What explains the prevalence of post-traumatic stress disorder, depression, anxiety and poor quality of life after intensive care?

An investigation of clinical, psychological and socio-demographic risk factors

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I, Dorothy Wade, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature…… Date……

Abstract

Although many lives are saved in intensive care, patients frequently fail to make a good recovery. In addition to physical weakness and cognitive impairment, patients suffer from clinical anxiety, depression and PTSD. The aim of this PhD was to establish the prevalence of poor mental health after intensive care and identify clinical, psychological and socio-demographic risk factors. First I carried out a systematic review of post-ICU psycho-social outcomes but found the quality of studies was variable and few consistent risk factors were identified.

I subsequently conducted a prospective cohort study of 157 intensive care patients who were assessed for mood, stress, delirium and memory in the ICU. Clinical and socio-demographic data were recorded. At three months, 64% completed valid measures of PTSD, depression and anxiety, and socio-economic circumstances (SEC). Incidence of mood disturbance, delirium and physical stress in the ICU were 78%, 66% and 77% respectively. At three months, prevalence of PTSD was **27.1%** (95%CIs: 18.3, 35.9%), depression **46.3%** (95%CIs: 36.5, 56.1%) and anxiety **44.4%** (95%CIs: 34.6%, 54.2%). A total of **55%** of patients had at least one outcome. PTSD was predicted by number of organs supported, drug groups used and sepsis bio-markers. Strongest clinical predictors were days of sedation (PTSD), benzodiazepine usage (depression), inotropes (anxiety) and steroids (better physical HRQL). SEC was a risk factor for depression, anxiety and mental HRQL. Psychological predictors including ICU mood, stress, delirium and memories were highly correlated with outcomes and partially mediated the relationships between clinical factors and outcomes.

A qualitative study of 17 patients with intrusive memories of ICU at three months revealed patients had highly disturbing hallucinatory flash-backs or distressing recurring images of bleeding, choking, tubes and pain. The PhD highlighted the need to reduce ICU stress and identified modifiable risk factors that could inform clinical interventions to help patients.

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List of Abbreviations

ARS	Advanced respiratory support
ACVS	Advanced cardiovascular support
APA	American Psychiatric Association
Apache	Acute physiology and chronic health evaluation
ARDS	Acute respiratory distress syndrome
BRS	Basic respiratory support
BCVS	Basic cardiovascular support
CABG	Coronary artery bypass graft
CCU	Critical care unit
CED-S	Center for epidemiologic studies depression scale
CHD	Coronary heart disease
CPAP	Continuous positive airway pressure
CV	Cardiovascular
CVP	Central venous pressure
CVVH	Continuous veno-venous haemofiltration
DM	Delusional memory
DSM-IV	Diagnostic and statistical manual of mental disorders (4^{th} edition)
FU	Follow-up
GABA	Gamma-aminobutyric acid
GAD	General anxiety disorder
GI	Gastro-intestinal
HADS	Hospital anxiety and depression scale
HRQL	Health-related quality of life
ICNARC	Intensive care national audit and research centre
ICS	Intensive care society
IES	Impact of events scale
ICUSS	ICU stress scale
ICU	Intensive care unit
IM	Intrusive memory
IMD	Index of multiple deprivation
ITU	Intensive therapy unit
LOS	Length of stay
MDD	Major depressive disorder
MOD	Multiple organ dysfunction
MOF	Multiple organ failure
MV	Mechanical ventilation
NICE	National institute for health and clinical excellence
NS-SEC	National statistical socio-economic classification
ONS	Office of national statistics
PDS	The Posttraumatic diagnostic scale
POMS	The Profile of mood states PTSD
PTSD	Post-traumatic stress disorder
SEC	Socio-economic circumstances
SIRS	Systemic inflammatory response syndrome
STAI	Stait-trait anxiety inventory
TISS	Therapeutic intervention scoring system

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Chapter 1 Introduction and literature review: background to intensive care and outcomes

1.1 Introduction

As the medical specialty of intensive care has developed over the past fifty years, the lives of increasing numbers of seriously ill people have been saved. Due to advances in the prevention and reversal of organ failure, it has become possible to keep some of the sickest patients, who previously could not have survived, alive (Audit Commission, 1999). But there is a serious question about what happens to such patients once they leave hospital. There is evidence that the health-related quality of life (HRQL) of intensive care survivors is often poor (Dowdy et al., 2005). Clearly patients' HRQL or well-being will be affected by their physical, cognitive and psychological state. It is known that in addition to physical problems such as muscle weakness, breathlessness and the inability to eat, former intensive care patients may also suffer from cognitive impairment, anxiety, post-traumatic stress disorder (PTSD) or depression, (Hopkins & Jackson, 2006; Davydow, 2010).

Clinicians are increasingly interested in discovering more about these psycho-social outcomes and intervening to improve them. Additionally, a recent clinical guideline from the National Institute of Health and Clinical Excellence (Tan et al., 2009) on rehabilitation after critical illness, promoted "optimisation of recovery" of ICU patients rather than mere survival as a key therapeutic objective. It states that all patients should be assessed by intensive care unit (ICU) staff for their risk of physical and psychological morbidity, and offered rehabilitation for any problems detected both in hospital and after discharge. However there is a lack of good evidence to guide rehabilitation efforts, about the HRQL of intensive care patients and about the prevalence, nature and extent of psychological morbidity in the months after intensive care.

There is even less evidence available about the risk factors or underlying causes that contribute to adverse psycho-social outcomes of intensive care (Jackson et al., 2007). Are certain patient groups at risk of morbidity because of the nature of their critical illness, or because of background vulnerability factors such as chronic physical illness, drug and alcohol use, past traumas, past psychiatric illness, age, gender, socio-economic circumstances or lack of social support? Or is it the nature of what happens to them in the ICU that puts them at risk? Patients in the ICU experience treatments that cause discomfort and distress, invasive monitoring and the effects of powerful psychoactive drugs. At the same time they are often unable to communicate (due to intubation for mechanical ventilation) and suffer both

sensory deprivation and sensory overload (Dyer, 1995; Russell, 1999). It has been suggested that these experiences often result in acute psychological stress, disorientation, and delirium while a patient remains in the ICU (Granberg et al., 1998). They may also lead to longer-term dysfunction including disturbing intrusive memories of intensive care and serious psychological distress long after a patient has left the ICU.

Factors relating to the ward transfer and the post-hospital recovery period must also be considered. After being discharged from an ICU, patients' anxiety may increase, as they leave the relative safety of one-to-one care, and are transferred to a medical or surgical ward where the nurse-patient ratio is lower. Once at home, many patients and families believe they will have a brief recovery period and swiftly return to normal life. In reality patients report that they are shocked by their weakness, and their inability to perform even the simplest activities such as walking up stairs. This can lead to depression and anger, and to conflict with relatives who find it difficult to cope with the debilitated patient (Griffiths & Jones, 1999).

It is becoming increasingly evident that a proportion of ICU patients need additional support at all stages of their illness – in the ICU, on the hospital ward and after their return home (Tan et al., 2009). Discovering which patients are most at risk of specific psycho-social outcomes, may enable staff to intervene to help those who are most vulnerable to psychological distress and poor HRQL after leaving the ICU.

The aims of this PhD were
(i) to determine what is already known about the prevalence and nature of post-ICU psycho-social outcomes and the identity of important risk factors, by carrying out a systematic review
(ii) to add to existing evidence by conducting a high-quality prospective cohort study of intensive care patients to investigate psycho-social outcomes at three months and to identify the most important clinical, psychological or socio-demographic risk factors
(iii) to explore the characteristics and content of patient's intrusive memories (IMs) of the ICU in a qualitative interview study, as the formation of IMs may be an important psychological process in the development of post-ICU psychological morbidity.

1.2 Overview of intensive care

Before examining the prevalence and causes of adverse psycho-social outcomes of intensive care, it is important to understand the nature of critical illness and the activities and interventions that take place in ICUs. This will help to build a picture of patients' experiences in intensive care, to inform the consideration of underlying causes of psycho-social outcomes. Intensive care can be defined as a service for patients with life-threatening but potentially recoverable conditions, who need constant monitoring and support to maintain organ function during recovery (Intensive Care Society, 2003). Patients admitted for intensive care usually require support for hemodynamic instability (hypertension or hypotension), airway or respiratory compromise, acute renal failure, potentially lethal cardiac arrhythmias, or the cumulative effects of multiple organ system failure. They may also be admitted for intensive and invasive monitoring, particularly in the hours after major surgery.

