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This study is based on original publications, which will be referred in the text by their roman numerals (I–III).

I. Vetkas, A., Lepik, T., Eilat, T., Rätsep, T., & Asser, T. (2013). Emotional health and quality of life after aneurysmal subarachnoid hemorrhage. *Acta Neurochirurgica*, *155*(6), 1107–1114. https://doi.org/10.1007/s00701-013-1683-3

II. Vetkas, A., Prans, E., Kõks, S., Rätsep, T., & Asser, T. (2020). Aneurysmal subarachnoid haemorrhage: Effect of CRHR1 genotype on fatigue and depression. *BMC Neurology*, *20*(1), 142. https://doi.org/10.1186/s12883-020-01727-y

III. Vetkas, A., Prans, E., Kõks, S., Rätsep, T., & Asser, T. (2020). Aneurysmal subarachnoid haemorrhage: Effect of CRHR1 genotype on mental health-related quality of life. *Scientific Reports*, *10*(1), 1–8. https://doi.org/10.1038/s41598-020-57527-4

Applicant's contributions for Papers I–III: Artur Vetkas was involved in the design of the study, assessment of patients, data collection, partially data analysis, and writing the manuscripts.

2 ABBREVATIONS

ACA – anterior cerebral artery
AcomA – anterior communicating artery
ACTH – adrenocorticotrophic hormone
aSAH – aneurysmal subarachnoid haemorrhage
AVP – vasopressin
BA – basilar artery
CI – confidence interval
CRH – corticotrophin releasing hormone
CRHR1 – corticotropin-releasing hormone receptor 1
DNA – deoxyribonucleic acid
DSA – digital subtraction angiography
DSMIV – Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
e.g. – example given
GCS – Glasgow Coma Scale
GxE – gene – environment interaction
HH – Hunt & Hess Scale
HRQoL – health related quality of life
ICA – internal carotid artery
ICD-10 – International Classification of Diseases, 10th Revision
MCA – middle cerebral artery
MM – major allele homozygote
mM – heterozygote
mm – minor allele homozygote
mRS – modified Rankin scale
n/a – not associated
OR – odds ratio
P – P value
PTSD – post-traumatic stress disorder
QoL – quality of life
SAH – subarachnoid haemorrhage
SD – standard deviation
SNP – single nucleotide polymorphism
SF-36 – Short Form Health Survey 36
VA – vertebral artery

3 INTRODUCTION

The rupture of an aneurysm leads to extravasation of arterial blood into the subarachnoid cisterns surrounding the brain causing aSAH (Petridis et al., 2017). Nontraumatic SAH accounts for approximately 5% of all strokes. An aneurysm rupture is the cause of nontraumatic SAH in 85% of cases (van Gijn, Kerr, & Rinkel, 2007). Incidence of aneurysmal SAH is around 7.9 per 100,000 person-years (Etminan et al., 2019).

It took more than 2000 years to associate the clinical picture of SAH – described by Hippocrates – with the existence of cerebral aneurysms in the 18th century (Longstreth, Koepsell, Yerby, & van Belle, 1985). The clinical presentation of SAH was further described by Byrom Bramwell (1847–1931) and neurologist Charles P. Symonds (1890–1978) (Smith et al., 1994). The first surgical treatment of aneurysms was performed by Norman Dott (1897 – 1973) in 1926 (Todd, Howie, & Miller, 1990) and resulted in wrapping. The first clipping of an aneurysm was performed by Walter Dandy in 1938 (Dandy, 1938). Treatment was further refined through the introduction of angiography in 1927 and microneurosurgery in 1972 (Artico et al., 2017; Krayenbühl, Yaşargil, Flamm, & Tew, 1972). Another step in managing aneurysms was taken when the first coiling of an aneurysm was achieved in 1991 by Guido Guglielmi (Guglielmi, Vinuela, Dion, & Duckwiler, 1991). Current treatment of aneurysms is focused on stopping bleeding, restoring normal cerebral blood flow, and preventing dire secondary complications, including delayed cerebral ischemia (H. Richard Winn, 2017).

aSAH is an acute illness that is associated with devastating long-term morbidity and socioeconomic burden (Rivero-Arias, Gray, & Wolstenholme, 2010). Outcomes after aSAH remain to be suboptimal in multiple domains, despite improvements in diagnostics and acute care. The mean age of aSAH occurrence is 55, and survivors have a good life expectancy (Rinkel & Algra, 2011). Due to this, any adverse long-term consequences of aSAH could affect a survivor's ability to continue their previous social roles – including returning to work (Al-Khindi, MacDonald, & Schweizer, 2010). Most patients do not exhibit severe neurological deficits measured with classical examinations, but up to 55% of patients report reduced HRQoL years after the haemorrhage, with a higher reduction in mental QoL (Kreitschmann-Andermahr et al., 2007; Nieuwkamp et al., 2009; Noble & Schenk, 2010). Reduction in QoL – with social and general health deficits – persists years after the disease (Scharbrodt, Stein, Schreiber, Böker, & Oertel, 2009; Von Vogelsang, Burström, Wengström, Svensson, & Forsberg, 2013).

Up to a half of patients after aSAH experience emotional health disturbances such as depression, anxiety, and fatigue (Kreiter et al., 2013; Kutlubaev, Barugh, & Mead, 2012; Von-Vogelsang, Forsberg, Svensson, & Wengström, 2015). Emotional health disorders can persist for years and become chronic in a significant number of patients (Al-Khindi et al., 2010). Emotional health disorders in aSAH survivors are associated with an impairment of HRQoL and disrupted

reintegration into normal life (Kreiter et al., 2013; Visser-Meily, Rhebergen, Rinkel, Van Zandvoort, & Post, 2009). Depression, and other emotional health disorders, in survivors of ischemic stroke leads to increased morbidity, mortality, and a poor functional outcome (Cojocaru, Popa-Wagner, Stanciulescu, Babadan, & Buga, 2013).

Stressful life-events and adverse environmental factors are important contributors to the pathogenesis of emotional health disorders (Paykel, 2003). Genetic factors account for up to 40% of the risk for developing depression (Sullivan, Neale, & Kendler, 2000). Dysregulation of the hypothalamic–pituitary–adrenal axis has been in the centre of neurobiological research for depression and other emotional health disorders (Buttenschon et al., 2017). CRH is involved in the regulation of stress responses; CRH is, also, associated with the formation of emotional health disorders following adverse life-events (Binder & Nemeroff, 2010). Therefore, CRHR1 genotype is a suitable biomarker for phenotypes vulnerable to the development of emotional health disorders after stressful life events (Liu et al., 2013).

Despite the potential benefit associated with the timely management of QoL and emotional health disorders after aSAH, these disorders often remain unrecognized and undertreated. aSAH patients require similar management to chronic neurological disease, and patient complaints should be measured with more precise instruments that include QoL, emotional, and cognitive assessment (He & Mack, 2014; Zweifel-Zehnder et al., 2015). Psychiatric disorders often coexist and their symptoms can overlap, but a more uniform diagnostic and management strategy is required to achieve better long-term outcomes (Zweifel-Zehnder et al., 2015). Biomarkers are needed to predict, diagnose, and potentially treat the long-term consequences of aSAH.

4 LITERATURE REVIEW

4.1 Epidemiology of aneurysmal subarachnoid haemorrhage

The prevalence of intracranial aneurysms is around 3% in general population based on autopsy studies (Etminan et al., 2014). The most common form of aneurysm is saccular, with a diameter below 1 cm, and most are in the anterior cerebral circulation (Figure 1) (Petridis et al., 2017). The incidence of aSAH is around 7.9 per 100,000 person-years and it has decreased in recent decades. In Europe, aSAH incidence has decreased by 40.6% from 1980 to 2010, which is likely associated with lifestyle changes (Etminan et al., 2019).

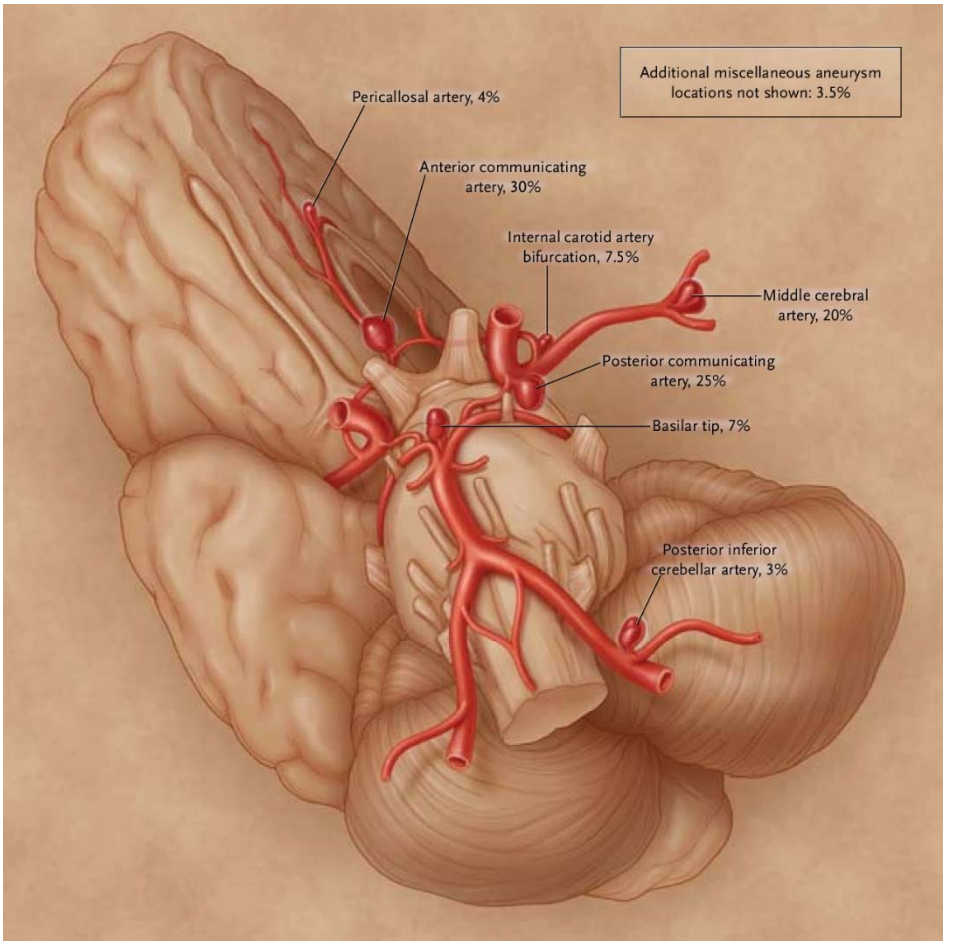

Figure 1. The circle of Willis and common location of intracranial aneurysms. Reproduced with permission from (Brisman, Song, & Newell, 2006). Copyright Massachusetts Medical Society.

A nationwide study from Finland illustrated that incidence of aSAH decreased from 11.7 in 1998–2000 to 8.9 per 100,000 persons in 2010–2012. At the same time, daily smoking decreased by 30% together with prevalence of hypertension (Korja, Lehto, Juvela, & Kaprio, 2016). Case fatality of aSAH is around 35%, which has decreased by 17% in the last three decades due to improved management in the subacute phase (Nieuwkamp et al., 2009).

4.2 Pathophysiology

Intracranial aneurysms are defined as focal outpouchings of an arterial wall originating at branching points of arteries of the circle of Willis. Pathologically, they are associated with vessel wall tissue degeneration and inflammation (Chalouhi, Hoh, & Hasan, 2013). In the case of aneurysm rupture, an acute extravasation of blood into subarachnoid space occurs during which intracranial pressure can shortly rise up to 100 mmHg leading to acute brain injury, hypoxemia and subsequent damage from blood products (Fujii et al., 2013). These events, together with mechanical damage from hydrocephalus, increased intracranial pressure, and other types of haemorrhages are the main causes of the initial neurological deficit seen in patients. aSAH is unique for having a secondary brain injury phase defined as delayed cerebral ischaemia (DCI) in 30% of patients on days 3 to 21. Angiographic vasospasm is seen in up to 70% of patients, but it does not always occur at the same time as DCI (Macdonald, 2014).

4.3 Risk factors, natural history, and diagnosis

Currently, aneurysms are considered to be acquired rather than congenital lesions (van Gijn et al., 2007). Up to 10% of patients have a familial history of aneurysm (Ronkainen et al., 1997). Genome wide association studies revealed multiple loci associated with aneurysm formation, but they explained only 5% of the genetic risk (Kurki et al., 2014). An aggregation of environmental factors is likely more important in determining the risk of aneurysms than genetic contributions, even in familial cases. Aneurysms are more common in females, in the elderly, and in patients with connective tissue disorders – e.g. autosomal dominant polycystic kidney disease or type IV Ehlers-Danlos syndrome (Muehlschlegel, 2018). Patients with history of aSAH have a 15-times higher chance of a new aneurysm formation (Anderson, Hankey, Jamrozik, & Dunbabin, 2000). Unruptured aneurysms usually remain asymptomatic, but they can manifest due to mass effect. Most aneurysms never rupture during a patient's life. The yearly rupture rate is highly variable; nevertheless, the yearly rupture rate is around 1% for aneurysms approximately 10 mm in size (H. Richard Winn, 2017). The risk factors for aSAH are the patient's age and the aneurysm's size, growth, morphological characteristics (e.g. irregular shape), location in posterior circulation, the existence of multiple aneurysms (30% of patients harbour more than one), a history of prior or familial

aSAH, and symptomatic aneurysms (Macdonald & Schweizer, 2017). Important modifiable factors that increase the risk of aneurysm rupture include smoking, hypertension, alcohol abuse, and sympathomimetic drugs (Andreasen, Bartek, Andresen, Springborg, & Romner, 2013). In recent decades, the global aSAH incidence declined by 7.1%, with decreases in every mmHG of systolic blood pressure, and by 2.4% with every percentage of decrease in smoking prevalence (Etminan et al., 2019).

The main sign of an aSAH is a sudden, severe 'thunderclap' headache, which is often described by patients as 'the worst pain in their life.' A headache is the only symptom in half of the cases, which can complicate the recognition of the disease and lead to a delay in diagnosis (Macdonald & Schweizer, 2017). Some patients experience weaker sentinel headache in the weeks preceding ictus. A headache might be accompanied by signs of meningitis, focal neurological symptoms (e.g. oculomotor nerve palsy), or epileptic seizures. A decrease in the level of consciousness is seen in two thirds of patients, of whom half are in a coma. The level of consciousness is commonly described according to the Glasgow Coma Scale (Table 1) (Teasdale & Jennett, 1974). In 10% of patients, an intraocular haemorrhage or Terson's syndrome occurs. A proportion of aSAH patients exhibit acute systemic effects, most likely due to a sympathetic reaction, which includes severe hypertension, arrythmias, myocardial dysfunction, pulmonary oedema, and gastroparesis (Petridis et al., 2017). Up to 21% of aSAH cases occur as sudden death before reaching hospital treatment (Korja et al., 2016).

Table 1. Glasgow Coma Scale (from Teasdale & Jennett, 1974).

