The role of posttraumatic stress disorder in explaining the psychosocial outcome of subarachnoid haemorrhage patients and their informal carers in both the short- and long-term

Adam J. Noble

The Role of Posttraumatic Stress Disorder in Explaining the Psychosocial Outcome of Subarachnoid Haemorrhage Patients and their Informal Carers in both the Short- and Long-Term.

Adam J. Noble

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Declaration

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Abstract

Surviving subarachnoid haemorrhage (SAH) patients' experience significantly reduced health-related quality of life (HRQoL) in both the short- and long-term, as well as mysterious symptoms of fatigue and sleep dysfunction. Patients' family members and friends – who often act as their informal carers – can also experience psychosocial disability. The cause for these poor outcomes remains unknown. Traditional explanations focusing on the neurological sequelae associated with SAH or the characteristics of the illness are not satisfactory; nor are attempts to explain family members' difficulties on the basis of carer burden.

The hypothesis which is tested in this thesis is that post-traumatic stress disorder (PTSD) may be abnormally high in both the SAH patient and 'significant other' (SO) population and that this may explain their outcomes. SAH patients are known to be at risk of suffering from PTSD, but it is unknown if this explains their outcome. In terms of patients' SOs, they are known to experience psychiatric *symptoms* and I suggest these could be caused by their development of PTSD, but this has never been examined.

In Part One (Chapter 2-5), I focus on patients' outcomes. Before examining my PTSD hypothesis, I present a meta-analysis (Chapter 2) I conducted of studies which have tried to explain patients' outcome using neurological factors. I conducted the meta-analysis as a tendency for prior studies to be underpowered and use unreliable statistics could have meant that the actual importance of traditional factors was obscured. The results of my meta-analysis however did not support this possibility and instead showed traditional neurological variables *did not* explain patients' outcome. With this in

mind, I then present a longitudinal study (Chapter 5) in which I examined one of the largest prospective series of SAH patients to establish PTSD's explanative importance. Using regression analyses, this study showed PTSD was the best predictor for patients' mental HRQoL – the domain most persistently impaired. It also helped predict patients' physical HRQoL. Moreover, PTSD was linked to sleep problems and may therefore cause fatigue. Crucially, to establish the cause of PTSD, logistic regression was performed. This showed that maladaptive stress coping strategies were the best predictor for PTSD development.

In Part Two of the thesis (Chapter 6), I present my longitudinal study of one of the largest prospective samples of SOs. All SOs were assessed with a diagnostic PTSD measure and coping skills were assessed. An elevated incidence of PTSD was found in both the short- and long-term. Although SOs' PTSD did not impinge on the recovery of the SAH patients being cared for, given that it is important to ensure SOs continue caring, regression results are presented which show the cause of SOs' PTSD was (at least in the short-term) due to the use of maladaptive coping strategies.

The overarching conclusion is that the elevated incidence of PTSD in SAH patients and SOs helps explain why they experience psychosocial disability. In the final part of the thesis (Chapter 8) the clinical and theoretical implications of this conclusion are considered, such as that teaching patients and their SOs more effective coping skills might prevent PTSD and psychosocial disability.

Chapter 1

General introduction

1.1 Introduction

A spontaneous subarachnoid brain hemorrhage (SAH) is a subtype of stroke that affects mainly middle-aged persons. Advances in treatment have reduced the mortality associated with this illness. In spite of these medical advances occurring, patients who survive an SAH experience a particularly poor psychosocial outcome in the short- and long-term. Evidence also suggests that patients' family and friends – who often act as their informal carers – can also experience a substantial reduction in their health and well-being.

After being ignored for a long-time, research has now begun to consider how best to rehabilitate and improve the outcome of both parties. Efforts to develop rehabilitation programs are however, hampered by a paradox. Specifically, patients' and their carers' high levels of psychosocial dysfunction are disproportionate to the relatively mild physical/ cognitive impairment induced by the SAH. Moreover, this psychosocial dysfunction cannot be explained using traditional neurological and illness-related factors. This thesis looks to try and resolve these paradoxes. Part One of this thesis primarily focuses upon explaining the paradoxically poor health-related quality of life (HRQoL) of SAH patients, whilst Part Two addresses the poor outcome of patients' family and friends.

1.2 Overview of Part One: SAH patients' health-related quality of life, psychosocial outcome and post-traumatic stress disorder

In **Chapter 2**, I provide a brief explanation of what SAH is, outline what is known about its patients' outcome and describe patients' mysterious reduction in HRQoL. SAH patients' puzzling problems of fatigue and poor sleep quality are also discussed. I hypothesise that two explanations could explain why SAH patients' problems remain difficult to explain. The first possibility is that previous studies have failed to explain HRQoL using traditional neurological and illness-related factors because they were both statistically underpowered and used notoriously unreliable statistics by which to judge the importance of traditional predictors. Specifically, rather than – as is ideal – examining the degree of variability which these traditional factors share with HRQoL, studies have typically only looked at the statistical significance of their relationship with HRQoL. This could have served to obscure the actual explanative value of traditional factors. The second possibility raised is that SAH researchers in the past have been too restrictive in the factors they have used to try and explain SAH HRQoL. It is contended that we may need to consider other, more novel aspects of SAH patients' symptom profile when trying to explain their poor outcome. I argue here that the psychiatric problems of an SAH patient are an aspect which could hold real promise for explaining these patients' HRQoL reduction, but that this has so-far been ignored.

In **Chapter 3**, I examine the first possibility – that the explanative value of traditionally considered variables for SAH patients' HRQoL has been obscured. In this chapter, I present the first ever meta-analysis on the cause

of SAH patients' HRQoL. The use of meta-analytic techniques allows for a more comprehensive examination of the explanative importance of traditional factors by considering criteria which are more appropriate than merely statistical significance – namely their predictive effect sizes for SAH HRQoL.

In **Chapter 4**, I review the literature to explore possibility two – that psychiatric disturbance has not yet been taken into account when trying to explain SAH HRQoL. I review the psychiatric aspects of an SAH and highlight how post-traumatic stress disorder (PTSD) elicited in patients in response to an SAH has recently been found to be the main psychiatric disorder affecting these patients. I then draw on findings from the wider literature and suggest that PTSD could potentially help us better explain SAH patients' HRQoL, as well as their puzzling symptoms of fatigue and sleep dysfunction.

Following this, in **Chapter 5**, I present a longitudinal study of a prospective sample of SAH patients in which I empirically examine whether PTSD in SAH patients can help us better explain their HRQoL reduction and their difficulties with fatigue and sleep. I also present analyses which look to try and predict which patients develop PTSD following an SAH, with particular attention being afforded to the role of the stress-coping strategies which a patient uses.

1.3 Overview of Part Two: Family and friends of SAH patients - psychosocial outcome and post-traumatic stress disorder

In **Chapter 6**, I describe how research to date on the family and friends of SAH patients has highlighted how these 'significant others' can experience

abnormally high levels of psychiatric difficulties and a poor psychosocial outcome, but that these difficulties remain unexplained. Following this, I detail my hypothesis that significant others' poor outcome could be explained by the never examined possibility that significant others could *also* develop PTSD in response to the trauma of an SAH. I then present a longitudinal study of a prospective sample of significant others in which I formally examine whether PTSD is abnormally present or not in this population. I also examine the impact of significant others' psychiatric status on SAH patients' cognitive, physical, psychiatric and psychosocial recovery in the early and later stages of recovery. Finally, I present analyses which look to determine whether it is possible to predict which significant others fare worst post-SAH.

1.4 Overview of Final Chapter

In **Chapter 7**, I summarise the main findings of both parts of this thesis, and discuss the implications of these findings for the treatment of SAH patients and significant others, as well the bearing they have on future research.

Part One

SAH patients' health-related quality of life, psychosocial outcome and post-traumatic stress disorder

Chapter 2

The impact of a subarachnoid haemorrhage on patients' health-related quality of life

2.1 Introduction

A spontaneous, non-traumatic subarachnoid brain haemorrhage (SAH) is a rare type of stroke (6:100,000 per year) [4, 403, 730], which has a disproportionately high impact upon society [321, 681, 682]. For example, as Figure 2.1 illustrates, despite its relative infrequency (accounting for only ~7% of all strokes) [19, 32, 672], the loss of productive life years associated with SAH is approximately double that of much more common types of stroke [681]. This is largely attributable to the following: (1) SAH affects much younger persons; with a mean age of 55 [4, 435], SAH strikes persons who are at the peak of their productivity and often supporting a young family [546, 548], (2) SAH is associated with a high mortality (~50%) [110, 284, 653] and (3) SAH survivors experience a particularly poor psychosocial recovery, in both the short- and long-term [90, 285, 286, 336, 540, 541, 546, 746]. With such high societal costs, it is important to look to address the outcome of surviving patients' and offer them evidence-based rehabilitation tailored to their disease. Such rehabilitative efforts are however, not currently possible, as at present we do not know which factors impinge upon SAH patients' well-being and cause their poor recovery. Indeed, we are yet to establish any factors which reliably predict patients' psychosocial outcome. Stark differences in patient age (the mean age of SAH patients being 55 years vs. 73 and 75 years for ischemic and intracerebral strokes, respectively [4, 32, 366]), as well as the kinds of brain damage (diffuse and focal vs. ischemic focal) and medical treatment (SAH patients typically undergo brain surgery whereas patients of other strokes do not), precludes simply looking to explain SAH outcome by referring to research which has examined the factors

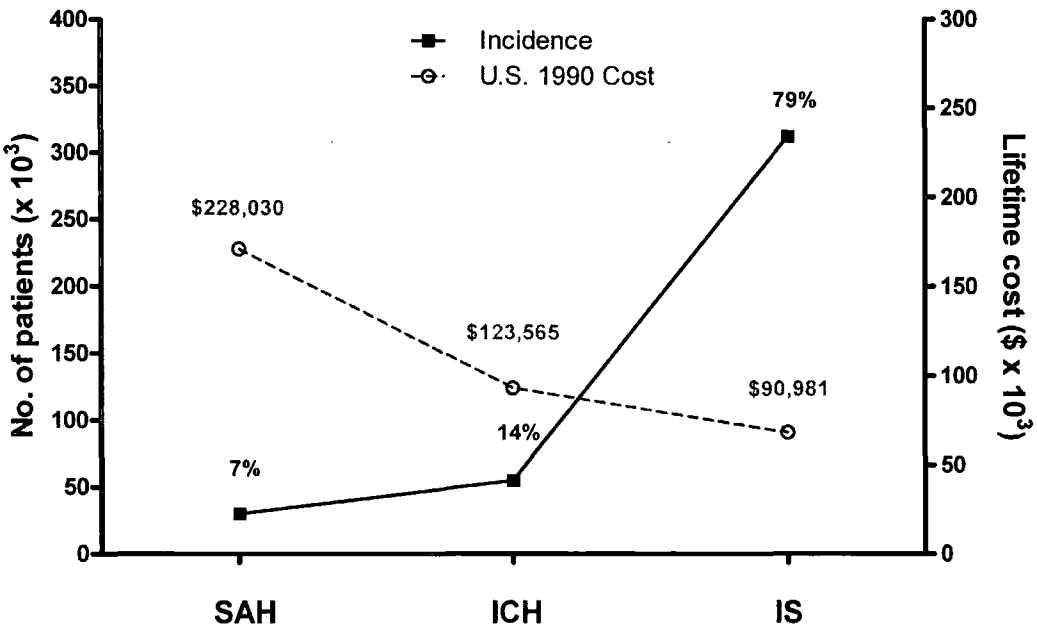

Figure 2.1 Associated life-time costs (U.S. dollars) to society in 1990 of different types of stroke measured in terms of loss of potential productive life years. Based on Taylor's (1997) data [681].

SAH=subarachnoid haemorrhage; ICH= intracerebral haemorrhage; IS= ischemic stroke

explaining outcome following more common (and better researched) types of stroke.

In this chapter, I introduce the concept of health-related quality of life (HRQoL) and highlight how it has become the prime criterion by which SAH patients' outcome should be judged. I highlight how the HRQoL of SAH patients is especially low, not only compared to normative levels, but also compared to levels in patients suffering from different illnesses. I then present the results of a systematic (non-quantitative) review of prior studies on SAH patients which have taken HRQoL as a dependent variable and have looked to determine which factors are statistically associated with (and as such, presumed to cause) it. This literature review serves to set up the subsequent studies as it illustrates how previous attempts to explain SAH patients' outcome have proved largely futile, with traditional factors appearing to be poorly

associated with SAH HRQoL. I then conclude the chapter with a discussion of whether the factors which are traditionally being used to explain SAH HRQoL are useful and whether it might not be more promising to examine the psychiatric aspects of this illness which have previously been ignored. Before discussing all of these points however, I first need to provide an introduction to SAH and its treatment. Such an introduction will serve to familiarise the reader with the specific neurological sequelae and the characteristics of SAH (such as bleed severity/ distribution, origin of haemorrhage, type of treatment received) as these are factors which have traditionally been used to try to explain SAH patients' HRQoL. It will also look to draw to the reader's attention how although an SAH is life-threatening in the immediate stages, the medical prognosis for a surviving SAH patient, once discharged from hospital, is very good (in terms of chances of re-bleeding and neurological sequelae), making such patients' poor psychosocial outcome all the more intriguing. And finally, the introduction aims to illustrate to the reader how having and surviving an SAH can potentially be psychologically traumatic.

2.2 Subarachnoid haemorrhage tutorial

2.2.1 *Pathology*

The subarachnoid space which is filled with cerebrospinal fluid is found between the arachnoid layer and the pia matter. Together with the dura, these comprise the meninges which loosely encase the brain and spinal cord [666]. A spontaneous non-traumatic subarachnoid haemorrhage (hereafter referred to as SAH) occurs when one or more blood vessels (which can run through the subarachnoid space) ruptures and extravasated blood enters into the space (Figures 2.2 and 2.3[a]) [33]. The rupture of a blood vessel is caused by a vascular abnormality. The most common cause – in around 75-85% of cases – is the rupture is of an intracranial aneurysm, which is a blister-like weakening in the wall of a cerebral artery [4, 335, 712]. The most common sites for aneurysms are at the bifurcation and junctions of cerebral arteries [710], typically at the base of the brain, near or on the circle of Willis (24-41% of SAH occur on the internal carotid artery; 30-40% on the middle cerebral artery; 13-33% in the vertebrobasilar system and 24-41% on a anterior cerebral artery [588, 654, 767]). In 10-20% of patients, repeated investigations fail to identify an origin for the patient's haemorrhage.[4] These idiopathic SAHs are typically referred to as an SAH of unknown aetiology, with the bleed typically being perimesencepahlic in nature [710]. This form of SAH is considered to be a benign subtype as it has an invariably uncomplicated clinical course [46, 115, 488, 710]. Other causes of SAH in ~5% of cases include leaking from a cerebral arteriovenous malformation, arterial dissection and dural arteriovenous fistulas [711].

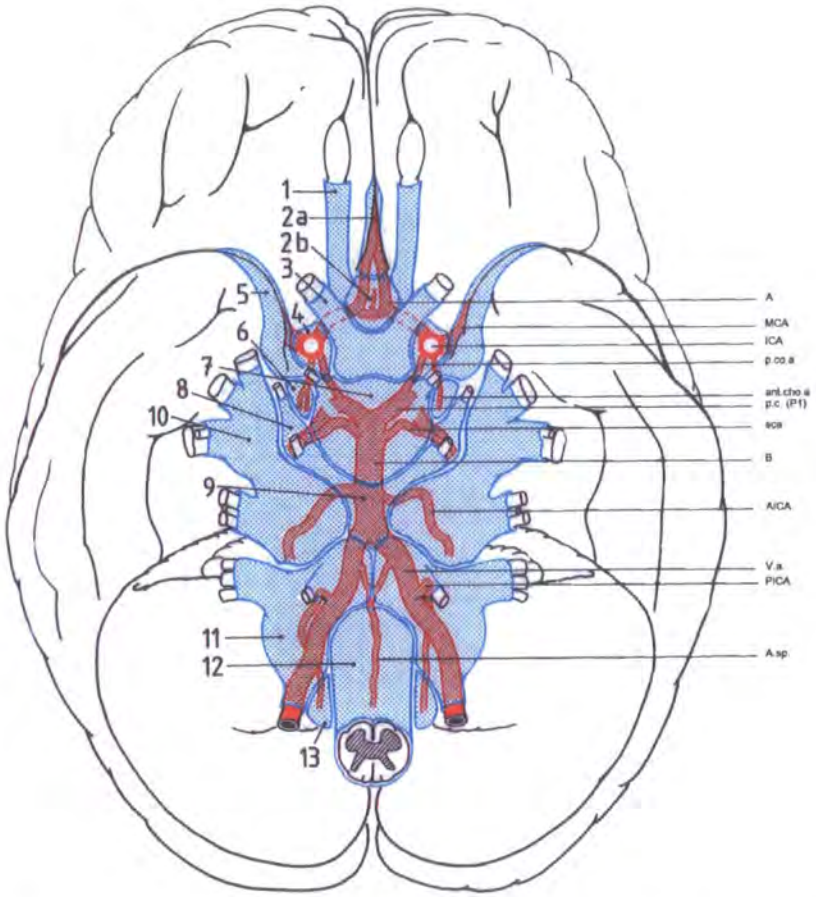

Figure 2.2 The relationship between the basal cisterns (Arabic numbers) and the ventral cerebral arterial system (p. 17; reprinted by permission) [767].

A	= A_1 + A_2 + Anterior communicating artery	1	=Olfactory cistern
MCA	= Middle cerebral artery	2a	= Callosal cistern
ICA	= Internal carotid artery	2b	= Lamina terminalis cistern
p.co.a.	= posterior communicating artery	3	= Chiasmatic cistern
p.c. (P1)	= posterior cerebral artery	4	= Carotid cistern
sca	= superior cerebellar artery	5	= Sylvian cistern
B	= Basilar artery	6	= Crural cistern
AICA	= anterior inferior cerebellar artery	7	= Interpeduncular cistern
V.a.	= Vertebral artery	8	= Ambient cistern
PICA	= posterior inferior cerebellar artery	9	= Prepontine cistern
A.sp.	= anterior spinal artery	10	= Superior cerebellar-pontine cistern
		11	= Inferior cerebellar-pontine cistern
		12	= Anterior spinal cistern
		13	= Posterior spinal cistern

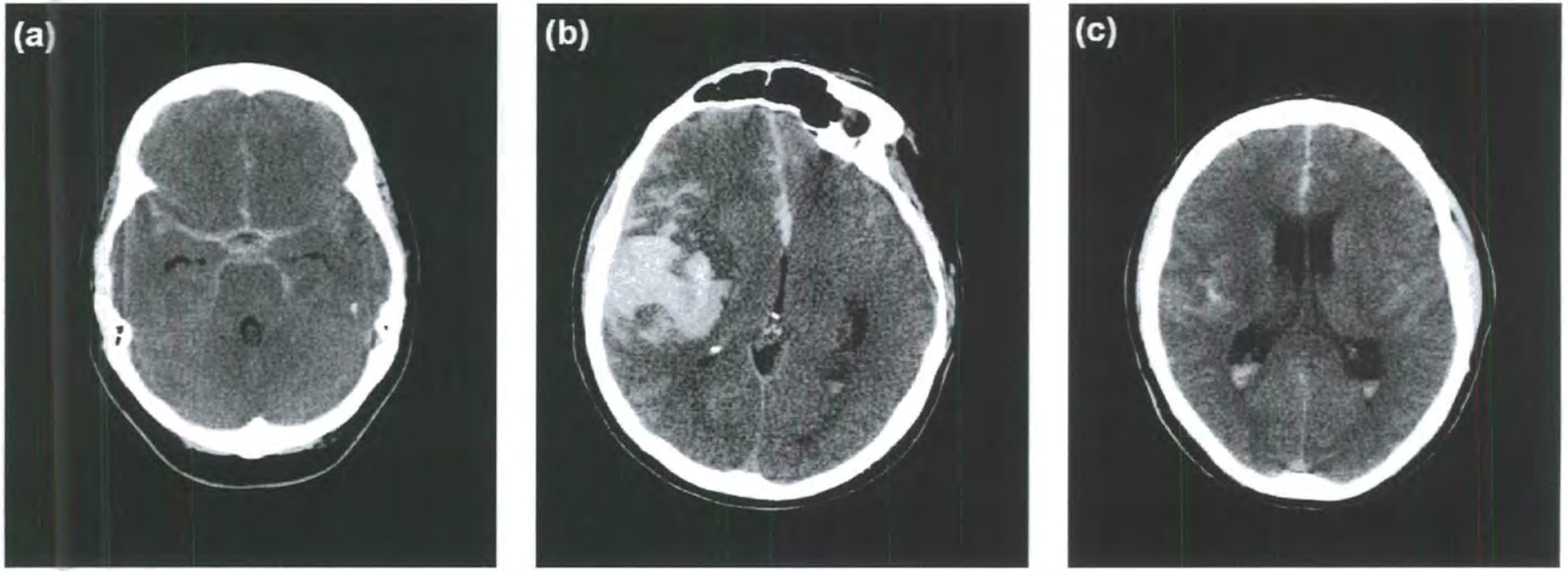

Figure 2.3 (a) Computed tomographic (CT) scan showing diffuse subarachnoid blood (basal cisterns; Sylvian fissures; anterior inter-hemispheric fissure) caused by ruptured left pericallosal aneurysm; (b) CT scan showing large temporoparietal intracerebral haematoma and extensive SAH caused by ruptured right middle cerebral artery aneurysm; (c) CT scan showing intraventricular blood and subarachnoid blood in interhemispheric fissure from rupture of an anterior-communicating artery aneurysm.

The subarachnoid space is not strictly a free-flowing space, but rather a collection of discrete cisterns formed by arachnoid partitions and trabeculae (Figures 2.2 and 2.4) [666, 767]. The walls of the cisterns serve to retard and direct the flow of any extravasated blood. Consequently, different distributions of bleed are associated with different anatomically-located sources [712, 767].

Depending on the direction of blood flow, an SAH can also invade adjacent brain areas, with intracerebral extension occurring in up to 43% of aneurysmal SAH patients (Figure 2.3[b]) [688], intraventricular extension in around 50% of aneurysmal SAH patients [306, 391] (Figure 2.3[c]) and more rarely, the occurrence of a subdural hematoma [295]. These subsequent problems have all been found to worsen immediate prognosis and can necessitate additional surgical procedures, including surgical evacuation, hemicraniectomy and the insertion of an external ventricular catheter [231, 486, 511, 574, 575].

It is postulated that the presence of subarachnoid blood (or substances derived from its degradation) in the meninges is neurotoxic causing a global encephalopathy which results in diffuse cortical damage [130, 158, 213, 236, 250, 408, 409, 597, 643, 720]. Although further research is needed [211], clinical and experimental evidence shows that blood in the subarachnoid space sets in motion a cascade of pathophysiological processes, including increased intracranial pressure which reduces cerebral perfusion and leads to ischemic damage [309], brain oedema and cerebral swelling [213] and blood-brain barrier dysfunction [158]. Germano et al. [213] for example, reported global brain dysfunction and enduring behavioural deficits in a rodent model after intracisternal injection of subarachnoid blood. The combination of this diffuse damage, as well as the focal brain damage resulting from intraventricular and intracerebral haemorrhage, means that an SAH

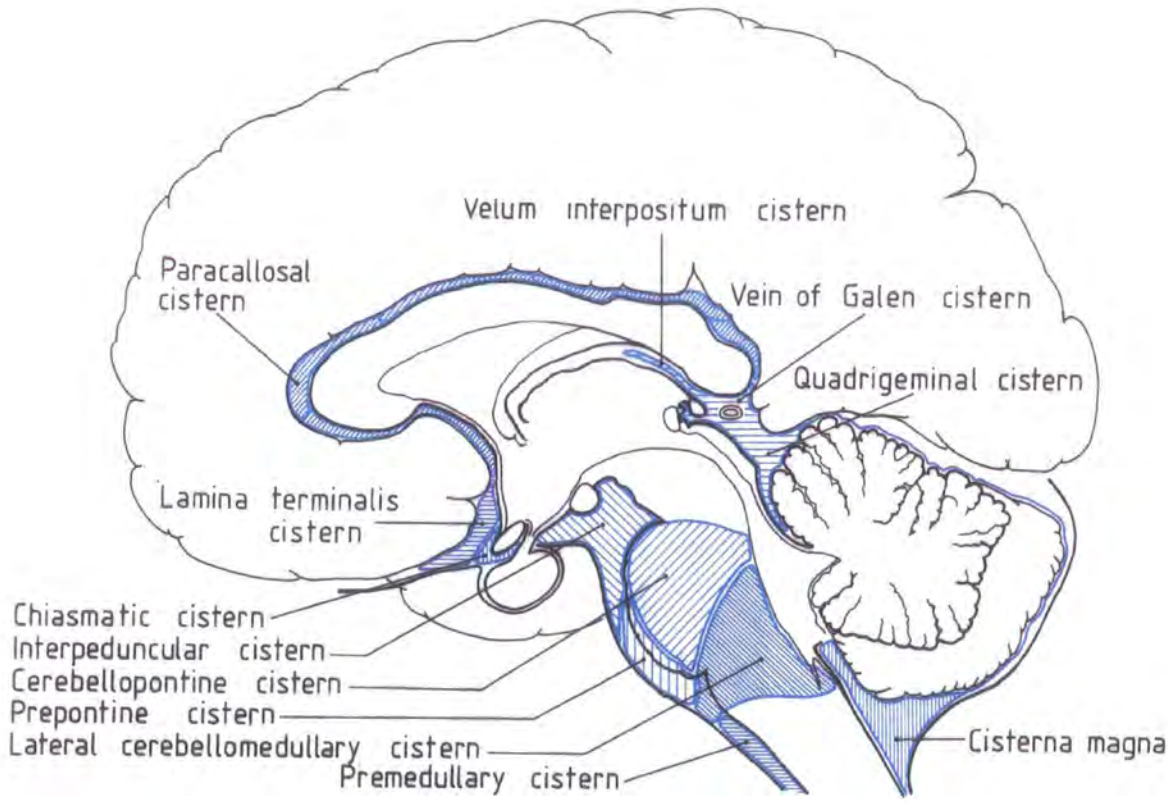

Figure 2.4 Schematic representation of some of the major subarachnoid cisterns in lateral view (p. 15. Reprinted with permission) [767].

is associated with a diverse array of difficulties, including cognitive impairment [750], behavioural disturbances [57, 544] and hormonal dysfunction [325, 604, 679].

2.2.2 Clinical presentation

An SAH precipitates one of the most dramatic and horrific clinical presentations in medicine [37], with the expelled blood immediately eliciting features of meningism (Figure 2.5) [338]. Though the initial symptoms depend upon the severity of the bleeding and the disruption to cerebral function, an unusually severe and sudden

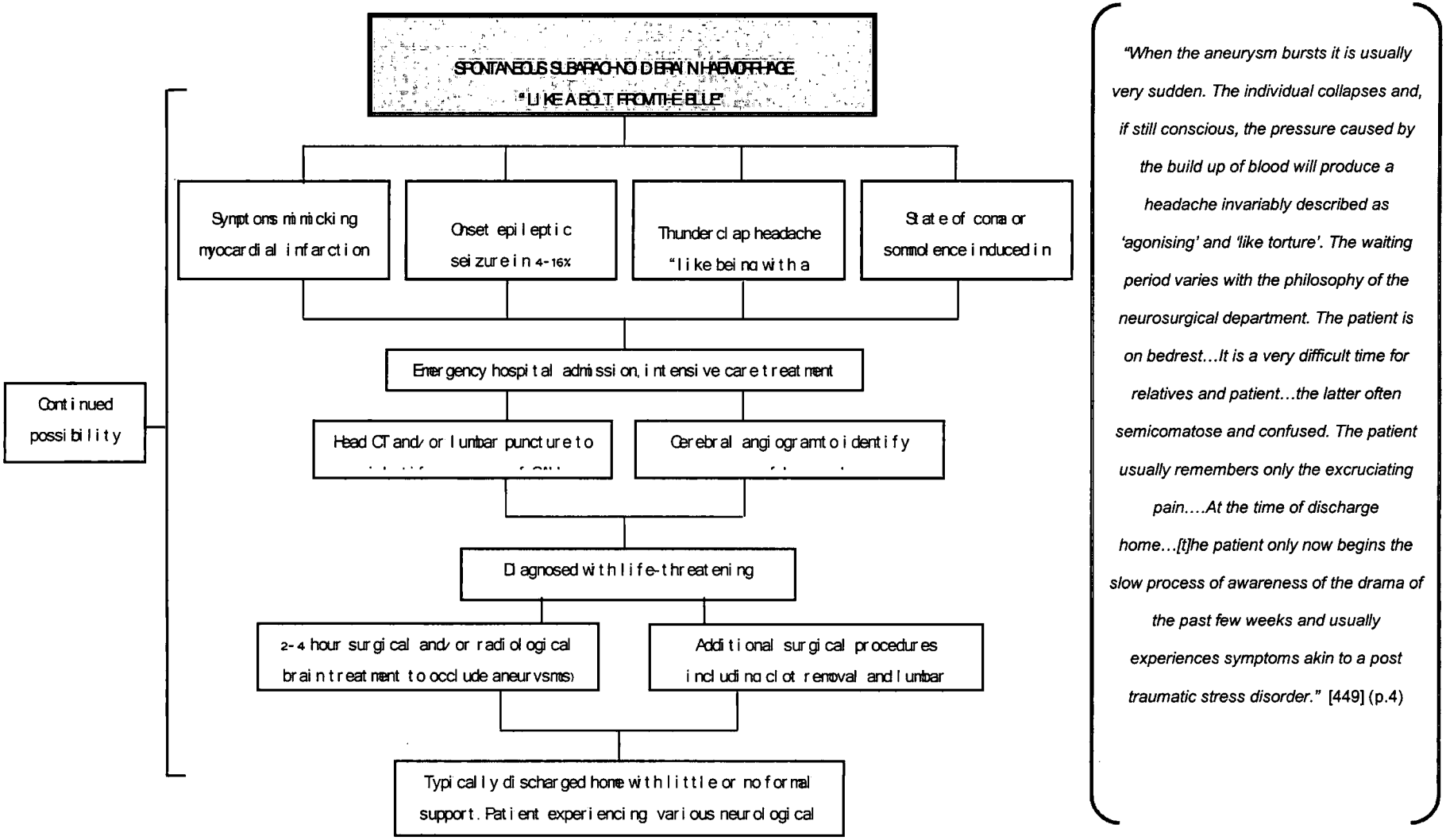

Figure 2.5 The potentially traumatic experience of suffering and surviving a spontaneous subarachnoid haemorrhage

thunderclap headache is characteristic of an SAH [402, 710]. This headache is generally diffuse and described by patients as the most severe headache possible (e.g., "like being hit with a cricket bat") [295, 449, 555, 707]. Increasingly severe bleeds result in a clinical presentation that is dominated by coma. Indeed, up to 40% of SAH patients are in a state of somnolence or coma upon admission to hospital [76, 221]. Other distressing symptoms include neck stiffness, vomiting, photophobia, focal neurological deficits and electrocardiographic changes mimicking myocardial infarction [353]. Onset seizures also occur in 4-16% of patients [94, 116, 533]. Importantly, an SAH can occur at any time, in states of rest (e.g., sleep), or in periods of activity (e.g., sexual intercourse, lifting) [184, 411, 497, 506, 602]. Although risk factors for SAH include smoking, alcohol consumption and cocaine use and hypertension [79, 330, 379], evidence suggests that for most patients, the SAH is their first experience of a serious illness [13, 187, 240, 502].

The severity of the patient's clinical presentation in hospital is judged according to their state of consciousness and the presence of certain neurological signs.[708] Two popular scales used to rate the severity are the World Federation of Neurological Surgeons scale (WFNS) [164] and the Hunt and Hess scale [293]. A higher score on both of these scales reflects a poor clinical status (for more details on these two scales which are both used in subsequent chapters, please refer to Appendices I and II where I provide further details on their contents and scoring). Clinical condition is largely related to the severity and impact of the initial haemorrhage [711]. The WFNS scale is the preferable scale because as well as having superior interrater reliability [401], it affords more weight to level of consciousness, which along with the patient's age and severity of bleed, is the most important prognostic factor for immediate outcome [164, 277, 334, 710].

2.2.3 Diagnosis

A diagnosis of an SAH is made if the presence of subarachnoid blood is confirmed, either by computed tomography (CT) or by lumbar puncture. In all patients, the first investigation is a CT scan of the head. The period of diagnosis (and hence access to appropriate treatment) in reality can be quite protracted for SAH patients (and their family) as misdiagnosis on first presentation to hospital occurs in 12-51% of cases [5, 112, 332, 369, 436, 482, 603, 715]. The diagnostic yield of the head CT depends on the time interval since ictus, the resolution of the scanner and the skills of the radiologist [6, 361, 691, 704]. Patients may therefore, also require a lumbar puncture to detect the occurrence of an SAH (namely, xanthrochromia in the cerebrospinal fluid).

Numerous scales exist to quantify and describe the severity and the anatomical distribution of a patient's bleed as seen on CT scans. Amongst the most commonly used is Fisher's-scale [191]. As Fisher's scale is used and discussed in subsequent chapters, I provide further details on its content and scoring in Appendix III.

To identify the source of a person's SAH, a comprehensive cerebral angiography is performed. In the traditional angiography technique, a catheter is fed through the femoral artery and up to the carotid and vertebral arteries. Contrast dye is then injected into the catheter so that the vessels of the circle of Willis can be visualised and any abnormalities, such as a cerebral aneurysm, detected. The aetiology of the patients bleed is often used to classify (be it 'unknown', aneurysmal, or the specific arterial location of the ruptured aneurysm) and to try to predict an SAH patient's outcome

2.2.4 Management

The initial haemorrhage is terminated by the "extravascular rise in pressure as a consequence of the bleeding and/ or by tamponade of the vacant surroundings" (p. 8) [295]. This termination is, however, only temporary. The cumulative risk of re-bleeding from a ruptured cerebral aneurysm is around 40% without intervention [278]. As these re-bleeds hold an extremely poor prognosis [573], the immediate therapeutic goal is to identify the source of the bleed and, where possible, permanently occlude it from circulation. Occlusion of a cerebral aneurysm is most commonly achieved via an invasive procedure, either neurosurgical clipping and/ or endovascular coiling. The former, more traditional procedure, entails a craniotomy and resection of the brain under general anaesthesia, where re-bleeding is prevented by the placement of a small spring-loaded metal clip across the neck of the aneurysm. This serves to exclude the aneurysm from circulation, whilst still preserving the parent and perforating arteries [468]. The coiling procedure on the other hand, entails an angiogram procedure (typically under general anaesthesia), whereby the tip of a catheter is positioned in the neck of the aneurysm, which is then packed with platinum coils, through a system of controlled detachment. The intent is to provoke reactive thrombosis of the aneurysm and so obstruct the lumen. No single craniotomy or coiling procedure is routine and can each take around 2-6 hours to complete [710]. Although both procedures carry independent risks for the life of the patient, the results from recent randomised controlled trials suggest an absolute advantage for the coiling technique in terms of the rate of death and dependence [466, 467, 702]. Coiling negates the need for craniotomy and hence damage to the brain parenchyma. Furthermore, unlike the clipping techniques, it does not increase the possibility of secondary ischemic brain damage [77].

In contrast to those patients whose haemorrhage is of an identified source, those with an SAH of an unknown origin, typically receive no surgical intervention and receive only conservative management. Given the potential differences in treatment impact, the type of intervention which a patient receives (be it conservative, clipping or coiling) is often used to classify patients and used to try and predict their outcome.

2.2.5 Risk of re-bleeding and further SAH

Empirical evidence indicates that re-bleeding in SAH patients is very rare [98, 131, 307, 333, 466, 611, 695, 745]. Although former aneurysmal SAH patients have a statistically higher chance of suffering a further SAH compared to the general population [702, 745], the actual number of re-bleeds is very small. For example, a recent meta-analysis [702], including data from the largest medical follow-up study to date (namely, the International Subarachnoid Aneurysm Trial [466]), found that only 1.2% of 1137 clipped patients and 2.6% of 1135 coiled patients had an episode of re-bleeding up to one year following treatment.

It can be concluded therefore, that coiling and surgical clipping procedures are effective treatments for the prevention of re-bleeding in the vast majority of patients. This, together with the fact that the majority (>95%) of deaths associated with the illness occur during the acute hospital stages of the illness [32, 413, 691], means that patients are naturally informed by their clinicians and patient information sources that they are very safe and should look to return to a normal, unrestricted life [202, 449, 503]. In addition, patients are often reassured that, unlike most in the general population, they have had a detailed examination of their cerebral architecture and had there been any cause for concern this would have been identified. Moreover, patients treated by coiling, those with multiple aneurysms and those with an

aneurysm that was incompletely obliterated by clipping are actually monitored and undergo repeated angiography following hospital discharge, which allows for pre-emptive treatment if required [449].

2.3 Health-related quality of life in the context of SAH

2.3.1 Background on HRQoL and the measuring of SAH patients' outcome

Progress in understanding the cause of SAH patients' poor psychosocial outcome has been particularly slow because research on this topic has only recently begun. The high mortality following SAH [110, 284, 653], as well as outcome research traditionally being conducted by neurosurgeons (for whom a "good" outcome constituted successful occlusion of a cerebral aneurysm), meant that research into patient recovery was for a long time, not considered a priority. Outcome had only been indexed in terms of mortality and patient survival time [268]. An improving survival rate and relatively stable incidence [284, 364, 370, 403, 653] has however, meant that it has become vital to now consider not only the quantity, but also the quality of SAH patients' survival [183].

With the increased attention on SAH patients' outcome, it became noticeable that researchers and clinicians needed to be equipped with sensitive measures to gauge patients' global outcome [214, 752]. A wealth of evidence has illustrated that the classic measures of outcome available within neurosurgery and neurology, measures such as the Glasgow Outcome Scale (GOS) [318], are far from satisfactory (please see Appendix IV for a description of the content and scoring of the GOS). Such crude, clinician-led measures were designed only to evaluate patient outcome with respect to physical disability, and are as such, too restricted in their focus to capture the broad array of difficulties which SAH patients can experience. An

infrequency of profound physical disability in the SAH population for example, means that although 80-85% of patients are rated as having made either a "good" or favourable outcome on such scales [303, 434], up to 60% of these patients illustrate chronic cognitive dysfunction [303, 438, 507, 540, 541, 643], around 50% experience personality change (including irritability, hostility, emotional lability) [57, 537, 746], 50% do not return to work [90, 540, 541], approximately 20% show reduced social participation [540, 541], 25% consider death preferable to the quality of their survival [90], and many also show severe hormonal disturbance [604].

The revelation that a positive appearance [17, 25, 45, 303, 313, 409, 507, 643] did not necessarily equate with a full recovery, forced neurosurgeons to engage in a debate on how it defined and measured SAH patients' outcome. Seminal contributions to this discussion revealed that neurosurgery's definition of outcome had been, for the most part, atheoretical. It was highlighted how the judgement of patient outcome following an SAH was not informed by the patient's own opinion, but rather was centred upon the treating neurosurgeon's own beliefs. Buchanan et al. [90] in a small, but important study, illustrated that this approach was wholly unsuitable because the frame of reference used by these two parties drastically differed. Whilst patients and their families evaluated outcome according to "what was", neurosurgeons, being acutely aware of the potential of an SAH to kill or profoundly disable, compared patients' outcomes "with what could have been". Consequently, though patients often experienced troublesome neurobehavioural sequelae, difficulties other than obvious physical impairment were viewed by neurosurgeons as 'minor' and permissible [44, 45, 90]. "Good" recovery, it was found, lay very much in the eye of the beholder.

As a result, the neurosurgical community recognised that it was crucial that a patient's perspective was taken into account when judging outcome after an SAH. It was seen that a more holistic approach to assessment was needed, whereby the entire patient as he/she exists and functions in his/her own world was evaluated [17, 44, 45, 295, 313, 383, 397, 398, 592]. As is the case for other illnesses [59, 234, 239, 384, 757], it is now widely accepted that measures of patients' 'health-related quality of life' (HRQoL) fulfil these aims and that such measures are well-suited to provide a sensitive index of the personal burden that an SAH places on its survivor [103, 137]. Indeed, in line with the US. Food and Drugs Administration's guidelines [137, 214], HRQoL is now used as "hard" criterion by which to evaluate different treatments for SAH [3, 91, 144, 239, 362, 410, 686, 693].

Despite this increased emphasis being placed on HRQoL, no single definition exists in the medical sciences [59, 186, 219, 329]. Nonetheless, HRQoL is commonly understood to be a multidimensional construct which measures the extent to which one's usual or expected physical, emotional and social well-being is affected by a medical condition or treatment [109]. HRQoL is distinct from the broader construct of quality of life which encompasses the influence of other aspects of life not amenable to health care services, such as adequacy of housing and income [59]. Importantly, it is recognised that HRQoL can only be effectively accessed by asking the patient themselves for their opinion [59, 186]. Furthermore, not only does HRQoL measure for some of the neurophysical impairments resulting from an illness (e.g., loss of movement in a limb) and its associated disability (i.e., the functional loss associated with these impairments), but it also heavily loads on the handicap which these impairments and disabilities cause (i.e., the disadvantages the person experiences as a result of the illness which limits or prevents them from fulfilling a normal role, such

as working). HRQoL therefore, represents an indicator of a patient's overall abilities in daily life. It exceeds the level of pure physical function and constitutes a more general outcome criterion than cognitive function [285, 305]. Given this multidimensional nature, HRQoL accords well with the World Health Organisation's models of disease [1, 2] which contend that an illness can affect a person in a multitude of ways, that its effects are context specific and can ultimately often only be evaluated by the patient themselves [84, 232, 748]. Importantly, HRQoL is a double-sided concept, allowing for both positive, as well as negative effects, of illness [59].

Both disease specific and generic HRQoL measures have been used to assess SAH patients' outcome [43, 546, 734]. These self-report questionnaires evaluate HRQoL by asking the patient to indicate their personal experience of the presence, frequency, or intensity of various symptoms, behaviours, capabilities and feelings. The key HRQoL domains which are commonly examined by such instruments include the person's physical functioning (i.e., limitations in performance due to their poor health in all physical activities including bathing and dressing), physical role limitations (i.e., problems with work and/ or daily activities as a result of their physical health), bodily pain (i.e., severity and limitations of pain), general health (i.e., evaluate their personal health as poor and asked whether it is likely to get worse), energy (i.e., whether they feel tired and worn out all the time), social functioning (i.e., whether they experience extreme and frequent interference with normal social activities due to physical or emotional problems) and mental health (i.e., whether they feel nervous and depressed all of the time) [735]. Principal component analyses reveal that scores from these domains essentially relate to two broad HRQoL dimensions – namely physical HRQoL and mental HRQoL [732]. Not only does the use of these summary scores obviously reduce the number of statistical

comparisons which are needed when analysing data, but it also simplifies interpretation and means that the two aspects can be examined separately.

Although disease-specific HRQoL instruments have the advantage that they can be highly sensitive, with items being tailored to the disease in question, such instruments have been slow to develop for SAH patients. To date, only one such SAH measure has been developed and it is still very much in the early stages of psychometric evaluation [546]. Consequently, the highly reliable and widely validated generic HRQoL measures – often referred to as health-status questionnaires [168, 186] – have been favoured in SAH studies. The Medical Outcomes Study Short Form questionnaires [731, 735] and the Sickness Impact Profile [43] are the most popular of the generic instruments in the field of SAH (as revealed by my review of the SAH HRQoL literature presented later in this chapter). The great advantage of such instruments is that normative data have been collected so that it can be determined to what degree SAH patients' HRQoL strays from normality [59]. Scores can also be compared to those reported in relation to patients with/after other illnesses which allows for SAH patients' impairment to be placed in the context of more thoroughly researched diseases.

2.3.2 Patients' HRQoL after SAH

Having been employed in SAH research since 1995, HRQoL measures have been instrumental in exposing the true extent and seriousness of an SAH for its survivors. Though a few exceptions exist [40, 75, 451], and a minority of patients note some positive consequences of the illness (e.g., a renewed sense of appreciation for life) [285], an overwhelming amount of literature now demonstrates that many SAH patients experience substantial degrees of HRQoL impairment compared to general

population controls [116, 144, 189, 240, 283, 285, 286, 302, 305, 336, 377, 438, 609, 639, 703]. This impairment is seen in both the early [144, 285, 336, 358, 438] and the later stages following the illness [116, 144, 189, 240, 286, 302, 305, 377, 609, 639]. For example, Hütter et al. [302] examined a sample of 58 SAH patients using a study-specific HRQoL measure and found that approximately 50% of those patients still reported impairment 1-5 years post-SAH.

The severity of SAH HRQoL impairment is reflected even at the group mean level, where it could be expected that its effect would be less pronounced. Using the data from 10 major studies which together examined over 600 SAH patients [144, 240, 283, 322, 336, 358, 377, 470, 569, 639], I present in Figure 2.6 the (weighted) average mental and physical HRQoL reported by SAH patients (as measured by the Medical Outcome Study Short-Form questionnaires [733, 734]). Crucially, I also include in the figure, the average HRQoL reported on the same measure by persons with health conditions which have been better researched and are recognised as being debilitating, such as cancer [676]. The use of a linear *t*-score transformation (where the mean normative score for each condition is 50) means that scores across the different health conditions can be compared. Although some caution should be exercised when interpreting the summary scores for SAH patients' HRQoL (since I did not formally examine the homogeneity of the scores from the contributing studies), the figure does nevertheless, quite clearly illustrate that an SAH – even at group-level – exerts a negative influence on HRQoL comparable to that of the other chronic illnesses. In fact, it can be observed that the HRQoL of SAH patients is worse than that caused by all other illnesses included in the figure, except Major Depressive Disorder. That an SAH can profoundly reduce a person's HRQoL agrees with those studies which more formally contrasted SAH patients' psychosocial outcome with

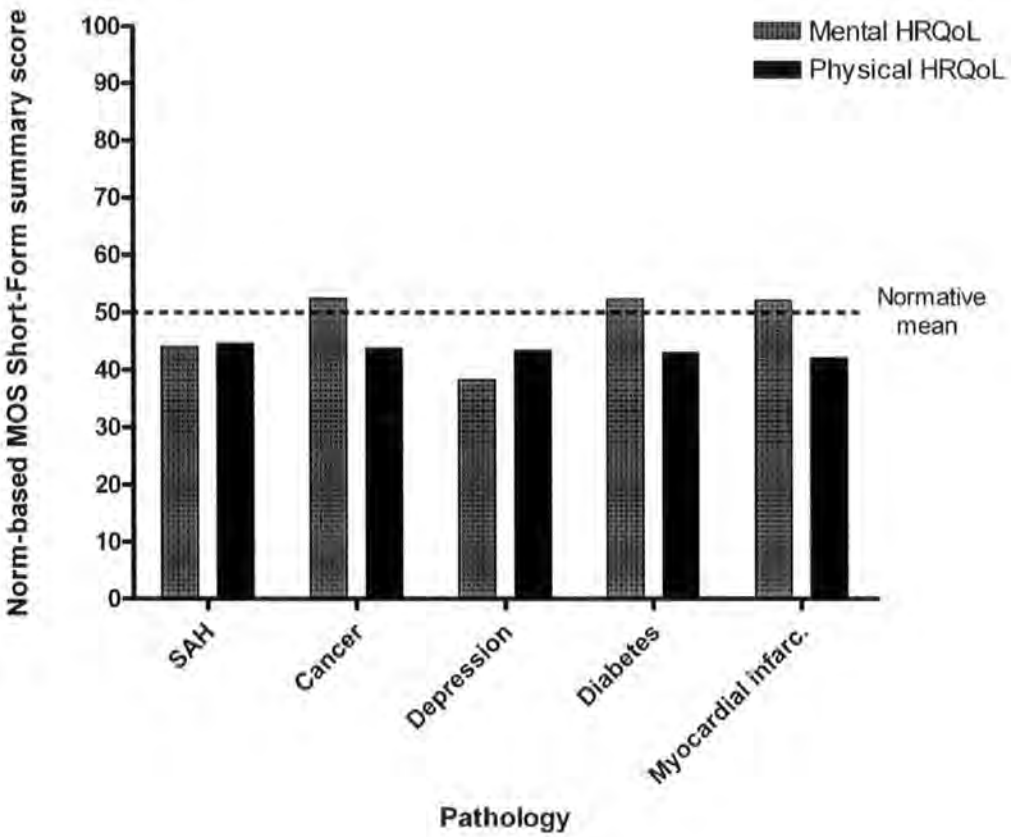

Figure 2.6 Comparison of Mental and Physical health-related quality of life associated with SAH and other illnesses.

SAH scores are weighted averages for 604 patients derived from 10 independent studies [144, 240, 283, 322, 336, 358, 377, 470, 569, 639]; Data for comparison health conditions from European Prospective Investigation into Cancer [676]; Scores less than 50 indicate a negative deviation from normality; Higher scores indicate better outcome; HRQoL= Health-related quality of life; MOS= Medical Outcome Study; Myocardial infarc.= myocardial infarction.

other patient groups [264, 304, 451, 465, 545, 627]. Though an SAH can cause significant reductions in all areas of HRQoL [189], the most prominent reduction has been found to occur in the Mental HRQoL. Katati et al. [336] for example, found that impairment in the domains mental health (47.1%), energy reduction (42.9%) and role

limitations due to emotional problems (40%) were amongst the most impaired areas of HRQoL post-SAH, whilst Kreitschmann-Andermahr et al. [377] found twice the impairment in Mental HRQoL compared to Physical HRQoL post-SAH.

2.4 Previous studies failure to explain SAH patients' reduced HRQoL

As we have seen, a person's HRQoL is especially impaired following an SAH. Does current the evidence allow us to explain this reduction? In order to answer this question, I conducted a systematic (non-quantitative) review of the literature to identify those studies which have looked to explain SAH HRQoL. Figure 2.7 illustrates the selection process for the articles used in this review. Further methodological details of this review, such as the terms used for the searching of electronic data-bases and exclusion criteria, are not presented here but instead can be found in the methods section of the next chapter (Chapter 3), as the current literature review forms the basis for the articles used in the meta-analysis which I present there.

The results from the systematic (non-quantitative) literature review are shown in Tables 2.1 and 2.2. These results show that whilst the complexity of an SAH has meant that a plethora of variables have so far been implicated in trying to explain SAH HRQoL (in fact, over 45), previous studies have failed to identify any factor which is reliably associated with SAH HRQoL and so can help explain these patients impairment (see column titled 'Findings' in the two tables). In addition to showing that most studies (81%; see Figure 2.7) on the topic have used either one of the MOS or SIP HRQoL questionnaires to measure HRQoL, the results also show that most

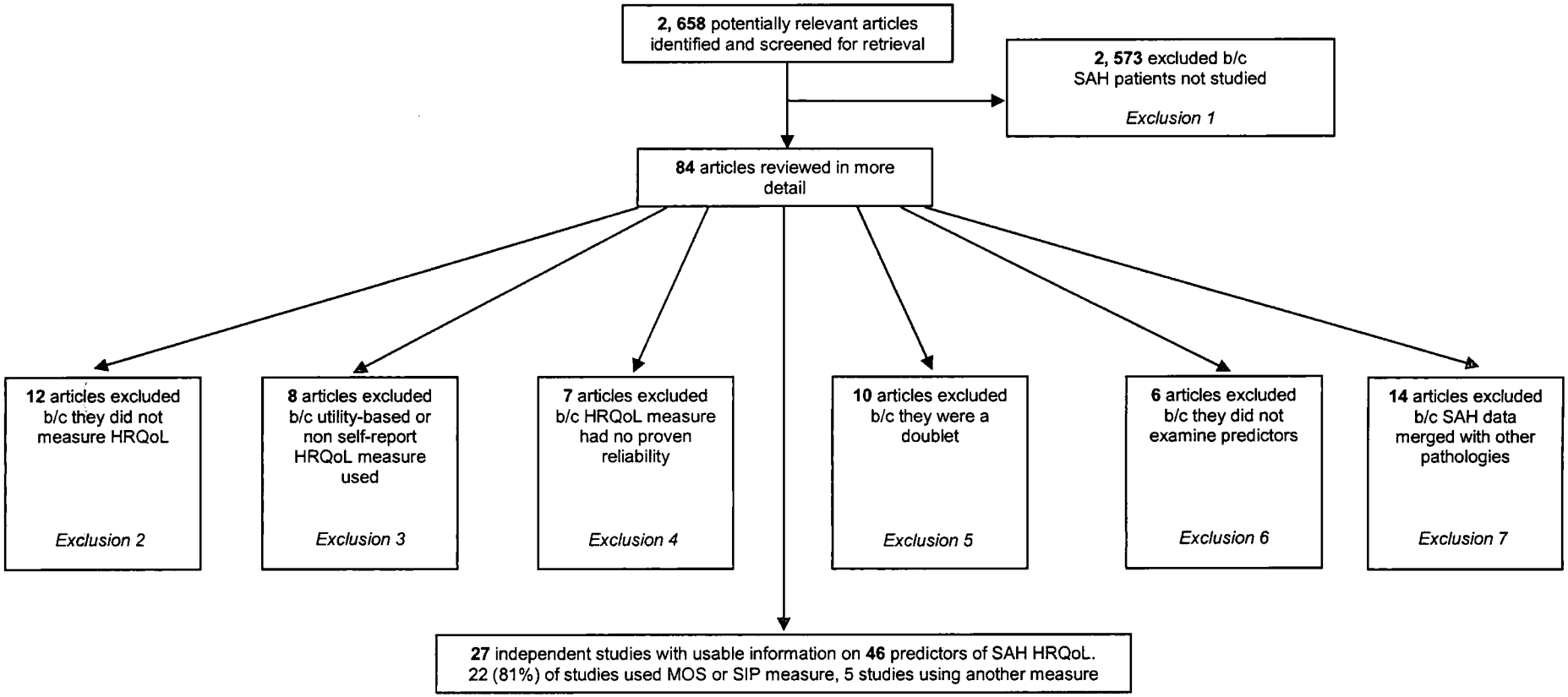

Figure 2.7 Flow diagram describing the selection process of the articles included in the systematic (non-quantitative) review.

b/c=because; HRQoL=health-related quality of life; MOS=Medical Outcomes Study Short-Form Questionnaires; SIP=Sickness Impact Profile.

Table 2.1 Acute SAH factors which have been examined for their value in explaining SAH patients' HRQoL

Acute factors	Study	N	HRQoL measure	Timing (yrs.)	Analysis	Finding(s)
Age	Claassen et al. [116]	247	SIP Total	1.0	Statistical MR	ns.
	Crago et al. [123]	74, 76	SF-36 PF	.25, .5, 1.0	Hierarchical LR	ns.
	Hackett et al. [240]	174	SF-36 all domains	1.2	Univariate	ns.
	Hütter et al. [305]	116	SIP† Total, PCS, MCS	4.0-5.0	Univariate; Stepwise MR; DF	**sig. Total, PCS**
	Katati et al. [336]	70	SF-36 Total and domains	.33	MR	ns. **except for PF**
	Kreitschmann-Andermahr et al. [377]	35	SF-36 PCS, MCS;	2.3	Covariate in MR for SF-36;	-
			NHP domains; QoL-AGHDS		Stepwise MR ± for others	ns. **except NHP social isolation**
	Lindberg et al. [397]	104	VAS	7.0	Univariate	ns.
	Pritchard et al. [546]	105	WPCQ	.5-1.0	Univariate	ns.
	Pritchard et al. [548]	136	WPCQ	.5	Univariate	ns.
Aneurysm	Hütter et al. [305]	116	ALQI Total, PCS, MCS	4.0-5.0	Univariate	ns.
Location	Pritchard et al. [546]	105	WPCQ	.5-1.0*	Univariate	ns.
	Pritchard et al. [548]	136	WPCQ	.5	Univariate	Ns
Aneurysm number	Hütter et al. [305]	116	ALQI Total, PCS, MCS	4.0-5.0	Univariate	ns.

Table 2.1 *Cont'd.*

Acute factors	Study	N	HRQoL measure	Timing (yrs.)	Analysis	Finding(s)
Aneurysm	Mocco et al. [463]	35	SIP Total, PCS, MCS	.25, 1.0	Univariate	ns.
treatment	Pritchard et al. [546]	105	WPCQ	.5-1.0	Univariate	ns.
	Pritchard et al. [548]	136	WPCQ	.5	Univariate	Ns
Anosmia	Wermer et al. [744]	74	VAS	7.33	-	-
Aspirin Therapy	Hop et al. [283]	42	SF-36 domains; SIP domains, PCS, MCS	.33	Univariate	ns. **except 'sleep and rest' on SIP**
Bleed	Crago et al. [123]	74, 76	SF-36 PF	.25, .5, 1.0	Hierarchical LR	ns.
Severity	Hütter et al. [305]	116	SIP† Total, PCS, MCS	4.0-5.0	Univariate; Stepwise MR; DF	ns.
	Katati et al. [336]	70	SF-36 Total and domains	.33	MR	ns.
	Kreitschmann-Andermahr et al. [377]	35	SF-36 PCS, MCS; NHP domains; QoL-AGHDS	2.3	Stepwise MR ±	ns.
	Pritchard et al. [546]	105	WPCQ	.5-1.0	Univariate	ns.
	Pritchard et al. [548]	136	WPCQ	.5	Univariate	ns.
	Soehle et al. [639]	29	SF-36 domains, PCS, MCS	1.0	Univariate	ns. **except for PF**
Brain sag	Komotar et al. [367]	48	SIP Total	.25	Univariate	ns.

Table 2.1 *Cont'd.*

Acute factors	Study	N	HRQoL measure	Timing (yrs.)	Analysis	Finding(s)
Cardiac Complications	Crago et al. [123]	74, 76	SF-36 PF	.25, .5, 1.0	Hierarchical LR	**Sig.** at 3 and 6 mo. only
Clinical severity	Claassen et al. [116]	247	SIP Total	1.0	Statistical MR	ns.
	Crago et al. [123]	74, 76	SF-36 PF	.25, .5, 1.0	Hierarchical LR	ns.
	Fertl et al. [189]	40	Lancaster QoL Profile	1.8	Univariate	ns.
	Hütter et al. [305]	116	ALQI Total, PCS, MCS	4.0-5.0	Univariate; Stepwise MR; DF	ns. **except DF Total**
	Katati et al. [336]	70	SF-36 Total and domains	.33	MR	ns. **except PF, PRL, EN**
	Kreitschmann-Andermahr et al. [377]	35	SF-36 PCS, MCS; NHP domains; QoL-AGHDS	2.3	Stepwise MR ±	ns.
	Pritchard et al. [546]	105	WPCQ	.5-1.0.	Univariate	ns.
	Pritchard et al. [548]	136	WPCQ	.5	Univariate	ns.
	Tseng et al. [694]	69	SF-36 PCS, MCS	.5	Statistical MR	Sig.
Co-morbidities	Hütter et al. [305]	116	ALQI Total, PCS, MCS	4.0-5.0	Univariate	**Sig.**
Delay to Treatment	Hütter et al. [306]	39	ALQI	2.0-3.0	Univariate	ns.
	Hackett et al. [240]	174	SF-36 all domains	1.2	Univariate	ns.

Table 2.1 *Cont'd.*

Acute factors	Study	N	HRQoL measure	Timing (yrs.)	Analysis	Finding(s)
Education	Claassen et al. [116]	247	SIP Total	1.0	Statistical MR	**sig.**
English fluency	Claassen et al. [116]	247	SIP Total	1.0	Statistical MR	ns.
Ethnicity	Claassen et al. [116]	247	SIP Total	1.0	Statistical MR	**sig.**
	Crago et al. [123]	74, 76	SF-36 PF	.25, .5, 1.0	Hierarchical LR	ns.
Fever	Fernandez et al. [188]	353	SIP poor/ good QoL cut-off	.25	Hierarchical LR	ns.
Hydrocephalus	Hütter et al. [305] ±±	116	ALQI Total, PCS, MCS	4.0-5.0	Univariate	ns.
	Tseng et al. [694]	69	SF-36 PCS, MCS	.5	Statistical MR	sig. for PCS only
Immediate Operative deficits	Tseng et a. [694]	69	SF-36 PCS, MCS	.5	Statistical MR	sig.
Infarction	Claassen et al. [116]	247	SIP Total	1.0	Statistical MR	ns.