ICUs are also known as intensive therapy units (ITUs) or, as currently recommended by the Department of Health, Critical care units (CCUs). The term Critical care encompasses both intensive care, the highest of four levels of care (0-3) available in a hospital, and High Dependency Care, the next highest level (Department of Health, 2000). ICUs are characterized by high staff-patient ratios, with intensive care (level 3) patients in the UK usually receiving one-to-one care from a nurse. ICU staff are very highly trained, and provision of facilities includes specialist technical equipment and medicines required to manage critically ill patients.

1.2.1 Critical care provision in UK and other countries

The proportion of seriously ill patients in hospital is growing in the UK, due to factors such as the ageing population and the increasing complexity of surgery, and therefore there is a growing demand for critical care beds (Hinds & Watson, 2008). There are currently around 3,700 critical care beds in England, with 1,989 beds in use for intensive care and 1,673 beds for high dependency care on the last census day (Department of Health, 2010). Some beds can be used interchangeably for level 2 or 3 patients, so the exact number of intensive care beds fluctuates. Approximately 110,000 people are admitted to critical care units in England and Wales each year (Tan et al., 2009). Around 56% of patients admitted during 2008-2009 were male, and mean age was 60.5 (Icnarc, 2010). They spent 5.0 days on average in a critical care unit and 23.3 days in hospital.

The costs of intensive care were estimated at £1000 - £1800 per bed-day, more than a decade ago (Edbrooke et al., 1999) and of course costs have risen since then. Intensive care is thought to be three or four times as expensive as ordinary ward care, and is equivalent to other costly health care such as heart transplantation. However, in spite of this expenditure, Edbrooke (1999) described intensive care in the UK as "neglected and under-resourced", and UK services still appear to be under-funded and under pressure in comparison with other developed countries. The UK spends 0.05% of GNP on intensive care, whereas the US spends up to 1% of GNP (Hinds & Watson, 2008). In the US between 6-20% of total hospital beds are dedicated to intensive care, compared to 1-2% of beds in the UK. The UK also has the smallest number of acute hospital beds allocated to critical care in Europe (The Intensive Care Society, 2006). As a result, patients who are admitted to ICUs in the UK are likely to be more severely ill than those admitted in other countries. There is usually a higher nurse:patient ratio in the UK than elsewhere in Europe where one nurse may care for either two or three patients. This may be because European units tend to be larger and to admit lower-risk patients.

1.2.2 Evolution of critical care

Critical Care is a relatively new branch of medicine, and was given the status of a specialty in the UK in 1999 (Intensive Care Society, 2003). Its evolution owes much to the development of new life-saving techniques in the twentieth century, together with improved understanding of the nature of critical illness. A significant step was made by medical staff treating severely injured soldiers during the two World Wars and the Korean War (The Society of Critical Care Medicine Ethics Committee, 1994; Intensive Care Society, 2003). They recognised the danger of septic shock and pioneered intra-vascular replacement using saline or colloid solutions. War-time surgeons improvised new procedures in the fields of neurosurgery and burns, and found that extensive supportive therapy was needed if patients were to survive. Another important innovation occurred in response to the poliomyelitis epidemic in Copenhagen in 1952 (Intensive care Society, 2003). Due to a shortage of negative pressure ventilators, ("iron lungs") doctors treated polio patients with manual positive pressure ventilation through a tracheostomy. The effect of this life-saving new treatment and of caring for patients in a separate area of the hospital rather than general wards, was that mortality was reduced from 90% to 40% (Bennett & Bion, 1999). In the early 1960s it also became apparent that cardiac surgery patients, who had high mortality rates, would benefit from post-operative care in specialized units, while ventilated patients' needs were better met in respiratory care units (Hinds & Watson, 2008). In 1962, the Progressive Patient Care report

(Ministry of Health, 1962) recommended "the systematic grouping of patients according to their illness and dependence on the nurse, rather than by classification of disease or illness." This was followed by the provision of funding to establish ICUs. There was to be "generous provision of working space" and 2-5% of acute beds should be allocated to intensive care, an optimistic prediction as we have seen. The trend in the UK was to establish general ICU units with some separate provision for neonatal, paediatric and occasionally other specialties.

1.2.3 What is critical illness?

Since the establishment of ICUs both their organisation and the medicine practised in them have evolved rapidly, resulting in new treatments for organ support and advances in the ability to save lives (Audit Commission, 1999). The modern concept of "critical illness" developed through the 70s and 80s. The focus of critical care specialists was on the identification and correction of physiological disturbance and the support of failing organ systems. Research and clinical experience provided a greater understanding of sepsis and multiple organ failure (MOF). It is now known that most illness and death in intensive care patients is caused by sepsis and systemic inflammation (Evans & Smithies, 1999). It is helpful at this point to consider definitions of sepsis, septic shock, systemic inflammatory response syndrome and multiple organ failure.

Sepsis is defined as a systemic response to infection manifested by signs including raised temperature, raised heart rate, tachypnoea and changes in white blood cell count (Bone et al., 1992). Septic shock is hypotension induced by sepsis despite adequate fluid replacement. Systemic inflammatory response syndrome (SIRS) is similar to sepsis, but is produced by the body's response to endothelial inflammation. Inflammation of the vascular endothelium has a number of possible causes such as pancreatitis, ischaemia, multiple trauma or infection. Activation of inflammatory cascades may lead to disruption of the microcirculation ensuring oxygenation of an organ, and of intracellular mechanisms that regulate use of oxygen. These may result in tissue hypoxia and ultimately to multiple organ failure. There is no consensus on the definition of the MOF syndrome, but organ dysfunction is defined as the presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention (Bone et al., 1992). Patients who develop multiple organ failure are highly likely to die; Those with prolonged three-system failure have a 50% mortality rate, while more than 90% of those with six-system failure die (Barton & Cerra, 1989). Thus there is increasing emphasis on the need to prevent critical illness rather than to react once organ failure is established.

1.2.4 Admission to intensive care

Patients are admitted to intensive care for a wide variety of clinical indications including both medical and surgical disorders. ICU admissions are categorized for data collection as either elective surgical, emergency surgical or medical patients. In 2008-2009 there were 22.6% elective surgical patients, 18.1% emergency surgical and 59.4% medical patients (Icnarc, 2010). Common medical indications for admission include respiratory failure, meningococcal infection, severe diabetic ketoacidosis, coma or obstetric emergencies. Surgical emergencies include acute intra-abdominal catastrophe such as ruptured abdominal aortic aneurysm or perforated viscus with faecal soiling of the peritoneum (Hinds & Watson, 2008). Many cases may be complicated by sepsis or septic shock. Elective surgical patients who require intensive care include cardiothoracic surgery and major head and neck surgery patients, especially when there is co-existing cardiovascular or respiratory disease. Patients with acute cardio-respiratory disorders often develop failure of other organ systems, prolonging the need for intensive care treatment. The most common reasons for ICU admission are shown in tables 1.1 and 1.2 below.

Table 1.1 Top five primary reasons for admission to ICU
(Icnarc, 2006)

Pneumonia (no organism isolated)	5.5%
Aortic or iliac dissection or aneurysm	4.2%
Large bowel tumour	3.9%
Septic shock	3.1%
Bacterial pneumonia	3.1%

Table 1.2 Top five primary systems involved in ICU admissions
(Audit Commission, 1999)

Cardiovascular	27.5%
Gastro-intestinal	21%
Respiratory	20.5%
Neurological	14%
Others	17%

Admission to ICU is usually from theatre/recovery (46%), wards (23%), other hospitals, including other ICUs (16%) or A&E (15%) according to the Audit Commission (1999). The Department of Health's admission guidelines (1996) stated that patients will be admitted to intensive care if they need support of two or more organ systems; or have chronic impairment of one organ system with acute failure of another, or need advanced respiratory care. Before being admitted to an ICU, all critically ill patients are assessed by a senior member of the medical team to determine the likelihood of the patient surviving a possibly protracted and

difficult illness. Patients who have an acute severe illness with a background of extensive chronic illness where the perceived benefit from ICU care is minimal, and patients without hope of recovering to an acceptable quality of life, should not be admitted according to the guidelines (Department of Health, 1996). However in practice it is not usually acceptable to refuse ICU admission to a critically ill patient. The long-term prognosis of patients is frequently uncertain and a precise diagnosis of underlying disorders may be difficult on initial referral (Hinds & Watson, 2008).