	Response	Score
Eye Opening (E)	None	1
	To Pain	2
	To Speech	3
	Spontaneous	4
Motor Responses (M)	No Response	1
	Extension	2
	Abnormal Flexion	3
	Withdraw	4
	Localizes Pain	5
	Obeys Commands	6
Verbal Response (V)	No Response	1
	Incomprehensible	2
	Inappropriate	3
	Confused	4
	Oriented	5

The main tool in diagnosing aSAH is computed tomography (CT), which might show an accompanying intracerebral haemorrhage (ICH) in 30% of cases, intraventricular haemorrhage in more than 50%, subdural haemorrhage in less than 5%, or hydrocephalus in 20% of cases (Figure 2). CT has a sensitivity of 97% in the first 72 hours, but after 5 days it is only 50% accurate (Macdonald & Schweizer, 2017). In cases where CT remains negative, a lumbar puncture is performed to check for xanthochromia. After diagnosing aSAH, vascular imaging is performed – usually a CT angiography, which has a sensitivity of 97–98% – to detect aneurysms compared to DSA (Westerlaan et al., 2010). The gold standard in aneurysm diagnostics remains to be DSA. In 10–20% of SAH cases, angiography does not reveal the source of bleeding. Repeat angiographic studies – in cases of non-perimesencephalic SAH – uncover the source of bleeding in 8% of cases (Dalyai et al., 2013).

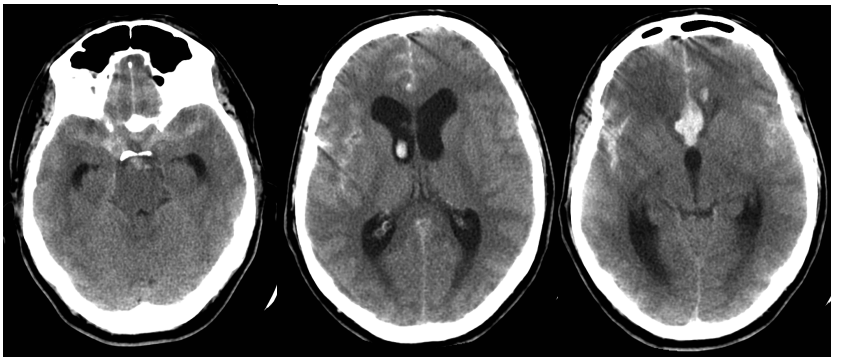

Figure 2. CT scan of SAH with an intraventricular and intracerebral hematoma.

4.4 Management

The initial treatment of aSAH requires the stabilisation of a patient's immediate condition, which follows the protocols of life support (airway, breathing, circulation) (Connolly et al., 2012). Any space occupying lesion (ICH, SDH), or hydrocephalus, is dealt with urgently. If left untreated, the risk of rebleeding from an aneurysm is 40% during the first month, with the highest probability during the first days after the original aneurysm (Brilstra, Algra, Rinkel, Tulleken, & Van Gijn, 2002). The risk of rebleeding in the hospital is around 15% (Vergouwen, Jong-Tjien-Fa, Algra, & Rinkel, 2016). If the patient's aneurysm rebleeds, the risk of death or permanent disability is 80% (Roos et al., 2000). The Hunt & Hess scale (Table 2) is a common classification system for grading aSAH patients. The scale holds important prognostic information (Hunt & Hess, 1968; Lantigua et al., 2015). Patients with an HH score of 5 are initially treated conservatively and monitored for improvement due to their poor prognosis. Patients in a better clinical condition should have their aneurysm occluded acutely due to the risk of rebleeding (Steiner et al., 2013). The choice between the two main ways of occluding a

ruptured aneurysm – endovascular or surgical – requires an interdisciplinary approach and depends on patient and aneurysm characteristics (Manhas et al., 2015). The treatment of aSAH does not end with the closure of the aneurysm, since severe complications exist which require prevention and management in an intensive care unit (de Oliveira Manoel et al., 2016).

Table 2. Hunt & Hess Scale with in-hospital mortality (from Lantigua et al., 2015).

Grade	Symptoms	Mortality rate (%)
1	Asymptomatic, mild headache	3.5
2	Moderate to severe headache, nuchal rigidity, no focal deficit other than cranial nerve palsy	3.2
3	Mild mental status change (drowsy or confused), mild focal neurologic deficit	9.4
4	Stupor, or moderate-to-severe hemiparesis	23.6
5	Comatose, or decerebrate rigidity	70.5

4.5 Short-term complications

aSAH has severe manifestations that can occur in the early phase after rupture. These include acute hydrocephalus in 20%, increased intracranial pressure in 50% and seizures in up to 26% of patients during the acute phase (Germanwala, Huang, & Tamargo, 2010; Heuer, Smith, Elliott, Winn, & Leroux, 2004; Lanzino, D'Urso, & Suarez, 2011). The medical complications are syndrome of inappropriate antidiuretic hormone (SIADH), cerebral salt wasting syndrome (CSW), fever, hyperglycaemia, anaemia, infections, gastric ulcers, renal dysfunction, intestinal necrosis, thromboembolic, and cardiopulmonary complications (Hall & O'Kane, 2018). The most problematic complication of aSAH is delayed cerebral ischemia. DCI accounts for up to 30% of poor outcomes, or deaths, after aSAH (Macdonald, 2014). Poor outcomes due to DCI can be reduced with prophylactic use of nimodipine, angioplasty procedures, and induced hypertension (Dorhout Mees et al., 2007; Kimball, Velat, & Hoh, 2011; Treggiar, 2011). Recently, deaths from DCI and rebleeding have decreased due to improved management techniques; nevertheless, up to 80% of patients still experience medical complications in the early phase which cause up to 23% of deaths among initial survivors (Lantigua et al., 2015).

4.6 Chronic complications

aSAH patients experience multiple chronic complications, which have a negative impact on clinical and general outcome among survivors. 7 to 19% of patients develop shunt-dependant hydrocephalus – this percentage varies due to diagnostics and management strategies (Lai & Morgan, 2013). Up to 30% of cases require ventriculoperitoneal shunt revisions (O'Kelly, Kulkarni, Austin, Urbach, & Christopher Wallace, 2009). 2% of patients develop long-term epilepsy (Lanzino et al., 2011). Up to 30% of patients develop anosmia (van Gijn et al., 2007). Pituitary dysfunction occurs in up to 31% of cases (Can et al., 2016).

4.7 Long-term outcome after aneurysmal subarachnoid haemorrhage

aSAH is a disease with a dramatic manifestation and a surgically treatable cause. Unfortunately, it is not a 'once in a life-time event.' Patients with aSAH are younger compared to patients with other types of strokes. Survivors of aSAH have a higher risk of new aneurysm formation and recurrent bleeding (Rinkel & Algra, 2011). The long-term standardised mortality ratio after aSAH is 1.5 times higher than in the general population, which is mostly related to cardiovascular and cerebrovascular deaths due to common risk factors, like hypertension and smoking (Huhtakangas et al., 2015). Survivors of aSAH experience long-term functional, emotional, and cognitive deficits. Functional deficit is related to the physical outcome of the patients and ability to manage everyday tasks. Emotional health deficit consists of depression, anxiety, panic disorder, and other psychological problems (including mental fatigue). Cognitive outcome is measured by neuropsychological studies (e.g. memory, language, attention). Different types of disorders, that aSAH patients develop, can affect QoL scores.

4.7.1 Functional and cognitive outcome

In the long-term, two-thirds of aSAH survivors are functionally independent (Nieuwkamp et al., 2009). Around 15% of survivors develop a focal neurological deficit or need assistance in ambulation (Mayer et al., 2002). A common measure of functional outcomes in stroke survivors is the modified Rankin Scale (Table 3) (Van-Swieten, Koudstaal, Visser, Schouten, & van Gijn, 1988). Based on the mRS score, 36% to 55% of patients are independent one year after aSAH (Nieuwkamp et al., 2009). Half of aSAH patients have sleep disturbances, and up to a third of patients with a good outcome experience sexual dysfunction (Al-Khindi et al., 2010; Epprecht et al., 2018). Clinical outcomes, after aSAH, depend on multiple factors, including the severity of the haemorrhage, the initial neurological condition, the posterior location of the aneurysm, the presence of IVH or

ICH, the occurrence of rebleeding, DCI, or hydrocephalus (Petridis et al., 2017; Rosengart, Schultheiss, Tolentino, & Macdonald, 2007). Activities of daily living – performed for self-care – are affected in 4% to 12% of cases. Instrumental activities of daily living – more complex tasks like housekeeping – are impaired in 44% to 93% of cases (Al-Khindi et al., 2010). Among patients older than 70 years at ictus, 50% are functionally independent at a 1 year follow-up (Proust et al., 2018).

Table 3. Modified Rankin Scale (from Van-Swieten, Koudstaal, Visser, Schouten, & van Gijn, 1988).

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability: unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability: requiring some help, but able to walk without assistance
4	Moderately severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability: bedridden, incontinent, and requiring constant nursing care and attention
6	Dead

Up to 50% of patients with a good functional outcome after aSAH experience some sort of cognitive impairment, most commonly in the form of verbal and visual memory, language, and executive function. Cognitive deficits are significant predictors of ADL and IADL impairment in survivors (Al-Khindi et al., 2010). Cognitive disturbances are more common in the first months after aSAH, but they can persist for years. The determinants of worse long-term cognitive outcome include older age, less years of education, poor neurological conditions, anterior circulation aneurysms, and more subarachnoid blood in the anterior interhemispheric fissure and sylvian fissures (Kreiter et al., 2002). A recent study described associations of hydrocephalus and brain infarctions with cognitive disturbances in the acute phase after aSAH (Haug Nordenmark, Karic, Sorteberg, & Sorteberg, 2019). According to a metanalysis and long-term data from the ISAT trial, coiling is associated with better cognitive outcomes in executive function and language tests than clipping (Egeto, Macdonald, Ornstein, & Schweizer, 2018; Scott et al., 2010).

4.7.2 Health related quality of life outcome

HRQoL is an ambiguous term, but it can be defined as 'those aspects of self-perceived well-being that are related to, or affected by, the presence of disease or treatment' (Ebrahim, 1995; Karimi & Brazier, 2016). QoL can be divided into physical, emotional, and social domains, and they are reasonably interconnected (Boosman, Passier, Visser-Meily, Rinkel, & Post, 2010). QoL is significantly impaired in all domains after aSAH, with a greater reduction in the emotional, rather than physical, domain (Kreitschmann-Andermahr et al., 2007; Wong et al., 2011). A decrease in QoL is reported even among patients regaining functional independence (Passier, Visser-Meily, Rinkel, Lindeman, & Post, 2013). The Short Form (36) Health Survey and EQ-5D are common questionnaires used to asses QoL after aSAH (Andersen, Fitzgerald, Delaney, & Finfer, 2019).

4.7.3 Social rehabilitation and work resumption

Deficits in social functioning persist for years after aSAH (Scharbrodt et al., 2009). More than 40% of patients are not able to return to their previous work, and up to one third of patients reduce working hours (Al-Khindi et al., 2010; Seule, Oswald, Muroi, Brandi, & Keller, 2020). The return to work is an important aspect of social reintegration with a significant effect on QoL. In 2005 in the United Kingdom, productivity losses related to aSAH reached almost 310 million euros, and the total economic healthcare burden of aSAH was around 565 million euros (Rivero-Arias et al., 2010). The occurrence of emotional and cognitive disturbances, neurological deficit, fatigue, and older age affect the return to work after aSAH (Al-Yassin, Ouyang, & Temes, 2017; Buunk, Spikman, Metzemaekers, Van Dijk, & Groen, 2019; Buunk et al., 2018; Crago et al., 2016; Turi et al., 2019; Westerlind, Persson, & Sunnerhagen, 2017).

4.7.4 Emotional health disorders and fatigue

Patients exhibit a high prevalence of multiple emotional health disorders in the months and years after surviving the haemorrhage. Experiencing a sudden threatening life event like an aSAH can be psychologically traumatic and leave a lasting fear of rebleeding, ultimately causing problems with reintegration into previous life (Hütter & Kreitschmann-Andermahr, 2014). As early as 1953, Walton et al. reported that 25% of aSAH patients in his cohort exhibited a severe and often persistent fear of rebleeding (Walton, 1953). Later, it was reported that about 25% of aSAH patients with a good neurological outcome had a substantial emotional maladjustment (Ropper & Zervas, 1984).

A recent metanalysis of depression following aSAH concluded that depression occurs in up to 61.7% of cases, with a weighted frequency of 28.1%, which is similar to other types stroke (Kwong Tang et al., 2020). Depression persisted for

longer than 2–5 years after aSAH in more than two thirds of the patients in one study (Ackermark et al., 2017). Anxiety occurs in 27% to 54% of patients and can persist for more than 2 years after aSAH (Al-Khindi et al., 2010). Harbouring an unsecured aneurysm might be associated with a higher anxiety score (King, Kassam, Yonas, Horowitz, & Roberts, 2005). Not all studies found a similar association between anxiety and an unsecured aneurysm (Van Der Schaaf et al., 2006; Von-Vogelsang et al., 2015; Von Vogelsang, Svensson, Wengström, & Forsberg, 2013). Post-traumatic stress disorder occurs in 18% to 37% of cases. Appearing usually in the initial months following aSAH, post-traumatic stress disorder can persist for more than 3 years (Al-Khindi et al., 2010; Hütter & Kreitschmann-Andermahr, 2014). The development of PTSD after aSAH is associated with younger age, passive coping styles, and neuroticism (Huenges Wajer et al., 2018; Noble et al., 2008; Visser-Meily et al., 2013). Active coping strategies after aSAH – such as positive reinterpretation, personal growth, and planning – lead to a better mental outcome in comparison with passive approaches, such as alcohol or drug use, disengagement, and denial (Tomberg et al., 2001).

Pathological fatigue is defined as "a state characterized by weariness unrelated to previous exertion levels and is usually not ameliorated by rest" (De Groot, Phillips, & Eskes, 2003). The occurrence of fatigue after aSAH is highest in the first 12-months, but fatigue can persist for years and even become worse with time. The frequency of fatigue in aSAH patients ranges from 31 to 90%. Various definitions of fatigue exist, but a distinction between mental and physical fatigue is important (Buunk et al., 2018; De Groot et al., 2003). Mental fatigue is a separate entity, and it occurs significantly more often than depression, anxiety, or other emotional health disorders. Mental fatigue after aSAH can lead to life dissatisfaction, the failure to return to work, and deficits in a patient's general well-being and social life (Kutlubaev et al., 2012). The occurrence of fatigue following aSAH has been associated with emotional health disorders, sleep disorders, physical and cognitive outcome of the patients (Noble et al., 2008; Ogden, Utley, & Mee, 1997; Passier et al., 2011). A recent study showed that mental fatigue occurs more frequently after aSAH than physical fatigue in 48% and 39% of cases, respectively. In that study, external cerebrospinal drainage in the acute phase after aSAH was the main factor associated with development of mental fatigue. Compared to mood disorders and physical fatigue, only mental fatigue was significantly associated with a poor long-term functional outcome among SAH patients (Buunk et al., 2018).

4.7.5. Associations between quality of life and emotional health disorders and their possible causes

Previous studies have reported associations between emotional health disorders and health related QoL after aSAH (Passier et al., 2012; Visser-Meily et al., 2009). Associations between emotional health disorders and QoL were confirmed by most studies, and only one study did not confirm the association of emotional

health disorders with social functioning after SAH (Powell, Kitchen, Heslin, & Greenwood, 2004).