Table 2.1 *Cont'd.*

Acute factors	Study	N	HRQoL measure	Timing (yrs.)	Analysis	Finding(s)
Initial Misdiagnosis	Kowalski et al. [369]	482	SIP	.25, 1.0	Univariate	ns. **except for just good grade patients at 3 mo.**
Intracerebral Bleed	Hütter et al. [305]*	108	ALQI Total, PCS, MCS	4.0-5.0	Univariate	**sig.**
Intraoperative aneurysm rupture	Hütter et al. [305]	116	ALQI Total, PCS, MCS	4.0-5.0	Univariate	ns.
Intraventricular Bleed	Hütter et al. [305]	116	ALQI Total, PCS, MCS	4.0-5.0	ANCOVA	ns.
Pravastatin treatment	Tseng et al. [694]	69	SF-36 PCS, MCS	.5	Statistical MR	**sig.**
Re-bleed	Claassen et al. [116]	247	SIP Total	1.0	Statistical MR	**sig.**

Table 2.1 *Cont'd.*

Acute factors	Study	N	HRQoL measure	Timing (yrs.)	Analysis	Finding(s)
Resection of the gyrus rectus	Hütter et al. [305]	116	ALQI Total, PCS, MCS	4.0-5.0	Univariate	ns.
Sepsis	Tseng et al. [694]	69	SF-36 PCS, MCS	.5	Statistical MR	**sig.**
Sex	Crago et al. [123]	74, 76	SF-36 PF	.25, .5, 1.0	Hierarchical LR	ns.
	Hackett et al. [240]	174	SF-36 all domains	1.2	Univariate	ns.
	Katati et al. [336]	70	SF-36 Total and domains	.33	MR	**sig. male better,** except SF
	Kreitschmann-Andermahr et al. [377]	35	SF-36 PCS, MCS;	2.3	Covariate in MR	-
			NHP domains; QoL-AGHDS		Stepwise MR ±	ns. **except NHP social isolation**
	Lindberg et al. [397]	104	VAS	7.0	Univariate	ns.
	Pritchard et al. [546]	105	WPCQ	5-1.0	Univariate	ns.
	Pritchard et al. [548]	136	WPCQ	.5	Univariate	ns.
	Tseng et al. [15]	69	SF-36 PCS, MCS	.5	Statistical MR	**sig. male better**
Temporary clipping	Hütter et al. [305]	116	ALQI Total, PCS, MCS	4.0-5.0	Univariate	**sig.** except for MCS

Table 2.1 *Cont'd.*

Acute factors	Study	N	HRQoL measure	Timing (yrs.)	Analysis	Finding(s)
Vasospasm	Hütter et al. [305]	116	ALQI Total, PCS, MCS	4.0-5.0	Univariate	ns. **except for PCS**
	Soehle et al. [639]	29	SF-36 domains, PCS, MCS	1.0	Univariate	ns.
Ventriculitis	Tseng et al. [15]	69	SF-36 PCS, MCS	.5	Statistical MR	**sig. for MCS**
ε4 allele	Morris et al. [470]	70	SF-36	1.2	Univariate	ns.

Note: ALQI= Aachen Life Quality Index; DF=discriminant function analysis; HRQoL=health-related quality of life; LR=logistic regression; MCS=Mental/ Psychosocial HRQoL Component Score; MR= Multiple regression n=number; NHP=Nottingham Health Profile; ns.=statistically non-significant; PCS=Physical HRQoL Component Score; PF=Physical Functioning; QoL-AGHDS=Quality of Life Assessment of Growth Hormone Deficiency; SF-36=Short Form-36; sig.=statistically significant; SIP=Sickness Impact Profile; VAS= Visual Analogue Scale; WPCQ=Wessex Patient Carer Questionnaire; yrs.=years; ±=Stepwise type unclear; ±±=Delayed hydrocephalus (3-48 weeks after discharge); *=Location of ICH in cohort was 'frontal' (11.2%), with the 6.8% of patients with ICH at other locations excluded from analysis.

Table 2.2 Other, non-acute SAH factors which have been examined for their value in explaining SAH patients' HRQoL

Other factor	Study	n	HRQoL measure	Timing (yrs.)	Analysis	Finding(s)
Anxiety	Mayer et al. [438]	137	SIP Total, PCS, MCS	.25	Hierarchical MR	excluded due to collinearity with depression
Cognitive	Mayer et al. [438]	137	SIP Total, PCS, MCS	.25	Univariate; hierarchical MR	**sig.**
Function	Scott et al. [613]	573	SIP Total, PCS, MCS	1.0	Univariate	**sig.**
Depression	Fertl et al. [189]	40	Lancaster QoL Profile	1.8	Univariate	**sig.**
	Lindberg et al. [397]	104	VAS	7.0	Univariate; DF	**sig.**
	Mayer et al. [438]	137	SIP Total, PCS, MCS	.25	Hierarchical MR	**sig.**
Epilepsy	Claassen et al. [116]	247	SIP Total	1.0	Statistical MR	**sig.**
Family functioning	Fertl et al. [189]	40	Lancaster QoL Profile	1.8	Univariate	ns.
Untreated aneurysm	van der Schaaf et al. [703]	69	SF36 domains; EURO-QOL	7.1, 9.1	Univariate	ns.

Table 2.2 *Cont'd.*

Other factor	Study	n	HRQoL measure	Timing (yrs.)	Analysis	Finding(s)
Hormone dysfunction	Kreitschmann-Andermahr et al. [377]	35	SF-36 PCS, MCS; NHP domains; QoL-AGHDS	2.3	Stepwise MR ±	ns. **except QoL-AGHDA, NHP mobility, sleep, social isolation, emotional reaction, energy**
					Univariate	ns.
Leisure and social activities	Lindberg et al. [7]	104	VAS	7.0	Univariate; DF	**sig.**
Physical disability	Hop et al. [285] ±±	55	SIP; SF-36; VAS	.3	Univariate	-
	Hop et al. [286]	48	SIP; SF-36; VAS	1.5	Univariate	sig. SIP 'household and SF-36 PF, PRL, ERL, MH, EN.
	Hütter et al. [305]	116	SIP† Total, PCS, MCS	4.0-5.0	Univariate	-
	Katati et al. [5]	70	SF-36 Total and domains	.33	MR	sig. except SF
	Kreitschmann-Andermahr et al. [377]	35	SF-36 PCS, MCS; NHP; QLAGHDS	2.3	Stepwise MR ±	ns. except SF-36 PCS, NHP pain
	Lindberg et al. [7]	104	VAS	7.0	Univariate	ns.
Number of children	Pritchard et al. [546]	105	WPCQ	.5-1.0	Univariate	ns.
	Pritchard et al. [548]	136	WPCQ	.5	Univariate	ns.
Sleep quality	Schuiling et al. [609]	83	SF-36 domains	1.7	Univariate	sig.

Table 2.2 *Cont'd.*

Other factor	Study	n	HRQoL measure	Timing (yrs.)	Analysis	Finding(s)
Smoking	Ballard et al. [31]	152	SIP Total	.25	Univariate	ns.
Time since illness	Hop et al. [286]	48	SIP; SF-36; VAS	1.5	Univariate	Sig. improve with time SF-36 PF & PRL. Sig. worse SIP 'household management', 'recreation and pastimes' & eating.
	Lindberg et al. [7]	104	VAS	7.0	Univariate	ns.
	Mocco et al. [10]	35	SIP Total, PCS, MCS	25, 1.0.	Univariate	sig.
	Pritchard et al. [8]	105	WPCQ	5-1.0	Univariate	ns.
	Pritchard et al. [9]	136	WPCQ	.5	Univariate	ns.
Working capacity	Fertl et al. [189]	40	Lancaster QoL Profile	1.8	Univariate	ns.
	Lindberg et al. [7]	104	VAS	7.0	Univariate	ns.

Note: ALQI=Aachen Life Quality Index; HRQoL=health-related quality of life; MCS=Mental HRQoL Component Score; NHP= Nottingham Health Profile; PCS=Physical HRQoL Component Score; QLAGHDS= Quality of Life Assessment of Growth Hormone Deficiency in Adults; SF-36= Short Form-36; ±=Stepwise method unclear; ±± Significance testing of associations precluded on the basis of small sample size [633]. When both summary and sub-domains scores available, the association with just summary scores is presented.

previous attempts to explain SAH patients' HRQoL reduction have centred on either (1) the clinical characteristics of the illness and the patient – such as patient age, sex, clinical severity on admission to hospital, severity and distribution of the haemorrhage, its aetiology and its treatment – or (2) on the neurological sequelae which they experience post-SAH. The reasons why these two sets of predictors have so dominated prior studies looking to explain SAH HRQoL are quite comprehensible.

In terms of clinical characteristics of the illness and the characteristics of patient, it is no doubt because these factors have previously been established as the best indicators for more *immediate* aspects of outcome following SAH, such as gross physical morbidity, mortality and some aspects of cognitive impairment [18, 52, 253, 271, 306, 334, 373, 381, 386, 387, 432, 511, 512, 540, 558, 560, 590, 595, 649]. Whilst in terms of the focus on neurological sequelae, it is because whilst SAH does not cause the cardinal neurological problems of 'stroke' (i.e., hemiplegia, aphasia, anosognosia and neglect) [302, 303, 382, 399, 460], it does nevertheless still cause cognitive dysfunction akin to that of closed-head injury in 25-55% of patients and to a lesser extent, some reduced physical independence [34, 295, 297, 303, 306, 505, 507, 687], which the wider literature on other illnesses suggest cold *potentially* be debilitating [35, 61, 180, 282, 344, 523, 719]. Specifically, whilst general intellectual function is unaffected [25, 228, 302, 303, 409, 412, 504, 507, 596, 617, 660], cognitive tests reveal that SAH patients can experience a pattern of chronic impairment in the areas of attention (such as in speed of information processing, sustained concentration and selective attention) [52, 146, 169, 242, 301, 304, 438, 450, 507, 644, 720] executive functioning (such as in tasks of planning, organisation, sequencing and monitoring of complex behaviours) [52, 146, 169, 242, 297, 300, 304, 382, 438, 450, 507, 644, 649, 720] and, to the largest extent, in learning and memory

(such as in figural short-term memory and verbal long-term memory) [13, 34, 145, 169, 242, 296, 300-304, 382, 388, 434, 438, 460, 507, 540, 541, 557, 649, 685, 687, 722]. This impairment it could be speculated could have been disruptive to a patients' quality of life. Indeed, the central place that neurological factors have been assumed to have in explaining SAH patients' psychosocial outcome is reflected in the rehabilitative programmes currently offered to SAH patients which predominantly look to moderate only the impact of the cognitive and physical consequences of the illness [159, 160, 462, 499, 555, 587, 661, 734, 747, 766]

So, how can the mysterious reduction in SAH patients' HRQoL be explained? Two possible explanations present themselves. The first possibility is that in most previous studies, only statistical significance has been used for the evaluation of a predictor's importance. This, combined with the fact that many studies have been statistically underpowered, could mean that the *actual* importance of the traditional factors which they had considered, may not have been revealed. The second explanation is that because SAH is a neurological illness, researchers have been blinkered into concentrating on only classical, neurological and illness-related factors to explain patient outcome and have not taken into account other possible explanations. In reading the literature, it is clear that SAH patients' symptom profile is also very often dominated by psychiatric disturbance [57, 469, 537, 544, 649, 652]. Psychiatric disturbance has however, not been incorporated into explanative models. This is surprising, considering that evidence from the wider psychiatric literature has shown that psychiatric disturbance can be highly debilitating [10, 49, 93, 532].

In the next three chapters, I empirically examine these two possibilities. In Chapter 3, I examine possibility one that traditional factors may be important in explaining SAH HRQoL but that the lack of statistical power in prior studies and their

reliance on notoriously unreliable statistics has served to obscure their actual importance. To do this I present a meta-analysis of prior research on the traditional predictors. In Chapters 4 and 5, I present a further literature review and my prospective study of a large sample of SAH patients, which together are used to explore the second possibility that there might be a so-far ignored consequence of an SAH which has not been taken into account.

Chapter 3

Possibility one – The explanative value of traditionally considered variables for SAH patients' health-related quality of life has been obscured

3.1 Introduction

A subarachnoid brain haemorrhage (SAH) can not only pose a serious threat to someone's life, but it can also negatively impinge upon the well-being of those who survive it [544]. Studies consistently find that a large proportion of its survivors – up to 55%, in fact [302, 377, 397] – report chronic and dramatic reductions on measures of both their Physical and Mental health-related quality of life (HRQoL). In Chapter 2, I showed how traditional efforts to explain SAH patients' reduced HRQoL have focused on the degree of neurological sequelae experienced post-SAH, intrinsic information about the patient and the characteristics of their haemorrhage (see Tables 2.1 - 2.2 in that chapter). It has for example, been argued in the SAH literature that increasing patient age [305, 306, 694], being female [336, 694], presenting in a worse neurological state on initial admission to hospital [188, 265, 305, 336, 639, 694], suffering a more severe haemorrhage [305, 306, 377, 639], greater physical disability and cognitive impairment [285, 286, 305, 336, 377, 438, 613] are associated with worse HRQoL scores. The time which elapses between haemorrhage occurrence and HRQoL assessment has also been proposed as being key when explaining patients' HRQoL outcome. It is those assessments which occur the soonest following haemorrhage which yield the worse HRQoL scores [286, 397, 463, 546, 548].

These traditional variables have not however, proved to be robust predictors [105, 116, 189, 286, 305, 397, 438, 689, 721]. Whilst some studies have found them to be associated with SAH patient HRQoL, the majority have not [116, 123, 189, 240, 285, 286, 305, 336, 397, 463, 546, 548, 639, 694]. This would suggest that future studies should focus on more novel aspects of SAH patients' outcome to explain the reduction in HRQoL. There remains the possibility however, that traditional factors *do* explain SAH HRQoL, but that the manner in which their importance has been

assessed has served to prevent their true importance from being recognised. To date, studies examining a predictor of HRQoL have almost exclusively relied upon the statistical significance of its association with HRQoL when evaluating its importance. By itself, this is however, a notoriously unreliable method. Specifically, any information which a *P*-value carries about the practical predictive importance of a relationship is always confounded by the statistical power of the study in question to actually detect the effect [108, 117, 210, 452, 751]. Studies with small samples for example, may find a large effect but this may not prove to be statistically significant because of inadequate statistical power [404]. Conversely, a small effect may prove statistically significant simply as a function of it being measured in a study with a large sample size. Therefore, the preferable means by which to judge the importance of these predictors is to examine the *size* of their predictive effect on SAH patients' HRQoL. In other words, how much variance in HRQoL can each of the predictors actually explain? This information is contained in standardised measures of effect size, of which there are two main families; the d family (such as Cohen's *d*, Hedges' *g* and Glass's delta) and the (correlation coefficient) *r* family [583]. Unlike *P*-values, these measures are relatively unaffected by sample size (although, as with any quantitative test, the larger the sample, the closer this statistic will approximate the true effect). Given the evidence that a lack of statistical significance does not necessarily equate with a lack of practical explanative importance, it is imperative that the ill-considered effect sizes of traditional predictors of HRQoL are considered before they are hastily discarded. An examination of their effect sizes will be able to inform us which, if any, of the predictors are truly important from an explanative perspective and should be retained.

With this in mind, the present chapter reports the results from a meta-analytic study which I conducted to examine the predictive effect size of each of the following 7 traditional predictors of SAH HRQoL: patient age, bleed severity, clinical severity on admission, cognitive function, physical disability, sex and time since illness. In the meta-analysis, the predictive effect sizes for the variables of Physical HRQoL and Mental HRQoL is examined separately. The basis for which predictors and articles to include in the meta-analysis were the results from the systematic (non-quantitative) literature review which I presented in the previous chapter. For each of the 7 predictors included, standard procedures [404, 472, 580] were used to calculate the size of their predictive effect in each of the included articles. In order to produce the most accurate estimates of their true effect size, meta-analysis pooled the effect size estimates from individual studies on the same predictor to produce single overall effect size estimates. When combining the effect size estimates from separate studies, the greatest weight was given to those estimates taken from the larger studies as these will usually be more precise in their measurement than the estimates from the smaller studies [260].

3.2 Methods

The meta-analysis presented in this chapter followed directly on from the results of the systematic (non-quantitative) literature review which I presented in Chapter 2. That particular review was conducted to examine which variables had been used in previous studies to try and explain SAH HRQoL. It revealed that a total of 46 predictors had, to differing extents, been examined for SAH HRQoL. It was this set of 46 predictors which formed the initial sample of predictors which were considered for inclusion in the meta-analysis. I shall now describe the process by which predictors/ articles were selected for both the initial systematic (non-quantitative) review and for the present meta-analysis.

Selection Procedures

For the initial systematic review presented in Chapter 2, several techniques were used to identify full journal articles, published in English, which had examined potential predictors of SAH patients' HRQoL. Firstly, a search of the *Medline* (1951 to June 2008), *ISI Web of Science* (1945 to May 2008) and *PsycINFO* (1887 to May 2008) databases was made. The databases were searched using the following key words in all relevant combinations: aneurysm, subarachnoid h(a)emorrhage, arteriovenous malformation, perimesencepahlic, quality of life, QoL, recovery, Short-Form 36, SF-36, Sickness Impact Profile, SIP, functional and psychosocial. Secondly, the journal *Stroke* (the highest impact journal for SAH studies) was hand-searched from January 1994 to June 2008 for potentially relevant studies. The starting date for this hand search was one year before the first SAH HRQoL study by Hütter et el. was published [302]. Finally, the bibliographies of all retrieved publications were examined

and a forward *Medline* search was made using the names of the author(s) of already identified studies.

Inclusion and Exclusion Criteria

For the systematic literature review, each identified predictor/ article was scrutinized and excluded if it met any of the following predetermined exclusion criteria: (1) SAH patients had not been studied in the article, (2) HRQoL had not actually been measured (studies measuring more specific aspects of psychosocial outcome, such as social participation or work status, were excluded), (3) a utility-based, rather than psychometric-based HRQoL measure had been used, (4) a HRQoL measure which had no proven reliability or validity had been used, (5) the article was a 'doublet' for another article in that it used the same data set and addressed the same question (when such multiple articles existed, I included the most comprehensive article or the article with the largest sample size), (6) the predictors of SAH HRQoL had not been examined and finally, (7) the article had merged the HRQoL data of SAH patients with that of other patient groups. The review initially identified 2,657 potentially relevant articles. The majority (*N*=2,573 articles) of these articles were however, excluded at the outset as their abstracts revealed that they had not studied SAH patients (Exclusion criteria 1). The full articles of the remaining 84 studies were then examined. Of these studies, 58 were excluded on the basis of the remaining six exclusion criteria. This resulted in the identification of 46 variables which had, to differing extents, been examined for their predictive value of SAH HRQoL by 27 articles (see Figure 2.7 in Chapter 2 for flow diagram describing the selection process for the systematic literature review). In the majority of studies (81.5%), either one of

the Sickness Impact Profile questionnaires [43, 298, 299] or Medical Outcomes Study questionnaires had been used to measure HRQoL [731, 734].

The selection process for the present meta-analysis involved examining the 46 predictors identified by the initial systematic review for possible inclusion. A visual presentation of the selection process for the meta-analysis is given in Figure 3.1. The meta-analysis included only predictors which were considered to be 'traditional predictors' – defined as having been examined in at least 3 independent and eligible articles (Exclusion criteria 8). Articles were only included if the dependent variable of HRQoL in the original study had been measured using either (1) the Sickness Impact Profile (SIP) HRQoL questionnaire (includes Sickness Impact Profile-136 [43], the Anglicized version known as the Functional Limitations Profile [525, 526]; and the Aachen Life Quality Index (ALQI) [298, 299]) or (2) the Medical Outcomes Study (MOS) Short-form HRQoL questionnaires (includes Short Form-36 [734] and Short Form-12 [731]; Exclusion criteria 9). Articles/ predictors were also excluded if insufficient data was provided in the article which meant that the effect sizes for its predictors could not be calculated (Exclusion criteria 10), or if only a limited part of the SIP or MOS instrument had been used to measure HRQoL (Exclusion criteria 11). It should be noted that if a study did fail to report sufficient information for the calculation of the effect size (or indeed, reported an effect size with more than one degree of freedom), attempts were made to contact author(s) of these articles, who were asked to provide either the univariate effect size(s) or the raw data necessary for their calculation (the positive response rate was 45%, with 9 of the 20 contacted authors being able to provide the necessary information for inclusion of their study in my meta-analysis; see Acknowledgements).

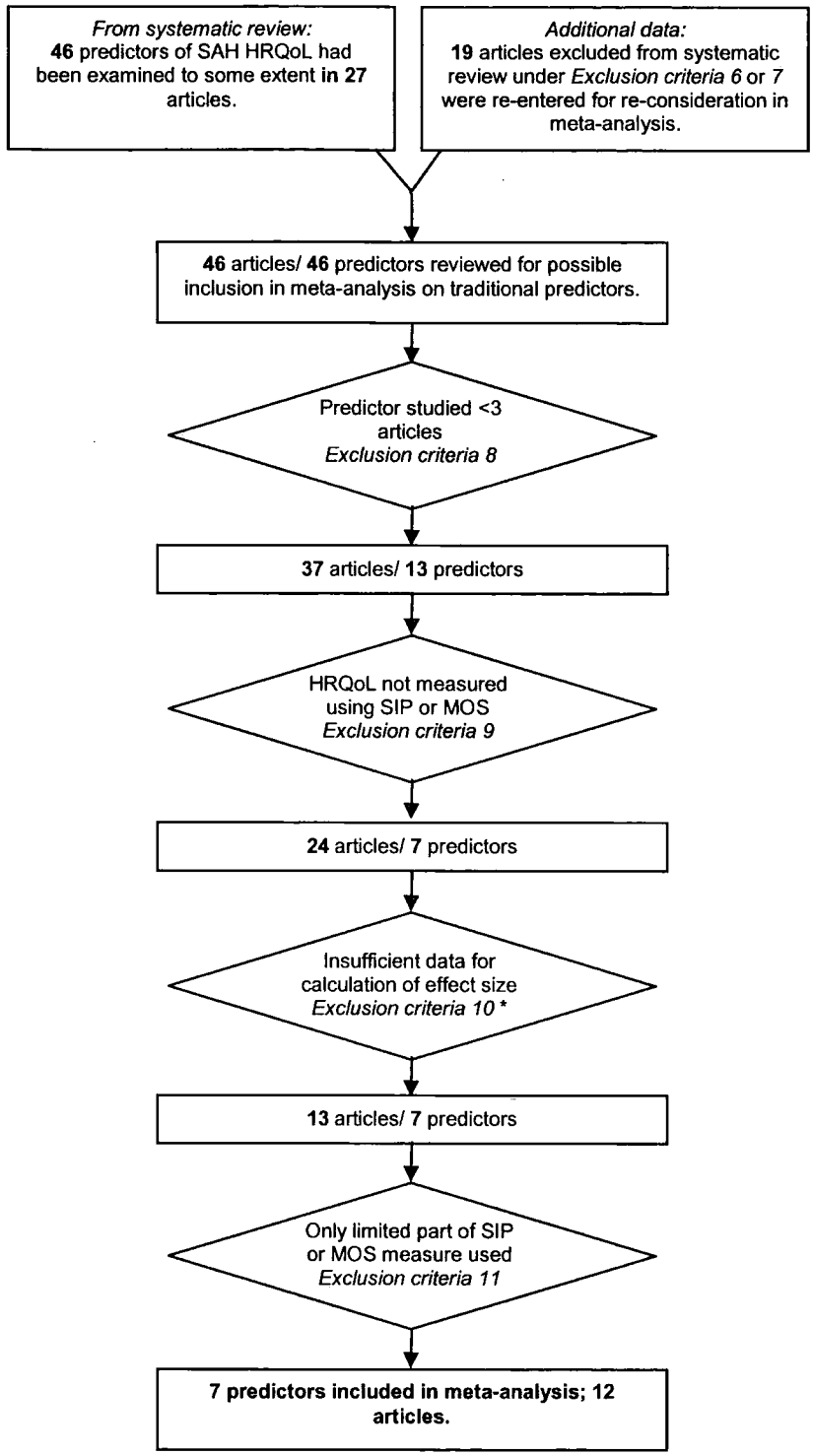

Figure 3.1 Selection of articles and predictors included in meta-analysis.

b/c=because; HRQoL=health-related quality of life; MOS=Medical Outcomes Study Questionnaires; SAH=subarachnoid haemorrhage; SIP=Symptom Impact Profile; *Anderson et al. [12], Brilstra et al. [75], Claassen et al. [116], Czechowsky and Hill [129], Deane et al. [144], Hamedani et al. [244], Hop et al. [286], Kim et al. [354], Komotar et al. [367], Mayer et al. [438] and Schuiling et al. [609].

The exclusion of studies which had not used a SIP or MOS instrument for the measurement of patients' HRQoL was necessary to ensure that the aggregation in the meta-analysis of results from different studies was statistically and conceptually meaningful. The comparability of the content and scoring of the SIP [43, 298, 299] and MOS [731, 734] measures meant that it was acceptable to merge the results from studies using them. To provide more detail, the MOS questionnaires assess patient HRQoL in the 8 areas: (1) physical functioning, (2) physical role limitations, (3) bodily pain, (4) general health, (5) energy, (6) social functioning, (7) emotional role limitations and (8) mental health. SIP questionnaires assess HRQoL in broadly similar areas: (i) ambulation, (ii) mobility, (iii) body care and movement, (iv) social interaction, (v) alertness behaviour, (vi) emotional behaviour and (vii) communication. Crucially, scores on both sets of measures can be reduced to two similarly composed summary scores – one which represents patient Physical HRQoL (scales 1-4 of the MOS and i-iii of the SIP) and one which represents Mental HRQoL (scales 5-8 of the MOS and iv-vii of the SIP; Figures 3.2 and 3.3). These two summary scores were used in the present meta-analysis as two separate dependent variables of patients' HRQoL. The effect sizes which the predictors had with these two dependent variables were examined separately. Although the ALQI [298, 299] is not an official version of the SIP, it was, nevertheless, here deemed to be such, because its German developers constructed it to specifically follow the SIP's content and structure. Like the other SIP measures, HRQoL scores on the ALQI can be represented by a Mental HRQoL summary score (composed of answers to questions concerning mobility, housework, ambulation, autonomy and activation) and a Physical HRQoL summary score (composed of answers to questions concerning free-time activities, family relations, social contacts, communication, and cognition).

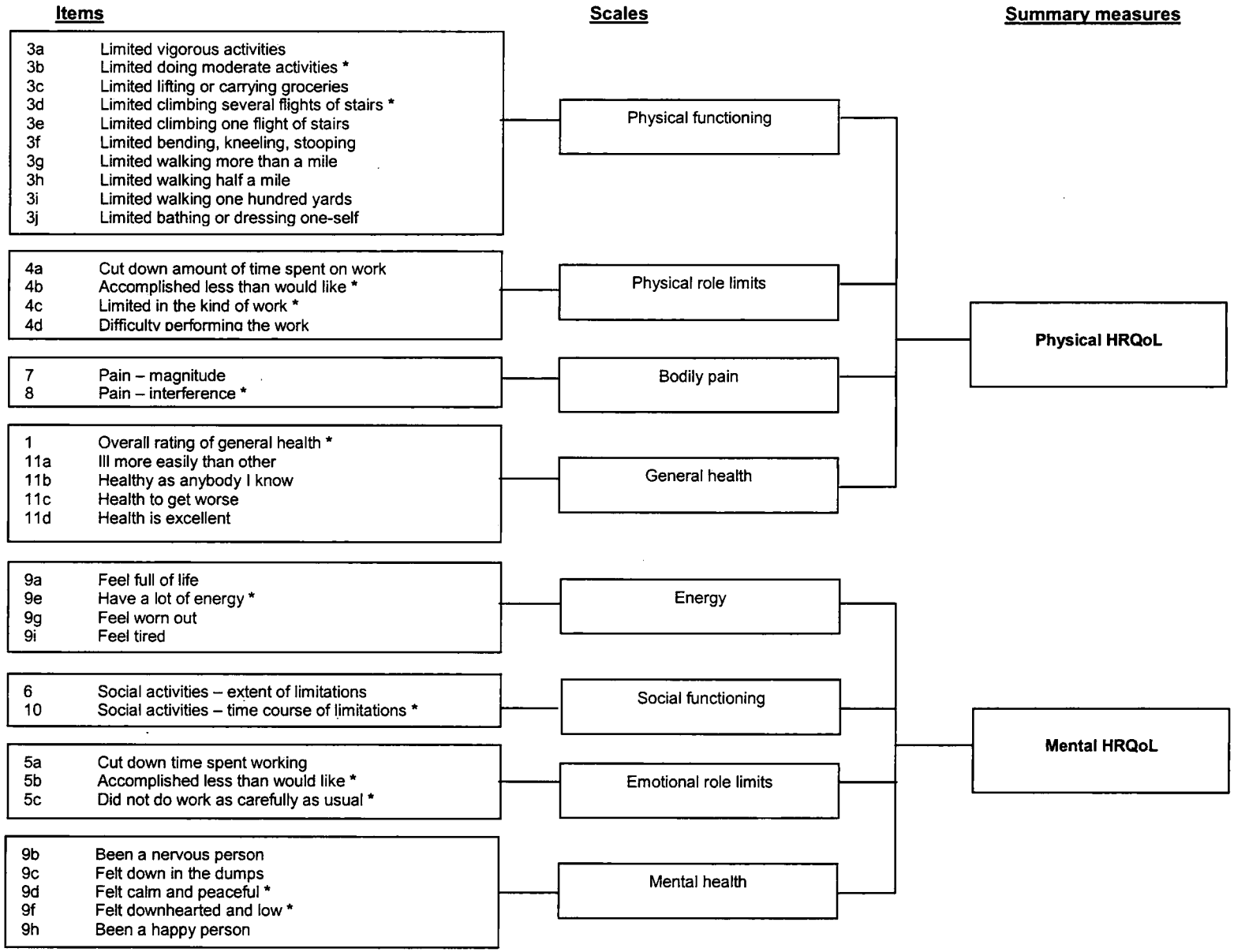

Figure 3.2 Schematic of the structure of the Medical Outcomes Study Short Form questionnaires.

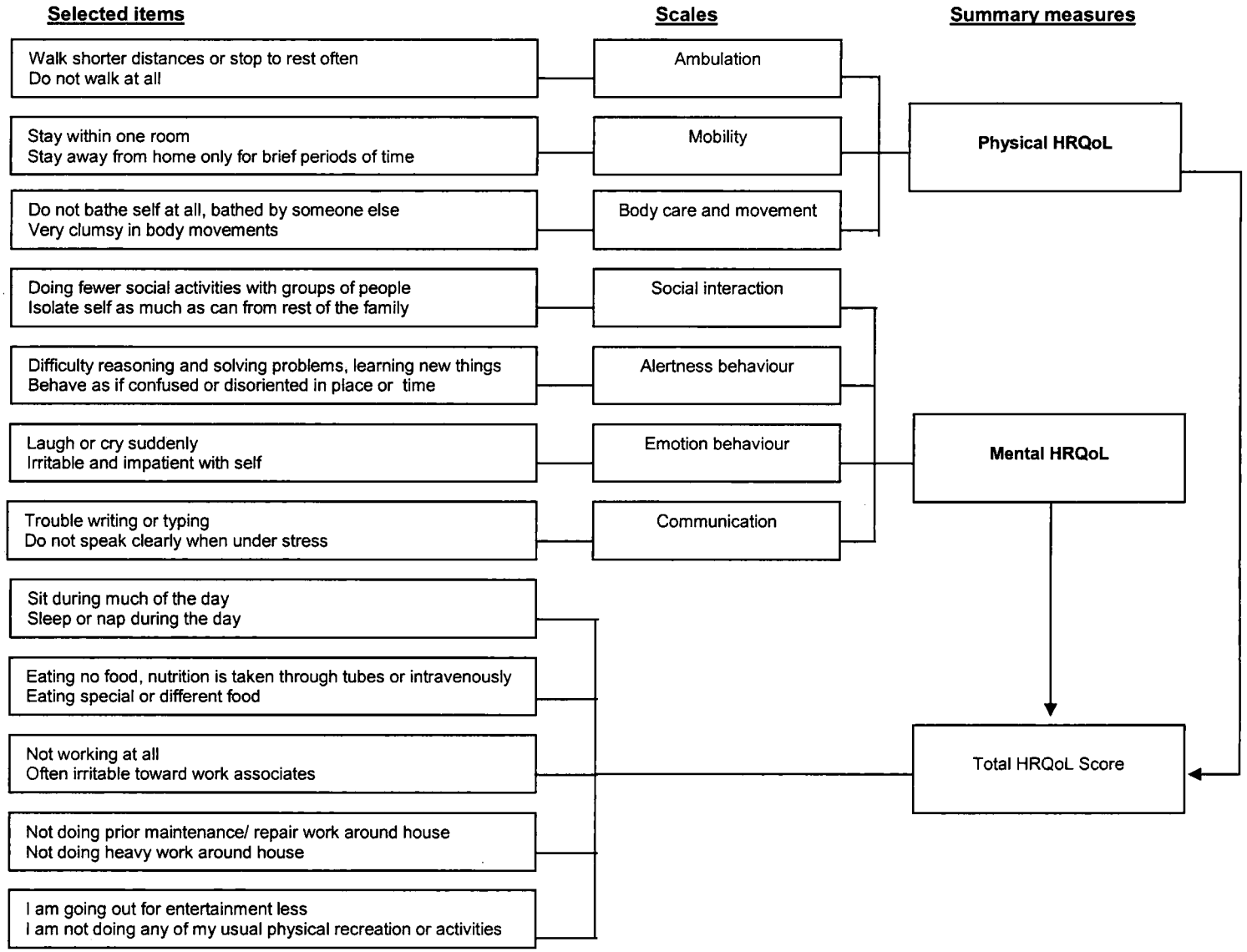

Figure 3.3 Schematic of the structure of the Sickness Impact Profile

HRQoL=health-related quality of life. Note the Mental Component of the SIP is officially referred to as 'Psychosocial HRQoL'.

Additional motivating factors for including studies using either the SIP or MOS were that, firstly, they are – by far – the most popular measures of HRQoL used within SAH studies. This meant that only a minimal number of studies had to be excluded (see Figure 2.7, Chapter 2). Secondly, both families of measures (including the ALQI) have been extensively validated and have been found to have satisfactory psychometric properties [59, 137, 138, 295, 731, 734]. Indeed, they are preferable to other HRQoL instruments used in SAH studies, such as the Euroqol [237] and the Nottingham Health Profile [292], as they have been found to illustrate superior sensitivity to gradations in poor health [59].

The use of all of the exclusion criteria in resulted in the inclusion in the meta-analysis of the following 7 traditional predictors of SAH patients' HRQoL: (1) patient age, (2) bleed severity, (3) clinical severity on admission to hospital, (4) post-SAH cognitive impairment, (5) post-SAH physical disability, (6) patient sex and (7) the time between illness onset and HRQoL assessment. In an attempt to increase the number of studies in the meta-analysis, the authors of those articles which were already identified for inclusion, but which had collected data on one (or more) extra predictor(s), but not included it in the original article, were contacted and asked to provide either the effect size or the raw data necessary for calculation. In addition, authors of those studies which had used the SIP or MOS to measure SAH patients' HRQoL, but which had been excluded from the initial systematic review because they had not explicitly examined predictors (Exclusion criteria 6) or because they had merged SAH patient data with that of other patient groups (Exclusion criteria 7), were also contacted. In total, 12 articles were finally included in the meta-analysis on the 7 predictors.

Data Analysis and Extraction

Using a standardized data extraction form, the 12 articles were coded for the following information: author name(s), year of publication, journal, sample size, participants' illness characteristics and population demographics, study context, location of study population and measures used to assess HRQoL and predictors. Each of the articles was examined and standard procedures [580], were used to calculate separate effect sizes for each of the predictors of Mental HRQoL and Physical HRQoL which had been studied. Effect size estimates from the studies for the individual predictors were then combined using the popular random-effects model to create overall estimates of the effect size for each of the predictors [274, 583]. In combining effect size estimates, the greatest weight was given to those estimates from studies with the least variance. It is for this reason that the combined effect size for each predictor is referred to as the weighted effect size. All effect sizes are presented in the familiar scale of the correlation coefficient *r*, along with their 95% confidence interval (CI). This interval reflects the precision of the effect size estimate [580, 582, 583]. An interval which does not incorporate zero indicates a significant effect at P=0.05. For the purposes of all computations, Fisher's [192] z-transformation was applied to the *r*-values from the original studies to normalize their distribution. Cohen's [117] effect size guidelines were used to judge the explanative importance of each predictor. Specifically, effect sizes of .10, .30 and .50 were taken to indicate small, medium and large effect sizes, respectively. Each weighted effect size was squared (R^2) to reflect the amount of variance in either Mental HRQoL or Physical HRQoL that it could explain. Finally, as recent guidelines suggest, the power of each of the meta-analyses to detect the weighted effect size was also calculated [260, 473, 474]. This was done as although it is often implicitly assumed that the issue of

statistical power is not important in meta-analyses, it is as pertinent as in primary studies. Moreover, presenting these figures serves to inform future studies on the topic of SAH HRQoL how large their sample size should be in order to detect certain effects. Muncer et al. [475] suggest that adequate power for a meta-analysis in the context of health-related studies constitutes a value of ≥.50. According to this guide, sufficient power was present in 11 of my meta-analyses, although it should be noted that in the 3 other meta-calculations, the size of the effect which was to be detected was so minute that the statistical power of the analysis was less than satisfactory.

As the studies included in the meta-analyses for each predictor had used diverse methodologies, the random-effects model – rather than the fixed-effects model – was deemed the most suitable for the combining of individual effect sizes. These between-study differences meant that it could not be assumed (as it is in the fixed-effects model) that any variance in effect size estimates between studies on the same predictor was simply due to within study variance (namely, sampling error). Rather, as the random effects model assumes, the true effect size was likely to vary from one study to the next, as a function of both within- and between-study variance. It should be borne in mind therefore, that the overall effect sizes calculated for each predictor using this model represent an estimate of the mean of a population of randomly distributed effect sizes, not an estimate of one true effect size for each of the predictors [149, 257]. As is recognised [621], the weighted effect size estimates produced under a random-effects model tend to be more conservative. For this reason and in order that their importance could be further explored in the meta-analyses, the weighted effect sizes for each predictor were also calculated under the fixed-effect model. Furthermore, weighted estimates were calculated when the influence of significant outlying study estimates was removed. An outlying study was

defined as one whose standardised residual effect size estimate exceeded (+/-) 2.00 [258].

The homogeneity between studies in terms of their effect size estimates for each predictor of Mental and Physical HRQoL was tested using the *Q*-test, with an alpha set of 0.05. The *Q*-test for a given predictor was computed by summing the squared deviations of each study's effect size estimate from the overall effect size estimate, with the contribution of each study weighted by its inverse variance. However, as this test is subject to a lack of power, the parameter *I*-squared (I^2) was also calculated to describe heterogeneity in between study effect sizes as it is not dependent on the number of studies included in the analysis [252, 275]. I^2 represents the percentage of the total variation between studies in effect sizes which was due to heterogeneity rather than chance [272]. Either a significant *Q*-statistic or a I^2 value of >50% was taken to indicate that the effect size estimates for a given predictor were more heterogeneous between studies than expected from sampling error alone [404].

The robustness of the calculated weighted effect size for the predictors from the (potential) impact of publication bias was assessed using the classic fail safe N calculation [581]. Publication bias is the tendency for journals to publish only those studies which report statistically significant results (or those based on larger studies) [156, 396]. Having largely included only published studies in the present meta-analysis, there was the potential that I introduced upward bias into the meta-analysis (i.e. significant effects for the traditional predictors were more likely to have been found than would have been the case if all actual completed studies had been included). For any significant effects detected by the meta-analysis, I therefore used the fail-safe N formulae to determine the number of unpublished (or un-retrieved) studies which on average found no significant effect of the predictor that would be

needed to reduce the significant effect to below the level of significance (alpha set at 0.05). The calculated number of studies was then judged in the context of SAH HRQoL research to evaluate the likelihood that such a number actually existed.

Meta-analysis assumes that the effect size estimates being combined are independent. Consequently, when the same predictor had been assessed within a study using more than one measure (e.g., several measures of physical disability were used), then the average of these effect size estimates was used for the analysis [404, 427, 472]. If a study presented an effect size for the relationship between a predictor and HRQoL from different assessment points, then the effect size for the assessment furthest away from illness onset was used. Such effect sizes, it was felt, would be most representative of the predictor's effect on patients' chronic HRQoL state.

Differences in the instruments used to measure HRQoL and some of the predictors in the studies, meant that higher scores did not always have the same meaning. For example, on the MOS measures, a higher score typically indicates a better HRQoL, whilst the opposite is true for scores on the SIP measures. To address this, when effect sizes were calculated the +/- sign of the *r*-value was changed, which ensured standardisation of the interpretation of the effect sizes. For the purposes of this meta-analysis, a high score on the MOS and SIP measures indicates a better HRQoL. The reader should also note that for the meta-analysis higher scores on the predictor variables, clinical severity, bleed severity, physical disability and cognitive impairment indicated worse neurological state on admission, a more severe bleed, worse physical disability and more cognitive impairment, respectively. Also, in coding the dichotomous variable 'sex', males were always scored as the baseline group. Thus, a positive correlation between sex and HRQoL meant that being female was

associated with a better HRQoL, whilst a negative correlation indicated that being male was associated with a better HRQoL.

The calculation of the effect sizes for a Brazilian study by Rocha-Filo et al. [569] which was included in this meta-analysis deserves mention here. Specifically, one of the standard steps used for the calculation of their patients' MOS Mental HRQoL and Physical HRQoL was not possible to complete exactly as stated by available guidelines [733]. The step that proved troublesome involved all eight of the patients' MOS subscale scores being standardised using a linear z-score transformation. Z-scores are usually calculated by subtracting the MOS subscale means for the local population from each individual's subscale score and then dividing the difference by the standard deviation of the local population. The documented lack of local MOS population scores for Brazil however [717], meant that it was necessary to use non-local normative data for the z-score calculations. My choice of which surrogate normative scores to use was informed by the limited Brazilian MOS normative data which *do* exist. Specifically, unpublished mean MOS scores (and not standard deviations) are available [619] and it is these that were used by Rocha-Filo et al. for crude visual comparisons in their original study. I however, used published normative scores from a large Swedish sample (N=8930) as these were the most comparable to the Brazilian population scores in terms of subscale means [673]. Appendix V presents a breakdown of the exact comparability of the Swedish MOS normative scores (as well as other countries) to those of Brazil.

Tests analogous to analysis of variance were conducted to examine the validity of my having combined effect size estimates for predictors from studies which differed in the HRQoL questionnaire they used. The individual effect sizes for each predictor were grouped according to whether they were derived from a study using

the MOS or the SIP and then contrasted to evaluate whether the measure used, moderated the effect size estimate. Significant heterogeneity was deemed to exist between the two groups' average effect size (Q_B statistic) if their mean effect size differed by more than sampling error [404].

All analyses were conducted using commercially available software (SPSS, Comprehensive Meta Analysis) and the freeware programme G*Power [174].

3.3 Results

Characteristics of the Studies included in the Meta-Analysis

As previously noted, 12 articles (Table 3.1) studying the 7 traditional SAH HRQoL predictors formed the basis of the meta-analysis. Of these articles, 10 had examined the predictor patient age, 9 had examined the predictor sex, 7 had examined clinical severity, 7 physical disability, 6 had studied bleed severity, 4 the time since illness and 3 cognitive impairment. Most of the studies reported in the articles had been conducted in Europe (67%), all were published between 2000 and 2008 (median= 2005) and were typically published in North-American neurological and neurosurgical journals. Most (67%) of the studies had used a MOS questionnaire to measure patients' HRQoL. In terms of their sample characteristics, most studies had focused exclusively on those SAH patients whose haemorrhage was of an aneurysmal origin (75%) and who were in a favourable clinical state on admission to hospital. Sample size ranged from 10 to 573 (median=63, interquartile [IQR] range=33-110). Nine of the 12 studies had assessed the SAH patients' HRQoL at only a single follow-up assessment: 3 studies had assessed SAH patients <6months post-ictus, 1 ≥6-12 months, 2 between 13-23 months and 2 ≥24 months post- SAH. In the studies, the predictor 'physical disability' had been measured using the Glasgow Outcome Scale

Table 3.1 Details of studies included in the meta-analysis

Study	Location	Treatment period	Sample size(s)	HRQoL measure	Follow-up point(s)	Clinical Severity	Bleed severity	Clinical details	Treatment	Age	Sex
Hackett et al.[240]	Australia	1995-1998	174	SF-36 (acute)	1.2	83% HH I-II	-	ASAH; SAHuo	Clipped (46% early)	50.9	Most female
Hop et al. [286]	Netherlands	1995-1996	48	SIP	.33, 1.5	86% WFNS I-II	-	ASAH	-	51.9	70.3% female
Hütter et al.[305]	Germany	1989-1992	116	ALQI	4.0-5.0	57% HH I-II	59% Fisher 4	ASAH	Clipped (74% early)	50.3	66% female
Jönsson et al. [322]	Sweden	2001-2002	10-13	SF-36	.33, 1.3	-	-	-	-	52.0	76.9% female
Katati et al. [336]	Spain	2003-2005	70	SF-36	.33	75.7% HH I-II; 71.4% WFNS I-II	43% Fisher 4	ASAH	Clipped or coiled.	48.9	57% male
King et al. [358]	U.S.	2001-2004	91	SF-12	-	-	-	ASAH	Most clipped.	51.3	Most female
Kreitsch'. [377]	Germany	1997-2002	35	SF-36	2.3	55% HH I-II	65% Fisher 3	ASAH	95% clipped	43.8	65% female

Table 3.1 *cont'd*

Study	Location	Treatment period	Sample size(s)	HRQoL measure	Follow-up point(s)	Clinical Severity	Bleed severity	Clinical details	Treatment	Age	Sex
Mocco et al. [463]	U.S.	1996-2002	35	SIP	.25, 1.0	64% HH IV; 36% HH V.	48% Fisher 3	ASAH	Clipped or coiled.	53.0	Most female
Morris et al. [470]	U.K.	1998-1998	32-49	SF-36	1.2	84% WFNS I-II.	53% Fisher 3	ASAH; SAHuo	77% clipped	45.2	Most female
Rocha-Filo et al. [569]	Brazil	2002-2003	66	SF-36	.4	All GCS 15	-	ASAH	Clipped	44.6	64% female
Scott et al. [613]	U.K.	1994-2002	512-573	FLP	1.0	Most WFNS I-II*	-	ASAH*	Clipped or coiled.	-	-
Tseng et al. [694]	U.K.	2004-2004	60	SF-36	.5	57.4% WFNS I-II.	86.2% Fisher 3-4	ASAH	65% clipped.	52.9	55% female

Note: AUQI=Aachen Life Quality Index; ASAH=aneurysmal subarachnoid haemorrhage; Fisher=Fisher CT grading scale; FLP=Functional Limitations Profile; GCS=Glasgow Coma Scale; HH=Hunt and Hess scale; Kreitsch'=Kreitschmann-Andermahr et al.; SAHuo=subarachnoid haemorrhage of unknown origin; SF-12=Short Form-12; SF-36=Short Form-36; SIP=Sickness Impact Profile; WFNS=World Federation of Neurological Surgeons Grading scale; -=unknown.

(original and extended version) [318, 758], the modified Rankin Scale [550] and the Barthel Index [421]. The predictor 'clinical severity' had been measured using either the World Federation of Neurological Surgeons Scale [164] or the Hunt and Hess Scale [293]. 'Bleed severity' on the other hand, had been measured in all studies using Fisher's CT rating scale [191]. For the measurement of the predictor 'cognitive impairment', one study used the Mini-Mental State Examination [197], a well-known global measure of cognitive impairment which has been found to be a sensitive and reliable measure of post-SAH cognitive dysfunction [354, 357, 438]. The other two studies employed comprehensive batteries of neuropsychological tests chosen primarily on the basis of their proven ability to detect post-SAH impairment [470, 613]. Measures of cognitive impairment, as well as physical disability, were completed almost always at the same appointment at which the patients' completed the HRQoL questionnaires. The measures of physical disability, clinical severity and bleed severity used in the studies included in the meta-analyses are further described in the appendices (Appendices I-IV and VI-VII).

Effect size for predictors of HRQoL

Physical HRQoL

Table 3.2 presents the weighted effect size estimates for the 7 traditional predictors of Physical HRQoL which were calculated using the random effects model. As can be seen, the weighted effect size for 6 of the 7 variables proved to be significantly associated with SAH patients' Physical HRQoL. Older age ($Z= -4.15$, $P<0.001$), a more severe bleed ($Z= -3.86$, $P<0.001$), a worse neurological state on admission to hospital ($Z= -2.88$, $P<0.001$), more post-SAH cognitive impairment ($Z= -3.42$,

Table 3.2 Summary of weighted effect sizes for predictors of Physical HRQoL

Predictor	r_w	R^2_w	No. of studies	Population size	CI		Q-statistic	Fail-safe N	Power
Age	-.20***	4.00%	10	1224	-.29	-.10	17.71*	87	1.00
Bleed severity	-.13***	1.69%	6	879	-.20	-.06	4.67	8	.98
Clinical severity	-.19***	3.61%	7	1055	-.30	-.06	18.22**	43	.99
Cognitive impairment	-.14***	1.96%	3	615	-.22	-.06	0.03	3	.96
Physical disability	-.54***	29.2%	7	865	-.63	-.44	13.74*	413	1.00
Sex	-.13*	1.69%	9	1070	-.24	-.02	19.29*	30	.99
Time since illness	.09	0.81%	4	127	-.12	.30	6.88	-	.26
Total		42.96%							

Note: CI=confidence interval; No.=number;r_w=weighted correlation coefficient (r_w=0.10, r=0.30 and r=0.50 are small, medium and large effect sizes, respectively); R^2_w.=variance explained; *=P<0.05; **=P<0.01; ***=P<0.001. For the dichotomous variable 'sex', males were scored as the baseline group. Thus, a positive correlation means that being female was associated with a better HRQoL, whilst a negative correlation indicates the opposite.

P<0.001), greater physical disability (Z= - 8.75, P<0.001) and being female (Z= -2.32, P<0.05) were all associated with a worse Physical HRQoL. Information about the time which had elapsed between a patient's SAH and assessment of their HRQoL was not significantly associated with SAH patients' Physical HRQoL: Z= 0.86, P>0.05. Importantly, with the exception of physical disability, the size of the effect of the significant predictors of Physical HRQoL was minimal, with each of these predictors being able to account for only 1.69-4% of the variance in patients' Physical HRQoL scores. As noted above, physical disability was the exception. It was found to have a

uniquely large predictive effect on SAH patients' Physical HRQoL. With a weighted effect size of-.54, this variable could, by itself, account for approximately 29% of variance in the SAH patients' Physical HRQoL.

The size of the fail-safe Ns associated with the predictors which were significantly associated with Physical HRQoL (see Table 3.2), suggests that most of these effects, namely age, clinical severity, physical disability and sex, were not susceptible to the potential influence of publication bias. The need for only a small number of studies to nullify the significance of the relationships that bleed severity and cognitive impairment hold with Physical HRQoL does however, raise the possibility that these variables' significant association with Physical HRQoL may not be reliable.

Figures 3.4 - 3.10 present Forrest plots for each of the traditional predictors of Physical HRQoL, illustrating the individual effect sizes found in each study included in the meta-analysis. Importantly, as these figures illustrate, the weighted effect size estimates for each of the traditional HRQoL predictors did not substantially change when calculated under the less constrained fixed-effect model or when the influence of outlying effect size/s had been removed. The heterogeneity statistics presented in Table 3.2 and Figures 3.4 - 3.10 indicate that 4 of the 7 predictors – namely, patient age (Q=17.71 (9), P<0.05; I^2= 49%), clinical severity (Q= 18.22 (6), P<0.01; I^2= 67%), physical disability (Q=13.74 (6), P<0.05; I^2= 56%) and sex (Q=19.29 (8), P<0.05; I^2= 59%) – did not uniformly predict Physical HRQoL between studies. This underlines that the use of the random-effects model was most appropriate.

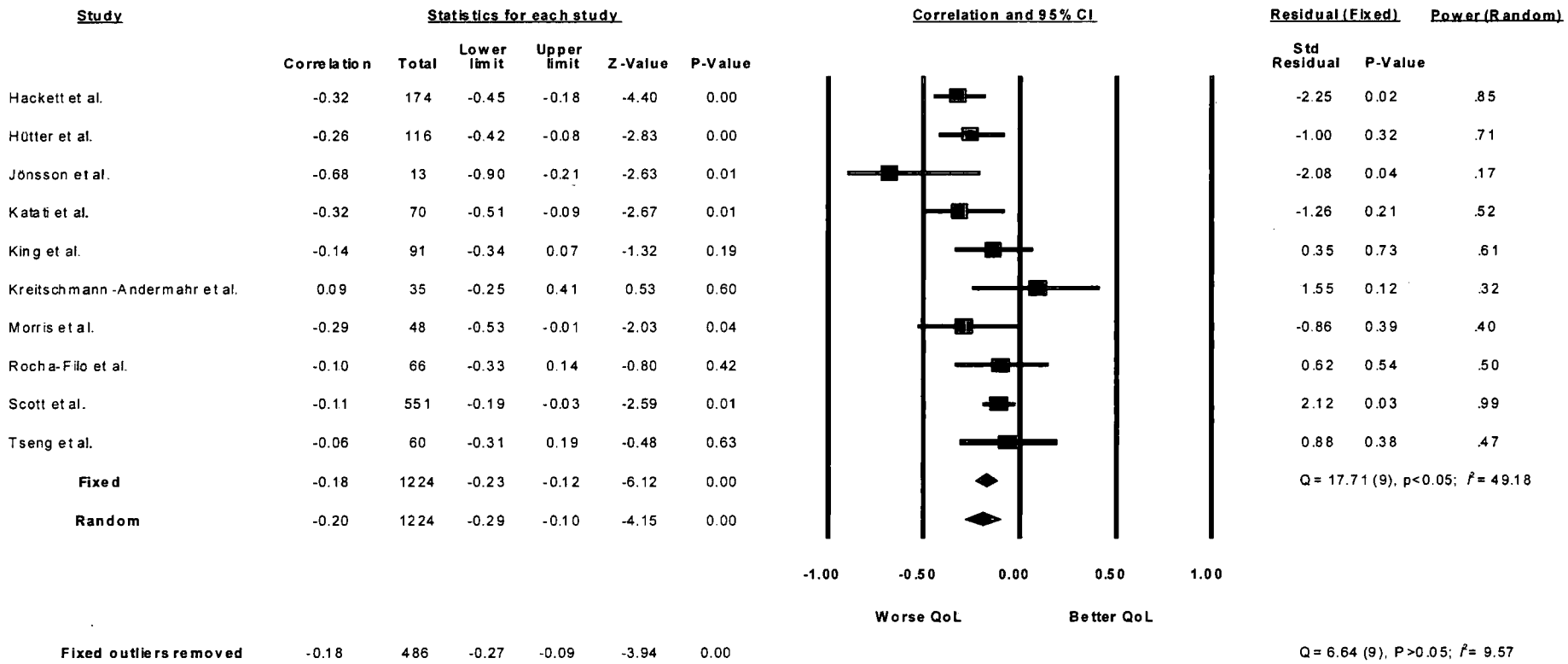

Figure 3.4 Forrest plot of effect size estimates of individual studies examining the association between age and Physical HRQoL.

Note: A negative correlation indicates that increasing age was associated with worse Physical HRQoL.

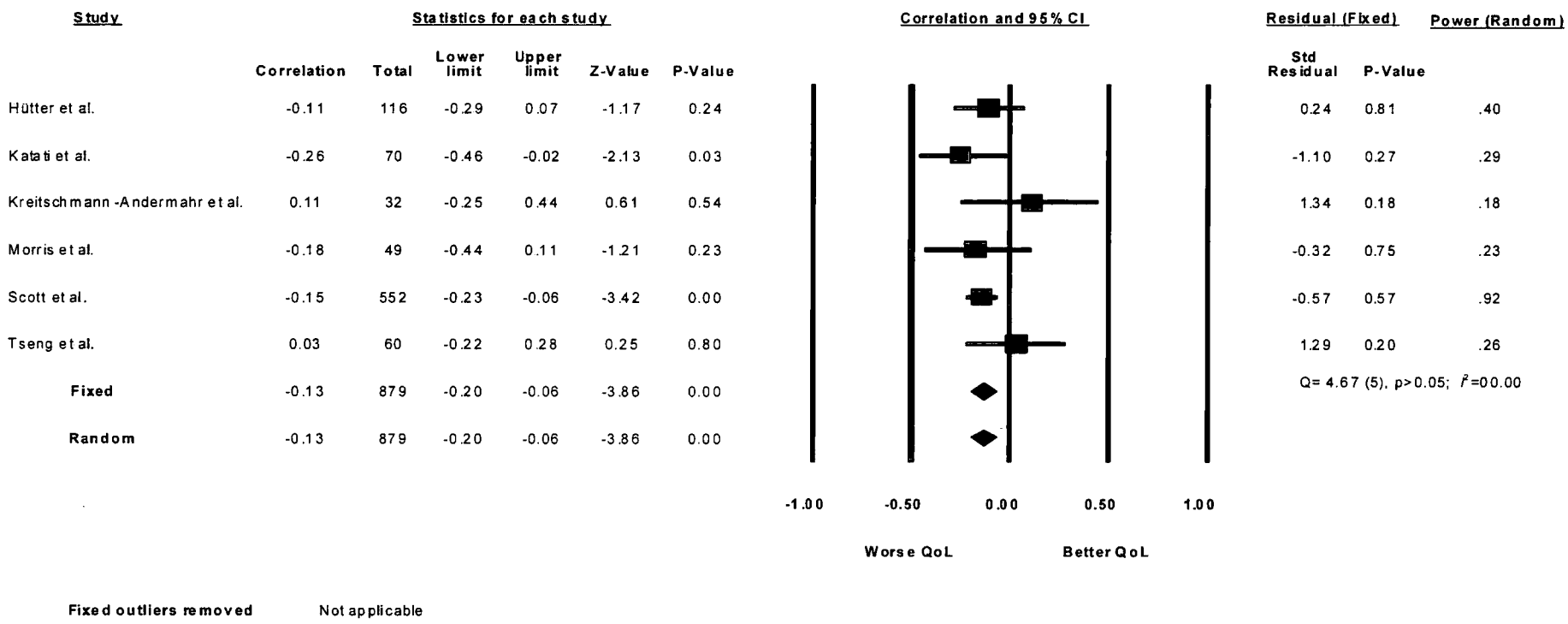

Figure 3.5 Forrest plot of effect size estimates of individual studies examining the association between bleed severity and Physical HRQoL.

Note: A negative correlation indicates that increasing bleed severity was associated with worse Physical HRQoL.

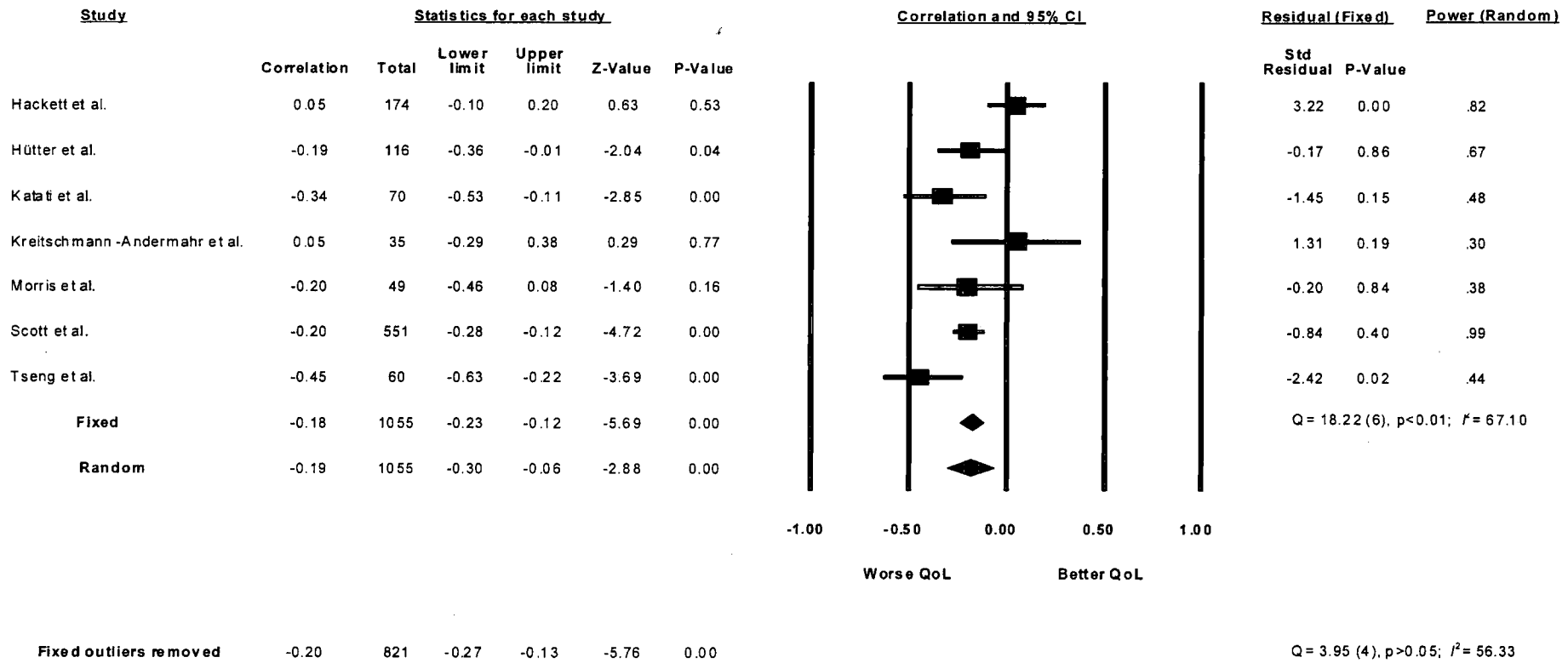

Figure 3.6 Forrest plot of effect size estimates of individual studies examining the association between clinical severity and Physical HRQoL.