1.2.5 ICU interventions

The information on types of ICU interventions in this and the following sections (1.2.6-1.2.8) was synthesised from a number of standard ICU text-books (Bersten & Soni, 2008; Hinds & Watson, 2008; Irwin & Ripp, 2008; Singer & Webb, 2009). Only very specific additional references are given in these sections. The immediate priority of interventions with all critically ill patients is to preserve life and prevent or minimise damage to vital organs. The key issue is usually to optimise respiratory and cardiovascular function in order to maintain perfusion pressure and deliver sufficient oxygen to the tissues to prevent organ dysfunction. Intensive care in the UK is categorized into nine types of organ system support (Department of Health, 2006). These are listed and described in table 1.3 below. There is a lack of rigorous, conclusive scientific evidence about the clinical effectiveness of many of the interventions carried out in Critical Care Units. This is probably due to the pace of change, to the heterogeneity of patients and to financial, logistical and ethical problems in carrying out large-scale randomized controlled trials using intensive care patients (Gunning & Rowan, 1999). The alternative has been to use observational methods that study the outcome of care patients receive as a natural part of their treatment. In order to draw inferences about outcomes of treatment in such studies, characteristics such as age and illness severity of the patients admitted to intensive care have to be taken into account. This is known as adjusting for case mix (Icnarc, 2010).

Table 1.3 Categories of organ support (Critical care minimum data set)
(Department of Health, 2006)

Organ system support	Description
Respiratory Advanced	Invasive mechanical ventilator support including BIPAP (biphasic positive airway pressure) or CPAP(continuous positive airway pressure) via a tracheal tube.
Respiratory Basic	More than 50% oxygen with face mask. Mask CPAP or non-invasive ventilation. Suction to clear secretions at least two hourly. Intubation to protect airway without ventilator support
Cardiovascular Advanced	Multiple vasoactive and/or rhythm controlling drugs to support arterial pressure, cardiac output or organ perfusion. Intra-aortic balloon pumping. Observation of cardiac output e.g. pulmonary artery catheter, oesophageal Doppler.
Cardiovascular Basic	Treatment of circulatory instability due to hypovolaemia. Use of CVP (Central Venous Pressure) line or arterial line for monitoring or access. Single vasoactive drug.
Renal	Acute renal replacement therapy e.g. haemodialyis, haemofiltration.
Neurological	CNS depression sufficient to prejudice airway and protective reflexes. Severely agitated or epileptic patients requiring constant nursing attention or heavy sedation. Invasive monitoring
Gastro-Intestinal.	Feeding with parenteral or enteral nutrition.
Dermatological	Major skin rashes, exfoliation or burns. Multiple trauma dressings. Complex dressings e.g. open abdomen or large skin area.
Liver	Extracorporeal liver replacement device, bio-artificial liver or charcoal haemoperfusion.

1.2.5(i) Respiratory support

The respiratory system is the most commonly supported organ system in ICU (Smith & Nielsen, 1999). Most ICU patients require some form of respiratory support due to hypoxaemia or respiratory failure (Esteban et al., 2000). Support may be in the form of oxygen therapy using a face mask, nasal prongs or cannulae. If high flow oxygen is not sufficient, a tight-fitting CPAP (continuous positive airways pressure) mask may be used or non-invasive ventilation can be delivered with a nasal or face mask. Alternatively it may be necessary to institute endo-tracheal intubation and ventilation. Indications for intubation and ventilation include profound hypoxaemia, as in pneumonia or acute respiratory distress syndrome; or postoperative care after major complicated or prolonged surgery. Several modes of ventilation may be employed from continuous mandatory ventilation, where breathing is completely controlled by the machine, to pressure support ventilation in which patients may initiate spontaneous breathing.

Complications caused by endotracheal intubation include nosocomial pneumonia and over-distention of the ventilated lung (Pinhu et al., 2003). Ventilation itself may damage delicate lung tissue or cause cardiovascular complications. Finally there are non-pulmonary complications including dysfunction of the renal, gastrointestinal and central nervous systems. Continuous monitoring of heart rate and blood pressure is essential during invasive ventilation. Patients mostly find it difficult to tolerate intubation and ventilation, and therefore require sedation with

opiates and anxiolytic or anaesthetic agents (Gehlbach & Kress, 2002). Sedatives commonly used are benzodiazepines such as midazolam, lorazepam and diazepam, or anaesthetics including propofol and clonidine. Opiates in common use in ICUs include morphine and fentanyl. Sedation may have adverse effects including hypotension, withdrawal symptoms and sleep deprivation. The sedative drugs may accumulate and thus have more prolonged action in patients with renal impairment.

Tracheostomies are usually performed if ventilation is likely to be prolonged. Complications of a tracheostomy include tracheal erosion, haemorrhage or migration of the tube orifice. However patients tolerate tracheostomies better than endotracheal intubation, so sedation can be reduced, weaning is more rapid and the stay in intensive care may be shorter (Griffiths et al., 2005). Several techniques can be used to wean patients off the ventilator. Patients should not be weaned until they are conscious and responsive, adequately oxygenated and able to meet the increased work of breathing. Weaning involves the patient breathing spontaneously for increasing periods or levels of ventilatory support gradually being reduced. If the patient is not well-prepared for weaning or is excessively anxious, weaning from the ventilator may fail, necessitating a longer stay in the ICU (MacIntyre et al., 2001).

1.2.5(ii) Cardiovascular support

Cardiovascular or circulatory support is required for hypotension, shock and to prevent complications in patients at risk of organ failure. Shock is a life-threatening medical emergency and can be defined as acute circulatory failure with inadequate or inappropriately distributed tissue perfusion resulting in generalised cellular hypoxia (Bersten & Soni, 2008). Shock may be caused by a variety of conditions such as acute myocardial infarction (cardiogenic shock), pulmonary embolus (obstructive shock), haemorrhage (hypovolaemic shock) or sepsis and anaphylaxis (distributive shock). The objective of treatment for shock is to restore oxygen delivery to the tissues while correcting the underlying cause. This should be done with minimum delay to prevent irreversible peripheral vascular failure and defects in oxygen use which can result in organ dysfunction. Shock treatment involves early respiratory support and cardiovascular support.

The aim of cardiovascular support is to maintain adequate cardiac output and blood pressure to maintain perfusion of vital organs. Volume replacement within minutes is essential in all cases. Fluids for volume replacement include blood, crystalloids, colloids (starches or gelatins) and in rare cases albumins. This can lead to the rapid restoration of cardiac output and tissue perfusion pressure and therefore reduce the risk of serious organ damage, particularly acute renal failure. If signs of shock

persist despite volume replacement, vasoactive drugs may be given to improve cardiac output and blood pressure. Some patients are given inotropes or vasopressors to restore cardiac output and blood pressure, while others are given inodilators to redistribute blood flow. Another group of patients who may benefit from intensive circulatory support are high risk surgical patients. Morbidity and mortality in these patients have been reduced by preoperative admission to intensive care to optimise cardiovascular function by volume replacement and administration of ionotropes or vasopressors (Hinds & Watson, 1999).

1.2.5(iii) Renal support

Renal failure is a common complication of acute illness or trauma. Acute renal failure is defined as a sudden, normally reversible impairment of the kidney's ability to excrete the body's nitrogenous waste products of metabolism, commonly accompanied by oliguria. In critically ill patients renal failure is not usually due to primary renal disease, but may result from hypovolaemia, impaired renal perfusion, sepsis, certain drugs, hepatic dysfunction or vascular occlusion. Management consists of optimising circulation and oxygenation, using ventilation if necessary and ensuring adequate intravascular volume, cardiac output and perfusion pressure. Renal replacement therapy may then be considered. Most critically ill patients in the UK are treated by continuous methods of haemofiltration (such as continuous veno-venous haemofiltration) rather than haemodialysis (Short & Cumming, 1999). As the patient recovers, urine volume will increase, but the kidney will have a reduced ability to conserve sodium, potassium, bicarbonate and water for some months.