The neural events behind a long-term decrease in quality of life and emotional health disorders after aSAH are largely unknown. MRI of aSAH patients have shown direct brain damage and morphological changes, which were associated with long- term cognitive deficits. Grey to white matter ratio, brain atrophy, focal lesions, hippocampal volume loss, and left-sided infarction following aSAH have been associated with a worse cognitive outcome (Ali et al., 2018; Bendel et al., 2010, 2006; Hadjivassiliou et al., 2001; Rass et al., 2020). In more than 30% of patients, pituitary dysfunction – which might lead to formation of emotional health disorders through various mechanisms – occurs (Buttenschon et al., 2017; Diringer et al., 2011). A recent metanalysis showed that the frequency of pituitary deficiency varies from 5% to 45% in studies performed up to 6 months after aSAH and from 0% to 55% in long-term investigations. Pooled frequencies were 31% in the short-term and 25% in long-term studies. Growth hormone deficiency was the most common finding in studies of aSAH patients. Growth hormone deficiency can lead to symptoms mimicking chronic fatigue (Can et al., 2016). Similar events occur after other types of stroke (Booij, Gaykema, Kuijpers, Pouwels, & den Hertog, 2018; Levada & Troyan, 2018). One study reported that depression following aSAH was associated with low basal cortisol values, and that low energy levels were associated with severe growth hormone deficiency (Kreitschmann-Andermahr et al., 2007). Central adrenal insufficiency was recently associated with reduced QoL after aSAH (Kronvall et al., 2016). Another small study found an association between higher hair cortisol values and depression, lower life satisfaction, hypochondriacal beliefs, and increased sleep disturbances following aSAH (Colledge et al., 2017). The loss of pituitary gland volume after aSAH is associated with worse self-perceived motivation and low initial volume with impaired executive functions at 1-year follow-up (Rass et al., 2020).

4.8 Hypothalamic-pituitary-adrenal axis and CRHR1 genotype relationship to emotional health disorders

4.8.1 Hypothalamic-pituitary-adrenal axis

The HPA-axis is an important regulator of homeostasis in response to different types of stress. The HPA-axis is activated with the release of CRH from the paraventricular nucleus in the hypothalamus into the portal circulation surrounding the pituitary gland. Two different CRH receptors exist, namely – CRHR1 and CRHR2 (Hauger et al., 2003). CRH and urocortin 1 bind mostly to CRHR1, whereas urocortin 1, 2, and 3 bind with higher affinity to the CRHR2 receptor (Hauger et al., 2003). The CRH activity is regulated by the CRH-binding protein (Behan et al., 1995). CRH stimulates the corticotropic cells in the anterior pituitary gland through the CHRH1 receptor. CRH leads to the release of ACTH. ACTH, in turn, stimulates the adrenal gland to release glucocorticoid hormones, mostly

cortisol (Figure. 3). Glucocorticoids regulate homeostasis through metabolic, immunologic, cognitive, and behavioural alterations (Goldstein & Kopin, 2007). A negative feedback loop exists in the HPA-axis, which leads to inhibition of both the pituitary and hypothalamus with cortisol acting on the NC3R1 receptor, and CRH acting on the CRHR2 receptor (Wasserman, Wasserman, & Sokolowski, 2010). This negative feedback also affects the limbic system (Naughton, Dinan, & Scott, 2014).

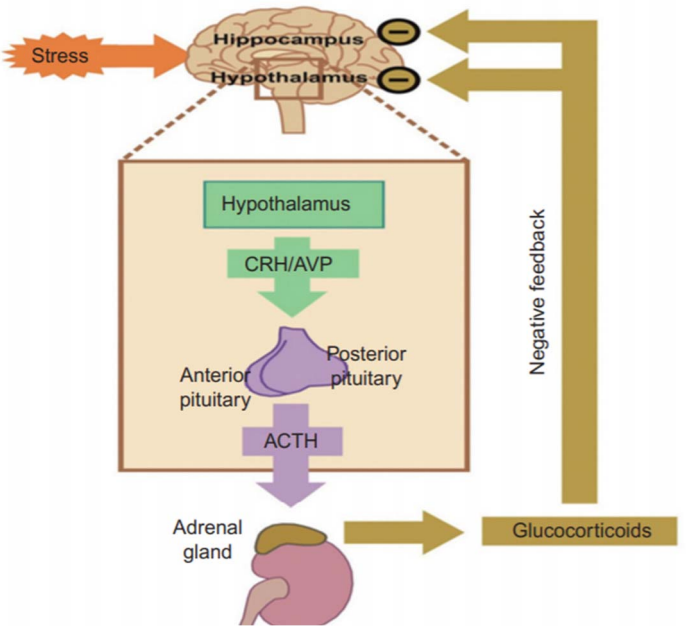

Figure 3. 4.8.1 Hypothalamic-pituitary-adrenal axis regulation. Abbreviations: CRH – corticotrophin releasing hormone; AVP – vasopressin, ACTH – adrenocorticotrophic hormone. Reproduced with permission from Naughton, Dinan, & Scott, 2014. Designed by Dr Marcela Julio. Copyright 2014 Elsevier B.V.

4.8.2 Corticotrophin releasing hormone receptor type 1 and emotional health disorders

Stress can be a trigger, or part, of the pathogenesis of mental illness. The stress-vulnerability model (Figure 4), described by Zubin et al. in 1977, is an extremely useful model for explaining, and approaching, mental disorders following adverse life events (Zubin & Spring, 1977). A person with an intrinsic vulnerability is at more risk of an inadequate psychological reaction and mental illness following a stressful life-event or acute brain damage. Intrinsic vulnerability might be caused by an abnormal functional organisation of the brain or the genetic setup of the organism. Due to these factors, adverse life-events could lead to the development of mental illness (Goh & Agius, 2010).

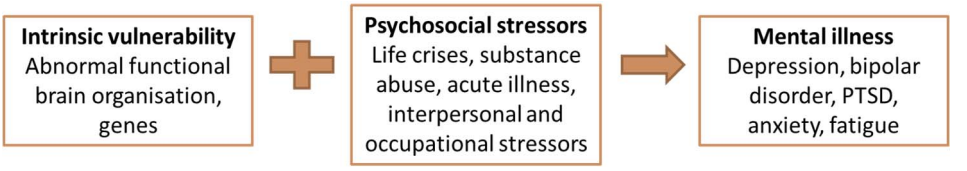

Figure 4. Stress-vulnerability model (modified from Goh & Agius, 2010).

The corticotropin releasing hormone receptor 1 (CRHR1) is a 7-transmembrane G-protein coupled receptor that is highly expressed in in the cerebral cortex, hippocampus, amygdala, pituitary gland, ventral tegmental area, substantia nigra, and cerebellum. To a lesser degree, CRHR1 is expressed in peripheral locations including the skin, ovaries, testes, and adrenal gland (Binder & Nemeroff, 2010). The CRHR1 gene is located on chromosome 17, spanning 20 kb of DNA (Chen, Lewis, Perrin, & Vale, 1993). CRHR1 contains 14 exons and three known isoforms arising due to alternative splicing (Pisarchik & Slominski, 2001).

Genes that regulate the function of the stress response system are probable moderators of the effect that adverse life events have on the development of emotional health disorders (Gerritsen et al., 2017; Gold, 2015). The corticotropin-releasing hormone is one of the main stress mediators in the central nervous system and it plays a role in the aetiology of emotional health disorders (Naughton et al., 2014). CRH acts together with vasopressin on the pituitary to release ACTH. CRH also acts on the limbic system through the type 1 receptor to activate functions relevant to the 'fight or flight' response, including increased fear and alertness, and decreased appetite and libido. The dysregulation of the HPA-axis is apparent in depression and anxiety disorders (Naughton et al., 2014). Overactivity of the CRH/CRHR1 receptor system is apparent following early life trauma in humans and in animal models. Overactivity of CRH/CRHR1 was also reported in post-mortem studies of depression and suicide (Binder & Nemeroff, 2010). CRHR1 knockout and CRH overexpressing mice, restricted to forebrain areas, have developed anxiety and depression-like phenotypes, which shows that development of depressive symptoms might also occur without HPA-axis involvement. Endocrine actions probably potentiate the effect of CRH/CRHR1 system (Lu et al., 2008; Müller et al., 2003). The CRHR1 gene has been shown to modulate negative memory consolidation in animal models (Hubbard, Nakashima, Lee, & Takahashi, 2007). CRH might have a possible neuroprotective function through direct effects in the central nervous system or the modulation of glucocorticoid activity (Koutmani et al., 2013).

The first report on associations between the CRHR1 genotype and depression focused on the effect of rs242939 and the G-G-T-haplotype (Liu et al., 2006). A polymorphism set in intron 1 of CRHR1 gene, that forms the rare TAT-haplotype (composed of rs7209436, rs110402, and rs242924), was originally associated with a protective effect against depression following early life stress (Bradley et al., 2008; Polanczyk et al., 2009). The TAT-haplotype has been also shown to be a risk factor for depression in later studies of patients with no, or minimal history

of, adverse life-events (Grabe et al., 2010; Kranzler et al., 2011; Laucht et al., 2013). GxE interaction plays an important role in an individual's resilience to stress and formation of emotional health disorders. GxE interaction refers to the difference in genetic effect depending on the environment or, alternatively, the way genetically different people respond to the same environment. The genetic diathesis model describes a trait or response that manifests after an exposure to a trigger. A more recent model, differential susceptibility, is distinct from simple diathesis by describing specific genetic polymorphisms that can manifest differently depending on environmental influences (Pluess, 2015). The differential susceptibility model states that individuals with the same genotype can be responsive to stressful and nurturing environments in separate ways, thus explaining variation in studies of the TAT-haplotype (Belsky & Pluess, 2009; Davis et al., 2018). Other SNP-s in the CRHR1 gene have been further associated with the risk of developing depression, panic, and posttraumatic stress disorder (Ishitobi et al., 2012; Liu et al., 2013; White et al., 2013). The CRHR1 genotype has been also associated with responses to antidepressant treatment (Geng et al., 2014; Ventura-Juncá et al., 2014).

It has been reported that the CRHR1 genotype is related to the reactivity of HPA-axis and cortisol to stress; this effect can be modulated by adverse life events (Heim, 2009; Mahon, 2013; Obasi et al., 2015; Sumner, McLaughlin, Walsh, Sheridan, & Koenen, 2014; Tyrka, Price, Gelernter, Anderson, & Carpenter, 2009). Cortisol reactivity to stress has been previously associated with emotional health disorders. A higher cortisol response to stress is usually associated with major depression, and a lower cortisol response is associated with PTSD and panic (Chopra et al., 2009; Fiksdal et al., 2019; McFarlane, Barton, Yehuda, & Wittert, 2011). CRHR1, together with other HPA-axis genes, has been shown to interact with chronic stress-moderating the diurnal cortisol slope and predicting fatigue (Starr, Dienes, Li, & Shaw, 2019).

Evidence suggests that the function of the CRHR1 gene is not limited to the HPA-axis, but an association with higher cognitive functions exists. When accounted for traumatic life-events in a gene-environment interaction model, the CRHR1 genotype was associated with impaired decision-making, psychotic symptoms of depression, the formation of emotional memories, rumination, and levels of neuroticism (Deyoung, Cicchetti, & Rogosch, 2011; Fuge et al., 2014; Guillaume et al., 2013; Polanczyk et al., 2009; Schatzberg et al., 2014; Woody et al., 2016). Better effect of interpersonal psychotherapy on depressive symptoms, social adjustment, and perceived stress was reported among women with no copies of the TAT-haplotype (Cicchetti, Toth, & Handley, 2014). The CRHR1 TAT-haplotype was recently associated with cognitive function in depressed patients, namely decision-making, rumination, worse learning, and memory (Davis et al., 2018).

4.9 Genetic factors and long-term outcome after aneurysmal subarachnoid haemorrhage

Previous studies, reporting a genetic association with outcome after aSAH primarily focused on pathophysiological topics of vasospasm, fibrinolysis or inflammation (Donnelly et al., 2015; Ducruet et al., 2010; Hendrix et al., 2017). Outcomes in these studies were mostly measured with general clinical scoring systems, like GOS or mRS, which do not give meaningful insights into the neuropsychological outcomes or QoL after aSAH. One small study reported an association of APOE-ε4 allele with worse scores in verbal fluency, visual memory, and colour naming tasks on long-term follow-up (Louko, Vilkki, & Niskakangas, 2006). Another study described an association of the APOE-ε4 allele with higher depression scores (Alfieri et al., 2008). A third study described that BDNF Met allele carriers with no cerebral infarctions had inferior learning and memory performance (Vilkki et al., 2008).

4.10 Summary of the literature review

Vascular diseases of the brain are a devastating cause of long-term morbidity and reduced QoL (Katzan, Schuster, Newey, Uchino, & Lapin, 2018). Despite substantial improvements in the management of aSAH in recent time, the psychosocial domain outcomes are still unsatisfactory both for patients and their proxies (Kapapa, Woischneck, & Tjahjadi, 2014). Recovery from aSAH leaves a significant strain on the personal and professional lives of patients, and recovery has a substantial impact on society (Al-Khindi et al., 2010).

More than half of patients have a reduced QoL following aSAH (Rinkel & Algra, 2011). Depression and anxiety occur in up to 50% of patients, and depression and anxiety can persist for more than 18-months (Al-Khindi et al., 2010; Powell et al., 2004). PTSD is reported in more than 30% of patients, and two-thirds of patients suffer from occasional or constant fear of rebleeding (Hütter & Kreitschmann-Andermahr, 2014). Changes in emotional health after aSAH are reported rather in-homogeneously and depend on the various instruments used to assess patient outcome (Hütter & Kreitschmann-Andermahr, 2014). One of the shortcomings of previous studies is that outcomes were often measured only with clinical scoring systems like the Glasgow Outcome Scale and the modified Rankin Scale, which are clinically relevant, but do not describe the psychosocial recovery (Rinkel & Algra, 2011).

Relatively little attention has been paid to the relationship between emotional health disorders and HRQoL impairment after aSAH. Emotional health disorders and social maladjustment are more prevalent than any clinical variable can explain (Lindberg, Angquist, Fodstad, Fugl-Meyer, & Fugl-Meyer, 1992; Noble & Schenk, 2010). This disparity cannot be explained by stigma from having a brain disease or by emotional strain from having a physical disability. This raises

questions about additional factors leading to psychological abnormalities after aSAH (Hütter & Kreitschmann-Andermahr, 2014).

There is a limited number of genetic studies on the topic of long-term psychosocial outcomes after aSAH, and their results are inconclusive (Alfieri et al., 2008). Adverse stressful life events are the most common risk factors for the development of emotional health disorders (Buttenschon et al., 2017). Genetic susceptibility to a maladaptive reaction, or dysfunctional central processing after a stressful life event, could lead to a poor psychosocial outcome after aSAH. The CRHR1 genotype is a possible biomarker of the susceptibility to poor psychosocial outcomes due to its implication in emotional health disorders, HPA-axis regulation, and influences on the cognitive and limbic systems (Naughton et al., 2014). The influence of the CRHR1 genotype on psychosocial disturbances after aSAH has not been previously studied. We chose to perform this study of long-term aSAH survivors treated in Tartu University Clinic as a group that represents the general outcome after aSAH. We aimed to explore the following hypotheses: QoL decrease occurs in all modalities after aSAH; emotional health disorders are common after aSAH; emotional health disorders are negatively associated with QoL after aSAH; CRHR1 genotype is associated with emotional health disorders and mental health related QoL after aSAH.