Note: A negative correlation indicates that increasing clinical severity was associated with worse Physical HRQoL.

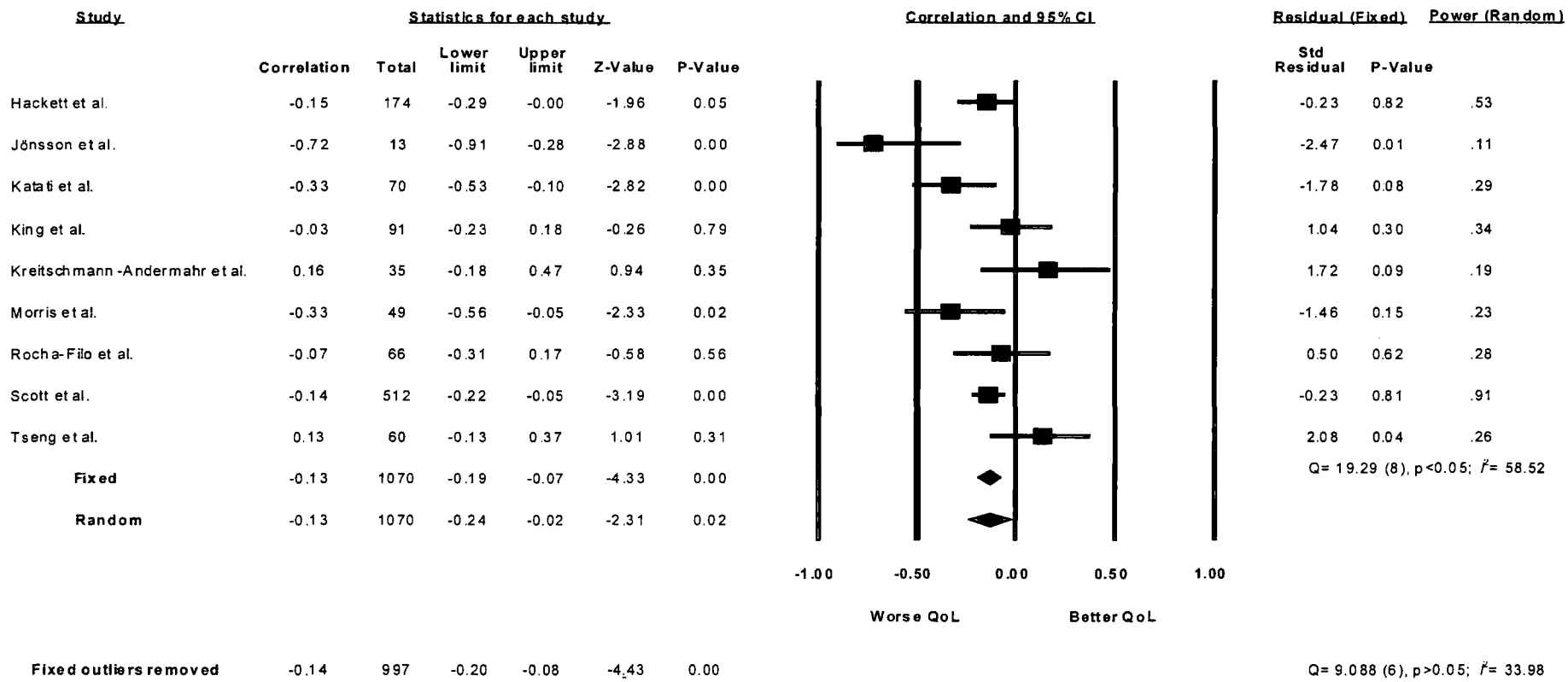

Figure 3.7 Forrest plot of effect size estimates of individual studies examining the association between sex and Physical HRQoL.

Note: For the dichotomous variable 'sex', males were scored as the baseline group. A negative correlation thus means that being female was associated with a worse Physical HRQoL.

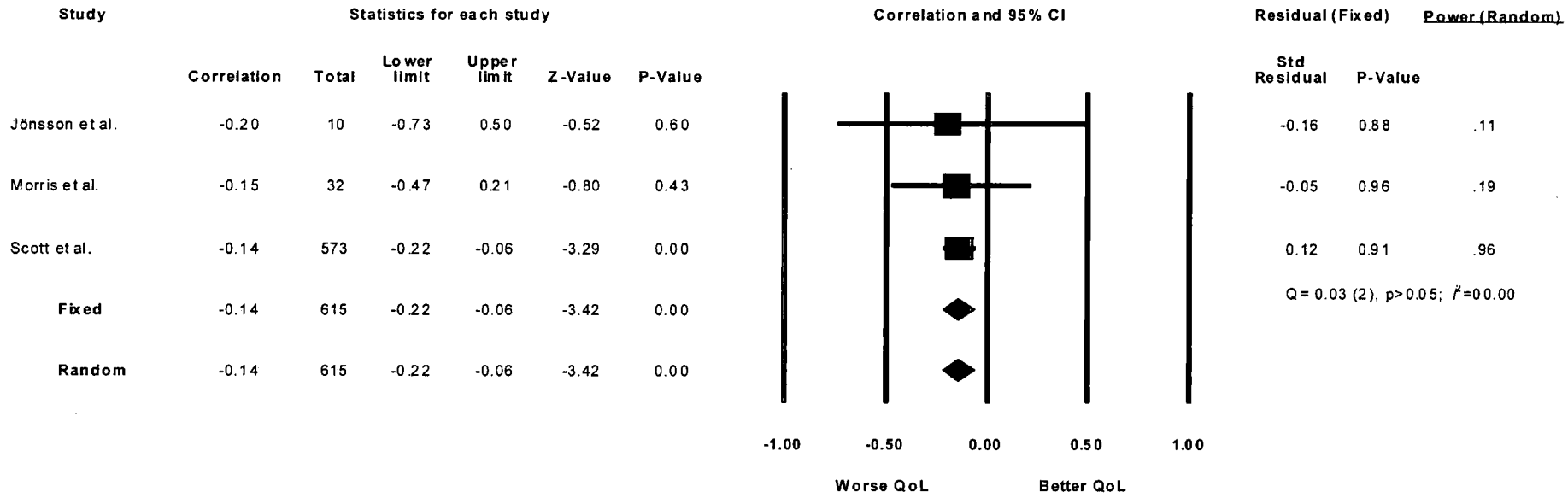

Figure 3.8 Forrest plot of effect size estimates of individual studies examining the association between cognitive impairment and Physical HRQoL.

Note: A negative correlation indicates that increasing cognitive impairment was associated with worse Physical HRQoL.

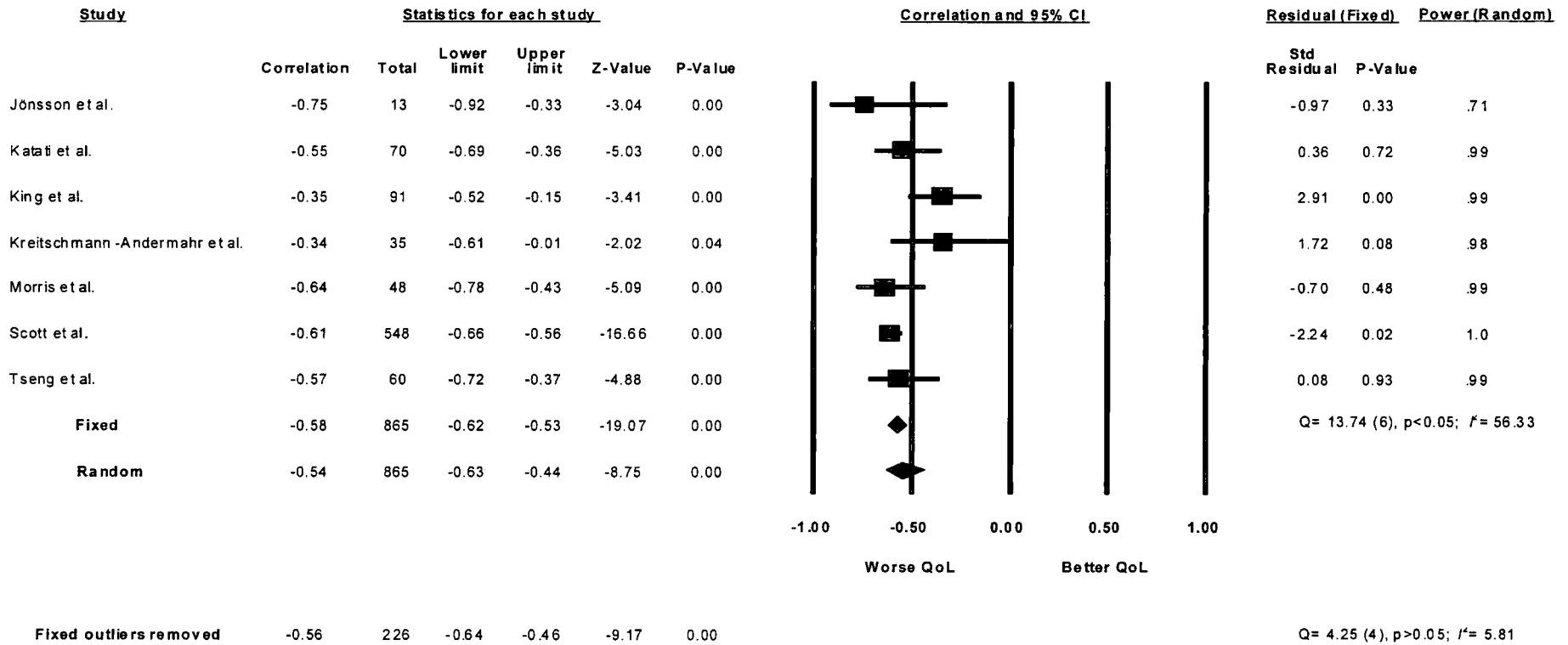

Figure 3.9 Forrest plot of effect size estimates of individual studies examining the association between physical disability and Physical HRQoL.

Note: A negative correlation indicates that increasing physical disability was associated with worse Physical HRQoL.

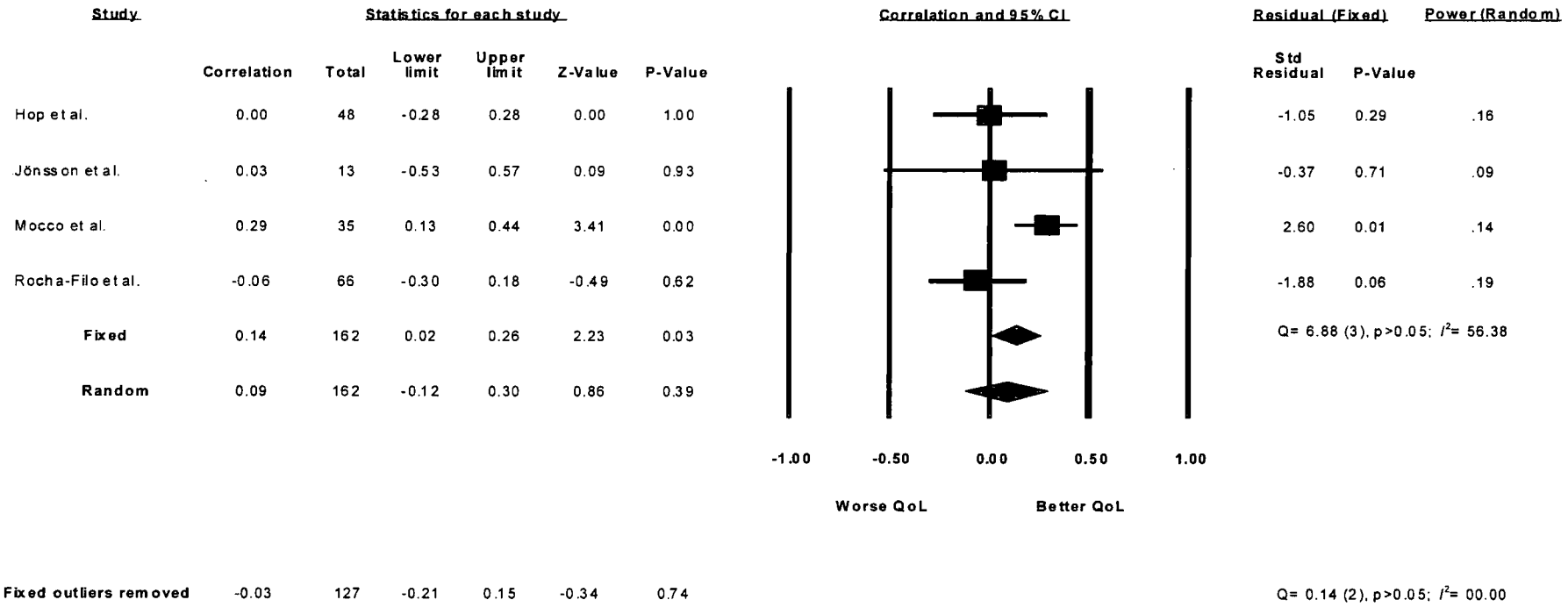

Figure 3.10 Forrest plot of effect size estimates of individual studies examining the association between the time between illness onset and assessment and Physical HRQoL.

Note: A positive correlation indicates that the longer the time between the HRQoL assessment and illness onset, the better the Physical HRQoL.

Mental HRQoL

Table 3.3 presents the weighted effect size estimates for each of the traditional predictors for patients' Mental HRQoL. Of all the predictors, only cognitive impairment proved to be significantly associated with patients' Mental HRQoL: Z= -3.26, $P<0.001$

Table 3.3 Summary of weighted effect sizes for predictors of Mental HRQoL

Predictor	r_w	R^2_w	No. of studies	Population size	CI		Q-statistic	Fail-safe N	Power
Age	0.07	0.59%	10	1225	-0.03	0.17	19.42*	-	.79
Bleed severity	0.01	0.01%	6	879	-0.13	0.14	12.38*	-	.08
Clinical severity	-0.08	0.64%	7	1044	-0.18	0.03	12.72*	-	.82
Cognitive impairment	-0.13***	1.69%	3	615	-0.21	-0.05	0.80	n/p	.94
Physical disability	-0.15	2.25%	7	866	-0.46	0.18	93.69***	-	.99
Sex	-0.05	0.25%	9	1070	-0.17	0.08	24.55**	-	.49
Time since illness	0.10	1.0%	4	162	-0.09	0.29	5.26	-	.35
Total		6.43%							

Note: CI=confidence interval; No.=number; n/p=calculation not possible due to differences between the formulae for classic fails safe N and modern meta analysis means that according to fail-safe formulae the weighted effects size was not statistically significant and so the fail safe N not computable; r_w= weighted correlation coefficient (r_w=0.10, r =0.30 and r =0.50 are small, medium and large effect sizes, respectively); R^2_w.= variance explained; *=$P<0.05$, **=$P<0.01$; ***=$P<0.00$. For the dichotomous variable 'sex', males were scored as the baseline group. A positive correlation thus means that being female was associated with a better HRQoL, whilst a negative correlation indicates the opposite.

(fail-safe N not calculable, see Discussion for comment). The weighted effect size estimate for this predictor was, nevertheless, still small (weighted r= -.13) – with cognitive impairment being able to account for only 1.69% of variance in SAH patients' Mental HRQoL. The Forest plots in Figures 3.11 - 3.17 illustrate that the effect size estimates for each of the predictors calculated using the random-effects model were comparable to those calculated using the fixed-effect model. Moreover, they were also comparable when calculated with any study with an outlying effect size estimate having been removed. It is also seen that significant heterogeneity existed in effect size estimates between studies for the predictors: patient age (Q=19.42 (9), P<0.05; I^2=54%), bleed severity (Q=12.38 (5), P<0.05; I^2=60%), clinical severity (Q=12.72 (6), P<0.05; I^2=53%), physical disability (Q=93.69 (6), P<0.001; I^2=94%) and sex (Q=24.55 (8), P<0.01; I^2=67%).

Validity of combining effect sizes from studies using the MOS and studies using the SIP

Tables 3.4 and 3.5 report the results from the analyses which examined whether the HRQoL measure used by a study moderated the effect size estimate which it found for a given predictor. The results show that in the vast majority of cases, the effect size estimates were homogenous between studies using different HRQoL measures. This result provides evidence that in most cases, it was valid to combine the results from studies using the SIP measure with the results from studies using MOS measures. Although no significant effect was found for any of the predictors of Physical HRQoL, significantly different effect size estimates were produced by studies

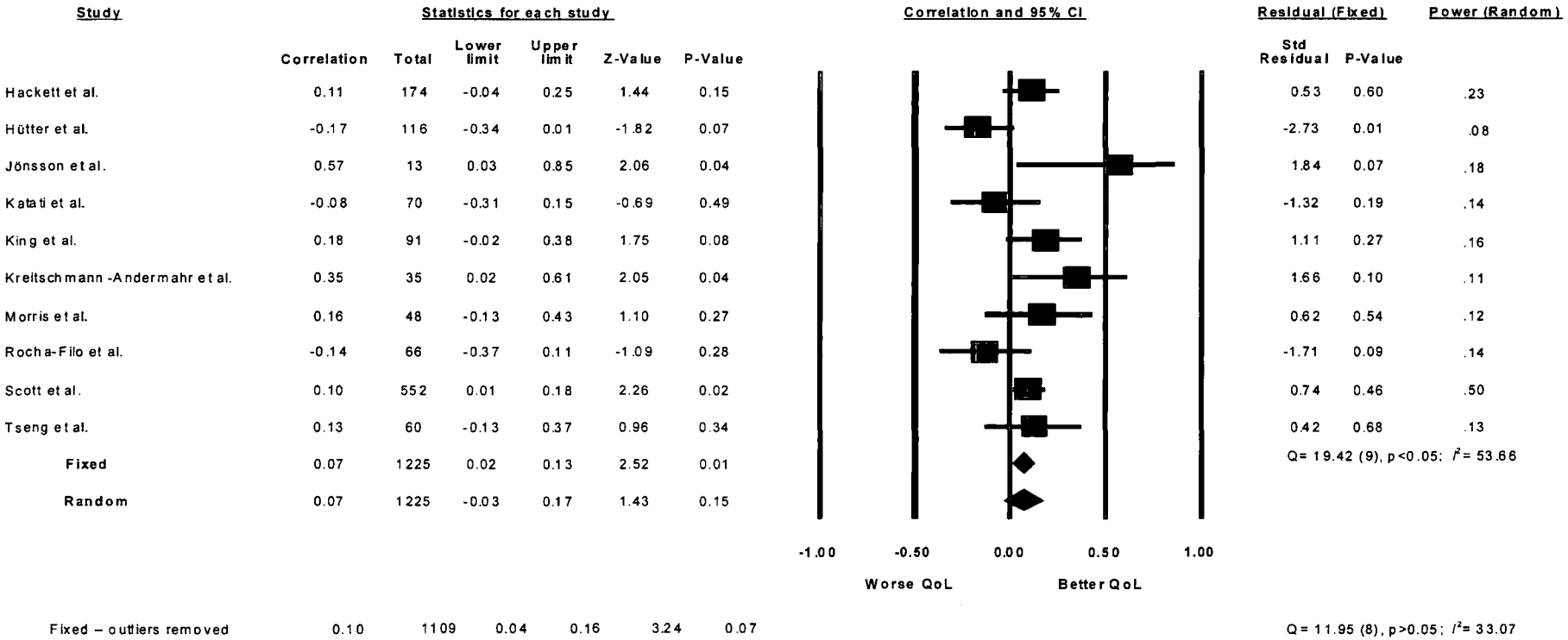

Figure 3.11 Forrest plot of effect size estimates of individual studies examining the association between age and Mental HRQoL.

Note: A negative correlation indicates that increasing age was associated with worse Mental HRQoL.

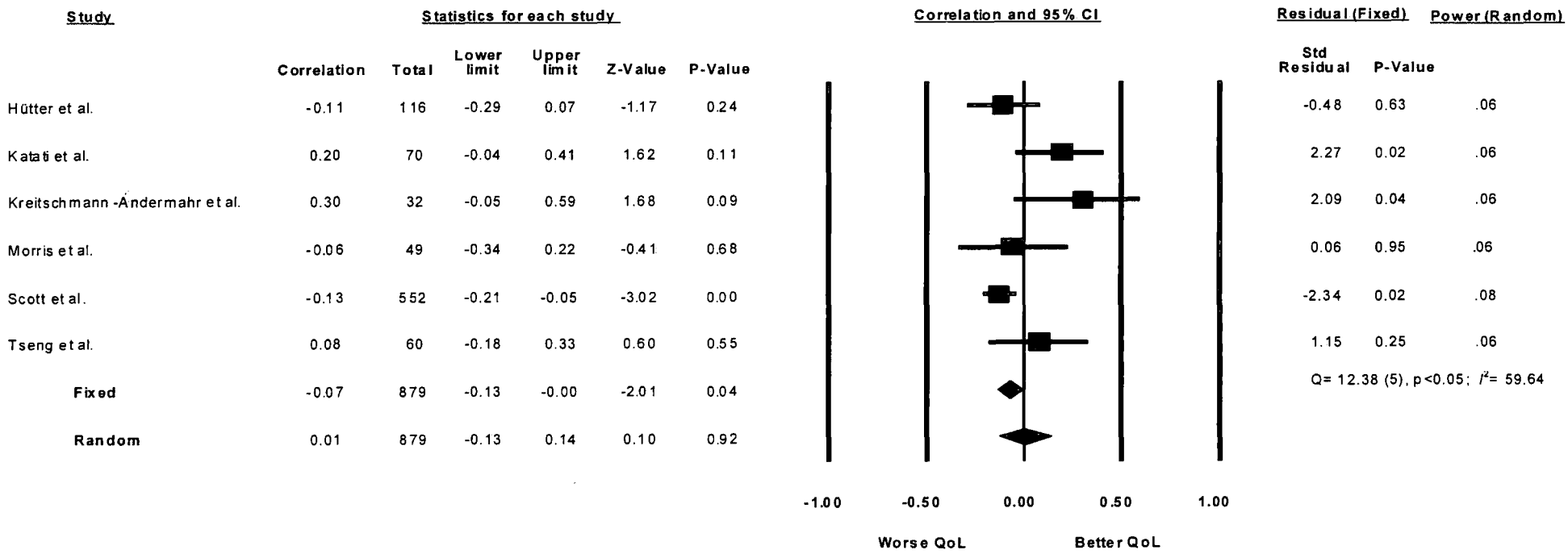

Figure 3.12 Forrest plot of effect size estimates of individual studies examining the association between bleed severity and Mental HRQoL.

Note: A negative correlation indicates that increasing bleed severity was associated with worse Mental HRQoL.

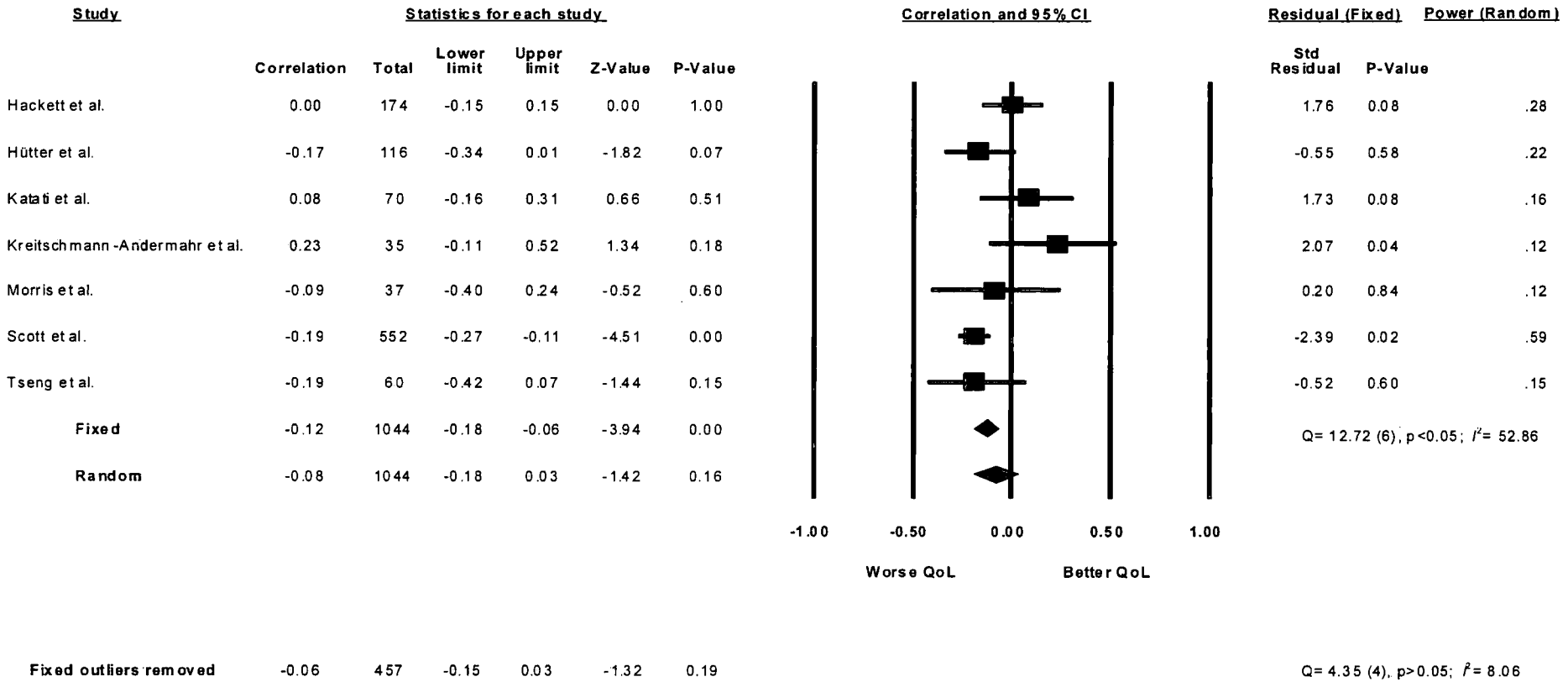

Figure 3.13 Forrest plot of effect size estimates of individual studies examining the association between clinical severity and Mental HRQoL.

Note: A negative correlation indicates that increasing clinical severity was associated with worse Mental HRQoL.

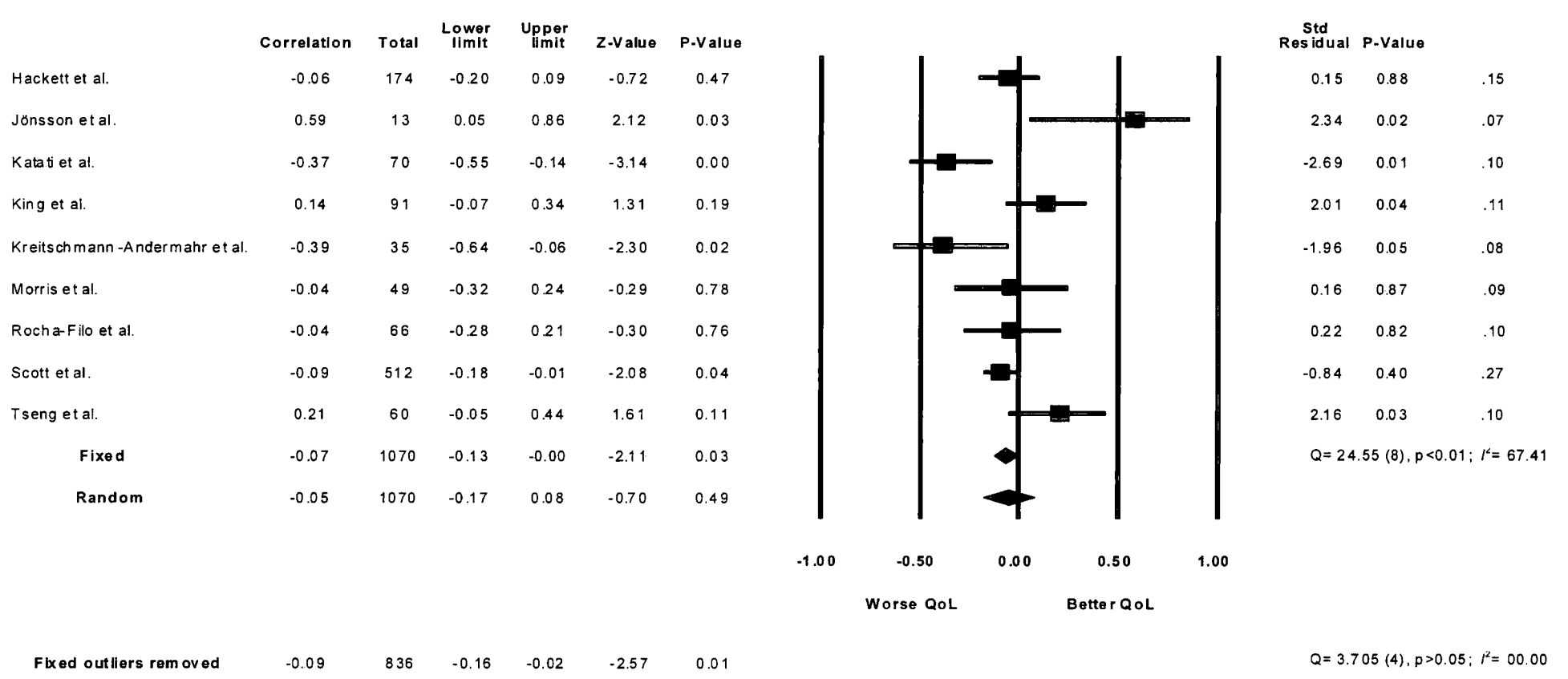

Figure 3.14 Forrest plot of effect size estimates of individual studies examining the association between sex and Mental HRQoL.

Note: For the dichotomous variable 'sex', males were scored as the baseline group. A negative correlation thus means that being female was associated with a worse Mental HRQoL.

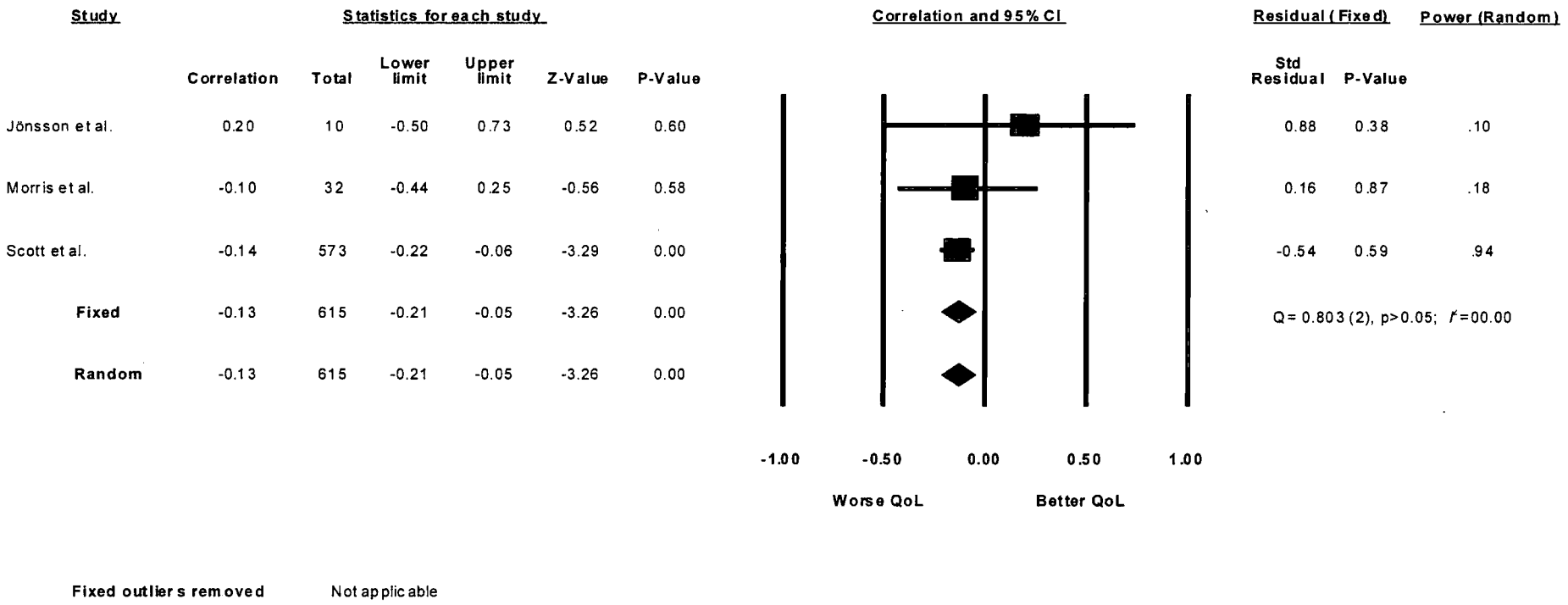

Figure 3.15 Forrest plot of effect size estimates of individual studies examining the association between cognitive impairment and Mental HRQoL.

Note: A negative correlation indicates that increasing cognitive impairment was associated with worse Mental HRQoL.

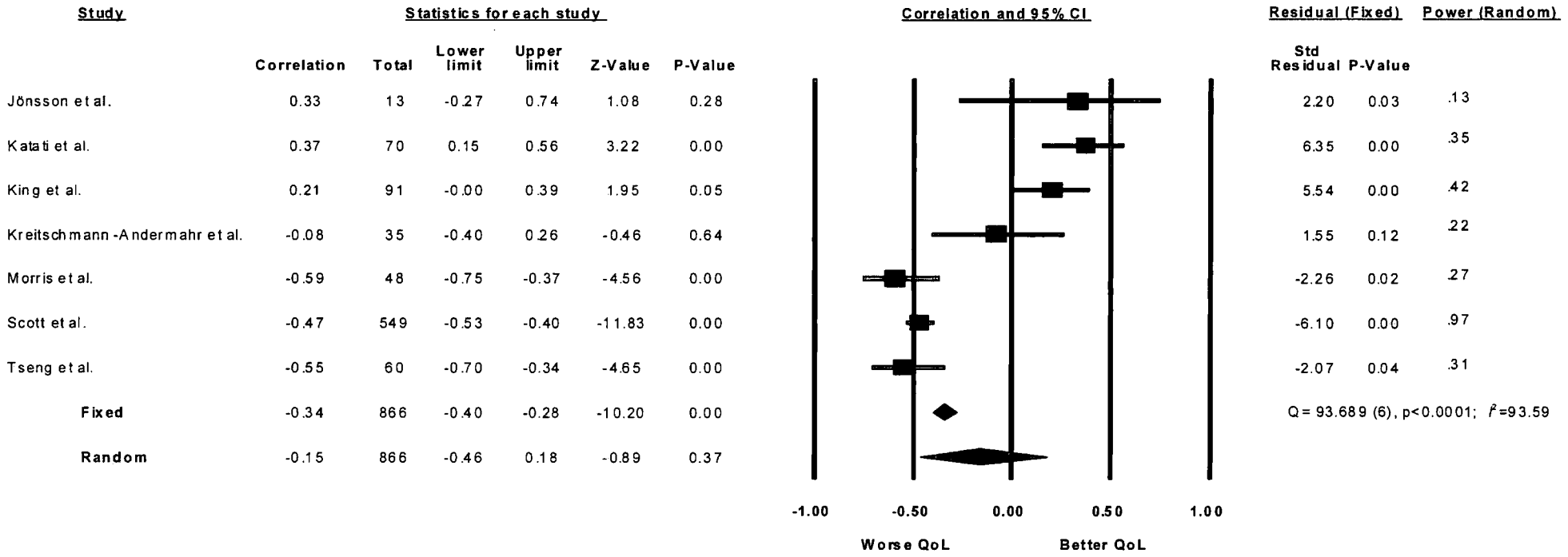

Figure 3.16 Forrest plot of effect size estimates of individual studies examining the association between physical disability and Mental HRQoL.

Note: A negative correlation indicates that increasing physical disability was associated with worse Mental HRQoL.

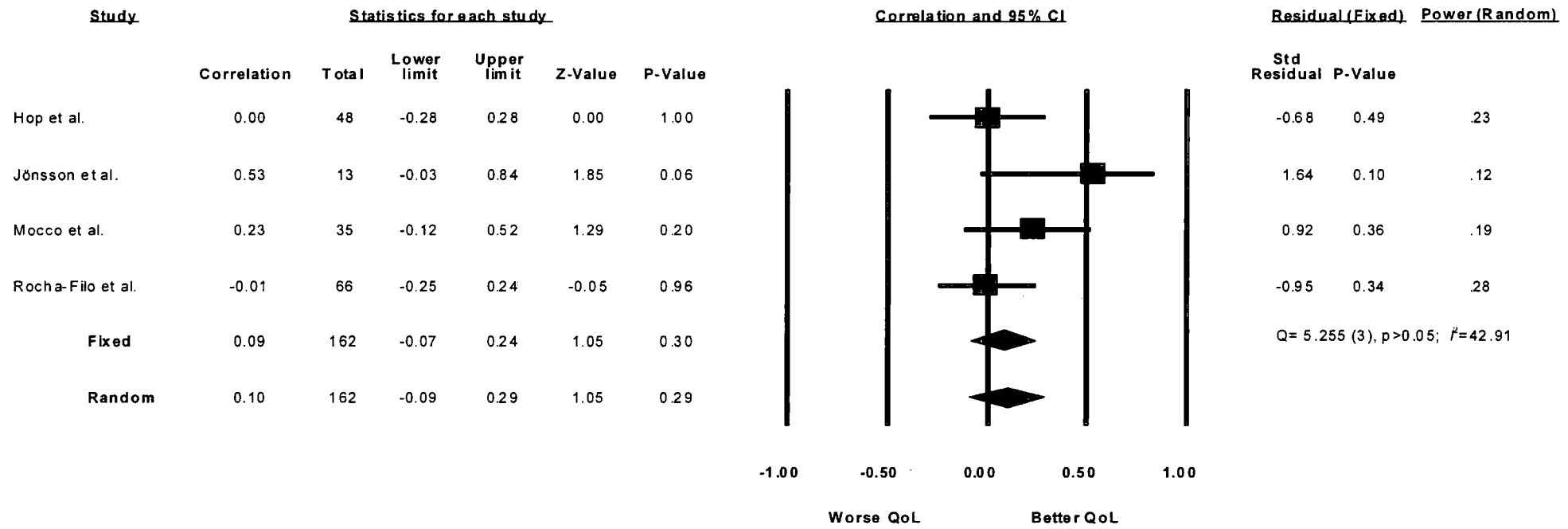

Figure 3.17 Forrest plot of effect size estimates of individual studies examining the association between the time between illness onset and assessment and Mental HRQoL.

Note: A positive correlation indicates that the longer the time between the HRQoL assessment and the illness' onset, the better the Physical HRQoL.

using the two sets of measures when examining the relationship between bleed severity and Mental HRQoL (MOS weighted r= .12; SIP weighted r= -.12; P<0.01) and between clinical severity and Mental HRQoL (MOS weighted r= -.002; SIP weighted r=-.19; P<0.01). The difference in effect sizes produced by studies using the different measures was .24 for bleed severity and .18 for clinical severity.

Table 3.4 Moderating effect of HRQoL measure on predictors of Physical HRQoL

Predictor	Measure	Studies	Correlation	Lower Limit	Upper Limit	Z-value	Between group heterogeneity
Age	MOS measure	8	-0.21***	-0.32	-0.09	-3.50	
	SIP measure	2	-0.17	-0.34	0.01	-1.90	Q_B=0.14 (1)
Bleed severity	MOS measure	4	-0.10	-0.24	0.04	-1.38	
	SIP measure	2	-0.14**	-0.23	-0.04	-2.78	Q_B=0.17 (1)
Clinical severity	MOS measure	5	-0.18*	-0.35	-0.1^{E-02}	-1.98	
	SIP measure	2	-0.19	-0.42	0.05	-1.56	Q_B=0.01 (1)
Cognitive impairment	MOS measure	2	-0.16	-0.45	0.17	-0.95	
	SIP measure	1	-0.14***	-0.22	-0.06	-3.29	Q_B=0.01 (1)
Physical disability	MOS measure	6	-0.51***	-0.62	-0.39	-7.12	
	SIP measure	1	-0.61***	-0.75	-0.43	-5.40	Q_B=0.87 (1)
Sex	MOS measure	8	-0.14	-0.28	0.01	-1.79	
	SIP measure	1	-0.14	-0.45	0.20	-0.82	Q_B=0.00 (1)
Time since illness	MOS measure	2	-0.04	-0.33	0.25	-0.29	
	SIP measure	2	0.19	-0.03	0.39	1.66	Q_B=1.52 (1)

Note: MOS=Medical Outcome Study Short Form questionnaires – either Short Form-36 or Short Form-12; SIP=Sickness Impact Profile questionnaires – Sickness Impact Profile-136 or Aachen Life Quality Index; *=P<0.05.; **=P<0.01; ***=P<0.001.

Table 3.5 Moderating effect of HRQoL measure on predictors of Mental HRQoL

Predictor	Measure	Studies	Correlation	Lower Limit	Upper Limit	Z-value	Between group heterogeneity
Age	MOS measure	8	0.11	-0.02	0.24	1.70	
	SIP measure	2	-0.02	-0.22	0.19	-0.16	Q_B=1.10 (1)
Bleed severity	MOS measure	4	0.12	-0.02	0.25	1.70	
	SIP measure	2	-0.12***	-0.20	-0.05	-3.23	Q_B=9.29 (1)**
Clinical severity	MOS measure	5	-0.2^{E-02}	-0.11	0.10	-0.05	
	SIP measure	2	-0.19***	-0.26	-0.11	-4.86	Q_B=8.11(1)**
Cognitive impairment	MOS measure	2	-0.04	-0.36	0.27	-0.27	
	SIP measure	1	-0.14***	-0.22	-0.06	-3.29	Q_B=0.29 (1)
Physical disability	MOS measure	6	-0.09	-0.45	0.30	-0.43	
	SIP measure	1	-0.47	-0.89	0.39	-1.08	Q_B=0.68 (1)
Sex	MOS measure	8	-0.03	-0.20	0.14	-0.36	
	SIP measure	1	-0.09	-0.45	0.29	-0.46	Q_B=0.78 (1)
Time since illness	MOS measure	2	0.16	-0.22	0.49	0.81	
	SIP measure	2	0.11	-0.24	0.43	0.60	Q_B=0.04 (1)

Note: MOS=Medical Outcome Study Short Form questionnaires – either Short Form-36 or Short Form-12; SIP=Sickness Impact Profile questionnaires – Sickness Impact Profile-136 or Aachen Life Quality Index; *=P<0.05; **=P<0.01; ***=P<0.001.

3.4 Discussion

This chapter has presented a study which used the techniques of meta-analysis to comprehensively examine the practical explanative importance of the variables traditionally used to explain SAH patients' reduced HRQoL – namely, patient's (1) age, (2) severity of bleed, (3) clinical severity on admission to hospital (4) post-SAH

cognitive impairment (5) physical disability, (6) sex and (7) the time occurring between the SAH and the assessment of HRQoL.

In respect to SAH patients' Physical HRQoL, the results from the meta-analysis showed that all, but one, of the traditional predictors were significantly related to patients' Physical HRQoL in terms of their *P*-values. Increasing age, a more severe haemorrhage, worse clinical status on admission to hospital, being female, and more cognitive impairment and physical disability were all (from a statistical perspective) significantly associated with a worse Physical HRQoL. The weighted effect sizes for 6 of these predictors calculated under random effects models showed that the practical importance of these variables was nevertheless typically small, thus emphasising the importance of not solely relying on *P*-values when judging importance. The variables could typically each explain only 2- 4% of actual variance in SAH patients' Physical HRQoL scores (effect sizes ranged -.13 to -.20). The exception to the rule was the degree of physical disability which the patient experienced. Physical disability, it was found, was an important predictor of Physical HRQoL, both statistically and practically. The variable physical disability could by itself, account for approximately 30% of variance in patients' Physical HRQOL scores (weighted r= -.54).

In striking contrast to the numerous significant predictors of Physical HRQoL, only 1 of the 7 traditional predictors – namely, cognitive impairment – proved to be associated with SAH patients' Mental HRQoL scores. Increasing cognitive impairment was seen to be associated with worse Mental HRQoL. The magnitude of this effect was however still small, with it explaining less than 2% of variance in patients' Mental HRQoL (weighted r= -.13).

To further examine the explanative value of the 7 traditional predictors for SAH HRQoL, the total variance accounted for by each of these predictors (i.e., the square of their weighted effect size [$R^2_{w.}$]) was summed together, regardless of whether or not an effect had proved statistically significant. It was found that together, the 7 variables could explain approximately 43% of variance in SAH patients' Physical HRQoL, but only 6% of variance in patients' Mental HRQoL scores. Consequently, a large proportion of variance in SAH patients' Physical HRQoL can be accounted for (although over 55% still remains mysterious), but nearly 95% of variance in SAH patients' Mental HRQoL remains unexplained. In fact, two reasons mean that the estimates of the total variance explained in Physical and Mental HRQoL by the traditional predictors could actually be too high. Firstly, it remains to be established whether the variance explained by each of the contributing predictors is actually unique. The summed R^2_w values were based on the squaring of the individual weighted effect sizes which are simply zero-order correlations . Given that many of the predictors are closely related to one another, it is highly plausible that much of the variance accounted for by the individual predictors was actually shared. Clinical severity on admission is known for instance, to be largely the function of the severity of a patient's bleed [711], whilst neurological impairment is known to be related to age, clinical severity and bleed severity [306]. The other reason for the estimate of total explained variance possibly being too high, is that I included in its calculation the effect sizes for all predictors regardless of whether they had proved to be statistically significant or not in the meta-analysis. A more conservative approach of including only those predictors which had actually proved significant and were not chance results would have reduced the variance explained. However, as noted earlier in the 'Data Analysis and Extraction' section of this chapter, the diminutive size of some of

the effects meant that despite the large sample size, in a few instances the power of the analysis was below the desired level (<.50). Given the resultant elevated chance of committing a Type II error for these particular predictors, I felt it wise to adopt a more relaxed inclusion criteria.

The findings of this meta-analysis are clear: Traditional predictors of SAH patients' HRQoL on the whole, demonstrate minimal predictive ability and cannot satisfactorily explain the concerning reduction in HRQoL which many of these patients illustrate. All traditional predictors (except physical disability when predicting Physical HRQoL) had only a small effect size ($r \leq .20$). These findings strongly suggest that the hypothesis that traditional predictors could actually explain patients' mysterious HRQoL reduction if only studies were sufficiently powered and considered more than statistical significance, cannot be supported. These findings strongly support the possibility that the reason researchers have struggled to explain SAH HRQoL is because they have so far failed to consider more novel aspects of these patients' outcome – aspects such as their psychiatric disturbance.

The failure of cognitive and physical disability and clinical information to explain the vast majority of SAH patients' profoundly low levels of HRQoL, although likely surprising to many people, is in fact, quite understandable. In terms of neurological sequelae, whilst important neurological changes *do* occur post-SAH – and we know from the wider literature that neurological impairment can be debilitating [35, 61, 180, 282, 344, 523, 719] – the actual nature of SAH patients' impairment tends only to subtle. Mild to moderate cognitive impairment is only revealed by the most complex of cognitive tasks [295, 541, 750] and profound physical disability is uncommon [220, 295, 302, 382, 398, 460]. It would be surprising therefore, if such mild impairment were to account for the profoundly poor HRQoL which SAH patients

experience. Indeed, testimony to the unhelpfulness of using neurological disability to explain SAH patients' HRQoL, are the findings reported by Pritchard et al. [545]. These researchers compared SAH patients' HRQoL to that of a group of patients with an acoustic neuroma (a benign form of brain tumour which develops on the vestibulocochlear nerve) who were broadly similar in demographics. It was reported that despite the acoustic neuroma patients experiencing greater neurological disability, it was the SAH patients who reported significantly worse HRQoL. The failure of clinical information to explain HRQoL even though it can explain immediate aspects of outcome after an SAH, is also in line with research on other health conditions (including other types of stroke). In several studies it has been suggested that those factors affecting long-term outcome are often different to those affecting immediate outcome [524, 759, 763]. The lack of a meaningful relationship between aspects of clinical information, such as patient age and sex, and HRQoL is even less surprising as in health psychology in general, it is recognised that the influence of these factors on HRQoL though significant, is not profound [10, 179].

It is important to note that the results and conclusions of this meta-analytic study do, however, need to be considered in the context of some potential limitations. Firstly, the inclusion of diverse studies meant that there was often a lack of homogeneity existing between studies in terms of their effect size estimates. This means that there is the possibility that the calculated weighted effect sizes for the predictors could be unrepresentative of their true effect size. As is typical for clinical research, the methodology often varied between the studies included in the meta-analyses and so this is a possible cause for the heterogeneity in effect size estimates for the same predictor. Unfortunately, the small number of studies which have so far examined SAH HRQoL and which were available for inclusion in the meta-analysis,

meant that there was not sufficient statistical power to formally examine which, if any, of the studies' methodological features moderated the effect size for predictors [259]. As is often the case in meta-analysis, there were simply too few studies to compare studies with different methodological aspects in a meaningfully way [273, 583]. As further empirical studies accumulate, patterns in effect sizes will possibly emerge and moderating variables identified [157, 256, 273]. The search for these moderator variables could however, be protracted given that the relative infrequency and high mortality of SAH means that generating a sufficient sample size to complete a HRQoL study can be difficult. It should also be noted that no index of the studies' methodological qualities was used because such indices remain to be validated for observational studies [323, 385, 404]. It is important to note however, that the standard degree of heterogeneity for the predictors was only moderate. Higgins and Thompson [275] who developed the I^2 measure used in this study to index heterogeneity, for example, suggested that notable heterogeneity constituted an I^2 value *substantially* greater than 50 percent. For the predictors included in this meta-analysis, the median heterogeneity value for Physical HRQoL was only 56.33 (IQR=00.00-58.52) and 52.86 (IQR=29.64-67.41) for Mental HRQoL. Moreover, as I previously noted, the re-calculated effect sizes under the fixed-effect model when outlying studies were removed, were broadly similar. Nevertheless, one instance in which substantial and significant heterogeneity in effect sizes did exist warrants comment. Specifically, it was found that the effect of physical disability when predicting Mental HRQoL illustrated a large amount of heterogeneity (see Figure 3.16), with some studies finding that physical disability was associated with worse Mental HRQoL (up to -.59), whilst an equal number of studies found a positive effect on Mental HRQoL (up to .37). This discrepancy is hard to explain. One obvious

explanation could be that a data entry mistake occurred, especially given that high scores on the different measures of physical disability which studies used did not always carry the same meaning (e.g., a high score on the Barthel Index in its original format indicates less disability, whilst the opposite is true for the modified Rankin Scale). A re-examination of the data however, showed that the scoring directions had been suitably standardised. Methodological characteristics of the divergent studies also do not seem to explain the discrepancy, with the studies being similar in terms of the samples they studied, the instruments they used and the timing of their HRQoL assessment. The only discernible difference between the studies finding the different effects is that those reporting a negative impact of physical disability on Mental HRQoL were conducted in the U.K. and that two of these were conducted as part of clinical trials. Still, it is hard to see how this can explain the appreciable discrepancy, even if the potential for increased bias resulting from demand characteristics introduced as part of a trial are considered. Instead, the explanation for what moderates the impact of physical disability on SAH patients' Mental HRQoL needs to await further study. The large discrepancy between the two groups of studies in their effect size estimates does nevertheless, raise the possibility that the actual effect of physical disability on SAH Mental HRQoL is not well represented by the overall weighted effect size calculated for it by this meta-analysis. The presence of substantial heterogeneity means that the overall effect size for this predictor is an average (albeit weighted) of two sets of extreme values and so physical disability may better explain SAH Mental HRQoL than the results of this meta-analysis would suggest. Nevertheless, even if we assume one of the largest of the extreme effect size estimates (i.e., either -.59 or .37) is more representative of the actual effect of

physical disability, the magnitude of the size of these effects means that a large majority (65-86%) of variance in Mental HRQoL still remains unexplained.

A second limitation of the meta-analysis was that it was only possible to include just over half of the studies which the systematic review identified as having (or were likely to have) measured the relationship between the traditional predictors and SAH patients' HRQoL. The remaining articles which had (or were likely to of have) considered the predictors could not be included because insufficient data was provided in the articles to calculate effect sizes and the corresponding authors could not provide any further information (because for example, the data was un-retrievable or the authors had yet to publish some of the data themselves) [12, 75, 116, 129, 144, 244, 285, 354, 367, 438, 609]. It is however unlikely that including the data from these studies would have noticeably changed the results of the meta-analysis since the results of these un-included studies (where available) broadly support the conclusions of this meta-analysis (Table 3.6). As in the meta-analysis, age, sex and cognitive status are seen to be either largely unimportant predictors of SAH HRQoL or to have only a modest effect. Moreover, when significant effects are reported, these traditional predictors seem to be more relevant for Physical HRQoL than Mental HRQoL. Finally, as was the case in the present meta-analysis, physical disability seems to be the most important of all the traditional predictors.

A third potential limitation to this study is a problem common to all reviews (both qualitative and quantitative), namely publication bias. Given that there is a greater likelihood that studies with significant results and the largest samples are published, there is the possibility that meta-analyses which – such as this one – are (mostly) based on published data, could result in an overestimation of true effects [39, 63]. In response to this argument, I would highlight that as the effect sizes estimates

Table 3.6 Summary of studies identified by systematic review which could not be included in meta-analysis

		Which predictors did the study examine?							
Study	**Sample size**	Age	Bleed severity	Clinical severity	Sex	Cognitive impairment	Physical disability	Time since illness	**Comments**
Anderson et al.[12]	~17	X	.	.	X	.	X	.	-
Brilstra et al.[75]	25	X	.	.	X	.	.	X	-
Claassen et al.[116]*	247*	X	X	X	X	X	X	.	Age and clinical severity not included in final multivariate model as predictors of Total SIP.
Czechowsky & Hill [129]	2	X	.	X	X	.	X	X	-
Deane et al.[144]	29	X	.	X	X	.	X	X	-
Hamedani et al. [244]	83	X	.	.	X	X	X	X	-
Hop et al.[285]	55	X	.	X	X	.	X	.	According to an asymmetrical index (Somers' D), physical disability had a small-moderate relationship with mental HRQoL (0.2-0.4) and a moderate-strong relationship with physical HRQoL (0.3-0.06).[633]
Kim et al.[354]	385	X	.	X	X	X	X	X	A composite SF-36 score was sig. correlated (r= -.37) with physical disability and cognitive impairment (r= -.38).
Komotar et al.[367]	48	X	X	X	X	X	X	.	-

Table 3.6 *cont'd.*

		Which predictors did the study examine?							
Study	**Sample size**	Age	Bleed severity	Clinical severity	Sex	Cognitive impairment	Physical disability	Time since illness	**Comments**
Mayer et al.[438] *	113	**X**	**X**	**X**	**X**	**X**	**X**	.	PCS- Sig. multiple adjusted r^2-value of 18.8% for 'demographic variable' (effect direction unknown). After controlling for demographics and depression, global cognition and psychomotor function sig. associated with reduced PCS: additive adjusted r^2-value of 10.7%. MCS- Sig. multiple adjusted r^2-value of 0.08% for 'demographic variable' (effect direction unknown). After controlling for demographics and depression, global cognitive function and visuospatial function were sig. associated with MCS: additive adjusted r^2-value of .06%.
Schuiling et al.[609]	247	**X**	**X**	**X**	**X**	.	**X**	**X**	-
Total number of studies		11	4	8	11	5	10	6	
Physical HRQoL Fail-safe N		87	8	43	30	25	45	n/a	
Mental HRQoL Fail-safe N		n/a	n/a	n/a	n/a	n/p	n/a	n/a	

Note: HRQoL=health-related quality of life; n/a=calculation not applicable as weighted effect size not statistically significant; n/p=calculation not possible; r^2=variance explained; SF-36= Short Form-36; sig.=significant; SIP= Sickness Impact Profile; **X**= variable examined by study; *=these two studies are not independent. Mayer et al.'s [438] study was an earlier assessment of the same sample studied by Claassen et al. [116]. =variable not examined by study.

produced by the present meta-analysis were typically small and often insignificant, the possible impact of publication bias for most of this study's results seems negligible. In fact, it could even be argued, that the data used in this meta-analysis was *less* prone to the forces of publication bias (at least directly). For example, the effect size data on predictors of HRQoL often came from studies where the examination of the predictors of HRQoL was not actually the prime concern and/or novelty of published articles [240, 358, 470, 613, 694]. Therefore, a non-significant effect of a predictor for HRQoL could still have been published as a function of it being part of a much broader publication which had significant findings in response to its primary research question. Even with this in mind, for those effects in this meta-analysis which did prove to be statistically significant, the number of unpublished (or not included studies) with non-significant effects needed to nullify each significant effect was so high for most that it seemed unlikely that they existed (in the context of the SAH research field; see last three rows of Table 3.6). In fact, the number of required studies was often large enough that it approximated the criteria used for meta-analyses of much broader research fields (i.e., where the potential impact is felt to be negligible if the fail-safe $N>5K+10$, where K is the number of studies in the meta-analysis) [582]. Nevertheless, the significance of the effects of cognitive impairment and bleed severity when predicting Physical HRQoL were potentially less robust, with only 3 and 8 studies respectively being needed to nullify their significant effects. This implies that the ability of traditional variables to explain SAH Physical HRQoL could be even less important than suggested to be the case by this meta-analysis. Differences in the formulae used by contemporary meta-analysis and the classic fail safe N to calculate statistical significance (i.e., fail-safe N algorithm computes a *P*-value for each study and then combines these *P*-values, whereas

meta-analysis computes an effect size for each study, combines the estimates, and then computes the *P*-value for the weighted effect), meant that whilst the effect size for cognitive impairment when predicting Mental HRQoL proved to be significant according to the meta-analysis, it did not according to the fail-safe N calculation. Regrettably, it was therefore, not possible to determine the number of studies needed to nullify its significant effect. Alternative techniques for determining the robustness of this effect, such as inspection of Funnel plots, were not feasible because they are suitable only for meta-analyses which are based on a much larger number of primary studies [39, 170].

A fourth limitation that needs highlighting is that only those studies which had originally measured the dependent variable of HRQoL using either an MOS or SIP measures were included in the meta-analysis. This restriction was necessary as the other measures which have been used to assess SAH HRQoL are so diverse that to involve the results from studies using those measures would not have been meaningful, or indeed, at times, even possible. Some instruments for instance, measure HRQoL using a single question (such as the visual analogue scale), whilst others measured HRQoL using multidimensional questionnaires whose scores cannot be collapsed to one single score. To have included data from studies using measures other than MOS or SIP questionnaires would have meant that even further heterogeneity in effect sizes would have introduced into the meta-analysis data and I would have committed what some have evocatively referred to as combining "apples and oranges" [243, 583]. I chose to include studies using either MOS or SIP questionnaires as not only were they the most popular HRQoL measure used in SAH studies (used in 81% of all SAH HRQoL studies; see Figure 2.7), but, the two sets of measures are broadly similar in their content and structure. Although there is some

preliminary evidence from a few SAH studies (mostly published in abstracts) that the MOS and SIP measures may exhibit different sensitivities, responsiveness and discriminative properties [121, 286, 437, 439], by far the majority of evidence from the literature suggests that these two sets of instruments do measure the same construct of HRQoL [102, 241, 337, 480, 484, 699, 737]. This conclusion corresponds with the evaluation undertaken as part of this meta-analysis to assess the validity of combining results from those studies using these two sets of measures. It was found that for all but 2 of the 14 predictors, the effect sizes were homogenous between studies using the different measures. The exceptions were bleed severity and clinical severity when predicting Mental HRQoL. In these two cases, the use of the SIP was associated with a larger, more negative effect of bleed severity and clinical severity on Mental HRQoL. One likely explanation for this is that there are subtle differences in the content of the Mental HRQoL scales of the two sets of measures. Whilst the MOS Mental HRQoL summary is composed of questions relating to the patient's perception of how much their health has impacted upon their energy, social activities and emotional and mental well-being, the SIP scale *in addition* includes questions pertaining to the person's performance on cognitive tasks, such as reasoning, orientation and communication. Therefore, given that bleed severity and clinical severity are both known to be related to cognition post-SAH, it could be that the larger, negative relationship of the predictors with the SIP reflects the undue influence of the relationship between the predictors and cognition. Other differences between the SIP and MOS measures, such as the time of reference for their questions (the SIP uses the day of examination, whilst the MOS uses either the past week or 4-weeks) and that the SIP questions are more behaviour-based, whilst the MOS are

directed more at the subject's perceptions [241], could also be involved in explaining the difference. The reasons for this are however, less clear.

