion of participants that had mTBI, moTBI, or sTBI was not reported.
ǂ TBI measured by the GCS
CBG = cortisol-binding globulin, CoD = corticotropin deficiency, CPP = cerebral perfusion pressure, CT = computerized tomography, d = days, F = female, FSH = follicular stimulating hormone , fT3 = free triiodothyronine, fT4 = free thyroxin, GCS = Glasgow coma scale, GD = gonadotropin deficiency, GH = growth hormone, GHD = growth hormone deficiency, GHRH-arg = growth hormone releasing hormone and arginine test, GHRH/GHRP-6 = growth hormone releasing hormone and growth hormone releasing peptide 6, GnRH = Gonadotropin releasing hormone, h = hours, HPRL = hyperprolactinemia, ICP = intracranial pressure, IGF-1 = insulin like growth factor 1, IGFBP-3 = insulin like growth factor 1 binding protein 3, ITT = insulin tolerance test, LH = luteinising hormone, M = male, m = months, mTBI = mild traumatic brain injury, moTBI = moderate traumatic brain injury, NA = not associated, PRL = prolactin, SBT = screening blood tests, sGHD = severe growth hormone deficiency, SST = Short synacthen test, sTBI = severe traumatic brain injury, TBI = traumatic brain injury, TRH = thyrotropin releasing hormone, TSH = thyroid stimulation hormone, y = years.
(Aimaretti et al., 2004; Aimaretti et al., 2005; Bondanelli et al., 2004; Kelly et al., 2000; Klose et al., 2007a; Klose et al., 2007b; Tanriverdi et al., 2006).

Author (year)	Sample	Brain injury	Pituitary evaluation	HP	Affected axes	Predictive factors for HP
Bavisetty (2008)	n = 70 57M, 13F	mTBI moTBI sTBI ¥	Tested after 3m and 6-9m SBT**, GHRH-arg, SST, GnRH test	3m: 25% 6-9m: 21%	3m: GD (18%), GHD (16%) 6-9m: GHD (16%), GD (11%)	Increased disability and TBI severity on acute CT, especially diffuse brain swelling.
Schneider (2006) & Schneider (2008)	n = 78 52M, 26F	mTBI moTBI sTBI ¥	Tested after 3m and 1y: SBT*, SST, GHRH-arg	3m: 56% 1y: 36%	3m: GD (32%), CoD (20%), HPRL (12%) 1y: GD (20%), GHD (10%), HPRL (14%)	3m: Disability after TBI 1y: DAI NA with TBI severity ǂ.
Tanriverdi (2008) ƛ	n = 30 25M, 5F	mTBI (63%) moTBI (20%) sTBI (17%)	SBT**, fT3, ACTH, GH, SST, GHRH/GHRP-6	30%	GHD (23%), CoD (7%)	— §
Krahulik (2009)	Acute phase: n = 186 After 1y: n = 89 69M, 23F	mTBI moTBI sTBI ¥	Acute phase: cortisol, ACTH, TSH, fT4 3 – 6m and 1y: cortisol, TSH, fT4, IGF-1, SHBG, testosterone (M), oestradiol (F), LH, FSH, PRL, SST, GHRH–arg or GST	Acute phase: 53% 1y: 21%	Acute phase: GHD (19%), GD (17%) 1y: GHD (14%), GD (6%)	Diffuse brain swelling and BSF.
Tanriverdi (2013) ƛ	n = 25 20M, 5F	mTBI (64%) moTBI (20%) sTBI (16%)	SBT**, fT3, ACTH, GH, SST, GHRH/GHRP-6	32%	GHD (28%), CoD (4%) and GD (4%)	— §
Silva (2015)	n = 166 117M, 29F	mTBI (69%) moTBI/sTBI (31%)	SBT*, SST, GST.	31%	GH (15%), CH (10%)	Post-traumatic seizures, intracranial haemorrhage, and focal cortical contusions.
You (2019)	n = 193 128M, 65F	mTBI (51%) moTBI (25%) sTBI (24%)	SBT*, ITT	17%	CH (13%), GD (4%)	Increased ICP, longer hospitalization and ICU stay, increased TBI severity ǂ

Table 2 Studies on HP after TBI from 2008 – 2020
* IGF-1, fT4, TSH, PRL, LH, FSH, oestradiol (F), testosterone (M).
** IGF-1, cortisol, fT4, TSH, PRL, LH, FSH, oestradiol (F), testosterone (M).
ƛ These three studies are all part of a prognostic follow up over a five year period.
§ No prognostic factors were reported.
¥ The proportion of participants that had mTBI, moTBI, or sTBI was not reported.
ǂ TBI measured by the GCS.
ACTH = adrenocorticotropic hormone, BSF = basal skull fracture, CH = central hypothyroidism, CoD = corticotropin deficiency, CT = computerized tomography, DAI = diffuse axonal injury, F = female, FSH = follicular stimulating hormone, fT3 = free triiodothyronine, fT4 = free thyroxin, GCS = Glasgow coma scale, GD = gonadotropin deficiency, GH = growth hormone, GHD = growth hormone deficiency, GHRH-arg = growth hormone releasing hormone and arginine test, GHRH/GHRP-6 = growth hormone releasing hormone and growth hormone releasing peptide 6, GnRH = Gonadotropin releasing hormone, GST = glucagon stimulation test, HPRL = hyperprolactinemia, ICP = intracranial pressure, ICU = intensive care unit, IGF-1 = insulin like growth factor 1, ITT = insulin tolerance test, LH = luteinising hormone, M = male, m = months, mTBI = mild traumatic brain injury, moTBI = moderate traumatic brain injury, MVA = motor vehicle accidents, NA = not associated, PRL = prolactin, SBT = screening blood tests, SHBG = sex hormone binding globulin, SST = Short synacthen test, sTBI = severe traumatic brain injury, TBI = traumatic brain injury, TSH = thyroid stimulation hormone, y = years.
(Bavisetty et al., 2008; Krahulik et al., 2010; Schneider et al., 2006b; Schneider et al., 2008; Tanriverdi et al., 2013; Tanriverdi et al., 2008a; You et al., 2019)

Author (year)	Participants	Pituitary evaluation	HP	Most commonly affected axes	Predictive factors for HP
Bondanelli (2004) ¥	n = 16 11M, 5F	SBT*, ACTH, GHRH-arg	38% (n = 6)	GHD 25% (n = 4)	–
Kelestimur (2004)	n = 18 M (11 boxers, 7 controls)	SBT**, GHRH/GHRP-6	Boxers: 45% (5/11)	Only GHD was diagnosed 45% (n = 5)	–
Aimaretti (2005) ¥	n = 33 §	After 3m and 1y: SBT* and 24h urinary free cortisol, GHRH-arg	39% (n = 13)	GHD 33% (n = 11)	–
Tanriverdi (2007)	n = 22 kickboxers 16M, 6F	SBT*, fT3, GST, GHRH/GHRP-6	27% (n = 6)	GHD 23% (n = 5), CoD 9% (n = 2)	IGF-1 was negatively associated with age, duration of sports and number of competitions
Tanriverdi (2008)	N = 61 M boxers	SBT*, ACTH, fT3, GST, GHRH/GHRP-6	18% (n = 11)	GHD 15% (n = 9), CoD 8% (n = 5)	Age, age at retirement and number of competitions were higher in boxers with PD.
Ioachimescu (2014)	n = 20 M veterans	IGF-1, TSH, fT4, cortisol, GST, SST	25% (n = 5)	Only GHD was diagnosed 25% (n = 5)	–
Kelly (2014)	n = 68 M, retired players in American football	SBT**, ACTH, SST, GST	24% (n = 16)	GHD 15% (n = 10), GD 4% (n = 3), GHD + GD 4% (n = 3)	Age, years in NFL, and number of mTBI were similar between players with HP and nPF
Silva (2015)	n = 114 76M, 38F	SBT*, SST, GST	29% (n = 33)	GHD 10% (n = 11), GD 10% (n = 11)	
Giuliano (2017)	n = 48 34M, 14F*** Tested after 1y (n = 23) and 5y (n = 25)	SBT**, ACTH, GHRH-arg	Total: 42% (n = 20) 1y: 35% (8/23) 5y: 48% (12/25)	GHD was diagnosed in all patients, 1y 35%, 5y 48%. One patient in each group also had CH.	

Table 3 Studies on HP following mTBI
*IGF-1, fT4, TSH, PRL, LH, FSH, oestradiol (F), testosterone (M).
**IGF-1, cortisol, fT4, TSH, PRL, LH, FSH, oestradiol (F), testosterone (M).
*** Participants had complicated mTBI defined as mTBI with any anatomical changes on initial CT or MRI, acute pituitary hormone changes, need for hospitalization for > 24 h, need for ICU monitoring and/or any neurosurgical intervention
§ Information regarding the proportion of male and female participants was not available
¥ The study included all TBI (mTBI, moTBI, sTBI), mTBI statistics were calculated from the study data.
ACTH = adrenocorticotropic hormone, CH = central hypothyroidism, CoD = corticotropin deficiency, F = female, FSH = follicular stimulating hormone, fT3 = free triiodothyronine, fT4 = free thyroxin, GD = gonadotropin deficiency, GHD = growth hormone deficiency, GHRH-arg = growth hormone releasing hormone and arginine test, GHRH/GHRP-6 = growth hormone releasing hormone and growth hormone releasing peptide 6, GST = glucagon stimulation test, h = hours, HP = hypopituitarism, IGF-1 = insulin like growth factor 1, LH = luteinising hormone, M = male, m = months, mTBI = mild traumatic brain injury, NFL = National Football League, nPF = normal pituitary function, nr = number, PD = pituitary dysfunction, PRL = prolactin, SBT = screening blood tests, SST = short synacthen test, TSH = thyroid stimulation hormone, y = years.
(Aimaretti et al., 2005; Bondanelli et al., 2004; Giuliano et al., 2017; Ioachimescu et al., 2015; Kelestimur et al., 2004; Kelly et al., 2014; Silva et al., 2015; Tanriverdi et al., 2008b)

1.3.3 Pathophysiology of traumatic hypopituitarism

The pathophysiology of HP following TBI appears to result from primary or secondary injury to the pituitary gland or hypothalamus. The same pathophysiological mechanism may cause HPRL after TBI although studies are lacking. Primary pituitary injury occurs when direct mechanical trauma to the pituitary stalk or gland occurs while secondary injury is caused by vascular injury, neuroinflammation, autoimmune reaction, or uncontrolled release of neurotransmitters as a result of TBI (Figure 9) (Dubourg and Messerer, 2011; Dusick et al., 2012; Gasco et al., 2021; Khan et al., 2018; Sav et al., 2019).

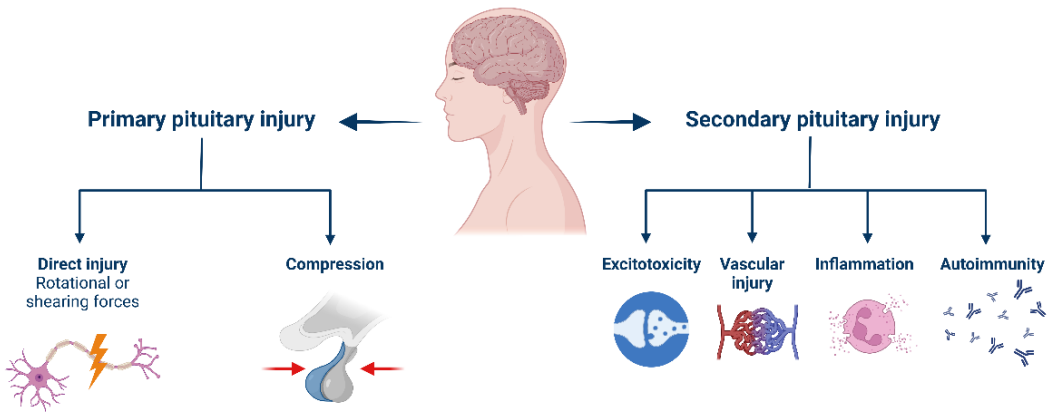

Figure 9 Pathophysiology of hypopituitarism following traumatic brain injury
Created with BioRender.com

1.3.3.1 Vascular injury

The long hypophyseal portal vessels (Figure 10) supply the lateral aspects of the pituitary gland (Adams et al., 1965; Sav et al., 2019; Xuereb et al., 1954a; Xuereb et al., 1954b). These vessels originate within the subarachnoid space and are especially vulnerable to mechanical injury (Dusick et al., 2012; Kelly et al., 2000; Xuereb et al., 1954a). The short hypophyseal portal vessels supply the medial portion of the anterior pituitary gland and the posterior pituitary gland. As these vessels originate below the sellar diaphragm they are less vulnerable to injury (Adams et al., 1965; Dusick et al., 2012; Kelly et al., 2000; Xuereb et al., 1954a).

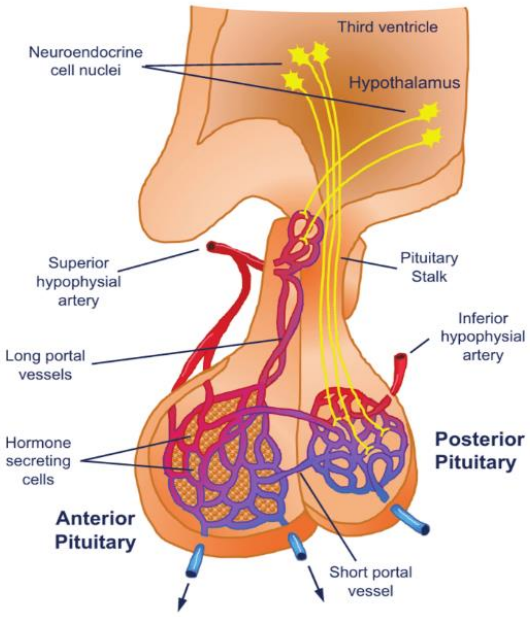

Figure 10 Vascularization of the pituitary gland. Source: www.ebrary.net *„The hypothalamo-pituitary complex: Vascular connections and DA levels in portal blood."*

Thus, somatotroph cells may be more vulnerable to vascular injury as they are located laterally within the anterior pituitary gland and the corticotrope and thyrotrope cells may be less susceptible to injury as they are located within the medial portion (Figure 11) (Adams et al., 1965; Ben-Shlomo and Melmed, 2022; Dusick et al., 2012; Gasco et al., 2021; Kelly et al., 2000).

1.3.3.2 Excitotoxicity

Similar to the pathophysiology of mTBI (Figure 2), release of uncontrolled excitatory neurotransmitters following TBI may contribute to HP by disrupting intra- and extracellular electrolyte homeostasis (Gasco et al., 2021).

1.3.3.3 Neuroinflammation

The neuroinflammatory mechanisms that occur following mTBI likely affect the entire brain parenchyma, including the pituitary gland possibly resulting in HP (Gasco et al., 2021; Meier et al., 2020; Nitta et al., 2019; Sun et al., 2019; Visser et al., 2022).

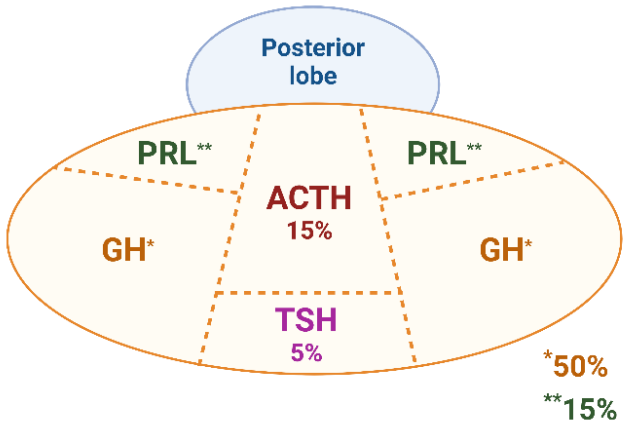

Figure 11 Distribution and percentage of anterior pituitary hormone cell subtypes.
Gonadotroph cells are scattered throughout the anterior pituitary and consistute ~10% of cells.
ACTH = adrenocorticotropic hormone, GH = growth hormone, PRL = prolactin, TSH = thyroid stimulating hormone.
Based on Figure 3 (Gasco et al., 2021)

1.3.3.4 Autoimmunity

Anti-pituitary and anti-hypothalamus antibodies have been reported in patients following TBI possibly due to an autoimmune reaction to exposed hypothalamic or pituitary antigens or ischemia due to vascular injury. Thus, it is unclear whether anti-pituitary and anti-hypothalamus antibodies cause HP following TBI or generally indicate that an injury to the pituitary gland or hypothalamus has occurred (Gasco et al., 2021).

1.3.4 Clinical presentation of pituitary dysfunction

Clinical symptoms of PD depend on which axes are affected, speed of onset, and the severity of PD (Table 4) (Kim, 2015; Schneider et al., 2007a).

1.3.5 Signs and symptoms of pituitary dysfunction

Hypopituitarism

Symptoms of GHD (Table 4) can be subtle and may overlap with symptoms of mTBI (Figure 3). Furthermore, patients with GHD have increased risk of cardiovascular disease (CVD) and cerebrovascular morbidity and mortality due to metabolic alterations that occur with GHD, such as increased abdominal adiposity, insulin resistance, and unfavourable lipid profile. As bone metabolism is also affected by GHD, risk of osteopenia and osteoporosis is increased (Table 4) (Carroll et al., 1998; Rosén and Bengtsson, 1990; Rosén et al., 1995; Verhelst et al., 2011).

Acute corticotropin deficiency (CoD) has severe and possibly life-threatening symptoms due to risk of adrenal crisis making prompt diagnosis essential (Puar et al., 2016). Although symptoms of chronic CoD can be insidious (Table 4), adrenal crisis can also occur due to chronic CoD (Hahner et al., 2010; Smans et al., 2016). If left untreated, CoD results in death in 2 – 4 years (Dunlop, 1963).

GHD	CoD	CH	GD	HPRL
Symptoms: Decreased strength, stamina and exercise capacity, fatigue, impaired psychological well-being, depressed mood, emotional lability, anxiety, decreased QOL, and social functioning. **Clinical signs:** Decreased muscle mass, thin and dry skin, cool peripheries; poor venous access, increased abdominal adiposity, premature atherosclerosis, osteoporosis, and dyslipidaemia.	**Symptoms:** Acute: abdominal pain, fever, fatigue, weakness, dizziness, nausea, vomiting. Chronic: fatigue, lack of stamina, loss of energy, reduced muscle strength, myalgia, arthralgia, and increased irritability. **Clinical signs:** Adrenal crisis (mostly in acute CoD: severe hypotension, hypovolemic shock, abdominal pain), pallor, hyponatremia and normokalaemia, hypoglycaemia, anorexia, weight loss, and postural hypotension.	**Symptoms:** Tiredness, cold intolerance, constipation, hair loss, dry skin, myalgia and arthralgia, slow mental processes such as difficulties with concentration and memory impairment **Clinical signs:** Weight gain, bradycardia, hypotension, and dyslipidaemia.	**Symptoms:** Women: oligo- or amenorrhea (pre-menopausal), infertility, loss of libido, dyspareunia, depressed mood, loss of interest, and poor concentration. Men: loss of libido, impaired sexual function, fatigue, depressed mood, poor concentration, and memory. **Clinical signs:** Osteoporosis Women: premature CVD, and hyperlipidaemia. Men: anaemia, decreased muscle mass, increased body fat, and loss of facial, scrotal, and truncal hair.	Women: oligo- or amenorrhea, galactorrhoea, and infertility. Men: hypogonadism, loss of libido, erectile dysfunction, and infertility. **Clinical signs:** Men: Osteopenia and gynecomastia.

Table 4 Clinical symptoms and signs of PD
CH = central hypothyroidism, CoD = corticotropin deficiency, CVD = cardiovascular disease, GD = gonadotropin deficiency, GHD = growth hormone deficiency, HPRL = hyperprolactinemia, PD = pituitary dysfunction, QOL = quality of life.
(Arlt and Allolio, 2003; Carroll et al., 1998; Martin-Grace et al., 2020; Schneider et al., 2007a; van Aken and Lamberts, 2005)

Symptoms of central hypothyroidism (CH) can be subtle (Table 4) (Schneider et al., 2007a). Untreated CH causes metabolic alterations such as increased body mass index (BMI) and dyslipidaemia possibly increasing the risk of CVD (Biondi et al., 2019; Klose et al., 2013).

Clinical symptoms of GD depend on gender and age (Table 4) (Schneider et al., 2006a). Changes in lipid profile and increased risk of CVD has also been reported in women with functional hypothalamic amenorrhea (Rickenlund et al., 2005).

Hyperprolactinemia
As elevated levels of PRL suppress gonadotropin release, symptoms of HPRL overlap with symptoms of GD (Table 4). Thus, HPRL is often detected sooner in women than in men due to oligo- or amenorrhoea prompting them to seek medical attention (Barber et al., 2021; Koike et al., 1991).

1.3.5.1 Psychological and neuropsychological symptoms of hypopituitarism

Psychological and neuropsychological symptoms of mTBI have previously been attributed to the brain injury itself. However, these symptoms may also result from HP following mTBI (Slagboom et al., 2021a, 2021b).

Untreated GHD can lead to decreased QOL and psychological well-being, and neuropsychological symptoms such as decreased memory and attention (Deijen et al., 1996; Rosén et al., 1994). Women with GHD following pituitary surgery have also been reported to have a higher incidence of mental disorders and worse neuropsychological outcome compared to controls (Bülow et al., 2002). However, these symptoms may improve with hormone replacement therapy (Deijen et al., 1998; High et al., 2010; Oertel et al., 2004; Rosén et al., 1995), even when GHD occurs following TBI (Szarka et al., 2021).

Other pituitary hormone deficiencies can also affect psychological and neuropsychological outcome. Patients treated for primary adrenal insufficiency or CoD appear to have an increased rate of depressive disorders (Thomsen et al., 2006), impaired attention, and prolonged reaction time compared to controls (Blacha et al., 2021). Increased symptoms of anxiety and depression, decreased QOL, and impaired verbal memory have been reported in patients with untreated primary hypothyroidism although evidence is lacking with regards to CH (Correia et al., 2009; Gulseren et al., 2006; Miller et al., 2006, 2007). Working memory and attention appear to be affected by HPRL in patients with prolactinoma regardless of tumour size (Bala et al., 2022; Bala et al., 2016). Reducing PRL levels with medical treatment may improve neuropsychological function (Montalvo et al., 2018).

1.3.5.2 Hypopituitarism – Increased morbidity and mortality

Increased morbidity and mortality has consistently been reported in patients with HP compared to normal population, especially in women (Bülow et al., 1997; Jasim et al., 2017; Nielsen et al., 2007; Olsson et al., 2016; Olsson et al., 2015; Rosén and Bengtsson, 1990; Tomlinson et al., 2001).

The association between increased mortality and HP may be related to the higher prevalence of metabolic syndrome in patients with HP including higher BMI, dyslipidaemia, and increased insulin resistance (Abe et al., 2020), especially in female patients (Khang et al., 2016), which increases the risk of CVD and cerebrovascular disease (Bülow et al., 1997; Jasim et al., 2017; Olsson et al., 2016; Rosén and Bengtsson, 1990; Tomlinson et al., 2001). Although these metabolic alterations have mainly been attributed to untreated GHD, CH and GD, overly treated CoD can also affect metabolism (Abe et al., 2020; Klose et al., 2013; Rickenlund et al., 2005; Rosén et al., 1995; Zueger et al., 2012). In fact, untreated GD has been independently associated with increased mortality, especially in women (Tomlinson et al., 2001).

1.3.6 Diagnosis of pituitary dysfunction

Considering PD in patients with persistent symptoms following mTBI is important as PD represents a possibly reversible cause for symptoms following mTBI (Figure 3 and Table 4) (Szarka et al., 2021).

1.3.6.1 Diagnosis of hypopituitarism

The diagnostic methods used for HP diagnosis vary depending on which pituitary hormonal axis is suspected to be insufficient.

Due to the pulsatile nature of GH release measurements of serum GH (s-GH) levels have no diagnostic value when GHD is suspected (Steyn et al., 2016; Surya et al., 2006). Measurements of serum IGF-1 (s-IGF-1) have been proposed as a screening tool for GHD as it may reflect GH levels although s-IGF-1 within normal reference value (RV) does not exclude GHD (Lithgow et al., 2018). Definite diagnosis of GHD involves stimulation tests such as the GHRH and arginine (GHRH-arg) test, and the insulin tolerance test (ITT) (Berg et al., 2010; Biller et al., 2002; Popovic et al., 2003). The ITT has potential risks, some contraindications, and can be unpleasant, thus, the GHRH-arg test is a safe alternative diagnostic method (Biller et al., 2002). Although both the ITT and GHRH-arg tests can diagnose GHD due to pituitary disease, only the ITT can diagnose GHD due to hypothalamic dysfunction (Darzy et al., 2003; Glynn and Agha, 2012; Schneider et al., 2006a).

Measurements of morning serum cortisol (s-cortisol) at 9 A.M. can be used to screen for CoD with s-cortisol levels below 100nmol/L indicating possible hypothalamic-pituitary-adrenal axis insufficiency (Le Roux et al., 2002; Perton et al., 2017). Plasma ACTH should also be measured to differentiate between primary adrenal insufficiency (high levels of ACTH) and CoD (low levels of ACTH). Stimulation tests, such as the short Synacthen test (SST) or the ITT, are needed to establish the diagnosis of CoD (Bancos et al., 2015; Dorin et al., 2003; Wallace et al., 2009). The ITT is considered the gold standard for hypothalamic-

pituitary-adrenal axis evaluation as it also assesses hypothalamic function (Ammari et al., 1996; Bancos et al., 2015; Wallace et al., 2009). However, the SST test is often used as an alternative by measuring baseline cortisol levels before and 30 and 60 minutes after administrating either a low dose (1 µg) or, more commonly, a high dose (250 µg) of synthetic ACTH (Synacthen) (Table 6) (Dorin et al., 2003; Mayenknecht et al., 1998; Wallace et al., 2009).

In the relevant clinical setting, the absence of elevated serum TSH (s-TSH) when serum free thyroxine (s-fT_4) levels are low or within the lower quartile of the normal RV may indicate CH (Feldt-Rasmussen et al., 2021). Although a thyrotropin-releasing hormone stimulation test can be used to differentiate between pituitary or hypothalamic origin of CH, its routine use does not have any advantages compared to basal s-TSH and s-fT_4 measurements (Hartoft-Nielsen et al., 2004).

Women with GD usually have decreased levels of serum oestrogen (s-oestrogen) and serum progesterone (s-progesterone) with inappropriately low or normal levels of serum LH (s-LH) and serum FSH (s-FSH) (Rothman and Wierman, 2008). In men, morning serum total testosterone and sex hormone binding globulin should be measured (Fraietta et al., 2013). A gonadotropin-releasing hormone stimulation test can be performed although it adds little diagnostic value to baseline hormonal measurements and does not reliably differentiate between pituitary and hypothalamic defects (Rothman and Wierman, 2008; Silveira and Latronico, 2013).

1.3.6.2 Screening for hypopituitarism after mild traumatic brain injury

There is no widely accepted consensus regarding screening for HP following mTBI although a few guidelines have been published. Screening for HP has been suggested following complicated mTBI (hospitalization for >24 hours, intensive care monitoring or neurosurgical intervention is required, anatomical changes are visible on computerized tomography imaging or MRI) (Figure 12), if admission is required for >48 hours, or if symptoms of mTBI are persistent (Glynn and Agha, 2019; Tan et al., 2017; Tanriverdi et al., 2015; Tanriverdi et al., 2010).

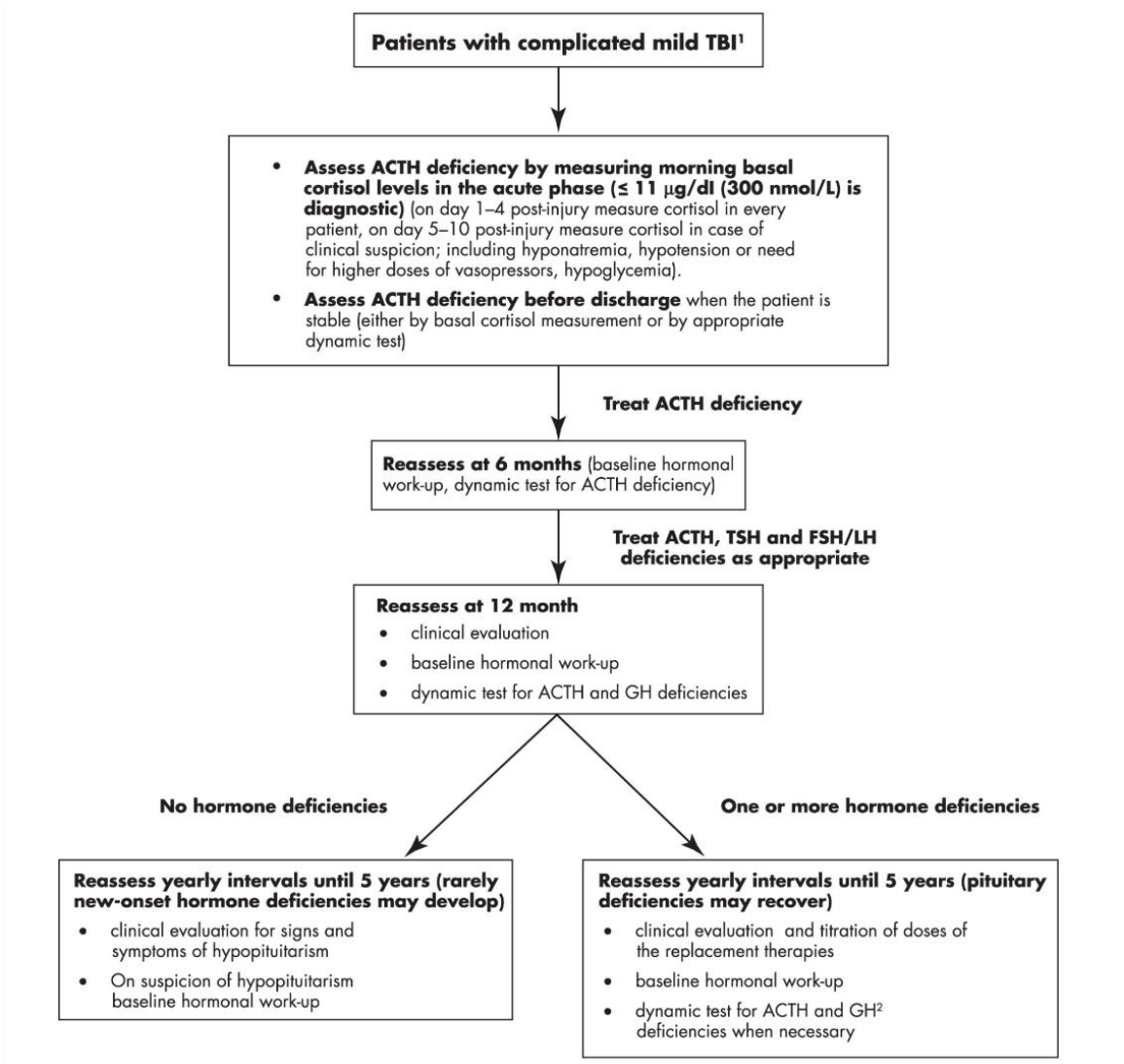

Figure 12 Suggested screening strategy for anterior pituitary function after complicated mTBI.
The screening recommendations after 12 months are not strong enough and need further confirmation.
[1]All the mTBI patients who will be screened have to fulfill the criteria for complicated mTBI
[2]Dynamic tests for GHD need to be done with an "intent to treat" and according to clinical context throughout the follow-up period.
ACTH = adrenocorticotropic hormone, AHA = anti-hypothalamic antibodies, APA = anti-pituitary antibodies, CT = computerized tomography, DI = diabetes insipidus, GHD = growth hormone deficiency, ICU = intensive care unit, MRI = magnetic resonance imaging, mTBI = mild traumatic brain injury.
Tanriverdi F et al. Pituitary dysfunction after traumatic brain injury: a clinical and pathophysiological approach. *Endocrine Reviews*, Volume 36, Issue 3, 1 June 2015, Pages 305–342, https://doi.org/10.1210/er.2014-1065, by permission of Oxford University Press.