5 AIMS OF THE STUDY

The focus of this dissertation is aSAH and its long-term consequences. QoL and emotional health disorders are common among long-term survivors of aSAH. The relationship between associated clinical variables, biological risk factors, and long-term consequences after aSAH has not been thoroughly examined.

With studies included in this dissertation we aimed:

1. To assess the long-term quality of life in patients after aSAH.
2. To describe the long-term emotional outcome after aSAH.
3. To analyse the relationship between emotional health disorders and HRQoL in long-term survivors of aSAH.
4. To explore the effect of the CRHR1 genotype on the emotional health and quality of life of patients after aSAH.

6 PATIENTS AND METHODS

6.1 Study population

6.1.1 Article I

A study cohort for article I was collected retrospectively from the charts of all patients with aSAH treated at Tartu University Hospital from January 2001 to December 2010. We identified 384 cases with aSAH. Patients with SAH from other causes or intracerebral haemorrhages were not included. The contact information was available for 134 survivors. All patients were contacted by phone or mail, and all patients were asked to participate in the study. 20 patients were excluded due to following reasons: 7 were unreachable, 10 declined to take part in the study, and 3 were unable to take part due to logistic reasons or severe comorbidities. Eventually, 114 patients treated for aSAH were included in the study.

6.1.2 Articles II–III

Based on the medical records, 467 patients were diagnosed with aSAH during the period from January 2001 to November 2013 in Tartu University Hospital. All identified patients were included in the study. 185 survivors, with available contact information, were approached and asked to participate in the study. 60 patients were excluded due to following reasons: 31 were unreachable, 19 declined to take part in the study or donate blood, and 10 were unable to take part due to logistic reasons or severe comorbidities. A flow diagram describing the selection protocol is presented in Figure 5. A study cohort for articles II and III was composed of patients included in article I – who agreed to donate blood samples after the interview – and additional patients who were treated for aSAH in the same university clinic from 2010 to 2013 and agreed to participate in the study. Patients described in the articles II and III will be referred to as ‘extended cohort.’ The final study group consisted of 125 patients.

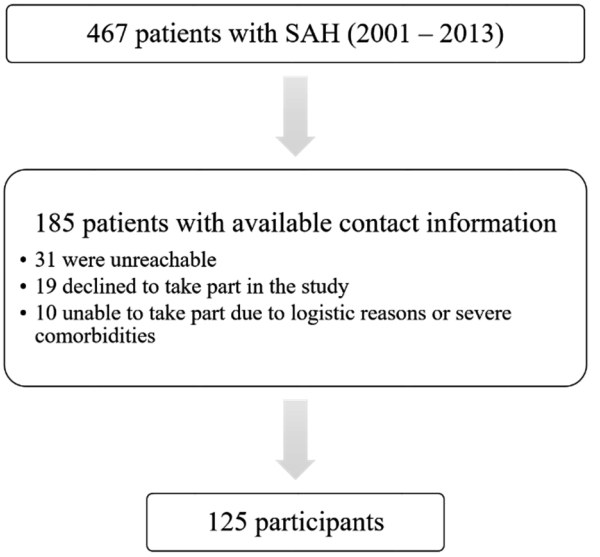

Figure 5. Flow diagram.

6.1.3 Consent and ethics committee approval

All individuals who participated in the studies gave their informed consent, and all procedures in all three articles were performed according to ethical standards and the latest Helsinki declaration. Tartu University ethics committee approved (no. 214/T-2/2012) the study.

6.2 Patient management (Articles I–III)

All patients were hospitalised during the acute phase of aSAH. SAH was diagnosed by computed tomography (CT) or lumbar puncture. The location of the aneurysm and its morphology were assessed by CT-angiography or digital subtraction angiography. Patients were initially treated at the neurointensive care unit, and their neurological status was closely monitored. Almost all of the patients were acutely operated – mostly via pterional approach – and aneurysms were clipped using standard microsurgical techniques. Endovascular procedures were preferentially performed in a different institution. Laboratory analysis and radiological procedures (computed tomography and transcranial doppler sonography) were routinely performed during postoperative management. Treatment was directed at preserving normal body physiology, decreasing risk of DCI, and treating DCI and other secondary complications. In all patients with acute hydrocephalus – diagnosed by CT – ventriculostomy was performed and intracranial pressure was monitored. All patients received 60 mg nimodipine p/o every 4 hours, and therapeutic hypertension was initiated in cases of vasospasm.

6.3 Procedure (Articles I–III)

Clinical data was recorded at admission. During follow-up interviews, patients were interviewed in person with a structured questionnaire. Clinical recovery was evaluated with the mRS. Information regarding treatment for emotional health disorders after aSAH, existing comorbidities, and patients' education levels and social situations was gathered. EST-Q was used to measure the patient's emotional health, and SF-36 (The RAND 36-item Health Survey 1.0) was used to assess QoL. Estonian and Russian versions of SF-36 and EST-Q were used to evaluate the patients. Blood samples were collected by the interviewing physician after the assessment.

EST-Q is a self-rating questionnaire that is composed of depression, anxiety, agoraphobia-panic, fatigue, and insomnia scales. The items of EST-Q were derived from diagnostic criteria from the Diagnostic and Statistical Manual of Mental Disorders IV and the International Classification of Diseases 10. Each item was rated for occurrence by a patient on a five-point scale ranging from 0 to 4 (from 'not' to 'all the time'). Participants of the study were asked how much the various problems troubled them during the past 4 weeks. EST-Q's total scale and subscales demonstrated good internal consistency (Cronbach α 0.69–0.88). The EST-Q questionnaire was demonstrated to be a reliable instrument in the assessment of depression, general anxiety, agoraphobia–panic, fatigue, and insomnia. EST-Q keeps nonspecific symptoms such as fatigue and insomnia apart from core symptoms of anxiety and depression (Aluoja, Shlik, Vasar, Luuk, & Leinsalu, 1999). To determine the optimal screening threshold, the sensitivity and specificity for various cut-off scores was calculated. The cut-off points for clinically important symptomatology are: ≥ 12 points for depression and anxiety, ≥ 8 points for fatigue, ≥ 7 points for agoraphobia– panic, and ≥ 6 points for insomnia (Aluoja A, Luuk K, Shlik J, 2001). Scoring more than the cut-off point in a specific subscale shows that the subscale score is in the same magnitude as that of most patients with the given diagnosis. EST-Q also includes a question about the frequency of 'recurrent thoughts of death or suicide'. The data was compared with the age and gender matched control group of 3,923 subjects (obtained from the 6,434 respondents of the Estonian Health Interview Survey) (Matsi A, 2009).

SF-36 is a validated instrument to assess general QoL that is widely used in clinical outcome research, including stroke and aSAH research. The RAND-36 version has a slightly different scoring method, but it allows results from the SF-36 to be compared (Hays, Sherbourne, & Mazel, 1993). SF-36 has been translated and adapted in Estonian and Russian languages (Herodes, Õun, Haldre, & Kaasik, 2001; Ivanova et al., 2005; Kalyadina et al., 2008; Novik, Ionova, & Gandek, 2001). SF-36 consists of 36 questions and has 8 scales: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health (McHorney, Ware, Lu, & Sherbourne, 1994; McHorney, Ware, & Raczek, 1993). SF-36 scores are transformed by the assignment of predefined weights to the different items and calculated separately for each scale. Results can range from 0 (low QoL) to 100 (high QoL). SF-36 has a correlation around

0.7 with other QoL questionnaires (Linde, Sørensen, Ostergaard, Hørslev-Petersen, & Hetland, 2008; McDonough et al., 2005; Richardson, Iezzi, Khan, Chen, & Maxwell, 2016). Mean component scores are separately calculated for mental (MCS-36) and physical (PCS-36) health. The results of our study group were compared with corresponding values from an age and gender matched group of the general population (996 subjects) obtained from respondents of a health survey of 1,989 individuals (Lai T, Kallikorm R, Salupere R, 2001).

6.4 Genetic analysis (Articles II–III)

A standard salting-out method was used to extract the genomic DNA from venous blood samples in 4 ml EDTA containing vaccuettes. The EDTA tubes were stored at –20 ºC. Isolated DNA was dissolved in the Tris-EDTA (TE) buffer. The purity and concentrations of the DNA were measured by a spectrophotometer (Nano-Drop, ND-1000). The gDNA samples were aliquoted and stored at –80 ºC until usage (Miller, Dykes, & Polesky, 1988). Genotyping of marker single nucleotide polymorphisms (SNP) rs7209436, rs110402, rs242924 and rs242939 was carried out by using the TaqMan SNP Genotyping Assay (Applied Biosystems, Foster City, CA, USA). PCR reactions were run on the ViiA7 instrument (Applied Biosystems, Foster City, CA, USA) by using the following cycling parameters: after the first step at 95 ºC for 10 minutes, 40 cycles of denaturation at 92 ºC for 15 seconds, and extension at 60 ºC for 1 minute. Genomic DNA (20 ng/µl) was amplified in a total volume of 10 ul containing 1x Amplification Master Mix (Applied Biosystems, Foster City, CA, USA) and 1x probe. Genotypes were analysed by using the allelic discrimination function of the system (Table 4).

Table 4. CRHR1 allele distribution (n=125).

SNP	Genotype (n)			Minor allele (n)	Major allele (n)
Rs7209436	C/C (34)	C/T (69)	T/T (22)	T (91)	C (103)
Rs110402	G/G (29)	A/G (68)	A/A (28)	A (96)	G (97)
Rs242924	G/G (31)	G/T (67)	T/T (27)	T (94)	G (98)
rs242939	T/T (95)	C/T (28)	C/C (2)	C (32)	T (218)

6.5 Statistical analysis

6.5.1 Article I

The Shapiro-Wilk's W test was used to check for normality of all continuous variables. The student's t-test was used to compare the mean scores of SF-36 and EST-Q of the patients with the matched controls. A two-sample t-test was used to study the associations between the scale scores and clinical/sociodemographic

or treatment factors. A Pearson correlation analysis was used to analyse the associations between EST-Q scores and SF-36 scale scores. A multiple linear regression analysis was performed to describe the impact of emotional health disorders diagnosed with EST-Q on SF-36 scale scores. EST-Q scores were used as indicator variables to diagnose emotional health disorders (those who scored higher than the cut-off were coded as '1,' the rest were coded as '0'). $p<0.05$ was defined as level of significance. JMP-9 (SAS Institute Inc., Cary, NC) and SPSS software (IBM Corp., NY) were used for the statistical analysis.

6.5.2 Article II

Beta-binomial regression analysis was used to analyse the association of the CRHR1 genotype with SF-36 scale scores and calculate the subsequent odds ratios. We chose between additive/dominant/recessive model based on the AIC (Akaike information criterion) of the unadjusted model in the SNP analysis. In the results of the SF-36 analysis, odds ratios higher than 1 indicate a better QoL in the respective group (recessive model – minor allele homozygote; dominant model – major allele homozygote; additive model – heterozygotes, in which case OR is multiplied with minor allele addition); odds ratios lower than 1 indicate a reduced outcome in SF-36 scales. When the recessive genotype was rare (3 or less patients) then dominant model was preferred. More precisely, OR shows the probability of having a higher score in the selected scale by 1 point (1 point bring equal to 5 points in physical functioning, vitality, general health scales; 25 points in role-physical scale; about 11 points in pain scale; about 33 points in role-emotional scale, 12,5 points in social functioning scale; and about 8 points in emotional wellbeing scale) (Arostegui, Núñez-Antón, & Quintana, 2007; Najera-Zuloaga, Lee, & Arostegui, 2018). Pearson's correlation and multiple logistic regression models were used to analyse the impact of genotype (frequency of minor alleles) and patient related variables on SF-36 scores. Statistical analysis was performed with Stata 14.2 (StataCorp LLC) and SPSS 24 (IBM).

6.5.3 Article III

Logistic regression analysis was used to study the association of CRHR1 genotype and EST-Q scores. Odds ratios were calculated. EST-Q scores were used as indicator variables to diagnose the emotional health disorders according to cut-off values. Pearson's correlation was used to assess internal correlation in EST-Q scales and multiple logistic regression analysis was used to describe the influence of the CRHR1 genotype (frequency of minor alleles) and patient related factors on fatigue scale results. Statistical analysis was performed with R (The R Foundation) and Stata 14.2 (StataCorp LLC).

7 RESULTS

7.1 Article I

7.1.1 Patient characteristics

The mean age at the time of aSAH was 54±13 years (range 21–80). 68% of the patients were female. 92% (n=105) of the aneurysms were clipped, mostly via a pterional approach. In 8% of the cases (n=9), aneurysms were occluded through coiling.

The mean time from initial hospitalisation to assessment was 4.5±3 years (range 1–10). 53% (n=60) were evaluated more than 3 years after experiencing an aSAH. The mean age at follow-up was 59±13 years (range 29–82) and 61% (n=70) were older than 55. Patient and aSAH characteristics are presented in Table 5. 55% of the patients had a mRS score of 0–2, and 38% had a score of 3, which equates to a good neurological outcome. 28% of the patients attended a psychiatrist or psychologist, and 36% of patients used antidepressants during their recovery from aSAH. Only 36% of patients reported complete subjective recovery from aSAH, and 45% of the patients required assistance with everyday activities. 80% (n=91) of the patients had more than 10 years of education.

Table 5. Patient and aSAH characteristics for article I (n=114) and articles II and III (n=125).

Characteristics		Article I N (%)	Articles II and II N (%)
Female		78 (68%)	88 (70%)
Male		36 (32%)	37 (30%)
Hunt Hess score	1	12 (10%)	17 (14%)
	2	58 (51%)	66 (53%)
	3	25 (22%)	23 (18%)
	4	13 (12%)	14 (11%)
	5	6 (5%)	5 (4%)
Aneurysm location	ICA	35 (30.7%)	40 (32%)
	AcomA	35 (30.7%)	44 (35%)
	MCA	25 (21.9%)	22 (18%)
	ACA	6 (5.3%)	8 (6%)
	BA	10 (8.8%)	9 (7%)
	VA	3 (2.6%)	2 (2%)
Intracerebral haemorrhage		20 (18%)	22 (18%)
Symptomatic vasospasm		27 (24%)	34 (27%)
Hydrocephalus	acute	37 (32%)	34 (27%)
	chronic*	10 (9%)	14 (11%)

Table 5. Continue

Characteristics		Article I N (%)	Articles II and II N (%)
Modified Rankin Score	0	1 (1%)	4 (3%)
	1	3 (2.6%)	7 (6%)
	2	59 (51.8%)	57 (46%)
	3	43 (37.6%)	49 (39%)
	4	8 (7%)	8 (6%)
Returned to work after aSAH		40 (35%)	–
Employed at assessment		32 (28%)	–
Complete subjective recovery		41 (36%)	–
Daily help requirement		51 (45%)	51 (41%)
Treatment during recovery:			
Antidepressants		41 (36%)	47 (38%)
Psychologist/psychiatrist		32 (28%)	30 (24%)
Education (years)	4–9	23 (20%)	27 (22%)
	10–12	75 (66%)	80 (64%)
	13–…	16 (14%)	18 (14%)

*Patients that received a ventriculoperitoneal shunt

7.1.2 Quality of life outcome after aneurysmal subarachnoid haemorrhage measured with SF-36

Patients had lower SF-36 QoL scores in all scales when compared to an age and gender matched controls (Table 6). The PCS-36 score was 42.3±9.4 and MCS-36 score was 47.3±10.2.