On a final note, I would like to briefly discuss a possible reason why some of the traditional variables – namely bleed severity and cognitive impairment – proved so poor in predicting HRQoL (i.e., for bleed severity 1.69% of Physical HRQoL and 0.01% of Mental HRQoL; for cognition 1.96% of Physical HRQoL and 1.69% of Mental HRQoL). Rather than bleed severity/distribution and cognitive impairment not being related to HRQoL, the explanation could be that they are actually better related than the current evidence suggests, but that the instruments used in studies to measure these aspects are too crude to capture the information needed. In terms of bleed severity for example, the crudeness of Fisher's CT rating score [191] (which is almost always used to index bleed severity/distribution) means that it does not capture the variability in bleed severity. The rationale for this particular speculation comes from a single study by Hütter et al. [305] which suggested that specific characteristics of a person's haemorrhage, not sufficiently captured by Fisher's scale, may be better related to HRQoL than the results of the present meta-analysis would suggest. Using univariate tests, Hütter et al. examined the predictive value of firstly, an SAH with intracerebral bleed extension (ICB) on SAH patients' HRQoL and then of SAH with intraventricular bleed extension (IVB). Crucially, it was found that ICB and IVB had different predictive values for SAH HRQoL, but Fisher's scale affords equal weight to ICB and IVB, grouping persons with either haemorrhage extension type together. Specifically, Hütter and colleagues found that thirteen aneurysmal SAH patients with frontal intracerebral invasion experienced a significantly worse physical (r=-.27) and mental (r=-.21) HRQoL compared to 95 SAH patients with no ICB who were treated contemporaneously and who were socially and clinical comparable. The

presence of IVB however, was not associated with HRQoL. Indeed, the effect sizes for ICB are potentially even larger than those which I cite above as Hütter et al. only examined the effect of *frontal* ICBs. The use of the Fisher scale in prior studies could therefore, serve to obscure the unique HRQoL explanative value associated with bleed severity and explain why studies (including this meta-analysis) find bleed severity to explain *so* little variance in SAH HRQoL. It is quite plausible that ICB and IVB could have a different impact on patient HRQoL. We already know for instance, that ICB and IVB each hold unique predictive values for mortality and gross morbidity following SAH [261, 306, 441, 442], and that they each can cause different types of focal brain damage [261, 626, 709]. The potential drawback of this scale is not something which I was able to address in this thesis, but which future studies would be wise to consider (see discussion section 3.3.3, Chapter 7). In relation to the measurement of cognitive impairment, previous studies have not assessed cognitive impairment using instruments with a high degree of ecological validity. Instead prior studies have typically used only classic neuropsychological tests which are designed not to predict behaviour, but rather to localise lesions [203, 276]. It may be therefore, that the use of such measures serves to artificially attenuate the actual relationship between cognitive impairment and HRQoL. Given this, in my subsequent empirical study of SAH patients which I present in Chapter 5, I made an explicit effort to use only cognitive tests with a high degree of ecological validity.

3.5 Conclusions

The results of this meta-analysis lead to the conclusion that traditional predictors (with the exception of physical disability when predicting Physical HRQoL) cannot satisfactorily explain SAH HRQoL. Moreover, their importance has not been overly

obscured by previous studies' over-reliance on statistical significance when evaluating their effect on SAH HRQoL. According to this meta-analysis, even after traditional predictors have been taken into account, between 53-57% of variance in SAH patients' Physical HRQoL and 90-94% of variance in SAH patients' Mental HRQoL remains unaccounted for. Future studies therefore, need to consider more novel aspects of patients' outcome when looking to explain SAH HRQoL.

Although most of the traditional predictors seem unimportant for explaining SAH HRQoL, now that this meta-analysis has comprehensively established their predictive value, these values could be used as a useful yardstick by which to make an informed judgement on the importance of other predictors.

Chapter 4

Possibility two: Psychiatric disturbance has not been taken into account

4.1 Introduction

Following a spontaneous subarachnoid haemorrhage (SAH), many patients experience an extremely poor health-related quality of life (HRQoL). This reduction however, remains largely unexplained. Classical neurological factors – such as bleed severity, clinical severity and neurological disability – which have traditionally been employed to try and explain the reduction have proved (in both primary studies and in my meta-analysis presented in the previous chapter) inadequate. How then can the HRQoL reduction be explained? Following injury to the brain, there is an understandable tendency to assume that it is this damage which is central to a patient's ultimate outcome. We know however, from pioneering studies following other illnesses, such as traumatic brain injury and stroke [61, 180, 344, 405, 591], that while classical neurological factors are key to *immediate* outcome, a patient's later recovery and HRQoL is also determined by 'non-neurological' factors. One possibility therefore, is that the failure to explain much of SAH patients' HRQoL is because research to date has not considered these 'non-neurological' factors. One highly promising 'non-neurological' candidate variable which could help us further explain SAH HRQoL, but which has so-far been ignored is the psychiatric disturbance which SAH patients can often experience.[57, 469, 537, 746]

In this chapter, I shall provide a review of the psychiatric problems faced by SAH patients, the studies which have measured these problems, how SAH psychiatric problems are best conceptualised and finally, discuss the potential of certain conceptualisations to explain SAH patients' reduced HRQoL (and other aspects of their psychosocial outcome).

4.2 Psychiatric disturbance in SAH patients

As several commentators have concluded [46, 57, 306, 537, 544, 750], it is clear that SAH patients experience alarmingly high levels of psychiatric disturbance compared to healthy controls. In Table 4.1, I present a review of studies of psychiatric problems in SAH patients. It was necessary to exclude many studies from this review as, although rich in description of patients' psychiatric outcome, they were limited by their use of unofficial nomenclature, their measurement of nebulous concepts (such as 'emotional disturbance' and 'psychiatric problems') and/or their use of non-validated instruments [8, 25, 78, 99, 150, 185, 409, 412, 428, 501, 510, 513, 553, 632, 643, 649, 659, 667-669, 678, 685, 721, 722].

My review highlights that the psychiatric profile of SAH patients is largely dominated by a state of anxiety (≤54%) [48, 265, 314, 469, 540, 541, 652, 703, 725, 746]. An examination of the literature reveals that a sense of worry and fear over haemorrhage recurrence dominates SAH patients' anxiety (18-89%) [295, 412, 652, 728, 729]. Generalised psychological disturbance [48, 90], personality change (e.g., increased irritability, impulsivity, apathy) [8, 58, 302, 419, 504, 510, 643, 659, 685, 721], as well as more peculiar symptoms of sleep dysfunction and fatigue are also seen to be part of patients' psychiatric profile [313, 314, 409, 510, 609, 649, 746]. As seen in Table 4.1, although symptoms of depression/ mood reduction are also reported by SAH patients [44, 45, 105, 189, 265, 280, 302, 377, 397, 418, 504, 507, 508, 540, 609, 687, 703, 746, 752], they have not been found to be the main symptoms [265, 314, 377, 469, 540, 541, 703, 746]. For example, Jarvis et al. [314] in one of the largest studies to date (with a sample of 62 aneurysmal SAH patients), found that 14% of patients reported clinical levels of depressive symptoms, but 35%, reported clinical levels of anxiety. The tendency of SAH studies to have utilised

Table 4.1 Summary of studies examining psychiatric disturbance in SAH patients using a validated instrument(s)

Study	N	Type	Sample characteristics	Measure	Follow-up (yrs)	Findings
Bellebaum et al.[40]	32	ASAH	100% GOS I-II. 81% H&H I-II	BDI	1.9-2.4	**BDI:** Compared to healthy controls, SAH patients treated with aneurysm clipping showed sig. more depression. Clipped patients also reported sig. higher depression compared to SAH patients treated by aneurysm coiling (unadjusted r=.31, 9.7%; adjusted r=.41, 16.9%*‡). Coiled patients depression scores not sig. different compared to controls.
Beristain et al. [44, 45]	15	ASAH	53% H&H I-II; 93% GOS I-II	BDI; BRS	.5	**BDI:** 20% of SAH patients mild-moderately depressed (13-19), 25% moderately-severely depressed (20-29) and 6.6% severely depression (>29). **BRS:** Merging data with other patient groups precludes reporting of results.
Berry et al. [48]	48	ASAH	Most WFNS I-II	BDI; GHQ; STAI	.7	**BDI:** SAH patients were sig. more depressed than healthy controls. **GHQ-28:** SAH patients reported sig. more psychological and psychiatric disturbance. **STAI:** Compared to health controls, SAH patients reported sig. more STAI-state anxiety, but not SATI-trait anxiety. Depression and general psychiatric disturbance was not sig. associated with memory performance. State anxiety sig. associated with worse verbal recognition and recall (both unadjusted *r*=.33, 11.3% and adjusted *r*=.44, 19.9%*‡). Psychiatric disturbance not sig. associated with physical independence.

Table 4.1 *Cont'.d*

Study	N	Type	Sample characteristics	Measure	Follow-up (yrs)	Findings
Berry et al. [47]	28	ASAH	Referrals to clinical psychology service. 100% good neurological recovery	Diagnostic interview (DSM-III-R PTSD)	.5	**Diagnostic interview:** 32% met the diagnostic criteria for PTSD in relation to their SAH.
Buchanan et al. [90]	24	ASAH; SAHavm	100% GOS I-II	BSI	1.6	**BSI:** 58% met caseness criteria (≥63) for psychological distress. 13% of patients acknowledged suicidal ideation during the previous 7 days.
Carter et al. [105]	179	ASAH	96% GOS I-II; 61% H&H I-II	ZSRDS	1.0-6.0	**ZSRDS:** 11.7% of patients reported mild depression (50-59) and 25.1% severe depression (60-100). Time, clinical severity and age not sig. associated with depression. Physical disability was sig. associated with depression (r= .29, 8.9%*)
Claassen et al. [116]	247	ASAH; SAHuo	53% H&H I-II	CES-D; STAI	1.0	**CES-D:** Depression scores not sig. associated with post-SAH 12-month epilepsy.

Table 4.1 *Cont'd.*

Study	N	Type	Sample characteristics	Measure	Follow-up (yrs)	Findings
Claassen et al. cont'd.						STAI-state: In multiple regression, worse state anxiety sig. associated with non-white ethnicity (OR=4.0) and 12-month post-SAH epilepsy (OR=4.8). Age, education, fluency in English, clinical grade (GCS), aneurysm re-bleed, infarction and delayed cerebral ischemia did not enter into final model.
Fertl et al. [189]	40	ASAH	100% GOS I-II;.65% H&H I-II	BDI	1.8	**BDI:** 27.5% of SAH patients mildly-moderately depressed (12-26). Depression sig. associated with cognitive and physical impairment (r= .36, 13.5% variance) and reduced working capacity (r= .56, 31.8% variance)*±.
Fontanella et al. [198]	53	ASAH; SAHuo	100% WFNS I-II; 100% GOS I.	BDI; STAI	.5	**BDI:** No sig. mood disturbance compared to healthy controls. STAI: No sig. disturbance on both 'state' and 'trait' scales. Psychiatric state not associated with treatment (clipping vs. coiling) or aetiology of bleed (aneurysmal vs. unknown origin).
Germanò et al. [212]	20	ASAH	100% GOS I; 100% H&H I-II; Patients selected as, considered to likely make favourable recovery:	HARS; HDRS	1.0	**HARS:** 100% of SAH patients mildly anxious. SAH patients' mean anxiety score was not sig. different to controls. **HDRS:** 15% of SAH patients mildly-moderately depressed, 5% moderately- severely depressed. SAH patients' mean depression score was not sig. different to controls.

Table 4.1 *Cont'd.*

Study	N	Type	Sample characteristics	Measure	Follow-up (yrs)	Findings
Hadjivassiliou et al. [242]	80	ASAH	91% GOS I-II; 78% WFNS I-II	BDI	1.0	**BDI:** Depression scores not sig. associated with aneurysm treatment type (clipping vs. coiling).
Hellawell et al. [265]	26, 23, 19	ASAH; SAHuo	Most WFNS I-II	HADS	.5, 1.0, 2.0	**HADS-Anxiety:** At 6 months, 11% borderline anxiety, 8% clinically anxious. At 12 months, 17% were borderline and 13% clinically anxious. At 24 months, 21% borderline and none were clinically anxious. **HADS-Depression:** At 6 months, 92% scored in the normal range. Just 8% illustrated clinically significant depressive scores. At 12 months, 9% reported borderline depression and 9% scored in the clinically depressed range. At 24 months, 5% of patients scores were borderline and 5% of patients' scores were in the clinical range. Note that at 12 month appointment, total HADS score sig. positively correlated with clinical severity (unadjusted r=.46, 21.2%; adjusted r=.64, 42.0%*‡‡). Note no corrections were made for multiple comparisons.
Hillis et al. [280]	27, 6	ASAH	Average H&H II	ZSRDS	.25	**ZSRDS:** 36% were minimally to moderately depressed (50-59), 23% moderately to markedly depressed (60-69), and 5% severely depressed (≥80). SAH patients' depression scores not sig. higher than those of non-SAH patients surgically treated for an un-ruptured aneurysm. 6 patients were seen again at 1 year post-SAH and no sig. change in their depression scores was found.

Table 4.1 *Cont'd.*

Study	N	Type	Sample characteristics	Measure	Follow-up (yrs)	Findings
Hütter et al. [297, 302]	58	ASAH; SAHuo	100% GOS I-II	BDI	3.0	**BDI:** 30% of patients reported clinically relevant depression scores (BDI >10). No sig. differences in depression scores by SAH type (ASAH vs. SAHuo) or aneurysm location (ACoA vs. other sources).
Hütter et al. [295]	45	ASAH; SAHuo	-	BDI; IES;; Diagnostic interview (DSM-IV PTSD)	4.0	**IES:** Compared to a control group of 25 medical studies who had dissected their first corpse a week before, SAH patients had sig. higher IES avoidance and total traumatisation symptoms, but not intrusion symptoms. No sig. difference between IES scores by SAH type (ASAH vs. SAHuo). IES intrusions sig. associated with clinical severity (r=.32, 10.2%) and bleed severity (9.6%), but not vasospasm. Intrusion score also sig. correlated with score on measure of fronto-cortical function completed 4 years earlier. (r= -.35, 12.3%). IES intrusion (*r*=.52, 27.0%) and avoidance (*r*=.45, 20.3%) scores both sig. correlated with concurrent BDI depression scores. **Diagnostic interview:** 26% of SAH met diagnostic criteria for PTSD.
Jarvis & Talbot [314]	62	ASAH	-	HADS; IES	.25	**HADS-Anxiety:** 35% of SAH patients reported clinically relevant anxiety (11+). **HADS-Depression:** 14% of SAH patients reported clinically relevant depression (11+). **IES:** 37% of SAH patients reported clinically relevant PTSD score (15+).

Table 4.1 *Cont'd.*

Study	N	Type	Sample characteristics	Measure	Follow-up (yrs)	Findings
Kreitschmann' [377]	35-40	ASAH	90% GOS I-II; 55% H&H I-II	BDI; IES	2.3	**BDI:** 27.5% of SAH patients reported mild-moderate depression (11-17) and 10% severe depression (>17). Depression sig. associated with basal cortisol value (r= -.56, 31.3%) and physical disability (r= -.44, 19.3%). **IES:** 34% of SAH patients reported mild-moderate PTSD response (IES<15).
Lindberg et al. [397]	104	ASAH	-	ZSRDS	7.0	**ZSRDS:** 22% of SAH patients were reported to be experiencing clinically relevant levels of depression (40-80). Depression not sig. associated with time between SAH and assessment, age, sex, cognitive impairment or physical disability. Depression was sig. associated with ability to work (r=.27, 7.5%* †) and a decrease in leisure activity (r= .26, 7.2%*).
Madureira et al. [418]	18	PMSAH	94% H&H I-II	HDRS	3.25	**HDRS:** 33% of SAH patients scored in the depressed range (≥13). Depression not sig. associated with age, sex or time between SAH and assessment. Depression sig. correlated with memory deficits (r=.72, 53.0%*±), but not global cognitive function.
Mayer et al. [438]	113	ASAH; SAHuo	84% NIHSS 0; 56% WFNS I-II	CES-D; STAI	.25	**CESD:** After controlling for age, education and race, global cognitive function sig. associated with depression (r=.24, 5.8%* †). Domain-specific cognition not sig. associated with depression. **STAI:** After controlling for age, education and race, global cognitive function sig. associated with state anxiety (r=.29, 8.4%* †), but not trait anxiety. Domain-specific cognition not sig. associated with either state or trait anxiety scores. Anxiety and depression sig. correlated, but coefficient not provided in article.

Table 4.1 *Cont'd.*

Study	N	Type	Sample characteristics	Measure	Follow-up (yrs)	Findings
Morris et al. [469]	52	ASAH; SAHuo	44% had a good GOS-E; 84% WFNS I-II	BDI; GHQ; HADS;STAI	1.4	**BDI:** 28% of SAH patients reported mild-moderate depression (10-18) and 22% reported moderate-severe depression (≥19). **GHQ:** 41% of the 46 SAH patients who completed the measure scored above the 4/5 threshold indicating poor subjective mental health. **HADS-Anxiety:** 16% of SAH patients reported mild anxiety (8-10) and 38% reported moderate-severe anxiety (≥11). **HADS-Depression:** 21% of SAH patients reported mild depression (8-10) and 17% reported moderate-severe depression (≥11). **STAI:** 58% of SAH patients reported trait anxiety scoring above 80th percentile and 46% above 80% on state anxiety. None of the mood scores were sig. associated with clinical severity, bleed severity, aneurysm location, type of SAH (ASAH vs. SAHuo), delay to treatment or sex. HADS and STAI scores scales were all sig. correlated with physical disability (unadjusted *r*s=.42, 18.4%; adjusted *r*s=.50, 25.2%).*‡‡
Morris et al. [470]	70§	ASAH; SAHuo	84% WFNS I-II	HADS; STAI; BDI	1.2	Possession of ε4 allele not sig. associated with any anxiety or depression scores.
Ogden et al. [504]	16	ASAH; SAHuo	100% GOS=I; 56% Botterel Grade 1-2	ZSRDS	4.0	**ZDRS:** 25% of SAH patients reported at least moderate depression (≥50).

Table 4.1 *Cont'd.*

Study	N	Type	Sample characteristics	Measure	Follow-up (yrs)	Findings
Ogden et al. [507]	89, 66	ASAH; SAHuo	98% GOS I-II; 89% GCS 13-15	BDI	.2, 1.0	**BDI:** At 10 weeks, 19% of SAH patients reported mild-moderate depression (10-19) and 5.6% moderately severe depression (20-29). At 12 month assessment, 17% of SAH patients reported mild-moderate depression and 3% moderately severe depression. Depression was not sig. associated with cognitive performance.
Ogden et al. [508]	71, 62	ASAH; SAHuo	98% GOSI-II; 57% good clinical admission state as per Mee et al. scale.	BDI	.20, 1.0	**BDI:** At 10-week assessment, 13% of SAH patients reported mild depression (10-15), 10% moderate depression (16-23) and 1% severe depression (24-63). At 12 month assessment, 14% of SAH patients reported mild depression, 3% moderate depression and 2% severe depression. Depression score was not sig. associated with age, sex, aneurysm site, type of SAH (ASAH vs. SAHuo), clinical complications (vasospasm; ischemic deficit; hydrocephalus), marital status, pre-morbid occupational status, pre-morbid IQ, estimated BDI for month preceding SAH or severity of life stress for preceding year. 10-week depression scores were sig. associated with worse a clinical grade (effect size not calculable). Significant reduction in BDI scores with time (r=.16; 2.56%).

Table 4.1 *Cont'd.*

Study	N	Type	Sample characteristics	Measure	Follow-up (yrs)	Findings
Ogden et al. [510]	123	ASAH; SAHuo	Most GOS=I; Mean GCS 13.2 (*SD*=2.14)	ESS	4.0-7.0	**ESS:** 35% of SAH patients reported experiencing excessive daytime sleepiness/ fatigue. Excessive sleepiness/ fatigue sig. correlated with reports of difficulties maintaining night-time sleep (reported by 26%; *r*=.34, 11.6%), personality changes (*r*=.30, 9.0%) and complaints of poor memory (*r*=.32, 10.2%).
Oyebode et al. [519]	20	ASAH; SAHavm	Referrals to clinical psychiatry unit.	Diagnostic interview	8.0	**Diagnostic interview:** 70% of SAH patients met criteria for major depressive disorder, 5% bipolar depression with mania, 10% schizoaffective disorder, 10% generalised anxiety and 5% erectile impotence.
Powell et al. [540]	44-50	ASAH	100% GOS I-II;.100%I WFNS I-II	BDI; HADS; IES	.25, .75	**BDI:** At the 3 month assessment, 9.1% of SAH patients reported clinical relevant depression (19+). At the 9 month assessment, 11.4% of SAH patients reported clinically relevant depression. **HADS-Anxiety:** At the 3 month assessment, 16.0% reported clinically relevant anxiety (11+). At the 9 month assessment, 17.0% reported clinically relevant anxiety. At both 3 and 9 months, SAH patients reported sig. more anxiety than controls. **HADS-Depression:** At the 3 months assessment, 14.0% of SAH patients reported clinically relevant depression (11+) At the 9 months assessment, 8.5% of SAH patients reported clinically relevant depression. SAH patients' depression scores were sig. higher than controls at 3 month assessment, but not at 9 month assessment.

Table 4.1 *Cont'd.*

Study	N	Type	Sample characteristics	Measure	Follow-up (yrs)	Findings
Powell et al. cont'd.						**IES:** At the 3 month assessment, 30% scored in the clinically indicative PTSD range on both the intrusion (≥12) and avoidance (≥14) scales. At the 9 month assessment,15% scored in the clinically indicative range on both the intrusion and avoidance scales. There was a sig. reduction with time on IES scales (both r= .33, 11.5%). Univariate analysis showed no significant recovery on either HADS scales or BDI with time. In predicting overall of mood outcome (HADS + IES), 45% of variance in this composite was accounted for by a final model made up of information about a patient's prior mental health (15%), prior physical health (12%), experience of dysphasia (8%) and prose recall at the 3 month assessment (5%). Age, sex, physical disability and stresses for the year proceeding SAH did not enter into final model.
Powell et al. [541]	49	ASAH	100% GOS I-II; 100% WFNS I-II	BDI;HADS; IES	1.5	**BDI:** 16.3% of SAH patients reported clinically relevant depression (≥19). **HADS-Anxiety:** 18.4% of SAH patients reported clinically relevant anxiety (≥11). Compared to controls, SAH patients reported sig. higher anxiety. **HADS-Depression:** 10.2% of SAH patients reported clinically relevant depression (≥11). Patients did not report more depression than controls.

Table 4.1 *Cont'd.*

Study	N	Type	Sample characteristics	Measure	Follow-up (yrs)	Findings
Powell et al. cont'd.						**IES:** 6% of SAH patients scored in the clinically indicative PTSD range on both the intrusion (≥12) and avoidance scales (≥14). Compared to 9 month (cf. [540]), was no sig. improvement in HADS Anxiety or Depression scores or BDI scores. Compared to data from 9 month assessment (cf. Powell et al. 2002), there was a sig. recovery for PTSD IES intrusion scale score (r=.38; 14.85% variance*), but not on avoidance scale. No sig. predictive model could be established for overall mood outcome at 18 months (HADS+IES) – potential variables included age, sex, physical disability, dysphasia, prose recall at 3 months, prior life stresses and prior physical and mental health problems. In univariate analysis, overall mood was sig. associated with prior mental health (r= -.29; 8.4% *).
Preiss et al. [543]	75	ASAH	100% GOS I-II.	BDI-II	1.0	**BDI:** Mean depression scores of two groups of SAH patients treated differently (clipping vs. coiling) were both within the minimal depression range. Depression scores not sig. related to aneurysm treatment or sex.
Salmond et al. [589]	20	ASAH	Average WFNS I-II. Only MCA or PCoA aneurysm bleeds.	BDI	5.7	**BDI:** Depression scores not sig. higher compared to healthy controls.

Table 4.1 *Cont'd.*

Study	N	Type	Sample characteristics	Measure	Follow-up (yrs)	Findings
Samra et al. [590]	185	ASAH	96%WFNS Grades I-99% GOS I-II.	BDI	.75	**BDI:** SAH patients had sig. more symptoms of depression than healthy controls.
Satzger et al. [594]	44	ASAH	100% no neurologic deficit.91% H&H I-II;	Befindlickeits-Skala	2.9-3.2	**Befindlickeits-Skala:** Mean score of two SAH patient treatment groups (early surgery vs. late surgery) both indicated no presence of depression (<56). Age, timing of surgery, clinical severity and aneurysm location (ACoA vs. other) were not sig. associated with depression.
Schuiling et al. [609]	83	ASAH; SAHuo	82% WFNS Grades I-II,	APSG; BDI; SDL,	1.7	**SDL:** 34% had severe sleep problems (a score of ≥3 on either the SDL sleepiness or excessive daytime sleepiness scales). **APSG:** In 20 of the patients with SDL scores indicating severe sleep problems scores APSG was conducted. None of these patients had a normal sleep. Severe sleep fragmentation, sleep apnoea, restlessness leg syndrome/ periodic limb movement, or a combination these disorders of sleep and wake occurred in 19 patients (95%). **BDI:** Four patients (including the 1 patient without sleep fragmentation) had insomnia from inadequate sleep hygiene (staying in bed too long and daytime napping). 45% of patients had depression (BDI>16). Sleep dysfunction on the SDL was not sig. associated with treatment (clipping vs. coiling), physical disability or bleed severity.

Table 4.1 *Cont'd.*

Study	N	Type	Sample characteristics	Measure	Follow-up (yrs)	Findings
Sheldrick et al. [627]	27-38	ASAH; SAHuo	-	DTS	≤.04, .10-.15,23-.29	**DTS:** At ≤2 week assessment 18.4% reported clinically relevant PTSD Symptoms (>40). At 5-7 week assessment, 35.5% reported clinically relevant PTSD symptoms. At 11-14 week assessment, 18.5% reported clinically relevant PTSD symptoms. Compared to myocardial infarction patients, SAH patients' scores at all time points were higher, but the difference was not sig. A mixed design analysis found time to be sig. related to PTSD scores for both groups. Change over time was homogenous between groups. Pair-wise comparisons found there to be a sig. decrease in scores between assessments two and three for the two groups as a whole (effect size not calculable).
Stegen & Freckman [652]	87	ASAH	93.1% good neurological recovery.	STAI	1.0	**STAI:** Increased anxiety noted. Patients whose SAH was caused by rupture of an MCA aneurysm had sig. worse anxiety than those with ACA aneurysms (r=.17, 3.1%).
Tidswell et al. [687]	37	ASAH	-	BDI	2.2	**BDI:** 16% of patients in the "depressed" range (>13). Depression was not sig. associated with cognitive performance or aneurysm location (anterior vs. non-anterior).

Table 4.1 *Cont'd.*

Study	N	Type	Sample characteristics	Measure	Follow-up (yrs)	Findings
van der Schaaf et al. [703]	69	ASAH	76.8% mRS 0-1	HADS	7.1 & 9.1	**HADS-Anxiety:** 17.4% of SAH patients reported possible anxiety (8-10) and 5.8% reported probable anxiety (>10). **HADS-Depression:** 15.9% of SAH patients reported possible depression (8-10) and 7.2% reported probable depression (>10). Neither anxiety nor depression was sig. associated with having a small identified aneurysm being left untreated.
von Vogeslang et al. [725]	62	ASAH	All good neurological recovery (GOS I-II).	STAI-state	.08-.25	**STAI-state:** Compared to general population guidelines, SAH patients illustrated higher STAI-state scores, but this was not statistically compared. Using a quasi-experimental design, anxiety scores were compared between a retrospective 'treatment as usual' control group and a prospective intervention group who received enhanced oral and written information about their illness (including its treatment, potential consequences and contact information for patient associations). There was no sig. difference in anxiety scores between these two groups or between sexes.
Wermer et al. [746]	584	ASAH	57%mRS 0-1	HADS	8.75	**HADS-Anxiety:** 13.5% of SAH patients reported possible anxiety and 11.1% probable anxiety. SAH patients' mean anxiety score was not sig. higher than that of controls. **HADS-Depression:** 19.5% of SAH patients reported possible depression (8-10 score) and 9.4% probable depression. SAH patients' mean depression score was significantly higher than controls. Time since SAH was not sig. associated with either anxiety or depression.

Table 4.1 *Cont'd.*

Study	N	Type	Sample characteristics	Measure	Follow-up (yrs)	Findings
Will & Philipp [752]	65	ASAH	Mean H&H=2.4 .	BDI	4.0	**BDI:** 13%of SAH patients reported mild depression and 19% clinically relevant depression.

Notes: ACoA= Anterior communicating artery; APSG=Ambulatory polysomography; ASAH=Subarachnoid haemorrhage of aneurismal origin; Befindlickeits-Skala=self mood evaluation scale [700]; BDI=Beck Depression Inventory [36]; BRS=Behavioral Rating Scale [269]; BSI=Brief Symptom Inventory [148]; CES-D=Center for Epidemiologic Studies-Depression Scale [549]; DSM-III-R= Diagnostic and Statistical Manual of Mental Disorder Third Edition-Revised [21]; DTS=Davidson Trauma Scale [132]; ESS=Epworth Sleepiness Scale [320];GCS=Glasgow Coma Scale (range 3-15; 15= best clinical presentation) [683];GHQ=General Health Questionnaire [227]; GOS=Glasgow Outcome Scale (range I-V; grade I-II=good/ favourable neurological recovery no/modest physical impairment, needs no help in daily activities) [318]; GOS=E=Glasgow Outcome Scale-Extended version [758]; H&H= Hunt and Hess grading scale for neurological state on admission (range I-V; grades I-II good clinical presentation) [293]; HADS=Hospital Anxiety and Depression Scale [772];HARS/ HDRS=Hamilton Anxiety/ Depression Rating Scales [245, 246];IES= Impact of Events Scale [[288]; Kreitschmann'= Kreitschmann-Andermahr et al; MCA= middle cerebral artery; Mee et al. scale=Clinical status neurological grading scale (range 1-6; 1-2= good neurological status, oriented with only minimal cranial nerve deficit) [456]; mRS=modified Rankin Scale score (range 0-6; 0-1=good neurological recovery, needs no help in daily activities) [550]; NIHSS= National Institute of Health Stroke Scale (range 0-30;0 =no neurologic impairment) [230]; OR=odds-ratio; PCoA=posterior communicating artery; PTSD=Posttraumatic stress disorder; SAHavm=Subarachnoid haemorrhage resulting from an arteriovenous malformation; SAHuo=Subarachnoid haemorrhage of unknown origin; SDL=The Sleep Disorders Questionnaire [163]; sig.=significant(ly); STAI=State-Trait Anxiety Inventory [647]; WFNS= World Federation of Neurological Surgeons grading scale for neurological state on admission (range I-V; grades I-II good clinical presentation) [164]; ZSRDS=Zung Self-Report Depression Scale [774]; * effect sizes (*r*)for 1 df tests calculated where possible [580, 583]; ‡ adjusted effect size also presented as per Glass et al. [222] formulae to account for 5% power reduction associated with use of Mann-Whitney test; ‡‡ adjusted effect size also presented to account for 9% power reduction associated with use of Spearman's-correlation test [633]; ± effect size based on p-value and conversion to z-value, but not corrected for less power associated with non-parametric test as Fisher exact used in this case is the most powerful tests for the dichotomous, nominally scaled data [633]; † effect size could be slightly larger as exact sample size for calculation based on entire population, rather than just who completed measure/ or were of working age as these number were not available in the article;§ exact sample size likely smaller, but only starting sample number not account for missing data is cited in article.

Studies not included in table if psychiatric data merged with that of non-SAH patients,[17, 244, 359, 569] if the study used only a personality inventory,[247, 308] provided insufficient details on psychiatric outcome,[25, 377, 433, 570, 571] was not an independent study [31] or was a case report.[312, 577]

screening measures for depression, rather than anxiety when exploring psychiatric disturbance in this population (seen in Table 4.1), should not be taken to indicate that symptoms of depression are most prominent. Instead, it reflects the influence within the neurosciences of the seminal work by Robinson and colleagues on ischemic stroke patients, which publicised the possibility of depression following cerebrovascular incidents [565-568].

It is important to note at this point, that the psychiatric problems of SAH patients are considered to be new difficulties which occur following their haemorrhage. There is – despite some early proposals [506] – no convincing evidence to suggest that this population experienced abnormal levels of psychopathology or stress prior to their haemorrhage [540].

As noted earlier, one particularly distinctive feature of SAH patients' anxiety is a sense of fear and a preoccupation with the possibility of a further SAH occurring, despite their relative safety [25, 47, 57, 75, 99, 295, 313, 314, 412, 449, 465, 559, 643, 652, 728, 729]. "Oh God, I'm on my own, I'm out now. Will it happen to me again?" (p.1433) is something repeatedly stated by SAH patients [313]. Hütter [295] for example, found that in a sample of 45 aneurysmal SAH patients assessed 4 years post-SAH, only 11% never feared recurrence and 33% were either 'frequently' or 'permanently' afraid of a haemorrhage recurring. Crucially, many SAH patients also have flashbacks and often feel as if the haemorrhage is recurring [47, 313, 314, 449, 716]. This can be precipitated by a tendency in the SAH population to catastrophically misinterpret normal bodily sensations (such as headaches and tingling sensations in the operation site) as indicating the onset of another SAH [47, 285, 545, 546, 548].

The sense of fear reported by SAH patients is of clinical concern because it is considered to be both persistent and potentially debilitating [25, 57, 78, 295, 313, 437,

465]. Its abnormality is illustrated by the fact that significantly less patients following treatment for other types of brain pathology exhibit such fear [545]. Although it has often been presumed that SAH patients' worries could reflect a lack of knowledge about their illness [302, 313, 314, 449, 469, 546, 548, 627, 652], it has been found that this anxiety and fear is not abated through clinicians providing the patients with extensive reassurance about their relative safety [47, 313, 652, 725]. Stegen and Freckman [652] for example, assessed a sample of 69 aneurysmal SAH patients 12 months post-SAH and found that despite admitting that the illness had been sufficiently explained and being aware of their safety, 79% of patients still feared recurrence. The functional impairment caused by SAH patients' fear is illustrated by these patients' avoidance of thinking about their haemorrhage and by placing restrictions on themselves, such as not participating in certain activities (such driving, lifting, sexual intercourse) in case they elicit sensations which are similar to those experienced at the time of the haemorrhage and/or trigger harmful processes which *they* feel could cause a further bleed [57, 285, 314, 437, 449, 703].

Patients' fears can also place extra strains on relationships with their family and friends. For instance, patients may continually seek reassurance from their loved-ones about their health and may not allow themselves to be left alone [314, 664]. Their array of symptoms is concisely depicted in the following typical patient comment derived from Jarvis' [313] qualitative study of SAH patients: "I felt very very (sic) frightened about it happening again. I thought if it's happened once, it can happen again. I felt very vulnerable – I had flashbacks of the night it happened. When I went to bed...I was reliving everything of it and couldn't get it out of my mind. I learned to open my eyes when this happened so I would forget about it ...Even though I knew

the facts about the chance of another haemorrhage, I still have the flashbacks of the night it occurred because I'm so frightened of it happening again" (p.1433).

In order for the psychiatric difficulties of SAH patients to be better understood and ultimately treated, it is necessary to move beyond the simple description of symptoms and to determine which psychiatric disorder (or disorders) underlies their symptoms. Whilst the results from studies using screening measures have been important in highlighting that the dominant presenting symptoms of SAH patients are anxiety and a sense of fear, the ubiquitous nature of these symptoms to many major psychiatric disorders [23, 190, 576], means that these studies alone cannot delineate which specific disorder is responsible for the difficulties experienced by SAH patients [53, 96, 122, 341, 345, 453, 561, 610, 636, 736]. According to the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) [23, 190], when patients present with a symptom profile dominated by anxiety and fear, the set of potentially relevant disorders includes, generalised anxiety disorder, adjustment disorder and posttraumatic stress disorder (PTSD). As Figure 4.1 illustrates, although these various conditions are associated with symptoms of anxiety and fear, they are not synonymous and they can be differentiated on the basis of the nature and content of the anxiety which they produce (e.g., whether or not the anxiety is in response to a stressor, what the patient is afraid of, what situations are avoided) [190, 340]. Fortunately, efforts have now been made to determine which of the potential psychiatric disorders seen in Figure 4.1 best accounts for SAH patients' symptom profile. Indications from these recent studies suggest that PTSD is the best explanation for SAH patients' psychiatric symptom profile. Therefore, in the next section I shall discuss why PTSD is so good at accounting for SAH patients' psychiatric difficulties.

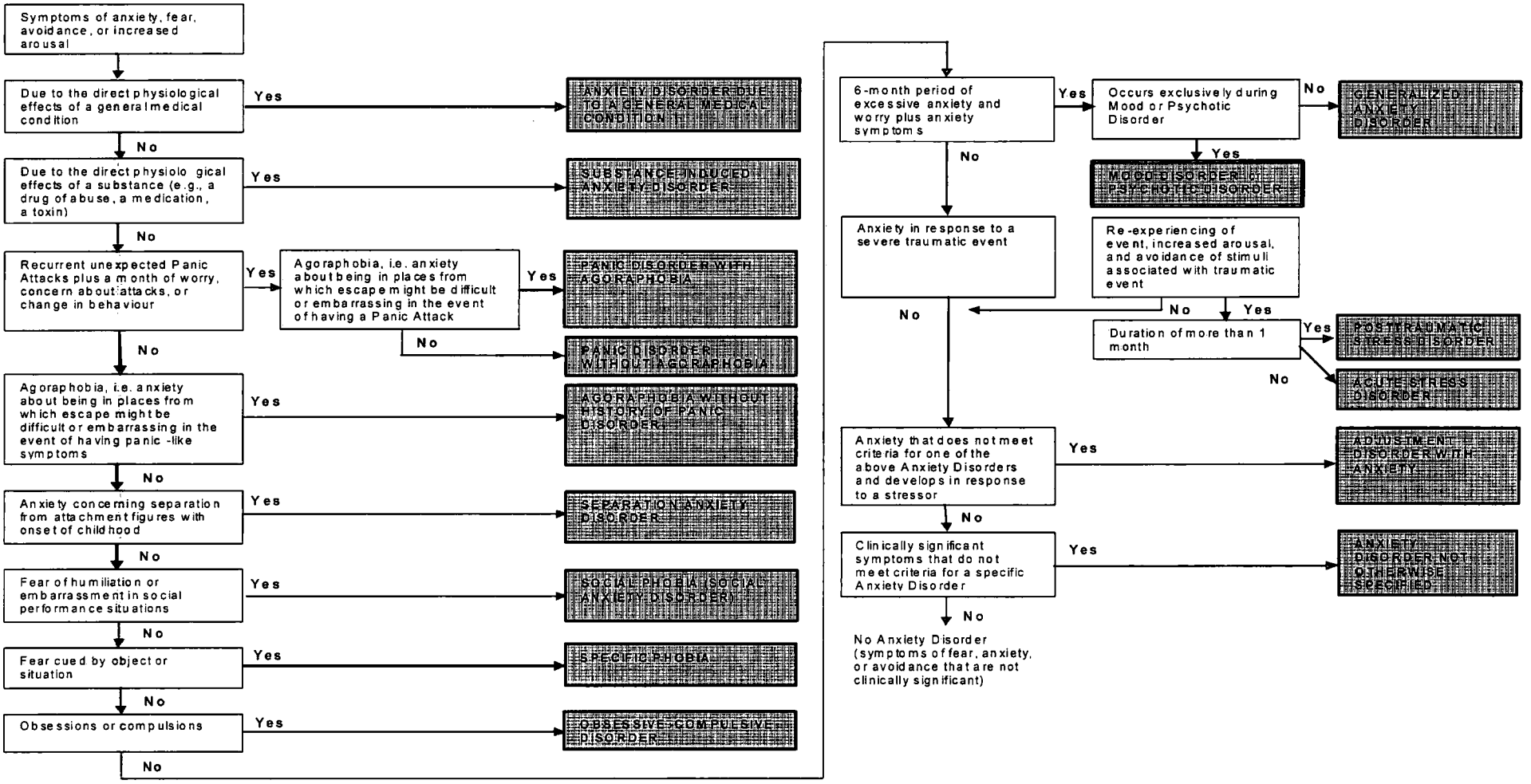

Figure 4.1 Decision tree for differential diagnosis of psychiatric disorders accounting for anxiety symptoms (Adapted from DSM-IV-TR [23]).

4.3 Post-traumatic stress disorder (PTSD) provides best explanation for SAH patients' psychiatric difficulties

Before discussing the evidence on PTSD being the disorder which can best account for SAH patients' psychiatric difficulties, it is first necessary to discuss the diagnosis of PTSD in general, its characteristics and risk factors.

First recognised by psychiatry in 1980 [20], PTSD is an abnormal and highly distressing psychiatric reaction that follows the experience of a traumatic event that involves "actual or threatened death or serious injury, or a threat to the physical integrity of self or others" (p.467) [23]. Characterised by intrusive recollections of the trauma, active avoidance of stimuli associated with the trauma, emotional numbing and persistently increased arousal (Table 4.2), it is an independent disorder whose pathophysiology and treatment is distinct from other psychiatric conditions [23, 100, 204, 205, 339, 495, 554, 630, 631, 670, 765]. PTSD is known to interfere with interpersonal relations, cause marital conflict and lead to job loss on the part of the patient. In addition to its diagnostic symptoms, patients who develop PTSD can also illustrate impulsive behaviour, somatic complaints, hostility, social withdrawal and a change in personality [23]. It is a complex disorder, with a high rate of psychiatric co-morbidity. Major depression, panic disorder and social phobia are amongst the most common disorders that are also found in persons with PTSD [351]. Although persons can spontaneously recover from PTSD, those individuals who still meet its diagnostic criteria at around 6 months post-trauma are, without intervention, unlikely to recover [351]. Crucially, we know a great deal about PTSD's causes/ risk factors and how best to treat it. Recent research has, for example, established that who does and does not develop PTSD following a trauma is not a purely random phenomenon, but rather its development can be reliably predicted by several established risk

Table 4.2 American Psychiatric Association's [23] criteria for PTSD in adults

A. The person has been exposed to a traumatic event in which both of the following were present:

(1) person experienced, witnessed, or was confronted with event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others

(2) the person's response involved intense fear, helplessness, or horror

B. The traumatic event is persistently re-experienced in one (or more) of the following ways:

(1) recurrent and intrusive distressing recollections of the event, including images, thoughts, or perceptions.

(2) recurrent distressing dreams of the event

(3) acting or feeling as if traumatic event were recurring (e.g., a sense or reliving the experience, illusions, hallucinations, and dissociative flashback episodes, including those that occur on awakening or when intoxicated)

(4) intense psychological distress at exposure to internal or external reminders of the traumatic event

(5) physiological reactivity on exposure to internal or external reminders of the traumatic event

C. Persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness (not present before the trauma), as indicated by three (or more) of the following:

(1) efforts to avoid thoughts, feelings, or conversations associated with the trauma

(2) efforts to avoid activities, places, or people that arouse recollections of the trauma

(3) inability to recall an important part of the trauma

(4) markedly diminished interest or participation in significant activities ("psychic numbing" or "emotional numbing")

(5) feeling of detachment or estrangement from others

(6) restricted ability to feel emotions (especially those associated with intimacy, tenderness and sexuality)

(7) sense of foreshortened future (e.g., does not expect to have a career, marriage, children, or a normal life span)

D. Persistent symptoms of increased arousal (not present before the trauma), as indicated by two (or more) of the following:

(1) difficulty falling or staying asleep (often due to recurrent nightmares during which the trauma is relived)

(2) irritability or outbursts of anger

(3) difficulty concentrating or completing tasks

(4) hypervigilance

(5) exaggerated startle response

E. Duration of the disturbance (symptoms in Criteria B, C and D) is more than 1 month.

F. The disturbance causes clinically significant distress or impairment in social, occupation, or other important areas of functioning.

factors [521]. It has been found, for example, that key to the development of PTSD is the manner by which the person reacts and responds to the stress of the trauma [328, 390]. This response is mediated by the coping strategies which the person consciously employs when confronted with stress [217]. Therefore, whilst meta-analyses find that factors such as age, sex, education and psychiatric history have only a minimal predictive effect for PTSD development [73, 521], coping strategies are found to be one of the most powerful and robust predictors for PTSD development [87, 88, 172, 217, 328, 490, 493]. In a variety of studies, including those which fortuitously measured coping style prior to exposure to a real-life trauma [217, 490], a causal relation appears to exist between coping and PTSD development. Those who tend to use denial as a coping strategy (e.g., "I say to myself 'this isn't real'"), self-distraction (e.g., "I turn to work or other activities to take my mind off things"), self-blame (e.g., "I blame myself for things that happened"), venting (e.g., "I express my negative feelings"), substance abuse (e.g., "I use alcohol or other drugs to help me get through it") and behavioural disengagement (e.g., "I give up trying to deal with it") when dealing with stress are most likely to develop PTSD. The classic explanation for why these coping strategies prove maladaptive and promote PTSD refers to the slightly paradoxical phenomenon that by actively avoiding thoughts or situations which lead to anxiety and fear, we in fact maintain their fear-inducing quality. A host of experimental evidence for example, shows that attempts to suppress unwanted thoughts are doomed to failure, and are, in fact, counterproductive with the thoughts returning even more strongly [743]. In contrast, successful adaptation to the experience of a trauma (as reflected in most psychological treatments for PTSD which involve exposure therapy) appears to involve the accessing of aversive emotions about the event, which permits habituation

to anxiety and the modification of one's trauma-related beliefs (i.e., disconfirming beliefs) through the processing, assimilation and accommodation to the experience [88, 165, 193].

Studies now consistently demonstrate that the experience of having suffered an SAH can be so traumatic that the patient can develop PTSD (see Table 4.1). Crucially, recent studies also provide compelling evidence that it is PTSD which is the most parsimonious explanation for SAH patients' psychiatric disturbance [47, 295, 314, 377, 540, 541, 627], with PTSD being found to account for more of SAH patients' psychiatric symptoms than any other psychiatric disorder [47]. Supporting PTSD's ability to explain SAH patients' abnormally high psychiatric disturbance is the finding of an abnormally high incidence of PTSD in the SAH population. Whilst the life-time prevalence of PTSD in the general population is between only 1-8% [23, 267, 351], two studies (using diagnostic criteria) have reported that 26-32% of SAH patients warrant a clinical diagnosis of PTSD following SAH [47, 295]. This represents *at least* three-times the normal rate.

Although there are some obvious caveats to applying the DSM-IV-TR diagnostic criteria and its associated features in a "rote or cookbook fashion" (p. xv), [190], it is clear that the symptom profile of SAH patients corresponds extremely closely to PTSD. SAH patients' misinterpretation of bodily sensations and feeling as if the haemorrhage were recurring for example, can be seen to reflect the PTSD symptoms of re-experiencing, whereby patients can act or feel as if they are actually reliving the traumatic experience [47, 313]. In addition, avoidant symptoms can be seen to be reflected in SAH patients' self-imposed restrictions which prevent them from thinking about their haemorrhage or from participating in activities and frequenting places that could remind them of the SAH [437]. Finally, the sense of

perpetual fear which SAH patients experience concurs closely with the well-known feature of PTSD [74, 171], whereby patients are found to feel anxious about the future, even though the trauma lies in the past. Such patients alter their beliefs, attributions and expectations about themselves, others and the world, in an extreme and maladaptive way [372]. For example, in the case of a female rape victim who develops PTSD, the woman comes to believe that all men could be potential rapists and/ or that the world is not a safe place. In line with the suggestion that SAH patients' unfounded fears of re-bleeding are a consequence of the development of PTSD is Hütter's [295] finding that SAH patients' degree of fear of haemorrhage recurrence is highly correlated in a positive manner with the degree to which they experienced different PTSD symptoms (r's ≥.62, all $p<0.001$).

To date, the available evidence suggests that PTSD is the best explanation for SAH patients' psychiatric symptom profile. Even though most SAH studies have examined relatively small samples (median size=47, interquartile range 39-59) [47, 295, 314, 377, 540, 541, 571, 627], the effect of PTSD in SAH patients has been of a sufficient magnitude that all but one of these studies [571] has detected concerning levels of PTSD (please note that this latter study is not included in Table 4.1 as insufficient details on SAH patients' psychiatric outcome was provided in the article which precluded its inclusion). It is important to recognise that the studies identifying PTSD in SAH patients have not only relied on screening measures, but also used more rigorous and comprehensive techniques, including the "gold-standard" technique of differential diagnosis [365]. This is important as many screening instruments often only measure for the presence of some PTSD symptoms, do not separate new from pre-existing symptoms, do not ask about the duration of the symptoms and do not assess the resultant functional impact that these symptoms

have [483]. Such measures can, therefore, potentially inflate the number of patients who are identified as having PTSD [615, 684].

As SAH patients' psychiatric symptoms occur within the context of the patients having a medical illness, it is important to highlight that the possibility of an alternative DSM-IV-TR diagnosis of Anxiety due to a General Medical Condition has been considered. However, it has not been found to be a more appropriate explanation for patients' symptoms. Such a diagnosis is appropriate only when the psychiatric disturbance is the direct physiological consequence of a medical condition and another primary disorder does not better account for the symptoms [23, 637]. No evidence suggests that SAH patients' psychiatric disturbance is aetiologically related to the haemorrhage (or its treatments). For example, no acute illness index, such as the severity and distribution of the person's SAH, its treatment, or its cause, has proved to be reliably associated with SAH psychiatric disturbance [105, 116, 242, 265, 280, 295, 297, 302, 469, 507, 543, 594, 687]. Moreover, indirect mechanisms by which medical conditions can cause psychiatric disturbance, such as via induced neuroendocrine dysfunction, have also not proved important [315, 539]. For example, Kreitschmann-Andermahr et al. [377] found that PTSD symptoms in SAH patients were not associated with any concurrent measure of their hormonal function.

Psychiatry officially recognises that medical events can precipitate PTSD [23, 455]. This is illustrated by its definition of a traumatic event as one which involves "actual or threatened death or serious injury, or a threat to the physical integrity of self or others" (p.467) [23]. Despite this official stance, the conceptualisation of a medical event (and hence an SAH) within the PTSD nosological framework is not without its difficulties [92, 476, 684], with some persons having questioned the validity of diagnoses of PTSD in medical patients. As this is an important point of debate, I will,

in the next section, briefly discuss some of the proposed difficulties in diagnosing PTSD in medical patients. Importantly, I will describe how I believe most criticisms over these persons' diagnoses can be potentially resolved and how the case for PTSD in SAH patients should not be viewed as ill-fated.

4.4 The validity of PTSD diagnoses in medical patients

Prior to 1994 [22], psychiatry did not officially recognise that a medical illness could elicit PTSD because it had been stated that *only* events 'outside the range of usual human experience' (p.236) could precipitate such a reaction [21]. It was epidemiological research however, which forced psychiatry to adopt its current, much broader definition of what actually constitutes a trauma, as it was repeatedly illustrated that there are few events which are *truly* rare from a statistical perspective and so outside usual human experience. Moreover, the actual events which caused PTSD were found to be more common than uncommon (e.g., assault, rape, motor vehicle accidents) [70, 134, 491]. Therefore, despite traditionally being associated with external traumatic events, such as natural disasters [417] and military combat [640], it is now officially recognised that medical events [30, 81, 89, 128, 167, 476, 534, 684], such as HIV infection (≤35%) [355], myocardial infarction (≤16%) [380] and cancer (≤32%)[479] can elicit PTSD. In re-examining the clinical events which SAH patients will typically experience (see Figure 2.5 in Chapter 2), it becomes clear that a spontaneous SAH and its treatment are (as the DSM-IV-TR's PTSD diagnostic criteria necessitates) not only life-threatening, but also have the potential to be intensely frightening [23]. In fact, it is already known that intensive care treatment (which SAH patients often receive) can alone frequently elicit PTSD [684].

Amongst the main reasons for current scepticism over the diagnosing of PTSD following a medical event are: 1) the methods of diagnosis (e.g., self-report measures) have not been validated on patients who have experienced a medical illness and patients could therefore confound traumatological symptoms with the direct effects of the illness and/ or its treatment (e.g., Criterion D symptoms of hyperarousal, such as insomnia, concentration difficulties, irritability) [20,21], 2) differences exist in the manner in which some patients experience some PTSD symptoms. For example, 're-experiencing' (Criterion B) is defined in terms of thoughts about past events (e.g. flashbacks to event, feeling like it was happening again), but some patients (e.g., cancer patients) who face the real possibility of relapse, have intrusions which are more future-orientated (e.g., 'Will the cancer progress to the point that I'm in so much pain that I would want to die?' 'Will my family be provided for once I am gone?') [14,22,23], and 3) it is unclear how a minority of patients develop PTSD following a medical trauma, despite having lost consciousness at the time. It has been understood that a person needs to have felt fear, helplessness or horror at the time of the trauma and that explicit memories of the trauma are necessary for the generation of and maintenance of PTSD (Criterion A).

There are some clinical difficulties in awarding a diagnosis of PTSD following a medical trauma (such as SAH). However, I do not believe that these issues raise any serious threat to the validity of diagnoses of PTSD in SAH patients, rather they represent theoretical and diagnostic challenges which future studies will need to address. In support of my argument is the fact that there is still much debate about the way PTSD expresses itself even in the case of more *traditional* traumas. For example, some question the diagnosis of PTSD in children who have experienced a *traditional* trauma because their symptomatology can be expressed in divergent ways

[136]. With regards to the issue of lack of memory of the event and how it is that persons following medical events can still develop PTSD, work is already beginning to emerge (from the field of traumatic brain injury) that helps to explain this. The work shows that a lack of consciousness at the time of the trauma does not preclude PTSD because the person can (1) still experience the traumatic event after they regain consciousness, (2) processing can occur at an implicit level, by-passing cortical structures (i.e., through the amygdala and related structures) during periods of impaired consciousness and (3) because some people appear to reconstruct memories or experiences which then 'become memories' that may provide the basis for the generation of PTSD symptoms [86, 218, 599]. Also, in the case of the difficulties of symptom overlap, evidence from the use of screening measures such as the Hospital and Anxiety Depression Scale [772], which are used for more general psychiatric disturbance, suggests that with the refinement of measures, it is possible to begin to control for the 'noise' of concurrent somatic disorders which can potentially present themselves when assessing a patient's psychiatric status. One of the most important pieces of evidence that supports the diagnoses of PTSD in some medical patients comes from a recent study by Pitman et al. [534] of cancer patients who had been diagnosed with PTSD using interview techniques. Pitman et al.'s study built upon the finding that classical PTSD patients are known to illustrate a triad of *unique* correlates on psychophysiological measures – namely, elevated arousal during periods of rest, an exaggerated startle response and physiological reactivity on exposure to cues symbolising or resembling an aspect of the traumatic event [516, 517, 535, 536, 624]. Crucially, Pitman et al. found that the cancer patients with PTSD illustrated exactly the same psychophysiological 'signature' as those persons who had suffered more traditional traumas (including military combat, sexual assault and

terrorism). Such findings appear to provide a 'biological' validation of medical patients' PTSD diagnoses, as the precision of 'objective' psychophysiological tests is not, like traditional interview techniques, vulnerable to the reliability of patients' reports or a clinician's ability to differentiate whether patients' symptoms are psychiatric in origin or not.

In summary, the available evidence supports the diagnosing of PTSD in SAH patients. With this in mind, in the next section I shall discuss some anecdotal evidence which motivates me to examine if the abnormally high incidence of PTSD in the SAH population can help explain SAH patients' poor psychosocial outcome.

4.5 Potential of PTSD to explain SAH patients' HRQoL and other unexplained disturbances?

Although it has never been comprehensively examined, the following tentative evidence hints that the abnormal incidence of PTSD in the SAH population could help explain SAH patients' reduced HRQoL. Firstly, PTSD in the wider literature is known to cause particularly severe levels of disability and handicap [82, 177, 348-350, 352, 459] which lead to a pattern and level of HRQoL impairment very comparable to that generally reported by SAH patients. Both conditions (i.e., SAH and PTSD in general) have been found to lead to worse HRQoL than that caused by other illnesses, including heart disease and diabetes (see Figure 2.6 Chapter 2 for SAH HRQoL profile compared to other illnesses) [10, 249, 422, 459, 514, 551, 585, 608, 662, 760]. In fact, the severity of this reduction in HRQoL in both conditions is second only to that associated with a Major Depressive Disorder. Secondly, although PTSD sufferers (like SAH patients) are known to experience impairment in *both* the Physical and Mental domains of HRQoL, they too experience especially pronounced

reductions in Mental HRQoL [10]. Although most evidence on the link between PTSD in general and HRQoL comes from cross-sectional studies, which precludes causal statements (e.g., it is not possible to conclude that HRQoL did not pre-date the onset of PTSD [464]), evidence is amounting to suggest a causal link between PTSD and HRQoL, as the treatment of PTSD results in improvement in HRQoL [56, 64, 422, 429, 454, 552, 656, 696].

In the context of discussing PTSD's potential explanative power for SAH HRQoL, it is interesting to note that PTSD could also explain two other mysterious aspects of SAH patients' outcome, namely, post-SAH chronic fatigue and sleep dysfunction [8, 90, 176, 185, 264, 265, 285, 313, 314, 360, 400, 409, 428, 465, 487, 504, 508, 510, 513, 572, 579, 609, 617, 643, 646, 649, 667, 669, 685, 718, 746]. SAH patients report persistently feeling excessively tired, weak, without energy and needing rest following even the most menial of tasks [313]. They also note that they have difficulty falling asleep, repeat awakenings and difficulty returning to sleep [609]. Even the most conservative of estimates suggests that a third of patients experience debilitating levels of fatigue [579], whilst around 20% report severe sleep dysfunction up to 7 years after the haemorrhage [510].

Although prior studies considering SAH patients' fatigue and sleep quality are limited by a failure to use validated instruments or to compare patients' complaints to normative levels, the two sets of difficulties have recently come to the fore as preliminary evidence suggests that they could be integral to patients' post-SAH social participation, including their work and socialisation [118, 313, 487, 541]. Unfortunately, these difficulties have gone untreated within clinical practice, often dismissed because their severity has not been properly gauged, but also because their origin has never been established [544]. Efforts have been made to explain their

presence as a result of the brain damage induced by an SAH (and its treatment) [65, 377, 509], but this mechanism does not stand up to much scrutiny (at least not as the principle cause of the problems). Kreitschmann-Andermahr et al. [377] for instance, reported that whilst in a group of 35 patients, SAH-induced neuroendocrine dysfunction was related to sleep and fatigue, 84% and 70% of variance in these respective scores was not accounted for by the hormonal dysfunction. In another study, Brandt et al. [65] found that in 10 patients reporting post-SAH fatigue, only 3 experienced obvious neuroendocrine disturbance. PTSD could potentially much better explain the development of the fatigue and sleep disturbance. Sleep dysfunction (as a result of intrusive nightmares and/or a difficulty getting to sleep and staying asleep) is a DSM-IV-TR symptom of PTSD [23, 251, 420], and increased somatic complaints, including fatigue, are well known to form part of the PTSD syndrome following other traumatic events [143, 199, 326, 392, 481]. Despite this strong indication that PTSD could cause these symptoms, this has never been examined. Nor has the relationship between sleep dysfunction and fatigue in SAH patients been determined.

As can be seen in Table 4.3, several small studies have found that psychiatric symptoms *in general* could be useful in explaining other aspects of SAH patients' psychosocial outcome. An exhaustive review of the literature identified only one (somewhat obscure) study published in a small book chapter [295], which had considered the value of PTSD symptoms for SAH patients' HRQoL. Although the study in question did provide some important insights and suggested a potential role for PTSD, it did not, for several reasons, satisfactorily resolve its importance. Firstly,

Table 4.3 Studies which formally examined the relation between SAH patients' psychiatric difficulties and psychosocial outcome

Study	N	Psychiatric predictor	Psychosocial measure	Follow-up (yrs)	Finding(s)
Artiola i Fortuny & Prieto-Valiente[17]	204	GHQ	Work; Leisure activities	1.5-5.5	**Work**: Psychiatric disturbance sig. associated with reduced work capacity. (Effect size not calculable). **Leisure activities:** Psychiatric disturbance sig. associated with reduced work capacity. (Effect size not calculable).
Carter et al. [105]	179	ZSRDS	Work; Social participation (RNL)	1.0-6.0	**Work:** In multivariate model, reduced mood sig. associated with reduced working capacity (odds ratio converted *r*=-.54, 29%*). **Social participation:** In multivariate model, reduced mood negatively associated with participation (odds ratio converted *r*=-.60, 36%*).
Fertl et al. [189]	40	BDI	Work; Life satisfaction (LQoLP)	1.8	**Work:** Reduced mood sig. associated with a reduced working capacity (*r*= -.56, 31%). **Life satisfaction:** Reduced mood sig. associated with reduced life satisfaction (*r*= -.46, 21%).
Hütter et al. [294]	58	BDI	Life satisfaction (FPI-R)	3.0	**Life satisfaction:** Reduced mood sig. associated with reduced life satisfaction (*r*= -.40, 16%).
Hütter [295]	45	IES	HRQoL (ALQI); Life satisfaction (FPI-R)	4.0	**HRQoL:** PTSD symptoms of avoidance and intrusion sig. associated with reduced HRQoL: Physical HRQoL *r*= -.40, 16%, Mental HRQoL *r*= -.50, 25%.
Lindberg et al. [397]	104	ZSRDS	Work; Leisure activity HRQoL (VAS)	7.0	**Work:** Reduced mood sig. associated with reduced working capacity (*r*= -.27, 8%). **Leisure activity:** Reduced mood sig. associated with reduced leisure activity (*r*= -.26, 7%). **HRQoL:** Reduced mood sig. associated with reduced HRQoL (*r*=.21, 4.4%).