1.3.6.3 Diagnosis of hyperprolactinemia

Elevated levels of serum PRL (s-PRL) confirm the diagnosis of HPRL. Suppression tests are available although they have limited diagnostic value (Melmed et al., 2011).

Several aetiologies of HPRL need to be considered in the evaluation of HPRL such as macroprolactinemia, medications, prolactinoma, and pituitary stalk or hypothalamic injury following mTBI or TBI of all severity (Melmed et al., 2011; Sav et al., 2019).

1.3.7 Treatment of pituitary dysfunction

Optimal treatment of HP is important as HP is associated with increased morbidity and mortality (Bülow et al., 1997; Jasim et al., 2017; Olsson et al., 2016; Olsson et al., 2015; Rosén and Bengtsson, 1990; Tomlinson et al., 2001).

Treatment of GHD with GH replacement therapy improves body composition, bone health, decreases the risk of CVD (Fleseriu et al., 2016; Molitch et al., 2011; Reed et al., 2013; Rosén et al., 1995), and may improve neuropsychological and psychological functioning, and QOL (Deijen et al., 1998; Oertel et al., 2004; Rosén et al., 1995). Improvements in processing speed and memory capacities, decreased severity of depression, and improvements in QOL have also been reported in patients with GHD following TBI after 6–12 months of hormone replacement therapy (Szarka et al., 2021).

Hydrocortisone treatment should be initiated immediately after the diagnosis of CoD has been confirmed with increased doses during times of physical and mental stress to prevent adrenal crisis (Ceccato and Scaroni, 2019; Higham et al., 2016).

Once CH is confirmed, levothyroxine treatment should be started. Hormone replacement therapy may reduce CVD risk by reversing the metabolic effects of CH (Filipsson Nyström et al., 2012; Klose et al., 2013).

The increased mortality reported in patients with untreated GD is reversible with hormone replacement therapy (Tomlinson et al., 2001). Combined treatment with oestrogen-progestogen preparations is advised in premenopausal women with GD. Unopposed oestrogens can be used in women who have undergone hysterectomy (Fleseriu et al., 2016). Testosterone replacement therapy is also beneficial in men with GD (Alexandraki and Grossman, 2019; Fleseriu et al., 2016).

Treatment of HPRL using dopamine agonists, such as cabergoline, is indicated in symptomatic patients with microadenomas and without a visible tumour on MRI (Melmed et al., 2011; Serri et al., 2003; Wang et al., 2012). Treatment reverses symptoms of HPRL such as oligo- or amenorrhoea, infertility, and bone loss in women as well as bothersome galactorrhoea.

2 Hypothesis

PD, including both HP and HPRL, can occur in female athletes with a prior history of mTBI in sport.

PD following mTBI can cause physical, psychological, and neuropsychological symptoms resulting in decreased QOL in female athletes.

3 Aims

The aim of this thesis was to:

- investigate whether female athletes needing further endocrinological evaluation for possible PD following mTBI can be identified
- find the prevalence of PD following mTBI in female athletes
- explore possible predictive factors for PD following mTBI in female athletes
- evaluate psychological and neuropsychological symptoms as well as QOL in female athletes diagnosed with PD following mTBI
- evaluate possible differences in psychological and neuropsychological symptoms and QOL in female athletes diagnosed with PD following mTBI compared to female athletes who had normal pituitary function after mTBI
- explore psychological or neuropsychological factors that may have predictive value with regards to PD following mTBI in female athletes

4 Materials and Methods

4.1 Study design

This thesis focuses on the third and last part of an extensive study on female athletes after mTBI conducted in three parts starting in the year 2018 and proceeding through the year 2020:

- Part I focused on mTBI history and mental health of female athletes after mTBI and involved an online questionnaire regarding mTBI history, mental health scales, and QOL. The questionnaire was distributed through social media including a Facebook page for the study and sports-related Facebook pages (snowball sampling) and was open from the end of January 2018 to the end of April 2018 (Jónsdóttir et al., 2021; Kristjánsdóttir et al., 2020).

- Part II involved a detailed interview where symptoms of mTBI and sleep disturbances were evaluated. Neuropsychological tests were also performed to evaluate neuropsychological symptoms after mTBI. The interviews in part II were performed over a one year period from 2018 to 2019 (Kristensen, 2022).

- Part III of the study, which is the focus of this thesis, involved a medical interview, physical and neurological examination, screening blood tests (SBT) and further endocrinological evaluation for possible PD following mTBI in female athletes. The medical interview, SBT, and further endocrinological evaluation were performed from 2018 – 2020 (Eggertsdóttir Claessen et al., 2023b; Eggertsdóttir Claessen et al., 2024b). Psychological and neuropsychological symptoms of female athletes with PD following mTBI were also explored by comparing results of the mental health scales and the neuropsychological tests in part I and part II of the study between women with PD and normal pituitary function (nPF) (Eggertsdóttir Claessen et al., 2024a).

4.1.1 Study population in part I and II

The population included female athletes aged 18 to 45 years, currently active in or retired from contact sports including soccer, team handball, basketball, ice hockey, and martial arts in Iceland (Figure 13).

- In part I of the study, 508 female athletes participated by responding to the online questionnaire.
- Of these 508 women, 308 (60.6%) reported one or more mTBI after reading a definition of mTBI and were invited for further participation in part II of the study.
- Of the 308 women invited to participate in part II of the study, 166 (53.9%) women accepted.

4.1.2 Study population in this thesis (part III of the study)

All 166 of the female athletes participating in part II of the study were invited for further participation in part III of the study, which is the focus of the current thesis, with 151 (90.9%, n = 166) accepting (Figure 13).

4.1.2.1 Medical interview and physical examination

A medical interview, including a physical and a neurological examination was performed for all 151 participants who had accepted further participation in part III of the study. Participants were interviewed and examined by the same medical doctor, Lára Ósk Eggertsdóttir Claessen.

4.1.2.2 Hormonal screening blood tests

Of the 151 women, 133 (88.1%) accepted further participation in hormonal SBT, nine were pregnant, and nine were lost to follow up (Figure 13). Women who had SBT outside reference value (O-RV) for each hormonal measurement in two or three repeated blood tests were referred to an endocrinologist for a detailed endocrinological evaluation (Figure 13).

4.1.2.3 Endocrinological evaluation

Women who had repeated SBT O-RV (n = 88) were referred for a medical interview and physical examination by an endocrinologist, Helga Ágústa Sigurjónsdóttir (HÁS). Two of the 88 participants did not attend the interview and were excluded from the study. One was pregnant and one was lost to follow up despite repeated attempts to contact (Figure 13). Thus, of the 131 participating in SBT, 86 were interviewed further by an endocrinologist (HÁS). Following the interview with the endocrinologist, further endocrinological tests were requested when further evaluation was needed. The women were followed by the same endocrinologist (HÁS).

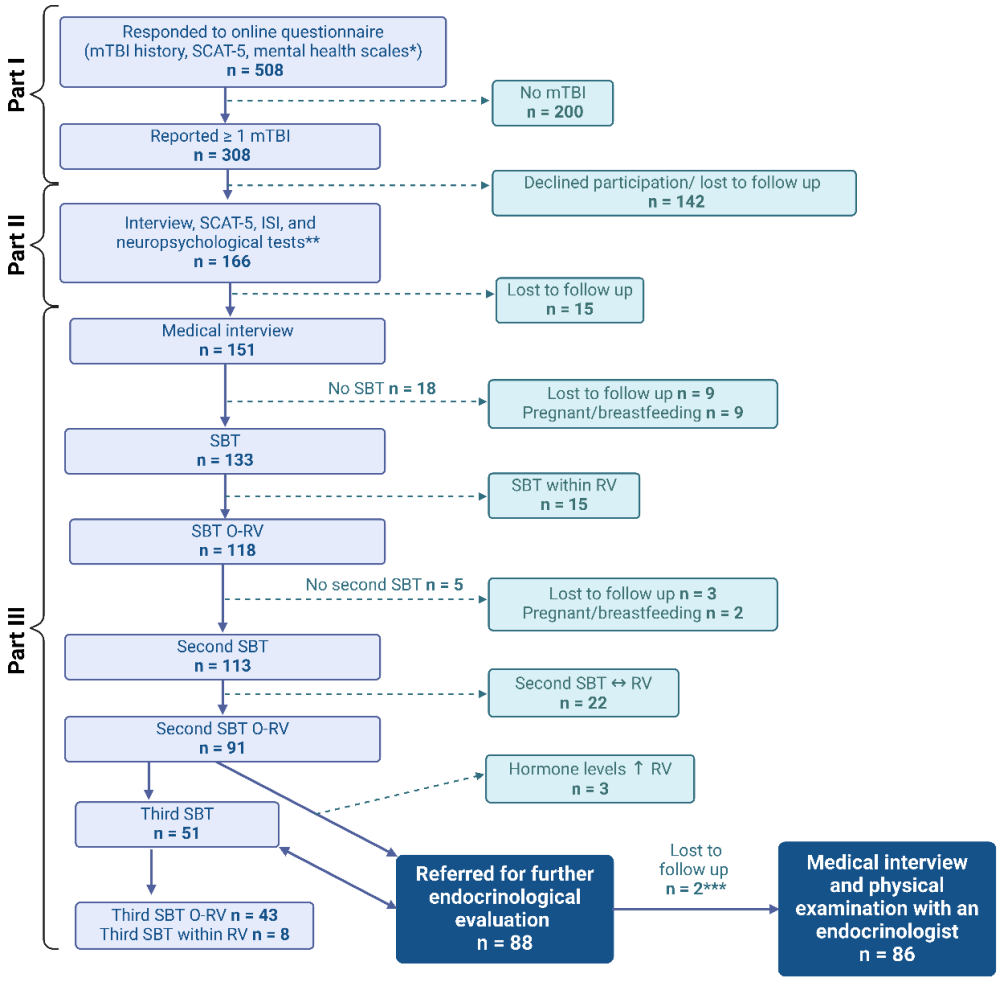

Figure 13 Overview of study design and study population

* The mental health scales were Patient Health Questionnaire-9 (PHQ-9), General Anxiety Disorder-7 (GAD-7), Perceived Stress Scale 4 (PSS4), and the Quality of Life Scale.

** Current mTBI symptoms were evaluated using The Sport Concussion Assessment Tool 5 (SCAT-5). Insomnia was evaluated using the Insomnia Severity Index (ISI). Neuropsychological tests included the Sustained Attention to Response Test (SART), the Stroop Colour-Word test (SCWT), Trail Making Test (TMT), and subtests of The Wechsler Abbreviated Scale of Intelligence (WASI) and the Wechsler Adult Intelligence Scale (WAIS).

*** As two of the 88 women who needed further endocrinological evaluation did not attend the medical interview with the endocrinologist they were excluded from the study. Thus, 131 women instead of 133 had SBT and 86 women instead of 88 had a detailed endocrinological evaluation.

↔ = within RV, ↑ = above RV, mTBI = mild traumatic brain injury, O-RV = outside reference value, RV = reference value, SBT = screening blood test.

(Eggertsdóttir Claessen et al., 2023b). Reprinted from NeuroRehabilitation, with permission from IOS Press. The publication is available at IOS Press through http://dx.doi.org/[10.3233/nre-220194].

4.1.2.4 Psychological and neuropsychological tests

Prior to the medical interview in part III, the mental health scales from part I of the study were repeated to reflect mental health at the time of the SBT. This was done as, in some cases, months passed between the online questionnaire and the SBT. As the neuropsychological tests were complex and time consuming to perform, they were not repeated even though, in some cases, months also passed between the neuropsychological tests and the SBT. Of the 131 women who participated in the SBT, 123 repeated the mental health scales and eight did not (one with PD, seven with nPF). Thus, these eight women were excluded from the statistical analysis of the mental health scales (Figure 14). All the 131 female athletes participated in the neuropsychological tests in part II of the study (Figure 13).

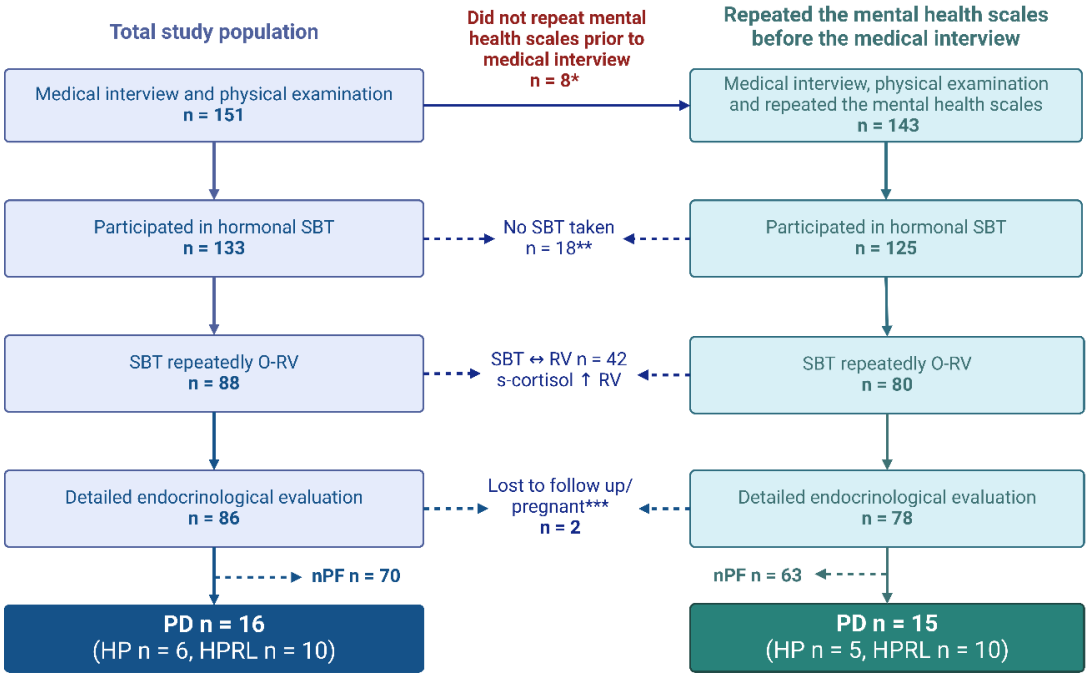

Figure 14 Overview of repeated mental health scales in paper III.
* Of the eight women who did not repeat the mental health questionnaires before the medical interview, one was diagnosed with PD and seven had nPF following detailed endocrinological evaluation.
**Pregnant n = 9, lost to follow up n = 9
***Two women who were referred for further workup for possible HP did not attend the endocrinological interview and were excluded from the study. Thus, the final number of women who participated in SBT was 131, the number of women who repeated the mental health questionnaires was 123 and the number of women referred for further workup was 86.
HP = hypopituitarism, HPRL = hyperprolactinemia, nPF = normal pituitary function, O-RV = outside reference value, PD = pituitary dysfunction, RV = reference value, SBT = screening blood tests.
Based on Figure 1 from paper III (Eggertsdóttir Claessen et al., 2024a). Submitted for publication.

4.2 Measurements

4.2.1 Medical interview and physical examination

Prior to the medical interview, participants answered a questionnaire regarding previous medical history, medications, HoC use, menstruation, and the timing of the first and most recent mTBI. A physical examination was performed, including a neurological examination of the motor and sensory systems, and cranial nerves, including eye movements. Blood pressure, heart rate, oxygen saturation, height, and weight were measured, BMI was calculated, and an electrocardiogram was performed (Eggertsdóttir Claessen et al., 2023b).

4.2.2 Hormonal analysis in screening blood tests for hypopituitarism

Hormonal SBT were taken at 8 A.M. including s-IGF-1, s-cortisol, s-TSH, s-fT4, s-FSH, s-LH, s-oestrogen, s-progesterone, and s-PRL (Table 5). Participants were in different phases of the menstrual cycle when the SBT were taken. All SBT results were reviewed by the same endocrinologist (HÁS) and were defined as abnormal when results were O-RV for each hormonal measurement (Table 5). As s-IGF-1 within RV does not exclude GHD, s-IGF-1 was considered abnormal if measurements were below median RV (Table 5) and clinical symptoms of GHD were present (Table 4) (Lithgow et al., 2018). If the first SBT was O-RV for any of the hormonal measurements, the SBT were repeated to re-evaluate those particular hormonal measurements for a second and sometimes the third time (Figure 13).

Analyte	Assay	Manufacturer	Instrument	CV%			Reportable range	Reference value	Specimen	
				Low cont	Med cont	High cont			Type	Storage
IGF-1	IGF-I	Siemens	Immulite 2000	6.3	3.1	2.5	15 – 1,000 µg/L	Manufacturer's age dependant reference range *	Serum	+2 – 8°C or –20°C
Cortisol	Cortisol II	Roche	Elecsys	5.4	1.5	1.6	1.5 – 1,750 nmol/L	133 – 537 nmol/L**, 68.2 – 327 nmol/L***	Serum	+2 – 8°C
TSH	TSH	Roche	Elecsys	11.1	1.3	2.2	0.005 – 100 mIU/L	0.270 – 4.20 mIU/L	Serum	+2 – 8°C
fT4	FT4 III	Roche	Elecsys	4.3	1.5	2.6	0.5 – 100 pmol/L	12 – 22 pmol/L	Serum	+2 – 8°C
FSH	FSH	Roche	Elecsys	2.6	2.5	-	0.100 – 200 IU/L	FP 3.5 – 12.5 IU/L; OP 4.7 – 21.5 IU/L; LP 1.7 – 7.7 IU/L	Serum	+2 – 8°C
LH	LH	Roche	Elecsys	1.8	0.8	-	0.100 – 200 IU/L	FP 2.4 – 12.6 IU/L; OP 14.0 – 95.6 IU/L; LP1.0 – 11.4 IU/L	Serum	+2 – 8°C
Oestradiol	Oestradiol III	Roche	Elecsys	6.7	1.6	1.9	18.4 – 11,010 pmol/L	FP 45.4 – 854 pmol/L; OP 151 – 1,461 pmol/L; LP 81.9 –1,251 pmol/L	Serum	+2 – 8°C
Progesterone	Progesterone III	Roche	Elecsys	11.9	3.7	2.4	0.159 – 191 nmol/L	FP 0.181 – 2.84 nmol/L; OP 0.385 – 38.1 nmol/L; LP 5.82 – 75.9 nmol/L	Serum	+2 – 8°C
Prolactin	Prolactin II	Roche	Elecsys	1.5	3.0	2.4	0.0470 – 470 µg/L	4.79 – 23.3 µg/L Ψ	Serum	+2 – 8°C

Table 5 Analytical methods of serum hormonal measurements

* ("Immulite 2000 IGF-1," 2018)

**morning measurements (6 – 10 A.M.)

***afternoon measurements (4 – 8 P.M.)

Ψ Female (not pregnant).

CV= coefficient of variation, FP = follicular phase, FSH = follicle stimulating hormone, fT4 = free thyroxine, High cont = high control, IGF-1 = insulin-like growth factor 1, LH = luteinising hormone, Low cont = low control, LP = luteal phase, Med cont = median control, OP = ovulation phase, PMP = post-menopausal phase, TSH = thyroid-stimulating hormone.

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4.2.3 Endocrinological evaluation and endocrinological tests

In the medical interview with the endocrinologist (HÁS), information regarding mTBI history, previous medical history, medications, and clinical symptoms of mTBI or PD was gathered again without comparing with the first medical interview and physical examination. Height, weight, blood pressure, and heart rate were measured.

Women with s-IGF-1 below median RV in SBT (Table 5) and symptoms of GHD (Table 4) were evaluated further for possible GHD with a GHRH-arg test. If s-IGF-1 was below median RV without any symptoms of GHD, further endocrinological evaluation was not performed. The GHRH-arg test was performed by administering 1 µg/kg of GHRH (max 100 µg) at 0 minutes and 0.5 g/kg (max 30 g) of arginine from minute 0 to minute 30 by an infusion. Blood samples were drawn for s-GH analysis (Table 6) at − 15 minutes, 0 minutes, +30 minutes, +45 minutes, +60 minutes and +90 minutes. GHD was defined as a peak s-GH levels ≤ 11.0 µg/L, ≤ 8.0 µg/L, and ≤ 4.0 µg/L for BMI < 25 kg/m^2, 25 – 30 kg/m^2 and BMI ≥ 30 kg/m^{2,} respectively (Ho, 2007). One woman had an ITT due to practical reasons and strong clinical symptoms indicating possible GHD. It was performed by administering 0.10 – 0.20 U/kg soluble insulin intravenously (Actrapid, Novo Nordisk). The dosage depended on pre-test blood glucose and weight according to clinical practice. Hypoglycaemia was defined as blood glucose < 2.1 mmol/L. Blood was collected for the measurement of serum glucose, s-GH, s-cortisol and plasma ACTH at − 10 minutes, 0 minutes, +10 minutes, +20 minutes, +30 minutes, +40 minutes, +60 minutes, +90 minutes and +120 minutes. GHD was defined as a peak value of s-GH < 3 µg/L (Ho, 2007).

If s-cortisol was < 350 nmol/L (Perton et al., 2017), plasma ACTH was measured (Table 6), and a high dose short Synachten test was performed. The test was performed between 8 – 10 A.M. by intramuscular injection of 250 µg Synachten (Alphasigma). Blood samples for s-cortisol and plasma ACTH were collected at baseline before the Synacthen injection, at +30 minutes and +60 minutes after (Dorin et al., 2003). A normal response was defined as s-cortisol ≥440 nmol/L after either 30 or 60 minutes (Dorin et al., 2003).

When s-fT4 was below RV and s-TSH levels were low or normal (Table 5), serum anti-thyroid peroxidase antibodies (s-anti-TPO) was measured to exclude autoimmune hypothyroidism (Table 6). If s-anti-TPO was negative CH was suspected and an MRI was requested for further evaluation.

Further endocrinological evaluation for possible GD was not indicated in any of the female athletes as s-FSH, s-LH, s-oestrogen, and s-progesterone were within RV in SBT (Table 5).

When s-PRL levels were above RV a macroprolactin analysis was performed to differentiate between monomeric PRL and macroprolactin. If s-PRL was repeatedly above RV (Table 5) an MRI was performed.

Analyte	Assay name	Manufacturer	Instrument	CV %			Reportable range	Reference value	Specimen	
				Low cont	Med cont	High cont			Type	Storage
ACTH	ACTH	Roche	Elecsys	2.7	0.6	0.7	1.0 – 2,000 ng/L	7.2 – 63.3 ng/L	Plasma	+2 – 8°C
GH	Growth hormone	Siemens	Immulite 2000	6.5	5.5	6.6	0.05 – 40 ng/ml	Females: up to 8 ng/ml	Serum	+2 – 8°C
Anti-TPO	EliA anti–TPO	Thermo Fisher	Phadia™ 250	–	–	–	–	<25 IU/ml = negative, 25 – 35 IU/ml = equivocal, >35 IU/ml = positive	Serum	+2 – 8°C

Table 6 Analytical methods for GH, ACTH, and anti-TPO measurements

ACTH = adrenocorticotropic hormone, anti-TPO = anti-thyroid peroxidase antibodies, CV = coefficient of variation, GH = growth hormone, High cont = high control, Low cont = low control, Med cont = median control.

Based on Table 1 from paper II (Eggertsdóttir Claessen et al., 2024b). Reprinted from Endocrine Connections, with permission from Bioscientifica. The publication is available at through Bioscientifica http://dx.doi.org/[10.1530/ec-23-0363].

4.2.4 Mental health scales

Symptoms of depression were evaluated using The Patient Health Questionnaire 9 (PHQ-9), with symptom severity ranging from mild (5 – 9), moderate (10 – 14), moderately severe (15 – 19) to severe (20 – 27). The psychometric properties of both the English and Icelandic version of the questionnaire, have been reported as good (Kroenke and Spitzer, 2002; Pálsdóttir, 2007). The clinical cut-off for symptoms of depression was defined as a PHQ-9 score of ≥10 (Kroenke et al., 2001).

The General Anxiety Disorder Questionnaire 7 (GAD-7) was used to assess symptoms of anxiety ranging from mild (5 – 9), moderate (10 – 14) and severe (15 – 21) symptoms. The reliability and validity of GAD-7 is good for measuring symptoms of anxiety in the general population (Löwe et al., 2008; Spitzer et al., 2006). The psychometric properties of the Icelandic version are also considered good (Omarsdottir et al.). The clinical cut-off for symptoms of anxiety was defined as a GAD-7 score of ≥10 (Spitzer et al., 2006).

The Perceived Stress Scale 4 (PSS4) was used for the evaluation of stress with scores ranging from 0 – 16, with higher scores indicating increased stress (Cohen et al., 1983). The psychometric properties of the scale are adequate (Cohen et al., 1983) although the psychometric properties of the Icelandic version of the scale are unknown.

The Quality Of Life Scale was used to measure QOL with scores ranging from 16 – 112 (Burckhardt and Anderson, 2003). The scale is a reliable and valid measurement QOL (Burckhardt and Anderson, 2003) and the Icelandic version of the scale also has good psychometric properties (Hrafnsson and Guðmundsson, 2007).

4.2.5 Symptoms of mild traumatic brain injury and sleep disturbances

The Sport Concussion Assessment Tool 5 (SCAT-5) symptom evaluation scale was used to evaluate the total number of mTBI symptoms ranging from 0 – 22 symptoms. The SCAT-5 is a useful sideline evaluation tool for mTBI diagnosis although its role in tracking recovery remains debated as symptoms of mTBI are often unspecific (Echemendia et al., 2017; McCrory et al., 2017). Sleep disturbances were evaluated using the Insomnia Severity Index (ISI). The clinical cut-off for symptoms of insomnia were defined as an ISI score of ≥10 (Morin et al., 2011).

4.2.6 Neuropsychological tests

The neuropsychological tests performed included the Sustained Attention to Response Task (SART) (Robertson et al., 1997), the Stroop Colour- and Word Test (SCWT) (Magnusdottir et al., 2021; Scarpina and Tagini, 2017), the Trail Making Test A and B (TMT) (Bowie and Harvey, 2006; Magnusdottir et al., 2021), and two sub-tests from the Icelandic standardization of the Wechsler Abbreviated Scale of Intelligence (WASI-IS)

(Guðmundsson, 2016), and four from the Wechsler Adult Intelligence Scale-III (WAIS-III) which has not been standardized in Icelandic (Wechsler, 1997).

The SART is a cognitively demanding computerized test evaluating inhibitory performance and impulsivity (Stevenson et al., 2011) as well as sustained attention by measuring the mean SART response time (SARTrt) and the SART error score (SARTes) (Robertson et al., 1997). Participants were presented with a series of single digit numbers on a computer and were asked to respond to each digit with a key press. However, when the digit 3 appears, participants must withhold a key press. Icelandic norms for the general population are not available for this test.

The SCWT has three parts (Stroop I, Stroop II, and Stroop III) measuring cognitive interference which is the ability to inhibit the processing of a well learned stimulus (i.e. reading) in favour of a less familiar reaction (i.e. naming a colour) (Scarpina and Tagini, 2017). During Stroop I, participants are asked to read the names of four colours (red, blue, green, and yellow) displayed in black ink. In Stroop II, participants name the same four colours presented on colour pads rather than in print. In Stroop III, the name of the four colours is printed in one of the other four colours and participants are asked to name the colour that the word is printed in instead of reading the word. The time it took to finish each part was measured and a Stroop interference score was derived according to the formula Stroop III – (Stroop II + Stroop I)/2. Results were compared to Icelandic norms based on age, gender, and education (Magnusdottir et al., 2021).

The TMT has two parts. The TMT A measures visual search and motor speed by having participants connect 25 numbers in numerical order. The TMT B measures cognitive flexibility, divided attention, and working memory by having participants connect 25 numbers and letters in numerical and alphabetical order alternating between the numbers and the letters. The total time to completion is measured for parts A and B (Bowie and Harvey, 2006; Crowe, 1998) and the TMT difference (TMT B – TMT A) was used to obtain a derived t-score based on age, gender, and education. Results were compared to Icelandic norms based on age, gender, and education (Magnusdottir et al., 2021).

Subtests of the WASI-IS and the WAIS-III were used to measure intellectual abilities, working memory, and processing speed. The WASI-IS subtests performed were the Vocabulary and Matrix Reasoning tests. The Vocabulary test involves defining printed words presented to the examinee. The Matrix Reasoning test consists of incomplete pattern series where participants are asked to select an option that completes the series (Guðmundsson, 2016). The WAIS-III subtests performed were the Digit Span (digits forwards and backwards) test, the Digit Coding test, the Letter-Number Sequencing test, and the Symbol Search test. During the Digit Span test, the examiner reads a series of number sequences which the participant is asked to repeat in a forwards or backwards order. The Digit Coding test includes a series of symbols paired with numbers. Using a key, the participant has 120 seconds to connect the

right symbol to each number. The Letter-Number Sequencing Test involves a combination of letters and numbers which are read out loud by the examiner and the participant is asked to recall the numbers first in ascending order and then the letters in alphabetical order. The Symbol Search test contains a target group of symbols and a search group. The participants are asked to identify as many target symbols matching the symbols in the search groups as possible in 120 seconds (Silva, 2008; Wechsler, 1997). Total raw scores of the WASI-IS subtests are converted to t-scores with a mean normal score of 50 with a standard deviation of ±10 (Guðmundsson, 2016). The mean normal score for the sub-tests of WAIS-III was 10 with a standard deviation of ±3 (Wechsler, 1997).

4.3 Statistical analysis

All statistical analysis was performed using R (version 3.6.1). Statistical analysis of study data was performed under the guidance of a statistician, Sigrún Helga Lund.

In paper I, a univariate logistic regression was performed to identify possible predictive factors for having SBT results O-RV following mTBI (Table 7). An association was considered significant when $p < 0.05$ and presented as OR with a 95% confidence interval (Table 7).

The Fisher's exact test was used in paper I to evaluate associations between categorical data such as having ≤ three symptoms of mTBI or > three symptoms of mTBI and having one affected hormonal axis or ≥ two affected hormonal axes. It was also used to evaluate associations between having ≤ three symptoms or > three symptoms of mTBI and having PD and whether having menstrual disturbances or not was associated with having HPRL in paper II.

Poisson regression was used in paper I to compare counted data (the number of mTBI and mTBI symptoms) between women with normal or abnormal eye movements, between retired or currently playing female athletes, and between women using HoC or not.

A two-sample t-test was used to compare women with PD and women with nPF to identify possible risk factors for PD following mTBI in paper II (Table 11). It was also used for the comparison of mean results of the mental health scales and neuropsychological tests between women with PD and women with nPF in paper III. An association was considered significant when $p < 0.05$ (Table 13, 15, and 16).