1.2.6 Invasive monitoring

In addition to organ support, most patients in intensive care require continuous invasive monitoring to assess their condition and alert staff to changes. Variables monitored both invasively and non-invasively usually include heart rate, respiratory rate (RR), oxygen saturation (SaO_2), pulse oximetry, blood gases, arterial blood pressure (ABP), central venous pressure (CVP), urinary output, electrolyte levels and temperature. In some cases cardiac output, intra-cranial pressure (ICP), jugular bulb oxygen saturation or abdominal compartment pressure may also be measured. As well as allowing early recognition of changes in the patient's condition, monitoring is used to establish or confirm a diagnosis, to gauge the severity of the condition, to follow the evolution of the illness, to guide interventions and to assess the response to treatment. However invasive monitoring is associated with significant risk of complications as well as cost and patient discomfort. Therefore it should only be used when there are clear benefits and monitors should be removed as early as possible (Hinds & Watson, 2008).

1.2.7 Other supportive care

Other interventions required in intensive care to maintain organ function and prevent further damage include chest physiotherapy to improve respiratory function, and mobilization to counter muscle wasting and weakness (Bersten & Soni, 2008). Patients also require frequent turning and repositioning to prevent pressure sores, and regular care to prevent damage to eyes and mouth. Most patients are too sick to eat, so they may require enteral or parenteral nutrition or both. Finally patients in intensive care are five times more likely to develop a nosocomial infection than other hospital patients (Adam & Forrest, 1999), so a vigorous infection control policy is needed. Specific causes of infection in the ICU are multiple vascular access sites; endo-tracheal tubes; sedation, ventilation and immobility leading to pneumonia; urinary catheters, compromised immune function, poor nutrition, overcrowding and high use of antibiotics.

1.2.8 Environment and organisation

As well as illness and interventions, other factors such as the environment and organisation of ICUs are thought to have an effect on patient outcomes. A few background details about design, equipment and staffing factors will suffice here, as the ICU environment will be discussed more fully in Chapter Three.

1.2.8(i) Design

The ideal size of an ICU is between four and about 20 beds, although larger units may operate effectively if they are adequately staffed. The average size of a UK District General Hospital's ICU is between six and ten beds. It is recommended that ICU facilities should be both spacious and light (Hinds & Watson, 2008). There should be large open-plan areas containing several beds, to make the most efficient use of nursing staff, with some adjacent single rooms to prevent cross-infection, and to accommodate long-stay patients. Each bed space should be of 20-21m² (Intensive Care Society, 1997). All bed areas should be well lit with natural daylight and ideally patients should have a view of the outside world from a window (Wilson, 1972). Noise levels in an ICU also need to be considered. One study (Bentley et al., 1977) found that ICUs were noisier than any other hospital ward, with noise levels reaching 70 decibels, equivalent to the sound of heavy traffic. In reality of course not all ICUs conform to ideal standards, particularly in old hospital buildings.

1.2.8(ii) Equipment for monitoring and intervention

Part of the patient's environment in the ICU is determined by the presence of large amounts of equipment, some of it attached to themselves and much of it arranged

around their bed spaces. Equipment used for monitoring in the ICU includes cannulae in the veins and arteries to measure venous and arterial pressure and to allow blood gas and acid-base analysis; urinary catheters; oxygen saturation monitors on fingers or ears; naso-gastric catheters to measure gastric mucosal pressure, and more rarely nowadays, pulmonary artery catheters. Each bed space is equipped with monitors, suction apparatus, piped oxygen and air, and a vacuum supply. Equipment for respiratory therapy includes oxygen masks, self-inflating bags for manual ventilation, humidifiers, ventilators, anaesthetic machine and bronchoscope. For cardiovascular therapy there will be infusion pumps, syringe pumps, pacemakers, defibrillators and intra-aortic balloon pumps. Additionally there may be equipment for continuous veno-venous haemodiafiltration and possibly access to a haemodialysis machine.

1.2.8(iii) Organisation and staffing

Research has shown that the organisation and staffing of ICUs also has an impact on outcomes. For example excessive unit workload seems to increase mortality (Tarnow-Mordi et al., 2000). Frequent night-time discharges are also associated with worse outcomes (Goldfrad & Rowan, 2000). The under-provision and under-resourcing of intensive care was highlighted in section 1.2.1 above. In Critical to Success, the Audit Commission (1999) concluded that intensive care medicine in the UK was fragmented, overcrowded, expensive and under pressure. ICU services had evolved in an ad hoc haphazard manner since the 1960s and there existed great diversity in ICUs in terms of quality, care management, unit management and efficiency.

In spite of modernisation and extra money (Department of Health, 2000) ICU bed and staff shortages are still common in the UK. A shortage of ICU beds may lead to high occupancy rates, cancelled elective surgery, frequent refused admissions and premature discharge of patients. An excessive workload will exacerbate the occupational stress of ICU staff, which is already considerable. Causes of work stress in ICUs include death and dying, staff shortages, fatigue, increasingly sophisticated technology, conflict between staff and families, and difficulty communicating with patients (Hinds & Watson, 2008). Although moderate stress can be helpful, excessive, prolonged stress may lead to the syndrome of "burn-out" which has been documented in ICU staff (Roberts, 1986). This could have an impact on the quality of care, particularly psychological care, which staff are able to give to patients.

1.3 Intensive care outcomes

1.3.1 Mortality

In the early days of intensive care, the emphasis was, quite understandably, on saving lives, and mortality was the main outcome of interest. The most recent UK mortality statistics available were based on almost 90,000 admissions to 180 units between April 2008 and March 2009 (Icnarc 2010). In those 12 months ICU mortality was 17.1% of patients, while ultimate hospital mortality was 25.8%. In non-surgical patients, both ICU mortality (23.8%) and hospital mortality (34.4%) were higher than for surgical groups, both planned and emergency. A further group of patients are likely to die at home after hospital discharge. Of a UK cohort of 370 general ICU patients (Eddleston et al., 2000), 29% of patients died in the ICU, 39% of patients had died by three months after discharge from the ICU, 41% by six months and 43% by one year. Death rates do not return to normal population levels until two-four years after intensive care (Griffiths & Jones, 1999).

It has been argued that death is "a sensitive, appropriate and meaningful" measure of outcome, given the high mortality amongst intensive care patients (Gunning & Rowan, 1999, p.32). However mortality rates are difficult to compare between one ICU and another. One audit showed that mortality across units varied more than three-fold. This may be in part because patients admitted to intensive care units are a heterogeneous group with a wide range of conditions. Intensive care units admitting a large proportion of high risk patients would be expected to have higher mortality. Therefore the characteristics of patients or "casemix" must be taken into account or adjusted for. One method of doing this is to use a scoring method to quantify case mix. The most commonly used scoring system in ICUs is the Apache (Acute physiology and chronic health evaluation) II system (Knaus et al., 1981). This system assigns up to four points for the most abnormal values of 12 physiological variables during the first 24 hours in the ICU. Points are also given for age, clinical history and surgical status, yielding a score ranging from 0-71 with higher scores representing greater severity of illness. Even after adjusting for case mix, variation in mortality rates of ICUs has been found, suggesting that some differences may be due to clinical approach (Audit Commission, 1999). However an alternative explanation would be that the Apache II score does not address casemix adequately or completely.

Survival rates from intensive care have improved over time. Enhanced understanding of the nature of critical illness has led to a sharp decline in mortality rates for conditions such as sepsis and the acute respiratory distress syndrome

(ARDS) over the past two decades (Milberg et al., 1995; Martin et al., 2003). However the Audit Commission national survey (1999) found that although 63% of ICU patients (N not provided) survived until 6 months, only 16% of patients had made a *good* recovery by that time. As many as 38% of the original cohort had some limitations to daily living, while 9% had severe limitations. With ever more people surviving intensive care, it is recognised that HRQL, as well as survival, is an important outcome. Key questions should be: Do intensive care survivors have optimal long-term outcomes and would ICU decisions change if more were known about such outcomes? There has been a call for more critical care research that studies the effects of treatments on endpoints that are important to patients and society (Rubenfeld et al., 1999). It is now recommended that clinical trials of ICU therapies should include long-term follow-up of survival, HRQL, morbidity, functional status and costs of care (Angus et al., 2003).