Table 4.3 *Cont'd.*

Study	N	Psychiatric predictor	Psychosocial measure	Follow-up (yrs)	Finding(s)
Mayer et al. [438]	133	CES-D	HRQoL (SIP)	.25.	**HRQoL:** In multivariate model controlling for demographics, reduced mood sig. associated with reduced HRQoL: Physical HRQoL, additive adjusted r^2=15%; Mental HRQoL, additive adjusted r^2=56%.
Morris et al. [469]	36-52	HADS-Anxiety HADS-Depression	Work; Leisure activities		**Work:** Reduced mood on both scales associated with reduced working capacity: HADS-Anxiety r= -.36, 13%; HADS-Depression r= -.27, 8%).* **Leisure activities:** Reduced mood associated with reduced leisure activities: HADS-Anxiety r= -.48, 23.0; HADS-Depression r= -.56, 31%.**
Ogden et al. [504]	16	ZSRDS	Broad measures of social outcome (PAI)	5.0	**Social outcome:** ns.
Powell et al. [540]	48	Composite score (HADS; IES)	Work status (BICRO-39)	.75	**Work:** ns.
Powell et al. [541]	49	Composite score (HADS; IES)	Work status (BICRO-39)	1.5	**Work:** ns.

Note: ALQI=Aachen Life Quality Index [299, 302];BDI=Beck Depression Inventory [36]; BICRO-38=The Brain Injury Community Rehabilitation Outcome-39 scales [542]; CES-D=Center for Epidemiologic Studies Depression Scale [549]; FPI-R=Freiburger Personality Inventory-Revised [181, 182];GHQ=General Health Questionnaire [226]; HADS=Hospital Anxiety and Depression Scale [772]; HRQoL=Health-related quality of life; IES=Impact of Events Scale [288]; LQoLP=Lancaster Quality of Life Index [515]; sig.=significantly; ns=not statistically significant; PAI=Portland Adaptability Inventory [393]; RNL=the Reintegration into Normal Living Index [764]; SIP=Sickness Impact Profile [43]; VAS=Visual Analogue Scale [7]; ZSRDS=Zung Self Rating Depression Scale [774]; *effect size *r* for depression converted from odds ratio from multivariate model using conversion (ln(odds ratio)/1.81) [114, 580, 677]; ** effect not adjusted for use of non-parametric data as Fisher exact test most powerful test for nominal data used.[633] Three studies which are doublets for Mayer et al. [438] have also been published as abstracts, but these are not included in the table. [118, 440, 578]

the SAH patients' PTSD symptoms were indexed using only a screening measure (i.e., the Impact of Event Scale [288]), rather than an instrument which was explicitly tied to the DSM-IV-TR's diagnostic criteria. Secondly, only bivariate statistical analyses were conducted between PTSD and HRQoL. Therefore, we know nothing about the *relative* importance of PTSD compared to the traditional predictors used for HRQoL, such as age, clinical severity, cognitive impairment and physical disability. Thirdly, the relationship between PTSD and HRQoL came only from a single follow-up assessment with the patients, 4-years following their SAH. Therefore, the study tells us nothing about the importance of PTSD over time and whether or not it can help us to explain patients' HRQoL in both the short- and the long-term – information that is clearly important from a clinical, rehabilitative perspective. Fourthly, the sample on which the results were based was small (N=45) and seemingly selective, which raises questions as to the generalisability of the study's findings for the SAH population as a whole. And finally, the study in question did not examine whether any of the robust risk factors for PTSD in the wider literature – such as the use of maladaptive coping – were useful in predicting the development of PTSD in SAH patients, in either the short- or long-term.

4.6 Conclusions

In this theoretical review chapter I have argued that PTSD seems to hold great promise in being able to help us better explain SAH HRQoL. With this in mind, in the next chapter (Chapter 5), I present a comprehensive study in which I empirically examined the value of PTSD in explaining SAH patients HRQoL. The study also examined whether SAH patients' trait-coping style can help to predict the development of PTSD in both the short- and long-term. In respect to patients' fatigue and sleep dysfunction, I also measured SAH patients' complaints of these

difficulties using validated instruments, compared their scores to those of the general population (i.e. matched control subjects), and finally, evaluated the usefulness of PTSD in explaining their presence.

Chapter 5

An examination of the explanative value of PTSD in predicting patients' short- and long-term psychosocial outcome after a subarachnoid haemorrhage

Work presented in this chapter has previously appeared in:

Noble, A.J., Baisch, S., Mendelow, A.D., Allen, L., Kane, P. & Schenk, T. (2008). Posttraumatic stress disorder explains reduced quality of life in subarachnoid hemorrhage patients in both the short- and long-term. *Neurosurgery*, **63**: 1095-1105.

5.1 Introduction

Outcome research on subarachnoid haemorrhage (SAH) is confronted with a paradox. Conventional clinical measures such as the Glasgow Outcome Scale [318], which focus on the disability level of the disorder, suggest most SAH survivors can expect a moderate to good outcome, with little disability [90, 303]. In contrast, the more handicap-orientated measures of health-related quality of life (HRQoL) show that SAH patients experience a significantly reduced perceived sense of well-being in both the short- and long-term [377, 746]. Put simply: While neurologists/ neurosurgeons are mostly pleased with the outcome, patients and their carers are typically not [90]. How can this discrepancy be explained?

Neither the physical nor the cognitive impairments which are typically experienced post-SAH are severe enough to explain the HRQoL reduction [540, 541]. A meta-analysis which I presented in the previous chapter has also shown that other traditional SAH outcome predictors, such as age, sex, clinical severity and bleed severity are not useful explanative variables. As such, we have to look beyond traditional factors to find an explanation. One particularly promising candidate is post-traumatic stress disorder (PTSD).

Numerous recent studies have reported that an SAH can be sufficiently traumatic to elicit a PTSD-reaction, with SAH patients illustrating aspects of the disorder in both the short- and long-term [47, 295, 314, 377, 540, 541, 627]. Two such studies used diagnostic criteria and reported (at least) three times the 'normal' rate of PTSD in the SAH population [23, 47, 267, 295, 351]. Since PTSD has only recently been recognised as a disorder which can follow an SAH, its value in explaining patients' poor HRQoL has however, never been examined. Given that this disorder in general is known to cause significant functional impairment to its sufferers [10, 249, 422, 459, 514, 551, 585, 608, 662, 760], together with the fact that it is, on the whole, readily treatable and has known risk

factors (such as the use of maladaptive coping) [255], means that it is imperative that we examine and confirm whether or not it is a key determinant of SAH patients' poor HRQoL.

Interestingly, the arrival of the concept of PTSD to SAH research could also mean that other mysterious aspects of SAH patients' psychosocial outcome could be explained. In particular, patients frequently complain of excessive fatigue and sleep difficulties following their haemorrhage [541, 553, 571]. The failure for them to be properly measured and for their cause to be established though, has meant that they are often dismissed by neurosurgeons (who tend to classify them as purely subjective and therefore not deserving of treatment [544]). PTSD could however, offer a reasonable explanation for their presence. After all, we know that sleep dysfunction (in the form of nightmares and difficulties falling and staying asleep) is a diagnostic symptom of PTSD [23] and that somatic complaints are highly associated with the presence of PTSD. Therefore, SAH patients' reports of fatigue and sleep dysfunction could simply be illustrations of the abnormal presence of PTSD in the SAH population [29, 135, 143, 173, 291, 326, 531, 769]. In fact, it is even plausible, that the sleep dysfunction induced by PTSD causes their fatigue with day-time somnolence [119, 254, 663]. This proposed causal path from PTSD to sleep dysfunction to fatigue however has never been examined. Any such examination however in SAH patients, would also need to take into account the possible role of patients' neuropsychological deficits and neurological impairments which could also plausibly lead to fatigue and sleep dysfunction [705, 714].

To summarise the main points of the first part of this chapter, the evidence suggests that elevated levels of PTSD are found in the SAH population. This raises the possibility that PTSD could explain why SAH patients have low HRQoL, despite comparatively little physical/ cognitive disability [314, 409, 540, 541]. The

presence of PTSD could also explain these patients' mysterious symptoms of fatigue and sleep.

In this study, I therefore address the following questions:

(1) Can PTSD explain reduced HRQoL in SAH patients in both the short- and long-term?

(2) Is PTSD a better predictor of HRQoL than more traditional predictors, including physical/ cognitive disability?

(3) Is PTSD in the acute stages of recovery associated with worse HRQoL in the long-term?

(4) Why do some SAH patients develop PTSD while others do not?

(5) What is the relationship between PTSD, fatigue and sleep dysfunction?

To do this, a sample of SAH patients were followed with consecutive neuropsychological examinations at approximately 3 and 13 months post-ictus (assessment one and assessment two respectively). Patients were assessed with a comprehensive battery and regression analysis established the predictive values of PTSD, age, sex, clinical severity, time since illness and physical and cognitive disability for patients' HRQoL in the early and later stages of recovery. The relationship between PTSD, fatigue and sleep dysfunction was also examined and the role of coping-strategies in PTSD development following SAH was explored.

In designing this study to answer the above questions, I paid particular attention to addressing limitations within previous SAH studies. It is necessary to briefly discuss some of the resultant features of my study and the rationale behind them.

Firstly, the study examines a prospectively recruited sample, rather than a retrospective sample as is common to many prior SAH studies [12, 83, 129, 144, 189, 279, 302, 358, 376, 548, 752]. Prospective recruitment involves waiting for new SAH cases to occur and then attempting to recruit these participants. Given

the relative infrequency of SAH, retrospective techniques have proved more popular because these involve drawing participants from a large pool of patients who have already been treated (e.g., searching neurosurgical department records and recruiting from follow-up review clinics) [692]. This approach has the obvious advantage of (potentially) being able to generate sufficient numbers of participants in a shorter period of time as one can search departmental records as far back as needed until a sufficient sample size has been established. Retrospective recruitment techniques are however, amongst other things, especially susceptible to recruitment bias. For example, patients still under medical care or who have not been able to return to work may be more likely to participate in studies due to their increased availability [507]. Another disadvantage is that the samples of SAH participants generated by this technique are very heterogeneous, in terms of for example, the time since they had their SAH. Moreover, the rapid developments in the medical care of SAH, means that patients who have received different standards of treatment may be combined to form a single sample. Thus, in short, retrospective samples are not representative and are heterogeneous; prospective ones are more representative, homogeneous and therefore more likely to have the required sensitivity.

Secondly, despite their tendency to use retrospective designs, previous studies have typically examined only small samples of patients [123, 129, 189, 240, 244, 305, 306, 336, 367, 369, 377, 397, 470, 546, 548, 609, 613, 694, 703]. I on the other hand, study a large sample (in the context of the infrequent occurrence of SAH), by recruiting patients from two, rather than one regional neurosurgical treatment centre. This meant that a sample of 105 patients was recruited. This ensured that the statistical results are robust (e.g., the case-variable ratio assumption for multiple regression models was met).

Thirdly, a representative sample of patients was recruited. This is in contrast to nearly all previous studies which used very restrictive inclusion criteria which resulted in only a select group of the SAH population typically being included – namely those who presented at hospital in the acute stages, in a good clinical state and had made a favourable physical recovery at the point of discharge. Though these patients are less challenging to recruit, the restricted inclusion criteria meant that a proportion of patients who are perfectly able to provide informed consent and participate are always excluded. Studies have also often excluded the 15-25% of SAH patients whose haemorrhage was not due to the rupture of a cerebral aneurysm. This is because it has been assumed that most of these excluded patients – namely, those whose bleed was of an unknown origin – have suffered what is considered a benign sub-form of SAH because it is associated with a less dramatic clinical course (i.e., a more gradual onset, no ischemic damage, no surgical intervention, limited extension of blood [710]). Increasing evidence however, suggests that this assumption is incorrect and that SAH patients' neuropsychological and psychosocial outcome is largely independent of the aetiology of the bleed, with a common pattern of deficits resulting regardless of the origin of the haemorrhage [78, 176, 301, 302, 324, 428, 502, 504, 572, 628, 644]. In fact, some contend that those patients whose bleed was of an unknown origin could experience a worse psychiatric outcome. It has been argued for example, that a patient whose bleed was of an identifiable origin, such as a ruptured aneurysm, may leave the hospital more confident as the source of their haemorrhage has been "cured" and knowing that their chances of a further SAH are minimal. In contrast, a person whose bleed was of an unidentified origin and so remains untreated, may worry more about the likelihood of a further SAH. It has been postulated that these patients may be burdened by this additionally, (though unfounded) ever-present peril [211, 295, 306, 504, 572].

A final limitation of previous studies addressed by the present study is that patients' neurological disabilities have not previously been measured using instruments with a high degree of ecological validity. Prior studies for example, used only classic neuropsychological tests which are designed not to predict behaviour, but rather to localise lesions [203, 276]. The use of these measures could have served to attenuate the relationship between patients' scores on cognitive tests and their HRQoL. Since in this chapter I am examining the relative value of PTSD, I felt it sensible to adopt a conservative approach and compare its explanative value next to neurological variables indexed using sensitive measures with a high degree of ecological validity.

5.2 Methods

Patients

A prospective and consecutive series of 105 non-institutionalised patients was studied. Patients were recruited from a potential population of 186 first-time victims of spontaneous SAH, admitted to Newcastle General or James Cook University Hospital between April 2005 and August 2006. Of the non-participators, 6 were excluded for geographic reasons, 1 did not speak English and 74 declined participation.

SAH diagnosis was established by CT, or if negative, xanthrochromia in cerebrospinal spinal fluid was considered diagnostic. Aneurysms were demonstrated by spiral computed tomography or catheter angiography.

Age and sex-matched controls were recruited from the U.K. general population to provide sleep and fatigue data to compare to that of SAH patients. Control subjects were recruited through personal contacts and recreational clubs.

This study was granted multi-centre approval by the Central Manchester Research Ethics Committee. Informed consent was obtained from all participants.

Procedure

Patients completed two comprehensive neuropsychological assessments at their homes or at a laboratory at Durham University. Following a brief introductory interview, the patient's HRQoL, attention, memory and executive function were examined. Patients were then left with a series of self-report measures to examine their psychiatric status, fatigue and sleep dysfunction. These were then either returned to me using a pre-paid envelope or collected at a later date. The two appointments were conducted at approximately 3 (Assessment 1) and 13 (Assessment 2) months post-ictus. The neuropsychological appointments lasted

approximately 3.5 hours (including regular breaks taken according to the requirements of the individual patient).

Measures

Instruments were chosen on the basis of having robust psychometric properties and ecological validity for cognitive tasks [95, 107, 139, 194, 197, 238, 563, 657, 734, 754-756]. Each of these items is detailed below. A complete list of these instruments along with a shortened description can also be found in Table 5.1. Please note that parallel versions of the TEA and RBMT-E were used at assessments one and two.

The Short-Form 36 (SF-36) [734] assesses HRQoL across 8 domains: 1) 'Physical Functioning', 2) 'Physical Role Limitations', 3) 'Bodily Pain', 4) 'General Health', 5) 'Energy', 6) 'Social Functioning', 7) 'Emotional Role Limitations' and 8) 'Mental Health'. Scores range from 100 (no reduction) to 0 (maximum reduction). Standard algorithms – derived from principal component analyses – aggregated scores from the eight domains into two summary scores for regression: 'Physical HRQoL' and 'Mental HRQoL'. Scores from domains 1-4 mostly contribute to 'Physical HRQoL', whilst domains 5-8 contribute most to 'Mental HRQoL' (see Figure 3.2, Chapter 3 for schematic of the structure and questions of the SF-36) [733].

The Post-traumatic Diagnostic Scale [194] assesses whether patients warrant a DSM-IV-TR diagnosis of PTSD (see Table 4.2, Chapter 4 for diagnostic symptoms of PTSD) [23]. It provides a PTSD symptom severity score and a functional impairment index for those diagnosed. For use in some regression analyses, a 'PTSD Symptom Severity' score was calculated for all patients regardless of PTSD diagnosis. PTSD is usually only diagnosed if patients have experienced intense fear, helplessness or horror at the time of the trauma. Given

Table 5.1 Summary of neurological, neuropsychological and psychosocial instruments used in the study

Purpose	Test	Information
Screening	*Behavioural Inattention Test (BIT)* [756]; *Short Token Test* [139].	These tests screened for unilateral visual neglect and linguistic deficits. They were completed at assessment one and were used to establish whether administration of the remaining battery was appropriate.
Global mental status	*Mini-Mental State Examination (MMSE)* [197].	This was completed at assessment one only and was used to establish global cognitive status for all patients. This brief index was then used in missing value analysis to assess if those failing to complete a subsequent test significantly differed in cognitive status from those with complete data.
Health-related quality of life	*Short-Form-36 (SF-36)* [734].	Measured health-related quality of life (HRQoL) across 8 domains (see Figure 3.2, Chapter 3). 'Physical HRQoL' and 'Mental HRQoL' summary scores were generated for regression analyses using standard algorithms.
Post-traumatic stress disorder	*Post-traumatic Stress Diagnostic Scale (PDS)* [194].	This measure assesses whether a patient warranted a DSM-IV diagnosis of post-traumatic stress disorder (PTSD) in relation to their SAH experience. It provides a PTSD symptom severity score and a functional impairment index. PTSD is usually only diagnosed if patients experienced intense fear, helplessness or horror at the time of the trauma. Given SAH can lead to loss of consciousness at the time of trauma, this criteria was relaxed. The effect of this modification was minimal and merely permitted diagnosis of PTSD in two more patients at assessment one and three more patients at assessment two.
Fatigue	*Multidimensional Fatigue Symptom Inventory–Short Form (MSFI-SF)* [657].	Fatigue measured across the following scales: General Fatigue, Physical Fatigue, Mental Fatigue, Emotional Fatigue and Vigour. The sum of the fatigue subscales minus the 'Vigour' scale generated a Total Fatigue Score.

Table 5.1 *Cont'd.*

Purpose	Test	Information
Cognition	*Test of Everyday Attention (TEA)* [563]; *Behavioural Assessment of the Dysexecutive Syndrome (BADS)* [754]; *Rivermead Behavioural Memory Test – Extended (RBMT-E)* [755].	Attention tasks: 'Visual Elevator', 'Telephone Search', 'Telephone Search Dual Task', 'Elevator Counting' and 'Lottery'. Executive subtests: 'Rule Shift Cards', 'Key Search', 'Modified Six Elements', 'Temporal Judgment', and 'Zoo Map'. Memory subtests: 'Story Immediate' and 'Delayed', 'Picture Recognition', 'Face Recognition', 'Orientation and Date', 'First Names 'Second Names', and 'Appointments and Belongings'.
Sleep	*Pittsburgh Sleep Quality Index (PSIQ)* [95].	Sleep measured across the following scales: Subjective Sleep Quality, Latency, Duration, Habitual Sleep Efficiency (hours slee hours in bed), Disturbances, Sleep Medication Use, Daytime Dysfunction and Global Sleep score.
Physical disability	*Functional Independence Measure – Motor Scale (FIM-MS)* [238].	Independence was measured across 13 tasks. Increasing values indicate greater levels of independence in mobility, self-ca and continence.
Coping	*Brief Cope Inventory* [107].	Measured patients' dispositional use of 'Maladaptive Coping Strategies', 'Venting', 'Denial', 'Substance Use', 'Behaviour Disengagement' and 'Self-Distraction'. This measure was completed at assessment one only.

that SAH can sometimes lead to loss of consciousness around ictus and so the aforementioned feelings are not necessarily experienced, this criterion was relaxed. The effect of this modification in my use of the diagnostic criteria was minimal, but allowed me to include two more patients at assessment one and three more patients at assessment two (patients who would have otherwise been excluded). The prevalence of sub-threshold/ sub-syndromal PTSD (i.e., a syndrome of symptoms below the threshold for the DSM-IV diagnosis of full-PTSD) in the patient sample was also recorded. Sub-threshold/ sub-syndromal PTSD (hereafter referred to as just sub-syndromal PTSD) was defined, according to recent guidelines [477], as a syndrome in which the threshold for Criterion C (Avoidance) and/or D (Arousal) was not reached, but there was at least one symptom of each of these criterion present. These symptoms, along with those of Intrusion (Criterion B), must have been present for at least one month (Criterion E) and have caused significant distress and/ or functional impairment (Criterion F).

The Multidimensional Fatigue Symptom Inventory – Short Form (MFSI-SF) [657] assesses how much patients experience fatigue symptoms. The MFSI-SF is comprised of the following 5 subscales: 1) General Fatigue (e.g., "I feel shattered"), 2) 'Physical Fatigue' (e.g., "My legs feel weak"), 3) 'Mental Fatigue' (e.g., "I am confused"), 4) 'Emotional Fatigue' (e.g., "I am distressed") and 5) 'Vigour' (e.g., "I feel energetic). Subjects are asked to base their responses on their experience of the preceding week. Higher scores, except for 'Vigour', indicate more fatigue (0-24). The sum of the fatigue subscales minus the 'Vigour' subscale generates a Total Fatigue Score (ranging from -24 to 96).

The Functional Independence Measure – Motor Subscale (FIM-MS) [238] measures physical disability. Physical independence is measured on 7-point scales across the following 13 tasks: eating, grooming, bathing, dressing (lower body, upper body), toileting, bladder management, bowel management, transfers

to/from bed/chair/wheelchair, transfers to/from toilet, transfers to/from bath/shower, walking and stairs. Increased values indicate greater levels of independence in mobility, self-care and continence.

The Test of Everyday Attention (TEA) [563] assesses attention. The following tasks were used: 'Visual Elevator', 'Telephone Search', 'Telephone Search Dual Task', 'Elevator Counting' and 'Lottery'.

The Behavioural Assessment of the Dysexecutive Syndrome (BADS) [754] measures executive skills. The following tests were used: 'Rule Shift Cards', 'Key Search', 'Modified Six Elements', 'Temporal Judgment', 'Key Search', 'Zoo Map' and 'Modified Six Elements'.

The Rivermead Behavioural Memory Test - Extended (RBMT-E) [755] measures everyday memory function. This battery was specifically designed to detect milder, more subtle memory deficits. The following tests were used: 'Story Immediate' and 'Delayed', 'Picture Recognition', 'Face Recognition', 'Orientation and Date', 'First Names', 'Second Names' and 'Appointments and Belongings'. For further details on the specific memory tests which comprise this battery, as well as for the tests included in the attention and executive batteries, please refer to Appendix VIII.

The Pittsburgh Sleep Quality Index (PSIQ) [95] measures sleep quality over the preceding month. The sleep component scores generated were: 'Subjective Sleep Quality', 'Latency', 'Duration', 'Habitual Sleep Efficiency' (hours sleep: hours in bed), 'Disturbances', 'Use of Sleep Medication' and 'Daytime Dysfunction'. Component scores ranged from 0-3. The sum of these yielded a 'Global PSIQ Sleep' score (0-21), where higher scores indicate worse sleep.

The Brief COPE Inventory [107] measured patients' dispositional use of 'Maladaptive Coping Strategies' ('Venting', 'Denial', 'Substance Use', 'Behavioural Disengagement', 'Self-Distraction' and 'Self-Blame'). Higher scores denote more

frequent use. Internal consistency was satisfactory. This measure was only taken at assessment one.

The Mini-Mental State Examination (MMSE) [197] was completed at assessment one only and was used to establish global cognitive function in patients. This brief index was then used in missing value analyses to assess whether those failing to complete a subsequent test significantly differed in cognitive status from those with complete data.

Behavioural Inattention Test (BIT) [756]. The BIT Line Bisection and Star Cancellation tests were used to screen for signs of unilateral neglect.

The Short Token Test [139] screens for linguistic deficits by asking patients to follow increasingly complex commands. This and the two previous tasks were used to establish whether administration of the remaining test battery was appropriate.

Data Analysis

With large numbers of comparisons in some analyses, alpha levels were adjusted (Bonferonni) as appropriate to compensate for family-wise error and keep the alpha-level at 5%. The adopted values are reported in the corresponding paragraphs of the Results section. When missing data exceeded 5%, a missing value analysis assessed its impact on the results' generalisability by examining if incompleteness was dependent on any variable (Little MCAR test) and whether cases with missing data were comparable to those without (t-tests; variables considered age, sex, clinical severity, haemorrhage type, treatment type and MMSE). For the purposes of brevity, I only report on the results of missing variable analyses when a significant result was found. Spearman's correlations were used to examine the correlations between the main outcome measures of 'Mental HRQoL', 'Physical HRQoL', PTSD, fatigue and sleep at each assessment. For

regression analyses, beta values (*standardized ß*) and squared semi-partial correlations (sr^2_i) indicated relative and unique predictor contributions. The backward elimination method of variable entry/ selection (likelihood ratio test for logistic regression) was used in the regression analyses to identify the most parsimonious predictor variables. Stepwise block entry regression was also used in a few instances to examine the unique explanative ability of a variable once the variance accounted for by other variables was controlled for. Case-variable ratios were satisfactory for regression models. Where possible, effect sizes (ES) in the form of the correlation coefficient *r* are reported for all results. Analyses were conducted using commercially available software (SPSS).

Health-Related Quality of Life (HRQoL). Kruskal-Wallis one-way analyses of variance determined the normality of patients' SF-36 scores by comparing their scores to reference values [60]. Three- and thirteen month 'Physical HRQoL' and 'Mental HRQoL' determinants were explored using Spearman's correlation and multiple linear regression. Parametric regression techniques were most appropriate for this ordinal data due to the number of occupied categories, and due to the fact that it was fair to assume an underlying continuum and an equal distance between each ordinal point of the SF-36 [727]. Predictors considered were: age, sex, clinical severity as indexed by the World Federation of Neurological Surgeons (WFNS) scale [164], history of previous illness vs. none, the 'Overall Cognitive Function' index, 'FIM-MS' score and 'PTSD Symptom Severity' score from the same assessment point. Further regression analyses, this time using stepwise variable entry (2 blocks), were conducted to examine 1) the *unique* ability of SAH patients' PTSD detected at the short-term assessment to predict the HRQoL these patients reported at the long-term assessment and 2) any change that had occurred between patients' short-term HRQoL and long-term HRQoL (indexed as a patient's long-term HRQoL minus their short-term HRQoL).

In the first block, traditional variables from the acute stages of a patient's illness and short-term assessment – namely their age, sex, WFNS score, history of previous illness vs. none, 'Overall Cognitive Function' score and 'FIM-MS' score – were entered and formed the predictive model. The variance which these predictors accounted for was therefore controlled. In the second entry block, the patient's 'PTSD Symptom Severity' score from the short-term assessment was then entered into the model and its unique explanative value was established. The Wilcoxon matched-pairs signed-ranks test compared patients' assessment one and assessment two SF-36 scores.

Post-traumatic Stress Disorder (PTSD). The severity and functional impairment of the PTSD for those diagnosed is described. The rate of PTSD in the SAH sample (both at assessments one and two) was compared to that expected in the general population [23]. Logistic regression examined the following predictors for PTSD at both time points: age, sex, WFNS grade, psychiatric history vs. none, aneurysmal SAH (ASAH) vs. non-ASAH, surgery vs. not, endovascular vs. not, education and dispositional use of 'Maladaptive Coping Strategies'. For this kind of analysis the odds ratio (OR) can be used to interpret the two regression models. The OR indicates the change in the odds of having or not having PTSD when the value of a predictor increases by one unit. The c-statistic measures the discriminative power of the two regression equations. Varying from 0.5 (predictions are no better than chance) to 1.0 (model predicts without error), it is the percentage of case pairs to which the models correctly assigns a higher probability. The Wilcoxon matched-pairs signed-ranks test and McNemar's test of symmetry were used to compare the PTSD reported at assessments one and two.

Sleep and Fatigue. Kruskal-Wallis analyses compared patients' PSQI and MFSI-SF scores to those of controls to determine the normality of SAH sleep and fatigue. Fatigue or sleep levels which were equal to or greater than the levels

found at the lower borders of the 90th quantiles were judged to be abnormal. The proportion of abnormal fatigue ('Total Fatigue' score) and sleep ('Global PSIQ Sleep' score) were calculated. Determinants of fatigue ('Total Fatigue' score) and sleep quality at assessments one and two ('Global PSIQ Sleep' score) were explored by regression. Again, with assumptions (see comments in the paragraph on the use of linear regression analysis for HRQoL), parametric regression procedures were used to identify the predictors for these two ordinal variables. Predictors considered for sleep were: age, sex, WFNS grade, ASAH vs. other type, 'Overall Cognitive Function' index, 'psychiatric history vs. none' and 'PTSD Symptom Severity' score. The predictors of fatigue were the same except for the addition of a 'Global PSIQ Sleep' score. Mann-Whitney U tests were used to further explore the sleep and fatigue experienced by those with and those without PTSD, whilst Spearman's correlation tests examined the relationship between sleep quality and concurrent fatigue. The Wilcoxon matched-pairs signed-ranks test compared the quality of sleep and fatigue reported at assessments one and two.

Physical Disability. Median scores across 'FIM-MS' items were calculated. The proportion of patients with disability at assessments one and two was calculated (<6 indicates dependence). The Wilcoxon matched-pairs signed-ranks test compared FIM-MS scores from assessment one and two.

Cognition. Using normative data [564, 754, 755], 'Attention', 'Memory' and 'Executive Function' indexes were generated from performances on the assessments. Indexes are based on the following scale: 4-Exceptional, 3-Good, 2-Average, 1-Poor and 0-Impaired. Scoring instructions from the RBMT-E and BADS manuals generated the 'Memory Function' and 'Executive Function' indexes respectively. For the 'Executive Function' index, the labels adopted were mapped onto the labels used in the BADS as follows: "very superior" = 4-excellent, "high

average/ superior" = 3-good, "average" = 2-average, "borderline/ low average" = 1-poor and "impaired" = 0-impaired. As no standard TEA procedure exists for generating an 'Attention Function' index, I scored TEA subtest performances (directed by accepted guidelines [248]) as follows: TEA ≥98% = 4-excellent, ≥75% = 3-good, ≥25% = 2-average, ≥2% = 1-poor and <2% = 0-impaired. TEA lottery task performance, which in its original format is scored according to cut-offs, was awarded the following: TEA "impaired" = 0-impaired; "borderline" = 1-poor and "normal" = 3-good. The 'Attention Function' index was the median score on the subtests. For the purposes of regression analyses, 'Overall Cognitive Function' indices were generated for patients to represent cognitive performance on each respective assessment. These indices were calculated by summing the 'Attention', 'Memory' and 'Executive' indexes from the respective assessment. Changes in cognitive performance from assessment one to assessment two were analysed by Wilcoxon test.

5.3 Results

The recruited patient group consisted of 60 women and 45 men. No differences existed between participators and non-participators in age, sex, WFNS grade, haemorrhage type, or treatment (all $P>0.05$; Little's MCAR: $P=.082$). All 105 patients were examined at assessment one, but 10 patients (9.5%) were lost from the sample at assessment two (Table 5.2). The reason for the reduced sample was due to one patient death and the remaining nine patients declining to participate in assessment two. No significant differences existed between the patients who were examined at assessment two and those who were not ($P>0.05$), with no pattern to the missing data being found (Little's MCAR: $P=.549$). Average follow-up for assessment one was 109 days after SAH (SD 49.95; range 24-251) and 406 days after SAH for assessment two (SD 47.82; range 335-672). In total,

Table 5.2 Demographic and clinical data of patients examined at assessments one and two

Factor	Value (%)	
	Assessment one (N=105)	Assessment two (N=95)
Mean age at assessment ± SD (range) (yr)	52.4 ± 11 (31-80)	53.0 ± 11 (32-81)
Women	60 (57.1)	54 (56.8)
Education (yr)	11.6± 1.51 (10-20)	11.6± 1.6 (10-20)
Aneurysmal SAH	77 (73.3)	67 (70.5)
Location of ruptured aneurysm		
ACoM/ ACA	34 (44.2)	31 (46.3)
ICA	19 (24.7)	14 (20.9)
MCA	19 (24.7)	17 (25.4)
Vertebrobasilar	5 (6.5)	5 (7.5)
Unknown origin	25 (23.8)	25 (26.3)
Other origin	3 (2.9)	3 (3.2)
WFNS grade		
I	74 (70.5)	66 (69.5)
II	15 (14.3)	13 (13.7)
III	5 (4.8)	5 (5.3)
IV	10 (9.5)	10 (10.5)
V	1 (1)	1 (1.1)
Primary treatment		
Endovascular	47 (44.8)	40 (42.1)
Surgery	32 (30.5)	29 (30.5)
Conservative	26 (24.8)	26 (27.4)
Significant history *		
Physical only	18 (17.1)	15 (15.8)
Psychiatric only	15 (14.3)	15 (15.8)
Both	16 (15.2)	15 (15.8)

Note: ACA=anterior cerebral artery; ACoM=anterior communicating artery; ICA=internal carotid artery; n=number; MCA=middle cerebral artery; N=number; SD=standard deviation; Vertebrobasilar =vertebrobasilar system artery; WFNS=World Federation of Neurological Surgeons; yr=year. *Self-reported illness receiving/ received formal treatment. Physical illness: benign intracranial hypertension; cancer; epilepsy; Guillain-Barre syndrome; human immunodeficiency virus; hypothyroidism; ischemic stroke; kidney cyst; meningioma; multiple sclerosis; myocardial infarction; pulmonary emphysema; Raynaud's phenomenon; recurrent pneumothorax; rheumatoid arthritis; road traffic accident injuries; sleep apnoea; spondylosis; transient ischemic attack; tuberculosis. Psychiatric illness: Anxiety unspecified diagnosis; Depression unspecified diagnosis and Alcohol abuse.

87 controls were recruited to complete the sleep and fatigue measures. Controls were comparable to their matched SAH patient in age (assessment one M=53.28, SD 9.68, range 28-77; assessment two M=52.73, SD 10.94, range 28-77) and sex (assessment one 43 females; assessment two 51 females; all $P>0.05$).

Outcome measures

Assessment one

Health-Related Quality of Life (HRQoL). HRQoL was assessed in 103 patients, with patients scoring significantly worse across all domains compared to reference values (Adjusted alpha $P<0.006$; Figure 5.1).

Post-traumatic Stress Disorder (PTSD). PTSD was assessed in 97 patients. Thirty-six (37.1%) patients were diagnosed with PTSD. In the general population a prevalence of ≤8% is expected [23, 267, 351]. Symptom severity for those diagnosed at assessment one was "moderate to severe" (median 22, interquartile range [IQR]=14-31) and caused "severe" functional impairment (75%). A further 10 patients (10.3%) met the criteria for sub-syndromal PTSD. The severity of these patients' PTSD syndrome was categorised as mild (median=9.5, IQR=6-10), but nevertheless, still severely impaired the majority (80%). A missing value analysis revealed that those with missing data (7.6%) were more cognitively impaired at a global level (MMSE; $t_{7.4}= 3.2$, $P<0.02$).

Fatigue and Sleep. Fatigue and sleep measures were completed by 73 patients. Patients showed significantly worse fatigue compared to controls across all domains, with 59% experiencing pathological fatigue (all $P<0.002$; Adjusted alpha $P<0.008$). The sleep of 45% of patients at assessment one was pathological. SAH patients illustrated significantly poorer sleep quality in terms of

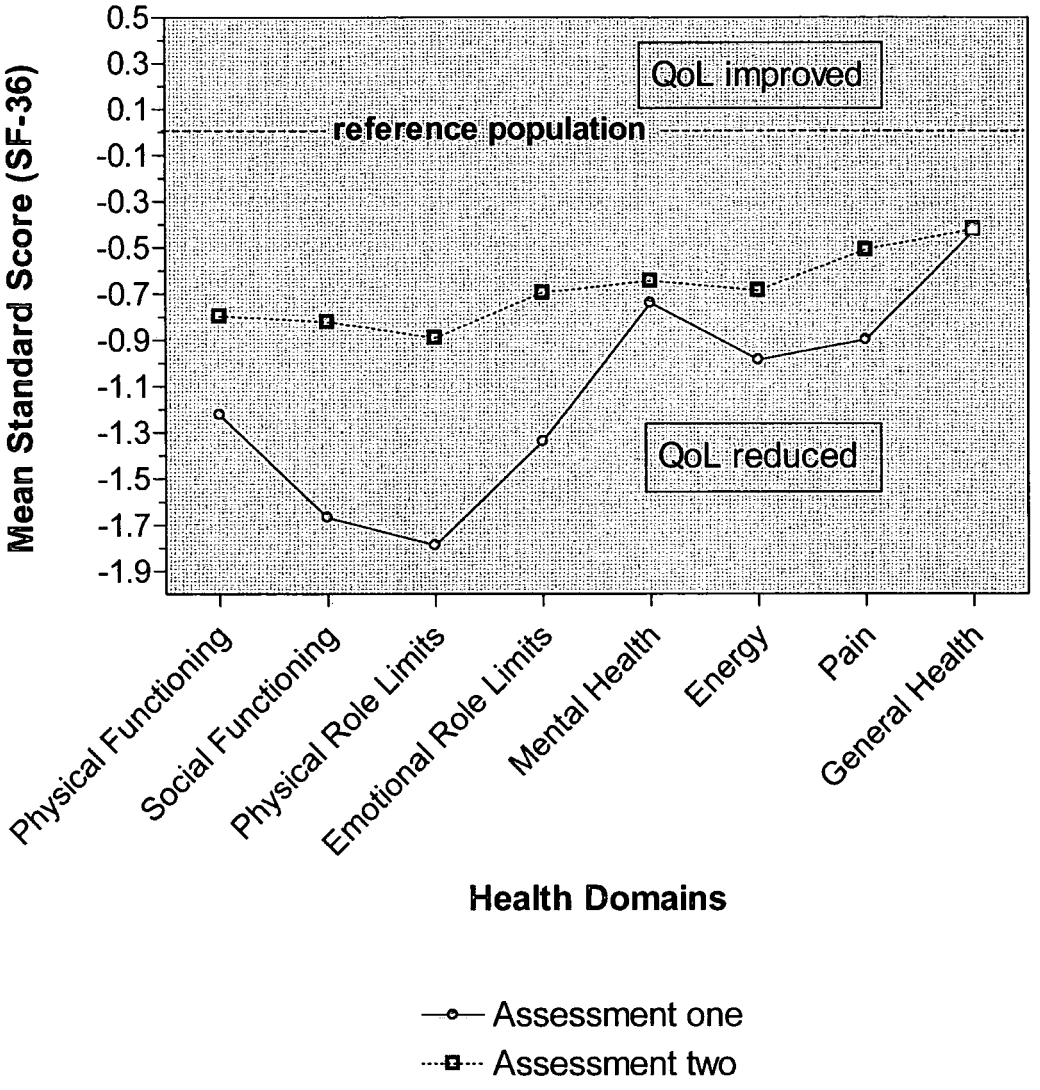

Figure 5.1 Graph showing the SF-36 HRQoL profile of patients at assessments one and two. Deviations from reference data are expressed in mean standard scores. All deviations from reference values are significant ($P<0.05$), except 'Emotional Role Limitations' at assessment two.

Table 5.3 Comparison of fatigue and sleep of patients and controls at assessments one and two

Factor	Assessment one SAH patients			Assessment one Matched controls			Assessment one patients vs. controls *P*-value	ES	Assessment two SAH patients			Assessment two Matched controls			Assessment two patients vs. controls *P*-value	ES	Assessment one vs. assessment two patients *p*-value	ES
	N	Median	IQR	N	Median	IQR			N	Median	IQR	N	Median	IQR				
Fatigue - MFSI-SF																		
General Fatigue	73	13.0	5.0 - 16.5	73	5.0	2.0 - 8.0	<0.0001	.41	87	8.0	4.0-17.0	87	4.0	2.0-8.0	<0.0001	.28	ns	.11
Physical Fatigue	73	6.0	3.0 - 12.0	73	1.0	0.0 - 4.0	<0.0001	.47	87	5.0	2.0-10.0	87	2.0	0.0-5.0	<0.0001	.34	ns	.05
Emotional Fatigue	73	5.0	1.0 - 11.0	73	2.0	0.0 - 5.0	<0.002	.28	87	4.0	1.0-10.0	87	2.0	0.0-5.0	<0.002	.25	ns	.05
Mental Fatigue	73	8.0	4.0 - 13.5	73	3.0	2.0 - 6.0	<0.0001	.36	87	8.0	5.0-13.0	87	3.0	1.0-6.0	<0.0001	.41	ns	.19
Vigour	73	8.0	5.0 - 12.0	73	13.0	9.0 - 15.0	<0.0001	.41	87	8.0	6.0-12.0	87	13.0	10.0-17.0	<0.0001	.44	ns	.16
Total Fatigue	73	26.0	3.0 - 44.0	73	0.0	-8.0 - 13.0	<0.0001	.45	87	18.0	2.0-39.0	87	-2.0	-10.0-12.0	<0.0001	.43	ns	.04
Sleep - PSIQ																		
Subjective Sleep Quality	73	1.0	0 - 2.0	73	1.0	0 - 1.0	ns	.14	87	1.0	1.0-2.0	87	1.0	0.0-1.0	<0.02	.20	ns	.18
Sleep Latency	73	1.0	0 - 3.0	73	1.0	1 - 2.0	ns	.11	87	1.0	0.0-2.0	87	1.0	0.0-2.0	ns	.08	ns	.01
Sleep Duration	73	0.0	0 - 1.5	73	1.0	0 - 1.0	ns	.07	87	1.0	0.0-2.0	87	1.0	0.0-1.0	ns	.05	ns	.09
Habitual Sleep Efficiency	73	1.0	0 - 3.0	73	0.0	0 - 1.0	<0.007	.33	87	1.0	0.0-2.0	87	1.0	0.0-1.0	ns	.14	ns	.05

Table 5.3 *Cont'd.*

Factor	Assessment one SAH patients			Assessment one Matched controls			Assessment one patients vs. controls *P*-value	ES	Assessment two SAH patients			Assessment two Matched controls			Assessment two patients vs. controls *P*-value	ES	Assessment one vs. assessment two patients *P*-value	ES
	N	Median	IQR	N	Median	IQR			N	Median	IQR	N	Median	IQR				
Sleep – PSIQ Cont'd.																		
Sleep Disturbances	73	1.0	1 - 2.0	73	1.0	1 - 2.0	ns	.13	87	1.0	1.0-2.0	87	1.0	1.0-2.0	ns	.06	ns	.08
Use of Sleep Medication	73	0.0	0 - 0.0	73	0.0	0 - 0.0	ns	.14	87	0.0	0.0-0.0	87	0.0	0.0-0.0	ns	.07	ns	.04
Daytime Dysfunction	73	1.0	1 – 2.0	73	1.0	0 – 1.0	<0.009	.22	87	1.0	1.0-2.0	87	1.0	0.0-1.0	<0.007	.21	ns	.10
Global PSIQ Sleep Score	73	7.0	3.5 – 10.5	73	6.0	3.5 – 8.0	<0.04	.17	87	6.0	4.0-11.0	87	6.0	4.0-8.0	ns	.14	ns	.01

Note: ES=effect size (*r*); IQR = interquartile range; MFSI-SF = Multidimensional Fatigue Symptom Inventory – Short Form; N = number; ns = non significant. PSIQ = The Pittsburgh Sleep Quality Index; higher PSIQ scores denote greater sleep difficulties. For comparisons between patients and controls, the critical alpha =<0.05. The adjusted alphas for comparison of patients' fatigue and sleep scores from assessment one and two were <0.008 and <0.006 respectively. Higher MFSI-SF scores denote more fatigue, except for the factor 'vigour'. Values are expressed as medians

'Habitual Sleep Efficiency' (Adjusted alpha P<0.007; Table 5.3).

Physical Disability. The physical status of 99 patients was examined. Only 4.0% of patients illustrated dependence (Table 5.4).

Cognition. There was notable decline in memory function, with 33.3% of the 102 assessed patients being classified as "impaired". This contrasts with the 2.12% found within healthy controls as reported by test makers. Less attentional (5.8%) and executive (12.7%) impairment was found (Table 5.4).

Assessment two

Health-Related Quality of Life (HRQoL). HRQoL was assessed in 94 patients. Compared to reference values and using an unadjusted alpha level of 0.05, patients scored significantly worse across all domains at assessment two, except in 'Emotional Role Limitations' (P=0.202; Figure 5.1). According to an adjusted alpha of P<0.006, SAH patients' HRQoL was also no longer different to reference values in terms of Physical Functioning (P=0.023) and General Health (P=0.031). Patients' scores did however, still significantly differ in the areas of Physical Role Limitations (P<0.003), Bodily Pain (P<0.006), Energy (P<0.0001), Social Functioning (P<0.001) and Mental Health (P<0.004).

Post-traumatic Stress Disorder (PTSD). PTSD was assessed for in 89 patients. Thirty-three (37.1%) patients were diagnosed with the disorder. Symptom severity for those diagnosed was "moderate" (median=18, IQR=12-30) and caused "severe" functional impairment for the majority (82%). A further 12 (13.5%) patients fulfilled the criteria for sub-syndromal PTSD. These patients' syndromes were typically only mild in severity (median=6.0, IQR=5-10), but still caused 41.7% of the patients "severe" functional impairment.

Fatigue and Sleep. Fatigue and sleep measures were completed by 87 patients. Patients showed significantly worse fatigue compared to controls across

Table 5.4 Summary of results from cognitive and physical examinations in assessments one and two

Factor	Assessment one SAH patients				Assessment two SAH patients				Assessment one versus two *P*-value	ES
	N	Median	IQR	Percentage in clinical range	N	Median	IQR	Percentage in clinical range		
Cognition										
RBMT-E Memory Function	102	1.0	0.0 - 1.0	33.3	95	1.0	0.0 - 1.0	29.5	ns	.15
BADS Executive Function	102	2.0	1.0 – 2.0	12.7	95	2.0	1.0 - 3.0	13.7	ns	.06
TEA Attention Function	103	2.0	1.0 – 2.0	5.8	95	2.0	1.0 - 3.0	8.4	ns	.04
Physical										
FIM-motor scale	99	7.0	7.0 - 7.0	4.0	87	7.0	7.0 - 7.0	8.0	ns	.09

Note: BADS=Behavioural Assessment of the Dysexecutive Syndrome; FIM-motor scale=Functional Independence Measure motor scale items. FIM-motor scale scores range from 1 (total dependence) to 7 (totally independent); IQR=interquartile range; N=number; ns=non significant; RBMT-E=Rivermead Behavioural Memory Test; TEA=Test of Everyday Attention. Cognitive function indexes range from 0 (impaired) to 4 (Excellent). Percent in clinical range for FIM was a median total motor score <6 (dependent on other person) and for cognitive tests it was a function score of 0 ("impaired"). For comparison of assessment one and two cognitive performances adjusted alpha *P*=0.01. Alpha for comparison of FIM-motor scale score *P*=0.05. Values are expressed as medians.

all domains – 36% reported pathological levels of fatigue (all P <0.002; Adjusted alpha P<0.0008). The only significantly reduced sleep score was seen in the domain of 'Daytime Dysfunction' (Adjusted alpha P<0.007). Sleep function was pathological in 37% of patients (Table 5.3).

Physical Disability. The physical status of 87 patients was examined. Eight percent of patients illustrated dependence (Table 5.4).

Cognition. In total, 95 patients were cognitively assessed. There was substantial memory dysfunction, with 29.5% of patients classified as "impaired" at assessment two. Much less attentional impairment (8.4%) and executive impairment (13.7% at assessment two) impairment was found (Table 5.4).

Comparison of assessment one and two performances

Health-Related Quality of Life (HRQoL). For the 93 patients who completed the SF-36 at both assessments, significant improvements in scores were seen at assessment two in the domains of 'Physical Functioning' (P<0.001, r=.36), 'Physical Role Limitations' (P<0.0001, r=.54), 'Bodily Pain' (P<0.006, r=.29), 'Social Functioning' (P<0.001, r=.57) and 'Emotional Role Limitations' (P<0.001, r=.36; Adjusted alpha P<0.006). Importantly, no significant improvement in SF-36 was seen in 'General Health' (P= 0.77, r=.03), 'Energy' (P= 0.03, r=.22) or 'Mental Health' (P= 0.13, r=.16).

Post-traumatic Stress Disorder (PTSD). For the 82 patients who completed PTSD assessments at both time points, the Wilcoxon test did not detect any significant difference in the number (P= 0.80; r=.03) or severity of PTSD symptoms experienced (P= 0.33; r=.11). Nor did it detect any significant difference in the experience of intrusive (P= 0.632; r=.05), avoidant (P= 0.189; r=.15) and arousal symptoms (P= 0.693; r=.04) at the two assessments (Adjusted alpha P< 0.01). A non-significant McNemar's test of symmetry indicated that the proportion of

patients with and without PTSD at the two assessments was comparable (P>0.05): Specifically, 75.6% of patients had the same PTSD status at the two assessments. A missing value analysis found that those without complete PTSD data (21.9%) from the first and second assessment were more cognitively impaired according to the MMSE ($t_{25.7}$= 2.9, P<0.009).

Fatigue and Sleep. Wilcoxon analyses of the Global PSIQ Sleep score and MFSI-SF Total Fatigue score from the 58 patients examined at both assessment points, revealed no significant change in sleep quality or fatigue levels (both P>0.05; Table 5.3).

Physical Disability. A Wilcoxon analysis of the physical disability scores of the 86 patients with complete 'FIM-MS' data from both assessments did not detect any significant change in physical status between assessments (P>0.05; Table 5.4).

Cognition. Wilcoxon analyses found there to be no significant improvement between assessments one and two, as measured by the 'Memory' (n=94; P= 0.157), 'Executive' (n=93; P= 0.542) or 'Attention' (n=93; P= 0.694) indexes (Adjusted alpha P<0.02; Table 5.4).

Correlation matrix

Tables 5.5 and 5.6 present the correlations between the main outcome variables of 'Mental HRQoL', 'Physical HRQoL', 'PTSD Symptom Severity', 'Total Fatigue' score and 'Global Sleep Quality' score at assessment one and assessment two respectively.

Table 5.5 Matrix of correlations between main outcome variables at assessment one

Assessment one	'Mental HRQoL' (SF-36 MCS)			'Physical HRQoL' (SF-36 PCS)			'Total Fatigue Score' (MFSI-SF)			'Global Sleep Quality' (PSQI)		
	N	r_s	***P-value***	**N**	r_s	***P-value***	**N**	r_s	***P-value***	**N**	r_s	***P-value***
'Mental HRQoL' (SF-36 MCS)	-	-	-	-	-	-	-	-	-	-	-	-
'Physical HRQoL' (SF-36PCS)	93	.010	ns	-	-	-	-	-	-	-	-	-
'Total Fatigue Score' (MFSI-SF)	68	-.588	<0.0001	68	-.272	<0.03	-	-	-	-	-	-
'Global Sleep Quality Score' (PSQI)	69	-.475	<0.0001	69	-.243	<0.05	68	.507	<0.0001	-	-	-
'PTSD Symptom Severity' (PDS)	93	-.630	<0.0001	93	-.240	<0.0001	68	.783	<0.0001	69	.575	<0.0001

Note: Assessment one= approximately 3 months post-ictus; MCS= Mental Component Score; MFSI-SF= Multidimensional Fatigue Symptom Inventory – Short Form; N=number; ns= non-significant *P*>0.05; PCS= Physical Component Score; PDS= Post-traumatic Stress Diagnostic Scale; PSIQ= Pittsburgh Sleep Quality Index; SF-36= Short-Form-36.

Table 5.6 Matrix of correlations between main outcome variables at assessment two

Assessment one	'Mental HRQoL' (SF-36 MCS)			'Physical HRQoL' (SF-36 PCS)			'Total Fatigue Score' (MFSI-SF)			'Global Sleep Quality' (PSQI)		
	N	r_s	***P-value***	**N**	r_s	***P-value***	**N**	r_s	***P-value***	**N**	r_s	***P-value***
'Mental HRQoL' (SF-36 MCS)	-	-	-	-	-	-	-	-	-	-	-	-
'Physical HRQoL' (SF-36PCS)	85	.267	<0.02	-	-	-	-	-	-	-	-	-
'Total Fatigue Score' (MFSI-SF)	78	-.782	<0.0001	78	-.365	<0.002	-	-	-	-	-	-
'Global Sleep Quality Score' (PSQI)	79	-.450	<0.0001	79	-.188	Ns	78	.509	P<0.0001	-	-	-
'PTSD Symptom Severity' (PDS)	80	-.688	<0.0001	80	-.310	<0.006	78	.761	P<0.0001	79	.535	<0.0001

Note: Assessment two= approximately 13 months post-ictus; MCS= Mental Component Score; MFSI-SF= Multidimensional Fatigue Symptom Inventory – Short Form; N=number; ns= non-significant *P*>0.05; PCS= Physical Component Score; PDS= Post-traumatic Stress Diagnostic Scale; PSIQ= Pittsburgh Sleep Quality Index; SF-36= Short-Form-36.

Predictive models

Table 5.7 provides a survey of those factors which proved significantly predictive in regression analyses for each outcome measure.

Table 5.7 A survey of those factors which proved to be significant risk factors in regression analyses

Outcome	Risk factor	Assessment one			Assessment two		
		ß/ OR	*sr^2_i*	*P-value*	*ß/ OR*	*sr^2_i*	*P-value*
Mental HRQoL*	Age	-	-	ns	-	-	Ns
(SF-36 MCS)	Sex	-	-	ns	-	-	Ns
	Clinical severity (WFNS)	-	-	ns	-	-	Ns
	History of previous illness	-	-	ns	-	-	Ns
	Overall cognitive function (TEA; RBMT-E; BADS)	-	-	ns	-	-	Ns
	Physical disability (FIM-MS)	-	-	ns	-	-	Ns
	PTSD symptom severity (PDS)	-.581	30%	<0.0001	-.626	35%	<0.0001
	Model Summary	R^2= 0.44; $F_{4,84}$= 16.70, *P*<0.0001			R^2 = 0.48; $F_{2,79}$ = 35.98, *P*<0.0001		
Physical HRQoL*	Age	-	-	ns	-	-	Ns
(SF-36 PCS)	Sex	-	-	ns	-	-	Ns
	Clinical severity (WFNS)	-	-	ns	-	-	Ns
	History of previous illness	-.334	11%	<0.0001	-	-	Ns
	Overall cognitive function (TEA; RBMT-E; BADS)	-	-	ns	-	-	Ns
	Physical disability (FIM-MS)	.424	18%	<0.0001	.429	18%	<0.0001
	PTSD symptom severity (PDS)	-	-	ns	-.411	15%	<0.0001
	Model Summary	R^2= 0.30; $F_{2,86}$= 18.80, *P*<0.0001			R^2 = 0.43; $F_{3,78}$ = 19.42, *P*<0.0001		
PTSD** *(PDS)* §	Age	0.92	-	<0.005	-	-	Ns
	Sex	-	-	ns	-	-	Ns
	Clinical severity (WFNS)	-	-	ns	-	-	Ns
	Psychiatric history	-	-	ns	-	-	Ns
	Aneurysmal vs. non aneurysmal haemorrhage	-	-	ns	-	-	Ns
	Surgery vs. non-surgical intervention	-	-	ns	-	-	Ns
	Endovascular vs. non-endovascular intervention	-	-	ns	-	-	Ns
	Education	-	-	ns	-	-	Ns
	Maladaptive coping (Brief COPE)	3.67	-	<0.0001	3.22	-	<0.0001
	Model Summary	c=.85; χ^2[3, N=95] =32.77, *P*<0.0001			c=.78; χ^2[1, N=81] =18.41, *P*<0.0001		

Table 5.7 *Cont'd.*

Outcome	Risk factor	Assessment one			Assessment two		
		ß/ OR	*sr^2_i*	*P-value*	*ß/ OR*	*sr^2_i*	*P-value*
Fatigue***	Age	-	-	Ns	-	-	Ns
(MFSI-SF)	Sex	-	-	Ns	-	-	Ns
	Clinical severity (WFNS)	-	-	Ns	-	-	ns
	Aneurysmal vs. non aneurysmal haemorrhage	-	-	Ns	-	-	ns
	Overall cognitive function (TEA; RBMT-E; BADS)	-	-	Ns	-	-	ns
	Psychiatric history	-	-	Ns	-	-	ns
	Sleep function (Global PSIQ Score)	-	-	Ns	-	-	ns
	PTSD symptom severity (PDS)	.786	49%	<0.0001	.796	58%	<0.0001
	Model Summary	R^2= 0.64; $F_{3,65}$= 37.75, *P*<0.0001			R^2= 0.58; $F_{2,84}$= 58.31, *P*<0.0001		
Sleep* *(PSIQ)*	Age	-	-	Ns	-	-	ns
	Sex	-	-	Ns	-	-	ns
	Clinical severity (WFNS)	-	-	Ns	-	-	ns
	Aneurysmal vs. non aneurysmal haemorrhage	-	-	Ns	-	-	ns
	Overall cognitive function (TEA; RBMT-E; BADS)	-	-	Ns	-	-	ns
	Psychiatric history	-	-	Ns	-	-	ns
	PTSD symptom severity (PDS)	.532	27%	<0.0001	.652	42%	<0.0001
	Model Summary	R^2= 0.38; $F_{2,67}$= 20.71 *P*<0.0001			R^2= 0.45; $F_{2,85}$= 34.98 *P*<0.0001		

Note: *= <0.007; **= <0.005; ***= <0.006; Assessment one= approximately 3 months post-SAH; assessment two= approximately 13 months post-SAH; ß=standardised beta coefficient; MFSI-SF= Multidimensional Fatigue Symptom Inventory – Short Form; OR= Odds-ratio; P= P-value; PDS= Post-traumatic Stress Diagnostic Scale; PSIQ= Pittsburgh Sleep Quality Index; SF-36 MCS= Short-Form-36 Mental component health-related quality of life score; SF-36 PCS= Short Form-36 Physical health-related quality of life component Score; sr2i= squared semi-partial correlations; §= Logistic regression, rather than linear regression. -= Predictor not significant. This table presents the explanative importance and P-values of significant predictors in the regression analyses. Backward elimination methods (likelihood ratio tests in the case of logistic regressions) were used to identify parsimonious predictors. Please refer to the 'Data analysis' section for further information on the predictors included in each regression model.

Assessment one

Health-Related Quality of Life (HRQoL). Due to missing data of some of the patients, regression analysis was based on 93 patients. Bonferonni-correction led to the adoption of a test-wise alpha of *P*<0.007.

'Mental HRQoL': 44% of variance in 'Mental HRQoL' was accounted for (R^2= 0.443; $F_{4,84}$= 16.698, P<0.0001). Only 'PTSD Symptom Severity' scores were significantly predictive (squared semi-partial correlation [sr^2_i]=30%; *standardized ß*= -.581; P<0.0001). Demographic, cognitive and physical disability information demonstrated no predictive value for 'Mental HRQoL' (Figure 5.2).

'Physical HRQoL': 30% of variance in 'Physical HRQoL' was accounted for (R^2= 0.304; $F_{2,86}$= 18.801, P<0.0001). Physical disability contributed most (FIM-MS; sr^2_i= 18%; *standardized ß* = .424; P<0.0001), followed by history of significant illness (sr^2_i = 11%; *standardized ß* = -.334; P<0.0001).

Post-traumatic Stress Disorder (PTSD). Due to missing data, this regression analysis was based on 95 patients. Bonferonni-correction led to the adoption of a test-wise alpha of P<0.005.

A significantly effective logistic model to predict PTSD was generated (χ^2 [3, N= 95] = 32.767, P< 0.0001). Predominant use of 'Maladaptive Coping Strategies' (OR= 3.670, CI 1.967 – 6.845; Wald= 16.707 (1) P<0.0001) and younger age (OR= 0.917, CI 0.867 – 0.971; Wald= 8.726 (1), P<0.005) significantly increased the probability of PTSD. Using a probability criterion of .5, predictive classification was excellent (c= 0.85), with the model assigning 85% of all possible pairs the correct probability of having PTSD (sensitivity= .71; specificity= .87; Figure 5.3). Table 5.8 presents a comparison of the symptoms and coping skills of those patients with and without PTSD.

Fatigue. Bonferonni-correction led to the adoption of a test-wise alpha of P<0.006.