The chi-squared test was used for the comparison of categorical variables between women with PD and nPF in paper II to identify possible risk factors for PD following mTBI when it was appropriate with regards to sample size (Table 11). In paper III it was used to compare scores above clinical cut-off for symptoms of insomnia. An association was considered significant when $p < 0.05$. The chi-squared was not used in paper III for the comparison of categorical variables including history of attention deficit hyperactivity disorder, depression

history, education level, anxiety and depression symptom severity or scores above the clinical cut-off for depression and anxiety symptoms between women with PD and nPF as women with PD were too few (Table 12 and 14).

Effect size was calculated in paper II using Cohen's d for the two-sample t-test, Phi (ϕ) for chi-squared test with 2x2 contingency tables, and Cramer's V for contingency tables larger than 2x2 (Table 11, 13, 15 and 16). Population size needed for 80% power was calculated using Lehr's formula.

In paper III, a linear regression was performed to evaluate whether there was an association between the number of mTBI and mTBI symptoms and scores above the clinical cut-off for symptoms of depression, anxiety, and insomnia. An association was considered significant when $p < 0.05$.

4.4 Ethics

Informed consent was obtained from all subjects upon participation in the study. Procedures were performed in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration. This study was approved by the Icelandic National Bioethics Committee (no: VSN-18-091), the Icelandic Data Protection Authority, the Institutional Research Committee of Landspitali University Hospital of Iceland, and Laeknasetrid outpatient clinic. As, in some cases, months passed from the part I and II of the study until the hormonal SBT in part III were performed, female athletes with a history of mTBI had to repeat the mental health scales prior to the medical interview. These changes to the study protocol were approved by the National Bioethics Committee (No: 17-183-V1).

5 Results

5.1 Medical history and clinical characteristics

Demographic and clinical characteristics of the female athletes who participated in SBT are presented in Table 7.

	Total (n = 133)	SBT within RV (n = 45)	SBT O-RV (n = 88)	OR [95%CI]	p - value
Still playing (%)	72 (54.1%)	28 (62.2%)	44 (50.9%)	–	
Retired (%)	61 (45.9%)	17 (37.8%)	44 (50.0%)		0.182
Age, mean (min; max)**	29.2 (17; 46)	31.2 (20.0; 46.0)	28.2 (17.0; 46.0)	*0.94 [0.90 – 0.99]*	*0.034**
BMI, mean (SD)	26.2 (4.7)	25.8 (3.7)	26.4 (5.2)	–	0.442
Previous medical history (%)	56 (42.1%)	18 (40.0%)	38 (43.2%)		
No previous medical history (%)	77 (57.9%)	27 (60.0%)	50 (56.8%)	–	0.725
Previous hormonal disease (%)	13 (9.8%)	3 (6.7%)	10 (11.3%)	–	
No previous hormonal disease (%)	120 (90.2%)	42 (93.3%)	78 (88.6%)	–	0.806
No HoC (%)	54 (40.6%)	18 (40.0%)	36 (40.9%)		
HoC before mTBI (%)	21 (15.8%)	9 (20.0%)	12 (13.6%)	–	0.442
HoC after mTBI (%)	22 (16.5%)	10 (22.2%)	12 (13.6%)	–	0.322
HoC before and after mTBI (%)	36 (27.1%)	8 (17.8%)	28 (31.8%)	–	0.257
Menstrual changes (%)	17 (12.8%)	5 (11.1%)	12 (13.6%)		
No menstrual changes (%)	116 (87.2%)	40 (88.9%)	76 (86.4%)	–	0.680
Time from mTBI, mean (min; max)***	5.0 (0.04; 35.2)	5.8 (0.04; 35.2)	4.7 (0.04; 25.6)	–	0.308
Number of mTBI, mean (min; max)	2.2 (1;4)	2.2 (1;4)	2.1 (1;4)	–	0.568
Number of mTBI symptoms, mean (min; max)	3.88 (0; 13)	2.9 (0;12)	4.3 (0;13)	*1.15 [1.01 – 1.33]*	*0.045**

Table 7 Demographic and clinical characteristics of the study population.
* Significant p-value < 0.05
**Age in years
***Time from mTBI in years
HoC use before mTBI: oral contraception (n = 19), contraceptive ring (n = 1), hormone coil (n = 1).
HoC use after mTBI: oral contraception (n = 17), contraceptive injections (n = 1), hormone coil (n = 3), birth control patch (n = 1).
HoC before and after mTBI: oral contraception (n = 27), contraceptive injections (n = 1), hormone coil (n = 2).
Six women switched HoC before and after mTBI, four from oral contraception to the hormone coil, one from oral contraception to contraceptive injections and one from contraceptive injection to the contraceptive ring
BMI = body mass index, CI = confidence interval, HoC = hormonal contraception, max = maximal value, min = minimal value, mTBI = mild traumatic brain injury, OR = odds ratio, RV = reference value, SBT O-RV = screening blood tests outside reference value, SD = standard deviation.
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5.1.1 Age distribution

The age distribution of the study population is presented in Figure 15. Retired athletes were significantly older with a mean age of 31.1 years than athletes who were still active in their sport where the mean age was 27.6 years (p < 0.001).

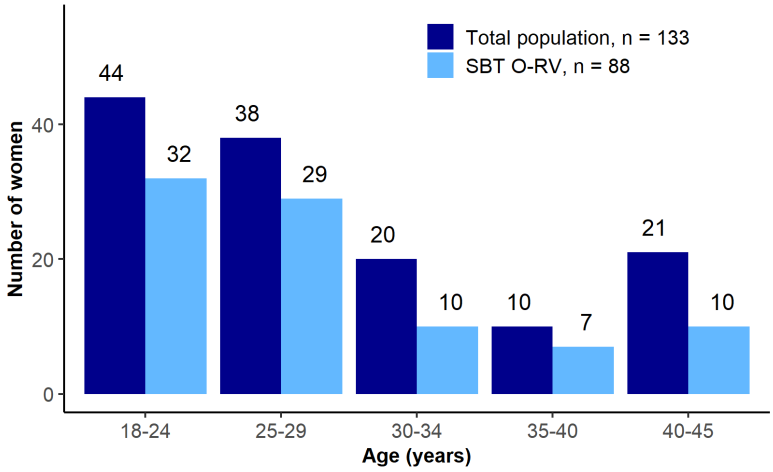

Figure 15 Population age distribution
Total study population (n = 133), women with SBT O-RV (n = 88).
SBT O-RV= screening blood test outside reference value.
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5.1.2 Previous medical history

The use of HoC was reported by 59.4% of women before mTBI, after mTBI or both with 47.4% taking oral contraception (Table 7).

Previous history of hormonal disease was reported by 13 women (Table 7) (decreased levels of sex hormones and HPRL n = 1, polycystic ovary syndrome n = 5, HPRL n = 1, hyperthyroidism n = 1 and hypothyroidism n = 5). Ten of these 13 women had SBT O-RV (s-IGF-1 below median RV n = 7, s-IGF-1 and s-cortisol below RV n = 1, thyroid hormone levels and s-IGF-1 below RV n = 1, s-cortisol and s-PRL levels above RV n =1). The SBT results that were O-RV in these ten women were not previously known to be abnormal except for one woman who had a prior history of HPRL although she had never been evaluated further (Eggertsdóttir Claessen et al., 2023b).

Prior history of depression and/or anxiety was self-reported by 17 women (12.8%, n =133) with 15 being currently treated with selective serotonin reuptake inhibitor. There was not a significant association between reporting a prior history of depression and/or anxiety and SBT O-RV (p = 0.45) (Eggertsdóttir Claessen et al., 2023b).

Medication use reported by participants included; antihypertensive medicine (n = 3), medications for attention deficit hyperactivity disorder (n = 5), salbutamol for asthma (n = 4), levothyroxine for hypothyroidism (n = 5), flecainide for premature atrial complexes (n = 1), gabapentin (n = 3) and nonsteroidal anti-inflammatory drugs (n = 4) for pain management, melatonin (n = 1), amitriptyline (n = 2) and zolpidem (n = 1) for sleep disturbances, allergy medications (n = 3), insulin for type 1 diabetes mellitus (n = 1), and oestrogen supplementation with tibolone (n = 1) (Eggertsdóttir Claessen et al., 2023b).

5.1.3 Symptoms of mild traumatic brain injury

Symptoms of mTBI reported at the time of the medical interview are presented in Table 8. Retired athletes reported a significantly greater number of mTBI symptoms (mean number of symptoms = 4.9) than athletes still active in their sport (mean number of symptoms = 3.1) ($p < 0.001$) although they did not report a higher number of mTBI ($p = 0.55$). There was not a significant difference in the number of mTBI symptoms between women reporting HoC use and women who were not using HoC ($p = 0.99$).

Symptoms of mTBI	Number of women (%)
Drowsiness	60 (45.1%)
Decreased concentration	58 (43.6%)
Headache	56 (42.1%)
Memory disturbances	50 (37.6%)
Light sensitivity	33 (24.8%)
Dizziness	33 (24.8%)
Fatigue	29 (21.8%)
Visual disturbances	26 (19.5%)
Noise sensitivity	25 (18.8%)
Balance disturbance	18 (13.5%)
Nausea	16 (12.0%)
Tinnitus	12 (9.0%)

Table 8 Reported symptoms of mTBI.
This mTBI symptom checklist was part of the questionnaire prior to the medical interview. Some women reported more than one symptom.

5.1.4 Time from mild traumatic brain injury to screening blood tests

The mean time from the medical interview and physical examination until SBT were taken for the entire population (n = 133) was 2.2 months (range 0.03 – 19 months). The time from the most recent mTBI was 5.0 years for the entire population and 4.7 years for those who had SBT-ORV (Table 7). The time from the latest mTBI until SBT divided into intervals is presented in Figure 16. More than two years passed from the most recent mTBI until the SBT were performed in 63 (47.4%) women and more than ten years for 24 (18%). The time from the latest mTBI was significantly longer in retired athletes (6.5 years) than in athletes who were still active in their sport (3.8 years) (p = 0.02).

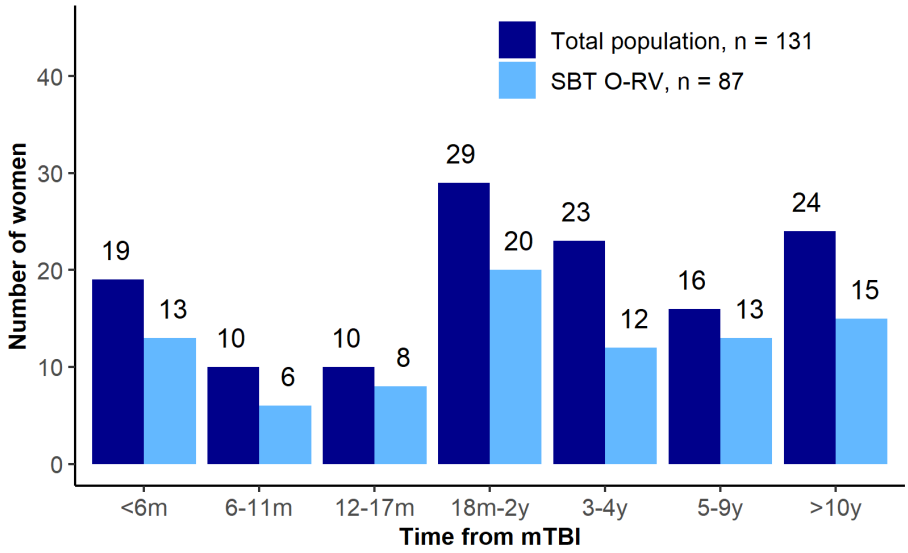

Figure 16 Time from mTBI until SBT.
Two women, one of which had SBT O-RV, did not recall the exact time of mTBI. Thus, the total study population in this figure includes 131 women and 87 women with SBT O-RV.
m = months, y = years, SBT O-RV= screening blood test outside reference value.
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5.2 Physical and neurological examination

Physical examination and electrocardiogram were normal for all participants and none of them had features suggesting hypercortisolism or acromegaly. Neurological examination was only remarkable for discomfort during eye movement evaluation in eight women. One of these eight women had visibly abnormal eye movements with slight lateral deviation of the left eye on convergence. Women with eye movement discomfort had a significantly greater number of mTBI symptoms (p < 0.001) although they did not report a significantly

greater number of mTBI (p = 0.76) than women with normal eye movements. There was not a significant association between eye movement discomfort and SBT O-RV (p = 0.26) (Eggertsdóttir Claessen et al., 2023b).

The population BMI classification according to World Health Organization is presented in Figure 17 ("Body Mass Index - BMI,"). There was not a significant difference in BMI between retired athletes (mean BMI 26.6) and athletes still active in their sport (mean BMI 25.9) (p = 0.418).

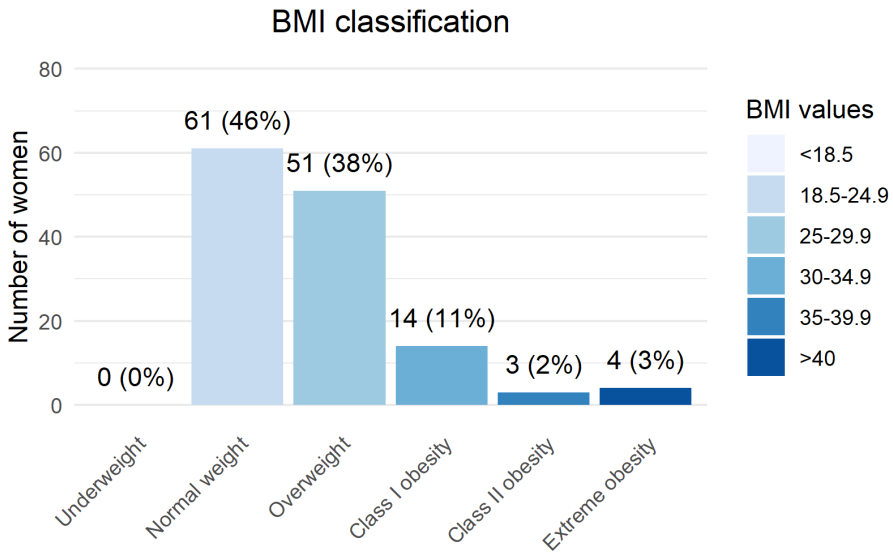

Figure 17 BMI classification of participants.
BMI = body mass index, WHO = World Health Organization.

Hypertension severity classification is presented in Figure 18 (Unger et al., 2020).

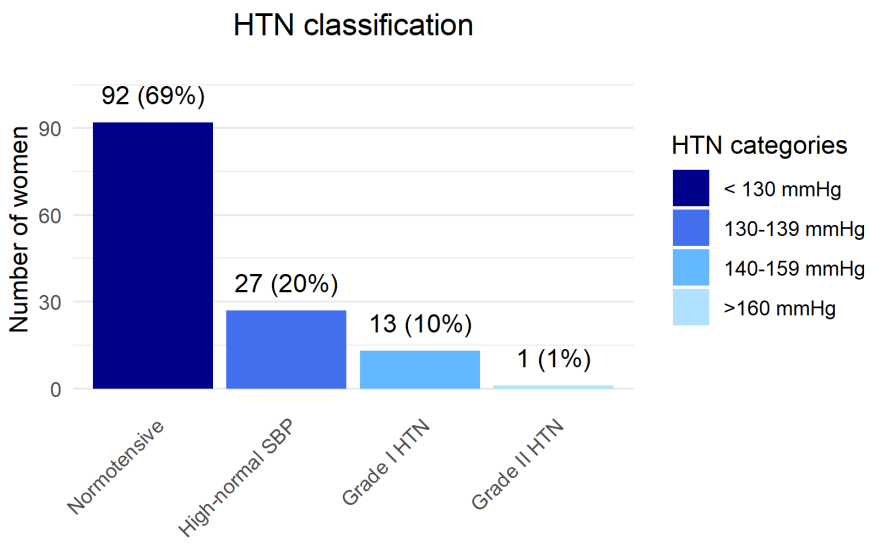

Figure 18 Hypertension severity classification.
HTN = hypertension, SBP = systolic blood pressure

5.3 Hormonal screening blood tests

The mean levels of the first, second, and third SBT for each hormonal measurement is presented in Table 9.

Hormonal measurement	First SBT n = 133 mean (min;max)	Second SBT n = 113 mean (min;max)	Third SBT n = 51 mean (min;max)
		n= 30	**n = 14**
s-TSH	2.6 (0.01; 8.7)	2.9 (0.13;6.7)	2.8 (0.01; 9.5)
s-fT4	15.1 (10.2; 20.4)	13.9 (10.9; 18.6)	14.3 (11.0; 18.2)
		n = 57	**n = 24**
s-PRL	25.8 (3.7; 169.7)	33.7 (0.5; 196.1)	35.9 (12.6; 184.7)
s-cortisol		**n = 63**	**n = 18**
	520.1 (96.0; 1339.0)	616.2 (231.0; 1236.0)	536.3 (170.0; 1141.0)
s-IGF-1		**n = 94**	**n = 33**
	169.4 (44.0; 329.0)	158.7 (61.0; 272.0)	165.2 (61.0; 272.0)
		n = 4	**n = 1**
s-FSH	4.5 (0.1; 13.0)	4.2 (2.0; 7.2)	3.7
s-LH	8.1 (0.1; 68.6)	7.1 (2.0; 11.7)	5.3
s-oestrogen	267.5 (18.4; 1558.0)	325.4 (18.4; 949.0)	167.0
s-progesterone	7.4 (0.2; 50.4)	17.5 (0.3; 64.4)	3.6

Table 9 Mean levels of serum hormonal measurements for each hormonal axis.
More than one hormonal axis was re-evaluated in the second and third SBT in some women
max = maximal value, min = minimal value, SBT = screening blood test, s-cortisol = serum cortisol, s-FSH = serum follicle stimulating hormone, s-fT4 =serum free thyroxine, s-IGF-1 = serum insulin like growth hormone 1, s-LH = serum luteinising hormone, s- oestrogen = serum oestrogen, s-PRL = serum prolactin, s-progesterone = serum progesterone, s-TSH = thyroid stimulating hormone.
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Of the 133 female athletes who participated in SBT, 88 women (66.2%) had results O-RV for one or more hormonal axes necessitating further endocrinological evaluation for possible PD (Table 10). Hormonal SBT normalized in 30 women when they were repeated for a second (n = 22) or third time (n = 8) (Figure 13). Compared to women with SBT O-RV for one hormonal axis, women with SBT O-RV for two or more hormonal axes were not more likely to have > 3 symptoms of mTBI (p = 0.645).

Number of axes O-RV	SBT results	SBT O-RV n = 88 (%)	Total n = 133 (%)
0	---	---	45 (33.8%)
1	↑ s-PRL	7 (7.9%)	54 (40.6%)
	↓ s-IGF-1	42 (47.7%)	
	↔ s-TSH, ↓ s-fT4 (n = 3) ↑ s-TSH, ↔ s-fT4 (n = 2)	5 (5.7%)	
2	↑ s-PRL, ↓ s-IGF-1	17 (19.3%)	30 (22.6%)
	↓ s-cortisol, ↓ s-IGF-1	5 (5.7%)	
	↑ s-PRL, ↓ s-cortisol	1 (1.1%)	
	↔ s-TSH, ↓ s-fT4, ↓ s-IGF-1	6 (6.8%)	
	↑ s-TSH, ↔ s-fT4, ↑ s-PRL	1 (1.1%)	
3	↑ s-PRL, ↓ s-cortisol, ↓ s-IGF-1	1 (1.1%)	3 (2.3%)
	↑ s-PRL, ↑ s-TSH, ↔ s-fT4, ↓ s-IGF-1	2 (2.3%)	
4	↑ s-PRL, ↓ s-cortisol, ↑ s-TSH, ↔ s-fT4, ↓ s-IGF-1	1 (1.1%)	1 (0.7%)

Table 10 Screening blood test results.
↔ = within RV, ↓ = below RV, ↑ = above RV, RV = reference value, SBT = screening blood tests, SBT O-RV = screening blood tests outside reference value, s-cortisol = serum cortisol, s-fT4 = thyroxine, s-IGF-1 = insulin like growth factor, s-PRL = prolactin, s-TSH = thyroid stimulating hormone.
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Most commonly, s-IGF-1 levels were below the median RV in 74 women (55.6%, n = 133). Eight women (5.3%, n = 133) had s-cortisol levels below the RV and thyroid hormone levels were below RV in 15 women (11.3%, n = 133). Elevated levels of s-PRL were present in 30 women (22.6%, n = 133) who had a mean time of 2.95 years (range 2 weeks – 11.1 years) from the latest mTBI until the SBT. One woman had gonadotropin levels below the RV in all three SBT. However, further endocrinological evaluation was not indicated as she was taking oral contraception (Eggertsdóttir Claessen et al., 2023b).

Age and the number of mTBI symptoms was associated with SBT O-RV. With older age, there was decreased likelihood of SBT O-RV (OR 0.94, CI 0.90 – 0.99, p-value = 0.034) and with higher numbers of reported mTBI symptoms there was increased likelihood of SBT O-RV (OR 1.15, CI 1.01 – 1.33, p-value = 0.045) (Table 7). Women with two or more affected axes were not significantly more likely to have > 3 symptoms of mTBI than women with one affected hormonal axis (p = 0.645) (Eggertsdóttir Claessen et al., 2023b).

5.4 Further endocrinological evaluation

Further endocrinological evaluation was performed in 86 women (65.6%, n = 131) who had repeated SBT O-RV (Figure 19). Population characteristics and comparison between women with PD and women with nPF following mTBI are presented in Table 11.

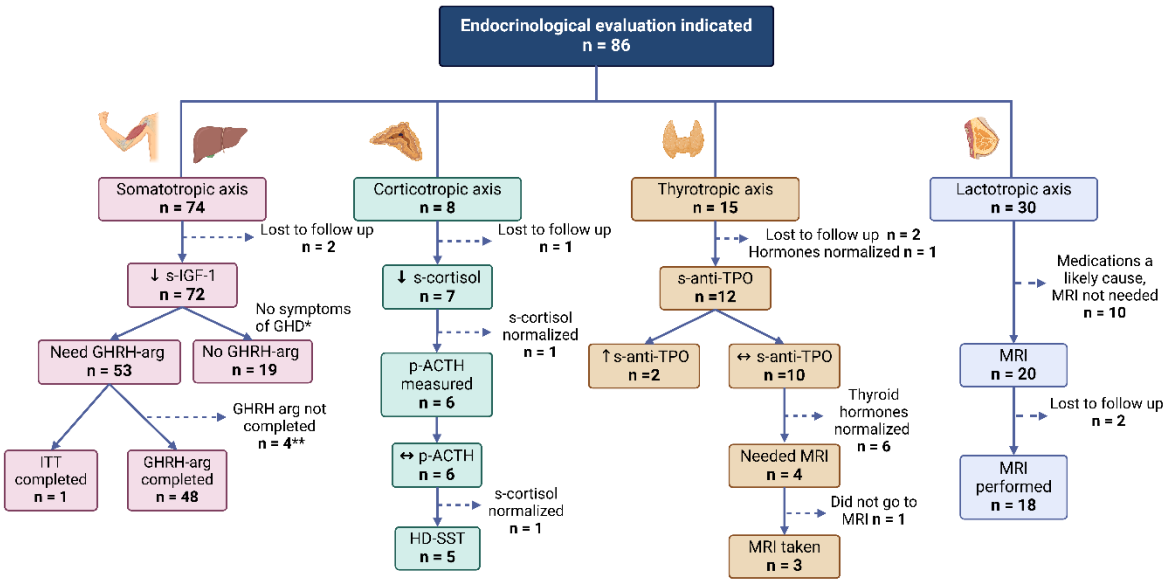

Figure 19 Overview of the endocrinological evaluation

* GHRH-arg tests were not performed for 19 women who did not have symptoms indicating possible GHD.

** Lost to follow up (n = 1), pregnant when the test was to be conducted (n = 2) and one woman was being treated for HPRL and followed by the endocrinologist before the GHRH-arg test can be performed if indicated.

↔= blood test results within RV, ↑ blood test results above RV, ↓ blood test results below RV, GHRH-arg = growth hormone releasing hormone and arginine, HD-SST = high dose short Synachten test, HPRL = hyperprolactinemia, ITT = insulin tolerance test, MRI = magnetic resonance imaging, p-ACTH = plasma adrenocorticotropic hormone, s-anti-TPO = serum anti-thyroid peroxidase antibodies, s-cortisol = serum cortisol, s-IGF-1 = serum insulin like growth factor 1.

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There were 74 women (56.5%, n = 131) with s-IGF-1 levels below median RV in repeated SBT (Fig 19). Of these 74, 53 women were referred for further endocrinological testing (ITT n =1, GHRH-arg test n = 52) as they also had clinical symptoms indicating possible GHD

(Figure 19). The GHRH-arg test was completed in 48 of the 52 women (92.3%) women and four were not tested as one was lost to follow up, two were pregnant at the time of the planned test, and one was being treated for HPRL before the GHRH-arg test could be performed if indicated (Figure 19). Two women were diagnosed with GHD, one with an ITT and one with a GHRH-arg test.

Eight women (6.2%, n = 131) had s-cortisol levels below RV (< 350 mmol/L) (Figure 19). Six of these eight women were evaluated further with plasma ACTH measurements, one woman was lost to follow up, and s-cortisol levels normalized in one woman (Figure 19). All six women had plasma ACTH measurements within the RV. Following the plasma ACTH measurements, a high dose short Synachten test was performed in five of the six women. One woman was not tested as s-cortisol levels normalized. The high dose short Synachten test was normal (peak s-cortisol ≥ 440 nmol/L) for all five women (Figure 19).

Of the 15 women (11.5%, n =131) who had thyroid hormone levels O-RV in repeated SBT, s-anti-TPO was measured in 12 women. Two were lost to follow up and serum thyroid hormone levels normalized in one woman with follow up (Figure 19). Measurements of s-anti-TPO were positive in two of these 12 women indicating autoimmune hypothyroidism and negative in ten women (Table 6). Of the ten women who had negative s-anti-TPO measurements, four (3.1%, n = 131) were suspected of having CH as they had low to normal s-TSH and low s-fT4 levels during follow up with an endocrinologist (HÁS) where thyroid hormone measurements were repeated at an interval ranging from 1 – 9 months (mean 3.2 months). The other six of the ten women who did not have s-anti-TPO antibodies were not suspected of having CH as thyroid hormone levels normalized during follow up (Figure 19). All four women suspected of having CH were examined with an MRI for further evaluation. Three of them had normal MRI results and one did not attend the MRI despite repeated attempts to contact her and was lost to follow up.

		Total n = 131	nPF n = 115	PD n = 16	Effect size	p-value
Sport* (%)	Soccer	52 (39.7%)	45 (39.1%)	7 (43.8%)	–	–
	Basketball	12 (9.2%)	9 (7.8%)	3 (18.8%)		
	Handball	48 (36.6%)	44 (38.3%)	4 (25.0%)		
	Ice Hockey	9 (6.8%)	7 (6.1%)	2 (12.5%)		
	Martial arts	8 (6.1%)	8 (6.9%)	0 (0.0%)		
Still playing (%)		71 (54.2%)	64 (55.7%)	7 (43.8%)	0.08	0.42
Retired (%)		60 (45.8%)	51 (44.3%)	9 (56.3%)		
Age, mean (SD)		29.3 (7.6)	29.5 (7.7)	27.6 (7.5)	0.25	0.36
BMI, mean (SD)		26.3 (4.7)	26.0 (4.5)	28.0 (6.2)	0.42	0.12
Previous medical history (%)		55 (42.0%)	51 (44.3%)	4 (25.0%)	–	–
No previous medical history (%)		76 (58.0%)	64 (55.7%)	12 (75.0%)		
Previous hormonal disease (%)		13 (9.9%)	12 (10.4%)	1 (6.3%)	–	–
No previous hormonal disease (%)		118 (90.1%)	103 (89.6%)	15 (93.7%)		
No HoC (%)		53 (40.5%)	46 (40.0%)	7 (43.4%)	–	–
HoC before mTBI (%)		21 (16.0%)	18 (15.7%)	3 (18.8%)		
HoC after mTBI (%)		22 (16.8%)	21 (18.3%)	1 (6.3%)		
HoC before and after mTBI (%)		35 (26.7%)	30 (26.0%)	5 (3.1%)		
Menstrual changes after mTBI (%)		16 (12.2%)	14 (12.2%)	2 (12.5%)	–	–
No menstrual changes (%)		115 (87.8%)	101 (87.8%)	14 (87.5%)		
Years from mTBI, mean (SD)		5.1 (6.2)	5.2 (6.5)	4.3 (4.2)	0.14	0.58
Number of mTBI, mean (SD)		2.2 (0.8)	2.2 (0.7)	2.0 (1.0)	0.23	0.40
Number of mTBI symptoms, mean (SD)**		3.4 (1.7)	3.4 (1.6)	3.5 (1.9)	0.06	0.86
Number of mTBI symptoms in endocrinologist interview, mean (SD)		2.0 (1.5)	2.1 (1.5)	1.8 (1.4)	0.20	0.52

Table 11 Demographic and clinical comparison between women with PD and nPF.
For the entire population (n = 131) the number of mTBI ranged from 1.0 – 4.0, BMI ranged from 19.1 – 46.5, time that passed from mTBI until SBT ranged from 0.04 – 35.2 years, the number of mTBI symptoms in endocrinologist interview ranged from 0 – 6.0, and the number of mTBI symptoms right after concussion from 1.0 – 8.0.
*The total number of women who answered questions regarding the sport they participated in was n = 129, as two women did not report which sport they participated in. Of the 129 women, 113 had PD and 16 did not.
** the number of mTBI symptoms reported in the questionnaire prior to the medical interview in part III of the study.
BMI = Body mass index, HoC = hormonal contraception, mTBI = mild traumatic brain injury, nPF = normal pituitary function, PD = pituitary dysfunction, SD = standard deviation.
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Elevated levels of s-PRL were present in 30 women (22.9%, n = 131) (Figure 19). However, further evaluation for HPRL was not indicated in ten women who were taking medications that can cause HPRL (selective serotonin reuptake inhibitors (SSRI) n = 2, HoC n = 5, SSRI and HoC n = 3) (Torre and Falorni, 2007). There were 20 women (15.3%, n = 131) who had elevated levels of s-PRL and were not taking medications that can affect s-PRL levels. Of these 20 women, 18 had an MRI of the pituitary gland and two were lost to follow up (Figure 19 and 20). Seven of the 18 women had visible changes of the pituitary gland (hypopituitary atrophy and signs of a regressing prolactinoma n = 1, microadenoma n = 2, cystic/haemorrhagic adenoma n = 1, concentric enlargement of the adenohypophysis with no visible tumour n = 1, concentric enlargement of the pituitary gland n = 1, arachnoid cyst n = 1) and 11 had normal MRI results (Figure 20). Four (3.1%, n = 131) of the seven women with abnormal MRI results had a prolactinoma (hypopituitary atrophy and signs of a regressing prolactinoma n = 1, microadenoma n = 2, cystic/haemorrhagic adenoma n = 1) (Figure 20) (Eggertsdóttir Claessen et al., 2024b). Thus, the prevalence of prolactinoma in this study population was 3.1% or 3,053 per 100,000 inhabitants.