Table 6. SF-36 quality of life scores of aSAH patients compared to the matched controls.

	Patients with SAH (n=114)		Matched controls (n=917)		
SF-36 subscales	Mean	SD	Mean	SD	P-value
Physical Functioning	61.4	26	79.7	25	< 0.0001
Role Physical	32.7	40	72.8	39	< 0.0001
Emotional Health	65.9	19	70	17	0.02
Role Emotional	48.8	42	77.3	39	< 0.0001
Vitality	47.8	21	55.8	18	< 0.0001
Social Functioning	70.8	26	78.8	28	0.004
Bodily Pain	64.9	28	74.2	24	0.0004
General Health	46.1	21	57.2	17	< 0.0001

7.1.3 Prevalence of emotional health disorders after aneurysmal subarachnoid haemorrhage measured with EST-Q

Patients scored significantly higher on all EST-Q scales when compared to the matched controls. Based on cut-off values, almost half of the patients had fatigue (47%; n=54) and insomnia (46%; n=52). About one third of aSAH patients exhibited scores consistent with depression (30%, n=34) and anxiety (31%, n=35). 15% of the patients (n=17) had higher than cut-off scores on the agora-phobia-panic scale, which was 5 times more than in controls (Figure 6).

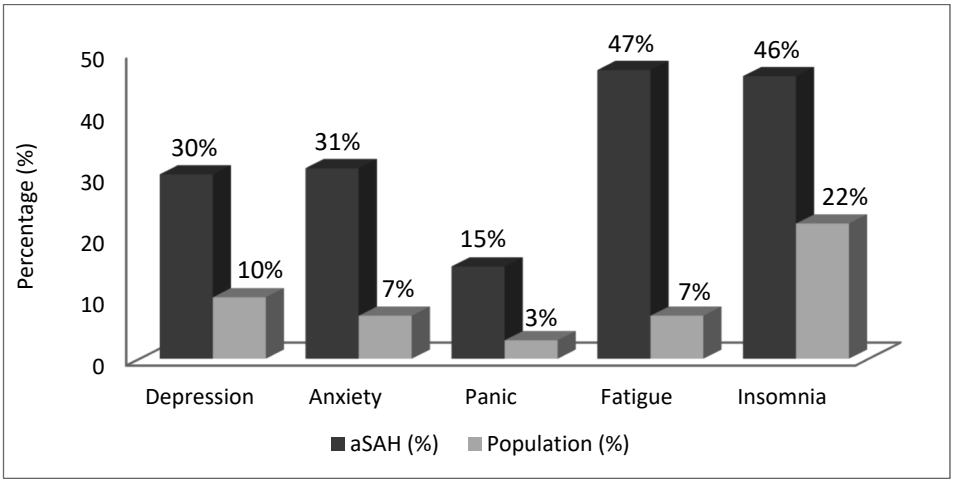

Figure 6. Prevalence of emotional health disorders among aSAH patients (n=114) compared to the matched controls (n=3,923) based on the EST-Q cut-off scores.

7.1.4 Variables associated with quality of life and emotional health after aneurysmal subarachnoid haemorrhage

Quality of life

Out of all sociodemographic and clinical variables, only a better HH score (1–3) – indicating a better clinical condition on admission – had a significant association with higher scores in vitality (49.5, SE=2.1 vs. 39.2, SE=4.7; p=0.02), emotional health (67.4, SE=1.9 vs 58.3, SE=4.3; p=0.03), and general health (47.7, SE=2.1 vs. 38.2, SE=4.8; p=0.04) scales.

Emotional Health

More time between aSAH and the follow-up interview (>3 years) was significantly associated with a higher panic score (3.5, SE=3.5 vs. 2.3, SE=0.5; p=0.04). Lower education (<10 years) was also associated with a higher panic score (4.7, SE=0.9 vs. 2.5, SE=0.4; p=0.01).

Using antidepressants during the recovery phase was associated with higher insomnia (6.0, SE=0.5 vs. 4.3, SE= 0.4; p=0.01), agoraphobia-panic (4.3, SE=0.8 vs. 2.2, SE=o.4; p=0.006), depression (11.0, SE=1.0 vs. 7.0, SE=0.8; p=0.002), fatigue (8.7, SE=0.5 vs. 6.0, SE=0.5; p=0.001), and anxiety (10.4, SE=0.7 vs. 7.0, SE=0.6; p=0.001) scores. Requiring psychological help during recovery was related to higher depression (11.5, SE=1.1 vs. 7.2, SE=0.7; p=0.002) and fatigue (8.3, SE=0.8 vs. 6.4, SE=0.5; p=0.04) scores.

7.1.5 Association of emotional health disorders with quality of life outcomes after aneurysmal subarachnoid haemorrhage

All SF-36 QoL scores had a significant negative correlation with EST-Q subscale scores (Pearson's r = –0.27–0.74).

Based on the multivariate regression analysis, fatigue was significantly associated with all SF-36 scale results (Table 8). Depression was significantly associated with the mental domain of QoL. Emotional health disorders explained 23–47% of the results in the SF-36 scales. Most of the variance in MCS-36 scores were explained by emotional health disorders, but less variance was indicated in the PCS-36 score (53% vs 29%).

Table 8. Multiple linear regression of SF-36 and EST-Q scores.

SF-36 subscales	EST-Q scales					R^2
	Anxiety	Depression	Panic	Fatigue	Insomnia	
Physical Functioning			b=–20	b=–16.4		0.23
			SE=6.5	SE=4.6		
			p=0.003	p=0.0006		
Role Physical				b=–38.9	b=–15.9	0.33
				SE=6.8	SE=7.2	
				p<0.0001	p=0.03	
Emotional Health		b= 15.9		b=–16.2		0.47
		SE=3.1		SE=2.9		
		p<0.0001		p<0.0001		
Role Emotional		b1=–23.9		b2=–33.1	b3=–16.8	0.44
		SE=7.4		SE=6.7	SE=7.1	
		p=0.002		p<0.0001	P=0.02	
Vitality		b=–10		b=–21.7		0.42
		SE=3.6		SE=3.3		
		p=0.007		p<0.0001		
		b1=–19.6		b3=–17.6		0.34

Table 8. Continue

SF-36 subscales	EST-Q scales					R^2
	Anxiety	Depression	Panic	Fatigue	Insomnia	
Social Functioning		SE=4.7		SE=4.3		
		p<0.0001		p<0.0001		
Bodily Pain	b1=–14.2			b2=–15.6	b3=–11.6	0.32
	SE=5.7			SE=5.2	SE=5.2	
	p=0.01			p=0.003	p=0.03	
General Health		b1=–15.5		b2 =–15.8		0.37
		SE=3.8		SE=3.5		
		p<0.0001		p<0.0001		
MCS		b1=–8.8		b2=–9.5		0.53
		SE=1.6		SE=1.5		
		p<0.0001		p<0.0001		
PCS			b1=–5.9	b2=–8		0.29
			SE=2.2	SE=1.6		
			p=0.0099	p<0.0001		

7.1.6 Returning to work following aneurysmal subarachnoid haemorrhage

Despite good clinical and neurological recovery, only 35% (n=40) of patients returned to work after aSAH, and 28% (n=32) of patients were employed at the follow-up. Not returning to work after aSAH was associated with higher insomnia (5.6, SE=0.4 vs. 3.8, SE=0.5; p=0.007), panic (3.8, SE=0.5 vs. 1.2, SE=0.4; p=0.001) and depression scores (9.7, SE=0.9 vs. 6.2, SE=0.8; p=0.007). Unemployment during the follow-up assessment was associated with higher insomnia (5.4, SE=0.4 vs. 3.9, SE=0.6; p=0.04), panic (3.5, SE=0.5 vs. 1.5, SE=0.4; p=0.01), depression (9.3, SE=0.8 vs. 6.4, SE=1.0; p=0.04), and fatigue scores (7.5, SE=0.5 vs. 5.7, SE=0.7; p=0.04).

7.2 Articles II and III

7.2.1 Patient characteristics

The mean age of aSAH occurrence was 54±13 years (range 24–82). 70% (n=88) of the patients were female. The average time between initial admission and the follow-up assessment was 4±2.8 years (range 1–13). The mean age at the follow up assessment was 58±12 years (range 26–82). 41% (n=51) of the patients were

studied more than 3 years from ictus. The patient characteristics of the extended cohort are presented in Table 5.

55% (n=68) of the patients had an mRS score of 0–2, and 39% (n=48) of patients had a score of 3. Daily help was required by 41% (n=51) of the patients. A lower mRS score was associated with female gender (2.5±0.8 vs 2.1±0.8, p=0.019) and requiring daily help (3.1±0.5 vs 2.0±0.7, p<0.001). 78% (n=97) lived with family or significant other. 78% (n=97) had more than 10 years of education.

24% (n=30) of the patients required psychological help, and 38% (n=47) of patients used antidepressants or similar medication during their recovery from aSAH. One patient had a prior diagnosis of depression based on the national database available from 2009. Patients reported having the following comorbidities: hypertension in 67% (n=84), joint pain or rheumatoid arthritis in 14% (n=18), diabetes in 7% (n=9) and 2% had a myocardial infarction.

7.2.2 Quality of life outcome in the extended cohort

All SF-36 quality of life scores among patients from the extended group were lower than that of the matched controls (Table 3 of Article II). The mean physical health component score (PCS-36) was 43±9.6, and the mean mental health component score (MCS-36) was 48.6±9.4.

Female gender was associated with worse physical functioning – 56.9±26.4 vs 76.6±19.1, p<0.001; role-physical – 32.4±38.6 vs 51.4±45.6, p=0.019; mental health – 64.9±18.9 vs 74.1±13.7, p = 0.08; and a worse PCS-36 score – 41.6±9.2 vs 46.8±9.5, p=0.005.

Age (older than 55 years at admission) was associated with a worse physical functioning – 54±25.4 vs 68±25, p=0.003 and a worse PCS-36 score – 40.6±9.4 vs 44.6±9.5, p =0.024. More than 3 years from aSAH to assessment was associated with a worse physical functioning – 58.3±26.7 vs 67.4±24.5, p=0.048; worse general health – 43±20.5 vs 54.2±21.1, p=0.003; and a worse PCS-36 score – 40.8±8.8 vs 45.4±9.9, p=0.008. After adjusting for age, the difference in the physical functioning score was statistically insignificant.

Diabetes was associated with a worse physical functioning score – 40±24.1 vs 64.6±25.4, p=0.016. Hypertension was associated with a worse physical functioning score – 58.9±25 vs 70.9±26.3, p=0.018. Joint pain or rheumatoid arthritis were associated with a worse role-physical score – 18.1±26.9 vs 41.5±42.8, p=0.004.

The modified Rankin Scale score – indicating a worse neurological outcome – was negatively correlated to all SF-36 scales with a higher correlation to physical functioning (Pearson's r=−0.62)

7.2.3 Prevalence of emotional health disorders in the extended cohort

Patients had significantly worse scores on all EST-Q scales compared to the matched controls (Table 3 of Article III).

Worse EST-Q scores were associated with female gender: depression – mean 9±6.8 vs 5.6±4.7, p=0.006; anxiety – mean 9.2±5.8 vs 6.7± 4.9, p=0.021; agora-phobia-panic – mean 3.8±4.3 vs 1.2±2, p< 0.001; fatigue – mean 7.2±4.2 vs 5.4±4, p=0.03; and insomnia – mean 5.1±3.3 vs 3.7±3.6, p=0.04.

A worse fatigue score was associated with hypertension – mean 7.5±4.2 vs 4.9 SD±3.6, p< 0.001; and having joint pains – mean 8.6±3.4 vs 6.4±4.3, p=0.021. A worse depression score was associated with receiving amlodipine – 10.7± 6.9 vs mean 7.5±6.3, p=0.035.

aSAH patients exhibited a high prevalence of emotional health disorders – based on the cut-off values of EST-Q – at the long-term follow-up. Fatigue (45%, n=56) and insomnia (41%, n=51) occurred in almost half of the patients. About one third of the patients demonstrated depression (29%, n=36) and anxiety (30%, n=38). 15% of patients (n=19) scored above cut-off values on the agoraphobia-panic scale, which is 5-times higher than the matched controls. 14% (n=18) of aSAH patients reported frequent thoughts of death or suicide (ranging from sometimes to constant) compared to 3% (n=126) in the matched controls (p<0.001).

7.2.4 Association of CRHR1 genotype with emotional health related quality of life after aneurysmal subarachnoid haemorrhage (Article II)

Patients who had more minor alleles of CRHR1 (Rs7209436, Rs110402, Rs242924) exhibited better scores in the mental domain of QoL. Statistically significant results are presented in Table 9. The CRHR1 genotype was not associated with other scales of SF-36. The TAT-haplotype – formed by the three minor alleles – and rs242939 did not show any statistically significant effect on QoL scores.

Table 9. Mean scores of SF-36 scales after aSAH according to CRHR1 genotype (only statistically significant associations presented).

Genotype	Mental health	Vitality	Role-emotional
Rs7209436			
MM	63.5±24.0	43.4±15.3	41.2±40.5
mM	67.2±18.5	52.5±21.4	55.6±43.1
mm	75.5±15.4	59.5±17.6	63.6±36.1
Rs110402			
MM	63.3±17.4	44.0±15.1	36.8±39.5
mM	66.6±18.5	51.7±22.1	55.9±42.6
mm	74.7±14.9	57.9±16.3	63.1±38.2

Table 9. Continue

Genotype	Mental health	Vitality	Role-emotional
Rs242924			
MM	65.9±17.9	43.7±15.3	n/a
mM	65.3±18.3	52.0±21.9	n/a
mm	75.7±14.2	58.1±16.6	n/a

We performed a beta-binomial regression analysis to explore the association of the CRHR1 genotype with QoL scores measured with SF-36 after aSAH (Table 10). All results remained significant after adjustment for the neurological state at admission (HH score), gender, age, and time from aSAH to assessment.

Table 10. Association of CRHR1 SNP-s with SF-36 outcomes (only statistically significant results are reported).

SNP	Allele	Model	OR	95% CI	p	OR*	95% CI*	p*
Mental health								
Rs7209436	Minor	Additive	1.31	1.07–1.6	0.009	1.31	1.07–1.6	0.009
Rs110402	Minor	Additive	1.29	1.06–1.57	0.011	1.26	1.04–1.54	0.019
Rs242924	Minor	Recessive	1.60	1.14–2.24	**0.006**	1.59	1.14–2.22	**0.007**
Vitality								
Rs7209436	Minor	Additive	1.38	1.13–1.7	**0.002**	1.38	1.13–1.69	**0.002**
Rs110402	Minor	Additive	1.31	1.07–1.6	**0.008**	1.31	1.07–1.6	0.009
Rs242924	Minor	Additive	1.33	1.09–1.62	**0.005**	1.32	1.08–1.62	**0.006**
Role-emotional								
Rs7209436	Minor	Additive	1.57	1.01–2.44	0.044	1.53	0.98–2.4	0.063
Rs110402	Major	Dominant	0.43	0.21–0.87	0.019	0.44	0.22–0.91	0.026

*adjusted for Hunt & Hess scale score, gender, age, and time from aSAH. P-values that survived Bonferroni correction are marked with bold.