A significantly predictive model for the 73 who completed the MFSI-SF at assessment one was generated – accounting for 64% of variance in 'Total Fatigue' scores (r= 0.797; R^2= 0.635; $F_{3,65}$= 37.750, P<0.0001). The model was based solely

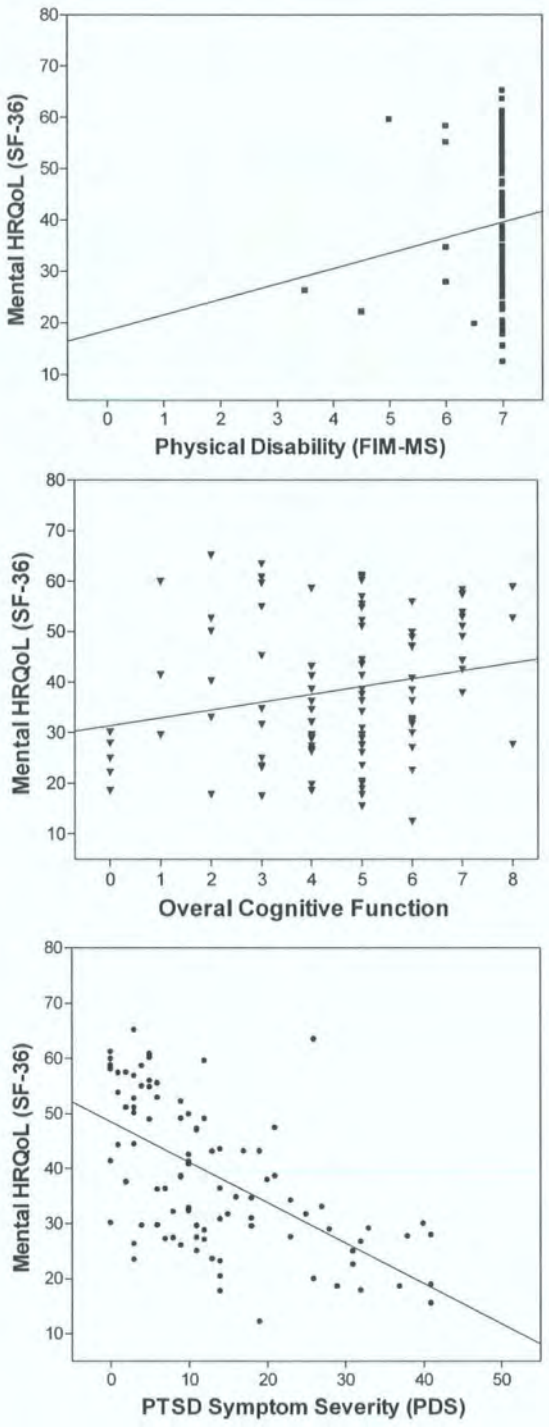

Figure 5.2 Graphs of relationship between 'Mental HRQoL' and 'PTSD Symptom Severity' (upper), 'Cognition' (middle) and 'Physical Disability' (lower) at assessment one.

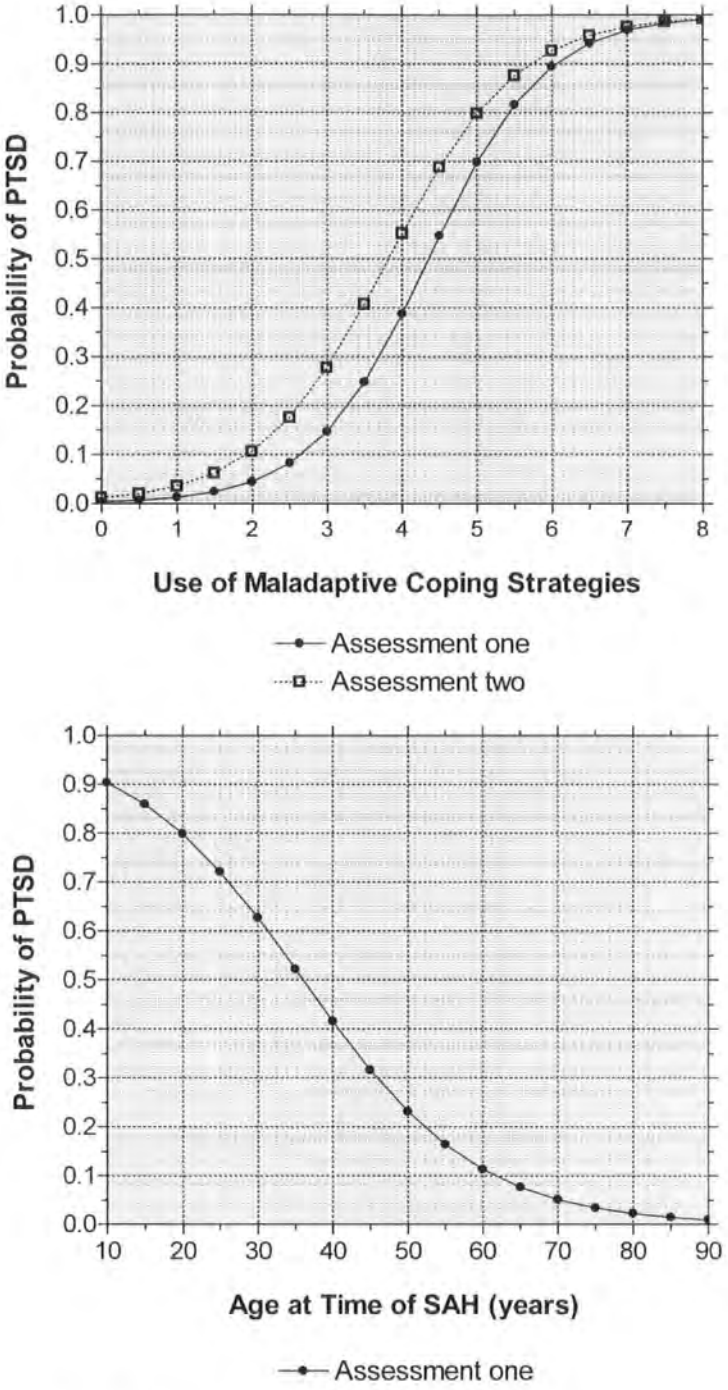

Figure 5.3 Graph depicting the relationship between probability of PTSD at assessments one and two with use of maladaptive coping strategies (upper; assessment one OR = 3.670; age held at mean; assessment two OR = 3.216) and relationship between PTSD and age at assessment one (lower; OR = 0.917; with use of maladaptive coping strategies held at mean level).

Table 5.8 Comparison of symptoms and coping skills of patients with and without post-traumatic stress disorder at assessments

Factor	Assessment one With PTSD			Assessment one Without PTSD			*P*-value	ES	Assessment two With PTSD			Assessment two Without PTSD			*P*-value	ES
	N	Median	IQR	N	Median	IQR			N	Median	IQR	N	Median	IQR		
PTSD – PDS																
Intrusions	36	4.0	2.0 - 5.0	61	1.0	0.0 - 2.0	<0.0001	.62	33	3.0	2.0 - 5.0	56	1.0	0.0 - 2.0	<0.0001	.66
Avoidance	36	5.0	4.0 - 6.0	61	2.0	1.0 - 3.0	<0.0001	.67	33	4.0	4.0 - 7.0	56	1.0	0.3 - 2.8	<0.0001	.74
Arousal	36	4.0	3.0 - 5.0	61	2.0	1.0 - 3.0	<0.0001	.58	33	4.0	3.0 - 5.0	56	2.0	1.0 - 3.0	<0.0001	.60
Symptom Severity	36	22.0	14.0 - 31.0	61	5.0	3.0 - 11.0	<0.0001	.69	33	18.0	12.0 - 30.0	56	5.0	3.0 - 8.0	<0.0001	.73
Coping - Brief COPE §																
Maladaptive coping	35	4.0	3.2 - 4.7	59	2.8	2.3 - 3.3	<0.0001	.45	29	3.7	3.0 - 4.6	53	2.5	2.3 - 3.4	<0.0001	.47
Self Distraction	35	5.0	3.0 - 7.0	59	4.0	3.0 - 5.0	<0.005	.32	29	5.0	3.5 - 7.0	53	4.0	2.0 - 5.0	<0.01	.29
Denial	35	4.0	2.0 - 6.0	59	2.0	2.0 - 3.0	<0.0001	.45	29	3.0	2.0 - 5.0	53	2.0	2.0 - 3.0	<0.0001	.39
Substance Use	35	2.0	2.0 - 3.0	59	2.0	2.0 - 2.0	Ns	.10	29	2.0	2.0 - 4.0	53	2.0	2.0 - 2.0	ns	.14
Behavioural Disengagement	35	3.0	2.0 - 5.0	59	2.0	2.0 - 3.0	<0.005	.30	29	2.0	2.0 - 4.0	53	2.0	2.0 - 3.0	ns	.18
Venting	35	3.0	2.0 - 5.0	59	3.0	2.0 - 4.0	Ns	.16	29	3.0	3.0 - 4.5	53	2.0	2.0 - 3.0	<0.005	.33
Self-Blame	35	4.0	3.0 - 6.0	59	2.0	2.0 - 4.0	<0.002	.35	29	4.0	3.0 - 5.5	53	2.0	2.0 - 4.5	<0.003	.34

Notes: ; IQR = interquartile range; N = number; ; ns = non significant p>0.05; PDS = Posttraumatic Stress Diagnostic Scale; PDS scoring is presented as the median number of intrusive (e.g., "reliving the brain haemorrhage, acting or feeling as if it was happening again"), avoidant (e.g., "trying to avoid activities, people or places that remind me of the brain haemorrhage") and arousal (e.g., "feeling irritable or having fits of anger") symptoms experienced; § Brief COPE results taken at assessment one (3-months post-SAH) used for prediction of PTSD at both assessment points. Brief COPE scoring ranges from 1 ("strategy usually not used") to 4 ("strategy usually used a lot"). Values are expressed as medians.

on 'PTSD Symptom Severity' scores (sr^2_i= 49%; *standardised ß*= .786; *P*<0.0001). Patients with PTSD reported significantly more 'Total Fatigue' than those without (Mann Whitney, *P*<0.0001; *r*=.44).

Sleep. Bonferonni-correction led to the adoption of a test-wise alpha of *P*<0.007.

A significantly predictive model for the 73 who completed the PSIQ accounted for 38% of variance in 'Global PSIQ Sleep' scores (*r*= 0.618; R^2= 0.382; $F_{2,67}$= 20.708 *P*<0.0001). The model was based solely on 'PTSD Symptom Severity' scores (sr^2_i= 27%; *standardised ß*= .532; *P*<0.0001). Significantly worse sleep ('Global PSIQ Sleep' score) was reported by patients with PTSD (Mann Whitney, *P*<0.0001; *r*=.28). Sleep quality was significantly associated with concurrent fatigue (r_s= .49, P<0.0001).

Assessment two

Health-Related Quality of Life (HRQoL). Due to missing data, regression analysis was based on 89 patients. Bonferonni-correction led to the adoption of a test-wise alpha of *P*<0.007.

'Mental HRQoL': 48% of variance in 'Mental HRQoL' was accounted for (R^2 = 0.477; $F_{2,79}$ = 35.979, *P*<0.0001). Only the 'PTSD Symptom Severity' score was significantly predictive (sr^2_i = 35%; *standardised ß* = -.626; *P*<0.0001). Demographic, cognitive and physical disability information demonstrated no predictive value (Figure 5.4).

'Physical HRQoL': 43% of variance in 'Physical HRQoL' was accounted for (R^2 = 0.428; $F_{3,78}$ = 19.415, *P*<0.0001). Physical disability scores (FIM-MS; sr^2_i = 18%; *standardized ß* = .429; *P*<0.0001) contributed most, followed closely by 'PTSD Symptoms Severity' scores (sr^2_i = 15%; *standardised ß* = -.411; *P*<0.0001).

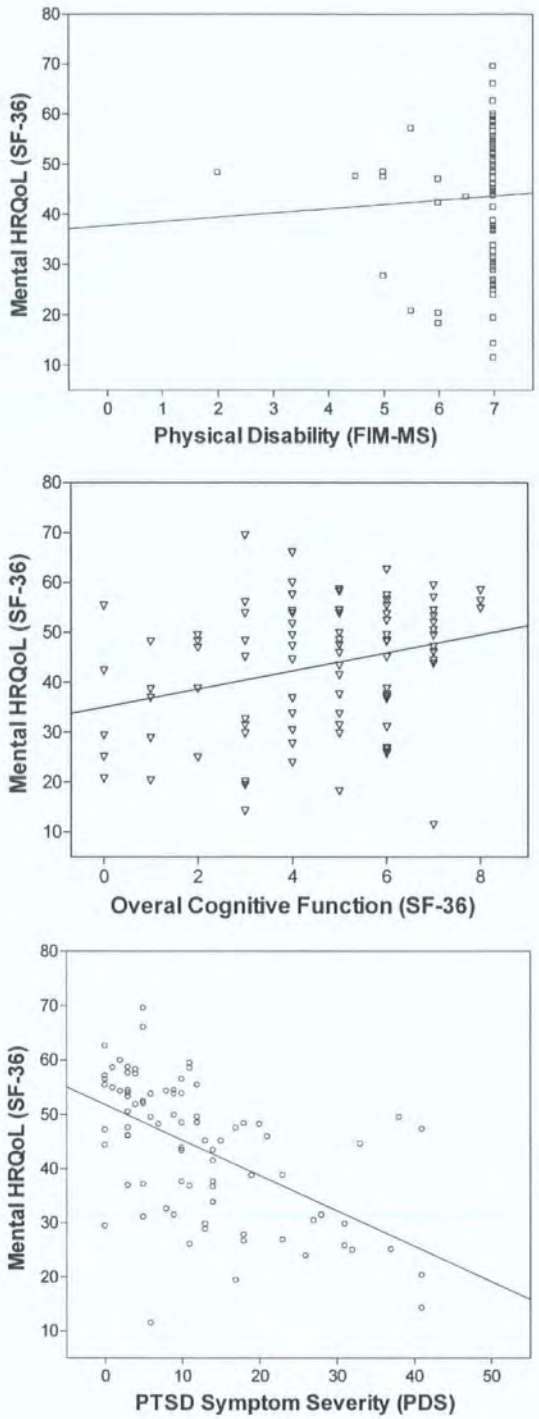

Figure 5.4 Graphs of relationship between 'Mental HRQoL' and 'PTSD Symptom Severity' (upper), 'Cognition' (middle) and 'Physical Disability' (lower) at assessment two.

Prediction of patients' long-term HRQoL by their experience of PTSD in the acute stages: Due to missing data, analysis was based on 83 patients. Bonferonni-correction led to the adoption of a test-wise alpha of $P<0.007$.

'Mental HRQoL': A patient's experience of PTSD in the short-term ('PTSD Symptom Severity' assessment one) held a large and negative relationship with the 'Mental HRQoL' which they experienced in the later stages (assessment two): $r_s = -.597$, $P<0.0001$.

Regression analysis using stepwise block entry revealed that the degree to which a patient experienced PTSD in the short-term had a unique predictive effect for their longer-term 'Mental HRQoL' (Table 5.9). An initial predictive model based on information about the severity of a patient's illness, their demographics and the degree to which they experienced neurological sequelae in the short-term could explain around 23% of variance in patients' long-term 'Mental HRQoL': $R^2 = 0.226$, $F_{6,76} = 3.703$, $P<0.004$). The addition of information about the patient's experience of PTSD in the acute stages – namely 'PTSD Symptom Severity' score from assessment one – significantly improved the model's overall predictive ability: $F_{1,75} = 20.101$, $P<0.0001$. With its inclusion, a total 39% of variance in 'Mental HRQoL' could be accounted for ($R^2 = 0.390$, $F_{7,75} = 6.843$, $P<0.0001$). Increasing PTSD severity was associated with a worse 'Mental HRQoL': $ß = -.484$; $t = -4.483$, $P<0.0001$.

'Physical HRQoL': A patient's experience of PTSD in the short-term ('PTSD Symptom Severity' assessment one) held only a small and negative relationship with the 'Physical HRQoL' which they experienced in the later stages (assessment two): $r_s = -.248$, $P<0.03$.

Stepwise regression analysis revealed that once the variance accounted for by traditional predictors was controlled for, patients' PTSD symptomatology in the short-term holds no unique significant predictive effect for long-term 'Physical

HRQoL': $F_{1,75}$= 3.595, *P*>0.05; Table 5.9. The initial predictive model based on traditional predictive information was however, significantly predictive – explaining approximately 30% of variance in patients' long-term ' Physical HRQoL': R^2 = 0.284, $F_{6,76}$= 5.031, P<0.0001.

Prediction of improvement in patients' HRQoL between assessment one and two by information about the patients' experience of PTSD in the acute stages: Due to missing data, analysis was based on 83 patients. Bonferonni-correction led to the adoption of a test-wise alpha of *P*<0.007.

'Mental HRQoL': A patient's experience of PTSD in the short-term ('PTSD Symptom Severity' assessment one) did not hold a significant bivariate relationship with the change in their 'Mental HRQoL' that occurred between assessment one and two: r_s= .148, N=85 *P*>0.05.

The subsequent stepwise regression analysis revealed that it was not possible to significantly predict the change in patients' 'Mental HRQoL' that occurred between assessments one and two using either the initial model based on traditional predictors (R^2 = 0.133, $F_{6,76}$= 1.939, *P*>0.05), or with the addition of information about the patients' experience of PTSD at assessment one (R^2 = 0.137, $F_{7,76}$= 0.368, *P*>0.05; Table 5.9).

'Physical HRQoL': A patient's experience of PTSD in the short-term ('PTSD Symptom Severity' assessment one) did not hold a significant relationship with the change in their 'Physical HRQoL' that occurred between assessments one and two: r_s= -.032, N=85 *P*>0.05.

Table 5.9 The unique predictive ability of PTSD at assessment one (short-term) for patients' HRQoL at assessment two (long-term)

Factor	Model 1				Model 2			
	N	ß	sr^2_i	*P-value*	N	ß	sr^2_i	*P-value*
Predicting improvement in HRQoL								
'Mental HRQoL' (*SF-36 MCS*)								
Age	83	-.152	.022	ns	83	-.128	.014	Ns
Sex	83	.188	.032	ns	83	.164	.021	Ns
Clinical severity (WFNS)	83	.175	.025	ns	83	.175	.030	Ns
History of previous illness	83	.039	.001	ns	83	.022	$.441^{E-03}$	Ns
Overall cognitive function (TEA; RBMT-E; BADS)	83	-.038	.001	ns	83	-.034	$.961^{E-03}$	Ns
Physical disability (FIM-MS)	83	.273	.062	<0.03	83	.291	.070	<0.02
PTSD Symptom Severity	-	-	-	-	83	078	.004	Ns
Model summary	R^2= 0.13; $F_{6,76}$= 1.94, *P*>0.05				R^2= 0.14; $F_{1,75}$= 0.37, *P*>0.05			
'Physical HRQoL' (*SF-36 PCS*)								
Age	83	-.156	.023	ns	83	-.196	.032	Ns
Sex	83	.005	$.256^{E-03}$	ns	83	.046	.002	Ns
Clinical severity (WFNS)	83	.018	$.289^{E-03}$	ns	83	.017	$.256^{E-03}$	Ns
History of previous illness	83	.120	.013	ns	83	.148	.020	Ns
Overall cognitive function (TEA; RBMT-E; BADS)	83	.110	.010	ns	83	.104	.010	Ns
Physical disability (FIM-MS)	83	.032	.001	ns	83	.003	$.100^{E-04}$	Ns
PTSD symptom severity (PDS)	-	-	-	-	83	-.129	.012	Ns
Model summary	R^2= 0.05; $F_{6,76}$= 0.61, *P*>0.05				R^2= 0.06; $F_{1,75}$= 0.93, *P*>0.05			
Predicting long-term HRQoL								
'Mental HRQoL' *(SF-36 MCS)*								
Age	83	.247	0.060	<0.02	83	.099	0.008	Ns
Sex	83	-.036	0.001	ns	83	.133	0.010	ns
Clinical severity (WFNS)	83	.190	0.030	ns	83	.186	0.030	ns
History of previous illness	83	-.274	0.070	<0.02	83	-.169	0.024	ns
Overall cognitive function (TEA; RBMT-E; BADS)	83	.166	0.022	ns	83	.144	0.016	ns
Physical disability (FIM-MS)	83	.185	0.030	ns	83	.075	0.005	ns
PTSD Symptom Severity	-	-	-	-	83	-.484	0.163	<0.0001
Model Summary	R^2= 0.23; $F_{6,76}$= 3.70, *P*<0.004				R^2= 0.39; $F_{1,75}$= 20.10, *P*<0.0001			

Table 5.9 *Cont'd.*

Factor	Model 1				Model 2			
	N	ß	sr^2_i	*P-value*	N	ß	sr^2_i	*P-value*
Predicting long-term HRQoL Cont'd.								
'Physical HRQoL' (*SF-36 PCS*)								
Age	83	-.115	0.013	ns	83	-.180	0.030	83
Sex	83	-.009	0.640^{E-04}	ns	83	0.058	0.003	83
Clinical severity (WFNS)	83	.046	0.002	ns	83	.044	0.002	83
History of previous illness	83	-.247	0.060	<0.02	83	-.201	0.034	83
Overall cognitive function (TEA; RBMT-E; BADS)	83	.010	0.810^{E-04}	ns	83	.000	0.000	83
Physical disability (FIM-MS)	83	.435	0.160	<0.0001	83	.386	0.120	83
PTSD Symptom Severity	-	-	-	-	83	-.216	0.033	83
Model Summary	R^2= 0.28; $F_{6,76}$= 5.03, *P*<0.0001				R^2= 0.32; $F_{1,75}$= 3.60, *P*>0.05			

Note: Assessment one= approximately 3-months post-ictus; Assessment two= approximately 13-months post-ictus; ß= standardise beta coefficient; BADS=Behavioural Assessment of the Dysexecutive Syndrome; FIM-MS=Functional Independence Measure-Moto HADS-A=Hospital Anxiety and Depression Scale – Anxiety score; HADS-D=Hospital Anxiety and Depression Scale – Depression score HRQoL= Health-related quality of life; MCS= Mental Component Score; MFSI-SF=Multidimensional Fatigue Symptom Inventory-Sho Form; N=sample size; ns= non-significant (*P*>0.05); PCS=Physical Component Score; PDS=Posttraumatic Stress Diagnostic Scale PSQI=Pittsburgh Sleep Quality; R^2=variance explained by model; RBMT-E=Rivermead Behavioural Memory Test-Extended; SF 36=Short Form-36; sr^2_i=squared semi-partial correlation; TEA=Test of Everyday Attention. Hierarchical step-wise entry (2 blocks) wa used to examine the *unique* predictive ability of patients' experience of PTSD in the acute stages for their later HRQoL. In Model traditional predictors of SAH patients' outcome from assessment one were entered into the model and the variance in assessment tw HRQoL which these predictors accounted for was controlled (constant + Patient age + Sex, Clinical severity + History of previous illnes + Overall cognitive function + Physical disability). In Model 2 patients' experience of PTSD at assessment one (PTSD Symptor Severity) was entered into the predictive model and its additive explanative importance established.

Stepwise regression analysis revealed that it was not possible to significantly predict the change in patients' 'Physical HRQoL' that occurred between assessments one and two using the initial model based on traditional predictors (R^2 = 0.046, $F_{6,76}$= 0.611, *P*>0.05), nor with the addition of information about patients' experience of PTSD at assessment one (R^2 = 0.058, $F_{7,76}$= 0.929, *P*>0.05; Table 5.9).

Post-traumatic Stress Disorder (PTSD). Due to missing data this regression analyses was based on 81. Bonferonni-correction led to the adoption of a test-wise alpha of $P<0.005$.

A significantly effective logistic model to predict PTSD was generated (χ^2 [1, N= 81] = 18.409, $P< 0.0001$). The only variable included in the final model was information about the patients' coping skills. A disposition to use 'Maladaptive Coping Strategies' (OR= 3.216, CI 1.761 – 5.873; Wald= 14.452 (1), $P<0.0001$) significantly increased the probability of having PTSD. Using a probability criterion of .5, predictive classification was excellent (c= 0.78), with the model assigning 78% of all possible pairs the correct probability of having PTSD (sensitivity= .48; specificity= .79; Figure 5.3). Table 5.8 presents a comparison of the symptoms and coping skills of those patients with and without PTSD.

Fatigue. Bonferonni-correction led to the adoption of a test-wise alpha of $P<0.006$.

A significantly predictive model for the 87 patients who completed the MFSI-SF at assessment two was generated – accounting for 57% of 'Total Fatigue' variance ($r= .762$; $R^2= 0.581$; $F_{2,84}= 58.310$, $P<0.0001$). The model was based solely on 'PTSD Symptom Severity' (sr^2_i= 58%; *standardised* ß= .796; $P<0.0001$). Patients with PTSD reported significantly more Total Fatigue than those without (Mann Whitney, $P<0.0001$; $r=.56$).

Sleep. Bonferonni-correction led to the adoption of a test-wise alpha of $P<0.007$.

A significantly predictive model for the 88 who completed the PSIQ at assessment two accounted for 45% of variance in 'Global PSIQ Sleep' scores ($r=$ 0.672; $R^2= 0.451$; $F_{2,85}= 34.977$ $P<0.0001$). The model was based solely on 'PTSD Symptom Severity' scores (sr^2_i= 42%; *standardised* ß= .652; $P<0.0001$). Significantly worse sleep ('Global PSIQ Sleep' score) was reported by patients

with PTSD (Mann Whitney, $P<0.0001$; $r=.38$). Sleep quality was significantly associated concurrent fatigue ($r_s= .51$, $P<0.0001$).

5.4 Discussion

Post-traumatic stress disorder (PTSD) is a severe psychiatric condition that can be elicited by the experience of traumatic, life-threatening events. In line with earlier reports, this study has confirmed that the experience of having and surviving a subarachnoid haemorrhage (SAH) can elicit PTSD [23, 47, 295]. Moreover, PTSD was found to be abnormally prevalent in the SAH population. Crucially, PTSD was found to be the single best predictor of patients' Mental health-related quality of life (HRQoL) – the domain most persistently impaired – in both the short- and long-term. In accord with the results of my meta-analysis presented in Chapter 3, none of the other variables in the model (including clinical grade, physical and cognitive disability) made significant contributions to the patients' Mental HRQoL. PTSD also proved to be significantly predictive of Physical HRQoL at the second follow-up assessment. Importantly, I also found that the degree to which patients experienced PTSD in the short-term held a large and unique predictive effect for patients' long-term HRQoL. Specifically, it was those patients who experienced more severe PTSD symptoms in the early stages post-ictus who experienced worse Mental HRQoL in the long-term. Together the findings from my study suggest that it is the frequent occurrence of PTSD (37%) after SAH which is partly to blame for the surprisingly low HRQoL found in many SAH patients who, in other respects, make a good recovery. Although it has not traditionally been considered as a high priority within SAH care, my findings highlight the importance of recognizing and addressing the psychological adjustment of patients to their experience of SAH. In particular, given that the experience of PTSD in the short-term is uniquely predictive of a poor *long-term* Mental HRQoL, the evidence

indicates that patients' psychiatric dysfunction should be treated aggressively as *early* as possible.

The proposal that PTSD can affect a patient's Mental HRQoL seems intuitive given that this domain is concerned with the degree to which the person *feels* their health has impinged upon their mood and vitality and the degree to which their emotional well-being has limited their social interaction and ability to work [23, 514]. The means by which PTSD can affect the physical aspects of an SAH patient's HRQoL may however, seem counterintuitive, given that Physical HRQoL concerns patients' physical functioning (e.g., "my health severely limits me from lifting or carrying"), physical role limitations (e.g., "my physical health has caused me to cut down on the amount of time spent on work"), bodily pain and general health (e.g., "I expect my health to get worse"), whereas PTSD presumably causes primarily non-physical impairment. Interestingly though, the association between PTSD and Physical HRQoL which I found is not unique to the present study. Indeed, several reviews in the wider literature have now concluded that in contrast with other psychiatric disorders, PTSD can impact on Physical HRQoL. In fact, its effect on Physical HRQoL can at times, be almost as severe as its effect on Mental HRQoL [514, 614]. The means by which PTSD could reduce Physical HRQoL include the fact that those who develop PTSD are known to experience increased physical symptoms, including elevated pain, headaches, joint and muscle aches, bowel symptoms and dizziness, which together with core PTSD symptoms, such as avoidance and anxiety, would simply make it harder for the patient to complete physical tasks, or to simply *do things* as one commentator notes [69, 133, 175, 229, 289, 368, 406, 415, 437, 438, 448, 530, 622, 641, 761].

PTSD was highly prevalent in my sample at both assessment points post-haemorrhage and most patients who warranted a diagnosis of PTSD at approximately 3 months, still warranted the diagnosis at 13 months. Obviously, my

conclusions on the incidence of PTSD are limited to 13 months post-SAH, but they are in line with evidence that PTSD is often a persistent and chronic disorder [417, 529]. Evidence from two recent studies does however, suggest that mood disturbance is a persistent problem post-SAH [295, 746]. Hütter, for example, assessed patients four years post-SAH and found PTSD in a similar proportion of patients [295]. It is likely that the largely stable nature of SAH patients' PTSD explains why in regression analyses, I found that PTSD could not account for the improved HRQoL which patients reported at the second assessment. It is interesting to note that I also found that more traditional predictors, such as patients' cognitive function and physical disability, also could not account for the improvement in patients' HRQoL between assessments. This is not surprising given that these factors, as revealed by my comparison of patients' performances at the two assessments, also had not significantly improved at the second assessment. The improvement in patients' HRQoL scores is instead, likely due to improvement between assessments in other aspects of the patients' outcome which I did not measure/ incorportate into the predictive models (for example, the de-conditioning associated with their convalescence) and/ or the possible insensitivity to change of my measures.

It is interesting to note that in the present study the incidence of PTSD detected in the SAH patient population is remarkably high. At both the short- and long-term follow-up appointments, 37% of SAH patients were found to warrant a diagnosis of full-PTSD. It is usually assumed that that the prevalence of PTSD (and psycho-pathology in general) following such *internal* traumas is lower relative to that which follows traditional traumas [476, 701]. For example, whilst approximately 35-50% of patients are expected to develop PTSD following traditional traumas such rape or military combat [71, 125, 351], 0-16% develop PTSD following myocardial infarction [41, 42, 152, 380, 500, 616, 706], 10-18%

following cardiac surgery [151-153, 665, 671], 3.3% following variceal haemorrhage [498], 9.8% following others strokes [615] and 1-5.6% following child-birth [26, 126, 749]. Indeed, even the DSM-IV-TR [23] notes in its discussion of PTSD that the disorder tends to be more severe (or long-lasting) when the stressor event is external and of human design (e.g., rape, torture). So how can this high incidence in the SAH population be explained? The similarity of the results from the present study and prior SAH studies which used "gold standard" diagnostic interview techniques (full-PTSD estimates 26-32%) [47, 295], means that the high incidence I detected cannot be explained by my use of a questionnaire measure of PTSD which can at times, 'over-diagnose', particularly with medical patients [500, 674, 675]. Indeed, unlike many of the aforementioned studies on other medical illness, the methodology of the current study could have potentially underestimated the incidence of PTSD as it involved the patients being left with the PTSD questionnaire and having them return it to me. One could speculate that this method would have led to an underestimation of the disorder, with those patients with PTSD (who by definition wish to avoid thinking about their illness) having been less likely to have completed and returned the measure [684]. The high incidence is also surprising as it has been suggested that in certain medical populations, symptoms of PTSD are frequently expressed in nuanced and idiosyncratic ways which may make the likelihood of them fulfilling its diagnostic criteria less likely, or at least, being captured by a generic PTSD questionnaire [310, 327, 498, 684]. For instance, an SAH typically occurs in a patient's everyday environment (such as in their homes), many experience ongoing internal consequences (e.g., neuropsychological sequelae) and external consequences (e.g., surgical scars) of their illness and can have reminders of the SAH externally imposed upon them (e.g., follow-up angiograms, medications). This means that SAH patients may, unlike those who have experienced more traditional traumas,

find it more difficult to actually avoid trauma reminders and so not fulfill the 'avoidance' criteria for the diagnosis of PTSD. SAH patients do however, still often fulfill this criteria and this could be explained by the fact that in reality the questions which ask patients about their avoidance behaviours only ask whether they have made *efforts* to avoid reminders and *not* about the *success* of their attempts [23]. Given that methodological features do not seem able to explain the high incidence of PTSD in the SAH population, it could be that there is something uniquely traumatising about the experience of an SAH. This is something deserving of future study, a point which I discuss further in Chapter 7 (see section 7.4.1).

Studies in the past had reported a comparatively good physical and cognitive recovery after SAH [432, 507, 558, 590, 649]. It was suspected that the relative infrequency of severe problems post-SAH might in part, be a consequence of those studies having used insensitive tests and pre-selected samples. I avoided these problems in the present study by investigating a large unselected sample and using ecologically valid instruments. Nevertheless my findings confirm that on average, patients surviving SAH show a good physical and cognitive recovery. This underlines the importance of shifting focus from classical neurological/neuropsychological problems to the less examined field of neuropsychiatric sequelae in order to understand the poor HRQoL experienced by patients. Furthermore, where considered, no significant value was found to be associated with clinical information for HRQoL [306, 469, 510, 543, 546, 577, 590, 609, 649, 722].

That I did not detect any significant improvement in cognition between assessment one and assessment two in the present study is not entirely unexpected. Whilst some prospective studies have reported improvements [507, 590, 649], others, like mine, have not [432, 558]. When improvements in cognition have been found, it appears that the effect is only modest and tends to be

detected by studies with the largest samples [432, 507, 558, 590, 649]. Moreover, the findings appear very dependent on the specific neuropsychological test that a study has employed and improvement often disappears when statistical corrections are made for multiple comparisons. The largest prospective study to date for example conducted by Samra et al. [590] examined a starting sample of 185 ASAH patients with a restricted (but sensitive) battery of 4 cognitive tests tapping memory, executive function, attention and visuospatial skills at 3, 9, and 15 months post-SAH. This study reported that no improvement occurred between 9 and 15 months, but that a significant improvement in overall cognition did occur between 3 and 9 months. Nevertheless, the size of the effect of improvement was small (r=.13) and even with the large sample size studied, its statistical significance was borderline (P=0.05) [117].

Since PTSD is a major determinant of how well a patient mentally and physically adjusts after an SAH, an understanding of why these patients develop PTSD is relevant for the design of rehabilitation regimes. I found that use of maladaptive coping strategies (and to a lesser extent also young age in the early stages) significantly predicted a higher likelihood of post-SAH PTSD. In fact, using only these predictors led to a classification accuracy of between 78-85%. This means it is possible to predict who is at risk of developing PTSD after an SAH.

Maladaptive coping likely promotes PTSD because evidence suggests that successful adaptation to the experience of a trauma involves the accessing of aversive emotions about the event, which permits one to habituate to anxiety and the modification of trauma-related beliefs [193] – something not at all promoted by maladaptive coping strategies. The predictive value of maladaptive coping for PTSD found in this study complements evidence that they are also key in the development of PTSD after a variety of other traumas [88, 172, 217]. It has long been speculated that coping style is somehow involved in explaining SAH patients'

poor outcome, but its role had never been seriously examined [189, 294, 295, 297, 397, 469, 510, 689]. The important insight that this study's finding now offers is that it might be possible to reduce the incidence of PTSD and improve the HRQoL in patients after SAH by teaching patients better coping strategies. To my knowledge, there has been no evaluation of the clinical efficacy of programs to improve the coping strategies employed by SAH patients. However, findings from the wider literature show that patients' coping skills are amenable to change via brief and relatively inexpensive programs which could be delivered by trained volunteers or non-specialist clinicians [196]. Along with clinicians needing to be more aware that SAH patients are at a high risk of developing PTSD, these coping skills programs (with modifications for a cognitively impaired group) could lead to SAH patients increasing their use of adaptive skills and decreasing their use of maladaptive ones, thereby improving emotional well-being – as previously shown by persons with a variety of other health problems, including HIV+ [113], spinal cord injury [346] and breast cancer [742]. Encouraging in this context, is the finding by Rodholm et al. [571], which demonstrates an absence of PTSD in an SAH sample who received illness information and advice on how to cope with neuropsychiatric symptoms.

Although these findings are encouraging, it is important to acknowledge the fact that use of maladaptive coping strategies are probably not the only factor which leads to PTSD after SAH. This becomes particularly obvious when we look at the regression model for assessment two. This model had a substantially lower sensitivity (i.e., a lower proportion of true positives were correctly predicted by the model) than the predictive model for assessment one, suggesting that additional factors become involved at later stages. This is something which clearly warrants study in the future.

We also need to discuss alternative explanations for why maladaptive coping emerges as a significant predictor of PTSD. One possibility is that given that avoidant behaviours are both an aspect of maladaptive coping and a diagnostic symptom of PTSD (i.e., Criterion C 1-2), maladaptive coping may be a consequence, rather than the cause of SAH patients' PTSD. However, as Bryant et al. [88] note in regard to the relationship more generally, this seems unlikely as intentional avoidance behaviours describe only 2 of the 17 symptoms that define PTSD. Furthermore, evidence from studies that fortuitously measured individuals' preferences for coping skills prior to a trauma, show that it is *pre-trauma* preferences for maladaptive coping which are predictive of subsequent PTSD [172, 217].

A second possible explanation is that maladaptive coping is not actually a premorbid risk factor, but is a consequence of the cognitive deficits associated with an SAH. For example, it could be argued that the deficits lead the SAH patient to not remember adaptive strategies that they used pre-morbidly and/or patients post-SAH lack the attentional focus to maintain the use of (arguably) more demanding adaptive strategies and/ or because the patient now does not notice the problems that are caused by the use of maladaptive strategies [88]. Partial support for this suggestion comes from a recent small study by Tomberg et al. [689] which suggested that SAH patients use different coping skills compared to healthy-controls. This could be taken to imply that the brain damage experienced by SAH patients leads them as a group to cope differently to those without brain injury. The cross-sectional nature of the present study means that this possibility cannot definitely be ruled-out. The hypothesis that maladaptive coping is a consequence of the cognitive deficits associated with SAH does not however remain so convincing when it is considered that Tomberg et al. found only *subtle* differences in SAH patients' coping compared to controls. Specifically, only 2

meaningful and significant differences in SAH patients' coping compared to controls (both $P<0.05$) were found from a measure of *14* aspects of patients' coping. Indeed, it is even debatable whether these 2 significant differences in SAH coping were not simply chance results given no correction was made by the authors for the potential family-wise error that resulted from the 14 *t*-tests they conducted for the analysis. In any case, teaching patients more adaptive coping skills could still reduce the prevalence of PTSD in the SAH population.

Should the reader wish to consider another explanation for why maladaptive coping emerged as a significant predictor of patients' PTSD in the current study, they are directed to Appendix IX. There, I empirically examine and refute the possibility that the relationship was detected due to many patients having suffered a psychiatric illness prior to the SAH which could have promoted the use of such coping and so be the real predictive factor. In discussing the cause of SAH patients' PTSD, the reader may also wish to refer to Appendix X where I give empirical consideration to the predictive value of the location of SAH patients' ruptured cerebral aneurysms. Aneurysm location was not included as a potential predictive factor in my main examination of the cause of SAH patients' PTSD, as contemporary SAH studies (and indeed my own, presented in the supplementary analyses) have consistently found it unhelpful.

Fatigue and sleep disorders are two important aspects of the SAH sequelae which have not received sufficient attention. Although previous studies reported that patients complain about fatigue [507, 541, 553] and sleep difficulties [609], these problems were not properly assessed. Using standardised measures, I have reported, for the first time within the literature, that fatigue and sleep problems occur significantly more often in SAH patients than in a matched control sample. Fatigue and sleep dysfunction were persistent problems for SAH patients with over 30% of patients being afflicted by each difficulty more than a year post-

haemorrhage. No significant improvement in these domains was detected between assessments. Alarmingly, the fatigue in the SAH population was at times, in fact, even higher than in cancer patients undergoing chemotherapy – a group known to experience incapacitating fatigue [407]. Regrettably, due to restrictions in recording of control subjects' educational/ occupational levels, the recruited fatigue and sleep controls were matched to patients only on the basis of age and sex. This less-than-favourable matching procedure could potentially lead to an overestimation of fatigue and sleep dysfunction. However, as no appropriate normative values for the fatigue and sleep measures exist, my calculation of impairment results in a more conservative estimate than that which would result from the only alternative, namely employing non U.K.-based cut-off scores associated with the measures [95, 407].

Interestingly, as shown by my regression analyses, PTSD seems to consistently play a major role in the development of both fatigue and sleep problems. The likely mechanism linking these disorders is that PTSD induces sleep problems, which in turn leads to much of the fatigue. This model corresponds with previous findings where sleep disturbance is noted as core to PTSD and a much ignored association between sleeplessness and fatigue/daytime sleepiness which was previously found in SAH patients [510]. In fact, the nature of the studied SAH patients' sleep dysfunction (i.e. reduced sleep efficiency) accords with measurement of sleep functions in PTSD patients in general where persistent arousals cause impaired sleep continuity [420]. Indeed, in the only objective SAH sleep study, patients reporting primary insomnia were most afflicted by 'sleep fragmentation' [609]. However, PTSD cannot explain all SAH fatigue and sleep dysfunction. I would suggest on the basis of the literature [65, 377, 509] that diffuse neuronal damage and/ or neuroendocrine dysfunction are also involved and could help explain some of the remaining 36-43% and 55-

62% variance in fatigue and sleep dysfunction, respectively. In discussing the important predictive role which PTSD has for SAH patients' experience of fatigue and sleep dysfunction, it is important to draw attention to the high correlations which I found between patients' fatigue, sleep and Mental HRQoL at each respective assessment (Spearman's correlation coefficients ranged from= -.45 to -.78). Although the correlations were not large enough to indicate that the three concepts are synonymous with one another, these high correlations do, nevertheless, indicate that the variance which PTSD is found to explain in patients' fatigue, sleep and Mental HRQoL scores may not be independent, but partly the same. The likely explanation for this is that the content of the fatigue (MFSI-SF), sleep (PSQI) and Mental HRQoL (SF-36) instruments have a degree of overlap with one another. For example, in addition to asking the patient questions about their social functioning, emotional role limitations and mental health, the SF-36 Mental HRQoL scale also includes questions about vitality and tiredness. Fatigue and sleep in this sense, should be considered correlated sub-components of a more global concept of outcome which is being captured by the Mental HRQoL scale. It is important to emphasise this point so as not to risk exaggerating the explanative power which PTSD holds for SAH patients' outcomes.

There are two potential limitations to the present study. Firstly, in assessing the relative predictive value of clinical indices for patients' outcome it was possible to include only a selection of key factors. An obvious absence from the regression models was an index of bleed severity. Although this variable did not prove particularly useful in the meta-analysis I conducted (see Chapter 3), it would nevertheless have been preferable to have included it in the models. Unfortunately, with initial CT scans often being conducted in outside accident emergency and departments, scans were not available for most patients and so could not be systematically examined. The only CT scans which were accessible

for most of the patients were those derived from the angiographic examination which the SAH patients underwent. These are however not suitable for the rating of bleed distribution because not only are the angiograms conducted several hours/ days after the initial haemorrhage (which renders scans unreliable as blood rapidly becomes isodense [618]), but also the technical quality of these scans is not necessarily satisfactory [746]. A second limitation to the study which needs to be acknowledged is that given some SAH symptoms (such as anxiety and sleep disturbance) are ubiquitous to a variety of other psychiatric conditions, and that PTSD has a high psychiatric co-morbidity, there is the possibility that an alternate or concurrent disorder could be responsible for these symptoms. This is something my study cannot rule out.

5.5 Conclusions

It can be concluded that PTSD is largely responsible for the reduced HRQoL observed in SAH patients in both the short- and long-term. Moreover, PTSD appears to consistently lead to sleep problems and thereby contribute to patients' excessive fatigue. As such, it is important to prevent the development of PTSD post-SAH. Maladaptive coping strategies seem to be the best predictor for later PTSD. Teaching patients better coping strategies could potentially reduce the incidence of PTSD and fatigue – thus significantly improving HRQoL.

Part Two

Family and friends of SAH patients - psychosocial outcome and post-traumatic stress disorder

Chapter 6

Does post-traumatic stress disorder occur in subarachnoid haemorrhage patients' family and friends? Furthermore, what is its impact on patients' recovery?

Work presented in this chapter has previously appeared in:

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&

Noble, A.J. & Schenk, T. (2008). The impact of spontaneous subarachnoid haemorrhage on patient's families and friends (Invited review). *British Journal of Neuroscience Nursing*, **4**: 278-285.

6.1 Introduction

Increasing evidence suggests that it is not only subarachnoid haemorrhage (SAH) patients who are affected by the illness. Recent studies provide compelling evidence that the families and friends of these patients are also traumatised by this disorder [461, 710, 750]. Considering the life-threatening nature of a spontaneous subarachnoid haemorrhage (SAH), its dramatic clinical presentation and neuropsychological sequelae, it is understandable that overwhelming stress and distress can be experienced by an SAH patient's family and friends [90, 264, 285, 286, 461, 545, 547].

Although two studies note positive consequences of the SAH for family and friends, such as gratitude for having been given a 'second chance' with their loved-one [285] and a closer marriage [90], most concur in finding that the negative consequences far outweigh the positives. Patients' 'significant others' (SOs) report persistent psychiatric symptoms, with anxiety [285, 545], depression (18%) [90, 545], stress (25–40%) [48, 264, 265, 461, 546] and sleep disturbance [461] featuring heavily. The aforementioned symptoms often co-occur with impairment in an SO's work [286, 545, 546], quality of life [285, 286], and family functioning [90, 286, 451, 461, 501, 502, 519]. Buchanan et al. [90], even noted that 26% of these SOs reported that death was preferable to life in their current state. Importantly, these difficulties are not experienced solely by those SOs of patients with a poor outcome [48, 90, 264, 265, 286, 461, 545, 546, 746] and SOs can even experience higher levels of emotional distress than the patient does [90, 285, 546]. Pritchard et al.[545], for example, noted that 50% of SOs considered that the family had suffered as much as the patient as a result of the SAH.

Two particularly remarkable features of SOs difficulties are the following. Firstly, they report elevated feelings of being frightened (27%) [545] and report perpetual fears over their loved-one suffering a further haemorrhage (17%),

despite expert reassurance that the chances are extremely low [285, 652]. Secondly, they report finding discussing the event particularly harrowing [313]. In fact, over 25% have been found to require medication to help them with their anxieties [546].

The psychological problems of the friends and family of SAH patients present a significant concern for two main reasons. Firstly, it shows that the consequences of SAH extend beyond the patient, causing psychological problems also in the patient's friends and families. As things stand though, SOs of SAH patients hardly receive any medical attention [461]. On discharge from acute services, most SAH patients require continued care. With referral to rehabilitation centres restricted to a subset (10%) of patients [398, 579, 746], and involvement of a professional carer appearing rare [189, 264, 398, 752] the majority of care is therefore left to SOs [189, 264, 398, 461, 752]. Two studies for example, found that even up to 6.5 years after SAH, long after acute support is withdrawn, around 55% of patients still require a high level of care [264, 461]. A second concern therefore, is that with SOs often acting as informal carers [90, 264, 461, 545, 546], that their ill psychological-health could act as a deterrent to assuming this role and may mean that SOs become unable or unwilling to continue in the position. Replacing them with professional carers would be both difficult and costly. Furthermore, there is tenuous evidence suggesting that poor SO health can reduce the quality of the care which they might offer and thus reduce their patient's chance of a good recovery [423, 538, 690]. For example, in a cross-sectional study of 27 patients examined 15 months after SAH, Toomela et al. [690] reported that the degree to which SAH patients reported cognitive symptoms was associated with a low level of social support.

In light of these points, it is important to find ways to reduce, or even better, prevent the development of the psychological problems in SOs of SAH patients.

This however requires a better understanding of the origin of these difficulties. In the past, research on the impact of SAH has typically focused on the wellbeing of the patients only. A systematic review which I previously published [489] (see Appendix XI for further results of this review) showed that only 6 studies have looked into this aspect of SAH and out of this sample only one article focused exclusively on the SOs rather than the patients. It also showed that it is not useful to refer to the wider literature on stroke carers for any direction. With SAH being considered so different from the norm, SAH patients/ their SOs are typically excluded from studies which look to learn about the impact of stroke in general on SOs [147, 155, 235, 527, 741]. Our current lack of understanding of the cause of SOs' difficulties and hence how they should be treated, is no doubt the reason why the only study [548] so far which has examined the effect of an intervention (use of a specialist liaison nurse) for these persons, found the benefits of the treatment to be only negligible.[547, 548]

The most obvious explanation for SOs' reduced well-being is that providing instrumental and emotional support for an SAH patient with physical, cognitive, and/or emotional problems can be extremely draining and leads the SO to experience depression and other symptoms of psychological distress. This explanation is supported by a number of studies showing that SOs of patients who have had an SAH report significant degrees of carer burden—at times as high as those of dementia carers [90]. The studies also show that this burden is, in turn, linearly associated with the degree of neurobehavioural sequelae that the patient illustrates [90, 264, 265, 285, 286, 461, 504, 510, 746]. The explanation that SAH SOs' psychosocial difficulties could be explained by the burden of the SAH patients' condition is given some plausibility by evidence from the wider literature on other conditions, which shows that the neurobehavioural sequelae associated with injury to the brain hold unique stress-inducing qualities. For example, it has

been documented that families living with brain-injured patients experience greater stress than those families living with the effects of physical disability (e.g. spinal cord injury) or other debilitating illnesses (e.g. cystic fibrosis) [9].

The empirical support for this explanation for SAH SOs' difficulties is however, not as compelling as one might expect. Firstly, many of the family members and friends of SAH patients who have previously been found to illustrate psychiatric disturbance had not actually assumed a caring role for a patient [48, 90, 264, 265, 285, 286]. SOs therefore appear to be significantly affected by an SAH even if they do not directly provide the patient with care [48, 265, 285, 510]. Secondly, in the group of SOs who *had* been caring, if burden of care was the main determinant of their wellbeing, there should be a robust correlation between the patient's disability and the SO's wellbeing. This is not the case. Although correlations are found, they are not robust. They are based on small-to-moderate sized samples (median=52 participants), vary dramatically in size between studies [90, 265, 461] and in some cases, burden of care accounts for less than 10% of the variability in SOs' wellbeing [510]. It is thus clear that burden of care on its own, cannot explain the psychological impact of SAH on the SOs of affected patients.

A study by Pritchard et al.[545] provides a clue as to what might be in part responsible for much of these SOs problems. These workers found that compared to SOs of other neurosurgical patients with similar needs and disabilities, but which followed a non-emergency illness (namely, an acoustic neuroma), SOs of SAH patients have a significantly worse psychopathological outcome. SOs of SAH patients reported significantly more anxiety, depression and stress and took more time off from their formal occupation. Pritchard et al. postulated that it is the unpredictable (emergency) nature and sudden onset of SAH which is probably responsible for the SOs' increased psychopathology. This phenomenon of

persistent psychological problems following the experience of an unpredictably occurring traumatic event has been well-described in the psychiatric literature and is now recognised within the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR) as an independent psychiatric illness called post-traumatic stress disorder (PTSD) [23]. In my view, PTSD provides a plausible and attractive hypothesis in the search for an explanation of SAH patents' significant others' reduced well-being for several reasons: Firstly, the psychological problems typically described by SOs of SAH patients (e.g. anxiety, fear, stress and sleep dysfunction) are similar to those of the PTSD syndrome (see Table 4.2, Chapter 4 for PTSD's diagnostic symptoms) [23]. Secondly, it is known (as seen in my own study in Chapter 5) that the onset of an SAH often causes PTSD in the patients themselves [47, 295], illustrating that an SAH can be as traumatic an event as events which are more traditionally associated with PTSD. And finally, psychiatry formally recognises that PTSD can be experienced not only by those involved in a traumatic event (such as a medical illness), but also by those who witness it, or learn of its occurrence [23, 27, 771]. Evidence that SOs of SAH patients experience uniquely high (and unappreciated) degrees of stress in the acute stages of the illness could also be seen to lend credence to this possible explanation [90, 545]. However, since no study has formally assessed the incidence of PTSD in SOs of SAH patients, we do not know whether PTSD could be responsible for their observed psychiatric problems.

If it were established that the psychosocial difficulties observed in SOs of SAH patients correspond to PTSD, it would mean that the host of information already uncovered about this disorder by psychiatry could be made use of. In particular, it could be used to provide a more accurate prognosis and more effective treatment for the SOs [23]. It could also mean that the possibility of being able to improve these particular SOs' outcome is arguably more likely than it is for

SOs of different groups of patients. As although many interventions (such as employing the use of specialized community support, social workers and occupational therapists) for this group of persons are commonly cited as being effective, several recent reviews have now concluded that these interventions have in reality failed to actually prove effective for *any* carer population [67, 201, 723]. One finding that could have significant implications for the support of SOs is that the use of 'maladaptive' coping strategies (such as distraction, denial, venting and self-blame) can help to predict PTSD development. This means that there is the possibility of designing interventions to improve the coping strategies of people who are at risk of developing PTSD and thereby help them to avoid that fate [193, 217]. Importantly, such prediction of SOs' later well-being could alert practitioners to 'at-risk' SOs, allowing monitoring and targeting of appropriate interventions before, rather than after, a crisis has occurred. The predictive value of maladaptive coping strategies does, however, need to be considered alongside other potential predictors identified in the wider literature on the wellbeing of SOs. It has, as noted, for example, been suggested that the extent of neuropsychological and neuropsychiatric deficits in the patient can be related to the extent of psychosocial problems observed in the SO [264, 285, 286].

The aim of this study therefore is to address the following questions:

1) Can the experience of having a loved-one suffer and survive an SAH elicit post-traumatic stress disorder in SOs?
2) Is the incidence of SO PTSD in the short- and long-term beyond that normally expected?
3) Why do some SOs develop PTSD while others do not? In particular, are maladaptive coping strategies good predictors of PTSD in SOs of SAH patients?

4) What is the impact of SO well-being on the recovery of the patient they care for?

To do this, a representative sample of 86 SAH patients and their SOs were examined twice over the course of 13-months. Assessment one occurred at approximately 3 months post-ictus and assessment two approximately 13 months post-ictus. All SOs were assessed with a diagnostic measure for PTSD and were given a questionnaire to establish their dominant coping style. All patients underwent a comprehensive assessment of their cognitive, physical and emotional state. Regression analyses were then used to explore the predictive values of the patients' level of impairment and the SOs' coping style for the development of PTSD in the SOs of SAH patients. Finally, the unique contribution of SOs well-being – as indexed by their experience of PTSD symptomatology – to their patient's cognitive, neurological and emotional recovery was determined using sequential multiple regression analyses.

6.2 Methods

Patients and Significant Others

In this study, 86 SAH patients and their SOs were prospectively examined. All patients were non-institutionalised first-time victims of spontaneous SAH, admitted to Newcastle General Hospital or James Cook University Hospital, Middlesbrough between May 2005 and August 2006. SOs were approached through the patients, who passed an invitation on to the SO if they wished them to participate. An SO was defined as the person/s the patient felt closest to and who was most involved in helping to informally support them since their illness. Patients were recruited from a total of 188 patients admitted and who were eventually discharged home and who had a significant other. Of non-participating patient/ SO pairs, 6 were excluded for geographic reasons, 1 patient did not speak English, 16 recruited pairs had too much missing data and 79 declined to participate or were not available for testing.

Diagnosis of the patents' SAH was established by computed tomography (CT), or if negative, xanthrochromia of cerebrospinal fluid was diagnostic. In aneurysmal SAH patients (ASAH), aneurysms were demonstrated by spiral CT or catheter angiography.

This study was granted multi-centre approval by the Central Manchester Research Ethics Committee. Informed consent was obtained from all participants.

Measures

Instruments were chosen on the basis of having robust psychometric properties and ecological validity for cognitive tasks [53, 95, 107, 194, 238, 563, 657, 734, 754, 755]. Parallel versions of the attention and memory tests were used at assessments one and two.

Significant others

At both assessment one and two, SOs underwent a brief interview to determine their medical and psychiatric history, relationship with the patient, years of marriage (where appropriate) and whether the SO resided with the patient. The measures described below were then completed at both assessments (except the Brief COPE Inventory which was only completed at each SO's first appointment).

The Post-traumatic Diagnostic Scale (PDS) [194] assessed whether SOs warranted a DSM-IV-TR diagnosis of PTSD [23]. The PDS also provides a PTSD severity score and a functional impairment index. In order for a diagnosis of full-PTSD to be warranted SOs must have satisfied the following diagnostic criteria in response to their loved-ones SAH: experienced intense fear, helplessness, or horror at time of the event (Criterion A); persistently re-experienced the event (Criterion B Intrusion); persistently avoided stimuli associated with the event and numbing of responsiveness (Criterion C Avoidance); and had persistent symptoms of increased arousal (Criterion D Arousal). This full symptom picture must have been present for more than 1 month (Criterion E Duration) and the disturbance must have caused clinically significant distress or impairment in social, occupational or other important areas of functioning (Criterion F Functioning). The prevalence of sub-threshold/ sub-syndromal PTSD as defined by recent guidelines [477] was also recorded. In short, this syndrome was defined as one in which the threshold for Criterion C (Avoidance) and/or D (Arousal) was not reached, but there was at least one symptom of each of these criterion present. These symptoms, along with those of Intrusion (Criterion B), must have been present for at least one month (Criterion E) and have caused significant distress and/ or functional impairment (Criterion F). Finally, a 'PTSD Symptom Severity' score was calculated for all SOs regardless of PTSD diagnosis to examine the link between SO well-being and patient recovery through regression analyses.

The Brief COPE Inventory [107] measured SOs' dispositional use of 'maladaptive coping strategies' (Venting, Denial, Substance Use, Behavioural Disengagement, Self Distraction and Self Blame). Higher scores denote more frequent use of the strategies. Internal consistency of this scale was satisfactory (α=0.7) [494].

Patients

Patients' neurosurgical notes were examined and details of their medical and psychiatric history and SAH were recorded. Details obtained about patients' SAH included clinical severity on admission to hospital (World Federation of Neurological Surgeons grade; WFNS) [164], the origin of their haemorrhage, its primary treatment and, if appropriate, aneurysm location. Following a brief introductory interview, the following measures were completed at both assessments.

The Functional Independence Measure – Motor Subscale (FIM-MS)[238] was completed based upon information from the SOs to index their loved-ones' physical disability. Measured across 13 tasks on 7-point scales, increasing values indicate greater levels of independence in mobility, self-care and continence.

The Test of Everyday Attention (TEA) [563] assessed attention. The following tasks were used: Visual Elevator, Telephone Search, Telephone Search Dual Task, Elevator Counting and Lottery.

The Behavioural Assessment of the Dysexecutive Syndrome (BADS) [754] measured executive skills. All but one of the tests was used: Rule Shift Cards, Key Search, Modified Six Elements, Temporal Judgment and Zoo Map.

The Rivermead Behavioural Memory Test - Extended Version (RBMT-E) [755] measured everyday memory function. The following tests were used: Story Immediate, Story Delayed, Picture Recognition, Face Recognition, Orientation and

Date, First Names, Second Names, and Appointments and Belongings (see Appendix VIII for further details on all cognitive measures).

For the purposes of analyses, an Overall Cognitive Function index for each assessment was generated from the performances on the TEA, RBMT-E and BADS at the respective assessment. This was achieved by using normative data to generate attention, memory and executive function indexes for performance on the batteries [563, 754, 755]. Indexes were based on the following scale: 4= Exceptional, 3= Good, 2= Average, 1= Poor and 0= Impaired. These indexes were then summed to provide the Overall Cognitive Function index. Further details on how the two Overall Cognitive Function indices were computed can be found in the methods section in Chapter 5 (section 5.2).

The Hospital Anxiety and Depression Scale (HADS) [772] is a self report measure of patients' experiences of 7 anxiety (HADS Anxiety Score) and 7 depression (HADS Depression Score) symptoms over the preceding week. It reduces 'noise' from somatic disorders by excluding symptoms also related to physical disorders. Scores were compared to UK normative data [124]. The Total HADS score (anxiety and depression scores combined) was used as an index of a patient's overall mood disturbance.

The Post-traumatic Diagnostic Scale (PDS) [194] assessed to what degree patients experienced DSM-IV PTSD symptoms.[23] A 'PTSD Symptom Severity' score was calculated for all patients regardless of PTSD diagnosis to examine the link between SO well-being and patient recovery through regression analyses.

The Pittsburgh Sleep Quality Index (PSIQ) [95] measures sleep quality over the preceding month. Subjective 'Sleep Quality', 'Latency', 'Duration', 'Habitual Sleep Efficiency' (hours sleep: hours in bed), 'Disturbances', 'Use of Sleep Medication' and 'Daytime Dysfunction' are all measured. A 'Global PSIQ Sleep'

score (0-21) was calculated and used in the present study to represent patients' overall sleep quality. Higher scores indicate worse sleep.

The Multidimensional Fatigue Symptom Inventory – Short Form (MFSI-SF) [657] assesses how much patients experienced fatigue symptoms over the preceding week. The MFSI-SF comprises 5 subscales ('General Fatigue', 'Physical Fatigue', 'Mental Fatigue', 'Emotional Fatigue' and 'Vigour'). The sum of the fatigue subscales minus the 'Vigour' scale generates a Total Fatigue Score that was used in this study (ranging from -24 to 96). A higher score indicates more fatigue.

The Short-Form 36 (SF-36) [734] assesses patients' health-related quality of life (HRQoL) across 8 domains: 1) 'Physical Functioning', 2) 'Physical Role Limitations', 3) 'Bodily Pain', 4) 'General Health', 5) 'Energy', 6) 'Social Functioning', 7) 'Emotional Role Limitations' and 8) 'Mental Health'. U.K. normative scores exist for this measure [60]. Standard algorithms aggregated scores into two summary HRQoL scores: 'Physical HRQoL' and 'Mental HRQoL" [733]. Scores range from 100 (no reduction) to 0 (maximum reduction).