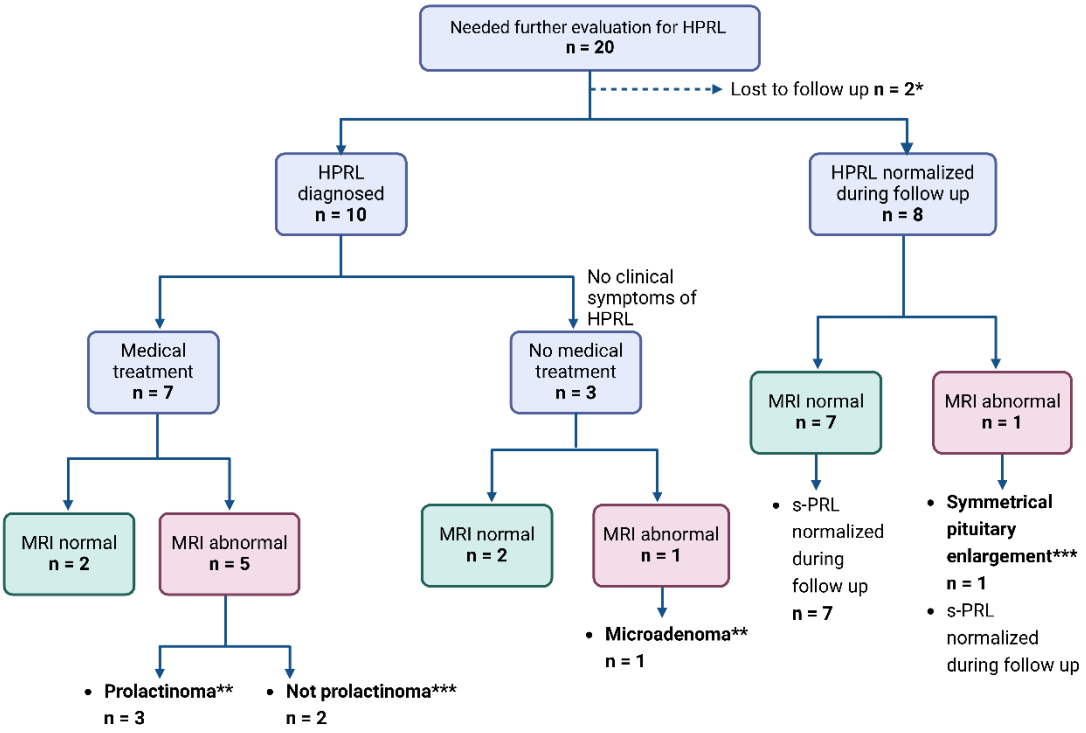

Figure 20 Results of the lactotroph axis evaluation.
18 women with elevated levels of s-PRL had an MRI for further workup.
* Both women had elevated S-prolactin levels in SBT and normal MRI results. Both were lost to follow up, one woman moved abroad, and the other did not respond to repeated requests to repeat blood tests for follow up.
** Prolactinoma, total count n = 4: microadenoma n = 2, regressing adenoma n = 1, cystic/haemorrhagic adenoma n =1.
*** Abnormal MRI without prolactinoma, total count n = 3: symmetrical pituitary enlargement n = 1 without a visible tumour, arachnoid cyst n =1, symmetrical enlargement of the adenohypophysis without a visible tumour n = 1.
s-PRL = serum prolactin, HPRL = hyperprolactinemia, MRI = magnetic resonance imaging.
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In summary, of the 20 women who had elevated s-PRL levels without medication use that may elevate s-PRL levels:

- Two women were lost to follow up during clinical follow up of elevated s-PRL levels and eight women were not diagnosed with HPRL as s-PRL normalized during follow up (Figure 20).
- Ten women (7.6%, n = 131) were diagnosed with HPRL as levels of s-PRL remained elevated in repeated blood tests during follow up (Figure 20).
- Four of the ten women diagnosed with HPRL (3.0%, n =131) had a prolactinoma and six (4.6%, n =131) did not (Figure 20).

Following a detailed endocrinological evaluation:

- 16 female athletes (12.2%, n = 131) were diagnosed with PD after mTBI and 115 (87.8%, n = 131) had nPF.
- Thus, PD was confirmed in 18.6% of the 86 women who had SBT O-RV and were referred for further endocrinological evaluation while 81.4% of the women who were referred for further endocrinological workup had nPF.
- Of the 16 women diagnosed with PD, six women (4.6%, n = 131) had HP (GHD n = 2, 1.5% and CH n = 4, 3.1%) and ten women (7.5%, n = 131) had HPRL (prolactinoma n = 4, 3.1% and HPRL without prolactinoma n = 6, 4.6%).
- Of the 16 women with PD, medical treatment was indicated for 13 (9.9%, n = 131).

Thus 81.3% of women diagnosed with PD received treatment. All six women diagnosed with HP received hormone replacement therapy, four were treated with levothyroxine for CH and two were treated with somatropin for GHD. Of the ten women diagnosed with HPRL, seven women were treated with a dopamine agonist (cabergoline) and three women were not as they were asymptomatic (Figure 20). Two of the seven women who received treatment had normal MRI results and five had abnormal MRI results (prolactinoma n = 3, no prolactinoma n = 2) (Figure 20).

The mean time from the most recent mTBI until the endocrinological evaluation was performed was 5.1 years for the entire population and 4.3 years (min 2.4 months, max 15.3 years) for the 16 women diagnosed with PD (Table 11). The mean time from the most recent mTBI until the endocrinological evaluation was 4.6 years (min 2.4 months, max 15.3 years) for the six women with HP, and 4.1 years (min 2.4 months, max 11.1 years) for the ten

women with HPRL. The time from mTBI until the endocrinological workup for the two women diagnosed with GHD was 2 months for one of them and 15 years for the other.

No statistically significant predictive factors for PD following mTBI were found when women with PD were compared to women with nPF after mTBI (Table 11). The effect size was largest for age, BMI, the number of mTBI, and the number of mTBI symptoms in the endocrinological interview (0.25, 0.42, 0.23 and 0.20 respectively) (Table 11). The calculated population size needed for 80% power was 261 participants for age, 89 participants for BMI, 296 for the number of mTBI, and 394 or the number of mTBI symptoms in the endocrinological interview (Eggertsdóttir Claessen et al., 2024b). Women with PD were not more likely to have >3 symptoms compared to women with nPF (p = 0.19), and women with HPRL were not more likely to have menstrual disturbances (p = 0.289).

5.5 Psychological findings

An overview of the education level, self-reported previous history of depression and attention deficit hyperactivity disorder for women with PD and nPF is presented in Table 12.

		Total n = 131 (%)	nPF n = 115 (%)	PD n = 16 (%)
No prior history of depression (%)		114 (87.0%)	99 (86.1%)	15 (93.8%)
Prior history of depression (%)		17 (13.0%)	16 (13.9%)	1 (6.3%)
No ADHD diagnosis (%)		124 (94.7%)	108 (93.9%)	16 (100.0%)
ADHD diagnosis* (%)		7 (5.3%)	7 (6.1%)	0 (0.0%)
Education level**	**Elementary school (%)**	15 (11.5%)	11 (9.6%)	4 (25.0%)
	College (%)	42 (32.1%)	38 (33.0%)	4 (25.0%)
	University (%)	73 (55.7%)	65 (56.5%)	8 (50.0%)

Table 12 Education level and previous history of depression and ADHD
* ADHD diagnosis was self-reported by participants.
**Total number of participants is n = 130 for education level as there was missing data for one participant with nPF.
ADHD = attention deficit hyperactivity disorder, PD = pituitary dysfunction, nPF = normal pituitary function.
Based on Table 2 from paper III (Eggertsdóttir Claessen et al., 2024a). Submitted for publication.

There was not a significant difference in the mean scores of the mental health scales between women with PD and nPF (Table 13).

Mental health scales	Total, n = 123 mean (SD)	nPF, n = 108 mean (SD)	PD, n = 15 mean (SD)	p – value	effect size
PSS4	8.1 (1.9)	8.1 (1.9)	8.2 (1.6)	*0.81*	*0.06*
PHQ-9	7.2 (4.7)	7.2 (4.7)	6.9 (4.7)	*0.79*	*0.06*
GAD-7	5.4 (4.2)	5.4 (4.1)	5.4 (4.6)	*0.98*	*0.00*
QOL scale	69.0 (12.0)	68.9 (12.1)	70.1 (11.4)	*0.72*	*0.10*

Table 13 Mean scores of the mental health scales
GAD-7 = General Anxiety Disorder Questionnaire 7, nPF = normal pituitary function, PD = pituitary dysfunction, PHQ-9 = The Patient Health Questionnaire 9, PSS4 = The Perceived Stress Scale 4, QOL = The Quality of Life, SD = Standard deviation.

Depression and anxiety symptom severity for women with PD and nPF is presented in Table 14. Further statistical analysis was not performed as participants with PD were too few.

	Symptom severity (scores)	Total n = 123 (%)	nPF n = 107 (%)	PD n = 16 (%)
GAD-7	**No anxiety (0 – 4)**	63 (51.2%)	55 (51.4%)	8 (50.0%)
	Mild (5 – 9)	37 (30.1%)	33 (30.8%)	4 (25.0%)
	Moderate (10 – 14)	18 (14.6%)	14 (13.1%)	4 (25.0%)
	Severe (15 – 21)	5 (4.1%)	5 (4.7%)	0 (0%)
PHQ-9	**No depression (0 – 4)**	46 (37.4%)	40 (37.3%)	6 (37.5%)
	Mild (5 – 9)	42 (34.1%)	35 (32.7%)	7 (43.8%)
	Moderate (10 – 14)	25 (20.3%)	24 (22.4%)	1 (6.3%)
	Moderately severe (15 – 19)	8 (6.5%)	6 (5.6%)	2 (12.5%)
	Severe (20 – 27)	2 (1.6%)	2 (1.9%)	0 (0%)

Table 14 Anxiety and depression symptom severity
GAD-7 = The General Anxiety Disorder Questionnaire 7, nPF = normal pituitary function, PD = pituitary dysfunction, PHQ-9 = Patient Health Questionnaire 9.

There were 35 women (28.4%, n = 123; nPF n = 32, PD n = 3) who had PHQ-9 scores above the clinical cut-off for symptoms of depression and 88 (71.5%, n = 123; nPF n = 76, PD n = 12) did not. The number of mTBI was not associated with results above the clinical cut-off for symptoms of depression (β = 0.15, p-value = 0.34). However, there was a significant association between the number of mTBI symptoms according to the SCAT-5 symptom evaluation scale and symptoms of depression above the clinical cut-off (β = 4.1, p-value < 0.001) (Eggertsdóttir Claessen et al., 2024a).

According to GAD-7 scale results 23 women (18.7%, n = 123; nPF n = 19, PD n = 4) had scores above the clinical cut-off for symptoms of anxiety and 100 (81.3%, n = 123; nPF n = 89, PD n = 11) women did not. The number of mTBI was not associated with results above the clinical cut-off for symptoms of anxiety (β = − 0.07, p-value = 0.71). A significant association was found between the number of mTBI symptoms according to the SCAT-5 symptom evaluation scale and results above the clinical cut-off for symptoms of anxiety (β = 2.0, p-value = 0.02) (Eggertsdóttir Claessen et al., 2024a).

5.6 Symptoms of mild traumatic brain injury and insomnia

There was not a significant difference in the mean scores of the ISI or the number of mTBI symptoms according to the SCAT-5 symptom evaluation scale between women with nPF and women with PD (Table 15). The mean number of the mTBI symptoms reported by the entire population was 7.6.

	Total, n = 131 mean (SD)	nPF, n = 115 mean (SD)	PD, n = 16 mean (SD)	p − value	effect size
ISI	8.5 (6.1)	8.6 (6.0)	7.6 (6.6)	0.54	0.16
SCAT-5*	7.6 (5.2)	7.9 (5.2)	5.8 (4.6)	0.12	0.41

Table 15 Results of the ISI and SCAT-5 symptom evaluation scale
*The SCAT-5 symptom evaluation scale was used to evaluate the number of mTBI symptoms ranging from 0 – 22 symptoms.
ISI = Insomnia severity index, nPF = normal pituitary function, PD = pituitary dysfunction, SCAT-5 = Sport Concussion Assessment Tool 5, SD = Standard deviation
Based on Table 3 from paper III (Eggertsdóttir Claessen et al., 2024a). Submitted for publication.

There were 54 women (41.2%, n = 131; nPF n = 48, PD n = 6) with ISI scores above the clinical cut-off for symptoms of insomnia and 77 (58.8%, n = 131; nPF n = 67, PD n = 10) did not. Thus, scores above the clinical cut-off for insomnia were not significantly more prevalent in women with PD compared to women with nPF (p = 0.80). An association between the number of mTBI and results above the clinical cut-off for symptoms of insomnia was not found (β = 0.03, p-value = 0.82). However, there was a borderline association between the number of mTBI symptoms according to the SCAT-5 symptom evaluation scale and results above the clinical cut-off for symptoms of insomnia although it was not statistically significant (β = 1.3, p-value = 0.05) (Eggertsdóttir Claessen et al., 2024a).

5.7 Neuropsychological findings

Female athletes with PD following mTBI had a significantly higher mean SARTes than women with nPF. No other significant difference in neuropsychological function was found (Table 16). Mean results of the WASI-IS and WAIS-III subtests for women with PD and those with nPF were within normal limits (Table 16) (Eggertsdóttir Claessen et al., 2024a).

		Total n = 131 mean (SD)	nPF n = 115 mean (SD)	PD n = 16 mean (SD)	p – value	effect size
SART	**Error score**	13.3 (7.0)	12.8 (7.1)	16.7 (5.2)	0.04*	0.56
	Response time	359 (82.7)	363 (85.2)	330 (55.5)	0.14	0.40
SCWT	**Errors**	2.0 (2.3)	1.9 (2.1)	2.8 (3.4)	0.18	0.39
	Interference score	23.9 (6.7)	23.9 (6.9)	24.5 (5.4)	0.71	0.09
	Interference score (t-score)	51.4 (7.1)	51.5 (7.3)	50.6 (5.5)	0.62	0.13
TMT	**Difference**	32.8 (24.1)	33.2 (25.1)	30.1 (15.3)	0.62	0.13
	Difference (t-score)	48.9 (13.3)	48.7 (13.9)	50.3 (8.7)	0.64	0.12
WASI-IS	**Vocabulary**	46.1 (9.7)	46.1 (9.8)	46.1 (9.1)	0.99	0.00
	Matrix Reasoning	46.8 (4.1)	46.8 (4.1)	46.8 (3.7)	0.96	0.00
WAIS-III	**Digit Span test**	9.6 (2.6)	9.7 (2.6)	8.6 (1.9)	0.09	0.44
	Letter Number Sequencing	9.7 (2.2)	9.7 (2.3)	9.1 (1.8)	0.28	0.27
	Digit symbol coding	11.7 (2.5)	11.7 (2.6)	11.8 (1.7)	0.89	0.04
	Symbol search	12.2 (2.8)	12.2 (2.9)	12.2 (2.2)	0.99	0.00

Table 16 Mean results of the neuropsychological tests
*Significant p – value < 0.05
nPF = normal pituitary function, PD = pituitary dysfunction, SART = The Sustained Attention to Response Task, SCWT = Stroop Colour-Word Test, SD = Standard deviation, TMT = Trail Making Test, WAIS-III = Wechsler Adult Intelligence Scale III, WASI-IS= Wechsler Abbreviated Scale of Intelligence Test.
Based on Table 3 from paper III (Eggertsdóttir Claessen et al., 2024a). Submitted for publication.

6 Discussion

In this study we aimed to investigate whether female athletes needing further endocrinological evaluation for possible PD following mTBI in sports could be identified. To the best of our knowledge, this is the first all-female study on PD following mTBI. Of the 151 women accepting participation in part III of the study, 133 women had SBT and 88 women (66.2%, n = 133) had repeated SBT results O-RV necessitating further endocrinological evaluation. The most commonly affected axis was the somatotroph axis followed by the lactotroph axis. Younger age and increased number of mTBI symptoms were found to be associated with SBT O-RV.

The study found the prevalence of PD following mTBI to be 12.2% (n = 131) as 16 women were diagnosed with PD including both HP and HPRL. The prevalence of HP following mTBI was 4.6% (n = 131) as six women had HP (GHD 1.5% and CH 3.1%). As ten women had HPRL (prolactinoma 3.0%, n = 131 and without prolactinoma 4.6%, n = 131), the prevalence of HPRL following mTBI was 7.6% (n = 131). There were no statistically significant predictive factors for PD following mTBI.

We also aimed to evaluate psychological and neuropsychological symptoms as well as QOL in female athletes with PD following mTBI compared to women with nPF and to identify psychological or neuropsychological factors that may have predictive value with regards to PD following mTBI. Women with PD following mTBI had a significantly higher mean SARTes than women with nPF indicating that screening for PD needs to be considered in women with higher SARTes following mTBI. The study found that women with symptoms of depression and anxiety above the clinical cut-off had an increased number of mTBI symptoms. Even so, there was not a significant difference between women with PD and nPF with regards to psychological symptoms or QOL.

6.1 Screening blood tests for pituitary function

As a substantial majority (66.2%, n = 133) of the study population had SBT O-RV in two or three repeated blood tests, possible PD following mTBI is a relevant consideration for doctors and other medical staff involved in the care of female athletes following mTBI. In a previous study on hormonal SBT after blast-related mTBI in a male sample, 42% had results O-RV which is lower than in our study (Wilkinson et al., 2012).

6.1.1 Possible hypopituitarism after mild traumatic brain injury

As 55.6% (n = 131) had s-IGF-1 levels below the median RV and clinical symptoms of GHD, the somatotropic axis appeared to be most commonly affected in SBT either in isolation or along with effect on other hormonal axes prior to further endocrinological testing for possible GHD. Earlier studies have also reported that GHD is the most common hormonal deficiency following mTBI or TBI (Table 1 – 3).

6.1.2 Elevated prolactin levels after mild traumatic brain injury

Interestingly, elevated levels of s-PRL were the second most common finding in the SBT possibly indicating impaired dopaminergic inhibitory control of PRL release as a result of pituitary stalk or hypothalamic injury (Gasco et al., 2021; Sav et al., 2019).

These findings differ from previous reports where GD or CoD have consistently been reported as the second most common hormonal deficiencies following TBI of all severity (Tables 1 – 2). Moreover, the prevalence of elevated s-PRL in SBT was higher (22.6%, n = 133) than has previously been reported (2 – 14%) following TBI (Agha et al., 2004b; Aimaretti et al., 2004; Aimaretti et al., 2005; Bensalah et al., 2020; Bondanelli et al., 2004; Kozlowski Moreau et al., 2012; Schneider et al., 2006b; Tanriverdi et al., 2006).

6.2 Pituitary dysfunction after mild traumatic brain injury

We aimed to find the prevalence of PD after mTBI. As 4.6% of the female athletes were diagnosed with HP following mTBI and 7.6% with HPRL, 12.2% of the female athletes had PD after mTBI. Thus, PD is an important consideration after mTBI especially since PD can be treated with hormonal replacement therapy. None of the women diagnosed with PD in the current study had ever been evaluated for possible PD following mTBI even though the injury had occurred up to 15.3 years (mean 4.3 years) prior to the study.

An estimated 69 million TBI cases occur globally each year (Dewan et al., 2018), with mTBI representing 70 – 90% (Capizzi et al., 2020; Cassidy et al., 2004; Feigin et al., 2013). Considering this, approximately 48 – 62 million mTBI cases occur globally each year and 5.8 – 7.4 million people can be estimated to be diagnosed with PD following mTBI according to the 12.2% prevalence of PD reported in the current study which is a substantial number of patients.

As female athletes appear to have a higher incidence of SRC (Black et al., 2017; Dave et al., 2022; Davis-Hayes et al., 2017; Vedung et al., 2020), experience more acute symptoms of SRC, (Broshek et al., 2005; Colvin et al., 2009), take longer to recover than men (Baker et al., 2016; Zuckerman et al., 2014), and may be more likely to have HP after TBI (Klose et al., 2007a), considering PD following mTBI and SRC may be particularly important in female athletes.

6.2.1 Hypopituitarism after mild traumatic brain injury

Six (4.6%, n = 131) women had HP following mTBI which is lower than the previously reported prevalence of 18 – 48% following mTBI (Table 3). The lower prevalence of HP following mTBI in the current study may be explained by the time (mean = 4.6 years) passing from the mTBI until the endocrinological evaluation was performed as HP can improve with time (Aimaretti et al., 2005; Bavisetty et al., 2008; Klose et al., 2007b; Krahulik et al., 2010; Schneider et al., 2007b; Schneider et al., 2006b; Tanriverdi et al., 2013; Tanriverdi et al., 2006; Tanriverdi et al., 2008a). It may also be explained by various definitions of HP (Klose et al., 2014; Kokshoorn et al., 2010). Moreover, there may be differences in the severity or number of mTBI between studies that is hard to standardize although results are conflicting regarding whether TBI severity increases the risk of HP after TBI (Agha et al., 2004b; Aimaretti et al., 2004; Aimaretti et al., 2005; Bensalah et al., 2020; Kozlowski Moreau et al., 2012; Schneider et al., 2006b). All six women received hormone replacement therapy (somatropin n = 2, levothyroxine n = 4) and experienced symptom relief with treatment during clinical follow up with an endocrinologist.

Although GHD is the most commonly reported pituitary hormone deficiency following mTBI (Table 3), we found that CH was the most common followed by GHD. This is an interesting finding as it has been suggested that HP following mTBI may result from vascular injury of the pituitary gland. The thyrotrope cells residing in the medial portion of the anterior pituitary gland should be better guarded from ischemic injury than the somatotroph cells as they are supplied by the short hypophyseal portal vessels. Conversely, the somatotroph cells, located in the lateral wings of the anterior pituitary gland, are presumably more prone to ischemic injury as they are supplied by the long hypophyseal portal vessels (Figure 11) (Adams et al., 1965; Ben-Shlomo and Melmed, 2022; Dusick et al., 2012; Kelly et al., 2000; Xuereb et al., 1954a).

The prevalence of GHD in our study (1.5%, n = 131) was lower than previously reported following mTBI (10 – 48%) (Table 3). The lower prevalence in our study may be explained by GHD improving with time as has been previously reported (Tanriverdi et al., 2013; Tanriverdi et al., 2008a). However, one of the two women diagnosed with GHD in our study suffered a mTBI only two months prior to the endocrinological evaluation while 15 years passed from the mTBI until the endocrinological evaluation was performed in the other woman. The lower prevalence of GHD in our study compared to previous studies on GHD after mTBI (Table 3) may also be explained by the use of the GHRH-arg test for GHD diagnosis rather than the ITT. Unlike the ITT, the GHRH-arg test does not evaluate the entire somatotroph axis. This may lead to falsely normal results if GHD is due to hypothalamic injury rather than pituitary gland injury (Darzy et al., 2003; Glynn and Agha, 2012; Schneider et al., 2006a).

6.2.2 Hyperprolactinemia following mild traumatic brain injury

Of the 30 female athletes who had elevated s-PRL levels in repeated SBT, 20 (15.3%, n = 131) had elevated levels of s-PRL that could not be explained by medications (Torre and Falorni, 2007). Thus, medication use does not explain the large proportion of women with elevated levels of s-PRL in our study.

Intriguingly, six of the ten women diagnosed with HPRL did not have a prolactinoma or medications to explain the persistantly elevated levels of s-PRL. Thus, the HPRL in these women may reflect long-term pituitary stalk or hypothalamic injury following mTBI as the time from mTBI until the endocrinological evaluation was performed for all of the ten women who had HPRL ranged from 2.4 months, to 11.1 years with a mean of 4.1 years (Sav et al., 2019). The prevalence of HPRL without a prolactinoma was comparable to the previously reported prevalence of HPRL after TBI of all severity ranging from 2 – 14% (Agha et al., 2004b; Aimaretti et al., 2004; Aimaretti et al., 2005; Bensalah et al., 2020; Bondanelli et al., 2004; Kozlowski Moreau et al., 2012; Schneider et al., 2006b; Tanriverdi et al., 2006).

As four of the 131 women in the current study were diagnosed with a prolactinoma, the prevalence of prolactinomas in the current study was 3.1% or 3,053/100,000 inhabitants. This is a remarkable finding as it is a much higher prevalence than previously reported in epidemiological studies on pituitary adenomas (Table 17). Although the prevalence of prolactinomas was not reported for women aged 18 – 45 years in an Icelandic study on the epidemiology of pituitary adenomas from 1955 – 2012 (Agustsson et al., 2015), the prevalence of prolactinoma for that age group was calculated using study data published as supplementary material. Only women aged 18 – 45 years diagnosed with prolactinomas during the last three years of that study period (2010 – 2012) were included in the calculations to improve the comparison with our study (2018 – 2020) yielding a period prevalence of 0.02% or 22.6/100,000 inhabitants (Agustsson et al., 2015). Prolactinomas are most common in women aged 30 – 40 years old (Agustsson et al., 2015; Gruppetta et al., 2013). However, as we compared women of the same age between the current study and the epidemiological study, the much higher prevalence in our study cannot be explained by age-related differences in the prevalence of prolactinomas

Author (year)	Study period	Number of prolactinoma cases	Total inhabitants	Period prevalence/100,000
Claessen (2023)	2018 – 2020	4	131	3,053
Agustsson (2015)	2010 – 2012	14	61,819*	22.6
Gruppetta (2013)	2000 – 2011	82	394,640 – 417,608 §	56.6**
Fainstein (2016)	2003 – 2014	63	81,422	77.4***

Table 17 Prolactinoma period prevalence/100,000 inhabitants
The period prevalence/100,000 is for women only (men have been excluded in this table).
* Mean number of women aged 18 – 45 years in Iceland from 2010 – 2012.
** Prevalence for the entire population of women aged 0 – 89 years.
*** Prevalence for the entire population of women aged 18 – 80 years.
§ The range of the number of inhabitants was given in the study and not the mean number of inhabitants over the study period.
(Agustsson et al., 2015; Fainstein Day et al., 2016; Gruppetta et al., 2013)

The prolactinomas diagnosed in our study were incidental findings as the participants were being evaluated for possible PD following mTBI rather than being clinically suspected of having a prolactinoma. Previously, a 10% prevalence of incidental pituitary adenomas has been reported in an asymptomatic population (Hall et al., 1994) which is even higher than in the current study. Thus, a more likely cause for the increased prevalence of prolactinoma in our study is that prolactinomas were being diagnosed in women who might not have been diagnosed if they had not participated in the study. These findings may indicate that prolactinomas, especially microadenomas, are underdiagnosed in women even though symptoms of HPRL are often more prominent in women than men due to menstrual disturbances (Barber et al., 2021; Koike et al., 1991).

6.3 Psychological symptoms

6.3.1 Self-reported depression and/or anxiety and mild traumatic brain injury

According to the questionnaire prior to the medical interview in part III of the study, 13.0% of the female athletes had a self-reported previous history of depression and/or anxiety. This is higher than the 5.4% prevalence of clinical depressive symptoms (PHQ-9 score ≥ 10) reported for a general population (Kocalevent et al., 2013; Kroenke et al., 2001). However, as mTBI regardless of pituitary function is associated with increased symptoms of stress,

anxiety, and depression (Jónsdóttir et al., 2021), our sample of female athletes who have all been exposed to one or more mTBI may not be comparable to a general population.

Compared to another athletic population, the prevalence of self-reported depression and/or anxiety in our sample was lower than the 19.1% prevalence of depression symptoms above clinical cut-off (PHQ-9 scores ≥10) reported in retired male players in American football exposed to repeated mTBI (Kerr et al., 2018).

6.3.2 Mental health scales and mild traumatic brain injury

Mental health scales for the evaluation of symptoms of depression and anxiety likely give a more accurate estimate of the prevalence of depression and anxiety than self-reported symptoms. Indeed, the results of the mental health scales indicated that 28.4% of the female athletes had depression symptoms above clinical cut-off (PHQ-9 scores ≥10) and 18.7% had symptoms of anxiety above the clinical cut-off (GAD-7 scores ≥10) regardless of pituitary function which is higher than the 13% self-reported prevalence of depression and/or anxiety.

Compared to the previously reported prevalence of depression symptoms above the clinical cut-off in a male population of athletes (19.1%), the female athletes in the current study had a higher prevalence of depression symptoms above the clinical cut-off possibly indicating a sex-based difference in depression symptoms following mTBI (Kerr et al., 2018). However, the prevalence of anxiety symptoms above the clinical cut-off was lower in the current study than the 24.2% prevalence of symptoms of anxiety reported in a previous study on women following SRC (24%) (D'Alonzo et al., 2022).

A dose-response relationship between the number of SRCs and symptoms of depression and anxiety has been reported in previous studies (Didehbani et al., 2013; Guskiewicz et al., 2007; Kerr et al., 2012; Kerr et al., 2018), including a report from part I of the study (Jónsdóttir et al., 2021). However, in the current study (part III), results above the clinical cut-off for symptoms of depression or anxiety were not associated with an increased number of mTBI. In part I of the study, symptoms of anxiety and depression above the clinical cut-off were compared between female athletes who reported a history of one or more mTBI and female athletes that did not report a history of mTBI while the entire population in the current study (part III) had a history of one or more mTBI. This may explain the different results with regards to symptoms of depression and anxiety above clinical cut-off and the number of reported mTBI.

6.3.3 Psychological symptoms of pituitary dysfunction

Although increased psychological symptoms and decreased QOL have been previously reported in patients with HP (Bülow et al., 2002; Rosén et al., 1994; Slagboom et al.,

2021b), increased symptoms of stress, depression, anxiety, or decreased QOL were not found in female athletes with PD following mTBI in the current study.

6.4 Neuropsychological effects

Results from earlier stages of the study indicated that women with a history of mTBI regardless of pituitary function require more attention and cognitive effort to maintain postural control and balance during a virtual reality simulation of being at sea (Jacob et al., 2022). Moreover, in part II of the study, women with a history of mTBI were found to have a higher SARTes and shorter SARTrt than women who had not sustained a mTBI (Kristensen, 2022).

When the neuropsychological symptoms of PD following mTBI were explored, neurophsychological test results indicated that women with PD also had a higher mean SARTes than women with nPF following mTBI. This difference in SARTes cannot be explained by a higher number of mTBI in women with PD as there was not a significant difference in the mean number of mTBI between women with PD and women with nPF (Table 11). Thus, women with PD following mTBI experience more difficulties with sustained attention (Robertson et al., 1997), inhibition or even both (Stevenson et al., 2011) compared to women with nPF following mTBI. The impaired sustained attention in women with PD may be explained by mental and neuropsychological fatigue due to HP as fatigue can affect attention during demanding tasks (Arlt and Allolio, 2003; Rosén et al., 1994; van Aken and Lamberts, 2005).

It is interesting that higher SARTes were observed in women with a history of mTBI regardless of pituitary function in part II of the study (Kristensen, 2022) and in women with PD following mTBI compared to women with nPF in the current study. It is possible that PD following mTBI has an additive effect on attention or inhibitory performance compared to mTBI alone, especially during challenging neuropsychological tests, such as the SART, that place high demands on simultaneous speed and inhibition.

Although lower scores in tests of vocabulary, perceptual speed, spatial learning, speed, and reaction time have been reported in women with GHD following pituitary surgery (Bülow et al., 2002), there were no other significant differences in neuropsychological function between women with PD following mTBI compared to women with nPF following mTBI. The similarities in neuropsychological function between women with PD and women with nPF after mTBI may be explained by the entire sample in our study being exposed to mTBI, which can also affect neuropsychological function (Belanger and Vanderploeg, 2005; Collins et al., 1999; Henry et al., 2016; Makdissi et al., 2010; McCrea et al., 2003).