1.3.2 Quality of life (HRQL)

A serious problem with research on quality of life is that there is little consensus about what it is, and no adequate theory to explain it. It is a subjective concept consisting of physical, emotional, psychological, social, economic, occupational and spiritual parameters. Different political, philosophical and health-related definitions exist. Health-related quality of life (HRQL) is a multi-dimensional construct relating health status to key components of quality of life. The core components of HRQL assessment should be physical, functional, psychological/emotional and social/occupational (Fallowfield, 2009). Many different instruments have been developed to assess it. Both the SF-36 (Ware, Jr. & Sherbourne, 1992) and the EQ-5D (Brooks et al., 2003) have been recommended as suitable tools for ICU outcome research (Rubenfeld et al., 1999).

A systematic review (Dowdy et al., 2005) of studies of HRQL of ICU survivors concluded that, compared with the general population, ICU survivors had lower HRQL in nearly all domains at baseline and at six months to 14 years after discharge. However HRQL improved over time after ICU discharge but not uniformly across domains. The scores in two important domains (mental health and perceived general health) did not show improvement between baseline and 6-12 months after discharge. Assessing the HRQL of ICU survivors is complicated by factors such as age and diagnostic category on admission to the ICU. Some sub-groups of intensive care patients such as younger patients and trauma patients (Ridley et al., 1997) are more likely to have had good HRQL before an ICU admission. Other groups, such as medical patients, may have had poor HRQL before going into ICU due to chronic illness. Therefore the first group are more likely to have a decrease in HRQL

after intensive care, whereas the second group are more likely to have an improvement in HRQL. Average HRQL statistics may not make much sense of these opposing trends.

1.3.3 Physical morbidity

The HRQL of intensive care survivors is influenced by both physical and psychological recovery after illness. Physical morbidity, cognitive impairment, psychological adjustment and support received during recovery will all have an effect. It is known that intensive care survivors have a range of physical problems during recovery. These may include residual pulmonary dysfunction, muscular weakness and wasting, reduced cough power, joint stiffness, numbness, taste changes, sleep disturbance, and breathlessness (Griffiths & Jones, 1999b). Patients in intensive care may lose up to 2% of muscle mass a day during their illness and rebuilding muscle loss may take up to a year (Herridge et al., 2003). In the early days after intensive care, patients may struggle to eat, swallow and cough, and are at increased danger of falls as muscle loss and peripheral neuropathies can affect balance. On returning home they may find they are too debilitated to climb stairs or carry out household jobs. Even at six months physical weakness may still hamper self-care activities such as getting out of the bath or delay returning to work. Patients can also have minor but distressing physical problems such as fatigue, hair loss and skin dryness (Eddleston et al., 2000).

1.3.4 Cognitive impairment

Additionally, it is now becoming clear that some patients have neuro-cognitive impairments after intensive care. Additional research is needed but early reports are alarming (Hopkins & Brett, 2005). Most of the evidence for cognitive impairment is found in specific sub-populations of ICU patients. For example, in patients with ARDS (acute respiratory distress syndrome) chronic cognitive impairments may be as high as 75% one year after ICU discharge (Hopkins et al., 1999) and 25% at six years (Rothenhausler, 2001). In an informal review of the evidence from 9 cohorts of ICU patients (mainly with ARDS), Hopkins & Brett (2005) concluded that neuro-cognitive impairments were extremely common at hospital discharge, and that despite improvement between six and 12 months, many patients had significant cognitive impairment at time-points between six months and six years. Domains most commonly affected were memory, attention and executive function.

Only a few small studies have been carried out to examine cognitive outcomes in a general cohort of intensive care patients with mixed diagnoses. In one of these, a

neuropsychological study of 34 mechanically ventilated patients in a medical intensive care unit (Jackson et al., 2003), 32% of patients were found to have significant cognitive impairment six months after intensive care. Deficits were found in several domains including psychomotor speed, visual and working memory, verbal fluency and visuo-construction. The rate of neuropsychological deficits in the ICU population was markedly higher than population norms for mild dementia. A neuro-cognitive evaluation of 32 critically ill medical patients who underwent mechanical ventilation for five days or more, found that 91% of patients at hospital discharge and 41% at 6 months, had cognitive impairments. The cognitive functions primarily affected were attention, memory, mental processing speed and executive function (Hopkins & Brett 2005). In a study of 45 general ICU patients, Sukantarat (2005) found that three months after ICU 35% of the cohort scored at or below the level of the lowest 5% of the normal population on tests of executive function and fluid intelligence. At nine months, cognitive performance remained below normal but there had been improvements since three months.

The study of the causes of cognitive dysfunction in critical care patients is at an early stage, but some evidence suggests that neurotransmitter abnormalities and occult diffuse brain injury could explain the dysfunction (Milbrandt & Angus, 2005). One hypothesis is that neurotransmitter abnormalities could be associated with drugs with anticholinergic properties that are commonly used in the ICUs. Examples are opiates, furosemide, digoxin, glucocorticoids and benzodiazepines. Excess GABA activity, such as that occurring after withdrawal from chronic alcohol or benzodiazepine use, or after ICU use of benzodiazepines and probably propofol for sedation, is known to lead to delirium. Whether it might also lead to long-term cognitive deficits is unknown. The possibility has been raised that long-term impairment is also caused by occult diffuse brain injury, as a consequence of hypoxia, hypoperfusion, inflammation and microvascular thrombosis, all of which commonly occur in critically ill patients (Sharshar et al., 2005).

1.3.5 Psychological adjustment and morbidity

It has frequently been observed that following their return home from the ICU, patients may undergo further considerable stress caused by physical disability, cognitive impairment, a prolonged recovery period, and conflict with families (Griffiths & Jones, 1999). Patients may become irritable or angry with relatives on whom they are dependent, show less affection to their partners and become socially isolated as they begin to avoid company and stop going out. Many worry that they will not return to normal health and will not be able to go back to work (if employed). Patients also suffer from sleep problems, sexual dysfunction, and

unusual psychological symptoms such as delusional memories (hallucinations and nightmares from the ICU) and flashbacks of traumatic experiences in the ICU (Bennun, 2001; Jones et al., 2001; Jones et al., 2004). If not resolved, these problems and reactions may contribute to depression, panic attacks or other anxiety disorders. Several studies have found that survivors of intensive care units frequently suffer from psychological disorders after leaving hospital. A review by Weinert (2005) found that up to 35% of patients discharged from ICUs had psychiatric symptoms and disorders including depression and PTSD.

1.3.6 Post-traumatic stress disorder

Most studies investigating post-ICU psychological distress have focused on PTSD as the main outcome. PTSD is an "anxiety disorder that often follows exposure to an extreme stressor that causes injury, threatens life or physical integrity" (American Psychiatric Association, 1994). To meet diagnostic criteria for PTSD, the person's response to the event or series of events must involve intense fear, helplessness or horror. Symptoms include persistent re-experiencing of the traumatic event in intrusive memories or nightmares, avoidance of stimuli associated with the trauma for example by emotional numbing or amnesia, and increased arousal symptoms such as insomnia, the startle response and hyper-vigilance. The disorder must be present for more than a month, and must cause distress or impaired functioning. PTSD is commonly accompanied by negative emotions such as sadness, anger, guilt and shame (Brewin & Holmes, 2003).

As well as being a highly unpleasant disorder involving extreme fearfulness and traumatic memories, PSTD has negative implications for physical health. People with PTSD report more chronic health problems and perceive their health as worse, compared to people without PTSD. Generally people who have experienced trauma use medical services more and have higher morbidity and mortality (Ballenger et al., 2000). It is known that PTSD sufferers experience physiological changes. For example high rates of circulating adrenaline and noradrenaline have been recorded, as well as a decreased cortisol response to stress. These changes to the HPA axis could help to explain problems with physical health. One study of Vietnam veterans found that having PTSD was as powerful a risk factor for long-term health problems as elevated white blood cell counts and other biological markers of disease risk (Boscarino, 2008).