Procedure

Patients completed the TEA, RBMT-E, HADS and BADS during an appointment at either their home or at our testing laboratory. The FIM-MS was then completed either during a face-to-face or by telephone appointment, whilst the remaining measures were left with the patients and SOs for completion in their own time and collected at a later date.

Data Analysis

With large numbers of comparisons in some analyses, alpha levels were appropriately adjusted (Bonferonni) to compensate for family-wise error and to

keep the alpha-level at 5%. The adopted values are reported in the corresponding paragraphs of the Results section. When missing data exceeded 5%, a missing value analysis assessed its impact on the results' generalisability by examining if incompleteness was dependent on any variable (Little MCAR test) and whether cases with missing data were comparable to those without (t-tests; variables considered SO age and sex and their patient's WFNS grade, haemorrhage type, treatment type and MMSE). For the purposes of brevity, I report only on the results of missing variable analyses when a significant result was found. The case-variable ratios for regression analyses were largely acceptable [290, 518]. Where possible, effect sizes (ES) in the form of the correlation coefficient *r* are reported for all results. All analyses were conducted using commercially available software (SPSS).

Incidence of PTSD. The frequency of PTSD in the SO sample at assessments one and two was compared to the frequency of PTSD normally expected within the general population [23]. The incidence of sub-syndromal PTSD was also calculated. Descriptive statistics were used to show the severity of, and functional impairment caused by, PTSD for those diagnosed. Mann-Whitney tests compared the number of symptoms experienced by SOs with PTSD with the number in those without PTSD. The functional impairment caused by full- and sub-syndromal PTSD compared to those not meeting its criteria at assessment one and two were also compared. Finally, the Wilcoxon matched-pairs signed-ranks test and Spearman's correlation were used to compare the PTSD reported by SOs who were examined both at assessment one and two.

Prediction of PTSD. Logistic regression examined the following SO- and patient-related predictors for PTSD at 3- and 13-months: the patient's WFNS grade, Overall Cognitive Function index, FIM-MS and Total HADS and the SO's age, sex, psychiatric history versus none and dispositional maladaptive coping

use. The patients' Overall Cognitive Function Index score, FIM-MS and Total HADS score from assessment one were used in the model to predict PTSD in SOs at assessment one, whilst the patients' scores on these measures from assessment two were used when predicting SO PTSD at assessment two. A backward elimination method (likelihood ratio test) revealed the most parsimonious predictors. The odds ratio (OR) was used here to indicate the change in the odds of having or not having PTSD when the value of a predictor increased by one unit. The c-statistic measured the discriminative power of the logistic equation. Varying from 0.5 (predictions are no better than chance) to 1.0 (model predicts without error), it is the percentage of case pairs to which the model correctly assigns a higher probability. Mann-Whitney U tests, box-plots and Kendall's tau (τ) measures of association were used where necessary to further explore relationships highlighted by regression.

Please note that due to a reduced SO sample size at assessment two and a smaller found frequency of SO PTSD, the full- and sub-syndromal SO PTSD categories were collapsed for regression analyses for assessment two to increase the number of cases of the rarer PTSD event (and hence satisfy an assumption of logistic regression). This merging of groups was deemed acceptable since at assessment two (unlike at assessment one), SOs with sub-syndromal and full-PTSD illustrated comparable levels of functional/ clinical impairment as a result of their PTSD syndromes (see Results incidence sections).

Impact of significant other well-being on patient recovery. Multiple linear and logistic regression using two sequential blocks of entry of variables was used. In the first block, patients' demographics (age, sex, education) and illness characteristics (clinical severity, time since illness and pre-morbid health) were entered and formed the predictive model. The variance in patient recovery which these predictors accounted for was therefore, controlled. In the second entry

block, SOs' PTSD symptom severity was then added to the predictive model and the unique explanative value which this predictor added to the model was established.

The aspects of patient short- and long-term recovery that were predicted were cognition (attention, memory and executive function individually and overall cognition) using logistic regression, and physical independence (FIM-MS), psychiatric disturbance (PTSD; HADS Anxiety; HADS Depression), fatigue (MFSI Total Score), sleep (PSIQ Global Score), and HRQoL (Mental HRQoL; Physical HRQoL) using linear regression. Parametric regression techniques were appropriate for most of the aspects of patient recovery (despite their ordinal nature), because of the number of occupied categories and the fact that it was fair to assume an underlying continuum and an equal distance between each ordinal point [677]. Logistic regression however, was used for exploring the predictors of patients' cognitive recovery ("impaired", score of 0/ "not impaired", score of 1-4) due to the limited number of categories by which cognition had been classified (i.e., the 4-0 scale). Due to the infrequency of impairment in attention and executive function, impairment in these two domains was, for the purposes of logistic regression defined as score that had originally been classified as either 'Impaired' (score of 0) or 'Poor' (score of 1) [677].

For the linear regression models, the significance of SOs' well-being in the prediction of patient recovery was determined by examining whether the addition of this variable significantly increased the variance which the predictive model explained. The significance of the improvement was determined by calculating the incremental change in the *F*-ratio – which is based upon the ratio of the improvement due to the model and the difference between the model and observed data. For logistic models, the goodness-of-fit chi-square test was used to examine whether a variable's addition improved the match between the observed

data and the model's predictive abilities. Due to differences in their calculation, a larger *F*-ratio statistic indicates better model prediction, whilst a smaller chi-square statistic compared to a baseline model indicates an improved predictive ability.

To increase the linearity between predictors and patient outcome measures – and hence enhance the prediction equations – square root, logarithm and (in one case) reflection and inversion transformations were made (where necessary) so that predictor variables better approached normality [677].

6.3 Results

Significant others and patients

The SO group consisted of 53 women and 33 men. All 86 SOs were examined at assessment one, but 12 SOs (14%) were lost from the sample at assessment two (Table 6.1). The reason for the reduced sample was due to one patient death and the remaining eleven SOs, either declining to participate or failing to complete the PDS at assessment two. No significant differences existed (in terms of their age, sex, or in their associated patients' WFNS grades, type of haemorrhage, treatment or cognitive, physical or mood disturbance at assessment one) between the SOs who were examined at assessment two and those who were not (all $P>0.05$), with no pattern to the missing data being found (Little's MCAR: $P=.114$). The majority of SOs (76.8% at assessment one; 79.7% at assessment two) were the spouse or partner of the patient. Average follow-up for assessment one was 112 days after SAH (SD 40.53; range 44-234) and 412 days after SAH for assessment two (SD 53.77; range 344-677).

Three patients informed me that the person they considered to be their SO had changed in the period between assessments one and two. In these cases, the SOs from assessment one were not assessed at appointment two, but instead, the patients' latest SOs were examined.

Table 6.1 Summary of demographic and characteristics of significant others examined at assessment one and two

Factor	Value (%)	
	Assessment one N=86	Assessment two N=74
Significant others		
Female	53 (61.6)	48 (60)
Mean age ± SD (range) (yr)	50.52 ± 13.68 (18-78)	51.41 ± 13.89 (19-79)
Relationship with patient		
Spouse/partner	66 (76.8)	63 (79.7)
Child	12 (14.0)	9 (11.4)
Parent	4 (4.7)	3 (3.8)
Sibling	2 (2.3)	3 (3.8)
Friend	2 (2.3)	1 (1.3)
Mean years of marriage ± SD (range) (yr)	27.16 ± 14.45 (0-62)	28.11 ± 14.63 (0-63)
Living in same residence	69 (80.2)	67 (84.8)
Mean years of formal education ± SD (range) (yr)	12.19 ± 1.97 (9-18)	12.23 ± 1.98 (9-18)
Significant history*		
Physical only	20 (23.3)	16 (21.9)
Psychiatric only	12 (14.0)	9 (12.3)
Both	2 (2.3)	2 (2.7)

*Note:*Assessment one=mean of 112 days post-ictus; assessment two=mean of 412 days post-ictus; N=number; SD=standard deviation; yr=year. *Self-reported illness receiving/ received formal treatment. Physical illness includes: acromegaly, brain tumour unspecified, diabetes, epilepsy, hypothyroidism, labyrinthinitis, myocardial infarction, normal pressure hydrocephalus, viral brain infection, rheumatoid arthritis, transient ischemic attack, traumatic head injury. Psychiatric illness includes: anxiety unspecified diagnosis, depression unspecified diagnosis, alcohol abuse, schizophrenia.

Recruited patients were representative of the population from which they were drawn (Table 6.2), with no differences between participators and non-participators in age, sex, WFNS, haemorrhage type, aneurysm location or treatment (all $P>0.008$). A detailed description of the included patients' cognitive,

psychiatric and physical status at the two assessment points is presented in Table 6.3.

Table 6.2 Summary of demographic and clinical data of patients who were examined at assessment one and two

Factor	Value (%)	
	Assessment one N=86	Assessment two N=74
Patients		
Female	49 (57.0)	40 (54.1)
Mean age ± SD (range) (yr)	52.40 ± 10.74 (27-80)	53.52 ± 10.62 (28-81)
Aneurysmal SAH	63 (73.3)	51 (68.9)
Location of ruptured aneurysm		
ACoM/ ACA	31 (49.2)	26 (51.0)
ICA	13 (20.6)	10 (19.6)
MCA	16 (25.4)	12 (23.5)
Vertebrobasilar	3 (4.8)	3 (5.9)
Unknown origin	21 (24.4)	21 (28.4)
Other origin	2 (2.3)	2 (2.7)
WFNS grade		
I	57 (66.3)	50 (67.6)
II	13 (15.1)	8 (10.8)
III	4 (4.7)	4 (5.4)
IV	12 (14.0)	12 (16.2)
V	0 (0)	0 (0)
Primary treatment		
Endovascular	37 (43.0)	28 (37.8)
Surgery	28 (32.6)	25 (33.8)
Conservative	21 (24.4)	21 (28.4)

Note: ACA=anterior cerebral artery; ACoM=anterior communicating artery; assessment one=mean of 112 days post-ictus; assessment two=mean of 412 days post-ictus; ICA=internal carotid artery; MCA=middle cerebral artery; N=number; SD=standard deviation; Vertebrobasilar=arteries of the vertebrobasilar system; WFNS=World Federation of Neurological Surgeons; yr=year.

Table 6.3 Summary of results from subarachnoid haemorrhage patients' cognitive, psychiatric, and physical examinations

Factor	N	Median	IQR	Percentage in clinical range*	N	Median	IQR	Percentage in clinical range*
Cognitive Impairment								
RBMT-E Memory Function	83	1.0	0.0-1.0	30.1	73	1.0	1.0-1.0	23.3
BADS Executive Function	83	2.0	1.0-2.0	10.8	73	2.0	1.0-3.0	9.6
TEA Attention Function	84	2.0	1.5-2.5	8.3	73	2.0	1.3-2.5	4.1
Overall Cognitive Function index	83	5.0	4.0-6.0	-	73	5.0	3.3-6.0	-
Psychiatric Status								
Total HADS Score	84	12.0	6.0-18.0	26.2	71	11.0	6.0-17.0	25.4
HADS Anxiety Score	84	7.0	3.0-10.0	34.5	71	8.0	6.5-8.0	18.3
HADS Depression Score	84	5.0	2.0-9.0	21.4	71	5.5	4.3-7.5	29.6
PTSD Severity Score	80	10.0	4.0-18.8	35.0	71	7.0	3.0-14.0	35.2
Physical Disability								
FIM-motor scale	86	90	89.0-91.0	5.8	74	7.0	7.0-7.0	12.2
Sleep								
Global PSIQ Sleep	59	7.0	4.0-11.0	49.2	74	6.0	3.0-10.0	35.1
Fatigue								
MFSI-SF Total Score	59	26.0	3.0-44.0	44.1	73	18.0	1.0-41.0	42.5

Table 6.3 *Cont'd.*

Factor	N	Median	IQR	Percentage in clinical range*	N	Median	IQR	Percentage in clinical range*
Health-Related Quality of Life								
SF-36 Mental HRQoL	83	38.6	29.1-51.0	69.9	72	47.8	36.7-54.2	50.0
SF-36 Physical HRQoL	83	36.4	29.8-43.9	74.7	72	42.9	31.4-51.5	51.4

Note: Assessment one=mean of 112 days post-ictus; assessment two= mean of 412 days post-ictus; BADS=Behavioural Assessment of the Dysexecutive Syndrome; FIM-motor scale=Functional Independence Measure motor scale items, with scores ranging from 13 (total dependence) to 91 (independent); HADS=Hospital Anxiety and Depression Scale, with scores ranging from 0 to 42 (higher values denote more disturbance); HRQoL=health-related quality of life; IQR=interquartile range; MFSI-SF=Multidimensional Fatigue Symptom Inventory-Short From, with scores ranging from -24-96 (higher scores indicate worse fatigue); N=number; PDS=Posttraumatic Stress Diagnostic Scale, PDS Symptom Severity score ranges from 0-51 (higher scores indicating more severity); PSQI=Pittsburgh Sleep Quality Index, with scores ranging from 0-21 (higher scores indicate poorer sleep); RBMT-E=Rivermead Behavioural Memory Test; SF-36=Short-Form 36 quality of Life measure, with scores ranging from 0-100 (lower values indicate worse HRQoL); TEA=Test of Everyday Attention. *=Percent in clinical range for RMBT-E, BADS and TEA was a function score of 0 ("impaired"); percentage in clinical range for HADS scores was determined by comparing patients' scores to sex-adjusted U.K. normative values and judged as abnormal ≥90th percentile percentage in clinical range for PDS was those with criteria for full-PTSD; clinical range for FIM was a median total motor score <6 (dependent on other person); percent in clinical range for PSIQ and MFSI-SF was ≥90th quartile compared to age-sex matched control sample (see Chapter 5); finally, percent in clinical range for SF-36 was those with a score below the ≤10th quartile compared to normative scores. Attention, Memory and Executive Function indices range from 0 (Impaired) to 4 (Excellent); Overall Cognitive Function classification ranges from 0 to 12 (increasing values indicate increased cognitive ability). Values expressed as median.

PTSD Incidence in significant others

Assessment one

PTSD was assessed in 86 SOs. Twenty-two (25.6%) SOs were diagnosed with PTSD. In the general population a prevalence of 8% is expected. Median symptom severity for those with PTSD was moderate (median=19.0, interquartile range [IQR]=14.0-30.8) and caused "severe" functional impairment for the majority (77.3%). Those SOs with full-PTSD exhibited significantly higher levels of intrusive, avoidant and arousal symptoms and more severe levels of symptomatology overall compared to those without (all $P<0.0001$; adjusted alpha= $P<0.01$; Table 6.4). An additional 12 (14%) SOs fulfilled the criteria for sub-syndromal PTSD. This caused mild functional impairment for 5 of these patients (41.7%), moderate impairment for 3 (25.0%) and severe impairment for the remaining 4 (33.3%) patients. Those with sub-syndromal PTSD experienced significantly less functional impairment/ distress as a result of their syndrome (median=4.0, IQR=2.0-9.0) compared to those with full-PTSD (median=9.0, IQR=8.0-9.0; $P<0.003$).

Assessment two

PTSD was assessed in 74 SOs. Twelve (16.2%) SOs were diagnosed with PTSD. The median symptom severity for those with PTSD was moderate (median=17.0, IQR=13.3-23.0) and caused "severe" functional impairment for the majority (75.0%). Those SOs with PTSD exhibited significantly higher levels of intrusive, avoidant and arousal symptoms and more severe levels of symptomatology overall (all $P<0.0001$; adjusted alpha= $P<0.01$; Table 6.4). An additional 5 (6.8%) of SOs met the criteria for sub-syndromal PTSD. This

Table 6.4 Comparison of significant others with and without PTSD

Factor	Assessment one								Assessment two							
	SOs with PTSD			SOs without PTSD			*P*-value	ES	SOs with PTSD**			SOs without PTSD			*P*-value	ES
	N	Median	IQR	N	Median	IQR			N	Median	IQR	N	Median	IQR		
PTSD – PDS *																
Intrusions	22	4.0	2.8-4.3	64	2.0	1.0-3.0	<0.0001	-.45	17	3.0	2.0-5.0	57	1.0	0.0-2.0	<0.0001	-.53
Avoidance	22	5.0	3.0-6.0	64	1.0	0.0-2.0	<0.0001	-.64	17	4.0	1.5-5.5	57	0.0	0.0-2.0	<0.0001	-.54
Arousal	22	4.0	3.0-5.0	64	1.0	0.0-2.0	<0.0001	-.60	17	3.0	2.0-5.0	57	0.0	0.0-2.0	<0.0001	-.55
Symptom severity	22	19.0	14.0-30.8	64	4.5	2.0-9.0	<0.0001	-.62	17	14.0	10.5-20.0	57	3.0	0.0-6.5	<0.0001	-.61
Coping – Brief COPE *																
Maladaptive coping	21	3.6	3.1-4.5	64	2.7	2.2-3.1	<0.0001	-.47	17	3.3	2.9-4.2	56	2.6	2.2-3.2	<0.007	-.32
Self distraction	21	5.0	3.0-6.0	64	3.0	2.0-7.0	<0.004	-.32	17	4.0	2.5-5.5	56	3.0	2.0-5.0	ns	-.16
Denial	21	4.0	2.0-6.0	64	2.0	2.0-3.0	<0.003	-.32	17	3.0	2.0-4.0	56	2.0	2.0-3.0	ns	-.22
Substance abuse	21	2.0	2.0-4.0	64	2.0	2.0-2.0	ns	-.23	17	2.0	2.0-3.0	56	2.0	2.0-2.0	ns	-.08
Behavioural disengagement	21	3.0	2.0-3.5	64	2.0	2.0-2.0	<0.0001	-.37	17	2.0	2.0-3.0	56	2.0	2.0-2.0	ns	-.14
Venting	21	4.0	2.0-5.0	64	2.0	2.0-3.0	ns	-.26	17	4.0	3.0-5.0	56	2.0	2.0-3.0	<0.0001	-.44
Self – blame	21	3.0	2.0-5.5	64	2.0	2.0-2.0	<0.004	-.33	17	3.0	2.0-4.0	56	2.0	2.0-3.8	ns	-.17
SOs demographics																
Mean age ± SD §	22	47.6	12.1	64	51.9	14.3	ns	.14	17	44.7	14.5	57	52.8	13.6	<0.05^	.06

Table 6.4 *Cont'd.*

	Assessment one								Assessment two							
	SOs with PTSD			SOs without PTSD			*P*-value	ES	SOs with PTSD**			SOs without PTSD			*P*-value	ES
	N	Median	IQR	N	Median	IQR			N	Median	IQR	N	Median	IQR		
SOs demographics cont'd.																
Females (%) ‡	22	12	55%	64	41	64%	ns	.06	17	13	76.5	57	25	43.9	ns	-
With psychiatric history (%) ‡	22	4	18%	64	10	16%	ns	-	17	5	29.4	57	6	10.5	ns	-

Note: ES=effect size (*r*); IQR=interquartile range; N=number; PDS=Posttraumatic Stress Diagnostic Scale; PDS scoring is presented as the number of intrusive (e.g., "reliving the brain haemorrhage, acting or feeling as if it was happening again"), avoidant (e.g., "trying to avoid activities, people or places that remind me of the brain haemorrhage") and arousal (e.g., "feeling irritable or having fits of anger") symptoms experienced; SOs=significant others; *=Comparisons made using Mann-Whitney tests. §=Comparison made using *t*-test for unequal groups; **PTSD group in assessment two comparisons includes 5 SOs with sub-syndromal PTSD in order to increase cell count for statistical purposes; ‡=Comparison made using χ^2 test/ Fisher exact test; ^=Equality of variances assumed. Brief COPE scoring ranges from 2 ("strategy usually not used") to 8 ("strategy usually used a lot"). Critical alpha level adjusted for each set of family comparisons: PTSD block *P*= 0.0125, Coping block *P*= 0.007 and SOs' demographic block *P*= 0.016. All values, other than age, expressed as medians.

caused severe functional impairment for the majority (60.0%). In fact, those with sub-syndromal PTSD illustrated levels of functional impairment/ distress as a result of their disorder comparable to those with full-PTSD (sub-syndromal median= 9.0, IQR 1.5-9.0 vs. full-PTSD median= 9.0, IQR 6.8-9.0, $P>0.05$).

Comparison of significant others' PTSD at assessment one and two

Missing data (17.4%), due to a reduced sample size at assessment two, meant that this analysis was based on the 71 SOs who completed the PTSD assessments at both assessments. There was no significant difference in PTSD prevalence ($P>0.05$), experience of intrusive ($P>0.05$), avoidant ($P>0.05$) or arousal symptoms ($P>0.05$) at assessments one and two (Adjusted alpha $P<0.01$). The Wilcoxon test however, detected a significant reduction with time in the number ($P<0.007$) and severity of PTSD symptoms ($P<0.01$) experienced by SOs (Table 6.5). Spearman's correlation between SOs' individual PTSD status (full, sub-syndromal or no PTSD) at the two assessments revealed that PTSD status was stable for many: $r_s= .317$, $P<0.0007$. In total, 67.1% of patients had the same status at both assessments.

Prediction of significant others' PTSD

Assessment one

Analysis was based on 82 patient/ SO pairs due to missing data (4.6%) on some measures considered. A logistic model that provided a significant relationship between predictors and the occurrence of PTSD was generated (χ^2 [2] = 26.195, $P<0.0001$). It was found that increased use of maladaptive coping strategies (OR= 4.292, CI 2.070 – 8.899; Wald statistic= 15.329 [1] $P<0.0001$) significantly increased the probability of PTSD (Adjusted alpha=$P<0.006$; Figure 6.1). Using a probability criterion of .5, predictive classification was excellent (c = 0.84), with the

Table 6.5 Comparison of significant others' PTSD symptoms at assessments one and two

Factor	Assessment one			Assessment two			*P*-value	ES
	N	Median	IQR	N	Median	IQR		
PTSD – PDS *								
Intrusions	71	2.0	1.0-4.0	71	1.0	0.0-3.0	Ns	-.20
Avoidance	71	1.0	0.0-4.0	71	1.0	0.0-3.0	Ns	-.18
Arousal	71	2.0	0.0-3.0	71	1.0	0.0-3.0	Ns	-.10
Number of symptoms	71	6.0	2.0-10.0	71	4.0	1.0-8.0	<0.007	-.32
Symptom severity	71	7.0	2.0-13.0	71	4.0	1.0-12.0	<0.01	-.21
Prevalence full PTSD (no. / %)**	71	15	21.1%	71	12	16.9%	Ns	-

Note: Assessment one= mean of 112 days post-ictus; assessment two= mean of 412 days post-ictus; ES=effect size (*r*); IQR=inter-quartile range; N=number; PDS=Posttraumatic Stress Diagnostic Scale; *=Adjusted alpha 0.0125; **=McNemar test with correction for continuity due to small cell size.[629] Values expressed as median.

model assigning 84% of all possible pairs the correct probability of having PTSD. The bivariate relationship between coping and PTSD diagnosis was τ = .404, P<0.0001. Those SOs diagnosed with PTSD were found to be more predisposed to use all but two types of maladaptive coping strategies compared to those SOs without PTSD (Table 6.4). Logistic regression analysis found no other variable – not SOs' demographic information, psychiatric history, nor patients' clinical severity (WFNS grade) or level of physical (FIM- MS), cognitive (Overall Cognitive Function index), or psychiatric (Total HADS) impairment – to hold any significant predictive value for the development of PTSD in SOs.

Assessment two

Due to missing data (2.7%), analysis was based on 72 patient/ SO pairs. A logistic model which provided a significant relationship between predictors and the

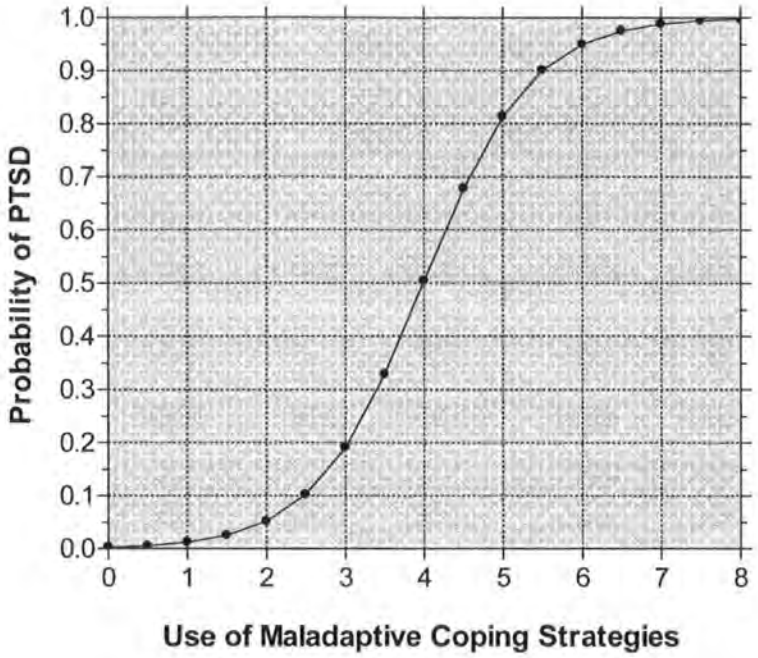

Figure 6.1 Graph depicting the relationship between probability of SO PTSD at assessments one and their use of maladaptive coping strategies (OR= 4.292).

occurrence of post-traumatic stress disorders was generated (χ^2 [3]=13.885, P<0.004). The backwards elimination model retained only two predictors in the final model. The use of maladaptive coping strategies (OR=2.445, CI 1.234 – 4.845; Wald statistic= 6.569 [1] P<0.01) had by far the largest effect on the development of full/ sub-syndromal PTSD, followed by patients' cognitive function (OR=0.693, CI 0.488 – 0.990; Wald statistic= 4.053 [1] P<0.05). These two predictors however, did not remain significantly predictive when judged according to the adjusted critical alpha value (Adjusted alpha = 0.006). Indeed, at assessment two, SOs with PTSD were mostly indistinguishable on the basis of

their disposition to use maladaptive coping skills from those SOs without PTSD (Table 6.4).

Bivariate correlations between maladaptive coping and PTSD at assessment two were calculated to further examine the reduced importance of maladaptive coping for the prediction of PTSD status at assessment two. It was seen that the correlation between coping and PTSD at assessment two was much smaller than that seen at assessment one (assessment two τ=.259, P<0.01 vs. assessment one τ= .404, P<0.0001). Box plots and Mann-Whitney tests (Figure 6.2) were used to compare the disposition to use maladaptive coping by those with PTSD at both assessments and those newly diagnosed with PTSD at assessment two. Though based on small groups, the results suggested that the reason for the reduced predictive importance of coping methods was that those SOs newly diagnosed with full-PTSD at assessment two formed a distinct subgroup for whom maladaptive coping was not predictive. These SOs (n=6) reported significantly less disposition to use of maladaptive coping than those SOs who were diagnosed with PTSD at both assessment points (n=6, P<0.001; r= -.44). On the other hand, those SOs who at assessment two no longer warranted the diagnosis of full-PTSD (n=15) reported significantly more of a disposition to use maladaptive coping than those who never warranted a diagnosis of PTSD at either assessment one or two (n=41, P<0.01; r= -.67). Therefore, in the longer-term a sub-group of SOs seemed to exist for whom maladaptive coping skills did not represent a PTSD risk factor. Corroborating this, is the finding that the use of maladaptive coping skills, did not significantly discriminate between those SOs who were newly diagnosed with PTSD at assessment two (n=15), and those who at assessment two, for the first

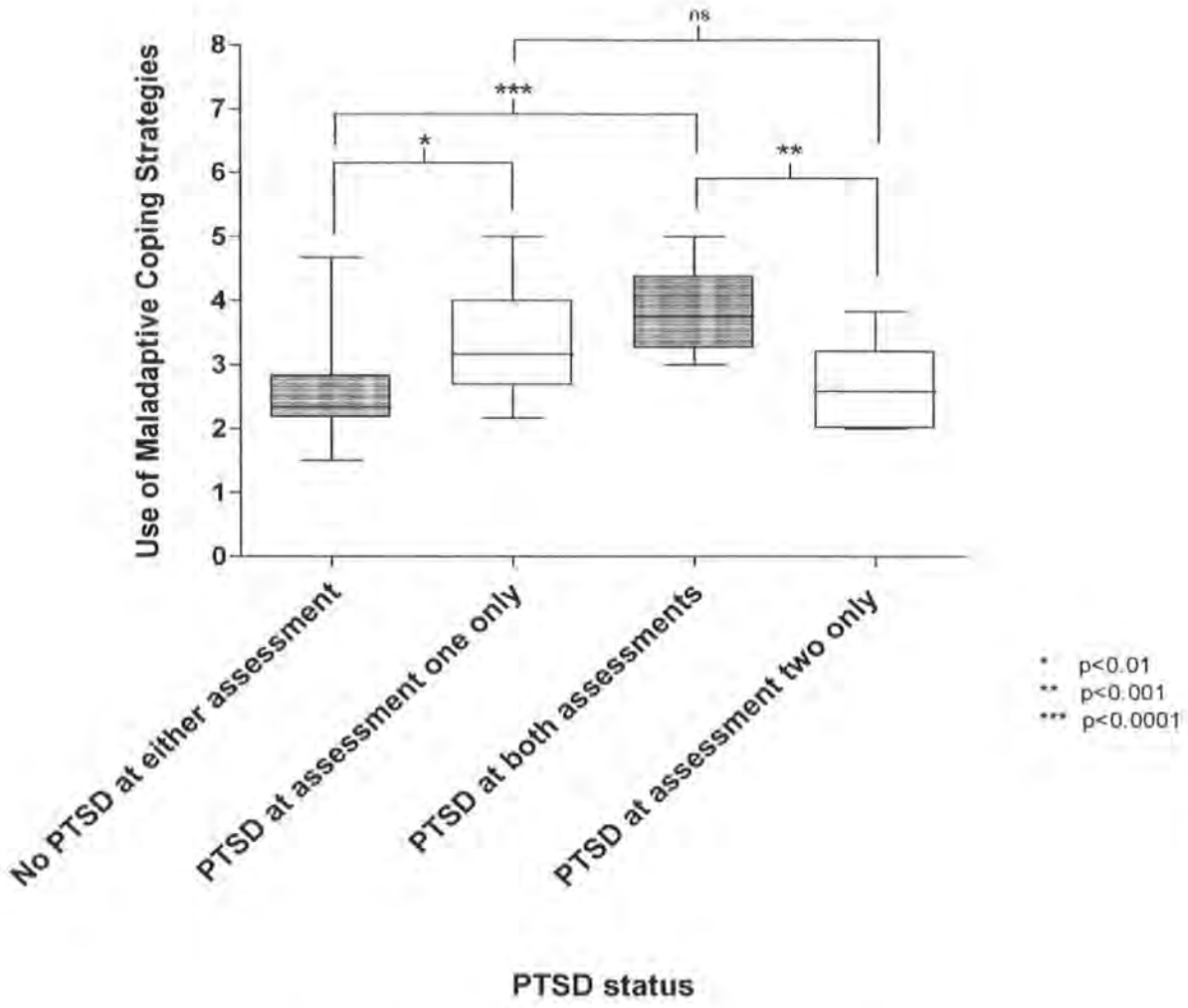

Figure 6.2 Use of maladaptive coping skills by significant others and their PTSD.

time, did not meet the diagnosis for PTSD (n=6, $P>0.05$; $r= -.37$). It should be noted that persons with sub-syndromal PTSD were excluded from these analyses due to their small number.

Impact of significant other well-being on patient recovery

Assessment one

The SOs' experience of PTSD symptomatology reported at assessment one did not significantly add to the predictive value of any aspect of patient recovery apart from patient anxiety ($F[1]=8.286$, $P<0.005$) (Table 6.6). Even in this one significant

Table 6.6 Results from hierarchical regression analysing the unique contribution of SO well-being to patient recovery

Factor	Assessment one					Assessment two				
	Model	N	R^{2*}	Step F/ χ^2 Improvement	*P*	Model	N	R^{2*}	Step F/ χ^2 Improvement	*P*
Attention (*TEA*)*	1	84	32.0	19.795	0.003	1	73	23.3	12.418	0.05
	2	84	32.0	0.009	ns	2	73	23.3	0.032	ns
Memory(*RBMT-E*)*	1	83	12.1	7.430	ns	1	73	19.3	9.997	ns
	2	83	21.8	6.446	0.011	2	73	20.0	0.392	ns
Executive (*BADS*)*	1	83	9.3	5.827	ns	1	73	18.2	10.210	ns
	2	83	14.6	3.494	ns	2	73	20.0	1.132	ns
Physical (*FIM-MS*)*	1	86	18.7	3.031	0.01	1	72	28.2	4.326	0.001
	2	86	21.9	3.213	ns	2	72	33.0	4.594	0.04
Sleep (*PSQI*)	1	60	12.1	1.218	ns	1	70	32.2	5.071	0.0001
	2	60	15.8	2.246	ns	2	70	33.1	0.795	ns
Fatigue (*MFSI-SF*)	1	59	29.3	3.592	0.005	1	69	19.2	2.489	0.04
	2	59	29.9	0.400	ns	2	69	19.5	0.284	ns
Physical HRQoL (*SF-36*)	1	83	13.6	1.988	ns	1	71	14.9	1.893	ns
	2	83	15.7	1.890	ns	2	71	17.2	1.799	ns
Mental HRQoL (*SF-36*)	1	83	27.8	4.884	0.0001	1	71	17.0	2.212	0.05
	2	83	30.9	3.363	ns	2	71	20.9	3.161	ns
Anxiety (*HADS-A*)	1	84	29.1	5.275	0.0001	1	70	18.2	2.375	0.04
	2	84	36.1	8.286	0.005	2	70	19.2	0.736	ns

Table 6.6 *Cont'd.*

Factor	Assessment one					Assessment two				Factor
	Model	N	R^{2*}	Step F/ χ^2 Improvement	*P*	Model	N	R^{2*}	Step F/ χ^2 Improvement	*P*
Depression (*HADS-D*)	1	84	23.1	3.859	0.002	1	70	12.9	1.578	ns
	2	84	25.2	2.074	ns	2	70	15.9	2.242	ns
PTSD (*PDS*)	1	80	26.1	4.300	0.001	1	70	18.5	2.422	0.05
	2	80	29.2	3.146	ns	2	70	25.4	5.851	0.03

Note: BADS=Behavioural Assessment of the Dysexecutive Syndrome; FIM-MS=Functional Independence Measure-Motor; HADS-A=Hospital Anxiety and Depression Scale – Anxiety score; HADS-D=Hospital Anxiety and Depression Scale – Depression score; MFSI-SF=Multidimensional Fatigue Symptom Inventory-Short Form; N=sample size; PDS=Posttraumatic Stress Diagnostic Scale; PSQI=Pittsburgh Sleep Quality; R^2=variance explained by model; RBMT-E=Rivermead Behavioural Memory Test-Extended; TEA=Test of Everyday Attention; SF-36=Short Form-36; *=The R^2 approximation for logistic regression model is the R^2 version devised by Nagelkerke (note this statistic can achieve a value of 1).[478] Model 1=Constant + Covariates (education, age, sex, pre-morbid health, WFNS grade, time since ictus), Model 2=Constant + Covariates + concurrent SO PTSD symptom severity.

aspect of patient recovery, only 7% of unique variance in patients' recovery was accounted for by SO well-being. SO wellbeing did explain 9.7% of unique variance in patients memory performance (F[1]=6.446, P=0.01), but this proved non-significant when judged according to the adjusted test-wise alpha (P=0.007).

Assessment two

The SOs' experience of PTSD symptomatology did not significantly predict any aspect of their patients' longer-term recovery (Table 6.6). Small associations of 5% and 7% were found between SO well-being and patients' physical recovery (F[1]= 4.595, P=0.04) and patients' own experience of PTSD symptoms respectively (F[1]= 5.851, P=0.03). Again though, these associations proved non-significant when judged according to the corrected alpha level (P=0.007).

6.4 Discussion

This study has shown for the first time that having a loved-one suffer, and survive a spontaneous subarachnoid haemorrhage (SAH) is sufficient to elicit post-traumatic stress disorder in patients' family members and friends. It was found that approximately 26% (over three times the normal rate) of these 'significant others' (SOs) warranted a diagnosis of PTSD in the early-stages following an SAH and 16% warranted a diagnosis over one year post-SAH. A further 14% (in the early stages) and 7% (at around 1 year post-SAH) met the criteria for its preclinical, debilitating sub-syndromal form. Given this considerably high prevalence and that PTSD is a disorder known to cause medical and psychosocial disability, it is clear that much more attention needs to be given to the outcome of SOs [23]. The present findings help to explain why SOs have previously been documented as exhibiting abnormal

levels of psychiatric symptoms and as having a reduced sense of well-being [48, 90, 264, 265, 285, 286, 461, 545, 546]. The need for an increased focus on SOs is underscored by evidence that they are the persons who typically act as informal carers to the patient [90, 264, 461, 545, 546]. If support is not provided, there may end up being two patients to support, where previously there was only one, supported by a SO [520]. The importance of this is highlighted when it is considered that the service rendered by families and other informal carers is invaluable and dramatically reduces the economic burden of SAH on society [154, 215]. Moreover, recent social trends, such as changes in family structure, increased geographical mobility and greater participation of women in the workforce, means that there are fewer potential replacements for those SOs who become ill and end up having to abdicate from the caring role [522]. Also, the incidence of SAH – unlike other stroke types – remains stable [140, 403, 711], but the number of people who survive an SAH and who require subsequent care is increasing all the time [284, 364, 653]. Therefore, the number of SOs who will be needed to act as informal carers can be expected to rise in the future.

My finding that SAH can elicit PTSD in an SO compliments the work of Pritchard et al. [545]. As noted in the introduction to this chapter, Pritchard and colleagues found that informal carers of aneurysmal SAH patients experienced a significantly worse psychosocial outcome (for example, feeling more frightened, depressed and stressed) than carers of acoustic neuroma (AN) patients, even though socially and clinically well-matched. The authors suggested that this difference in outcome could be due to the emergency (rather than elective manner as is the case for AN) onset of the SAH and its treatment. Pritchard et al. considered that the emergency onset of the SAH, which by its very nature, came without prior warning

and caused major disruption, was sufficiently traumatic for the SO to elicit a post-traumatic stress-reaction. Pritchard et al. however, did not use a diagnostic measure for PTSD and were therefore unable to confirm their hypothesis about PTSD. The present study did use such a diagnostic measure and can, therefore, confirm for the first time that an SAH leads to significantly elevated levels of PTSD in SOs of SAH patients.

It is important to highlight that it is not presumed that the finding of elevated PTSD is restricted to family members and friends of patients with SAH [23]. A few studies have indeed documented an abnormal level of PTSD symptoms in other populations of family and friends of patients, such as in parents of children involved in accidents [97, 142, 698, 771]. It is also likely that other neurological conditions could be sufficiently psychologically traumatic to elicit a PTSD-reaction in family or friends. The present findings therefore, serve to underscore the importance of considering the impact of an illness on persons other than the patient.

The finding that there was not a reduction in the prevalence of PTSD in those SOs examined at both assessment points, and that an SOs PTSD diagnosis was largely stable, leads to the conclusion that PTSD in this sample is, for the most part, a chronic problem. This concurs with evidence from the wider literature. One large epidemiological study of 5877 persons in the U.S., for example, found that the average duration of PTSD for those who did not seek treatment was over 5 years, and over one-third of persons suffering PTSD never fully recover [351]. There is some evidence to suggest that the greatest remission of PTSD occurs within the first 3 months [584] and that those persons who fulfil the diagnostic criteria beyond this point have a significantly high likelihood of their PTSD taking on a chronic course [266, 446, 458]. Indeed, the DSM-IV-TR does recommend that if PTSD endures in a person

for 3 months or more, then the treating clinician should consider it to have assumed a chronic course [23].

The existence of sub-syndromal PTSD in this study's SO sample (7-14%) also warrants discussion. The inclusion of these persons in the formal incidence of PTSD in the SAH SO population would obviously increase the prevalence of significant psychological impact of an SAH on SOs. It should be borne in mind, however, that a consensus on the definition of sub-syndromal PTSD has only recently begun to emerge [477], with some [55, 101] advocating less stringent diagnostic criteria for sub-syndromal PTSD than employed in the present study. Using such alternative criteria would have further increased the incidence of stress reactions found in SAH patients SOs. Previous research in other populations has illustrated that such sub-syndromal disorders are associated with similar levels of functional impairment and psychosocial difficulties as full-blown PTSD [72, 658, 739, 773], that it often assumes a chronic path [319, 605], and is a risk factor for delayed onset full-PTSD (i.e., PTSD which occurs more than 6 months following the trauma) [106]. In line with these findings, sub-syndromal PTSD in the present study was found to cause many SOs severe degrees of distress and/ or functional impairment. In fact, at the second assessment, the functional impairment caused to SOs by sub-syndromal PTSD was comparable to that experienced by SOs with full-PTSD. Findings such as these have, in fact, led many to criticise the diagnostic criteria for PTSD as being too restrictive and leaving many short of appropriate treatment [477, 586].

The high rate of PTSD in the current study clearly indicates a need to understand why SOs develop PTSD. It was found that for SOs of SAH patients, coping strategies are the single best predictor of PTSD in the short-term. The greater the use of maladaptive coping strategies, the higher the likelihood that an SO will

develop post-SAH PTSD. This mirrors similar findings obtained in persons who developed PTSD as a consequence of other traumatic events (such as accidents, terrorist incidents and having a medically ill child) [87, 206, 207, 217]. In fact, in this study it was found that use of information about an SO's coping strategies alone, allows a classification accuracy of 84%. The classic explanation for why maladaptive coping strategies promote PTSD refers to the slightly paradoxical phenomenon that by actively avoiding thoughts or situations which lead to anxiety and fear we in fact maintain the fear-inducing quality of those thoughts and situations. In contrast, successful adaptation to the experience of a trauma involves accessing of aversive emotions about the event, which permits habituation to anxiety and modification of trauma-related beliefs [88, 193]. It is therefore possible to predict at an early stage, which SOs are at risk of developing PTSD. Moreover, appropriate interventions, such as teaching SOs better coping strategies can be implemented, which should make possible a reduction in SO PTSD and its associated psychosocial disability. Encouraging in this context, are the findings from another of Pritchard et al.'s studies, which illustrated the potential to improve the psychosocial outcome of SAH carers through the enhancement of the support they are offered [547, 548]. Specifically, this enhanced service employed the use of a specialist liaison nurse who provided support and counselling for SAH patients and families from the first day of admission. Those receiving this enhanced support fared significantly better in their emotional response and employment than did a matched group of carers receiving the normal support. Knowing that the underlying problem in SOs is PTSD and identifying their use of maladaptive coping strategies should allow us to design a more specific and even more effective system for preventing and treating the psychosocial problems in SOs (the effect sizes for Pritchard et al.'s intervention were only modest).

It could be argued though, that maladaptive coping, which incorporates avoidant behaviors, rather than representing a PTSD risk factor, could instead be a symptom of it, especially given that avoidance behaviours are a diagnostic symptom of PTSD. As commented by other workers however, this seems unlikely given that avoidance behaviours describe only 2 of the 17 symptoms that define PTSD [88]. Furthermore, evidence from studies which fortuitously measured individuals' preferences for coping skills prior to a trauma, show that pre-trauma preferences for maladaptive coping are predictive of subsequent PTSD, suggesting that maladaptive coping is a cause rather than a consequence of PTSD [172, 217]. For the analysis in question, coping skills had been measured at the same time as PTSD. Thus, it was not possible to determine the causal relationship between these two variables. However, in light of the above-mentioned findings, it is more likely that maladaptive coping skills cause PTSD than the other way around. Ultimately, an intervention study would be required to settle this question.

Unfortunately, it was not possible to develop a significantly effective prediction model for longer-term SO PTSD. It was found that the dispositional use of maladaptive coping strategies, when judged against the adjusted critical alpha, were no longer sufficient to discriminate between those with and those without PTSD at assessment two. In exploring the reasons for the change in the association between coping and PTSD, the data suggests that those SOs with PTSD at only assessment two were unique in that their PTSD developed regardless of whether or not they used maladaptive coping. Further work on predicting the development of PTSD in the longer-term is obviously therefore needed. Fortunately, the results from the present study have illustrated that (at least in the first 13 months post-SAH) only a minority (~30%) of SOs' PTSD status actually changes between the short- and long-term.

Therefore, the short-term predictive model would efficiently highlight the majority of SOs who are likely to need targeted support in both the early and later stages following their loved-one's SAH.

Noteworthy, is the find finding that the degree of physical, cognitive and emotional disability an SO's patient exhibited was not associated with PTSD development at any point. This appears to be in conflict with other studies [394, 414], including two focusing on SAH SOs [265, 510], which have suggested that information on patient disability is important in predicting SO outcome. A close look at these studies however, shows that PTSD was not included in the reported outcome measures. Instead, more general measures such as "stress" or "incidence of divorce" were used. Moreover, the validity of some of these earlier findings is debatable given that they come from bivariate, rather than multivariate analyses and thereby did not control for possible confounding variables.

As has been stated, the well-being of SAH patients' SOs is of crucial importance not only from the perspective of their personal suffering, but also because of the important economic saving which they offer society. Increased attention on SO well-being has, however, also been motivated by evidence from the fields of ischemic stroke [161, 178, 225] and traumatic brain injury (amongst others) [528, 680], which suggests that the adjustment of an SO to a caring role (more broadly referred to as the patients' social support) has significant implications for the patient's ultimate recovery. At times, it is believed to be as significant as the initial disability resulting from the patient's illness. Such findings are very attractive from the perspective of rehabilitation, as SO well-being is potentially much more amenable to change through intervention than other, more stable predictors of patient recovery, like patient demographics and clinical aspects of the person's illness [593]. It has been asserted

within the fledgling SAH SO literature that the well-being of an SO is also a likely determinant for SAH patient recovery [461, 469, 690]. The present study employed hierarchical multiple regression techniques to further examine the impact/ association between SOs' well-being – here indexed by their experience of PTSD symptomatology – on different aspects of a patient's recovery, including objective measures of cognitive, physical and psychiatric status, as well as subjective measures of their health-related quality of life. Hierarchical multiple regression is well suited to this real-world, complex research question as it is not one which can be easily reduced to an orthogonal design for the laboratory setting. Through the entry of demographic and clinical characteristic in an initial block into the predictive models, it allowed the unique contribution of SO well-being to patient recovery to be gauged, as the variance explained by the demographic and clinical factors known already to predict patient recovery could be controlled [677]. The results of these analyses, however, largely contradicted the belief that the relationship holds for SAH patients, as on only 1 of the 22 measures of patient outcome that were considered was there a significant impact of SO well-being. How can this discrepancy be explained? The explanation probably lies in the fact that not only has the relationship between SO well-being and SAH patients' recovery simply been presumed (and not actually substantiated), but also because many of the studies in the wider literature which have claimed to have provided evidence for the relation between social support and patient recovery are actually seriously flawed by methodological limitations. In fact, as several commentators have recently noted [223, 753], there is, to date, little concrete evidence that ischemic stroke patients and traumatic brain injury patients actually have an improved outcome as a result of family interventions.

At time of writing, there has only been one SAH study, conducted by Toomela et al. [690], which has actually investigated the impact of SOs' well-being on SAH patients. Since that study reported evidence contrary to the present study, it is important to consider it in further detail. Specifically, it was reported by Toomela et al. that in a sample of 27 SAH patients, it was those SAH patients who felt the least supported post-discharge, who experienced the worst outcome, experiencing more headaches, memory problems and symptoms of dizziness [690]. It is quite obvious on closer examination why it should be that Toomela et al.'s study reported divergent findings to the present as it exemplifies the methodological limitations plaguing many of the studies on the topic in the wider literature [162, 224, 445, 528, 562, 650]. Firstly, the relative of significance of SO well-being was not considered. Specifically, SO well-being was not considered in the context of those predictors of patient outcome such as, the initial severity of the illness, patient's age, sex, education, premorbid health and the time that has elapsed since illness onset, which are *already* recognised as being important. Without controlling for these factors, it is not possible to ascertain what unique contribution SO well-being has for a patient's recovery. Secondly, many studies conclusions have been based on critically small samples, which raises concerns about how well their findings generalise. Toomela et al., for example, studied only 27 patients which, in fact, is so small that the discriminant function analyses which they used are rendered invalid according to accepted guidelines [677]. Finally, Toomela et al. considered only patients' subjective experience of headaches, memory problems, dizziness and absentmindedness. These aspects do not broadly encompass the key features of a patient's outcome after an SAH. Moreover, the use of only subjective based measures of such problems raises the question as to whether the impact of an SO's well-being extends to

objective measures. In the same study it was in fact reported that these patients' subjective reports of memory problems and absentmindedness did not correlate significantly with objective measures of the same problems. Therefore, given the greater methodological rigor of the present study, it is not surprising that results contrary to Toomela et al.'s were found. Although a larger sample size and a longer follow-up is required to rule out that SO well-being has no bearing on patients' recovery, the results of the present study do still strongly suggest that the influence of SO recovery is small. Indeed, the effect size of the only significant relationship that was found – namely between SO well-being and patient anxiety in the early stages of recovery – was of a negligible size, explaining only 7% of variance in patients' anxiety scores.

Two potential limitations to the present study require highlighting. Firstly, as SOs were recruited through the patients, there is the possibility of a selection bias. Secondly, it would have been preferable to have measured the SOs' psychiatric status using an interview, rather than questionnaire-based technique. Although the PDS is known to possess sensitivity and specificity levels which approach those associated with "gold-standard" interview techniques [54, 193], there exists the possibility, due to the ubiquitous nature of many of the SOs' symptoms to a variety of other disorders [23], that another disorder may be more appropriate to explain SOs' psychological distress. On the basis of my findings, this possibility cannot be ruled out. In any case, regardless of whether the observed psychological distress is most appropriately labelled as PTSD or not, it remains a fact that a substantial portion of SOs experience significant distress subsequent to a loved-one's SAH. More importantly, my findings suggest that the psychological distress of SOs might be

treatable and potentially preventable as maladaptive coping skills seem key to its development.

6.5 Conclusions

In conclusion, PTSD was found to be common in SOs of SAH patients at both 3 ½ - and 13-months post-ictus. The elevated incidence of this disorder helps to account for the previously noted psychiatric symptoms in and psychosocial disability of SOs. Greater attention and support needs to be given to assist with the adjustment of these persons to their recent experience, especially considering that they often act as informal carers to SAH patients. It is important to find ways to prevent the development of PTSD which would likely interfere with the willingness/ ability of SOs to care. Maladaptive coping strategies seem to be the best predictor of SO PTSD in the short-term, but it is unclear what predicts PTSD in the later stages. It is hoped that by teaching SOs better coping strategies early on, the incidence of PTSD could be reduced.

Final Chapter

Chapter 7

General discussion and conclusions

7.1 Introduction

Previous studies examining spontaneous subarachnoid haemorrahge (SAH) patients and their family and friends (who often act as their informal carers), had found that despite a seemingly good prognosis for surviving patients, many patients and their family and friends nevertheless suffered an particularly poor psychosocial outcome. The main aim of this thesis was to look to explain the mysterious difficulties of patients and their 'significant others' (SOs) by building upon previous evidence which led me to hypothesise that an abnormal prevalence of post-traumatic stress disorder (PTSD) in both groups – elicited by the trauma of an SAH – could be a way to explain their respective difficulties.

Two longitudinal studies were conducted – one focusing on SAH patients and one focusing on their SOs. Overall, the results show that the best explanation for the poor outcome of members of both groups is that an abnormal number of them find the experience of an SAH so traumatizing that they develop PTSD. However, rather than simply determining *what* the difficulties of these persons were, this thesis has also provided some important insights into *how* we could potentially treat/ prevent their difficulties. Specifically, I established that it is possible to reliably predict which patients and SOs develop PTSD on the basis of information about the stress-coping strategies that they employ. In the next section (7.2), I shall discuss the main findings and conclusions to this thesis. These are then followed by a discussion of their implications for the treatment of SAH patients and their SOs in section 7.3. Finally, future research directions are discussed in Section 7.4.

7.2 Main findings

The overarching finding emerging from the studies presented in this thesis is that the (previously mysterious) poor psychosocial outcome of SAH patients (defined in terms of health-related quality of life [HRQoL], fatigue and sleep dysfunction) and their SOs (defined in terms of their psychiatric disturbance) can, to a large extent be explained by the fact that an abnormal number of them find the experience of an SAH so traumatizing that they develop PTSD.

Evidence from Chapters 3, 5 and 6 showed that despite their very different roles in the event, both patients and significant others are united by the fact that they can experience an SAH as not only a medical emergency, but also as a psychologically stressful event. Overall, these findings support prior research which proposes that medical events can be highly traumatic for patients and that it is also important to consider the wider impact of medical events for patients' family and friends. The striking parallels between SAH patients' and their loved-ones' outcome accords well with previous research where similarly poor reactions have been found in both patients and their family members following other medical events, including breast cancer and heart transplant [28, 62, 85, 671].

Crucially, insights were provided into how patients and their family and friends PTSD could be reduced as findings from Chapters 5 and 6 showed that for both parties the degree to which they used certain psychological stress-coping strategies largely determined whether or not they developed PTSD as a result of the SAH. Those with a disposition to use 'maladaptive' coping strategies such as denial, avoidance, distraction, venting and behavioural disengagement, were the most likely to experience PTSD. Importantly, the SAH patients' PTSD was not found to be

associated with any characteristics of their illness, which strongly implies that the origins of these patients' PTSD are not neurological, but rather psychological.

In Chapter 5, I examined SAH patients' sleep and fatigue. For the first time within the literature, these symptoms were both measured using validated measures and the patients' scores were compared to those of a control group. Using these techniques evidence was found which strongly suggests that many SAH patients experience highly abnormal levels of fatigue and sleep. Importantly, PTSD helped explain many of the difficulties that these patients had with their sleep and energy levels. This evidence means that clinicians can no longer dismiss these symptoms and that they symptoms require medical attention.

Behavioural disturbances such as delirium, major depression, anxiety disorder, mania, psychosis, personality change and fatigue following neurological diseases have typically been assumed by clinicians to be the direct result of the brain damage associated with the disease and not a psychological disturbance [416, 531]. The finding of this thesis, that a psychiatric disturbance, namely PTSD (whose origins were psychological), is integral to understanding a patient's behavioural outcome following a neurological disease, is therefore highly novel and significant. In showing that not all behavioural disturbances or psychosocial impairment following neurological diseases can be understood as being the result of 'organic' brain damage, the findings of this thesis imply that a significantly different approach to the treatment of neurological patients' disturbances may be warranted. My study is amongst only a few studies which have considered such a 'non-organic' explanation for neurological patients' behavioural disturbances. For example, whilst a recent review article by Tedstone and Tarrier [684] revealed that a host of studies have considered the role of PTSD in explaining the behavioural disturbances following a

variety of medical incidents, including cardiac events, cancer and certain medical treatments, only a handful of primary studies were identified as having considered the possibility that this 'non-organic' disorder might explain the behavioural disturbances seen after *neurological* disease [89, 111, 615].

In Chapter 7, I looked at the outcome of patients' SOs in more detail. I felt that it was relevant to do so (a) because their health status is important for their own sakes and (b) because their health status is important due to their valuable role in supporting SAH patients. Contrary to many assertions, I found that although SO well-being was reduced, their poor psychiatric state, at least within the time frame of this particular study, did not appear to have any meaningful impact on patient recovery. The discrepancy between the finding of this study and the findings of other studies may at first seem concerning. However, close examination of the literature reveals that the relationship between significant others' psychiatric state and patient recovery, had largely been assumed, or based on research in the wider literature on other carer groups which have not adequately controlled for obvious confounding explanations for patients' poor recovery.

The key overall conclusion is that the treatment of PTSD in both SAH patients and their SOs could lead to a much improved outcome for both groups following an SAH.

7.3 Implications for treatment

The fact that both SAH patients and their SOs are often afflicted by PTSD and that the use of maladaptive coping reliably predicts its development, has significant bearing on neurosurgical practice and how these persons can be better treated.

One immediate implication of the finding that 37% of SAH patients and 16% of their SOs develop full-PTSD (and yet more its sub-syndromal form) post-SAH, is that health-professionals now urgently need to recognise and treat the psychiatric consequences of an SAH experienced by patient and significant other. At present, post-SAH rehabilitation programmes typically focus on only the patient, address only the neurological impact of an SAH and are offered to only a restricted subset of patients (~10%). The persistence and consequences of PTSD in the SAH population also add credence to calls for health-service providers to no longer simply view an SAH as an acute event, but rather a chronic disorder which necessitates the on-going support which is typically afforded to other such illnesses [240]. It is interesting to note when considering what support should be offered to SOs, that in my studies, I restricted the inclusion of SOs to only the person(s) which the patient felt were *most* involved in their support and excluded significant others whose loved-one had died. It is possible that additional members of the surviving patients' social networks (including their children) [762], as well as bereaved family members and friends, could have also developed PTSD as a result of the SAH [23].

PTSD following other traumas is known to be a readily treatable disorder [255]. This means that there is now a real possibility that the well-being of SAH patients and their SOs could be significantly improved [255]. It also provides a crucial insight for the rehabilitation of SAH patients and SOs, as traditionally it has been assumed that

the principle difficulties for this group were the consequence of patients' 'organic' brain damage, which is known to be extremely difficult to treat.

The failure to deliver an intervention targeted at treating PTSD could also help to explain why the effectiveness of interventions to improve SAH patients' and SOs' outcome in two previous studies proved disappointing [548, 725]. Only one of the studies [547, 548] – a non-randomised examination of a fairly non-specific intervention (support by a liaison nurse) – reported significant effects, but the benefit of this treatment (as revealed by calculated effect sizes) was small (*r* range=.12-. 21).

An array of formal psychological interventions [195] and pharmacological treatments (typically selective serotonin re-up-take inhibitors) [51, 429, 656, 696] are available for the treatment of PTSD and could prove much more efficacious in improving SAH patients' and significant others' well-being. But which specific treatment(s) should SAH patients and their SOs be offered? A psychological, rather than pharmacological treatment would seem preferable [24], as persons with brain damage in general are at increased risk of experiencing side effects (for example, nausea, dizziness and insomnia) from pharmacological treatments [281]. Medications could also increase patients' already heightened risk of suffering from seizures and the cognitive side-effects common to such treatments could serve to further impair patients' compromised cognitive function [645]. Moreover, the National Institute for Health and Clinical Excellence recently concluded from a comparison of treatment efficacy that psychological interventions are preferable to pharmacological interventions for the treatment of PTSD [255].

Psychological therapies for PTSD come in a variety of forms, but their central theme is similar. Like treatments for other anxiety disorders, psychological treatments consider that the best way to reduce or eliminate patient fear and anxiety is by

exposing (in a controlled and structured manner) the patient to those stimuli which provoke their fear and which they so ardently try to avoid. In the case of SAH PTSD, these stimuli are related to the "brain haemorrhage". In psychological interventions, the traumatized person is encouraged to confront the initial trauma in order to gain mastery over it and extinguish the considerable anxiety associated with the horrific event. A recent Cochrane review concluded that eye-movement desensitization and reprocessing (EMDR) and trauma-focused cognitive behavioural therapy (CBT) were the most efficacious of the psychological treatments [50]. In EMDR, the PTSD patient is asked to imagine an image, thought, emotion and a bodily sensation associated with the traumatic event whilst making rapid eye movements (which some consider facilitate processing of the traumatic event) [625]. Trauma-focused CBT on the other hand, generally employs an approach in which, (with the help of a therapist) the patient identifies distorted thinking patterns regarding themselves, the traumatic event and the world. The patient is encouraged to challenge these distorted thoughts by weighing up available evidence [50]. Future treatment of SAH patients and their SOs could look to use either of these two therapies for the treatment of PTSD.

An alternative treatment option would be to specifically focus on coping, since it was this which was found to be the best predictor of which SAH patients and SOs developed PTSD. In line with prior evidence, it was found that the use of coping strategies such as avoidance, denial, distraction and self-blame proved maladaptive to a patient's/ SO's mental health, increasing the risk of PTSD development. Mental health following an SAH may therefore be improved by the facilitation of more adaptive coping styles. This finding is very promising as a raft of evidence from the wider literature suggests that coping is amenable to intervention using relatively

inexpensive, psychosocial 'coping-effectiveness' group-based interventions [14, 16, 127, 216, 424, 556, 638].

'Coping-effectiveness' interventions are highly structured and draw on some elements of CBT. The interventions typically focus on teaching the individuals a structured problem-solving technique/ framework for choosing from various coping strategies. The central approach converts the major tenets of Lazarus and Folkman's [390] stress and coping theory into a series of practical and straightforward steps. Participants are encouraged to actively deal with problems by seeking information or by talking with others, rather than engaging in avoidant behaviours such as alcohol or drug use. Homework exercises and written handouts are used to encourage individuals to practise the strategies at home and to develop personal understanding of the effectiveness of the strategies.