6.5 Clinical characteristics

6.5.1 Screening blood tests, contraceptive medication, and the menstrual cycle

The evaluation of the gonadotroph axis in our study was likely affected by the large proportion of women taking HoC (59.4%). Moreover, the SBT were taken at various times during the menstrual cycle although SBT results were interpreted with regards to the hormonal changes that occur throughout the menstrual cycle (Rothman and Wierman, 2008).

Possible protective effects of HoC against clinical symptoms of mTBI have been suggested in previous studies (Gallagher et al., 2018; Wunderle et al., 2014). Conversely, HoC did not appear to have protective effects with regards to possible PD following mTBI as there was not a significant difference in HoC use between women who had SBT O-RV compared to women who had SBT within RV (Table 7).

6.5.2 Symptoms of mTBI

Even though 5.4 years had passed since the latest mTBI for the entire population, the female athletes reported a mean of 7.6 mTBI symptoms according to the SCAT-5 symptom evaluation scale which includes a list of 22 mTBI symptoms (Table 15). Thus, the women in our study population reported a considerable number of mTBI symptoms possibly reflecting prolonged symptoms of mTBI. However, the SCAT-5 is intended for the sideline evaluation of mTBI symptoms rather than the evaluation of persistent mTBI symptoms (Echemendia et al., 2017). Furthermore, the SCAT-5 symptom scale includes a number of unspecific symptoms such as "feeling slowed down", "don't feel right", and difficulties concentrating, which may explain the number of symptoms reported in our population (Echemendia et al., 2017; Patricios et al., 2023; "Sport concussion assessment tool - 5th edition," 2017),

6.5.3 Time from head injury until screening blood tests

A mean time of 4.7 years passed from the mTBI until the SBT for the women who had SBT O-RV (n = 88). Thus, it is remarkable that such a large proportion of the population had SBT results O-RV. However, SBT also normalized in 30 women when they were repeated for a second or third time (Figure 13) possibly reflecting normal hormonal fluctuations or improvement of pituitary gland injury with time as has been reported in previous studies (Aimaretti et al., 2005; Bavisetty et al., 2008; Klose et al., 2007b; Krahulik et al., 2010; Schneider et al., 2007b; Schneider et al., 2006b; Tanriverdi et al., 2013; Tanriverdi et al., 2006; Tanriverdi et al., 2008a).

6.5.4 Physical examination

As the study sample included female athletes either retired from or still active in their sport, it is surprising that 16% met the BMI criteria for obesity ("Body Mass Index - BMI,"). There was not a significant difference in BMI between retired athletes and athletes still active in their sport even though weight gain may be expected following retirement from sport. The proportion of female athletes who met the criteria for obesity may be explained by the BMI being overestimated as it does not distinguish fat from muscle. This could also explain the similar BMI between currently playing and retired athletes as the weight of muscle in female athletes still active in their sport may increase their BMI and decreased muscle mass in the retired female athletes may decrease their BMI (Prentice and Jebb, 2001).
There were 11% of the female athletes who met the criteria for hypertension (Unger et al., 2020). As a substantial proportion of the study sample reported HoC use, hypertension may be related to HoC which has been associated with elevated blood pressure (Liu et al., 2017).

6.6 Factors affecting symptoms of mild traumatic brain injury

6.6.1 Clinical characteristics

Retired athletes reported a greater mean number of mTBI symptoms even though they did not report a significantly greater number of mTBI. Thus, it can be speculated whether the increased mTBI symptom burden in retired athletes contributed to their retirement from sport.
Eight women had discomfort on eye movement evaluation during the neurological examination indicating vestibulo-ocular impairments which have been reported following mTBI and can be used for mTBI screening (Mucha et al., 2014). As dizziness, headaches, and visual disturbances can result from vestibulo-ocular impairment, it is unsurprising that the women with eye movement discomfort reported a significantly greater number of mTBI symptoms than women with normal eye movements.

6.6.2 Psychological symptoms

There was a significant association between results above the clinical cut-off for symptoms of depression and anxiety and increased number of mTBI symptoms according to the SCAT-5 symptom evaluation scale. Similar results have been reported in previous studies where patients with a history of mTBI and symptoms of depression reported a significantly higher number of mTBI symptoms compared to those who had a history of mTBI without depression symptoms (Lange et al., 2011). Moreover, affective symptoms or symptoms of anxiety appear to delay mTBI recovery (D'Alonzo et al., 2022) which might explain the increased mTBI symptom burden in female athletes with results above the clinical cut-off for symptoms of depression and anxiety.

However, it is important to consider that the role of SCAT-5 in tracking recovery of mTBI symptoms beyond 3 – 5 days after mTBI is limited (Echemendia et al., 2017). Furthermore, as symptoms of mTBI can overlap with symptoms of depression and anxiety (Figure 3), baseline SCAT-5 assessments can potentially identify depression and anxiety regardless of mTBI history in a sample of athletes (Burger et al., 2023).

6.6.3 Sleep disturbances

There was a borderline association between having results above the clinical cut-off for insomnia and increased number of mTBI symptoms according to the SCAT-5 symptom evaluation scale although it was not statistically significant. However, earlier studies have reported that increased symptoms of insomnia were significantly related to the total number of mTBI symptoms, mTBI symptom severity and decreased QOL (Blake et al., 2019). Sleep disturbances have also been associated with prolonged recovery of mTBI symptoms (Bramley et al., 2017).

6.7 Screening for pituitary dysfunction after mild traumatic brain injury

Although a majority (n = 88, 66.2%) of the study population had repeated SBT O-RV, PD was confirmed in 18.6% of the 86 women who had further endocrinological evaluation. Thus, identifying possible predictive factors for PD following mTBI is essential to facilitate more selective screening for possible PD following mTBI as the majority (81.4%) of the female athletes who had SBT O-RV possibly were not diagnosed with PD.

6.7.1 Predictive factors for pituitary dysfunction

By finding possible predictive factors targeted screening for possible PD following mTBI can be performed in those who need it. Thus, this was an important aim of the study. We found that SBT results were:

- less likely to be O-RV with increased age (OR 0.94, CI 0.90 – 0.99)
- more likely to be O-RV with increasing numbers of mTBI symptoms (OR 1.15, CI 1.01 – 1.33) (Table 7).

Thus, younger age and increased symptoms of mTBI and may indicate which women need SBT for possible PD following mTBI.

Even though the SART can also be affected directly by TBI (Robertson et al., 1997), the higher mean SARTes scores in women with PD and a prior history of mTBI may indicate that further endocrinological evaluation for possible PD following mTBI is needed. Although the population was large (n = 131), no other significant predictive factors for PD following mTBI

were found (Table 11). An even larger sample is needed to identify possible predictive factors for PD following mTBI according to the power analysis in Table 11.

6.7.2 Should we screen for pituitary dysfunction after head injury?

As untreated PD causes a range of serious physical, psychological, and neuropsychological symptoms, and affects QOL (Table 4), health care providers need to be aware of PD following mTBI since these symptoms may be reversible with hormone replacement therapy (Arlt and Allolio, 2003; Bülow et al., 2002; Deijen et al., 1996; Deijen et al., 1998; Rosén et al., 1994; Slagboom et al., 2021a, 2021b; van Aken and Lamberts, 2005).

Currently, there is no widely accepted consensus regarding screening for PD following mTBI although a few guidelines have been published (Glynn and Agha, 2019; Tan et al., 2017; Tanriverdi et al., 2015; Tanriverdi et al., 2010). Due to the vast number of new mTBI cases that occur annually, it is not feasible to evaluate pituitary function in all those who sustain a mTBI even though a substantial proportion (12.2%) of female athletes had PD following mTBI in the current study. Thus, we find it essential to be aware of, and further investigate possible predictive factors and clinical symptoms of PD after mTBI.

As evidence is conflicting regarding predictive factors for PD following TBI and mTBI as well as the appropriate timing of SBT (Table 1 – 3), it remains debated which women should be evaluated further for possible PD following mTBI, and when this endocrinological evaluation should occur. Although higher mean SARTes may indicate a need to screen for possible PD following TBI, it is not clinically practical to perform extensive neuropsychological tests to identify which women might need screening for PD following mTBI. As lower age and increased symptoms of mTBI were associated with SBT O-RV it can be suggested that screening should occur in individuals who have prominent symptoms of mTBI, if symptoms of mTBI persist despite correct treatment, and in younger individuals.

If SBT are performed for possible PD following mTBI, it is important to include measurements of all pituitary hormones (s-IGF-1, s-cortisol, s-TSH, s-fT4, s-FSH, s-LH, s-oestrogen, and s-progesterone) including s-PRL as elevated levels of s-PRL may reflect pituitary stalk or hypothalamic injury (Gasco et al., 2021; Sav et al., 2019).

6.8 Strengths and limitations

To the best of our knowledge, this study is the first study on possible PD after mTBI in an all-female population. Furthermore, it is the first to report psychological and neuropsychological functioning in women with PD following mTBI in an exclusively female sample. This is a strength of the study as studies on PD following mTBI have mainly been conducted for study populations where most participants are male (Table 1 – 3). Only 24.6% of the participants in the studies on HP prevalence following TBI of all severity were

women (Table 1 and 2) and in studies on HP after mTBI, only 17.2% of participants were women (Table 3). As female athletes remain an underreported population with regards to mTBI (D'Lauro et al., 2022), it is essential to study possible PD as well as psychological and neuropsychological function of PD in women following mTBI as results from studies with predominantly male populations cannot rightfully be generalized unto a female population.

Another strength of the study is that all 308 women reporting a history of one or more mTBI were invited to participate in neuropsychological tests. Moreover, all 166 women participating in the neuropsychological tests were invited to participate in a medical interview and a physical examination by the same medical doctor (Lára Ósk Eggertsdóttir Claessen), and all 88 women who had SBT repeatedly O-RV were invited to participate in a detailed endocrinological evaluation and follow up by the same endocrinologist (HÁS).

Our population (n = 131) is large compared to earlier studies (Table 1 – 3), which is a strength of the study. However, an even larger sample may be necessary to identify possible predictive factors for PD following mTBI and to determine differences in neuropsychological and psychological outcome between women with PD and women with nPF following mTBI. Thus, the population size can also be a limitation of our study. Furthermore, the association between the number of mTBI symptoms and SBT O-RV may be biased as female athletes with s-IGF-1 below median RV in SBT were only referred for further workup if they also had possible symptoms of GHD.

The study is retrospective, relying on participant reports on mTBI history (part I of the study), which is a limitation as mTBI tends to be underreported (Asken et al., 2016; Kerr et al., 2016; McCrea et al., 2004; Register-Mihalik et al., 2013). A previous report from part I of the study indicated mTBI underreporting as the proportion of women who reported a history of one or more mTBI increased from 40.2% to 64.8% after reading a definition of mTBI (Kristjánsdóttir et al., 2020). Thus, it is a strength of the study that we evaluated symptoms of mTBI objectively using the SCAT-5 symptom evaluation scale and included female athletes who reported history of one or more mTBI after reading a definition of mTBI.

Another possible limitation of the study is that we did not have a control group of women without a history of mTBI for the comparison of pituitary function between women with a history of mTBI and women without a history of mTBI. Instead, we relied on the RV of the SBT and the endocrinological tests as results within RV reflect hormonal measurements in a general population.

As the SBT were not taken at a predetermined time following mTBI, the time from mTBI until the SBT and, subsequently, the endocrinological evaluation varied between participants. This may be a limitation although it may also be considered a strength of the study as it provided insight into the long-term prevalence of PD following TBI. The time from the neuropsychological tests until the endocrinological evaluation was performed also varied

which can be considered a limiting factor as it may affect the ability of the neuropsychological tests to reflect neuropsychological symptoms of PD. Thus, future studies should aim to conduct the neuropsychological tests within a short period of the endocrinological evaluation.

Possible limitations of the diagnostic methods for GHD and CoD also need to be considered. The GHRH-arg was used to diagnose possible GHD although an ITT would have been preferable as it analyses the function of the whole somatotroph axis. This can be seen as a limitation of our study. Furthermore, even though measurements of s-cortisol and the high dose Synachten test were performed at 8 A.M. in the morning, variations in individual circadian rhythms may yield false negative results. Also, the use of the Synacthen test rather than the ITT, which evaluates the entire hypothalamic-pituitary-adrenal axis, can result in false negative results (Ammari et al., 1996). However, as the ITT requires medical supervision, is physically demanding on patients, and has several contraindications, the Synacthen test is often used as an alternative (Cho et al., 2014).

6.9 Discussion of the hypothesis

The results of this thesis support the hypothesis that PD, including both HP and HPRL, can occur in female athletes with a prior history of mTBI in sport. Furthermore, the results of this study support that PD following mTBI can cause neuropsychological symptoms such as decreased sustained attention or impaired inhibition although associations with physical and psychological symptoms as well as QOL were not found.

7 Summary of conclusions

Identifying which women needed further endocrinological evaluation for possible PD following mTBI was among the aims of the study. We found that a large proportion of female athletes (66.2%) had SBT results repeatedly O-RV necessitating further endocrinological evaluation for possible PD following mTBI.

Another aim of the study was finding the prevalence of PD in female athletes following mTBI. As the prevalence of PD following mTBI in female athletes was found to be 12.2%, with 9.9% requiring medical treatment, PD is an important consideration after mTBI. The prevalence of HP after mTBI in female athletes was lower (4.6%) than previously reported possibly reflecting recovery of pituitary injury over time. The HPRL diagnosed in six women who did not have a prolactinoma may indicate long-term pituitary or hypothalamic injury after mTBI. The prevalence of incidental prolactinoma in the current study was much higher than has been reported in previous studies indicating that prolactinomas are underdiagnosed in women.

Evaluating psychological and neuropsychological symptoms as well as QOL in female athletes with PD following mTBI was among the aims of this thesis. Sustained attention or inhibitory performance was affected in women with PD following mTBI as mean SARTes were higher in women with PD following mTBI compared to women with nPF. In part II of the study, women with a history of mTBI, regardless of pituitary function, had a higher SART and shorter SARTrt than women without a history of mTBI. Thus, PD following mTBI may have an additive effect on attention or inhibitory performance compared to mTBI alone. Other neuropsychological test results did not appear to be affected by PD following mTBI. Although women with symptoms of depression and anxiety above the clinical cut-off had an increased number of mTBI symptoms, there was not a significant difference between women with PD and nPF with regards to psychological symptoms or QOL.

We aimed to identify predictive factors, including psychological or neuropsychological predictive factors for PD following mTBI in female athletes. Lower age and an increased number of mTBI symptoms were associated with SBT O-RV. Higher mean SARTes is also a possible predictive factor for PD following mTBI. No other significant predictive factors were found in the current study although the study sample was large. Further studies with even larger samples are needed to establish predictive factors for PD following mTBI in female athletes.

8 Conclusions

We conclude that PD, including both HP and HPRL, can occur in female athletes with a prior history of mTBI in sport and that PD following mTBI in female athletes can cause subtle neuropsychological symptoms. As PD represents a treatable cause for symptoms of mTBI, screening for PD following mTBI in female athletes should be considered in younger women with prominent symptoms of mTBI.

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Original Publications

Paper I

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Screening for possible hypopituitarism following mild traumatic brain injury: The first all-female study. Who do we need to evaluate further?[1]

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Abstract.
BACKGROUND: Studies on hypopituitarism (HP) following mild traumatic brain injury (mTBI) have focused on male populations although women may be more susceptible to the sequelae of mTBI. This is, to the best of our knowledge, the first all-female study screening for HP following mTBI.
OBJECTIVE: Screening for possible HP in female athletes reporting a history of one or more mTBI.
METHODS: Pituitary hormone screening blood tests (SBT) were performed in 133 of the 151 female athletes included. Repeated results outside the reference value (O-RV) were considered abnormal necessitating further endocrinological evaluation.
RESULTS: Repeated SBT were O-RV in 88 women (66.2%). Decreased levels of serum insulin growth factor 1 (S-IGF1) were found in 55.6% of participants and elevated levels of serum prolactin (S-prolactin) in 22.6%. Serum cortisol levels were below the RV in 6.0% and thyroid hormonal levels in 11.3%. Lower age and increased number of mTBI symptoms correlated significantly with the risk of hormonal results O-RV.
CONCLUSION: The majority of the study population had SBT O-RV, warranting further workup of possible HP. Decreased levels of S-IGF1 were most commonly observed followed by elevated S-prolactin possibly indicating hypothalamic-pituitary impairment. Lower age and increased number of symptoms of mTBI may indicate the need to screen for HP.

Keywords: Head trauma, sport-related concussion (SRC), female athletes, pituitary hormones, hormone deficiency

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1. Introduction

Traumatic brain injury (TBI) can be divided into mild (mTBI), moderate (moTBI) and severe (sTBI). Mild TBI has a Glasgow coma score (GCS) of 13–15 in the first 24 hours after injury, normal neuroimaging studies and one or more of the following: loss of consciousness (LOC) for less than 30 minutes, post-traumatic amnesia (PTA) and altered mental state for less than 24 hours (Carroll et al., 2004; Corrigan et al., 2010). It can occur from trauma to the head, neck, or body, resulting in acceleration/deceleration movement of the brain. Symptoms of mTBI most often resolve within days or weeks, although persistent mTBI symptoms can arise. It is estimated that 1.6 to 3.8 million sport-related mTBI occur annually in the United States (Langlois et al., 2006). However, the incidence is likely underestimated, as diagnosis relies on self-reported symptoms and medical attention is not always sought (McCrea et al., 2004; McDonald et al., 2016).

Hypopituitarism (HP) can occur following mTBI with a prevalence of 13–48% (Giuliano et al., 2017; Kelestimur et al., 2004; Kelly et al., 2014; Klose et al., 2007; Northam et al., 2020; Schneider et al., 2007; Tanriverdi et al., 2007; Tanriverdi et al., 2008; Wilkinson et al., 2012). The somatotropic axis is most frequently affected with a prevalence of 15–45% (Aimaretti et al., 2005; Bensalah et al., 2020; Ives et al., 2007; Kelestimur et al., 2004; Kelly et al., 2014; Klose et al., 2007; Kokshoorn et al., 2010; Northam et al., 2020; Schneider et al., 2007; Tanriverdi et al., 2007; Tanriverdi et al., 2008; Wilkinson et al., 2012). Whether HP prevalence increases with TBI severity or not remains unclear as evidence is conflicting (Agha et al., 2004; Aimaretti et al., 2005; Bensalah et al., 2020; Bondanelli et al., 2004; Klose et al., 2007; Kokshoorn et al., 2011; Schneider et al., 2007; Schneider et al., 2006; Tanriverdi et al., 2006; You et al., 2019). Symptoms of HP may overlap with mTBI symptoms causing a delay in HP diagnosis. As HP is treatable, accurate diagnosis following mTBI is of great clinical importance. Moreover, any diagnostic delay can have dangerous consequences depending on which hormonal axes are affected (Kgosidialwa & Agha, 2019; Molaie & Maguire, 2018).

Studies on HP after mTBI have, so far, focused on male populations. Some included only male participants (Ives et al., 2007; Kelestimur et al., 2004; Kelly et al., 2014; Tanriverdi et al., 2008; Wilkinson et al., 2012), others both sexes with a male majority, where the greatest proportion of female participants was 65 women out of 193 participants (33.7%) (Agha et al., 2004; Aimaretti et al., 2005; Bensalah et al., 2020; Bondanelli et al., 2004; Kelly et al., 2000; Klose et al., 2007; Kokshoorn et al., 2011; Lieberman et al., 2001; Schneider et al., 2006; Tanriverdi et al., 2006; Tanriverdi et al., 2007; You et al., 2019). To the best of our knowledge, no previous study on HP after mTBI has had an all-female population even though female athletes seem more susceptible to the sequelae of mTBI and may take longer to recover (McGroarty et al., 2020). Contributing factors to these sex-based differences have been hypothesized, including sex related differences in head-neck stabilization (Tierney et al., 2005) and reporting biases (Kerr et al., 2016), as well as hormonal differences (McGroarty et al., 2020).

Although a few guidelines have been published, there is no widely accepted consensus for HP screening after mTBI (Glynn & Agha, 2013; Tan et al., 2017; Tanriverdi et al., 2015). It remains controversial which patients to screen, when, and how screening should occur. Further research on HP prevalence and screening for possible HP following mTBI is needed, particularly in a female population. The results presented here are part of a larger study which has three parts. Part I focuses on the definition of mTBI and mental health (Kristjánsdóttir et al., 2020), part II on neuropsychiatric outcome after mTBI (Jónsdóttir et al., 2021), and part III, presented here, focuses on screening for possible HP following mTBI. The aim of this study was to screen female athletes reporting a history of one or more mTBI for possible HP with the object of identifying which women need further endocrinological evaluation.

2. Materials and methods

2.1. Participants

In part I of the study, female athletes aged 18 to 45 years, currently active in or retired from soccer, team handball, basketball, ice hockey, and martial arts in Iceland participated by answering online questionnaires on mTBI history and mental health. The questionnaires were available from the end of January until the end of April 2018. Participants were contacted through sport-related social media groups or via email using information available through the national association for each sport (Kristjánsdóttir et al., 2020). There were 508 female athletes that

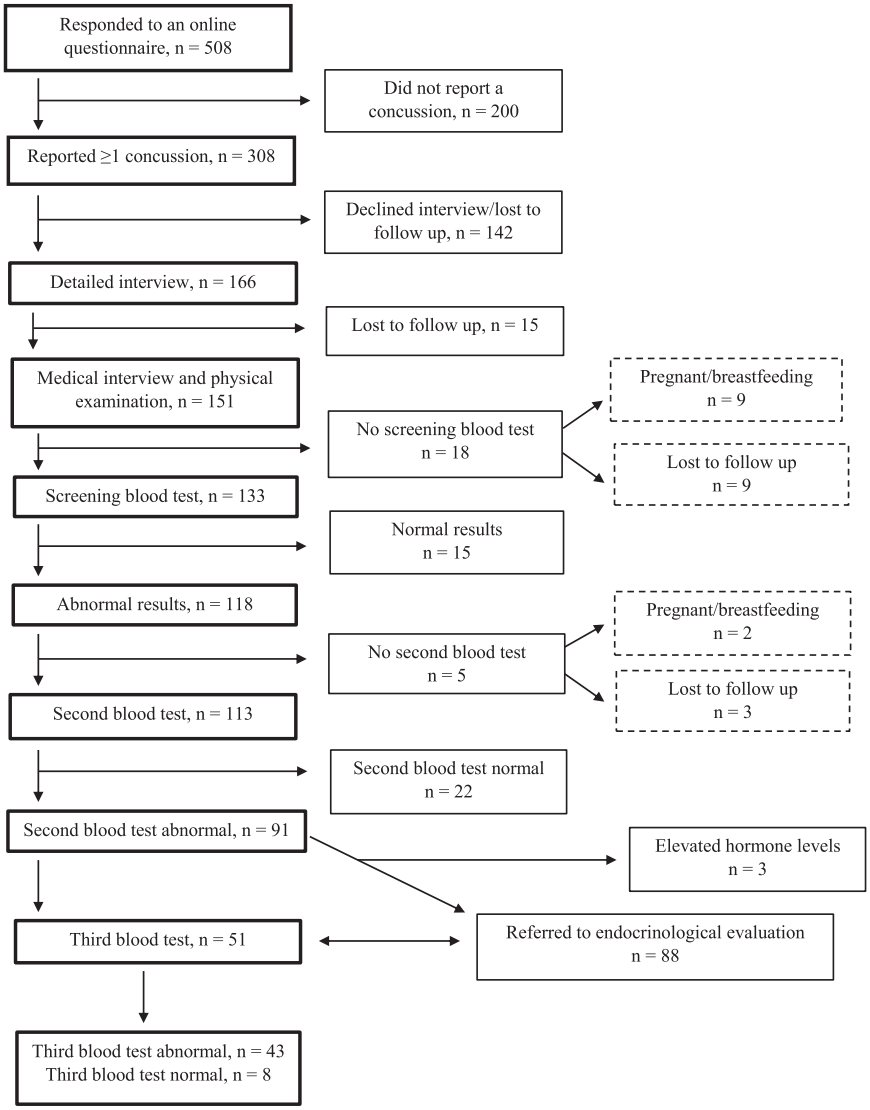

Fig. 1. Study design. Blood tests within reference value (RV) for each hormone were interpreted as normal, blood tests were interpreted as abnormal if they were above or below RV.

responded (Fig. 1) and they were offered further participation if they reported one or more mTBI ($n = 308$) after reading a definition of mTBI (Kristjánsdóttir et al., 2020).

2.2. *Study design*

In part II, 166 (53.9%) of the 308 women with a history of one or more mTBI accepted to have a detailed psychologist interview focusing on mTBI history and neuropsychological tests (this final number is explained in Fig. 1). Subsequently, they were offered to participate in part III, which included a medical interview and physical examination, with 151 (49.0%) women accepting (Fig. 1). All participants were interviewed and examined by the same medical doctor. Before the medical interview, the women answered a questionnaire regarding previous medical history and medications and the mental health questionnaires were repeated so that the assessment

would be done closer to the medical examination in time (data not reported here).

Following the medical interview, screening blood tests (SBT) were taken at their earliest convenience at 8 a.m. for hormonal evaluation. Unfortunately, the women were in different phases of the menstrual cycle when the SBT were taken. Results were defined as abnormal if they were outside the reference value (O-RV) for each hormonal measurement (Table 1). However, serum insulin-like growth factor (S-IGF1) was considered abnormal if clinical symptoms indicating possible growth hormone deficiency (GHD) were present and S-IGF1 measurements were below median RV (Reed et al., 2013) as normal S-IGF1 value does not exclude GHD (Ho, 2007). Similarly, women with S-IGF1 below RV without symptoms of possible GHD were not studied further. All SBT results were reviewed by the same endocrinologist. If the first SBT were O-RV or clinical symptoms of hormonal disease were present, blood tests were repeated for further evaluation. If the second blood test was O-RV, participants were referred to an endocrinologist for further assessment such as dynamic testing of pituitary function and magnetic resonance imaging (MRI) of the pituitary gland. Some of the women had a third SBT ($n = 51$) before being referred to an endocrinologist. Thus, either two or three blood tests were performed before referral.

2.3. Measurements and analytical methods

The questionnaire prior to the medical interview included mental health questionnaires, questions regarding previous medical history, medications, hormone contraception (HoC), menstruation, and the timing of the first and most recent mTBI. A physical examination was performed, including a neurological examination of the motor and sensory systems, reflexes, and cranial nerves, including eye movements. Blood pressure (BP), heart rate, oxygen saturation, height, and weight were measured, the body mass index (BMI) was calculated, and an electrocardiogram (ECG) was conducted. The following blood tests were subsequently taken at 8 a.m. for the whole population ($n = 133$): S-IGF1, serum cortisol (S-cortisol), serum prolactin (S-prolactin), serum thyroid-stimulating hormone (S-TSH), serum free thyroxin (S-fT4), serum follicle stimulating hormone (S-FSH), serum luteinizing hormone (S-LH), serum oestrogen (S-oestrogen), and serum progesterone (S-progesterone). The methodological description of each hormonal analysis is presented in Table 1.

2.4. Ethics

Informed consent was obtained from all subjects upon participation in the study. All procedures performed were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This study was approved by the Icelandic National Bioethics Committee (no. VSN-18-091), the Icelandic Data Protection Authority, the Institutional Research Committee of Landspitali University Hospital of Iceland and Laeknasetrid outpatient clinic.

2.5. Statistical analysis

All statistical analysis was performed using R (version 3.6.1). Univariate logistic regression was performed to analyse possible predictive factors for SBT O-RV. An association was considered significant when $p < 0.05$ and presented as odds ratios (OR) with a 95% confidence interval (CI) (Table 2). Poisson regression was used to compare counted data, such as the number of mTBI and mTBI symptoms between women with normal or abnormal eye movements and between retired or currently playing female athletes. A *t*-test was used for the comparison of mean BMI between retired and currently active athletes. Categorical data were examined for association significance using Fisher's exact test.

3. Results

There were 133 women who were evaluated with SBT for possible HP (Fig. 1), including currently active and retired athletes. Population characteristics are presented in Table 2 and the age distribution in Fig. 2. Retired athletes were significantly older ($p = 0.0002$) than athletes who were still active. Using BMI for classification ("Body Mass Index - BMI,"), 61 women (45.9%) were normal weight (BMI 18.5–24.9), 51 (38.3%) overweight (BMI 25–29.9), 14 (10.5%) in class I obesity (BMI 30–34.9), three (2.3%) in class II obesity (BMI 35–39.9), and four (3.0%) met the criteria for extreme obesity (BMI >40). No woman was underweight (BMI <18.5). According to international hypertension (HTN) guidelines (Unger et al., 2020), 92 (69.2%) women were normotensive (<130 mmHg), 27 (20.3%) had high-normal systolic blood pressure (SBP) (130–139 mmHg), 13 (9.7%) had

Table 1
Hormone measurements and analytical methods of serum hormones measured. CV = coefficient of variation, Low contr = low control, Med. contr = median control, High contr = high control. TSH = thyroid-stimulating hormone, fT4 = free thyroxine, IGF1 = insulin-like growth factor 1, FSH = follicle stimulating hormone, FP = follicular phase, OP = ovulation phase, LP = luteal phase, PMP = post-menopausal phase, LH = luteinizing hormone

				CV%					Specimen	
Analyte	Assay name	Manufacturer	Instrument	Low contr	Med. contr	High contr	Reportable range	Reference value	Type	Storage
TSH	TSH	Roche	Elecsys	11.1	1.3	2.2	0.005–100 mIU/L	0.270–4.20 mIU/L	Serum	+2–8°C
fT4	FT4 III	Roche	Elecsys	4.3	1.5	2.6	0.5–100 pmol/L	12–22 pmol/L	Serum	+2–8°C
Prolactin	Prolactin II	Roche	Elecsys	1.5	3.0	2.4	0.0470–470 μg/L	Female (not pregnant) 4.79–23.3 μg/L	Serum	+2–8°C
Cortisol	Cortisol II	Roche	Elecsys	5.4	1.5	1.6	1.5–1,750 nmol/L	Morning (6–10 a.m.): 133–537 nmol/L, afternoon (4–8 p.m.): 68.2–327 nmol/L	Serum	+2–8°C
IGF1	IGF-I	Siemens	Immulite 2000	6.3	3.1	2.5	15–1,000 μg/L	Manufacturer's age dependant reference range*	Serum	+2–8°C or –20°C
FSH	FSH	Roche	Elecsys	2.6	2.5	–	0.100–200 IU/L	FP 3.5–12.5 IU/L; OP 4.7–21.5 IU/L; LP 1.7–7.7 IU/L; PMP 25.8–134.8 IU/L	Serum	+2–8°C
LH	LH	Roche	Elecsys	1.8	0.8	–	0.100–200 IU/L	FP 2.4–12.6 IU/L; OP 14.0–95.6 IU/L; LP1.0–11.4 IU/L; PMP 7.7–58.5 IU/L	Serum	+2–8°C
Oestradiol	Estradiol III	Roche	Elecsys	6.7	1.6	1.9	18.4–11,010 pmol/L	FP 45.4–854 pmol/L; OP 151–1,461 pmol/L; LP 81.9 –1,251 pmol/L; PMP <18.4–505 pmol/L	Serum	+2–8°C
Progesterone	Progesterone III	Roche	Elecsys	11.9	3.7	2.4	0.159–191 nmol/L	FP 0.181–2.84 nmol/L; OP 0.385–38.1 nmol/L; LP 5.82–75.9 nmol/L; PMP <0.159–0.401 nmol/L	Serum	+2–8°C

*Immulite product booklet, IGF-1, Immulite 2000 IGF-1 (PIL2KIGF-4, 2018–07-02).