Estimates of the prevalence of PTSD in the months after discharge from intensive care range from 0% to 62% (Griffiths et al., 2007; Jackson et al., 2007). However many PTSD studies have been of low quality or based on small samples of patients

(see chapter two for systematic review of post-ICU psychological morbidity studies). Furthermore some studies were carried out in specific populations such as acute respiratory distress syndrome (ARDS) and sepsis patients, who may be expected to have higher rates of PTSD. For example Schelling (1999) reported PTSD rates of 38% among 54 septic shock survivors. Another study found that 27.5% of ARDS survivors had PTSD (Schelling, 1998). These ICU rates compare to 6-month prevalence estimates of PTSD in the community of 0.4% (Davidson et al., 1991) and 0.9% in elderly people (van Zelst et al., 2003). Prevalence of sub-threshold PTSD in the community was rated at 6.6% (Davidson et al. 1991). Lifetime prevalence of PTSD has been estimated as 1 - 9.2% (Hidalgo & Davidson, 2000). Prevalence of PTSD after other medical conditions has been estimated at 0-16% after myocardial infarction, 11-18% after cardiac surgery and 2-14% in cancer (Tedstone & Tarrier, 2003).

Risk factors for developing PTSD include socio-demographic factors (younger age, female gender, poor socioeconomic circumstances, lack of education, low intelligence, minority status), comorbidity (with a previous or current anxiety or depressive disorder) and past experience of trauma (having been abused as a child; having lived through other life-threatening events in the past; having recently been in a war zone or other area of social unrest or violent conflict). Factors operating during or after the trauma such as trauma severity, lack of social support and additional life stress had stronger effects than pre-trauma factors (Brewin et al., 2000).

Why should PTSD be particularly prevalent after ICU? According to current theoretical models, PTSD develops as a result of the abnormal cognitive processing of stressful events. The appraisal of continued threat is thought to be central to the disorder; Patients with PTSD continue to detect and react to threats in the environment even when a traumatic event is over (Ehlers & Clark, 2000). Ehlers and Clerk also found that PTSD patients react to the initial traumatic experience with "mental defeat" – a form of extreme helplessness and fatalism. This leads to negative thoughts of being weak, ineffective and unable to help one-self. Such thoughts impede psychological recovery as patients believe they are constantly vulnerable to danger and react accordingly.

Many psychological processes, including memory, attention, mood, beliefs and coping strategies are found to be disturbed in PTSD. However the most characteristic features of PTSD, compared to other disorders, are the unusual memory phenomena centred on the traumatic event (Brewin & Holmes, 2003).

Patients frequently recall vivid, emotional "snapshot" memories related to the trauma they have experienced but find it difficult to retrieve autobiographical, detailed memories of the incident (Brewin & Holmes, 2003). There is an unusual combination of experiencing some memories that are vivid and long-lasting (Rubin & Kozin, 1984) and others that are vague and lacking in detail (Loftus & Burns, 1982). Most notable are the reliving experiences or "flashbacks" to the trauma. They are dominated by sensory detail including visual images, sounds and other sensations. The images and sensations tend to be disjointed and fragmentary. They involve time distortion as they seem to be happening in the present rather than the past like ordinary memories and are often triggered involuntarily by some specific reminder of the trauma (e.g. a police siren).

There have been many theories to explain these phenomena (Brewin & Holmes 2003). One of the earliest theories - stress response theory (Horowitz, 1976) - proposed that after a trauma people experience information overload as they try to assimilate thoughts and memories about the traumatic event with their pre-trauma assumptions and world-view. If they use defence mechanisms such as denial and avoidance to keep trauma at bay, traumatic memories will break into consciousness in the form of flashbacks and nightmares. If people manage to work through this oscillation between denying and remembering, they will finally integrate the trauma information and recover. Those who do not may develop PTSD. Horowitz was influential as one of the first theorists to point out the impact of trauma on a person's beliefs about the world and the self, but the theory did not account for important phenomena of PTSD such as flashbacks (Brewin & Holmes, 2003).

Dual representation theory (Brewin et al., 1996; Brewin, 2001) draws on neuro-cognitive findings to explain the difference between ordinary memories and PTSD-type flashback memories. The theory proposes two different types of memory system that work in parallel using different pathways in the brain. Verbally accessible memories (VAM) are integrated with other autobiographical memories and can be deliberately retrieved as and when required. These memories are processed like all normal memories by the hippocampus which is responsible for laying down integrated, coherent representations of experience that are based on limited data registered by the conscious mind. However flashbacks are an example of situationally accessible memories (SAM) that contain information from a lower level processing of sights and sounds related to the trauma that were not consciously registered at the time. The SAM system is also thought to store information about physical responses to the trauma, so SAMs are more detailed and emotional than ordinary memories. SAMs tend to be triggered automatically by

perceptual reminders of the event and to bypass the hippocampus, taking a "direct" route to the amygdala. There is evidence that intense stress, associated with high levels of cortisol, impairs the functioning of the hippocampus (McEwen & Magarinos, 1997). This might be a mechanism that favours memory processing via the amygdala (LeDoux, 1996) after a stressful experience, heightening the risk of having automatic, vivid, emotional memories (i.e. flashbacks). A recent revision of this theory (Brewin et al., 2010) will be discussed later in the thesis (chapter 7).

It is perhaps not surprising that PTSD has been investigated as a potential outcome of treatment in an ICU. According to the literature, ICU survivors experience many of the vivid emotions and unusual memory processes known to occur in PTSD. Some are reported to have memory distortions after leaving ICU (Jones et al., 2001; Jones et al., 2007). Some patients have partial memories, while others have total amnesia for the ICU. Some have "delusional" memories of hallucinations or unreal experiences in the ICU but no recall of actual events. Others have traumatic but real memories of unpleasant procedures and pain (Schelling, 1998). Furthermore, being diagnosed with a life-threatening illness was added to the list of traumas that can be triggers for PTSD in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; American Psychiatric Association, 1994). Most ICU patients have been exposed to this "trauma" and may of course have been exposed to other stressors, either in the past, immediately before or during their ICU stay.

1.3.7 Depression

Very few studies have quantified the prevalence of other anxiety disorders or depression after intensive care. One study (Weinert & Meller, 2006), in which the SCID (First et al., 1998), a structured interview tool for DSM-IV disorders, was administered to 153 general ICU patients by mental health care professionals, found that 32% of patients had a depressive disorder two months after intensive care. Other studies have found prevalence rates of depression in former ICU patients ranging from 2.8 - 47%. This is in contrast to studies world-wide that have estimated prevalence of depression in the general population at 4 - 10% for major depression and 2.5 - 5% for dysthymia (Waraich et al., 2004). The high rates of depression estimated for post-ICU patients, if confirmed, would have serious implications for their well-being and recovery. Table 1.4 outlines the main symptoms of depression and other psychological outcomes after ICU. An important issue is the link between depression and suicide (Fawcett et al., 1987) as between 10 and 15 per cent of people with major depressive disorder are likely to commit suicide. Physical recovery is also threatened, as depression is associated with increased mortality due to medical problems or accidents. Heart disease is a

specific risk; It is known that depressive symptoms predict future coronary heart disease in originally disease-free samples (Stansfeld et al., 1993) and a worse prognosis after myocardial infarction (Ziegelstein, 2001).

Table 1.4 Possible psychological outcomes of ICU

Name of disorder	Defining symptoms*
Depression	*Low mood or loss of interest* usually accompanied by one or more of: low energy; changes in appetite, weight or sleep pattern; poor concentration; feelings of guilt or worthlessness; suicidal ideas
General Anxiety Disorder	Over-arousal; irritability; poor concentration; poor sleeping; worry about several areas *most of the time*
Panic Disorder	Intermittent episodes of panic or anxiety; taking avoiding action to prevent these feelings.
Post Traumatic Stress Disorder	1. Persistent re-experiencing of a traumatic event 2. Avoidance of stimuli associated with the trauma 3. Increased arousal symptoms such as insomnia or hypervigilance

**Sources: NICE clinical guidelines 22 (National Institute for Health and Clinical Excellence, 2004) and 26 (Middleton et al., 2005)*

Depression can be difficult to diagnose in patients who are or have been seriously ill. It may be unclear whether somatic symptoms (such as changes in appetite, weight, sleep and energy) are due to depression or underlying illness. Depression in seriously ill patients will be more readily manifested by the psychological or cognitive symptoms such as dysphoria, depressed mood, sadness, lack of pleasure, sense of worthlessness, hopelessness, helplessness, guilt and despair, tearfulness and loss of self-esteem (Block, 2005). Risk factors for depression include genetic vulnerability, poor social conditions, low levels of support, low self-esteem, childhood adversity, a family history of depression and a prior personal history of depression (Kendler et al., 1995). Advanced disease is also known to increase the likelihood of depression: The more symptoms, such as dyspnea, nausea, bowel problems or bladder problems, experienced, the more likely patients are to become depressed (Fine, 2001).