A higher SF-36 mental health scale score was associated with a minor allele (rs7209436, rs110402, and rs242924) of CRHR1 (OR=1.31–1.6, $p<0.05$) in additive and recessive models. A higher vitality scale score was associated with a minor allele (rs7209436, rs110402, and rs242924) of CRHR1 (OR=1.31–1.38, $p < 0.05$) in the additive model. A higher role-emotional scale score was associated with the Rs7209436 minor allele (OR=1.57, 95% CI, 1.01–2.44, p=0.044) in the additive model. A lower role-emotional scale score was associated with the rs110402 major allele (OR= 0.43, 95% CI, 0.21–0.87, p=0.019) in the dominant model.

After Bonferroni correction for multiple comparisons, the association of the Rs242924 minor allele with mental health and the association of rs7209436, rs110402 and rs242924 alleles with vitality scale scores remained statistically significant.

7.2.4.1 Factors associated with mental quality of life

We performed a multiple logistic regression analysis to explore the factors influencing mental QoL, including the CRHR1 genotype (Table 11). A model that included the mRS score, the physical health component score, antidepressant usage history, and the CRHR1 genotype (number of minor alleles) had the best predictive value with R^2=0.36 for role-emotional, R^2=0.32 for vitality, and R^2=0.3 for mental health score ($p < 0.001$).

The minor genotype of Rs110402 was associated with the role-emotional (β=0.15, p=0.044), and the minor genotype of Rs7209436 was associated with vitality scale scores (β=0.23, p=0.003). PCS-36 was associated with the role-emotional (β=0.45, p<0.001), vitality (β=0.5, p <0.001), and mental health scale scores (β=0.26, p=0.005). mRS score was associated with the role-emotional (β=−0.19, p= 0.032) and mental health scale scores (β=−0.23, p=0.013). A history of antidepressants during recovery was associated with the mental health scale score (β =−0.23, p=0.007).

Sociodemographic factors, the location of the aneurysm, and comorbidities were not associated with SF-36 mental scale outcomes in multiple regression analysis.

Table 11. Multiple logistic regression analysis for SF-36 mental quality of life scales.

Variables	B	SE	β	p-value	R^2
Role-Emotional					
PCS-36	1.96	.37	0.45	<0.001	0.36
mRS	–15.56	7.17	–0.19	0.032	
Rs110402	9.43	4.64	0.15	0.044	
Vitality					
PCS-36	1.04	0.16	0.5	<0.001	0.32
Rs7209436	6.85	2.3	0.23	0.003	
Mental Health					
PCS-36	0.48	0.17	0.26	0.005	0.3
Antidepressants	–8.41	3.06	–0.23	0.007	
mRS	–8.13	3.23	–0.23	0.013	

7.2.5 Association of CRHR1 genotype with depression and fatigue after aneurysmal subarachnoid haemorrhage (Article III)

We performed a multiple logistic regression analysis to explore the association of the CRHR1 genotype with emotional health disorders diagnosed after aSAH with EST-Q (Table 12). All results remained significant after adjustment for the neurological state at admission (HH score); the gender and age of the patients, and the time from aSAH to assessment. Only the association of Rs110402 with fatigue remained statistically significant after Bonferroni correction for multiple comparisons.

Table 12. Influence of CRHR1 genotype on emotional health after aSAH (only statistically significant results are reported).

SNP	Allele	Model	OR	95% CI	p	OR*	95% CI*	p*
Depression								
Rs110402	Minor	Additive	0.50	0.28–0.92	0.027	0.50	0.26–0.94	0.032
Fatigue								
Rs110402	Minor	Additive	0.46	0.26–0.8	**0.006**	0.48	0.27–0.85	0.012
Rs7209436	Minor	Recessive	0.22	0.07–0.69	0.009	0.23	0.07–0.75	0.015
Rs242924	Minor	Recessive	0.35	0.14–0.9	0.030	0.37	0.14–0.98	0.044
TAT-haplotype	Minor	Additive	0.26	0.08–0.81	0.021	0.27	0.08–0.88	0.030
Insomnia								
Rs242939	Minor	Additive	0.43	0.18–1.02	0.057	0.38	0.15–0.96	0.042

*adjusted for Hunt & Hess scale score, gender, age, and time from aSAH. P-values that survived Bonferroni correction marked with bold.

The minor genotype of Rs7209436, Rs110402, and Rs242924 had a protective effect against fatigue (OR=0.22–0.46, $p<0.05$) in additive and recessive models. The prevalence of fatigue in homozygotes for major and minor alleles of Rs110402 was 62% vs 25%, respectively (Figure 7). The TAT-haplotype was associated with a protective effect against developing fatigue (OR=0.26, 95% CI, 0.08–0.81, p=0.021) in the additive model.

Carriers of the Rs110402 minor genotype had a lower risk of depression (OR=0.5, 95% CI, 0.28– 0.92, p=0.027) in the additive model. The frequency of depression among homozygotes for Rs110402 minor alleles was close to the matched controls (14%), which was much lower than in homozygotes for major alleles (41%) (Figure 7).

The minor genotype of Rs242939 was associated with a protective effect against insomnia when adjusted for the HH score, gender, age of patients, and the time from aSAH (OR=0.43, 95% CI, 0.18–1.02, p=0.057) in the additive model (Table 11).

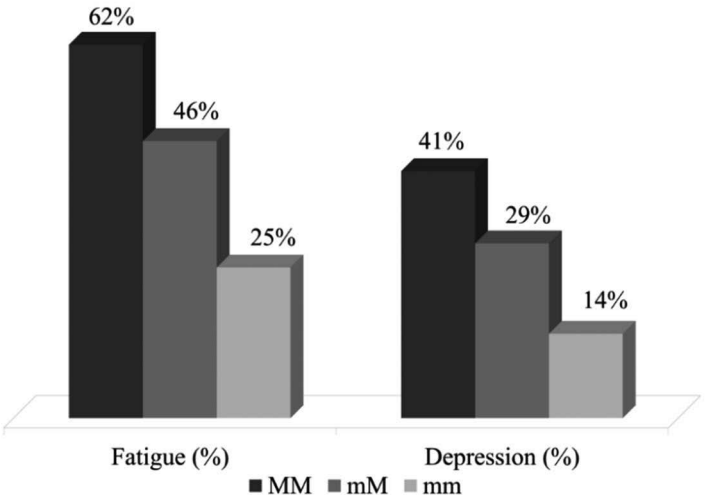

Figure 7. Prevalence of fatigue and depression in aSAH patients (n = 125) according to Rs110402 genotype. MM – homozygote for major allele, mM – heterozygote, mm – homozygote for minor allele.

7.2.5.1 Factors associated with fatigue and internal correlations

Fatigue was the most prevalent complaint among aSAH patients, and it had the most influence on QoL outcomes. Almost half of aSAH patients had EST-Q scores indicating fatigue (45%; n=56). Emotional health disorders – diagnosed by EST-Q cut-off values – were moderately correlated with each other (Table 5 in Article III). Fatigue had a higher correlation with anxiety and depression. Rs110402 and Rs7209436 SNP-s were statistically significantly correlated with fatigue, and Rs110402 was significantly correlated with depression.

We performed a multiple logistic regression analysis for fatigue to further explore the associated factors. The best model explaining fatigue had a R^2= 0.34, p<0.001 and it included anxiety, mRS, and Rs110402 genotype (number of minor alleles) (Table 13). A model where mRS was replaced with insomnia still had good explanatory value for fatigue, but R^2 decreased to 0.31, p<0.001. Socio-demographic factors and comorbidities were not associated with fatigue in this analysis.

Table 13. Multiple logistic regression analysis of fatigue.

Variables	B	SE	β	p-value
Anxiety	0.42	0.08	0.39	<0.001
mRS	0.016	0.05	0.27	0.001
Rs110402	–0.12	0.06	–0.17	0.027

8 DISCUSSION

aSAH has a presentation and natural history consistent with the description that patients attribute to a headache, its main symptom – 'it felt like being struck by thunder or hit in the head by an axe'. aSAH is an acute disease of the central nervous system with severe systemic complications. Despite being a subtype of stroke with a treatable cause, recovery from aSAH does not stop with the occlusion of the aneurysm. Complications are common in all phases of treatment and they leave a strain on the patient's potential recovery. Long-term psychosocial disorders after aSAH are recognized but remain an understudied issue. We aimed to assess the quality of life and the prevalence of emotional health disorders – their associations – and the effect of the CRHR1 genotype on outcomes after aSAH in a genetic association study.

In our study, the long-term quality of life was decreased on all scales in aSAH survivors compared to the matched controls. Emotional health disorders were common in aSAH survivors, and they were significantly associated with impairments of QoL. Fatigue was the most common disorder, and it was related to all SF-36 subscales. Fatigue was associated with both mental and physical complaints of the patients, including not returning to work. 53% of the variance in the mean mental component score (MCS-36) of SF-36 was explained by emotional symptoms after aSAH. Depression and anxiety occurred in one third of patients. The CRHR1 minor genotype was associated with a lower risk of fatigue, depression, and a higher score in mental domain of QoL after aSAH. Minor allele homozygotes of Rs110402 exhibited fatigue in 25% of patients and major allele homozygotes exhibited in 62% of the cases. Prevalence of depression in minor allele homozygotes of Rs110402 was 14%, compared to 41% in homozygotes for major alleles.

We performed a retrospective analysis of QoL and emotional health outcomes in a study of 125 aSAH survivors with a mean follow-up assessment period of 4.3 years. Almost half of the patients were studied more than 3 years after the haemorrhage. Patients were interviewed with a structured questionnaire using two validated assessment tools (SF-36 and EST-Q) to assess psychosocial outcomes. Both instruments measure multiple domains, and EST-Q allows a simultaneous assessment of various mental disorders based on diagnostic criteria. SNPs were selected in a marker gene (CRHR1) associated with susceptibility to emotional health disorders after adverse life-events based on previous research. Then SNPs were analysed in the aSAH patient group. We acknowledge the limitations imposed by the longevity of the study, small patient group, and the absence of a strict clinical assessment of premorbid psychiatric and postmorbid cognitive disorders.

8.1 Quality of life outcome after aneurysmal subarachnoid haemorrhage

In our cohort, aSAH patients scored significantly lower on all QoL scales measured with SF-36 compared to the matched controls. We described a more pronounced decrease in physical domain scores, but also a substantial reduction in the mental domain of QoL. There is variation in reports concerning the level of different domain involvement, and subsequent recovery, after aSAH (He & Mack, 2014). QoL disturbances improve with time, but disturbances can persist for years after the haemorrhage (Greebe, Rinkel, Hop, Visser-Meily, & Algra, 2010; Scharbrodt et al., 2009; Von-Vogelsang et al., 2015). Physical disabilities improve at a higher rate than emotional health disorders after aSAH (Mocco et al., 2006; Noble et al., 2008). This can be caused by the fact that a high number of patients receive rehabilitation focused solely on physical and language deficits, while the diagnostics and management of emotional health disorders remain poor (He & Mack, 2014; Malmivaara, Juvela, Hernesniemi, Lappalainen, & Siironen, 2012). For comparison, a group of Swedish patients studied with SF-36 after ischemic stroke had worse physical, but better mental health outcome (Almborg & Berg, 2009). Compared to a 4-year myocardial infarction survivors aged under 65 years aSAH patients experienced a worse QoL measured with SF-36 (Brown et al., 1999).

8.2 Emotional health outcome after aneurysmal subarachnoid haemorrhage

Based on cut-off values of EST-Q, patients showed a high prevalence of emotional health disorders. A significant number of patients reported thoughts of death and suicide (14%, n=18), which, to our knowledge, has not been previously assessed after aSAH.

Almost one third of the patients indicated depression and anxiety. In 20% of cases (n=25) both conditions coexisted. Depression was moderately correlated to anxiety (Pearson's $r=0.54$, $p<0.001$), and both conditions presented more often in women. After ischemic stroke, depression occurs in around 33% of cases, and anxiety presents in 25%, with a similar comorbidity (Towfighi et al., 2017; Wright, Wu, Chun, & Mead, 2017). In a recent meta-analysis, factors that increased the risk of depression, after aSAH, were female sex, premorbid psychiatric disorders, substance use, coping styles, cognitive impairment, fatigue, post-traumatic stress disorder, physical disability, and aSAH related brain infarctions. Depression after aSAH was associated with functional impairment, failure to return to work, and decreased HRQoL (Kwong Tang et al., 2020). Important explanatory factors for anxiety are low perceived recovery, lack of control over ones state, loss of belief into recovery, and living without social support (Sheldrick, Tarrier, Berry, & Kincey, 2006; Von-Vogelsang et al., 2015).

Patient perceived outcomes after different types of stroke (ischemic, intracerebral haemorrhage, and SAH) have been reported to be similar (Katzan et al., 2018). Ischemic stroke and aSAH patients experience a similar adverse life-event which requires habituation and acquiring a new social role.

The most prevalent self-reported disorder in our cohort was fatigue, and it occurred in 45% of the cases. Fatigue was moderately correlated to anxiety (Pearson's $r=0.49$, $p<0.001$) and depression ($r=0.42$, $p<0.001$). Anxiety, the mRS score, and the Rs110402 genotype explained 34% of variance in fatigue scores in a multiple regression model ($p<0.001$). Fatigue was related both to physical and mental health deficits, and it requires multidisciplinary rehabilitation – both cognitive and physical. Fatigue restricts everyday activities and leads to mental exhaustion from having to deal with processes of rehabilitation and daily adaptation that patients experience after stroke. Fatigue, after ischemic stroke, was associated with depression and anxiety, but fatigue also occurs separately (Ponchel et al., 2015). The successful treatment of depression does not always relieve symptoms of fatigue, which means it requires distinct interventions (Nierenberg et al., 1999). Fatigue is the most common complaint after stroke, and it occurs in around half of the patients (Cumming, Packer, Kramer, & English, 2016). The occurrence of fatigue after neurological disease is not explained by age and disability (Kluger, Krupp, & Enoka, 2013). Among younger stroke patients, fatigue has a stronger effect on QoL than neurological deficit (Becker et al., 2015).

Patients also showed a high prevalence insomnia (41%). It has been previously reported that up to 30% of aSAH patients experience sleeping disturbance, and sleeping disturbance is related to reduced QoL (Schuiling, Rinkel, Walchenbach, & De Weerd, 2005).

8.3 Association of emotional health and quality of life after aneurysmal subarachnoid haemorrhage

The factors most associated with QoL after aSAH in a metanalysis were age, sex, neurologic state at admission, the severity of the haemorrhage, physical disability, cognitive impairment, and time between ictus and assessment. Only one of the traditional factors – physical disability – had any notable effect on QoL. Changes in emotional health after aSAH have remained predominantly unexplained by traditional variables. Notably, up to 94% of variance in emotional health was left unexplained – a domain of HRQoL affected more commonly and persistently (Noble & Schenk, 2010; Wong et al., 2011).