Table 2
Demographic and clinical characteristics of the study population. OR = odds ratio, CI = confidence interval, BMI = body mass index, SD = standard deviation, SBP = systolic blood pressure, DBP = diastolic blood pressure, HoC = hormone contraception, mTBI = mild traumatic brain injury. * = significant p value <0.05, ** = mean (min;max)

		Total (n = 133)	Evaluation by an endocrinologist		OR [95%CI]	P value
			No (n = 45)	Yes (n = 88)		
Still playing	Yes	72 (54.1%)	28 (62.2%)	44 (50.9%)		0.182
	No	61 (45.9%)	17 (37.8%)	44 (50.0%)	—	
Age**	29.2 (17; 46)	31.2 (20.0; 46.0)	28.2 (17.0; 46.0)	*0.94 [0.95–0.99]*	*0.034**	
BMI, mean (SD)	26.2 (4.7)	25.8 (3.7)	26.4 (5.2)	—	0.442	
SBP, mean (SD)	124 (12.0)	123 (12.5)	125 (11.8)	—	0.361	
DBP, mean (SD)	78.3 (9.1)	77 (7.7)	78.9 (9.7)	—	0.268	
Previous medical	Yes	56 (42.1%)	18 (40.0%)	38 (43.2%)		0.725
history	No	77 (57.9%)	27 (60.0%)	50 (56.8%)	—	
Previous hormonal	Yes	13 (9.8%)	4 (8.9%)	9 (10.2%)	—	0.806
disease	No	120 (90.2%)	41 (91.1%)	79 (89.8%)	—	
HoC	No	54 (40.6%)	18 (40.0%)	36 (40.9%)		
	Before mTBI	21 (15.8%)	9 (20.0%)	12 (13.6%)	—	0.442
	After mTBI	22 (16.5%)	10 (22.2%)	12 (13.6%)	—	0.322
	Before and after mTBI	36 (27.1%)	8 (17.8%)	28 (31.8%)	—	0.257
Menstrual changes	After mTBI	17 (12.8%)	5 (11.1%)	12 (13.6%)		0.680
	No changes	116 (87.2%)	40 (88.9%)	76 (86.4%)	—	
Time from mTBI (years)**	5.0 (0.04; 35.2)	5.8 (0.04; 35.2)	4.7 (0.04; 25.6)	—	0.308	
Number of mTBI**	2.2 (1;4)	2.2 (1;4)	2.1 (1;4)	—	0.568	
Number of mTBI symptoms**	3.88 (0; 13)	2.9 (0;12)	4.3 (0;13)	*1.15 [1.01–1.33]*	*0.045**	

HoC use before mTBI: OC (n = 19), contraceptive ring (n = 1), hormone coil (n = 1). HoC use after mTBI: OC (n = 17), contraceptive injections (n = 1), hormone coil (n = 3), birth control patch (n = 1). HoC before and after mTBI: OC (n = 27), contraceptive injections (n = 1), hormone coil (n = 2). Six women switched HoC before and after mTBI, four from OC to the hormone coil, one from OC to contraceptive injections and one from contraceptive injection to the contraceptive ring.

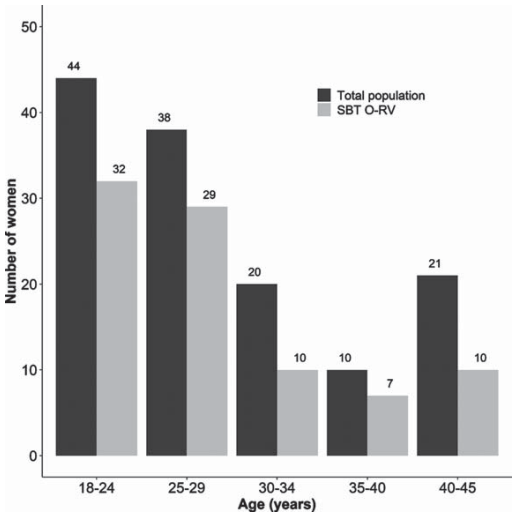

Fig. 2. The age distribution for the total study population ($n = 133$) and those with serum hormone levels outside reference values after two screening blood tests ($n = 91$). SBT O-RV = screening blood test outside reference value.

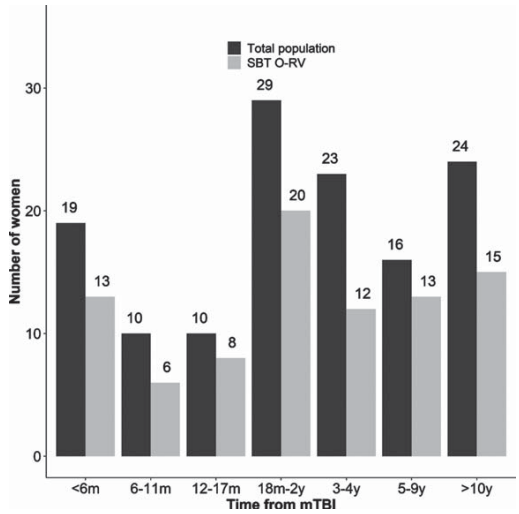

Fig. 3. Time from the latest mTBI until SBT for the study population ($n = 131$) and those with serum hormone levels O-RV ($n = 90$). Two women did not recall the exact time of mTBI and are therefore not included in the figure, one of which had SBT O-RV. m = months, y = years, SBT O-RV = screening blood test outside reference value.

grade 1 HTN (140–159 mmHg) and one (0.8%) had grade 2 HTN (≥160 mmHg). The use of HoC was reported by 59.4% of women with 47.4% taking oral contraception (OC) (Table 2). Thus, the gonadotropic axis was not evaluated further in these women. The time from the most recent mTBI until the SBT is presented in Table 2 and divided into intervals in Fig. 3. The mean time from the medical interview and physical examination until SBT were taken was 2.15 months (range 0.03–19 months).

The most common mTBI symptoms were drowsiness ($n = 60$, 45.1%), difficulties with concentration ($n = 58$, 43.6%), headache ($n = 56$, 42.1%) and memory disturbances ($n = 50$, 37.6%). Other symptoms included light sensitivity ($n = 33$, 24.8%), dizziness ($n = 33$, 24.8%), fatigue ($n = 29$, 21.8%), visual disturbances ($n = 26$, 19.5%), noise sensitivity ($n = 25$, 18.8%), balance disturbances ($n = 18$, 13.5%), nausea ($n = 16$, 12.0%) and tinnitus ($n = 12$, 9.0%). Although the retired athletes did not report a significantly higher number of mTBI ($p = 0.55$) they reported a significantly greater number of mTBI symptoms ($p = 1.39 \times 10^{-6}$) than the athletes who were still active in their sport.

There were 13 women with a previous history of hormonal disease (decreased levels of sex hormones and elevated S-prolactin $n = 1$, polycystic ovary syndrome $n = 5$, elevated s-prolactin $n = 1$, hyperthyroidism $n = 1$ and hypothyroidism $n = 5$). Ten of these 13 women had SBT O-RV (S-IGF1 below median RV $n = 7$, S-IGF1 and S-cortisol below RV $n = 1$, thyroid hormones, and S-IGF1 below RV $n = 1$ and S-cortisol and S-prolactin above RV $n = 1$). The hormones that were O-RV were not previously known to be abnormal except for one woman who had elevated S-prolactin in SBT and a prior history of elevated S-prolactin levels. However, the hyperprolactinemia had never been evaluated further.

A previous history of depression and/or anxiety was reported by 17 women (12.8%) and 15 of them were treated with selective serotonin reuptake inhibitor. No significant correlation was found between depression and/or anxiety and SBT O-RV ($p = 0.45$).

Other medications reported at inclusion were; antihypertensive treatment ($n = 3$), medications for attention deficit hyperactivity disorder ($n = 5$), asthma ($n = 4$), levothyroxine ($n = 5$), flecainide for premature atrial beat ($n = 1$), for pain treatment (gabapentin $n = 3$) and nonsteroidal anti-inflammatory drugs ($n = 4$), for sleep disturbance (melatonin $n = 1$, zolpidem $n = 1$, amitriptyline $n = 2$), anti-allergic drugs ($n = 3$), insulin for type 1 diabetes mellitus ($n = 1$), oestrogen supplementation with tibolone ($n = 1$).

The physical examination was normal for all participants, none had features suggesting hypercor-

tisolism or acromegaly. Three had abnormal heart sounds and were referred for a cardiological workup. All women had a normal ECG. The neurological examination was normal for all participants except eight women had discomfort on eye movement evaluation, although only one had visibly abnormal eye movements with slight lateral deviation of the left eye on convergence. Women with eye movement discomfort reported a significantly greater number of mTBI symptoms ($p = 8.1 \times 10^{-11}$) than those without eye movement discomfort. A significant correlation between eye movement discomfort and SBT O-RV was not found ($p = 0.26$).

The mean serum levels for each hormonal measurement in the SBT is presented in Table 3. The first SBT were O-RV in 118 women (88.7%) and within the RV in the remaining 15 women (Fig. 1). The second blood test was O-RV in 91 women (68.4%) and within RV in 22 women (16.5%). A third blood test was performed in 51 women prior to the evaluation with an endocrinologist (Fig. 1), 43 women had serum hormonal levels O-RV in the third blood test.

Further endocrinological evaluation with regards to possible HP was indicated for 88 (66.2%) of the 91 women with SBT O-RV (Fig. 1, Table 4). Two women had elevated S-cortisol levels and one had elevated S-IGF1 without abnormalities in other hormonal axes. Thus, these three women were not referred for further workup for possible HP. Of the 88 women referred for further evaluation, S-IGF1 levels were below the median RV in 74 women (55.6%). Eight women (5.3%) had S-cortisol levels below the RV and thyroid hormone levels were below RV in 15 women (11.3%). Elevated levels of S-prolactin were present in 30 women (22.6%) who had a mean time of 2.95 years (range 2 weeks - 11.1 years) from the latest mTBI until the SBT. One woman had gonadotropin levels below the RV in all three SBT but did not need further endocrinological evaluation as she was taking OC.

Women with SBT results indicating possible HP ($n = 88$) were compared to those with serum hormonal levels within the RV ($n = 45$) for possible risk factors (Table 2). A significant correlation for age and the number of mTBI symptoms was found. With older age, the likelihood of blood test results O-RV decreased (OR 0.94, CI 0.95–0.99) and increased with rising numbers of reported mTBI symptoms (OR 1.15, CI 1.01–1.33).

When comparing the number of mTBI symptoms ($\leq$3 symptoms or >3 symptoms) between the women with one affected hormonal axis and those with two or more affected axes, no statistical significance was found ($p = 0.645$).

4. Discussion

To the best of our knowledge, this is the first all-female study on screening for possible HP following mTBI. A considerable majority (66.2%) had SBT results indicating possible HP. Thus, HP may be a clinically important consideration for medical staff involved in the care of female athletes following mTBI. However, the diagnosis of HP following mTBI requires further endocrinological evaluation and testing. A much lower prevalence of possible HP was reported in a male population, where 42% of serum hormonal blood levels were O-RV (Wilkinson et al., 2012) possibly indicating a sex-related difference (McGroarty et al., 2020). In studies where further endocrinological tests were performed, HP prevalence following mTBI ranged from 13–48% (Ives et al., 2007; Kelestimur et al., 2004; Kelly et al., 2014; Klose et al., 2007; Northam et al., 2020; Schneider et al., 2007; Tanriverdi et al., 2007; Tanriverdi et al., 2008), which is also substantially lower than reported in this study. All participants with SBT O-RV in the current study were referred for further endocrinological evaluation for possible HP.

The somatotropic axis, evaluated by S-IGF1 and symptoms of GHD, was most commonly affected (Table 4), either in isolation or along with other hormonal axes O-RV, which is in line with earlier reports (Aimaretti et al., 2005; Bensalah et al., 2020; Ives et al., 2007; Kelestimur et al., 2004; Kelly et al., 2014; Klose et al., 2007; Kokshoorn et al., 2010; Northam et al., 2020; Schneider et al., 2007; Tanriverdi et al., 2007; Tanriverdi et al., 2008; Wilkinson et al., 2012). Despite symptoms indicating GHD and S-IGF1 below median RV, dynamic testing of growth hormone production is necessary to confirm or exclude GHD. However, the large proportion of women in the current study with possible somatotropic axis affection emphasizes the importance of being aware of GHD following mTBI. The lactotroph axis was the second most affected axis, followed by the corticotrope and thyrotrope axis, respectively. This differs from previous reports where the gonadotroph or corticotrope axes have been the second most affected following a TBI (Aimaretti et al., 2005; Bensalah et al., 2020; Ives et al., 2007; Kelestimur et al., 2004; Kelly et al., 2014; Klose et al., 2007; Northam et al., 2020; Schneider et al.,

Table 3
Mean values of screening blood test results for the entire population, $n = 133$. As seen in Fig. 1, five women were lost to follow up between the first and the second blood test. n = the number participants that needed repeated hormonal measurements, min = minimal value, max = maximal value, S-TSH = serum thyroid stimulating hormone, S-fT4 = serum free thyroxin, S-IGF-1 = serum insulin like growth factor 1, S-FSH = follicle stimulating hormone, S-LH = luteinizing hormone

		Blood test 1 $n = 133$	Blood test 2 $n = 113$	Blood test 3 $n = 51$
Hormone axis	Analysis	Mean (min;max)	Mean (min;max)	Mean (min; max)
Thyrotrope			$n = 30$	$n = 14$
	S-TSH	2.6 (0.01; 8.7)	2.9 (0.13;6.7)	2.8 (0.01; 9.5)
	S-fT4	15.1 (10.2; 20.4)	13.9 (10.9; 18.6)	14.3 (11.0; 18.2)
Lactotroph			$n = 57$	$n = 24$
	S-prolactin	25.8 (3.7; 169.7)	33.7 (0.5; 196.1)	35.9 (12.6; 184.7)
Corticotrope			$n = 63$	$n = 18$
	S-cortisol	520.1 (96.0; 1339.0)	616.2 (231.0; 1236.0)	536.3 (170.0; 1141.0)
Somatotroph			$n = 94$	$n = 33$
	S-IGF1	169.4 (44.0; 329.0)	158.7 (61.0; 272.0)	165.2 (61.0; 272.0)
			$n = 4$	$n = 1$
	S-FSH	4.5 (0.1; 13.0)	4.2 (2.0; 7.2)	3.7
Gonadotroph	S-LH	8.1 (0.1; 68.6)	7.1 (2.0; 11.7)	5.3
	S-oestradiol	267.5 (18.4; 1558.0)	325.4 (18.4; 949.0)	167.0
	S-progesterone	7.4 (0.2; 50.4)	17.5 (0.3; 64.4)	3.6

Table 4
Screening blood test results. Total number of women with SBT O-RV possibly indicating HP and the number of pituitary hormone axes O-RV

No. of affected PHA	Total $n = 133$ (%)	Affected PHA	SBT O-RV $n = 88$ (%)	Description
0	45 (33.8%)	—	—	—
1	54 (40.6%)	L	7 (7.9%)	↑ S-Prolactin, $n = 7$
		S	42 (47.7%)	↓ S-IGF1, $n = 42$
		T	5 (5.7%)	↔ S-TSH, ↓ S-fT4, $n = 3$
				↑ S-TSH, ↔ S-fT4, $n = 2$
2	30 (22.6%)	S + L	17 (19.3%)	↑ S-Prolactin, ↓ S-IGF1, $n = 17$
		S + C	5 (5.7%)	↓ S-Cortisol, ↓ S-IGF, $n = 5$
		C + L	1 (1.1%)	↑ S-Prolactin, ↓ S-Cortisol, $n = 1$
		S + T	6 (6.8%)	↔ S-TSH, ↓ S-fT4, ↓ S-IGF1, $n = 6$
		L + T	1 (1.1%)	↑ S-TSH, ↔ S-fT4, ↑ S-Prolactin, $n = 1$
3	3 (2.3%)	C + L + S	1 (1.1%)	↑ S-Prolactin, ↓ S-Cortisol, ↓ S-IGF, $n = 1$
		T + L + S	2 (2.3%)	↑ S-Prolactin, ↑ S-TSH, ↔ S-fT4, ↓ S-IGF1, $n = 2$
4	1 (0.7%)	S + L + C + T	1 (1.1%)	↑ S-Prolactin, ↓ S-Cortisol, ↑ S-TSH, ↔ S-fT4, ↓ S-IGF1, $n = 1$

↔ = within reference value (RV), ↓ = below RV, ↑ = above RV. No. = number, PHA = pituitary hormone axis, total = the total number of women with SBT O-RV, L = Lactotroph, *S* = Somatotroph, T = Thyrotrope C = Corticotrope.

2007; Tanriverdi et al., 2007; Tanriverdi et al., 2008; Wilkinson et al., 2012).

Following TBI, hypothalamic or pituitary impairment can cause elevated S-prolactin levels (Yousefvand et al., 2020) due to decreased transportation of prolactin inhibitory factors down the pituitary stalk (Scranton & Baskin, 2015). In our study, the time from mTBI to hormonal evaluation for the women with elevated S-prolactin levels ranged from two weeks to 11.1 years with a mean of 2.95 years. Despite this, we found a larger prevalence of S-prolactin levels above the RV, 22.6%, than previously reported (3.8%–16%) (Agha et al., 2004; Aimaretti et al., 2005; Bensalah et al., 2020; Bondanelli et al., 2004; Klose et al., 2007; Kokshoorn et al., 2010; Tanriverdi et al., 2006). It is intriguing that the S-prolactin levels in our study remained elevated for such an extended period following mTBI, possibly indicating long-term pituitary gland damage. Only ten of the 30 women with repeatedly elevated S-prolactin levels were taking medication that may affect S-prolactin levels (SSRI $n = 2$, hormone contra-

ception $n = 5$, SSRI and hormone contraception $n = 3$) (Torre & Falorni, 2007). Thus, the use of medications does not explain the large proportion of elevated S-prolactin found in our study. The elevated levels of S-prolactin may reflect pituitary or hypothalamic injury following mTBI and needs to be included in screening for possible HP after mTBI.

As many women in our study population were taking HoC (59.4%) and the SBT were taken at various times during the menstrual cycle, it likely affected the gonadotroph axis. It has been proposed that HoC use may have protective effects against symptoms of mTBI (Gallagher et al., 2018). Whether or not such protective effects against HP exist remains unclear as much of our study population will need further endocrinological evaluation for possible HP, despite a large proportion taking HoC.

There were 30 women who had SBT results O-RV which normalized when repeated for a second or third time, possibly representing normal hormonal fluctuations or improvement of pituitary gland injury. The time from the mTBI until the SBT varied substantially (Table 2, Fig. 3). More than two years passed for half of the study population and more than ten years for 18%. Therefore, it is remarkable that a majority of the population had SBT O-RV. This contradicts previous reports stating that HP following TBI tends to improve with time (Aimaretti et al., 2005; Schneider et al., 2006; Tanriverdi et al., 2006). However, as the somatotroph axis may not be affected shortly after the mTBI, GHD can be missed if hormonal evaluation is only performed right after the mTBI. The appropriate timing of hormonal evaluation after mTBI remains unclear (Glynn & Agha, 2013; Tan et al., 2017; Tanriverdi et al., 2015).

When comparing women with SBT O-RV to those that did not, a significant correlation with age and the number of mTBI symptoms was found (Table 2). With increasing age, the likelihood of blood test results O-RV decreased (OR 0.94, CI 0.95–0.99) but increased with the number of reported mTBI symptoms (OR 1.15, CI 1.01–1.33). Thus, younger age and symptoms of mTBI may indicate which women might need SBT for possible HP following mTBI.

Eight women had discomfort on eye movement evaluation, indicating vestibulo-ocular impairments which are known consequences of mTBI and can be used for mTBI screening (Mucha et al., 2014). As vestibulo-ocular impairment can cause symptoms such as dizziness, headaches, and visual disturbances (Mucha et al., 2014), it is unsurprising that women with eye movement discomfort reported a significantly greater number of mTBI symptoms ($p = 8.1 \times 10^{-11}$).

Depression is a known risk factor for mTBI (Holsinger et al., 2002) and a linear relationship seems to exist between depression prevalence and the number of mTBI (Didehbani et al., 2013; Finkbeiner et al., 2016; Guskiewicz et al., 2007). Furthermore, symptoms of mTBI and depression tend to overlap (Iverson, 2006). A previous history of depression and/or anxiety was reported by 17 women (12.8%) which is in line with depression prevalence (16.7%) reported in a general population of athletes not focusing on mTBI (Jensen et al., 2018) but lower than described in a general population after mTBI (23%) (Delmonico et al., 2021).

4.1. Strengths and limitations

To the best of our knowledge, this is the first all-female study screening for possible HP after mTBI which is a strength of the study. Additionally, the female study population ($n = 133$) is much larger than in previous studies focusing on both sexes (Agha et al., 2004; Aimaretti et al., 2005; Bensalah et al., 2020; Bondanelli et al., 2004; Kelly et al., 2000; Klose et al., 2007; Kokshoorn et al., 2011; Lieberman et al., 2001; Schneider et al., 2006; Tanriverdi et al., 2006; Tanriverdi et al., 2007; You et al., 2019). Blood tests were not taken at a predetermined time following mTBI. As a result, the time from mTBI until the hormonal evaluation differs considerably and may be a limitation of the study. Nevertheless, it might also be considered a strength since more than ten years passed from mTBI until SBT in some cases, possibly providing important information on the long-term hormonal effects of mTBI. Dynamic testing of pituitary function was not performed in this study which is a limitation although all female athletes with SBT O-RV were referred for further endocrinological evaluation.

The study is retrospective, relying on participant reports, which is a limitation as mTBI tends to be underreported (Anderson et al., 2016; Kerr et al., 2016; McDonald et al., 2016; Register-Mihalik et al., 2013). Indications of mTBI underreporting in the current study population have been reported from part I and II of the study. The proportion of participants reporting mTBI increased from 40.2% to 64.8% after reading a definition of mTBI (Kristjánsdóttir et al., 2020). Thus, it is a strength of the study that we included female athletes who reported a mTBI after reading a definition of mTBI. The correlation found

between the number of mTBI symptoms and SBT O-RV may be biased as women with S-IGF1 below median RV were only referred for further workup if symptoms of possible GHD were also present. Women with S-IGF1 levels below median RV and no symptoms of GHD were not. Despite the study population being large compared to previous studies (Agha et al., 2004; Aimaretti et al., 2005; Bensalah et al., 2020; Bondanelli et al., 2004; Kelestimur et al., 2004; Kelly et al., 2014; Kelly et al., 2000; Klose et al., 2007; Lieberman et al., 2001; Schneider et al., 2007; Schneider et al., 2006; Tanriverdi et al., 2015; Tanriverdi et al., 2006; Tanriverdi et al., 2007; Tanriverdi et al., 2008; Wilkinson et al., 2012; You et al., 2019), an even larger population may be required to identify possible risk factors of HP.

5. Conclusions and clinical implications

We conclude that a large proportion of the sample had SBT O-RV possibly indicating HP and necessitating further endocrinological evaluation. Most commonly, S-IGF1 levels were below median RV. Elevated levels of prolactin following mTBI may reflect pituitary or hypothalamic injury. Lower age and an increased number of mTBI symptoms may indicate the need to screen for HP after mTBI. Our results suggest that screening for possible HP needs to be considered following mTBI. Coaches, physiotherapists, doctors, and all relevant personnel need to be aware of this as pituitary dysfunction is treatable.

Conflict of interest

Sigrún Helga Lund is a statistician employed by deCODE Genetics Inc./Amgen Inc. The other authors have no conflict of interests to declare that are relevant to the content of this article

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Erratum

Erratum to: Screening for possible hypopituitarism following mild traumatic brain injury: The first all-female study. Who do we need to evaluate further?

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On page 264 there was an error in the layout of Table 2; some data was misplaced in the wrong column. The correct Table 2 is as follows:

		Total (n = 133)	Evaluation by an endocrinologist		OR [95%CI]	P value
			No (n = 45)	Yes (n = 88)		
Still playing	Yes	72 (54.1%)	28 (62.2%)	44 (50.9%)	---	0.182
	No	61 (45.9%)	17 (37.8%)	44 (50.0%)		
Age**		29.2 (17; 46)	31.2 (20.0; 46.0)	28.2 (17.0; 46.0)	*0.94 [0.95 – 0.99]*	*0.034**
BMI, mean (SD)		26.2 (4.7)	25.8 (3.7)	26.4 (5.2)	---	0.442
SBP, mean (SD)		124 (12.0)	123 (12.5)	125 (11.8)	---	0.361
DBP, mean (SD)		78.3 (9.1)	77 (7.7)	78.9 (9.7)	---	0.268
Previous medical history	Yes	56 (42.1%)	18 (40.0%)	38 (43.2%)		
	No	77 (57.9%)	27 (60.0%)	50 (56.8%)	---	0.725
Previous hormonal disease	Yes	13 (9.8%)	4 (8.9%)	9 (10.2%)	---	0.806
	No	120 (90.2%)	41 (91.1%)	79 (89.8%)	---	
HoC	No	54 (40.6%)	18 (40.0%)	36 (40.9%)		
	Before mTBI	21 (15.8%)	9 (20.0%)	12 (13.6%)	---	0.442
	After mTBI	22 (16.5%)	10 (22.2%)	12 (13.6%)	---	0.322
	Before and after mTBI	36 (27.1%)	8 (17.8%)	28 (31.8%)	---	0.257
Menstrual changes	After mTBI	17 (12.8%)	5 (11.1%)	12 (13.6%)		
	No changes	116 (87.2%)	40 (88.9%)	76 (86.4%)	---	0.680
Time from mTBI (years) **		5.0 (0.04; 35.2)	5.8 (0.04; 35.2)	4.7 (0.04; 25.6)	---	0.308
Number of mTBI **		2.2 (1;4)	2.2 (1;4)	2.1 (1;4)	---	0.568
Number of mTBI symptoms **		3.9 (0; 13)	2.9 (0;12)	4.3 (0;13)	*1.15 [1.01 – 1.33]*	*0.045**

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RESEARCH

Pituitary dysfunction following mild traumatic brain injury in female athletes

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Abstract

Objective: Pituitary dysfunction following mild traumatic brain injury can have serious physical and psychological consequences, making correct diagnosis and treatment essential. To the best of our knowledge, this study is the first to study the prevalence of pituitary dysfunction following mild traumatic brain injury in an all-female population following detailed endocrinological work-up after screening for pituitary dysfunction in female athletes.

Design: This is a retrospective cohort study.

Methods: Hormone screening blood tests, including serum blood values for thyroid-stimulating hormone, free thyroxin, insulin-like growth factor 1, prolactin, cortisol, follicle-stimulating hormone, luteinizing hormone, estrogen and progesterone, were taken in 133 female athletes. Results were repeatedly outside the reference value in 88 women necessitating further endocrinological evaluation. Two of those were lost to follow-up, and further endocrinological evaluation was performed in 86 participants.

Results: Six women (4.6%, $n = 131$) were diagnosed with hypopituitarism, four (3.1%) with central hypothyroidism and two with growth hormone deficiency (1.5%). Ten women (7.6%) had hyperprolactinemia, and four (3.1%) of them had prolactinoma. Medical treatment was initiated in 13 (9.9%) women. Significant prognostic factors were not found.

Conclusions: As 12.2% of female athletes with a history of mild traumatic brain injury had pituitary dysfunction (hypopituitarism 4.6%, hyperprolactinemia 7.6%), we conclude that pituitary dysfunction is an important consideration in post-concussion care. Hyperprolactinemia in the absence of prolactinoma may represent pituitary or hypothalamic injury following mild traumatic brain injury.

Significance statement

Mild traumatic brain injury (mTBI) has become a growing public health concern as 50 million people worldwide sustain a traumatic brain injury annually, with mTBI being the most common (70–90%). As studies on mTBI have

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focused on mostly male populations this study aims to explore pituitary dysfunction (PD) in female athletes following mTBI. To the best of our knowledge, it is the first all-female study on PD following mTBI.

The study found that 12.2% of the participating women had PD after mTBI. Six (4.6%) had hypopituitarism and ten (7.6%) had hyperprolactinemia. These findings suggest that PD following mTBI is an important consideration that endocrinologists and other medical staff working with athletes need to be aware of.

Keywords: hypopituitarism (HP); mild traumatic brain injury (mTBI); traumatic brain injury (TBI); sport-related concussion (SRC); female athletes; hyperprolactinemia

Introduction

Traumatic brain injury (TBI) is divided into mild (mTBI), moderate (moTBI), and severe (sTBI) injury. The most common is mTBI (1) which is caused by mechanical force being transmitted to the brain by a blow to the head, neck or body, acceleration–deceleration movement, or forces from a blast injury. Symptoms can present immediately, within hours or days and may or may not include loss of consciousness for less than 30 min (2, 3). Furthermore, recent diagnostic criteria for mTBI include a Glasgow coma scale (GCS) score of 13–15 after 30 min from the head injury, post-traumatic amnesia for less than 24 h, and normal neuroimaging studies (3, 4, 5). Symptoms of mTBI often resolve within a few weeks although prolonged cognitive and psychological effects can occur (6, 7). Furthermore, it has been demonstrated that mTBI can lead to hypopituitarism (HP) with a prevalence of 13–48% (8, 9, 10, 11, 12, 13, 14, 15), making it an important consideration of post-concussion care.

It has been speculated that HP following TBI may be due to direct or indirect injury to the pituitary gland or hypothalamus with four possible mechanisms of indirect injury (16):

1. Vascular injury to arteries supplying the pituitary gland resulting in ischemic damage (17).
2. Neuroinflammation and cytokine release can occur following mTBI causing pituitary damage (17).
3. Autoimmunity may also have a role in indirect pituitary injury following mTBI, as studies have found anti-pituitary antibodies in patients with previous mTBI (18).
4. Uncontrolled release of excitatory neurotransmitters following injury may damage neuronal cells in the pituitary gland by affecting cellular permeability (19).

Undiagnosed HP following mTBI can have serious physical and psychological consequences depending on which axes are affected (20, 21). While untreated glucocorticoid deficiency (GCD) can be life-threatening, symptoms of growth hormone deficiency (GHD) may be subtle and overlaps with symptoms of mTBI causing diagnostic delay. However, if left untreated, GHD can lead to decreased quality of life (22), metabolic alterations (23, 24, 25), osteopenia and osteoporosis (23, 25), and increased risk of cardiovascular and cerebrovascular morbidity and mortality (24, 25, 26). As hormonal supplementation therapy (HST) can reverse the metabolic and psychological effects of GHD (23, 25) accurate diagnosis and treatment is vital. Furthermore, even subclinical untreated hypothyroidism can have serious effects such as increased cardiovascular morbidity, and mortality (27) and gonadotropic deficiency can impact fertility and cause comorbidities of decreased gonadal hormones. Earlier reports indicate that the somatotropic axis is most commonly affected by mTBI with a prevalence of 8–48% (8, 11, 12, 13, 14, 15, 28, 29). The somatotroph cells may be prone to vascular injury as they receive blood supply via the long hypophysial portal vessels that are especially vulnerable (30).