Importantly, not only have coping effectiveness interventions proved to increase peoples' use of adaptive coping strategies (e.g., active coping, acceptance) and reduce the use of maladaptive coping (e.g., avoidance, denial, distraction), but these changes in coping are associated with improvements in mental health [16, 104, 113, 127, 216, 346, 424, 556]. Moreover, this finding has been illustrated in persons following a variety of medical events, including cancer, spinal cord injury, sickle cell disease and HIV+ infection [104, 113, 127, 216, 346, 556, 612]. Studies have also involved patients' family members and friends [342, 343, 424, 485, 612]. One study [634] even found a significant and clinically meaningful reduction in PTSD symptoms in a sample of adults who had experienced childhood sexual abuse and had HIV/AIDS. This improvement was found in comparison to both a wait-list and a support group control condition.

If coping effectiveness training proved effective for SAH patients and SOs, it could be extremely advantageous compared to traditional psychological treatments. As whilst EMDR and CBT are offered on a one-to-one basis (typically with repeated sessions often over the course of weeks or months, but sometimes years), coping training can be delivered to a group, including both SAH patients and their SOs. This means that such a treatment could be more cost-effective and allow a greater number of persons to be treated [14, 195, 483]. Furthermore, in several studies, the 'coping-effectiveness' intervention has been delivered by non-specialist staff [104, 263]. This raises the possibility that such programmes could be delivered to SAH patients and SOs by non-psychologist/ psychiatrists. It could even potentially be delivered by the large network of support groups and charities dedicated to brain damage which exist throughout the world.

Given that the maladaptive coping models developed in Chapters 4 and 6 proved to be quite reliable in predicting which SAH patients and SOs were most likely to develop PTSD, the possibility that the coping effectiveness training could actually be offered as a preemptive therapy is also raised. The Brief COPE measure [107] could be administered to all patients who are to be discharged and their SOs and those identified according to their score as being most 'at-risk' could be offered the intervention before the full PTSD syndrome develops. Indeed, preliminary evidence from one study on spinal cord injury suggests that the efficacy of coping effectiveness training interventions for mental health is maximized by reducing the time between onset of injury and the start of the intervention [347]. Moreover, early supportive interventions (but *not* single session debriefing techniques [444]) have long been considered helpful for acutely traumatized persons in general [24].

Regardless of which non-pharmacological treatment is deemed preferable, adjustments to the manner in which the therapy is delivered would need to be made, to account for the difficulties associated with SAH patients' brain injury [14, 15, 88]. Memory and attention problems could, for example, affect a patient's ability to take in and remember information and techniques discussed in the treatment sessions, whilst a dysexecutive syndrome may interfere with a patient's ability to generalise adaptive coping strategies learnt within the treatment session and implement them in their everyday life [14]. Employing a highly structured framework, as well as increased use of practical exercises, repetition and written reminders are obvious techniques which could help circumvent some of these problems. Importantly, it should be acknowledged that coping effectiveness treatment may not be effective for all persons with PTSD following SAH. As although the regression models presented in Chapters 5 and 6 were very useful, the development of PTSD in patients and SOs in the later stages was less reliably predicted on the basis of the coping skills which they used.

7.4 Implications for future research

The findings of the research presented in this thesis lead to extremely interesting directions for future studies. Some of the key questions which would it be useful to address are now described.

7.4.1 Why is the incidence of PTSD in the SAH patient population so high?

As I have already noted in the discussion section to Chapter 5, it is interesting that I detected a remarkably high incidence of PTSD in the SAH patient population – namely 37% in the both short- and long-term. This high incidence appears to be at odds with the usual pattern of low prevalence of PTSD (and psychopathology in general) that follows internal medical traumas [23, 476, 701]. So how can this high incidence in the SAH population be explained? The similarity of the incidence of PTSD in patients detected in this thesis and that of prior studies (full PTSD estimates 26-32% [47, 295]) on SAH which used "gold standard" interview techniques means that the high incidence cannot be explained by my use of a questionnaire measure of PTSD which can at times, 'over-diagnose', particularly with medical patients [500, 674, 675]. Rather, in my view, two (potentially complimentary) explanations could account for the high incidence. Firstly, I recruited a fairly large sample of patients and used broad inclusion sample. Previous studies examining PTSD following other medical events which have reported finding much lower incidences have often employed highly restrictive inclusion criteria which could serve to reduce their likelihood of finding PTSD. For example in cancer studies, it is often only early stage female breast cancer samples which are studied because of the relative ease of their recruitment [327, 476]. Evidence suggests that the relatively good prognosis of these

participants limits the likelihood of them developing PTSD and that the inclusion of persons with more advanced cancers would have increased the incidence of PTSD [311].

The second explanation for the high incidence of PTSD following an SAH is its unusually severe nature and its aftermath. Although the severity of an event is not by itself sufficient for the development of PTSD (hence 63% of SAH patients did not its fulfill its diagnostic criteria in this thesis), nor is it the most important determinant for who develops the disorder in general [73, 521], a dose-response model is nevertheless predictive to some extent [576]. Specifically, events of a higher a severity, intensity and physical proximity have been found to pose the greatest risk for the development of PTSD [23, 576]. This phenomenon has most recently been illustrated by an epidemiological study of the incidence of PTSD in residents in different areas of Manhattan, following the terrorist attacks of September 11th 2001 in New York on the World Trade Center. It was found in multivariate analysis that proximity to the World Trade Center was a significant predictor of PTSD development. Judged according to a U.S. normative population estimate of 3.6% of PTSD [620], it was found that following the attacks 6.8% of persons developed PTSD who lived towards the north of Manhattan and furthest away from the World Trade Center, whilst 20% of those persons living towards the southern end of Manhattan, in the vicinity of the attacks, developed PTSD [209]. This latter group was presumably more directly exposed to the trauma and/or its consequences. The phenomenon that being *directly* affected by a disaster carries a greater risk of developing PTSD [233, 492] explains why the incidence of PTSD is lower in SAH SOs than it is in SAH patients. So what is it about an SAH that makes it so severe? Not only would an answer to this question have significant implications for how we could possibly prevent SAH PTSD

(as I discuss in the next section), but it could have important ramifications for trauma research in general as it could help us to better understand the origins of PTSD reactions.

7.4.2 Prevention of PTSD in SAH patients

As noted by Weinert and Meller [738] with respect to the trauma of intensive care treatment, we are in a unique position with SAH because "[u]nlike subjects exposed to the stressors of combat, childhood neglect or physical assault who almost always present for treatment after the stressor is over...we can...intervene while the stressor is occurring...almost no other PTSD field can feasibly do this" (p.2). This means that identifying what it is about an SAH that precipitates PTSD in SAH patients could have significant implications for prevention as attempts could be made to make the event/s less traumatic. This idea of pre-emptive intervention for PTSD has previously been discussed by Bryant et al. [85] in the context of road-traffic accidents, who on the basis of their study, suggested that relatively simple changes in the future, such as the rapid removal of neck and back restraints on arrival to hospital and better communication about the trauma and its consequences, could help to reduce the incidence of PTSD.

Identifying the initial stressor event which precipitates PTSD in SAH patients is however, challenging compared to traditional traumatic events such as rape or assault, as it is not a discrete event. Instead, the nature of an SAH and its requisite treatments means that the event of having a 'brain haemorrhage' can be protracted, with patients potentially being exposed to multiple stressors (including the initial distressing onset of symptoms, the invasive treatments, the diagnosis, etcetera). Each of these individual events could be considered to satisfy the DSM-IV-TR

definition of a traumatic event (i.e., one which poses a threat to either a person's life or physical integrity). Pinning down the event which precipitated SAH patients PTSD has not so far been achieved by SAH patient studies (including the one in this thesis) because awarding the diagnosis does not necessitate knowing the *exact* stressor. Criterion A for a diagnosis of PTSD rather *only* requires that the person has a history of exposure to *one or more* traumatogenic events and that this event or events subsequently mobilises the three symptom clusters of re-experiencing, avoidance and hyperarousal which define PTSD [23]. The criterion A event can be as specific as a physical assault, or as broad as being involved in military combat. SAH studies, as was the case in this thesis, simply ask patients about their experience of PTSD symptoms with reference to their "brain haemorrhage". Future studies could employ two techniques to potentially help determine which event(s) is the actual stressor for SAH patients. The first would be to use qualitative interview techniques to explore the content of patients' intrusions. This could help ascertain which event(s) the patients' psychiatric response is centred upon. Alternatively, a novel approach would be to use psychophysiological techniques to determine which *specific* events of the whole SAH trauma are associated with the most stress. Patients could for example, be asked to generate personal scripts of their SAH experience. These could then be recorded in a neutral voice and recounted back to the patient. It may then be possible to identify the events which precipitated SAH patients' PTSD by determining which aspects of the recounted trauma were associated with the greatest physiological reaction in the patients.

It is interesting to note however, that it could actually be the complexity of an SAH and the fact that it exposes its patients to multiple traumas in a short space of time that causes an SAH to lead to such a high incidence of PTSD. Evidence is

available for instance, to suggest that individuals exposed to prolonged, repeated or multiple stressful events exhibit greater PTSD symptoms compared to individuals who experience discrete and single events [356, 447, 642].

In discussing the prevention of PTSD in SAH patients, it is also interesting to note that there has been recent interest in the administration of medication in the initial stages of a trauma to prevent PTSD – something possible in the case of SAH. Specifically, there is some evidence, albeit preliminary [51], that PTSD symptoms can be reduced following intravenous administration of hydrocortisone in victims of septic shock in intensive care [601], as well as in those undergoing cardiac surgery [740]. Such treatment is informed by studies – though not recent ones [770] – which found PTSD patients show neuroendocrine system alteration (such as lower basal cortisol concentrations [768] and high noradrenergic activity [457]). It is suggested that disrupting memory retrieval mechanisms with glucocorticoids during the initial stages of a trauma could act protectively against the development of PTSD by preventing recall of traumatic memories [600]. Future studies could consider the role of hydrocortisone and its ability to reduce PTSD in SAH patients.

7.4.3 What else can help explain HRQoL reduction in SAH patients?

Including PTSD into this thesis' explanative models of HRQoL substantially improves our ability to comprehend SAH patients' outcome. Nevertheless, even with the inclusion of this factor, there remains a proportion of variability in SAH patients' HRQoL that cannot be explained (52% of variance in Mental HRQoL and 67% of variance in Physical HRQoL). It is important for future studies to identify the factors that explain this reduction because currently there are some patients with a reduced HRQoL who we do not know how to help.

Given that conceptualising an SAH as a potential psychological stressor has proved useful in helping us to better explain SAH HRQoL, one possibility is to explore whether such a concepualisation could even *further* help to explain SAH patients' HRQoL. One interesting point raised by trauma-research in general is that it could be useful for future SAH studies to consider what psychiatric disorders other than PTSD are being elicited in patients by the trauma of their SAH [443, 607, 623]. A recent meta-analysis of psychiatric disorders following civilian traumas for instance, found that although PTSD was the most common psychiatric disorder to develop, generalised anxiety disorder, substance abuse, phobias and major depressive disorder are also common [80]. It could be that by measuring only PTSD symptoms, a group of patients who do not develop PTSD, but who do experience another psychiatric disorder post-SAH are excluded. This could explain their unexplained HRQoL reduction. Partial support for this possibility comes from three SAH studies which examined SAH patients' PTSD symptoms and found only modest correlations between the degree to which patients experienced PTSD and their scores on broader measures of psychiatric disturbance [295, 540, 541]. Hütter [295] for instance, measured the PTSD symptoms of intrusion and avoidance in a sample of 45 SAH patients and reported that their experience of these symptoms shared around only 25% of variance with their scores on a measure of mood disturbance (namely the Beck Depression Inventory [36]). This suggests that although a relationship exists between SAH patients' PTSD and mood disturbance, the two are relatively independent. Continuing along this theme of taking guidance from trauma research in general, future studies could also consider the added explanative value that comes from incorporating information into predictive models about the psychiatric co-morbidity experienced by those SAH patients with PTSD. It is well known from the

wider literature for example, that an additional formal psychiatric diagnosis is often warranted in PTSD patients [68, 125, 351] and that co-morbidity worsens a patient's HRQoL and functioning [431, 623].

With respect to which *non-psychiatric* factors could also potentially be involved, it is difficult to sift through the plethora of factors which have been implicated (see Tables 2.1 and 2.2 in Chapter 2) and suggest which hold the most promise. Studies examining them have typically not reported effect size data (or information necessary for its calculation). However, as I debated in the discussion section of my meta-analysis which I presented in Chapter 3 (see section 3.4), there is some evidence to suggest that it might be prudent for future studies to re-examine the relationship between bleed severity and SAH patients' HRQoL, but when bleed severity is indexed using a more detailed scale. The rationale for this suggestion being that Fisher's CT rating score [191] which is almost always used to index SAH bleed severity is potentially too crude to reflect the true variability in anatomical distribution and quantity of extravasated blood seen on patients' CT scans [306, 363, 371]. Indeed, it should be highlighted at this point that the Fisher scale was not designed to predict long-term HRQoL or describe bleed severity, but rather to simply categorise patients according to the risk that their bleed carried for the development of cerebral vasospasm [363, 496]. More appropriate scales for future HRQoL studies are however available. For example, Hidjra et al.'s [270] scale individually quantifies the presence of blood in the 10 major subarachnoid cisterns. The use of such scales could reveal that bleed distribution is better correlated with HRQoL than presently suggested.

7.4.4 What else can help predict PTSD development post-SAH?

Dispositional maladaptive coping proved to be highly predictive for the development of PTSD in SAH patients and SOs in the early stages post-ictus, as well as for most patients in the longer-term. This finding accords well with extensive evidence – from both prospective and retrospective studies – that shows that PTSD is highly associated with these types of coping strategies [87, 88, 165, 172, 217, 328, 493, 635, 655]. The failure however, to predict a subset of those SOs who develop PTSD in the later stages post-SAH and the reduced discriminative abilities of the model for long-term patient prediction, suggests that future work needs to look to refine the predictive models developed in Chapters 5 and 7 of this thesis and consider including additional, potentially predictive variables which have been implicated in the wider literature [73, 521].

7.4.5 What else predicts fatigue and sleep dysfunction in SAH patients?

In the current thesis, PTSD was found to be able to explain a staggering 58% and 42% of variance in SAH patients' experience of chronic fatigue and sleep symptoms, respectively. Previously these symptoms had remained unexplained. A large correlation in Chapter 5 between SAH patients' concurrent quality of sleep and fatigue (assessment one r=.53; assessment two r=.55) suggests that some of the fatigue was the consequence of impaired sleep which resulted from PTSD. This concurs with more general research on fatigue in sleep disorders,[166] where fatigue has been found to be elevated in those with sleep disorders (e.g., apnea, restless leg syndrome, narcolepsy [395, 471]) and a causal pathway is suggested, as treatment of these disorders leads to reduced fatigue [471]. Nevertheless, future research should examine how it is that PTSD can produce the remainder of SAH patients' fatigue, not

explained by induced sleep dysfunction. Possibilities could include the constant state of arousal which a PTSD patient can experience and the adverse health behaviours associated with the disorder (e.g., smoking, lack of exercise, alcohol use etc.) [351, 389, 606].

The finding that a proportion of fatigue and sleep dysfunction cannot be explained by PTSD, means that future studies need to determine which other factors are also involved. The fact that a proportion of fatigue remains unexplained is however, not unexpected as findings from the wider literature suggest that its cause is often multifactorial, with a variety of causes, including other health conditions (e.g., bacterial or viral infections, autoimmune illness) [120, 426], life-style choices (e.g., alcohol or caffeine intake, psychosocial stressors) [120, 426] and medications (e.g., anticonvulsants, analgesics) [38, 200, 648].

7.5 Conclusions

At the beginning of this thesis, it was stated that SAH is associated with very high societal and personal costs because the illness affects relatively young persons and because it causes its survivors and their family and friends to experience significant psychosocial disability. Unfortunately, it was not known what treatment could be offered to the survivors and their SOs to improve their outcome because the cause of their problems remained mysterious. This thesis has however, helped resolve this mystery by illustrating that the poor psychosocial outcome of SAH patients and their SOs is caused, to a large extent, by the fact that an abnormally high number of these persons develop PTSD as a result of the trauma of an SAH. Future studies are urgently needed to consider the implications of this finding. Importantly, studies need to determine whether offering treatment for PTSD to SAH survivors and their family

and friends reduces the burden associated with this illness. Studies would also be wise to determine whether teaching patients and their SOs more effective stress-coping strategies can reduce/ prevent PTSD and what it is that makes SAH so traumatizing that the illness stands out from other medical traumas as causing such a high degree of PTSD.

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Appendices

Appendix I:

World Federation of Neurological Surgeons scale

The World Federation of Neurological Surgeons (WFNS) scale [164] is a reliable scale for the rating of a subarachnoid haemorrhage patient's level of clinical severity on admission to hospital. Higher scores indicate worse clinical presentation.

The scoring for the scale is based upon the patient's score on the Glasgow Coma Scale (GCS) [683]. The GCS is a tool for the assessment of the level of consciousness (Table I.A). The GCS assesses responses to stimuli to measure the patient's ability to engage with his or her immediate surroundings. In the GCS a separate score is given for assessment of eye opening response, verbal response and motor response. These three scores are then added together to give a total score (between 3 and 15). The total GCS scores are then converted to a WFNS score as seen on the following page (Table I.B).

Table I.A The Glasgow Coma Scale

Glasgow Coma Scale						
	1	**2**	**3**	**4**	**5**	**6**
Eyes	Does not open eyes	Opens eyes in response to painful stimuli	Opens eyes in response to voice	Opens eyes spontaneously	-	-
Verbal	Makes no sound	Incomprehensible sounds	Utters words, but not coherent	Confused, disoriented conversation	Orientated, converses normally	-
Motor	Makes no movements	Extensor (rigid) response, decerebrate posture	Abnormal (spastic) flexion, decorticate posture	Flexion / withdraws to painful stimuli	Localizes pain	Obeys Commands

Table I.B The conversion of GCS to WFNS scores

WFNS Grade		
	Glasgow Coma Scale score	***Motor deficit***
1	15	Absent
2	13-14	Absent
3	13-14	Present
4	7-12	Absent or present
5	3-6	Absent or present

Appendix II:

The Hunt and Hess Scale

The Hunt and Hess scale [293] is a useful measure for the rating of a patient's clinical severity on admission to hospital (Table II.A). Higher scores indicate a worse clinical presentation.

Table II.A Hunt and Hess Scale

Hunt and Hess Grade	
Grade 0	Non-ruptured aneurysm
Grade 1	Asymptomatic or mild headache and/ or slight nuchal stiffness
Grade 2	Moderate to severe headache and/ or pronounced nuchal stiffness and/ or cranial nerve deficits, photophobia
Grade 3	Drowsiness and/ or mild disorientation and/ or slight pareses and/ or dysphasia
Grade 4	Stupor, moderate to severe hemiparesis and/ or dysphasia
Grade 5	Deep coma, decerebrate rigidity, moribund appearance

Appendix III:

Fisher's Rating Scale for Bleed Severity

Fisher's scale [191] for the rating of head computed tomographic scans for subarachnoid haemorrhage is presented below (Table III.A). A higher score indicates a more severe haemorrhage.

Table III.A Fisher's CT rating scale

Fisher Grade	
0	No scan available
1	No blood detected on CT
2	Diffuse deposition or thin, localised layer of blood in all vertical layers (interhemispheric fissure, insular cistern, ambient cistern), less than 1 mm in thickness
3	Localised blood clots and/or vertical layers of blood, 1mm or greater in thickness
4	Diffuse or no subarachnoid blood, with intracerebral or intraventricular blood present

Appendix IV:

Glasgow Outcome Scale

The Glasgow Outcome Scale (GOS) [318] for the rating of physical recovery following a subarachnoid haemorrhage is presented below (Table IV.A). A higher grade indicates more physical disability.

Table IV.A The Glasgow Outcome Scale

GOS Score	
1	Excellent recovery – Independent, no/ minimal neurological deficit
2	Good recovery – Moderate disability, independent with moderate deficit (e.g., aphasia, hemiparesis, ataxia or memory deficit)7
3	Poor recovery – Severe disability, dependent but conscious with severe deficits
4	Poor recovery – Vegetative state, dependent, persistent vegetative state
5	Dead

It should be noted that the scale is presented in the form in which it is typically used within SAH research. In its original form however, the scores were placed in reverse order (i.e., 5="good recovery", 1="death").

In the extended version of the GOS [758], the first three categories are each subdivided into two to increase its sensitivity for those patients with ratings in the upper end of the scale.

Appendix V:

Comparability in mean scores of limited Brazilian SF-36 population data and Swedish SF-36 population scores used to calculate summary scores for Rocha-Filo et al.'s study

Rocha-Filo et al. [569] examined a sample of Brazilian subarachnoid haemorrhage (SAH) patients' health-related quality of life (HRQoL) using the Medical Outcomes Study Short-Form 36 (SF-36) questionnaire. Unfortunately, only unpublished mean scores (and not standard deviations) are available for the Brazilian population for this measure [619]. Both population mean scores and standard deviations are needed however, for the calculation of the summary scores to represent patients' Physical HRQoL and Mental HRQoL scores. The means and standard deviations of a large Swedish population [673] for the SF-36 were used therefore for the purposes of calculating the summary scores, as the mean scores for this population on the SF-36 were the most comparable to the limited mean SF-36 scores available for the Brazilian population (see Tables V.A-B).

Table V.A Comparison of mean scores of Brazilian and Swedish population

MOS SF-36	Brazilian National Urban Population Norms [619]		Swedish General Population Norms [673]		
	Mean	*SD*	*Mean*	*SD*	*Difference in means*
Physical Functioning	83	-	87.9	19.6	-4.9
Physical Role Limits	87	-	83.2	31.8	3.8
Bodily Pain	73	-	74.8	26.1	-1.8
General Health	75	-	75.8	22.2	-0.8
Energy	70	-	68.8	22.8	1.2
Social Functioning	84	-	88.6	20.3	-4.6
Emotional Role Limits	86	-	85.7	29.2	0.3
Mental Health	73	-	80.9	18.9	-7.9

Table V.B Comparison of mean scores of Brazilian population to other norms

	PF	PRL	BP	GH	EN	SF	ERL	MH	Total difference in means
Brazilian[619]	83	87	73	75	70	84	86	73	
Difference in means									
Canadian [287]	-5.2	1.3	-5	-2.6	-7.6	-4.3	-1	-6	33
U.S 1998 [733]	1	8	0	4	12	-2	4	-3	34
U.K. 1996 [66]	2	7	-4	6	7	-1	2	-2	31
U.K. 91-92 [316, 317]	-5	1	-9	1	9	4	3	1	33
U.K. 92 ONS [60]	-7	3	-10	1	5	-5	-2	4	37
Croatian [430]	14	25	8	20	17	10	17	11	122
Spanish [11]	2	4	-6	7	3	-6	-3	0	31
Australian [651]	0	-7	-4	-3	-5	-1	3	-3	26
Swedish [673]	-5	4	-2	-1	1	-3	0	-8	24

Note: BP=Bodily Pain; GH=General Health; EN=Energy; ERL=Emotional Role Limitations; MH=Mental Health; ONS=Office of National Statistics; PF=Physical Functioning; PRL=Physical Role Limitations; SF=Social Functioning.

Appendix VI:

Modified Rankin Scale

The modified Rankin Scale is a reliable measure of physical/ functional disability (Table VI.A) [550, 713]. Higher scores indicate more physical disability.

Table VI.A The modified Rankin Scale

mRS Score	
0	No symptoms at all
I	No significant disability: despite symptoms, able to carry out all usual duties and activities
2	Slight disability: unable to carry out all activities as previously, but able to look after own affairs without assistance
3	Moderate disability: requires some help, but able to talk 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. (Also some studies include dead in this category)

It should be noted that this is a measure heavily focused on physical mobility. It mixes impairments and disabilities and is not a measure of "handicap" [726] as some have claimed.

Appendix VII:

Barthel Index

The Barthel Index is a measure of functional/ physical disability (Table VII.A) [421]. Although higher scores on this scale (in its original format) indicate less physical disability, for the purposes of my meta-analysis the direction of the effect size was reversed to standardise its interpretation with other measures of physical disability.

Table VII.A The Barthel Index

Barthel Area	
Bladder	0=incontinent, or catheterised and unable to manage alone
	1=occasional accident (max. once per 24 hours)
	2=continent
Grooming	0=needs help with personal care
	1=independent face/ hair/ teeth/ shaving (implements provided)
Toilet use	0=dependent
	1=needs some help, but can do some things alone
	2=independent (on and off, dressing, wiping)
Feeding	0=unable
	1=needs help cutting, spreading butter, etc.
	2=independent
Transfer	0=unable, no sitting balance
(bed to chair and back)	1=major help (one or two people, physical) can sit
	2=minor help (verbal or physical)
	3=independent
Mobility	0=immobile
	1= independent in a wheelchair, including corners
	2=walks with help of another person (verbal or physical)

Table VII.A *Cont'd.*

Barthel Area	
Mobility Cont'd.	3=independent (but may use aid, for example a stick)
Dressing	0=dependent
	1=needs help but can do about half unaided
	2=independent (including buttons, zips, laces, etc.)
Stairs	0=unable
	1=needs help (verbal, physical, carry aid)
	2=independent
Bathing	0=dependent
	1=independent (or in shower)
	Total 0-20

Note: Adapted from Wade [726]

Appendix VIII:

Further details on cognitive tasks used in patient study in Chapter 5

Attention

The Test of Everyday Attention [563, 564]

Visual Elevator: A timed task in which subjects count up and down as they follow a series of visually presented floors in the elevator. Factor analysis shows that this task is a measure of attentional switching (.78). It also loads on visual selective attention/ processing speed (.22) and working memory (.22).

Elevator Counting: Subjects are asked to pretend that they are in an elevator whose floor-indicator is not functioning. They therefore have to establish which floor they have arrived at by counting a series of auditory tones. This measure loads on sustained attention (.56), processing speed (.27) and attentional switching (.28).

Telephone Search: Subjects must look for key symbols while searching through pages in a simulated telephone directory. This test loads on 'selective attention' (.80), and to a lesser degree on attentional switching (.25) and working memory (.21).

Telephone Search while Counting: In this task, the subject must once again search through a telephone directory while simultaneously counting strings of auditory tones. Comparing search performance in this task to that illustrated in *Telephone Search*, allows for calculation of a divided attention score. This task loads on sustained attention (.72) and to a lesser extent on working memory (.31), attentional switching (.24) and visual selective attention/ processing speed (.21).

Lottery: Subjects have to listen for their winning lottery number, which ends in two numbers (e.g., '55') given to them at the beginning of the exercise. The patient must listen to a 10 minute series of audio-tape-presented numbers in the form

'BS143', 'LD'967', etc. The task is to write down the two letters preceding all numbers ending in their two numbers. The total number of 'relevant' combinations is 10. This task loads on sustained attention (.70), processing speed (.25) and attentional switching (.18).

Executive Function

Behavioural Assessment of the Dysexecutive Syndrome [754]

Rule-Shift Cards: A timed task in which participants are required to respond to stimuli (red or black playing card) according to one of two rules that are presented consecutively. Performance is scored according to how successfully the respondent shifts from applying the first rule to applying the second rule. This test looks to identify perseverative tendencies.

Key Search: The patient is presented with a square representing a field in which they have lost their keys. They are asked to draw a line, starting at a black dot, to show how they would walk to search the field to make absolutely sure that they would find their keys. This test assesses the person's ability to devise a solution to a problem. The person's search is scored according to its functionality (how systematic it was, its efficiency, its likely success and the time taken to complete the task).

Modified Six Elements: This time-management task involves the person having to divide a period of available time (10 minutes) between a number of tasks (2 picture naming, 2 arithmetic and 2 dictation), while not contravening a set of rules. The score is based on the number of tasks completed minus any errors for rule infringements and excessive time spent on single tasks. This is a measure of the person's ability to plan, organise and monitor behaviour.

Temporal Judgement: The respondent is required to estimate times of four everyday events. This task assesses judgement and abstract thinking, with the patients' answers being scored according the degree of deviation from the answers most commonly provided by a normative sample.

Zoo Map: In these two timed trials, subjects are given a map of a zoo and a set of instructions relating to places they have to visit and rules that they most follow (such as not cutting across paths or reusing a certain path). The patient must show how they would visit the series of designated locations on the map, whilst not contravening the set of rules. In this task, participants are assessed on their ability to minimise errors by modifying their performance on the basis of feedback, given when a rule is broken.

Memory

The Rivermead Behavioural Memory Test – Extended Version [755]

First and Second Names: The subject is shown three photographic portraits and asked to remember the first and second names of all three of the people in the photographs. This is a measure of short-term memory for names.

Appointments and Belongings: The subject is requested to ask, following a given prompt at the end of the memory battery test, for two of their belongings previously hidden by the examiner in different locations, and to remember where they have been hidden. They are also required to ask the examiner two set questions when a timer, which was set for 20 minutes, rings. This is a measure of prospective memory.

Picture Recognition: The subject must recognise 20 previously-seen line drawings and distinguish them from distractor items (a filled ~5 minute delay occurs between presentation and recall). This is a measure of visual memory.

Face Recognition: The subject must recognise 15 previously-seen faces and distinguish them from distractor items. This is a measure of visual memory.

Story Immediate and Delayed: The subject must recall a short passage of newspaper prose, immediately following it being read to them and then again after a delay (filled delay of 20 minutes). These two tests are measures of verbal memory.

Orientation and Date: The subject is asked 12 orientation questions and to give the correct date.

Appendix IX:

Supplementary analysis on the possible confounding impact of psychiatric history on the relationship between coping and SAH patients' PTSD

In Chapter 5, I contend that the dispositional use of maladaptive coping strategies is a risk factor for post-traumatic stress disorder (PTSD) subsequent to a subarachnoid haemorrhage (SAH). This conclusion was motivated by the results of the logistic regression analyses of assessments one and two PTSD which showed that dispositional use of maladaptive coping emerged as the most powerful predictor of PTSD in both the short- and long-term. Further supporting evidence for this conclusion is derived from previous studies which fortuitously measured individuals' preferences for coping skills prior to a trauma and found that pre-trauma preferences for maladaptive coping were predictive of subsequent PTSD [172, 217]. Up to approximately 30% of patients in the patient sample examined as part of the study presented in Chapter 5 do, nevertheless, have a history of other psychiatric illness, including depression, anxiety, and/or alcohol abuse (Table IX.A). Although this is not unusual and similar rates are reported in prior SAH studies [31, 159, 268, 305], there does remain the possibility that use of maladaptive coping skills does not represent a risk factor for PTSD, but that a significant association between coping and PTSD is found because those patients with PTSD could have experienced a prior psychiatric history which had promoted the use of maladaptive coping skills. This alternative explanation of the relationship between coping and PTSD was, however, not supported by the results of Chapter 5. 'Prior psychiatric history' had been included as a potential predictor in the original regression models for PTSD, but was eliminated

Table IX.A Psychiatric history in SAH patients examined for PTSD at assessment one and assessment two

Factor	Value (%)	
	Assessment one N=95	Assessment two N=81
Significant psychiatric history*	25 (26.3)	22 (27.2)

Note: N=number. *=Self-reported illness receiving/ received formal treatment. Psychiatric illnesses included: Anxiety unspecified diagnosis, Depression unspecified diagnosis, Alcohol abuse.

from the final model as it did not prove to be associated with PTSD in either the short- or long-term. In any case, the possibility that prior psychiatric history is a confounding variable for the relationship between coping and PTSD warrants further examination given the importance of establishing risk factors for the debilitating stress disorders which SAH patients experience. To do this, the unique and shared variance between PTSD, psychiatric history and coping was examined in order to further elucidate the relationship between these factors.

Methods

Nonparametric zero-order correlation and partial correlation coefficients were calculated between the following combinations of variables at both assessment one and assessment two: PTSD symptomatology and coping, PTSD symptomatology and prior psychiatric history and PTSD symptomatology and psychiatric history.

Results

The results of these supplementary correlation analyses are presented in Table IX.B. The results firstly show that the magnitude/ effect size of the relationship between coping and PTSD is consistently larger than the relationship between coping and psychiatric history. This substantial difference in effect sizes serves to underline the relative triviality of psychiatric history in explaining the presence of maladaptive coping. Secondly, the minimal reduction in the size of the correlation coefficients between PTSD and coping and between coping and psychiatric history when partial correlations are calculated which control for the shared variance between PTSD and psychiatric history, illustrates that these two factors are largely independent of one another in their relation to coping (Figures IX.A-B).

Discussion and conclusion

The results from the correlation analyses illustrate that PTSD holds a unique and substantial relationship with coping skills. Having controlled for the potential shared variance which PTSD and psychiatric history hold with coping, it is apparent that PTSD and psychiatric history are largely independent variables. In conclusion, psychiatric history holds little relevance for explaining the presence of poor coping skills or PTSD. The evidence therefore serves to corroborate the conclusion of Chapter 5, that coping skills seem largely the cause of PTSD in SAH patients in both the short- and long-term.

Table IX.B. Zero-order and partial correlation coefficients between PTSD, psychiatric history and maladaptive coping strategies

Variable	N	Zero-order correlation with coping		*P*-value	Partial correlation controlling for other variable		*P*-value
		r_s	r_s^2		$r_{sY(X1.X2)}$	$r_{sY(X1.X2)}^2$	
PTSD assessment 1	91	0.636	40.4%	<0.0001	0.623	38.8%	<0.0001
Psychiatric history assessment 1	91	0.216	4.67%	<0.05	0.066	0.4%	>0.05
PTSD assessment 2	81	0.459	21.1%	<0.0001	0.452	20.4%	<0.0001
Psychiatric history assessment 2	81	0.234	5.5%	<0.05	0.156	0.2%	>0.05

Note: N=sample size; PTSD=post-traumatic stress disorder; r_s=Spearman's rank order correlation; r_s^2 =Spearman's correlation r-squared equivalent; $r_{sY(X1.X2)}$=Spearman's partial rank order correlation; $r_{sY(X1.X2)}^2$=Spearman's partial rank order correlation r-squared equivalent..

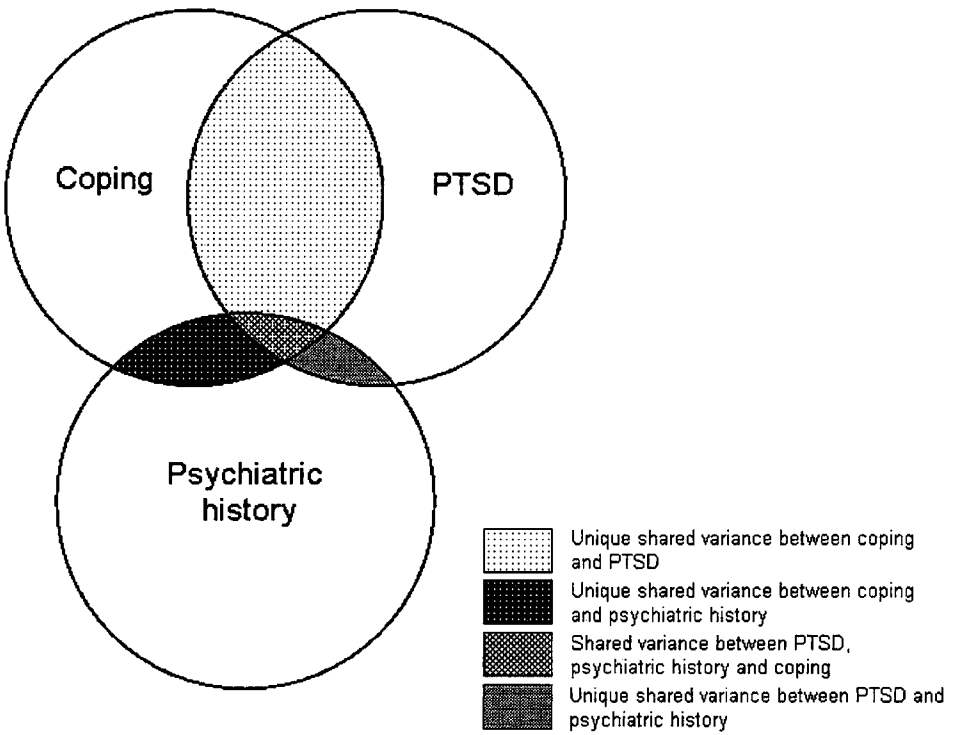

Figure IX.A Venn diagram illustrating the unique and shared variance between coping, PTSD and psychiatric history at assessment one.

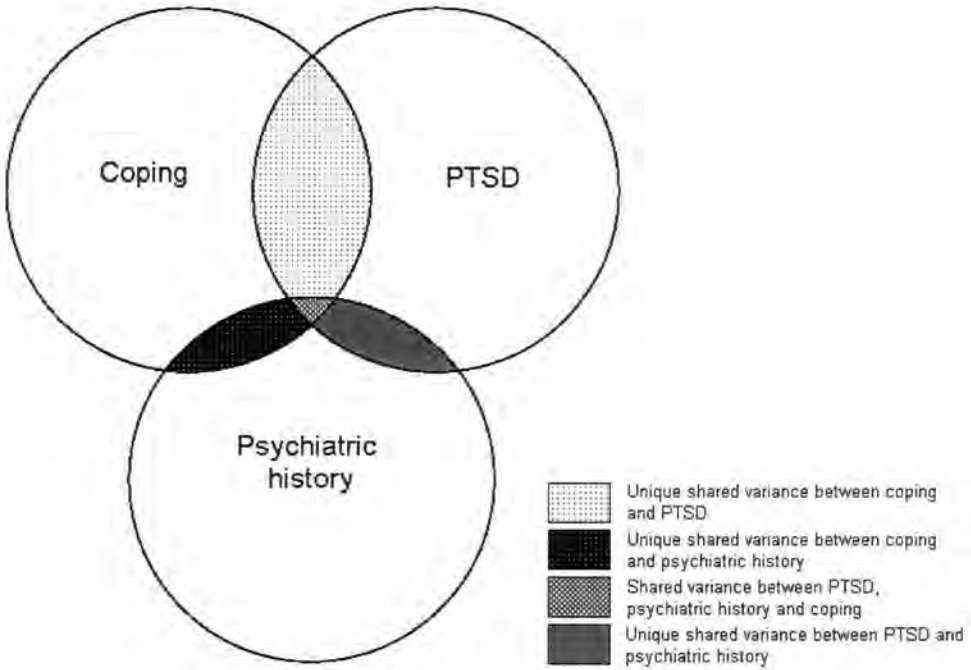

Figure IX.B Venn diagram illustrating the unique and shared variance between coping, PTSD and psychiatric history at assessment two.

Appendix X:

Supplementary analysis on the predictive value of aneurysm location for PTSD in SAH patients

The majority of surviving subarachnoid haemorrhage (SAH) patients examined in Chapter 5 had suffered their haemorrhage as the result of a ruptured cerebral aneurysm. As is typical, the neuroanatomical location of a patient's ruptured aneurysm varied between patients (Table X.A). Before further investigating other clinical explanations/ risk factors for post-traumatic stress disorder (PTSD) in SAH patients, it is important to comprehensively evaluate the effect of aneurysm location. Historically, it has been believed that differently located aneurysms pose different risks to the psychiatric sequelae which SAH patients' experience [57, 295, 537]. In particular, many traditionally believed that those patients whose SAH was due to a ruptured anterior cerebral artery aneurysm – especially those on the anterior communicating artery (ACoA) [8] – were likely to experience a unique pattern of psychiatric sequelae [295]. Older studies suggested that these patients could experience a psychiatric outcome akin to Korsakoff's syndrome [400, 513, 724]. ACoA patients for example, were seen to classically illustrate a distinctive neuropsychiatric profile of amnesia, confabulation and altered personality (including impulsivity, disinhibited behaviour, apathy, emotional lability and depression) [433]. The parallels between this profile and that of patients who had suffered damage to the prefrontal lobe [412] led to the belief that the type of neurobehavioural sequelae experienced post-SAH was largely due to the result of ischemic/ haemorrhagic damage in the territory supplied by the artery on which the aneurysm had ruptured [433]. Other factors, such as the fact that different locations of ruptured aneurysms

Table X.A Haemorrhage characteristics of those SAH patients who were examined for PTSD at assessment one and assessment two

Factor	Value (%)	
	Assessment one N=95	Assessment two N=91
Aneurysmal SAH	69 (72.6)	56 (69.1)
Location of ruptured aneurysm		
ACoA/ ACA	31 (44.9)	27 (48.2)
ICA	17 (24.6)	11 (19.6)
MCA	17 (24.6)	14 (25.0)
Vertebrobasilar	4 (5.8)	4 (7.1)
Unknown origin	23 (24.2)	23 (28.4)
Other origin	3 (3.2)	2 (2.5)

Note: ACA=anterior cerebral artery; ACoA=anterior communicating artery; ICA=internal carotid artery; MCA=middle cerebral artery; N=number; SD=standard deviation; Vertebrobasilar=arteries of the vertebrobasilar system; yr=year;

cause different bleed patterns (e.g., circle of Willis aneurysm results in symmetrically distributed basal blood, middle cerebral artery aneurysm asymmetrical pattern, anterior circulation blood accumulates between the frontal lobes and around the corpus callosum [666]), that intracerebral extension is more common with bleeds originating from aneurysms of the posterior communicating and middle cerebral artery, whilst intraventricular extension is characteristic of a bleed originating from an anterior cerebral artery [17, 43, 45], and that differently located aneurysms can require different neurosurgical approaches, also led many to assume that aneurysm

location was important in determining SAH outcome [295]. Nonetheless, the importance of the location of the ruptured aneurysm for SAH patients' neurobehavioural sequelae has in contemporary studies, proved debatable, with the majority studies, despite being well-powered, failing to detect a difference between the outcomes of patients with differently located aneurysms [57, 295, 433]. Instead, most now advocate that an SAH leads to unspecific brain damage that is, for the greater part, independent of the localisation of the ruptured aneurysm. In support of this position, is evidence that patients whose SAH was of an unknown origin, experience difficulties comparable to those patients whose bleed was caused by a ruptured aneurysm [34, 141, 296, 300, 302, 382, 409, 504, 507, 597, 643]. Yet further support can be found in the results presented in Chapter 5 which showed that aneurysmal SAH patients were no more, or no less prone to develop PTSD than other SAH patients. Even so, given the benefits of being able to reliably predict which patients will develop PTSD and also being able to understand the aetiology of the disorder, it is still important to explore the association between of aneurysm location and SAH PTSD.

With this in mind, this supplementary section now presents the results of bivariate/ univariate analyses of the association between aneurysm location (anterior vs. posterior; ACoA vs. other) and PTSD in both the short- and long-term. Also, to further explore the role of aneurysm location, PTSD severity and prevalence was compared between those patients whose bleed was of an aneurysmal origin and those patients whose bleed was of an unknown, non-aneurysmal origin.

Methods

The chi-square test (corrected for continuity [633]) and the Fisher exact test were used to determine the association between the experience of PTSD post-SAH and the location of a patient's ruptured aneurysm. The Mann-Whitney test examined the degree to which PTSD symptom severity in SAH patients was dependent on the location of the ruptured aneurysm. Comparisons were made between 1) ACoA aneurysms and all other locations, 2) anterior cerebral artery aneurysms (including ACoA) and all other locations and 3) between patients with an SAH of an aneurysmal origin and those who bleed was of an unknown origin. It was not possible to conduct a more detailed analysis of PTSD by specific aneurysm location because too small a number of patients had aneurysms of vertebrobasilar and too small a number of patients had aneurysms on arteries of locations other than the anterior cerebral artery. This is not however, a limitation specific to the present study, but a difficulty pervasive to many studies of SAH outcome which reflect the natural distribution of ruptured cerebral aneurysms in SAH patients [48, 300, 357, 374, 378, 507, 510, 687, 689].

Results

No significant association was found between PTSD prevalence or symptom severity and aneurysm location at either assessment one or assessment two (all $P>0.05$). Furthermore, there was no significant difference between the prevalence of PTSD or the severity of those patients' PTSD which resulted from a ruptured aneurysm and those whose bleed was of an unknown origin (Table X.B).

Table X.B The impact of aneurysm location on PTSD prevalence and severity

	Haemorrhage aetiology								
	ACoA	Other		ACA	Other		ASAH	Unknown	
	No. (%)	no.† (%)	*P*-value	no. (%)	no.‡ (%)	*P*-value	no. (%)	no. (%)	*P*-value
Assessment one									
PTSD									
Yes	5	22		11	16		27	7	
No	12	30	.510 *	16	26	1.00	42	16	.618
PTSD severity									
Median	10.0	10.5		11.0	10.0		10.0	10.0	
IQR	5.5-22.0	5.0-22.5	.775	5-28	4.5-19.5	.386	5.0-22.0	3.0-14.0	.308
Assessment two									
PTSD									
Yes	6	11		10	7		17	9	
No	10	29	.527 *	13	26	.137	39	14	.599
PTSD severity									
Median	10.5	6		10.	6		6.5	8	
IQR	3.5-12.0	3.0-11.75	.561	3.0-12.0	3.5-10.0	.339	3.0-12.0	5.0-14.0	.402

Note: ACoA = anterior communicating artery; ACA = anterior cerebral artery. * Fisher's exact test. † 'Other' location group includes aneurysms located on the internal carotid artery, middle cerebral artery, in the vertebrobasilar system and those of the anterior cerebral artery, excluding anterior communicating aneurysms. ‡ 'Other' location group includes aneurysms located on the internal carotid artery, middle cerebral artery and in the vertebrobasilar system.

Discussion

The results of this supplementary analysis show that the location of subarachnoid haemorrhage (SAH) patients' ruptured aneurysms does not significantly determine the likelihood of SAH patients developing post-traumatic stress disorder (PTSD), nor the severity of the PTSD that an SAH patient experiences. These findings concur with the multiple regression analyses presented in Chapter 5, where aetiology of bleed did not significantly add to the final predictive models for PTSD. It also accords with the majority of contemporary studies which have not found an association between long-term psychosocial outcome (such as anxiety, depression) and the location of a patient's ruptured aneurysm [17, 242, 247, 294, 297, 302, 425, 469, 507, 508, 546, 594, 649, 687, 722]. Indeed, aneurysm location is increasingly being seen as unrelated too to other aspects of SAH outcome, such as cognitive function [189, 247, 262, 357, 388, 432, 507, 543, 558, 590, 598, 649, 746, 750], fatigue [65, 247, 510, 649, 722], sleep dysfunction [510] and neuroendocrine dysfunction [375].

Historically however, many have proposed/ found that different aneurysm locations – particularly those of the anterior communicating artery (ACoA) – can cause different neurobehavioural sequelae of SAH [8, 331, 513, 617, 652]. How then can the discrepancy between these older and newer studies (including the current one) be explained? I would concur with the conclusions of two recent reviews on this important question produced by Hütter and colleagues [295, 306], who argue that aneurysm location (at least indirectly) was once an important explanation for SAH patients' neuropsychiatric changes, but that it is now largely irrelevant (and so not found to be important in contemporary studies) because of the drastically improved management of SAH which has occurred with the passage of time. These improvements include the introduction of the operating microscope, the use of

modern aneurysm clips, the abandonment of trapping procedures of the aneurysm bearing vessel, the principle of early surgical repair, as well as better techniques for the diagnosis and prevention of cerebral vasospasm (e.g., the calcium antagonist nimodipine and transcranial Doppler sonography, which reduce likelihood of cerebral infarction). It is commented that the introduction of the operating microscope and modern aneurysm clips for instance, has allowed neurosurgeons to spare the small perforators which originate from the AcoA that were previously inadvertently damaged during surgery and which caused distinct psychiatric problems. These perforators supply the anterior hypothalamus, septum pellucidum, anterior parts of the gyrus cinguli, parts of the fornix and anterior parts of the corpus callosum [697] and so damage to them can easily account for the elevated incidence of dysfunction – specifically, memory loss, confabulation and altered personality – that was previously found to be associated with ruptured AcoA aneurysms. Gade for example, provided compelling evidence showing a relationship between intraoperative trapping of the AcoA and the postoperative development of memory disturbance [208]. Increased methodological rigor to studies has also no doubt likely contributed to the discrepancy as older studies often only examined selective samples (case studies) rather than consecutive series of patients. Furthermore, older studies typically lacked adequate control patients whose ruptured aneurysms were of a different location.

Conclusion

In conclusion, the location of an SAH patient's ruptured aneurysm appears not to be associated with PTSD in SAH patients and so should not be considered a risk factor for its development or severity.

Appendix XI

Previous studies considering the impact of SAH on patients' SOs (From a published systematic literature review of mine [489])

Author	SAH details (1) type; (2) inclusion criteria.	Study population (i) number of participants; (ii) information source; (iii) sociodemographics; (iv) country of origin.	Design	Time (yrs)	Measures (a) psychological; (b) carer burden; (c) social health; (d) other.	Main results
Berry et al. [48]	(1) aneurysm; (2) age <60; clipped.	(i) 48; (ii) partner/ next of kin; (iii) not provided; (iv) England.	Cross-sectional	0.7	(a) BDI; GHQ-28; (b) nil; (c) nil; (d) nil.	-Significantly higher score on the GHQ-28 indicating psychological disturbance. No difference on BDI.
Buchanan et al.[90]	(1) aneurysm; AVM; (2) GOS I-II, surgically treated, Hunt and Hess I-IV.	(i) 27; (ii) supporting "primary relative"; (iii) not provided; (iv) Canada.	Cross-sectional	1.6	(a) BSI; (b) Likert Strain Scale; Zarit Burden Interview; (c) n-s measure; (d) Adjective Checklist.	- On BSI 65% illustrated clinical levels of stress. - Relatives were more stressed in the acute stages of the illness. - According to the burden interview, 66% of scores fell in the moderate or high range. Scores similar to Alzheimer carers. - Burden correlated with patient distress. - 26% considered death preferable to the quality of their outcome. - 3 spouses actively reinforced their husband's decreased libido.

Appendix XI *Cont'd.*

Author	SAH details	Study population	Design	Time	Measures	Main results
	(1) type; (2) inclusion criteria.	(i) number of participants; (ii) information source; (iii) sociodemographics; (iv) country of origin.		(yrs)	(a) psychological; (b) carer burden; (c) social health; (d) other.	
Fertl et al.[189]	(1)aneurysm; (2)GOS I-II;	(I) 40; (II) patients; (III) not provided; (IV) Austria.	Cross-sectional	1.8	(a) nil; (b) nil; (c) Patient QoL; (d) n-s measure.	-Of the patients, 33 had been living with a life partner. One patient had split from their partner which was attributed to be as a result of the 'sequelae of the SAH', whilst two further patients reported dissatisfaction with their relationships on QoL instrument.
Hellawell et al.[265]	(1) aneurysm; idiopathic; (2) CT confirmed SAH only.	(i) 36, 33, 28; (ii) relatives; (iii) not provided; (iv) Scotland.	Longitudinal	0.5, 1.0, 2.0	(a) RQ; (b) nil; (c) nil; (d) nil.	- Stress correlated with patient impairment at follow-up point.
Hellawell & Pentland [264]	(1) SAH; (2) CT confirmed SAH only.	(i) 58; (ii) close friend/ relative informant; (iii) 67% spouse or partner; (iv) Scotland.	Cross-sectional	6.5	(a) RQ; (b) nil; (c) nil; (d) nil.	- 55% of patients required care. - SAH informants experience stress as a result of patients SAH. - Correlation between informant stress and patients impairment. - Social behaviour, emotional disturbance, degree of dependency, and disturbed behaviour were most strongly associated with informant stress. Memory, language and physical impairment illustrated the weakest association.

Appendix XI *Cont'd.*

Author	SAH details (1) type; (2) inclusion criteria.	Study population (i) number of participants; (ii) information source; (iii) sociodemographics; (iv) country of origin.	Design	Time (yrs)	Measures (a) psychological; (b) carer burden; (c) social health; (d) other.	Main results
Hop et al. [285, 286]*	(1) aneurysm; (2) nil.	(i) 51; (ii) patient's closest significant other – 'partner'; (iii) 90% spouse or partner; (iv) Netherlands.	Longitudinal	0.3, 1.5	(a) nil; (b) nil; (c) SF-36; SIP; VAS; (d) n-s measure.	- At assessment one, carers illustrated reduced QoL on SIP, particularly psychosocial reductions. At assessment two, reductions found for SIP domains sleep and rest, emotional behaviour and recreation and pastimes. - SF-36 and SIP scores between 4 and 18 months varied, with some improvement (in social functioning, mental health), but also reductions (in pain, general health). Overall QoL, assessed by the VAS, did not improve between assessments one and two. - At assessment one, partners reported anxiety and uneasiness. Partners were afraid to leave the patient alone, especially if they had witnessed the initial event. Some expressed fear of having sex, especially if SAH was coital.

Table XI *Cont'd.*

Author	SAH details	Study population	Design	Time	Measures	Main results
	(1) type;	(i) number of participants;		(yrs)	(a) psychological;	
	(2) inclusion criteria.	(ii) information source;			(b) carer burden;	
		(iii) sociodemographics;			(c) social health;	
		(iv) country of origin.			(d) other.	
Hop et al. [285, 286]* *Cont'd.*						- At assessment two, 50% of employed carers reported occupation change related to SAH. 3 carers reported divorce/ "severe marital difficulties" caused by the patients' personality change. - Hop et al. [285] explored partners' QoL at assessment one and reported an association with patient dependence. Nevertheless, even partners of independent patients still experienced emotional role limitations – at times more than their patient.
Jarvis [313]	(1) SAH;	(I) 8;	Cross-	1.1-1.5	(a) nil;	- Common themes from qualitative interviews included: relationship
	(2) nil.	(II) patients;	sectional		(b) nil;	difficulties as a result of the SAH and relatives/ friends finding it very
		(III) not reported;			(c) nil;	traumatic to talk about the SAH event with the patient.
		(IV) England.			(d) n-s measure.	

Table XI *Cont'd.*

Author	SAH details (1) type; (2) inclusion criteria.	Study population (i) number of participants; (ii) information source; (iii) sociodemographics; (iv) country of origin.	Design	Time (yrs)	Measures (a) psychological; (b) carer burden; (c) social health; (d) other.	Main results
Mezue et al. [461]	(1) aneurysm; (2) GOS I-II.	(i) 52; (ii) carers; (iii) 74.6% spouse or partner; 13.6% other family member; (iv) England.	Cross-sectional	3.0	(a) GHQ-12; (b) Caregiver Strain Index; (c) nil; (d) Adjective Checklist.	- 54% complained of care-related strain, particularly in emotional and social areas. Emotional problems included upsetting patient behaviour (44.2%), emotional adjustment (28.9%), feeling overwhelmed (25%) and disturbed sleep (19.3%). - Social problems included changes in personal plans (28.9%), work (17.3%) and family (17.3%). - 25% of carers reported that they were distressed to an 'overwhelming' degree. - Carer distress/ strain correlated with neurobehavioural change in the patient. - No relation between clinical/ demographic variables and stress.

Table XI *Cont'd.*

Author	SAH details (1) type; (2) inclusion criteria.	Study population (i) number of participants; (ii) information source; (iii) sociodemographics; (iv) country of origin.	Design	Time (yrs)	Measures (a) psychological; (b) carer burden; (c) social health; (d) other.	Main results
Oder et al. [501]	(1) SAH; (2) Less severe and idiopathic cases overrepresented (61%).	(i) 67; (ii) patients; (iii) not reported; (iv) Austria.	Cross-sectional	7.1	(a) nil; (b) nil; (c) n-s measure; (d) nil.	- Patients rated the degree of disability in family relationships. - Association between amount of familial disturbance and patient disability. - Association between patients working status and familial handicap. - No relationship between clinical/ demographic variables and carer stress, although neurologic deficit on admission was predictive of later family disturbance.
Oder et al. [502]	(1) idiopathic; (2) Less severe patients.	(i) 41; (ii) patients; (iii) not reported; (iv) Austria.	Cross-sectional	7.6	(a) nil; (b) nil; (c) n-s measure; (d) nil.	- In total 17.1% of patients reported persistent "family tensions" after the SAH.

Table XI *Cont'd.*

Author	SAH details (1) type; (2) inclusion criteria.	Study population (i) number of participants; (ii) information source; (iii) sociodemographics; (iv) country of origin.	Design	Time (yrs)	Measures (a) psychological; (b) carer burden; (c) social health; (d) other.	Main results
Ogden et al. [510]	(1) aneurysm; idiopathic; (2) nil.	(i) 123; (ii) patients; (iii) not reported; (iv) New Zealand.	Cross-sectional	4.0-7.0	(a) nil; (b) nil; (c) n-s measure; (d) nil.	- Of the patients asked about changes in family structure, 4.1% reported divorcing as a result of SAH. Most due to partners failure to cope with SAH changes. - Association between family disruption and neurological status in the early stages of illness and experience of seizures.
Pritchard et al.[546]	(1) aneurysm; (2) nil.	(i) 98; (ii) carers; (iii) 76% partners, 63% female, 53% aged <54 years; (iv) England.	Cross-sectional	0.5-1.6	(a) nil; (b) nil; (c) Wessex Questionnaire; (d) nil.	- Carers were positive about in-patient care, though 63% remained fearful during the patient's hospital stay and 30% felt depressed. - Post-discharge, 50% felt unsupported, 40% stressed, 25% required medication and 14% said they made 'unnecessary' calls to their GP. Carers reported significantly more psychological burdens than patients.

Table XI *Cont'd.*

Author	SAH details (1) type; (2) inclusion criteria.	Study population (i) number of participants; (ii) information source; (iii) sociodemographics; (iv) country of origin.	Design	Time (yrs)	Measures (a) psychological; (b) carer burden; (c) social health; (d) other.	Main results
Pritchard et al.[546] *Cont'd.*						- No association between outcomes and clinical variables. - Criticism of 'Community Care'. It was the patients' families (96%) and neighbours (68%) who were the most involved in supporting patients. - 33% reported financial difficulties - 86% of carers lost 2 or more weeks and 15% lost 17 or more. -'Lost productivity' was estimated at £182,000.
Pritchard et al.[545]	(1) aneurysm; (2) nil.	(i) 98; (ii) primary carers; (iii) 63% male; (iv) England.	Cross-sectional	0.5-2.0	(a) nil; (b) nil; (c) Wessex Questionnaire; (d) nil.	- Compared outcome of a well-matched emergency cohort of SAH carers and an elective cohort of acoustic neuroma carers (AN). - SAH carers reported greater psychosocial disturbance than AN carers. In both the inpatient and post-discharge stages, SAH carers were more depressed, frightened, anxious and stressed - Economic cost: 85% of AN compared to 77% of SAH lost ≤16 weeks, but 23% of ASAH carers lost between 17-30 weeks. For AN, time off work cost £52,440. For SAH carers, it was £182,000.

Table XI *Cont'd.*

Author	SAH details	Study population	Design	Time	Measures	Main results
	(1) type;	(i) number of participants;		(yrs)	(a) psychological;	
	(2) inclusion criteria.	(ii) information source;			(b) carer burden;	
		(iii) sociodemographics;			(c) social health;	
		(iv) country of origin.			(d) other.	
Stegen & Freckman [652]	(1) aneurysm;	(i) 87;	Cross-	1.0	(a) n-s measure;	- 17% reported concerns about the possibility of re-bleeding.
	(2) nil.	(ii) next of kin;	sectional		(b) nil;	
		(iii) not reported;			(c) nil;	
		(iv) Germany.			(d) nil.	
Wermer et al.[746]	(1) aneurysm;	(i) 610;	Cross-	8.9	(a) nil;	- 75 of the 520 (14%) formerly married patients had divorced after
	(2) mRS ≤ 3; <71	(ii) patients;	sectional		(b) nil;	the SAH, 34 of whom (7%) reported that this was the result of the
	years old; clipping	(iii) not reported;			(c) nil;	SAH. The main reason was that the partner could not cope with the
	only.	(iv) Netherlands.			(d) n-s measure.	changes in the SAH patient.

Note: AN=acoustic neuroma; AVM=arteriovenous malformation; BDI=Beck Depression Inventory; BSI=Brief Symptom Inventory; GHQ-28=General Health Questionnaire-28; GOS I=Glasgow Outcome Scale I – no/ minimal impairment, "good recovery"; GOS II=Glasgow Outcome Scale II – modest impairment/ needs no impairment, "fair recovery; Hunt and Hess I=Grade I – mild headache and/ or nick stiffness on initial presentation; Hunt and Hess II=Grade II – severe headache and/ or pronounced neck stiffness and/ or cranial nerve deficits, photophobia; mRS=modified Rankin Scale; n-s measure=non-standardised measure; RQ=Relatives Questionnaire; SAH=subarachnoid haemorrhage; SF-36=Short-Form 36 Health Survey; SIP=Sickness Impact Profile; TBI=traumatic brain injury; QoL=Quality of Life; VAS=Visual Analogue Scale. *=Hop et al. (2001) contains data from 4 month assessment originally presented by Hop et al. (1998). For this review, searches of the *Medline* (1951 to April 2008), *ISI Web of Science* (1945 to April 2008) and *PsycINFO* databases (1887 to April 2008) was made using the term 'subarachnoid' plus: 'family', 'friend', 'carer', 'partner', 'relative' and 'rehabilitation'. The searches excluded 'stroke' as a term because SAH is considered a distinct form of stroke due to its differences in pathology (requiring differences in care), younger mean age of occurrence and differences in intervention (surgery for SAH) [710].