The traditional, though now controversial, distinction made between endogenous and reactive depression, stemmed from the idea that at least some depression occurs in reaction to stress. Research following a volcanic eruption found that the incidence of depression, as well as generalised anxiety disorder and PTSD, increased in the year after the disaster (Shore et al., 1989). Chronic stressors such as poverty, unemployment and care-giving are all associated with increased risk of depression (Schulz et al., 1995). However not all individuals become depressed after exposure to stress. Depression probably comes about through an interaction between chronic stress, acute stress and individual vulnerability factors. For

example Beck's cognitive model of depression (2008) suggests that people with negative early life experiences develop unhealthy core beliefs that predispose them to react to stressful events with depression (a negative view of the self, the world and the future). Learned helplessness (Miller & Seligman, 1975) is an alternative theory of depression that may have relevance for intensive care patients. It posits that people will become depressed and unmotivated when they are faced with stressful events that they cannot control.

1.3.8 Anxiety

The few studies that measured anxiety as an outcome of intensive care found that between 5% and 34% of patients had a "probable" anxiety disorder between three and nine months after leaving intensive care (see Chapter Two, systematic review). Anxiety has been defined as a state of emotional distress "resulting in feelings of being unable to predict, control, or obtain desired outcomes" (Barlow, 2004). It involves feelings of apprehension and fear often characterised by physical symptoms such as palpitations, sweating and feelings of stress. Anxiety may be experienced as agitation, insomnia, restlessness, tachycardia, hyperventilation, panic disorder, worry or tension. Some anxiety is a normal part of life, but the primary feature of an anxiety disorder is abnormal or inappropriate anxiety when a person's heart races, breathing increases and muscles tense without any reason for them to do so. Anxiety disorders are chronic, growing progressively worse if not treated.

There are a number of common anxiety disorders, such as GAD (generalised anxiety disorder) which involves worry about many areas of life most of the time, together with irritability, hyper-arousal, poor concentration and poor sleeping (American Psychiatric Association, 1994). The lifetime prevalence of GAD in the community is 5-6%. In panic disorder a patient will have recurrent unexpected panic attacks that lead to at least one month of persistent fear of more attacks, worry about the consequences, and behaviour change to avoid panic attacks (American Psychiatric Association 1994). Panic attacks are defined as "a discrete period of intense fear or discomfort, in which at least four of the following developed abruptly and reached a peak within ten minutes": palpitations, pounding heart or accelerated heart rate; sweating; trembling or shaking; sensations of shortness of breath or smothering; feeling of choking; chest pain or discomfort; nausea or abdominal discomfort; feeling dizzy, unsteady, lightheaded or faint; derealisation or depersonalisation; fear of losing control or going crazy; fear of dying; numbness or tingling; chills or hot flushes. Lifetime prevalence of panic disorder is 1-3% (Kumar & Malone, 2008).

1.3.9 Co-morbidity of outcomes

Identifying the nature of psychological morbidity can be complicated by the high rate of co-morbidity between psychological disorders. Depression and anxiety often co-exist (Gorwood, 2004), and a case has been made for a diagnosis of mixed anxiety-depression. In a US co-morbidity survey, 88% of men and 79% of women with PTSD were also diagnosed with another psychological disorder, including somatisation disorder, psychosis, anxiety disorder and depression (Davidson et al. 1991). The most frequent co-diagnoses are depression, GAD and substance abuse. Many authors have pointed out that there is a substantial symptom overlap with many depressive symptoms appearing in the DSM criteria for PTSD (e.g. markedly diminished interest in significant activities, restricted affect, sense of foreshortened future, difficulties with sleep, guilt). However it has been argued that distinctive features of PTSD are the exaggerated startle, the re-experiencing symptoms and physiological reactivity to trauma-related cues (Brewin et al., 1996; Brewin et al., 1996).

1.3.10 Conclusion

There are few studies that have examined the extent and nature of psychological morbidity after intensive care. Many are based on small samples of intensive care patients and are not generally of high quality. However, when results are considered along with evidence of poor HRQL (Dowdy et al. 2005), and clinical accounts by intensive care staff, it must be concluded that adverse psycho-social outcomes of intensive care are a matter for concern. The provision of psychological support to patients while they are undergoing intensive care has been advocated, as well as the establishment of follow-up clinics to provide both physical and psychological ICU after-care (Department of Health, 2000). A national survey (Griffiths et al., 2006b) found that only 80 ICUs (30%) had follow-up clinics; and of these, only 47 (59%) were funded. Evidence for the efficacy of follow-up clinics and their effect on long-term outcomes is lacking. A recent multi-centre randomised controlled trial of nurse-led follow-up clinics compared with standard care, showed no improvement of physical or psychological quality of life or cost effectiveness benefit in the first year after ICU discharge (Cuthbertson et al., 2009). It is not known to what extent ICUs provide psychological support in the acute setting; but few units have the services of a psychologist available to them (Bennun, 2001). However it is possible that a preventative, early intervention approach could prove more successful than the follow-up programmes. Increased knowledge about the nature of adverse psycho-social outcomes after intensive care and modifiable risk factors, is essential to inform the development of supportive interventions for ICU patients.

Chapter 2 Systematic review: psychological morbidity and poor HRQL after intensive care

2.1 Introduction

In chapter one it was argued that many former patients suffer severe psychological distress in the months after leaving intensive care. However little is known about the nature and extent of poor psychological outcomes after intensive care, nor about possible causal risk factors. As the first step in an investigation of post-ICU psychological morbidity, I carried out a systematic review of observational studies that estimated the prevalence of adverse psycho-social outcomes among general ICU patients and identified likely risk factors.

2.1.1 Prevalence of psycho-social outcomes of intensive care

Three previous systematic reviews (Jackson et al., 2007; Griffiths et al., 2007; Davydow et al., 2008) summarised evidence about the prevalence of post-traumatic stress disorder (PTSD) after intensive care. In a review of 15 studies of patients from general ICUs (medical, surgical or mixed) Davydow et al. (2008) reported that the median point prevalence of PTSD symptoms was 22% (range 8%-51%), while clinician-diagnosed PTSD was 19% (10% to 39%). Griffiths et al. (2007) found that the range of prevalence of PTSD reported in 30 studies of general ICU patients and sub-groups (ARDS, trauma, septic shock and cardiac surgery) was 0-64%. However the review concluded that the true prevalence of PTSD could not be known due to the poor design, methodology and reporting of the included studies. In a review of 16 studies of medical ICUs, Jackson et al. (2007) argued that the rates of PTSD (up to 63%) reported were likely to be over-estimates due to the methodological shortcomings of many studies.

These reviews provided useful data, but there is no empirical, clinical or theoretical reason to assume that PTSD is the only or even the most important psycho-social outcome occurring after intensive care treatment. Indeed after my systematic review was completed a review of studies of post-ICU depression was published (Davydow et al., 2009). Another systematic review by Dowdy et al. (2005) focused on evidence of the quality of life (or HRQL) of former intensive care patients from 21 studies of medical or surgical ICU patients. The majority of studies were rated high quality. Conclusions were not clear-cut because studies used four different measures to assess HRQL at diverse time-points, including pre-ICU, and no quantitative synthesis was possible. As already summarised in chapter one, Dowdy et al. (2005) concluded that the HRQL of former ICU patients was much lower than the general population from six months after discharge and up to 14 years later but that there was improvement over time.

The present systematic review built on work done in the previous reviews by encompassing studies that covered all adverse psycho-social outcomes reported for surviving ICU patients, including depression, anxiety disorders and cognitive dysfunction in addition to HRQL and PTSD. Anxiety disorders and depression are known to be important consequences of serious illness in other populations such as patients with heart disease (Davidson et al. 2004, Denollet et al. 2006) or cancer (Pirl, 2004). Anxiety and depression were measured as primary or secondary outcomes in a number of studies of ICU survivors. The review by Davydow et al. (2009) concluded that the median point prevalence of "clinically significant" depressive symptoms was 28% (using questionnaires) and 33% based on clinician diagnoses. The prevalence of post-ICU anxiety has not previously been estimated in a systematic review.