Contrary to other pituitary hormones, which can become deficient following mTBI, hyperprolactinemia (HPRL) can occur following TBI (mTBI, moTBI and sTBI) (15, 31, 32, 33, 34, 35, 36). Pituitary gland injury affects the dopaminergic inhibitory control of prolactin release, resulting in rising serum prolactin (s-prolactin) levels (30). Thus, HPRL may be a sign of pituitary or hypothalamic injury following TBI (36) and may be a marker of TBI severity, as it has been shown to correlate negatively with GCS (37).

Definite diagnosis of GCD or GHD involves stimulation testing, the synacthen test for GCD diagnosis (38) and the insulin tolerance test (ITT) for GHD and GCD diagnosis. Due to potential risks related to the ITT, a safer method such as the combined test with growth hormone releasing hormone and arginine (GHRH–arginine test) has been validated for GHD diagnosis (39, 40). As stimulation tests can be time consuming and expensive, a biochemical marker for GHD screening would be beneficial. Serum insulin-like growth factor 1 (s-IGF1) has been proposed as a screening tool for GHD as low s-IGF1 may indicate GHD. However, its use remains debatable as s-IGF1 within normal range does not exclude GHD (28, 40).

Female athletes remain an understudied population with regards to mTBI (41) and HP following mTBI even though they appear to be more susceptible to mTBI

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(42) and recovery time seems longer than with male athletes (43). The aim of this study was to explore pituitary dysfunction (PD) including HP in female athletes following mTBI in sport and, to the best of our knowledge, it is the first study to do so.

Materials and methods

Study design and subjects

This study is a part of more extensive research on female athletes. A comprehensive description of the population inclusion criteria has been published (44, 45, 46). The study included women aged 18–45 years currently active in or retired from soccer, handball, basketball, ice hockey and martial arts in Iceland. Of the 508 women included in part 1 of the study, 166 women accepted further participation in part 2 including a detailed psychological interview focusing on mTBI history and neuropsychological testing (44, 46). Following part 2, all 166 women were invited to participate in part 3 of the study, presented here, with 151 women (91.0%, $n=166$) accepting, 15 women (9.0%) were lost to follow-up. In part 3, a physical examination was conducted by the same medical doctor (LÓEC) for all participants including a neurological examination, and hormonal screening blood tests (SBT) for possible PD. Hormonal evaluation of all pituitary axes was performed with SBT taken in 133 women (88.1%, $n=151$), nine were lost to follow-up and nine were pregnant. All SBT results were reviewed by the same endocrinologist (HÁS). If SBT results were outside reference value (O-RV) in two or three repeated blood tests for each serum hormonal measurement, they were defined as abnormal (45).

Of the 133 women who had SBT taken, 88 women (66.2%, $n=131$) had results repeatedly O-RV necessitating further evaluation including a medical interview with an endocrinologist, physical examination and possibly further endocrinological testing (Fig. 1). Two of these 88 participants did not attend the visit despite repeated attempts to contact them and were thus lost to follow-up (Fig. 1). Thus, 86 women (64.6%, $n=131$) attended the medical interview with an endocrinologist followed by detailed endocrinological testing as indicated. All female participants diagnosed with PD requiring treatment or follow-up will be followed by the endocrinologist (HÁS).

Measurements and analytical methods

The SBT were taken at 08:00 h at the earliest convenient day for the participants and included serum thyroid-stimulating hormone (s-TSH), serum free thyroxin (s-fT4), s-IGF1, s-prolactin, serum cortisol (s-cortisol), serum follicle-stimulating hormone (s-FSH), serum luteinizing hormone (s-LH), serum estrogen (s-estrogen) and serum progesterone (s-progesterone). If the first SBT was O-RV for each hormone (Table 1), the blood tests were repeated for reevaluation.

In the endocrinological interview, further information regarding mTBI history was gathered as well as information regarding previous medical history, medications and possible clinical symptoms of mTBI or HP. Thus, information on mTBI symptoms was gathered at four different times during the study period (part 1, part 2 and twice in part 3). Height, weight, blood pressure and heart rate were measured. Further endocrinological tests were then requested as necessary.

Endocrinological tests

When s-fT4 was below reference value (RV) (Table 1) serum levels of anti-thyroid peroxidase antibodies (s-anti-TPO) were measured using the EliA method (fluoroenzymeimmunoassay) to exclude autoimmune hypothyroidism. Central hypothyroidism was suspected if s-anti-TPO was negative along with low or normal TSH levels and low s-fT4 levels. Consequently, magnetic resonance imaging (MRI) was requested for further work-up.

For s-IGF1, results below median RV (Table 1) were considered abnormal if clinical symptoms of GHD such as decreased vitality and energy, impaired psychological well-being (22, 25), and changes in memory and attention (47, 48) were also present and further evaluation with a GHRH–arginine test was performed as described in the consensus guidelines (40). If s-IGF1 was repeatedly below median RV without any symptoms of GHD, further endocrinological evaluation was not performed.

An ITT was performed in one woman due to practical reasons and strong clinical symptoms indicating GHD. It was performed as described in the consensus guidelines (40).

The lactotroph axis was evaluated using s-prolactin measurements. When s-prolactin level was found to be elevated, a macroprolactin analysis was performed to differentiate between monomeric prolactin and macroprolactin. When s-prolactin was repeatedly above RV (Table 1), an MRI was performed.

When s-cortisol was below 350 nmol/L (49), plasma adrenocorticotropic hormone (ACTH) was measured and a high dose (250 µg) synacthen test was performed as earlier described (50, 51). A normal response was defined as s-cortisol ≥440 nmol/L after either 30 or 60 min.

Ethics

The study was approved by the National Bioethics Committee (no. VSN-18-091), the Icelandic Data

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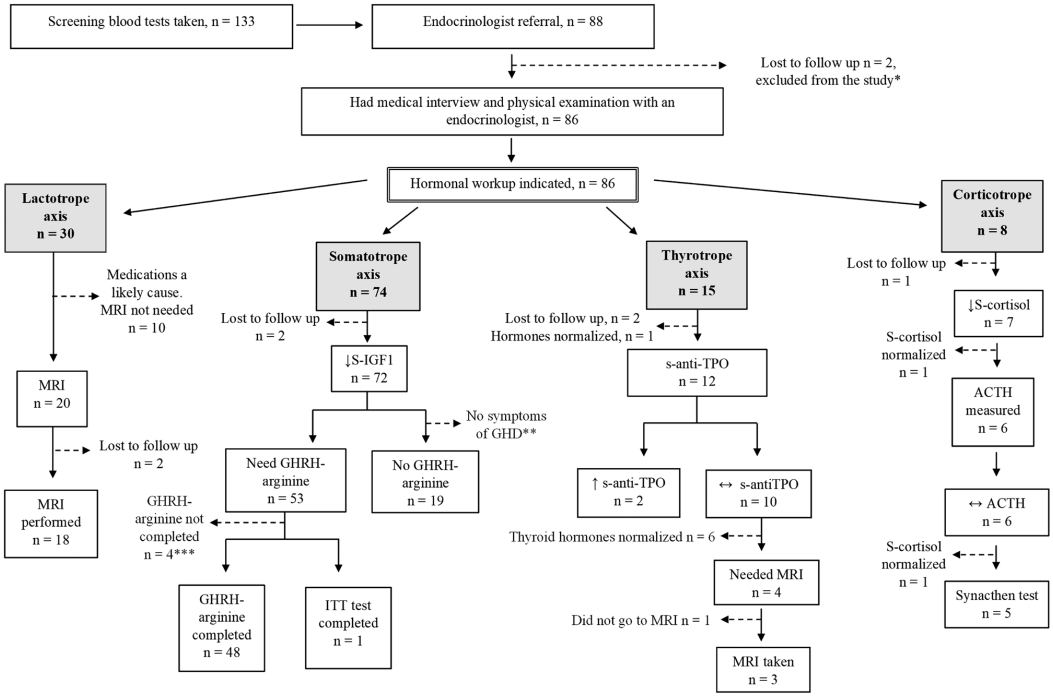

Figure 1

Overview of the study design and the detailed endocrinological work-up. *As two of the 88 women who needed further endocrinological evaluation did not attend the medical interview with the endocrinologist they were excluded from the study. Thus, 131 women instead of 133 had SBT and 86 women instead of 88 had a detailed endocrinological evaluation. **GHRH–arginine tests were not performed for 19 women who did not have symptoms indicating possible GHD. ***Lost to follow-up ($n = 1$), pregnant when the test was to be conducted ($n = 2$) and one woman is being treated for hyperprolactinemia and followed by the endocrinologist before the GHRH–arginine stimulation test can be performed if necessary. ↔ Blood test results within RV; ↑ Blood test results above RV; ↓ Blood test results below RV. ACTH, adrenocorticotropic hormone; anti-TPO, anti-thyroid peroxidase antibodies; GHRH–arginine, growth hormone-releasing hormone and arginine; ITT, insulin tolerance test; MRI, magnetic resonance imaging; S-cortisol, serum cortisol; S-IGF1, serum insulin like growth factor 1.

Protection Authority, the Institutional Research Committee of Landspitali National University Hospital, Iceland, the chief medical officer of Landspitali National University Hospital, Iceland and Laeknasetrid outpatient clinic (OB/ei Tilv. 16).

Statistical analysis

Statistical analysis was performed using R (version 3.6.1). A two-sample *t*-test and the chi-squared test were used to compare women with PD and women with normal pituitary function to identify possible risk factors for PD (Table 2). Categorical data were examined for association significance using Fisher's exact test. The effect size (Table 2) was calculated using Cohen's *d* for the two-sample *t*-test, Phi (ϕ) for chi-squared test with 2 × 2 contingency tables. Population size needed for 80% power was calculated using Lehr's formula.

Results

Of the 131 women who had SBT taken, 86 (65.6%, $n = 131$) had results repeatedly O-RV and were referred for further endocrinological evaluation. Following detailed endocrinological testing 16 women were diagnosed with PD (12.2%, $n = 131$), 115 had normal pituitary function. Population characteristics and comparison between the two groups are presented in Table 2 (see also Fig. 1).

Thyroid hormone levels were O-RV in 15 participants (11.5%, $n = 131$) and further work-up of the thyroid axis was performed in 12 (9.1%) of them (Fig. 1). Two of the 12 women had s-anti-TPO levels above RV and were diagnosed with autoimmune hypothyroidism. Six of the 10 women with s-anti-TPO within RV were not evaluated further as their thyroid hormone levels normalized during follow-up. Four women (3.1%,

Table 1 Hormone measurements and analytical methods of serum hormones measured.

				CV%					Specimen	
Analyte	**Assay name**	**Manufacturer**	**Instrument**	**Low contr**	**Med. contr**	**High contr**	**Reportable range**	**Reference value**	**Type**	**Storage**
TSH	TSH	Roche	Elecsys	11.1	1.3	2.2	0.005–100 mIU/L	0.270–4.20 mIU/L	Serum	+2–8°C
fT4	FT4 III	Roche	Elecsys	4.3	1.5	2.6	0.5–100 pmol/L	12–22 pmol/L	Serum	+2–8°C
Prolactin	Prolactin II	Roche	Elecsys	1.5	3.0	2.4	0.0470–470 µg/L	Female (not pregnant) 4.79–23.3 µg/L	Serum	+2–8°C
Cortisol	Cortisol II	Roche	Elecsys	5.4	1.5	1.6	1.5–1750 nmol/L	Morning (06:10 h): 133–537 nmol/L, afternoon (16:08 h): 68.2–327 nmol/L	Serum	+2–8°C
IGF1	IGF-I	Siemens	Immulite 2000	6.3	3.1	2.5	15–1000 µg/L	Manufacturer's age-dependent reference range[a]	Serum	+2–8°C or −20°C
ACTH	ACTH	Roche	Elecsys	2.7	0.6	0.7	1.0–2000 ng/L	7.2–63.3 ng/L	Plasma	+2–8°C
GH	Growth hormone	Siemens	Immulite 2000	6.5	5.5	6.6	0.05–40 ng/mL	Females: up to 8 ng/mL	Serum	+2–8°C
Anti-TPO	EliA anti-TPO	Thermo Fisher	Phadia™ 250	–	–	–	–	<25 IU/mL = negative, 25–35 IU/mL = equivocal, >35 IU/mL = positive	Serum	+2–8°C

[a]Immulite product booklet, IGF-1, Immulite 2000 IGF-1 (PIL2KIGF-4, 2018-07-02).

ACTH, adrenocorticotropic hormone; Anti-TPO, anti-thyroid peroxidase antibodies; CV, coefficient of variation; fT4, free thyroxine; GH, growth hormone; High contr, high control; IGF1, insulin-like growth factor 1; Low contr, low control; Med. contr, median control; TSH, thyroid-stimulating hormone.

$n = 131$) were suspected having central hypothyroidism as they did not have s-anti-TPO and their s-TSH were low to normal with low fT4 levels. During follow-up of these four women, thyroid function tests were repeated at an interval ranging from 1 to 9 months with a mean of 3.2 months. Three of these four women had normal MRI results. One woman did not attend MRI and was lost to follow-up despite repeated attempts to contact her.

Of the 74 (56.5%, $n = 131$) women with s-IGF1 levels in SBT below median RV (Fig. 1), 19 did not have clinical symptoms indicating GHD and were not evaluated further. Clinical symptoms of GHD were present in 53 participants who were referred to further endocrinological testing (ITT $n = 1$, GHRH–arginine test $n = 52$). A GHRH–arginine test was completed in 48 of the 53 women (90.6%) (Fig. 1).

Elevated s-prolactin was found in 30 women (22.9%, $n = 131$) (Fig. 1). Ten were taking medications that can cause HPRL (selective serotonin reuptake inhibitors (SSRI) $n = 2$, hormone contraception $n = 5$, SSRI and hormone contraception $n = 3$) (52). Thus, further work-up for HPRL was not indicated in those women. Of the remaining 20 women who had elevated levels of s-prolactin, 18 had an MRI of the pituitary gland and two were lost to follow-up (Fig. 1). Seven of the 18 women had visible changes of the pituitary gland (hypopituitary atrophy and signs of a regressing prolactinoma $n = 1$, microadenoma $n = 2$, cystic/hemorrhagic adenoma $n = 1$, concentric enlargement of the adenohypophysis with no visible tumor $n = 1$, concentric enlargement of the pituitary gland $n = 1$, arachnoid cyst $n = 1$) and 11 had normal MRI results (Fig. 2). Four (3.1%, $n = 131$) of the seven women with abnormal MRI results had a prolactinoma (hypopituitary atrophy and signs of a regressing prolactinoma $n = 1$, microadenoma $n = 2$, cystic/hemorrhagic adenoma $n = 1$) (Fig. 2). In summary, of the 18 women who had further work-up of the lactotroph axis, 10 women (7.6%, $n = 131$) had repeatedly elevated levels of s-prolactin and were diagnosed with HPRL. The s-prolactin levels normalized during follow-up in eight women who were not diagnosed with HPRL (Fig. 2). Four of the 10 women with HPRL were diagnosed with a prolactinoma and 6 women were not.

S-cortisol was below RV (below 350 mmol/L) in eight women (6.2%) (Fig. 1). Six were evaluated further with plasma ACTH measurements that were all within the RV. Five women needed further work-up with a synacthen test which was normal (peak s-cortisol ≥440 nmol/L) for all.

As has been reported, one woman had gonadotropin levels below RV in SBT. However, further endocrinological evaluation was not indicated as she was taking hormonal contraception (HOC) (45).

Following a detailed endocrinological work-up, 16 (12.2%) of the 131 participating women had PD. Six women (4.6%) had HP (GHD $n = 2$, 1.5% and

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Table 2 Demographic and clinical characteristics of the study population. Women with pituitary dysfunction were compared to women with normal pituitary to identify possible risk factors for pituitary dysfunction. Statistical comparison between the two groups was not performed for sport, previous medical history, previous history of hormonal disease, hormonal contraception or menstrual changes as there were too few participants with PD for statistical analysis with the chi-square test. For the entire population ($n = 131$) the number of mTBI ranged from 1.0 to 4.0, BMI ranged from 19.1 to 46.5, time that passed from mTBI until SBT ranged from 0.04 to 35.2 years, the number of mTBI symptoms in endocrinologist interview ranged from 0 to 6.0, and the number of mTBI symptoms right after concussion from 1.0 to 8.0.

		Total $n = 131$	No PD $n = 115$	PD $n = 16$	Effect size	*P*
Sport[a] (%)						
	Soccer	52 (40.3%)	45 (39.8%)	7 (43.8%)	–	–
	Basketball	12 (9.3%)	9 (8.0%)	3 (18.8%)		
	Handball	48 (37.2%)	44 (38.9%)	4 (25.0%)		
	Ice hockey	9 (7.0%)	7 (6.2%)	2 (12.5%)		
	Martial arts	8 (6.2%)	8 (7.1%)	0 (0.0%)		
Still playing (%)						
	Yes	71 (54.2%)	64 (55.7%)	7 (43.8%)	*0.08*	0.42
	No	60 (45.8%)	51 (44.3%)	9 (56.2%)		
Age (s.d.)		29.3 (7.6)	29.5 (7.7)	27.6 (7.5)	*0.25*	0.36
BMI (s.d.)		26.3 (4.7)	26.0 (4.5)	28.0 (6.2)	*0.42*	0.12
SBP (s.d.)		124 (12.1)	124 (12.4)	124 (10.1)	*0.00*	0.97
DBP (s.d.)		78.4 (9.1)	78.5 (9.1)	77.7 (9.4)	*0.09*	0.75
Previous medical history (%)						
	Yes	55 (42.0%)	51 (44.3%)	4 (25.0%)	–	–
	No	76 (58.0%)	64 (55.7%)	12 (75.0%)		
Previous hormonal disease (%)						
	Yes	13 (9.9%)	12 (10.4%)	1 (6.3%)	–	–
	No	118 (90.1%)	103 (89.6%)	15 (93.7%)		
HoC (%)						
	No	53 (40.5%)	46 (40.0%)	7 (43.4%)	–	–
	Before mTBI	21 (16.0%)	18 (15.7%)	3 (18.8%)		
	After mTBI	22 (16.8%)	21 (18.3%)	1 (6.3%)		
	Before and after mTBI	35 (26.7%)	30 (26.0%)	5 (3.1%)		
Menstrual changes (%)						
	Yes, after mTBI	16 (12.2%)	14 (12.2%)	2 (12.5%)	–	–
	No changes	115 (87.8%)	101 (87.8%)	14 (87.5%)		
Years from mTBI (s.d.)		5.1 (6.2)	5.2 (6.5)	4.3 (4.2)	*0.14*	0.58
Number of mTBI (s.d.)		2.2 (0.8)	2.2 (0.7)	2.0 (1.0)	*0.23*	0.40
Number of mTBI symptoms in endocrinologist interview (s.d.)		2.0 (1.5)	2.1 (1.5)	1.8 (1.4)	*0.20*	0.52
Number of mTBI symptoms right after concussion (s.d.)		3.4 (1.7)	3.4 (1.6)	3.5 (1.9)	*0.06*	0.86

[a]The total number of women who answered questions regarding the sport they participated in was $n = 129$, as two women did not report which sport they participated in. Of the 129 women, 113 had PD and 16 did not.
BMI, body mass index; DBP, diastolic blood pressure; HoC, hormonal contraception; mTBI, mild traumatic brain injury; PD, pituitary dysfunction; SBP, systolic blood pressure; s.d., standard deviation.

central hypothyroidism $n = 4$, 3.1%) and 10 (7.5%) had HPRL (prolactinoma $n = 4$, 3.1% and HPRL without prolactinoma $n = 6$, 4.6%). No woman had more than one abnormal hormonal axes. Thus, PD was confirmed in 18.6% of the 86 women referred for further endocrinological evaluation. The mean time from the most recent mTBI until the endocrinological evaluation for the 16 women with PD was 4.3 years (Table 2) (min 2.4 months, max 15.3 years). The six women with HP had a mean time of 4.6 years (min 2.4 months, max 15.3 years) from the most recent mTBI until HP diagnosis was confirmed and the 10 women with HPRL had a mean time of 4.1 years (min 2.4 months, max 11.1 years) until HPRL diagnosis was confirmed. The time from mTBI until the endocrinological work-up for the two women who were diagnosed with GHD was 2 months for one of them and 15 years for the other.

No statistically significant difference was found between the 16 female athletes with PD compared

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with those with normal pituitary function concerning prognostic factors (Table 2). The effect size in the current study was largest for age, BMI, the number of mTBI, and the number of mTBI symptoms in the endocrinological interview (0.25, 0.42, 0.23 and 0.20, respectively) (Table 2). The calculated population size needed for 80% power was 261 participants for age, 89 participants for BMI, 296 for the number of mTBI, and 394 or the number of mTBI symptoms in the endocrinological interview. When comparing the number of mTBI symptoms (≤3 symptoms or >3 symptoms) between the women with HP with those without HP, no statistical significance was found ($P = 0.19$). No statistical significance was found between women with and without HPRL with regards to menstrual disturbances ($P = 0.289$).

Medical treatment or HST was required for 13 (9.9%, $n = 131$) of the 16 women with PD, thus 81% of women with PD needed medical treatment. All six women diagnosed with HP were started on treatment with HST (levothyroxine for central hypothyroidism $n = 4$, somatropin for GHD $n = 2$). Seven of the 10 women with HPRL required treatment with a dopamine agonist (cabergoline). Two of these seven women had normal MRI results and five had abnormal MRI results (prolactinoma $n = 3$, no prolactinoma $n = 2$) (Fig 2). Three women with HPRL were asymptomatic and did not need medical treatment (Fig 2). One of them had a pituitary microadenoma and is being followed clinically and the need for treatment reevaluated as necessary.

Discussion

We found that 12.2% ($n = 131$) of female athletes with a history of mTBI had PD (HP 4.6%, HPRL 7.6%). As 50 million people worldwide sustain a TBI annually, with mTBI being the most common (70–90%) (1), this is a very important finding. Moreover, around 1.6 to 3.8 million sport-related mTBI occur annually in the United States (53) and the incidence is likely underestimated (54, 55). This highlights the importance of evaluating pituitary

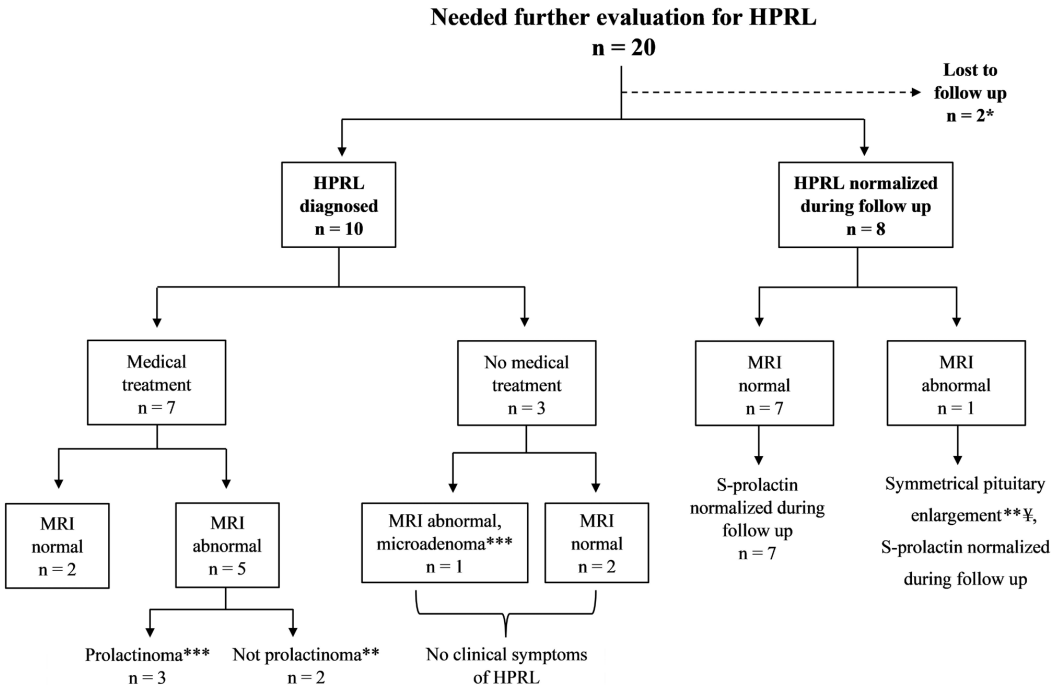

Figure 2

Results of the lactotroph axis evaluation. Ten women were diagnosed with HPRL, four of them were diagnosed with a prolactinoma. *Both women had elevated S-prolactin levels in SBT and normal MRI results. Both were lost to follow-up, one woman moved abroad and the other has not responded to repeated requests to repeat blood tests for follow-up. **Abnormal MRI without prolactinoma, total count $n = 3$: symmetrical pituitary enlargement $n = 1$ without a visible tumor, arachnoid cyst $n = 1$, symmetrical enlargement of the adenohypophysis without a visible tumor (¥) $n = 1$. ***Prolactinoma, total count $n = 4$: microadenoma $n = 2$, regressing adenoma $n = 1$, cystic/hemorrhagic adenoma $n = 1$. ¥ = symmetrical enlargement of the adenohypophysis without a visible tumor. HPRL, hyperprolactinemia.

function following mTBI, especially as symptoms of HP may overlap with mTBI symptoms and HP can be treated. None of the women diagnosed with PD in the current study had ever been evaluated for HP or HPRL despite prominent clinical symptoms following the mTBI which had occurred up to 15.3 years (mean 4.3 years) before the study.

PD was confirmed in 18.6% of the 86 women who had SBT repeatedly O-RV. As 81.4% of the women who were referred for further endocrinological evaluation, did not have PD (45), the question remains which women should be screened and evaluated further for possible PD following mTBI and when should this screening occur? Some studies suggest that increased TBI severity increases the risk of HP (10, 15, 56, 57). However, HP prevalence following moTBI, a more severe brain injury than mTBI, has been reported to be lower than following mTBI (9). Thus, this remains debatable.

We found 4.6%, or six of 131 women, to have HP which is lower than previously reported (13–48%) (8, 9, 10, 11, 12, 13, 14). All six women with HP were treated with HST and experienced symptom relief with treatment during follow-up. This lower prevalence of HP found in our study might be explained by the long interval from the most recent mTBI until the SBT were taken (45). A mean time of 5.1 years passed from the most recent mTBI until the endocrinological evaluation was performed for the entire population (Table 2) and 4.6 years passed from mTBI until the endocrinological evaluation for the six women diagnosed with HP. As it has been suggested that HP may improve with time (33, 58, 59, 60, 61), the extended time interval from mTBI until HP diagnosis may explain the results of our study.

Central hypothyroidism ($n=4$) was the most common form of HP, followed by GHD ($n=2$), whereas in previous reports GHD has been most common (9, 10, 12, 13, 14, 15, 33, 36, 62, 63). This is interesting considering the hypothesis that secondary ischemic injury of the pituitary gland may be a possible cause of HP following TBI (16). The TSH- and ACTH-secreting cells reside in the anteromedial portion and the central wedge of the anterior pituitary gland, and the growth hormone-secreting cells reside in the lateral portion of the anterior pituitary gland. As the anteromedial and central wedge of the pituitary gland receives its vasculature from both the long and short hypophyseal portal vessels it should be better guarded from ischemic injury than the lateral portion of the anterior pituitary which receives its vasculature from the hypophyseal portal vessels alone (16, 64, 65, 66).

The prevalence of GHD following mTBI in our study (1.5%, $n=131$) was lower than the previously reported prevalence of 8–48% (8, 11, 12, 13, 14, 15, 28, 29). Studies have suggested that GHD may improve with time which may explain the lower incidence of GHD in our study. One study found that 53.8% of patients with GHD had recovered after 3 years from TBI, although it is also discussed that GHD may arise as time passes (59). However, it is interesting that the time from the most recent mTBI until the endocrinological work-up for the two women with GHD was 2 months and 15 years. Thus, one had only recently suffered a mTBI while many years had passed for the other. Another possible explanation for the lower prevalence of GHD is that it may be caused by hypothalamic injury rather than by injury to the pituitary gland itself. As the GHRH–arginine tests was the diagnostic test for GHD rather than the ITT, results may be falsely normal as the GHRH–arginine test does not evaluate possible hypothalamic dysfunction (67, 68, 69).

Ten women (7.6%) had HPRL comparable to previously reported HPRL prevalence of 3.8–16% following mTBI, moTBI and sTBI (15, 31, 32, 33, 34). A mean time of 4.1 years passed from the most recent mTBI until HPRL was diagnosed. Thus, s-prolactin seems to remain elevated for an extended period in some cases following mTBI rather than improving with time as has been suggested for HP (33, 70).

The study did not find hypofunction in the gonadotropic or corticotropic axis (45).

No significant prognostic factors were found (Table 2). Although this is a large study of female athletes after mTBI, our power analysis (Table 2) show that a larger population is needed to identify possible prognostic factors to make PD screening following mTBI more targeted.

Strengths and limitations

To the best of our knowledge, our study is the first to report the prevalence of HP and HPRL following mTBI in an all-female study. This is a strength of the study as female athletes are an underreported population (41). A detailed endocrinological evaluation was conducted by the same endocrinologist and relevant testing were performed when indicated to confirm PD which is also a strength of the study. Furthermore, follow-up with the same endocrinologist was offered to all women who were diagnosed with PD.

It is a limiting factor that the study is retrospective as mTBI tends to be underreported (55, 71, 72, 73). Results from part 1 and part 2 of the study also indicate underreporting as mTBI reporting increased from 40.2% to 64.8% after participants read a definition of mTBI (44). The time from mTBI until the endocrinological evaluation varied between participants which may be a limitation of the study. However, it may also be a strength, as it gives an insight into the long-term prevalence of PD following TBI. Although the study population is larger compared to previous studies on HP following mTBI (8, 9, 10, 11, 12, 13, 14), an even larger study population is needed to identify possible prognostic factors for PD following mTBI. Limitations of the diagnostic methods for possible central cortisol

deficiency also need to be considered. Although measurements of s-cortisol and the high-dose (250 µg) synachten test were performed at 08:00 h, it is possible that variations in individual circadian rhythms could have resulted in false-negative results. Moreover, the use of the synacthen test rather than the gold-standard ITT for the assessment of the hypothalamopituitary–adrenal axis may not be reliable and can lead to false-negative results (74). However, as the ITT requires medical supervision, is physically demanding on patients, and can have contraindications, the synacthen test is often used as an alternative (75).

Conclusions

We conclude that PD is an important diagnosis in post-concussion care as 12.2% of the female athletes ($n=16$) had PD with 9.9% ($n=13$) requiring medical treatment. Following mTBI 4.6% of the female athletes had HP which is lower than previously reported and may possibly be explained by recovery over time. HPRL may indicate pituitary or hypothalamic injury after mTBI as six of the 10 women with HPRL were not diagnosed with a prolactinoma.

Declaration of interest
Sigrún Helga Lund is a statistician employed by deCODE genetics Inc./Amgen Inc.; she is not reimbursed for her work on this study. The authors have no competing interests to declare that are relevant to the content of this article.

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Compliance with ethical standards
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the National Bioethics Committee (no: VSN-18-091), the Icelandic Data Protection Authority, the Institutional Reasearch Commitee of Landspitali University Hospital of Iceland and Laeknasetrid outpatient clinic. Prior to participation, participants received information regarding the study design and gave their informed consent for participation and publication of the study results.

Data availability
As the participants of this study did not give written consent for their research data to be shared, the data is not available.

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Paper III

Pituitary dysfunction following mild traumatic brain injury in female athletes: neuropsychological and psychological findings.