In our cohort, emotional health disorders alone explained 23–47% of the results in SF-36 scales in a multivariate regression analysis. Mental health disorders diagnosed with EST-Q explained more than half of the variance of MCS-36. Fatigue was independently related to all subscales of SF-36. Fatigue was previously associated with a decrease in all scales of QoL, and fatigue reduced life satisfaction 2–4 years following aSAH (Passier et al., 2011; Visser-

Meily et al., 2009). Another study reported that 18 months after aSAH, subjective fatigue ratings were associated with less independence and socialising (Powell et al., 2004).

8.4 Returning to work following aneurysmal subarachnoid haemorrhage

35% of our patients were not able to return to work. Insomnia, panic, depression, and fatigue were related to self-reported inability to return to work after aSAH and unemployment at the time of assessment. The prevalence of emotional health disorders was previously reported to affect the 6-month return to work after aSAH (Al-Yassin, Ouyang, & Temes, 2017). The ability to return to work is also affected by neuropsychological complications and the ageing of the patients (Crago et al., 2016). Based on a recent report, a substantial amount of patients with a good neurological outcome could return to work with time and proper rehabilitation despite having reintegration issues in around 50% of cases (Sonesson, Kronvall, Säveland, Brandt, & Nilsson, 2018).

8.5 Association of quality of life and emotional health disorders with CRHR1 genotype after aneurysmal subarachnoid haemorrhage

Our results show that the CRHR1 genotype could be a significant factor associated with long-term outcomes in the mental domain of QoL after aSAH.

Carriers of the CRHR1 minor genotype had better QoL scores in mental health, role-emotional, and vitality scales. The Rs110402 major genotype was associated with a worse score in role-emotional scale. Results remained statistically significant after adjusting for the HH score, gender and age of patients; and the time from aSAH. The effect of the Rs242924 genotype on mental health, and Rs7209436, Rs110402, and Rs242924 on vitality scales, remained statistically significant after Bonferroni correction.

The three scales of SF-36 (mental health, role emotional, and vitality) that were affected by the CRHR1 genotype reflect on the mental domain of QoL. The role-emotional scale represents the limitations people add to everyday activities due to their perceived emotional state. Based on multiple regression analysis, the CRHR1 genotype, mRS score, PCS-36, and a history of antidepressant usage during recovery were related to outcomes in the mental domain of QoL. The effect of CRHR1 genotype on mental domain of QoL after aSAH might be explained by its association with the emotional health of the patients.

The CRHR1 genotype was associated with emotional health disorders in our cohort. Carriers of the minor genotype Rs110402 had a lower risk of depression. Based on EST-Q scores, depression occurred in 14% of minor allele homozygotes

and in 41% of homozygotes for major alleles of Rs110402. Rs110402, Rs242924, and Rs7209436 minor alleles, and the TAT-haplotype, had a protective effect against fatigue. Homozygotes for the minor allele Rs110402 scored for fatigue in 25% of cases, and homozygotes for the major allele in scored 62% of the cases. The association of Rs110402 with fatigue remained statistically significant after Bonferroni correction. Having less insomnia was associated with the Rs242939 minor genotype, but only in the adjusted model.

The CRHR1 receptor is an important moderator of HPA-axis reactivity to stress, and the CRHR1 receptor is associated with mental health disorders (Buttenschon et al., 2017; Liu et al., 2013). A follow-up of patients after severe illness and intensive care treatment showed an association of CRHR1 with the development of PTSD symptoms (Davydow et al., 2014). Corticosteroid administration has been associated with a decreased frequency of post-intensive care PTSD symptoms after major surgery (Schelling et al., 2006). Cortisol disbalance can occur in critical illness patients, with a possible deficiency after aSAH (Lanterna et al., 2013). It is unknown whether the studied SNP-s are functional. The pronounced effect of the CRHR1 genotype in the present study might be explained by its modulatory role in the HPA-axis's response to stress, or other central regulatory mechanisms (e.g. altering the regulation of CRH response in the hypothalamus, amygdala, hippocampus or other brain regions) including memory formation and fear processing (Naughton et al., 2014).

Neural events leading to psychosocial dysfunction after aSAH remain largely unexplained. There are multiple possible causes for maladjustment after a severe and stressful life-event such as an aSAH. A psychological reaction to an acute illness can occur, and fear of recurrence develops after aSAH (Hütter & Kreitschmann-Andermahr, 2014). The risk for post-traumatic stress disorder is higher after aSAH, than following other devastating illnesses, e.g. myocardial infarction (Brown et al., 1999; Sheldrick et al., 2006). Inadequate coping mechanisms could be responsible for an inability to return to an active life after a sudden illness (Lindberg et al., 1992). Maladaptive coping styles and premorbid psychiatric history are related to decreased QoL after SAH with a higher effect on the emotional domain (Hedlund, Zetterling, Ronne-Engström, Carlsson, & Ekselius, 2011). Even at 6-years following aSAH, patients describe that they were not prepared enough for potential long-term complications (Persson, Törnbom, Sunnerhagen, & Törnbom, 2017). A contrary positive experience has been reported by stroke survivors who have been discharged to a rehabilitation facility and received guidance (Luker, Lynch, Bernhardsson, Bennett, & Bernhardt, 2015).

Our results have confirmed that psychosocial disturbances are common and persist for years after aSAH. A significant part of reduction in QoL was caused by symptoms of emotional disease. Patient reintegration and the return to work is complicated by emotional health disorders and fatigue. A neurobiological predisposition for the development of depression, fatigue and lower QoL in the mental domain after aSAH could be associated with the CRHR1 genotype. The CRHR1 genotype could prove to be a useful biomarker for selecting patients at risk for psychological disturbances after aSAH and potentially guide their therapy.

8.6 Limitations of the study

This was a retrospective study that included 125 patients in the genetic analysis. Due to the longevity of the study, loss to follow-up and patient factors, a selection bias exists. Our study might be underpowered to draw certain conclusions in genetic analysis, and further replication studies are needed in this topic. We do not have information regarding the premorbid mental state of the patients included, but only one patient was diagnosed with depression according to the database available from 2009. The patient's cognitive status was not assessed, but all of them could attend the interview and answer the questions fully. The diagnosis of post-traumatic stress disorder might have added more information to the emotional profile of the survivors. There are differences among QoL questionnaires and they exhibit ceiling and floor effects (Almborg & Berg, 2009; Rautalin et al., 2018). Using EST-Q has allowed us to study various emotional health disorders simultaneously, but it is not well validated for post-stroke fatigue assessment. The vitality scale of SF-36 is reported to be an appropriate measurement of fatigue after stroke (Mead et al., 2007). Information about the translation and adaptation of EST-Q into Russian language has not been published. Cut-off values for the Estonian version of EST-Q have been validated and published, but possible differences with the official Russian translation of the questionnaire have not been taken into account during validation. Therefore, to increase the statistical power of the study, the Estonian cut-off values have been adapted for patients who spoke Russian as a native language. Cultural and social factors can influence the results.

9 CONCLUSIONS

With the performed studies we can conclude that:

1. In our cohort of aSAH survivors, a strong long-term reduction in the physical, mental, and social domains of QoL occurred in comparison with the matched controls.
2. The prevalence of long-term emotional health disorders, fatigue, and insomnia was high after aSAH. Fatigue was the most common disorder, and it was affected by the mental and physical state the patients. One third of the patients scored significantly for depression and anxiety, and both conditions coexisted frequently. A substantial number of patients reported frequent thoughts of suicide.
3. Emotional health disorders were significantly associated with impaired QoL after aSAH. Emotional health disorders explained more than half of the variance in the mental domain and almost one third of variance in the physical domain of QoL. Fatigue was significantly associated with all SF-36 scale results, and depression was associated with all scores in the mental domain of QoL. More than one third of the patients were not able to return to work, which was associated with mental disorders.
4. Carriers of the minor genotype of CRHR1 had significantly better scores in the mental domain of QoL. The CRHR1 minor genotype was associated with a lower risk of fatigue and depression after aSAH.

10 FUTURE DIRECTIONS

A better understanding of the long-term needs of patients after aSAH exposes the necessity to create timely and individualised rehabilitation strategies. A structured approach should be adapted in screening for psychosocial and cognitive disturbance after aSAH. With that in mind, stroke and aSAH specific outcome scales require local validation in Estonia.

Genetic association of CRHR1 with emotional health disorders after aSAH warrants further study as a potential biomarker.

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12 SUMMARY IN ESTONIAN

Aneurüsmaatilise subarahnoidaalse hemorraagia järgne elukvaliteet, emotsionaalne tervis ja nendega seotud faktorid

Sissejuhatus

Mittetraumaatiline subarahnoidaalne hemorraagia (SAH) ehk ämblikvõrkkesta-alune verejooks moodustab umbes 5% kõikidest insultidest. 85%-l patsientidest on SAH põhjustatud ajuarteri aneurüsmi lõhkemisest. Suuremal osal patsientidest leiab aneurüsmaatiline subarahnoidaalne hemorraagia (aSAH) aset keskeas (van Gijn et al., 2007). Koljusiseste aneurüsmide levimus üldpopulatsioonis on umbes 3% (Etminan et al., 2014). Aneurüsmi rebenemine põhjustab vere väljumist aju ümber paiknevasse ämblikvõrkkesta-alusesse ruumi (Petridis et al., 2017). Aneurüsmaatilise subarahnoidaalse hemorraagia (aSAH) haigestumus on 7.9:100,000 (Etminan et al., 2019).

aSAH-i peamiseks sümptomiks on äkkpeavalu, mida patsiendid kirjeldavad tihti kui kõige tugevamat peavalu nende elus. Teisteks sümptomiteks on meningisminähud (oksendamine, valguskartus ja kuklakangestus), teadvusehäire, fokaalsed neuroloogilised nähud ja epileptilised hood. aSAH-iga võivad kaasneda ägedad süsteemsed nähud – arteriaalne hüpertensioon, arütmia, kopsuturse ja hüpokseemia (Petridis et al., 2017). aSAH-i korral on peamisteks uurimismeetoditeks on kompuutertomograafia ja angiograafia. Umbes 21% aSAH haigetest surevad äkksurma enne haiglasse jõudmist (Korja et al., 2016). aSAH üldine suremus on 35%, kuid tänu paranenud käsitlusele haiguse varajases staadiumis on suremus viimastel aastakümnetel langustendentsiga, mõnedel andmetel on suremus langenud kuni 17% võrra (Nieuwkamp et al., 2009). aSAH-i esmane ravi on suunatud verejooksu põhjuse likvideerimisele (aneurüsmi mikrokirurgiline klipsimine või versoonesise sulgemine ehk koilimine) ja sekundaarsete tüsistuste ennetamisele.

Vaatamata sellele, et aSAH-i esmane käsitlus on viimastel aastakümnetel oluliselt paranenud, on haiguse psühhosotsiaalsed kaugtulemused ebarahuldavad nii patsientide kui ka nende lähedaste jaoks (Kapapa, Woischneck, & Tjahjadi, 2014). aSAH-ist paranemine jätab olulise jälje patsientide igapäevasele toimetulekule ja ka ühiskonnale (Al-Khindi et al., 2010).

Elukvaliteedi langust pärast aSAH-i on kirjeldatud 55%-l patsientidest (Rinkel & Algra, 2011). Kuni pooltel patsientidel esineb pärast aSAH-i depressioon ja ärevus, mis võivad püsida kauem kui 18 kuud (Al-Khindi et al., 2010; Powell et al., 2004). Posttraumaatilist stressihäiret (PTSH) pärast aSAH põdemist on kirjeldatud rohkem kui 30%-l patsientidest ja kahel kolmandikul patsientidest esineb aSAH põdemise järgselt korduva verejooksu kartus (Hütter & Kreitschmann-Andermahr, 2014). Suhteliselt vähe on uuringutes tähelepanu pööratud aSAH–ile järgnevate emotsionaalsete häirete ja elukvaliteedi languse seostele. Varasem uuring viitas seitsmele elukvaliteedi langust ennustavale tegurile:

patsiendi kõrge vanus, naissugu, raskem neuroloogiline seisund hospitaliseerimisel, raskem hemorraagia, raskem füüsiline puue, kognitiivne häire, ja väiksem ajaline vahe aSAH-i ja tervisega seotud elukvaliteedi hindamisel. Ainult füüsilisel puudel oli märkimisväärne mõju elukvaliteedi füüsilisele domeenile ja enamik elukvaliteedi languse põhjuseid oli välja selgimata. Elukvaliteedi vaimsete skaalade osas on 90% elukvaliteedi langusest jäänud traditsiooniliste ennustusväärtustega kirjeldamata (Noble & Schenk, 2010). aSAH-ile järgnevat psühhosotsiaalset defitsiiti ei saa seletada stigmaga, mis võiks kujuneda peale 'ajuhaigust', või füüsiliste piirangutega, mis esinevad kuni 15%-l ellujäänutest (Hütter & Kreitschmann-Andermahr, 2014).

aSAH kaugtulemusi on siiani käsitlenud piiratud arv geneetilisi uuringuid ja nende tulemused on vastuolulised (Alfieri et al., 2008). Üheks piiravaks teguriks on olnud üldiste kliiniliste klassifikaatorite kasutamine, mis ei peegelda patsiendi täieliku psühhosotsiaalset paranemist. Ebasoodsad elusündmused ja stress on kõige sagedasemad riskifaktorid emotsionaalsete häirete kujunemiseks (Buttenschon et al., 2017). Kehvad psühhosotsiaalsed kaugtulemused pärast aSAH-i võivad olla seotud geneetilise eelsoodumusega ebasoodsaks kohanemiseks, mis järgneb stressirohkele elusündmusele. Arvestades CRHR1 genotüübi seost emotsionaalsete häiretega ja selle olulist rolli hüpotalamuse-hüpofüüsi-neerupealise-telje (HPA-telg), limbilise süsteemi ja kognitsiooni regulatsioonis, on CRHR1 genotüüp võimalik biomarker ebasoodsa psühholoogilise kohanemise jaoks pärast aSAH-i (Naughton et al., 2014). CRHR1 genotüübi mõju psühhosotsiaalsetele häiretele pärast aSAH-i ei ole varem uuritud.

Uurimistöö eesmärgid

Väitekirja teemaks on aSAH-i psühhosotsiaalsed kaugtagajärjed. Elukvaliteedi langus ja emotsionaalsed häired on ellujäänute seas sagedased, kuid nende seosed, riskifaktorid ja võimalikud biomarkerid ei ole põhjalikult uuritud.

Uurimistöö eesmärgid:

1. Hinnata patsientide pikaaegset elukvaliteeti langust pärast aSAH-i.
2. Hinnata patsientide pikaaegsete emotsionaalsete häirete levimust pärast aSAH-i.
3. Analüüsida patsientide emotsionaalsete häirete ja elukvaliteedi seost pärast aSAH-i.
4. Kirjeldada CRHR1 genotüübi mõju emotsionaalsete häirete kujunemisele ja elukvaliteedi langusele pärast aSAH-i.