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Short running title: **Neuropsychological outcome in female athletes**

Key words: pituitary dysfunction, mild traumatic brain injury (mTBI), sport-related concussion (SRC), female athletes, cognition, neuropsychological outcome, mental health

Article type: Clinical research study

Abstract

Objective

Pituitary dysfunction (PD) and mild traumatic brain injury (mTBI) can affect neuropsychological and psychological functioning. To the best of our knowledge, this study is the first to report neuropsychological and psychological outcomes in female athletes with PD following mTBI.

Materials and methods

The study is a retrospective cohort study. Female athletes (n = 508) in Iceland participated by answering online questionnaires regarding mTBI history and mental health. Women reporting one or more mTBI (n = 308) were invited to participate in neuropsychological tests with 166 (53.8%) accepting. All 166 women were invited further participation in a medical interview with 151 accepting (90.9%). Pituitary hormone screening blood tests (SBT) were performed in 133 (88.1%) women, nine were lost to follow up and nine were pregnant. If SBT were repeatedly outside the reference value, detailed endocrinological tests were performed as indicated.

Results

Following a detailed endocrinological evaluation, 16 (12.2%) women were diagnosed with PD (hypopituitarism n = 6, hyperprolactinemia n = 10) after mTBI. Women with PD had a significantly higher mean Sustained Attention to Response Task (SART) error score than women with normal pituitary function (nPF) (16.7 and 12.8 respectively; p = 0.04). No other significant differences in neuropsychological or psychological outcome were found.

Conclusion

Sustained attention or inhibitory performance is affected in women with PD compared to women with nPF following mTBI. No other significant difference in neuropsychological or psychological outcome was demonstrated.

Introduction

The most common form of traumatic brain injury (TBI) is concussion or mild traumatic brain injury (mTBI)[1], referred to as sport-related concussion (SRC) when it occurs during sports[2]. From the year 2019 until 2023, participation of women and girls in soccer has increased by 24% which reflects increased interest and participation in women's sport[3]. Furthermore, the incidence of mTBI appears to be rising although this may reflect growing public awareness regarding mTBI[4]. The definition of mTBI includes a Glasgow coma scale (GCS) score of 13-15 after 30 minutes from the injury, post-traumatic amnesia for less than 24 hours, normal neuroimaging studies, and may include loss of consciousness for less than 30 minutes[5]. More severe forms of TBI are either moderate (moTBI) or severe TBI (sTBI). Causes of mTBI include transmission of mechanical force to the brain by a blow to the head, neck or body, acceleration-deceleration movement, or force from a blast injury[2, 5].

Symptoms can present immediately or within hours or days[2, 5] and typically resolve within a few days or weeks, although prolonged physical, neuropsychological, and psychological symptoms can occur[6-9]. Various cognitive symptoms have been described acutely following SRC such as problems with executive functioning, attention, memory, processing speed, and reaction time[6-9]. Cognitive symptoms generally improve within four weeks from SRC[6-9] although long-term cognitive effects have also been reported[10].

Mental health is also affected by mTBI as has been reported in a sample of retired football players where 19.1% of the players had moderate to severe depression following SRC or non-sport related mTBI[11] compared to 5.9% in the general male population[12]. Moreover, there appears to be a dose-response relationship between the number of SRCs and clinical depression in male and female athletes[11, 13]. Results from earlier stages of the current study indicate that women reporting 2 – 3 or ≥ 4 SRCs were 3.48 and 4.85 times more likely, respectively, to have clinical depression and 3.52 and 3.40 times more likely to have clinical anxiety than those who did not report a SRC[13].

Physical effects of TBI (mTBI,moTBI, sTBI) include hypopituitarism (HP) with systematic review reporting a prevalence of 15-50% where growth hormone deficiency (GHD) appears to be most common[14-16]. Hyperprolactinemia (HPRL) following TBI (mTBI, moTBI, and sTBI) has also been reported possibly indicating pituitary or hypothalamic injury[16] as such injuries affect the dopaminergic inhibitory control of prolactin release[17].

The physical, psychological, and neuropsychological symptoms following mTBI have previously been attributed to mTBI directly[2, 7]. However, these symptoms may in fact be due to pituitary dysfunction (PD) as neuropsychological effects of GHD have been reported[18-20]. Moreover, hormonal replacement therapy appears be beneficial with regards to neuropsychological outcome[21-23].

The current study is part of a larger study on female athletes in contact sports following mTBI[13, 24-26]. The aim of the part of the study presented here was to explore psychological and neuropsychological outcome in female athletes with PD following mTBI and identifying possible prognostic factors for PD following mTBI. To the best of our knowledge this is the

first study focusing on neuropsychological and psychological functioning of PD following mTBI in an all-female population.

Materials and methods

Participants and study design

The current study is a part of more extensive research on female athletes conducted in three parts. A detailed description of the inclusion process has previously been published (Figure 1). Currently active or retired female athletes aged 18 to 45 years (n = 508) participated in part 1 of the study by answering an online questionnaire regarding mTBI history and mental health (Figure 1)[13, 26].

A previous history of one or more mTBI after reading a definition of mTBI was reported by 308 female athletes who were invited to participate in part 2 of the study including a detailed interview and neuropsychological tests, with 166 women (53.8%) accepting (Figure 1)[13, 26].

Following the interview 151 women (91.0%) accepted participation in part 3 of the study including a medical interview and physical examination performed by the same medical doctor (LÓEC). The mental health scales were repeated before the medical interview to reflect mental health at the time of the medical interview and screening blood tests (SBT). This was done as in some cases months passed between the online questionnaire and the SBT. However, eight women did not repeat the mental health scales prior to the medical interview (Figure 1). Of the 151 women who participated in the medical interview, 133 had SBT taken for possible PD, nine were lost to follow up and nine were pregnant (Figure 1)[24, 25]. Results of the SBT were outside the reference value (O-RV) (Table 1) in 88 women (66.2%) who needed further endocrinological evaluation by an endocrinologist. Two of these 88 women did not attend the endocrinologist's interview and were excluded from the study. One was pregnant and one did not attend the visit despite repeated attempts for contact (Figure 1). Thus, the sample for the current study included 131 women who had SBT of whom 86 women had a detailed endocrinological evaluation.

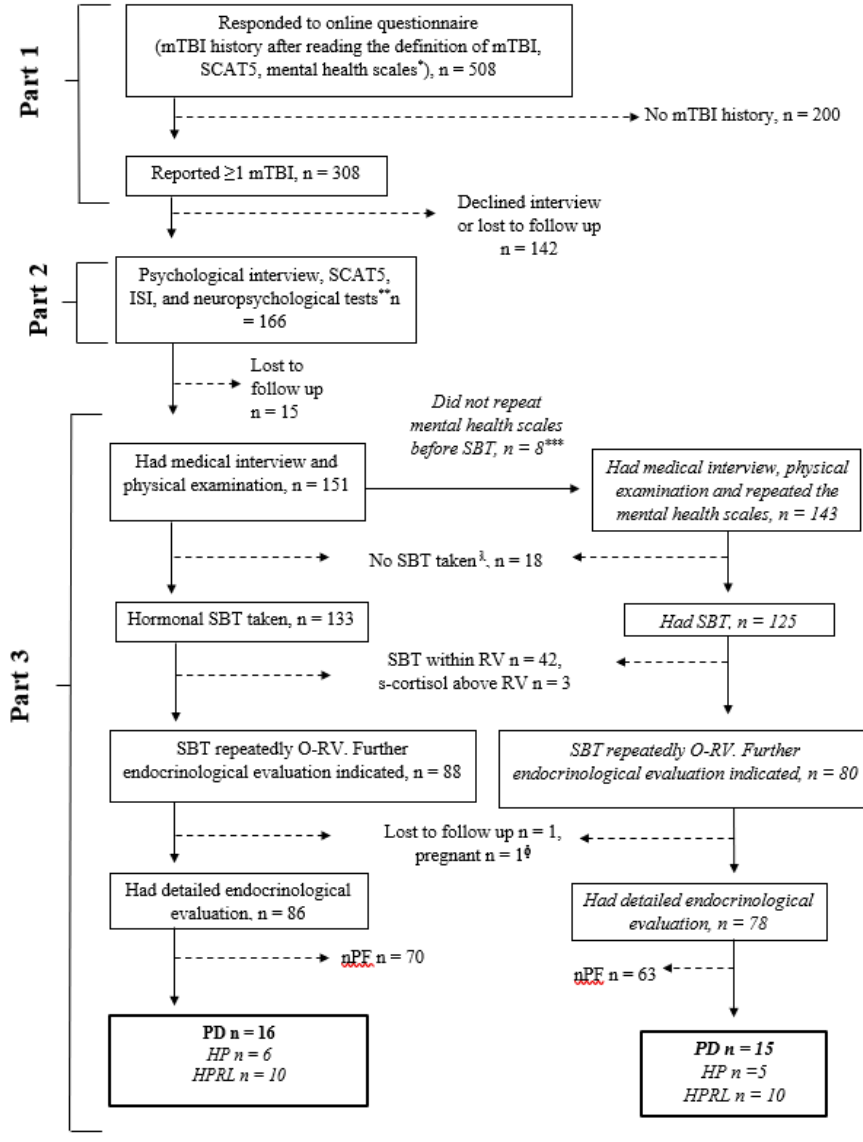

Figure 1 Overview of the study design and population.

* Online questionnaire regarding sports, education, mTBI history, mTBI symptoms. The mental health scales were Patient Health Questionnaire – 9 (PHQ – 9), General Anxiety Disorder – 7 (GAD – 7), Perceived Stress Scale 4 (PSS4), and the Quality of Life Scale (QOLS). They were repeated in part III of the study to reflect mental health at the time of the hormonal screening blood tests.

** Current mTBI symptoms were re-evaluated using The Sport Concussion Assessment Tool 5 (SCAT5). The Insomnia Severity Index (ISI) was used to evaluate insomnia. The neuropsychological tests included the Sustained Attention to Response Test (SART), the Stroop Colour-Word test (SCWT), Trail Making Test (TMT), and subtests of The Wechsler Abbreviated Scale of Intelligence (WASI) and the Wechsler Adult Intelligence Scale (WAIS).

*** Of the eight women who did not repeat the mental health questionnaires before the medical interview, one was diagnosed with PD and seven had nPF following detailed endocrinological evaluation.

λ Pregnant n = 9, lost to follow up n = 9

ϕ Two women who were referred for further workup for possible HP did not attend the endocrinological interview and were excluded from the study. Thus, the final number of women who participated in SBT was 131, the number of women who repeated the mental health questionnaires was 123 and the number of women referred for further workup was 86.

Measurements

Current and past mTBI symptoms were evaluated using the symptom evaluation scale of the Sport Concussion Assessment Tool, fifth edition (SCAT-5)[27]. Symptoms of anxiety, depression, stress, and quality of life (QOL) were evaluated using the General Anxiety Disorder Questionnaire 7 (GAD-7), Patient Health Questionnaire 9 (PHQ-9), the Perceived Stress Scale 4 (PSS4), and the QOL scale respectively[13]. The clinical cut-off for anxiety was defined as a GAD-7 score of ≥10 [28] and the clinical cut-off for depression was defined as a PHQ- 9 score of ≥10[29].

The SCAT-5 post-concussion symptom scale was repeated in part 2 of the study and sleep disturbances were evaluated using the Insomnia Severity Index (ISI) where the clinical cut-off for insomnia is defined as an ISI score of ≥10 [30].

The neuropsychological tests performed included the Sustained Attention to Response Task (SART)[31], the Stroop Colour- and Word Test (SCWT)[32, 33], the Trail Making Test (TMT)[33, 34], and two sub-tests from the Wechsler Abbreviated Scale of Intelligence (WASI-IS)[35], and four from the Wechsler Adult Intelligence Scale-III (WAIS-III)[36].

The SART is a cognitively demanding test intended to measure sustained attention and also reflects inhibitory performance and impulsivity[37]. It was used to assess processing speed and error in attention by measuring the mean SART response time (SARTrt) and the SART error score (SARTes)[31]. Participants are presented with a series of single digit numbers and are required to responded to each digit with a key press. However, when the digit 3 appears, participants withhold a key press. Icelandic norms for the general population are not available for this test.

The SCWT was performed to evaluate executive functioning and cognitive interference which is the ability to inhibit a well learned response (i.e. reading) in favour of a less familiar reaction (i.e. naming a colour)[32]. The test has three parts, Stroop I, Stroop II, and Stroop III. The time it took to finish each part was measured and a Stroop interference score was derived from the results according to the formula Stroop III – (Stroop II + Stroop I)/2. Results were compared to Icelandic norms based on age, gender, and education[33].

The TMT consists of two parts, the TMT A measuring visual search and motor speed, and the TMT B measuring cognitive flexibility, divided attention and working memory[34]. The TMT difference (TMT B -TMT A) was used to obtain a derived t-score based on age, gender, and education. Results were compared to Icelandic norms[33].

Subtests of the Icelandic version of the WASI-IS and the WAIS-III were used to measure intellectual abilities, working memory, and processing speed. The WASI-IS subtests performed were the Vocabulary and Matrix Reasoning tests[35]. The WAIS-III subtests performed were the Digit Span (digits forwards and backwards) test, the Digit Coding test, the Letter-Number Sequencing test, and the Symbol Search test[36]. Total raw scores of the WASI-IS sub-tests are converted to T-scores with a mean normal score of 50 with a standard deviation

of ±10 [35] The mean normal score for the sub-tests of WAIS-III was 10 with a standard deviation of ±3.

Screening blood tests and endocrinological testing

Hormonal SBT (n = 131) included hormonal measurements of all pituitary axes taken at 8 a.m except vasopressin which was clinically evaluated. Results of the SBT were defined as abnormal if they were O-RV for each hormonal measurement in two or three repeated blood tests (Table 1). Women with SBT O-RV had a detailed endocrinological evaluation and follow by the same endocrinologist (HÁS) as indicated (Table 1)[24, 25].

	Screening blood test (reference value)	Further endocrinological evaluation
Lactotroph axis	s-Prolactin (4.79 – 23.3 µg/L) *	MRI
Somatotroph axis	s-IGF1 (manufacturer's age dependant reference range) **	GHRH – arg test, ITT test
Thyrotrope axis	s-TSH (0.270 – 4.20 mIU/L)	s-Anti – TPO antibodies¥, MRI
	s-fT4 (12 – 22 pmol/L)	
Corticotrope axis	s-Cortisol (133 – 537 nmol/L) ***	s-ACTH measurement, Synacthen test
Gonadotroph axis	s-FSH (FP 3.5 – 12.5 IU/L, OP 4.7 – 21.5 IU/L, LP 1.7 – 7.7 IU/L	
	s-LH (FP 2.4 – 12.6 IU/L, OP 14.0 – 95.6 IU/L, LP 1.0 – 11.4 IU/L)	
	s-Oestrogen (FP 45.4 – 854 pmol/L, OP 151 – 1,461 pmol/L, LP 81.9 –1,251 pmol/L	Not indicatedϕ
	s-Progesterone (FP 0.181 – 2.84 nmol/L, OP 0.385 – 38.1 nmol/L, LP 5.82 – 75.9 nmol/L)	

Table 1 Overview of the screening blood tests and endocrinological tests performed.
Participants with repeated screening blood test results outside reference value were referred to an endocrinologist for endocrinological evaluation and testing for possible pituitary dysfunction. No women had gonadotroph hormone measurements repeatedly outside the reference value, thus no further endocrinological evaluation of that axis was necessary.
s-prolactin = serum prolactin, MRI = magnetic resonance imaging, s-IGF1 = serum insulin-like growth factor 1, GHRH – arg test = growth hormone releasing hormone arginine test, ITT = insulin tolerance test, s-TSH = serum thyroid-stimulating hormone, s-fT4 = serum free thyroxin, anti – TPO antibodies = anti – thyroid peroxidase antibodies, s-ACTH = serum adrenocorticotropic hormone, s-FSH = serum follicular stimulating hormone, FP = follicular phase, OP = ovulation phase, LP = luteinizing phase, s-LH = serum luteinizing hormone, s-oestrogen = serum oestrogen, s-progesterone = serum progesterone.
*Reference value for women who are not pregnant.
** Immulite product booklet, IGF-1, Immulite 2000 IGF-1 (PIL2KIGF-4, 2018–07-02).
*** Morning (6 – 10 a.m.) reference value
¥ <25 IU/ml = negative, 25 – 35 IU/ml = equivocal, >35 IU/ml = positive
ϕ Further evaluation for possible gonadotroph hormone deficiency was not indicated for any of the participants.

Ethics

Informed consent was obtained from all subjects upon participation in the study. The study was approved by the National Bioethics Committee (no: VSN-18-091), the Icelandic Data Protection Authority (no: 18-083), the Institutional Research Committee of Landspitali the National University Hospital of Iceland, the chief medical officer of Landspitali the National University Hospital of Iceland and Laeknasetrid outpatient clinic.

Statistics

All statistical analysis was performed using R (version 3.6.1). A two-sample t-test was used for the comparison of psychological and neuropsychological test results between women with PD and women with normal pituitary function (nPF). The chi-squared test was used for the comparison of categorical variables between the two groups when it was appropriate with regards to sample size. A linear logistic regression was performed to evaluate whether there was an association between the number of mTBIs and mTBI symptoms and having scores above the clinical cut-off for symptoms of depression, anxiety, and insomnia. A p-value of < 0.05 was considered statistically significant. Effect sizes were calculated using Cohen's d for the two-sample t-tests.

Results

As has been previously reported, 16 (12.2%) of the 131 women who had SBT, were diagnosed with PD following a detailed endocrinological evaluation (Table 1). Ten were diagnosed with HPRL and six with HP (central hypothyroidism n = 4, GHD n = 2)[25]. Population characteristics can be seen in Table 2 and a more detailed description of the study sample has also been previously reported[13, 24-26]. There was not a significant difference in the mean number of mTBI between the group or the time that had passed since the injury occurred (Table 2). Of the 16 women who were diagnosed with PD one reported a prior history of depression and none reported a previous history of attention-deficit hyperactivity disorder (ADHD) (Table 2).

		Total n = 131	nPF n = 115	PD n = 16	effect size*	p-value
Age (SD)		29.3 (7.6)	29.5 (7.7)	27.6 (7.5)	*0.25*	0.36
Still playing (%)		71 (54.2%)	64 (55.7%)	7 (43.8%)		
Retired from sport (%)		60 (45.8%)	51 (44.3%)	9 (56.3%)	*0.08*	0.42
No prior history of depression (%)		114 (87.0%)	99 (86.1%)	15 (93.8%)		
Prior history of depression[*] (%)		17 (13.0%)	16 (13.9%)	1 (6.3%)	..	..
No ADHD diagnosis (%)		124 (94.7%)	108 (93.9%)	16 (100.0%)		
ADHD diagnosis[**] (%)		7 (5.3%)	7 (6.1%)	0 (0.0%)	..	..
Education level[***]	**Elementary school (%)**	15 (11.5%)	11 (9.6%)	4 (25.0%)		
	College (%)	42 (32.1%)	38 (33.0%)	4 (25.0%)		
	University (%)	73 (55.7%)	65 (56.5%)	8 (50.0%)	..	..
Years from the last mTBI (SD)		5.1 (6.2)	5.2 (6.5)	4.3 (4.2)	*0.14*	0.58
Number of mTBI (SD) ¥		2.2 (0.8)	2.2 (0.7)	2.0 (1.0)	*0.23*	0.40

Table 2 Demographic and clinical characteristics of the study population.
There were too few participants with PD for statistical analysis with the Chi Square test. Thus, statistical comparison between the two groups was not performed for previous depression history, ADHD diagnosis or education level.
[*] Previous history of depression was self-reported by participants
[**] ADHD diagnosis were self-reported by participants.
[***]Total number of participants is n = 130 for education level as there was missing data for one participant with nPF.
¥ The number of mTBI ranged from 1.0 – 4.0.
SD = standard deviation, nPF = normal pituitary function, PD = pituitary dysfunction, ADHD = attention deficit hyperactivity disorder, mTBI = mild traumatic brain injury.

There was not a significant difference in the mean scores of the SCAT-5 post-concussion symptom scale or ISI between women with nPF and women with PD (Table 3). According to ISI scores, 54 (41.2%, PD n = 6, nPF n = 48) of the 131 women had scores above the clinical cut-off for insomnia and 77 (58.8%, PD n = 10, nPF n = 67) women did not. Scores above the clinical cut-off for insomnia were not significantly more prevalent in women with PD compared to women with nPF. The number of mTBI was not significantly associated with results above the clinical cut-off for symptoms of insomnia ($\beta = 0.03$, p-value = 0.82). However, there was a borderline association between the number of mTBI symptoms according to the SCAT-5 symptom evaluation scale and results above the clinical cut-off for symptoms of insomnia although it was not statistically significant ($\beta = 1.3$, p-value = 0.05).

Results of the neuropsychological tests performed in part 2 of the study are presented in Table 3. Women with PD following mTBI had a significantly higher mean SARTes than women with nPF (Table 3). No other significant difference was found between women with PD and nPF with regards to neuropsychological outcome (Table 3). Mean scores of the WASI-IS and WAIS-III subtests for women with PD and those with nPF were within normal limits (Table 3)[35, 36].

		Total n = 131 Mean (SD)	nPF n = 115 Mean (SD)	PD n = 16 Mean (SD)	p – value	effect size
ISI		8.5 (6.1)	8.6 (6.0)	7.6 (6.6)	*0.54*	*0.16*
SCAT5 concussion symptom scale		7.6 (5.2)	7.9 (5.2)	5.8 (4.6)	*0.12*	*0.41*
SART	**Error score**	13.3 (7.0)	12.8 (7.1)	16.7 (5.2)	*0.04**	*0.56*
	Response time	359 (82.7)	363 (85.2)	330 (55.5)	*0.14*	*0.40*
	Errors	2.0 (2.3)	1.9 (2.1)	2.8 (3.4)	*0.18*	*0.39*
SCWT	**Interference score**	23.9 (6.7)	23.9 (6.9)	24.5 (5.4)	*0.71*	*0.09*
	Interference score t-score	51.4 (7.1)	51.5 (7.3)	50.6 (5.5)	*0.62*	*0.13*
TMT	**Difference**	32.8 (24.1)	33.2 (25.1)	30.1 (15.3)	*0.62*	*0.13*
	Difference (t-score)	48.9 (13.3)	48.7 (13.9)	50.3 (8.7)	*0.64*	*0.12*
WASI	**Vocabulary**	46.1 (9.7)	46.1 (9.8)	46.1 (9.1)	*0.99*	*0.00*
	Matrix Reasoning	46.8 (4.1)	46.8 (4.1)	46.8 (3.7)	*0.96*	*0.00*
WAIS	**Digit Span test**	9.6 (2.6)	9.7 (2.6)	8.6 (1.9)	*0.09*	*0.44*
	Letter Number Sequencing test	9.7 (2.2)	9.7 (2.3)	9.1 (1.8)	*0.28*	*0.27*
	Digit symbol coding	11.7 (2.5)	11.7 (2.6)	11.8 (1.7)	*0.89*	*0.04*
	Symbol search	12.2 (2.8)	12.2 (2.9)	12.2 (2.2)	*0.99*	*0.00*

Table 3 Results ISI, SCAT5, and neuropshychological tests.

Mean scores of the ISI, SCAT5 concussion symptom scale and neuropsychological tests performed in the psycologist interview in part 2 of the study. Results were compared between women with nPF and women with PD.

SD = standard deviation, nPF = normal pituitary function, PD = pituitary dysfunction, ISI = Insomnia severity index, SCAT5 = Sport Concussion Assessment Tool 5, SART = The Sustained Attention to Response Task, SCWT = Stroop color-word test, TMT = trail making test, WASI = Wechsler Abbreviated Scale of Intelligence Test, WAIS = Wechsler Adult Intelligence Scale

Of the 131 participants, 123 repeated the mental health scales (PSS4, PHQ-9, GAD-7, and QOLS) before the medical interview (Figure 1). Eight women did not repeat the mental health questionnaires, one of them was diagnosed with central hypothyroidism following the detailed endocrinological evaluation and seven had nPF. No significant difference was found in the mean scores of the mental health scales between women with PD and nPF.

According to PHQ-9 scores, 35 (28.4%, PD n = 3, nPF n = 32) of the 123 women who repeated the mental health scales had scores above the clinical cut-off for depression and 88 (71.5%, PD n = 12, nPF n = 76) did not. Eight (PD n = 0, nPF n = 8) of the 35 women who had results above the clinical cut-off for depression had a self-reported prior history of anxiety or depression, and 27 (PD n = 3, nPF n = 24) women did not. The number of mTBI was not significantly associated with results above the clinical cut-off for symptoms of depression ($\beta = 0.15$, p-value = 0.34) although there was a significant association between the number of mTBI symptoms according to the SCAT-5 symptom evaluation scale and results above the clinical cut-off for symptoms of depression ($\beta = 4.1$, p-value = 3.6×10^{-5}).

Results of the GAD-7 scale indicated that 23 (18.7%, PD n = 4, nPF n = 19) of the 123 women who repeated the mental health scales had scores above the clinical cut-off for anxiety and 100 (81.3%, PD n = 11, nPF n = 89) women did not. Five (PD n = 0, nPF n = 5) of the 23 women who had results above the clinical cut-off for anxiety had a self-reported previous history of anxiety or depression and 18 (PD n = 4, nPF n = 14) did not. The number of mTBI was not significantly associated with results above the clinical cut-off for anxiety ($\beta = -0.07$, p-value = 0.71) although there was a significant association between the number of mTBI symptoms according to the SCAT-5 symptom evaluation scale and results above the clinical cut-off for symptoms of anxiety ($\beta = 2.0$, p-value = 0.02).

Discussion

The aim of the study was to evaluate neuropsychological and psychological functioning in women with PD following mTBI compared to women with nPF. Our study found that the 16 women who were diagnosed with PD had a higher mean SARTes than women with nPF suggesting greater difficulties with sustained attention in women with PD[31]. However, the higher SARTes in women with PD may also reflect problems with inhibition rather than with sustained attention or even both[37]. There were no indications of increased psychological symptoms, or decreased QOL in women with PD following mTBI.

Six of the 16 female athletes with PD were diagnosed with HP (GHD n = 2, central hypothyroidism n = 4). Mental and cognitive fatigue can be caused by HP[38, 39] possibly affecting attention during demanding tasks, such as the SART, which may explain the impaired sustained attention in women diagnosed with PD compared to women with nPF.

Neuropsychological symptoms, such as lower scores on tests of reaction time, vocabulary, perceptual speed, spatial learning, and speed have previously been reported in women with untreated GHD compared to controls[18]. Results of the current study are in contrasts to these findings, as women with PD following mTBI were comparable to women with nPF with regards to working memory, divided attention, and sub-tests of intelligence. As the entire sample in the current study was exposed to mTBI, which can affect neuropsychological

functioning[6-10], this may explain the similar neuropsychological outcome between women with PD and women with nPF after mTBI.

Indications of problems with cognitive control following mTBI alone have also been reported from the earlier stages of the study. Women with a history of mTBI demonstrated more theta activity in an electroencephalogram (EEG) during a virtual reality simulation of the sensation of being at sea, indicating that they required more attention and cognitive effort to maintain postural control and balance during the simulation[40]. Furthermore, women with a history of mTBI, regardless of pituitary function, were found to have a higher SARTes and shorter SARTrt than participants without a history of mTBI in another report from earlier stages of the study (Figure 1)[41]. It is intriguing that in the current sample, SARTes seems to be affected in women with PD following mTBI. This cannot be explained by a higher number of mTBI in that group as there was not a significant difference in the mean number of mTBI between women with PD compared to nPF[25]. These findings may indicate an additive effect of PD following mTBI on attention or inhibitory performance compared to mTBI alone, especially during challenging neuropsychological tests that place high demands on simultaneous speed and inhibition.

Although previous studies have reported higher depression and anxiety symptom scores in patients with untreated GHD[18, 39], we found no indications of increased stress, depression symptoms, anxiety symptoms, or decreased QOL in women with PD following mTBI in the current study.

There was an association between results above the clinical cut-off for symptoms of depression and anxiety and increased number of mTBI symptoms. Previous studies have also reported that patients with a history of mTBI and symptoms of depression reported a significantly higher number of mTBI symptoms compared to those who had a history of mTBI without depression symptoms [42]. However, it is important to consider that the SCAT-5 has a limited role in tracking recovery of mTBI symptoms beyond 3-5 days after mTBI[43] and that symptoms of mTBI can overlap with symptoms of depression and anxiety [44]. This may explain the increased mTBI symptom burden in female athletes with results above the clinical cut-off for symptoms of depression and anxiety.

Globally, an estimated 69 million people sustain a mTBI every year[45]. As a considerable proportion of those who sustain a mTBI are subsequently affected by HP (15-50%)[14-16], screening for possible HP following mTBI has been suggested[46] although which patients should be screened, when, and how screening should occur remains a debate. In a previous report from part 3 of the study, lower age, and an increased number of mTBI symptoms were suggested as predictive factors indicating the need for SBT for possible PD following mTBI[24]. Although the SART is also affected directly by TBI[31], the current study found that women with PD had higher mean SARTes. Thus, higher mean SARTes may indicate that further endocrinological evaluation for possible PD is necessary in women with a prior history of mTBI.

Strengths and limitations

To the best of our knowledge, this study is the first to report the psychological and neuropsychological functioning in women with PD following mTBI in a sample that consists

exclusively of female athletes. This is a strength of the study as female athletes remain an underreported population[47]. All 308 women reporting a prior history of mTBI were invited to participate in neuropsychological tests, a medical interview by the same medical doctor (LÓEC), and a detailed endocrinological evaluation and follow up by the same endocrinologist (HÁS) which is another strength of the study. Our study sample is large compared to earlier studies[18-21, 23]. However, an even larger sample may be necessary to determine differences in neuropsychological and psychological functioning between women with PD and women with nPF following mTBI and identify possible prognostic factors for PD following mTBI. Furthermore, the time from the neuropsychological tests until the medical interview and hormonal SBT varied in the current study which may be a limiting factor. Future studies should aim to perform neuropsychological tests within a short period from the endocrinological evaluation. It is also a limiting factor that the study is retrospective as mTBI tends to be underreported[48]. However, previous history of mTBI was evaluated objectively using the SCAT-5 post-concussion symptom scale and by presenting a definition of mTBI to participants before they reported whether they had a history of mTBI[26].

Conclusions

Women with PD following mTBI had higher mean SARTes than women with nPF following mTBI indicating the effects of PD following mTBI on sustained attention or inhibitory performance and that further endocrinological evaluation for possible PD may be necessary. Women with a history of mTBI, regardless of pituitary function, have been reported to have a higher SART and shorter SARTrt than women without a history of mTBI. Thus, PD following mTBI may have an additive effect on attention or inhibitory performance compared to mTBI alone. Performance on other neuropsychological tests did not appear to be affected in women with PD. Although women with symptoms of depression and anxiety above the clinical cut-off had an increased number of mTBI symptoms, there were no indications of increased stress levels, increased symptoms of depression or anxiety, or decreased QOL in women with PD compared with women with nPF.

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Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the National Bioethics Committee (no: VSN-18-091), the Icelandic Data

Protection Authority, the Institutional Reasearch Commitee of Landspitali University Hospital of Iceland and Laeknasetrid outpatient clinic. Prior to participation, participants received information regarding the study design and gave their informed consent for participation and publication of the study results.

Data availability

As the participants of this study did not give written consent for their research data to be shared, the data is not available.

Conflict of interests

The authors have no competing interests to declare that are relevant to the content of this article.

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