Uuritavad ja meetodid

Artikkel I. Retrospektiivsesse uuringusse oli kaasatud 384 patsienti, kellel oli aastatel 2001–2010 Tartu Ülikooli Kliinikumis diagnoositud aSAH. Kontaktinfo oli olemas 134 patsiendi kohta. Patsientidega võeti ühendust telefoni teel ja neid teavitati uuringu iseloomust. Väljaarvamise kriteeriumid olid: kättesaamatu

(n=7), keeldus osalemast (n=10), ei saa osaleda logistiliste probleemide või raskete haiguste tõttu (n=3). Lõplik uuringurühm koosnes 114 patsiendist. Patsientide keskmine vanus haigestumisel oli 54±13 (21–80). Keskmine aeg haigestumisest hindamiseni oli 4.5±3 (1–10) aastat. 68% (n=78) uuritud patsientidest olid naised.

Artiklid II ja III. Retrospektiivsesse uuringusse oli kaasatud osa esimese uuringurühma patsientidest (Artikkel I), kes olid nõus loovutama verd geneetiliseks analüüsiks, ja lisapatsiendid, keda oli ravitud Tartu Ülikooli kliinikumis aastatel 2010–2013. II ja III artikli patsiendid on nimetatud laiendatud kohordiks. Uuringusse oli kokku kaasatud 467 patsienti, kellel oli aastatel 2001–2013 Tartu Ülikooli Kliinikumis aSAH diagnoositud. Kontaktinfo oli olemas 185 patsiendi kohta. Patsientidega võeti ühendust ja neid teavitati uuringu iseloomust. Väljaarvamise kriteeriumid olid: kättesaamatu (n=31), keeldus osalemast (n=19), ei saa osaleda logistiliste probleemide või raskete haiguste tõttu (n=10). Lõplik uuringurühm koosnes 125 patsiendist. Patsientide keskmine vanus haigestumisel oli 54±13 (24–82). Keskmine aeg haigestumisest hindamiseni oli 4±2.8 (1–13) aastat. 70% (n=88) uuritud patsientidest olid naised.

Kõik uuringus osalejad allkirjastasid teadliku nõusoleku vormi. Uuringu teostamine oli kooskõlastatud Tartu Ülikooli Eetikakomiteega (214/T-2/2012).

SAH oli diagnoositud kompuutertomograafilise uuringu või lumbaalpunktsiooni abil haiguse ägedas faasis. Aneurüsm oli diagnoositud kompuutertomograafilise angiograafiaga või konventsionaalse angiograafiaga. Patsientide algne ravi toimus intensiivravi osakonnas. Ravi oli suunatud normaalse homeostaasi tagamisele, hilise isheemilise defitsiidi ennetamisele, ja tüsistuste käsitlusele. Kõik patsiendid said nimodipiini profülaktilises doosis (60 mg 4 tunni tagant). Peaaegu kõik patsiendid said opereeritud ägedas faasis – enamasti pterionaalse juurdepääsu kaudu – ja aneurüsmid klipsitud kasutades standardset mikrokirurgilist tehnikat. Patsientide operatsioonijärgne käsitlus hõlmas rutiinseid laboratoorseid analüüse ja radioloogilisi uuringuid (kompuutertomograafia ja transkraniaalne Doppleri ultraheliuuring). Kõikidele patsientidele ägeda hüdrotsefaaliaga (diagnoositud kompuutertomograafilise uuringu abil) tehti ventriikuli drenaaž, mille abil jälgiti koljusisest rõhku.

Kliinilised andmed olid dokumenteeritud haigestumise ajal (kaasa arvatud kliiniline seisund hospitaliseerimisel Hunt ja Hessi seisundi raskusastme skaala alusel). Patsiente uuriti struktureeritud küsimustiku abil. Kliiniline paranemine hinnati modifitseeritud Rankini skaala (mRS) järgi. Lisaks kogusime andmeid patsiendi kaasuvate haiguste, haridustaseme, töötamise, sotsiaalse elukorralduse ja paranemise kohta. Patsientide hindamiseks kasutati SF-36 (The RAND 36-Item Health Survey 1.0) küsimustikku ja EEK-2 (Emotsionaalse Enesetunde Küsimustik 2). Samaealise elanikkonna SF-36 ja EEK-2 andmed pärinevad Eesti Terviseuuringust 2006 ja Euroopa Sotsiaaluuringu 2004 Eesti raportist (Lai T, Kallikorm R, Salupere R, 2001; Matsi A, 2009). Vereproovid geenianalüüsiks koguti pärast küsitlust.

SF-36 on valideeritud instrument elukvaliteedi hindamiseks ja on uuringutes laialdaselt kasutusel. SF-36 koosneb 36 küsimusest ja 8 alaskaalast: kehaline

seisund, kehalistest häiretest tingitud piirangud igapäevaelus, emotsionaalsetest häiretest tingitud piirangud igapäevaelus, energia ja väsimus, vaimne heaolu, sotsiaalne toimetulek, füüsiline valu, ja üldtervislik seisund. SF-36 hindamine toimub 100 palli süsteemis – 0 (madal elukvaliteet), 100 (kõrge elukvaliteet) (McHorney et al., 1994, 1993). Alamskaalade tulemustest arvutatakse vaimse (MCS-36) ja füüsilise (PCS-36) tervise üldhindeid.

EEK-2 on enesehinnanguskaala depressiooni ja ärevushäirete sümptomite sedastamiseks viimase nelja nädala jooksul. EEK-2 on valideeritud esmatasandil depressiooni ja ärevuse skriinimiseks, kuid sisaldab alaskaalasid ka teiste vaimsete häirete uurimiseks. EEK-2 koosneb järgnevatest alaskaaladest: depressioon, ärevus, agorafoobia-paanika, asteenia (*fatigue*) ja unetus. Igale väitele vastatakse esinemissageduse alusel 5-pallisel skaalal vahemikus 0 kuni 4 (vastavalt „ei" kuni „pidevalt"). Alaskaalade piirhinnete ületamine tähendab seda, et vastava alaskaala hinne on patsiendil samas suurusjärgus nagu enamusel selle häire all kannatavatest haigetest (Aluoja et al., 1999).

CRHR1 geenis said varasema kirjanduse järgi valitud need SNP-d (rs7209436, rs110402, rs242924 ja rs242939), mis on näidanud olulist mõju vaimse tervise häirete kujunemisele pärast negatiivseid elusündmusi (Liu et al., 2013). CHRH1 geneetiline analüüs teostati vastavalt alleelide distributsioonile: minoorsed homosügoodid, mažoorsed homosügoodid, heterosügoodid.

Tulemused ja arutelu

Võrreldes samaealise üldpopulatsiooniga oli pärast aSAH-i elukvaliteet vähenenud kõikides SF-36 alaskaalades. Meie uuringu kohordis esines suurem elukvaliteedi langus füüsilise domeeni hinnetes. Vaimse domeeni hinded olid samuti oluliselt vähenenud. Võrdluseks saab tuua isheemilise insuldi üle elanud patsiente, kellel esinesid madalamad füüsilised hinded, kuid paremad vaimse domeeni hinded (Almborg & Berg, 2009). aSAH-i järgselt olid patsientidel madalamad SF-36 hinded kui sarnase vanusega müokardiinfarkti üle elanutel (Brown et al., 1999).

aSAH patsientidel esines EEK-2 piirhinnete järgi kõrge emotsionaalsete häirete levimus. Kõige sagedasemaks häireks oli asteenia, mis esines 45%-l (n=56) patsientidest. Asteenial oli mõõdukas korrelatsioon ärevusega (Pearsoni $r=0.49$, $p<0.001$) ja depressiooniga ($r=0.42$, $p<0.001$). Ärevus, mRS hinne ja Rs110402 genotüüp seletasid regressioonmudelis ($p<0.001$) 34% erinevusest asteenia hinnetes . Asteenia oli seotud patsientide füüsilise ja vaimse tervisega, mistõttu see vajab aSAH-i järgselt multidistsiplinaarset taastusravi. Asteenia on kõige sagedasem kaebus teiste insuldivormide järgselt (Cumming et al., 2016). Asteenia esinemine pärast neuroloogilist haigust ei ole seotud ainult vanuse ja füüsilise defitsiidiga (Kluger et al., 2013).

Pärast aSAH-i esinesid depressioon ja ärevus ühel kolmandikul patsientidest. 14%-l (n=18) patsientidest esinesid surma- ja enesetapumõtted, mida ei ole varem aSAH-i järgselt uuritud. Depressioon esineb pärast ajuinfarkti umbes 33%-l ja ärevus umbes 25%-l patsientidest (Towfighi et al., 2017; Wright, Wu, Chun, &

Mead, 2017). Patsientide poolt tajutud kaugtulemused on sarnased erinevate insuldivormide järgselt (isheemiline, intratserebraalne hemorraagia ja SAH) (Katzan et al., 2018).

41%-l (n=51) patsientidest esines unetus. Pärast aSAH-i oli paanika-agorafoobia hinne patoloogiline 15%-l (n=19) patsientidest.

Emotsionaalse tervise häired seletasid 23%–47% elukvaliteedi langusest pärast aSAH-i. Emotsionaalse tervise häired üksi seletasid 53% MCS-36 hinde erinevusest. Asteenia oli sõltumatult seotud kõikide SF-36 alaskaalade hinnetega. Asteeniat on varem seostatud aSAH-ile järgneva elukvaliteedi langusega (Passier et al., 2011; Visser-Meily et al., 2009).

35% (n=40) patsientidest aSAH-i kohordis ei suutnud tööle naasta. Unetus, paanikahäired, depressioon ja asteenia osutusid tööle naasmise puhul olulisteks riskifaktoriteks. Suutmatus tööle naasta on seotud neuropsühholoogiliste häirete ja patsientide vananemisega (Crago et al., 2016).

CRHR1 genotüüp oli seotud parema tulemusega elukvaliteedi vaimses domeenis. Rs242924 genotüübi mõju SF-36 vaimse heaolu skaalale ja Rs7209436, Rs110402 ning Rs242924 genotüübi mõju energia ja väsimuse skaalale oli statistiliselt oluline pärast Bonferroni korrektsiooni. CRHR1 minoorne genotüüp oli seotud väiksema riskiga asteenia ja depressiooni kujunemiseks. Rs110402 genotüübi mõju asteeniale oli statistiliselt oluline pärast Bonferroni korrektsiooni. Asteenia esines 25%-l Rs110402 minoorse alleeli homosügootidel ja 62%-l mažoorse alleeli homosügootidel. Depressiooni levimus oli Rs110402 minoorse alleeli homosügootidel 14%, mažoorse alleeli homosügootidel aga 42%.

Intensiivravi patsientide kauguuring kirjeldas CRHR1 genotüübi seost ravile järgnevate PTSH sümptomite tekkimisega (Davydow et al., 2014). CRHR1 retseptor on oluline HPA-telje funktsiooni moduleerija, mis on seotud emotsionaalse tervise häirete arenguga peale ebasoodsaid elusündmusi (Liu et al., 2013; Buttenschon et al., 2017). CRHR1 genotüübi mõju võib meie uuringus olla seotud selle regulatoorse toimega HPA-telje funktsioonis või selle rolliga mälu ja hirmu moodustumises (Naughton et al., 2014).

Meie tulemused kinnitasid, et psühhosotsiaalsed häired – mis võivad püsida aastaid peale haigestumist – on pärast aSAH-i sagedased. Patsientide naasmine tööle ja normaalse elu juurde on emotsionaalsete häirete ja asteenia tõttu raskendatud. Oluline osa elukvaliteedi langusest pärast aSAH-i oli seotud emotsionaalsete häiretega. Neurobioloogiline eelsoodumus depressiooni ja asteenia arenguks ja elukvaliteedi vähenemiseks võib olla seotud CRHR1 genotüübiga. CRHR1 genotüüp võib osutuda kasulikuks biomarkeriks patsientide skriinimiseks ja potentsiaalselt ka nende raviks.

Tunnistame, et uurimistöö piiranguteks on väike kohort, retrospektiivne iseloom ja patsientide kliinilise neuropsühholoogilise hindamise puudumine. EEK-2 kasutamine võimaldas mitme vaimse tervise häire samaaegset hindamist, kuid küsimustiku asteenia alaskaala ei ole piisavalt valideeritud. Varasema kirjanduse järgi asteenia hindamiseks peale insulti sobib ka SF-36 energia ja väsimuse alaskaala. EEK-2 eestikeelne versioon on valideeritud, kuid piirhinnete leidmisel pole keelelisi erinevusi arvestatud. Selleks, et parandada uuringu

statistilist võimsust, venekeelsete patsientide hindamisel kasutati küsimustiku ametliku tõlget ja eestikeelsete patsientide piirhindeid. Kultuurilised ja sotsiaalsed tegurid võivad mõjutada tulemusi.

Uurimistöö järeldused

Läbiviidud uurimistöö põhjal saab järeldada, et:

1. Uuritud aSAH-i patsientide kohordis esines üldpopulatsiooniga võrreldes väljendunud pikaaegne elukvaliteedi langus füüsilises, vaimses ja sotsiaalses domeenis.
2. Emotsionaalsete häirete, asteenia ja unetuse levimus aSAH-i kohordis on üldpopulatsiooniga võrreldes kõrge. Asteenia on kõige sagedasem patoloogiline seisund, mis oli patsientide vaimse ja füüsilise seisundiga seotud. Ühel kolmandikul patsientidest esines depressioon ja ärevus, mille sümptomid võivad avalduda samaaegselt. Olulisel arvul patsientidest esinevad surma- või enesetapumõtted.
3. Elukvaliteedi langus on olulisel määral seotud aSAH-ile järgnevate emotsionaalsed häiretega. Emotsionaalsed häired seletavad enam kui poole elukvaliteedi vaimse domeeni hinnete erinevusest ja peaaegu kolmandiku füüsilise domeeni hinnetest. Asteenia on seotud kõikide SF-36 skaalade tulemustega. Depressioon on seotud elukvaliteedi vaimse domeeni hinnetega. Enam kui kolmandik patsientidest ei suuda pärast aSAH-i tööle naasta ja see on seotud emotsionaalsete häirete esinemisega.
4. CRHR1 minoorse genotüübi kandjatel on oluliselt paremad tulemused elukvaliteedi vaimses domeenis. CRHR1 minoorne genotüüp on seotud väiksema riskiga asteenia ja depressiooni arenguks.

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14 PUBLICATIONS

15 CURRICULUM VITAE

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2016–…	University of Tartu, Faculty of Medicine, Curriculum Medicine, PhD studies
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Professional employment

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2010–2011	Tartu University Hospital, Orthopaedics Department, Nursing assistant
2011–2013	Tartu University Hospital, Department of Anaesthesiology and Intensive Care, Neurointensive Care Unit, ICU Nursing assistant
2012	North Estonia Medical Centre, Department of Emergency Care, Assistant doctor
2013	East Tallinn Central Hospital, Department of Neurology, Assistant doctor
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Scientific work and professional organizations

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Publications

1. Vetkas A., Lillemäe K., Rätsep T., Asser T. (2011). Delay in diagnostic management of spontaneous subarachnoid haemorrhage. *Eesti Arst*, 90 (8), 366–371
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16 ELULOOKIRJELDUS

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Teadus-ja erialane tegevus

Valdkonnad: peaaju vaskulaarsed haigused, neuroonkoloogia
Liikmelisus: Euroopa Neurokirurgia Selts

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