The existence of severe cognitive impairment has been highlighted in a number of studies of sub-groups of ICU patients. For example, patients with acute respiratory distress syndrome (ARDS) 75% had chronic cognitive impairment at 1 year (Hopkins et al., 1999), and 25% at 6 years (Rothenhausler at al., 2001). A small number of studies suggest that general ICU patients may also be at risk of cognitive impairment after discharge. These studies were not included in previous systematic reviews of psychological morbidity after ICU, but were included in my review.

By covering all known adverse psychological outcomes in one systematic review, my aim was to present a comprehensive picture of the possible consequences for patients who have undergone treatment in an ICU. This would provide valuable information to clinicians, especially those in the UK who are now required by the National Institute for Health and Clinical Excellence (NICE) to screen ICU patients for psychological morbidity and provide rehabilitation and follow-up in the community if necessary (Tan et al, 2009).

An important issue affecting the prevalence estimates from previous PTSD reviews is that all three included studies of diagnostic sub-groups of ICU patients as well as studies of mixed-diagnosis ICU patients. Griffiths et al. (2007) included 17 studies of ARDS, cardiac surgery, trauma or septic shock patients. Seven out of 16 studies reviewed by Jackson et al. (2007) were of sub-groups of patients (ARDS, septic shock or acute lung injury). The review by Davydow et al. (2008) included two studies of patients with sepsis. The inclusion of these sub-groups of patients would be likely to increase heterogeneity as some patient groups are likely to have much higher PTSD rates than general ICU patients. For example, rates for ARDS patients range from 29-43% (Deja, 2006; Kapfhammer et al., 2004; Schelling, 1998) and for sepsis patients from 39% to 64% (Schelling et al., 1999; Schelling, 2001). In

my systematic review I excluded studies of diagnostic sub-groups in order to estimate average PTSD prevalence rates of the general ICU population. The only sub-groups included are in studies of mechanically ventilated ICU patients. I included them because mechanical ventilation is the most common intervention in the ICU (68.3% of all admissions were mechanically ventilated within the first 24 hours (Icnarc 2007)) and outcomes of mechanically ventilated patients are of particular concern due to the invasive nature of treatment.

2.1.2 Predictors of psycho-social outcomes post-ICU

The second aim of the systematic review was to establish what is known about psychological, clinical and socio-demographic risk factors for adverse psycho-social outcomes after ICU. The reviews by Jackson et al. (2007), Davydow et al. (2008) and Dowdy et al. (2005) also considered the evidence for consistent risk factors of post-ICU psychological outcomes. Griffiths et al. (2007) did not report on risk factors. Their findings are summarised in table 2.1 below.

Table 2.1 Risk factors of post-ICU psycho-social outcomes from three reviews

	Psychological	**Clinical/Healthcare**	**Socio-Demographic**	**History**
Jackson et al. 2007 (PTSD)	Delusional memories Factual memories Social support	Length of stay Duration of MV Levels sedation	Younger age Female	Psychological history
Davydow et al. 2008 (PTSD)	Early delusional memories Later traumatic memories	Benzodiazepine administration	Younger age Female	Psychological history
Dowdy et al. 2005(HRQL)		Severity of illness	Older age	

The most consistent risk factors for PTSD according to the systematic reviews were memories of ICU (traumatic, delusional or factual), sedation, psychological history, younger age and female gender. However these factors were only found to be significant in one or few studies. Additionally there were some discrepancies between reviews concerning risk factors of PTSD. For example, Davydow et al. (2008) reported that there were no associations between length of stay and PTSD, or between duration of mechanical ventilation and PTSD, while Jackson et al. (2007) reported that those associations had been found. There was inconsistency in the way studies operationalised memory of the ICU. Memories were measured prospectively (a few days after leaving the ICU) in some studies or cross-sectionally (at follow up) in others. They were categorised in different studies as delusional, psychotic, frightening, traumatic or factual, yet it is not clear in some studies how those categories were differentiated or overlapped. The review by Dowdy et al. (2005) found few consistent predictors of HRQL across studies. Only severity of illness and old age were found to predict some HRQL domains. The only risk factor identified for post-ICU depression was early post-ICU depression (Davydow et al., 2009). In this review I tried to evaluate risk factors in the most detailed,

comprehensive way possible to establish more clearly where gaps in our knowledge lie.

2.1.3 Quality of previous reviews

In deciding to carry out a new systematic review, I considered the quality and coverage of the previous reviews. Quality was considered according to guidance for conducting and reporting systematic reviews in the Quorom statement (Clarke, 2000), recently updated by the Prisma statement (Moher et al., 2009). Strengths of the review by Griffiths et al. (2007) included explicit search and selection strategies and the use of quality assessment items including outcome assessment. However study quality assessment was not taken into account when reporting the range of prevalence estimates.

There were methodological weaknesses in the review by Jackson et al. (2007). The reviewers did not use explicit or systematic search and selection strategies, as recommended in Quorom (Clarke 2000). Quality scores were given to studies but the aspects of quality assessed were not described. It should also be noted that studies of medical ICUs only were included, so that results may not apply equally to general ICUs. The review by Davydow et al. (2008) conformed to recommended standards for search and selection strategies, but did not assess the quality of studies. Dowdy et al. (2005) conducted and reported the review of HRQL correctly. However there was very limited synthesis of results, and conclusions, due to the heterogeneity of included studies.

2.1.4 Summary

Previous reviews of psychological morbidity in the ICU had some methodological or other shortcomings. The current review adheres to recent recommendations (Moher et al., 2009) for carrying out systematic reviews by working from a protocol (Appendix 1) and using systematic and explicit methods to identify, select and critically appraise studies. The risk of bias in studies was assessed, including quality of outcome assessment. The review would be useful to clinicians because it includes studies of all recognised psycho-social outcomes after ICU and a comprehensive evaluation of risk factors. As no studies of diagnostic sub-groups of ICU were included, therefore estimates of prevalence were not inflated by patient groups with exceptionally high rates.

The aim of the review was to provide accurate estimates of the proportion of all ICU patients who suffer from adverse psycho-social outcomes in the months following hospital discharge and to investigate the nature of these outcomes. The review also examined the severity of psychological symptoms found in studies, and

determined whether consistent risk factors for adverse psycho-social outcomes could be identified.

2.1.5 Review questions

1. What proportion of ICU survivors suffer to what extent from adverse psycho-social outcomes (including PTSD, anxiety, depression, cognitive impairment and poor quality of life) in the months after intensive care?
2. What are the clinical, psychological and socio-demographic risk factors for adverse psychosocial outcomes in the months after ICU treatment?

2.2 Methods

2.2.1 Criteria for study selection

Three criteria were used to decide which studies should be selected for inclusion in the systematic review.

Type of studies: Prospective cohort studies, retrospective cohort studies, and cross-sectional surveys were included in the review. (A retrospective cohort study is defined here as one in which patients were recruited at the time when outcomes were measured and data from their ICU stay were then collected retrospectively.) Data from the control groups in RCTs of interventions to reduce psychological morbidity in ICU patients were also considered eligible.

Types of participants: The study populations were ICU patients who received intensive care >24 hours in general, medical or surgical ICUs. Studies of sub-groups of ICU patients such as patients with ARDS or pancreatitis were not eligible as they are not representative of general ICU patients. However studies that focused on ICU patients receiving mechanical ventilation (advanced respiratory support) were included, as it is the most common intervention received in an ICU. Patients who receive advanced respiratory support suffer from many different underlying conditions so they are approximately representative of the general ICU population.

Types of outcome measures: Studies were selected if they used reliable and validated questionnaires or interviews for PTSD, anxiety, depression, other psychological morbidity, cognitive impairment or quality of life. Studies that used single item measures or unvalidated bespoke questionnaires were excluded.

2.2.2 Search strategy

The search strategy for identification of studies followed the Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies (MOOSE, Stroup et al., 2000). Studies were identified in December 2007 from the following databases:

Medline	(Ovid, 1950-2007)
Embase	(Ovid, 1980-2007)
Psycinfo	(Ovid, 1806- 2007)
Cinahl	(EBSCO Host, 1982 – 2007)
Web of Science	(ISI Web of Knowledge, 1981-2007)

The initial search was carried out on Medline using the following strategy (figure 2.1). Similar searches were carried out on the other four databases.

Figure 2.1 Search strategy

1.	**MEDLINE**
	Search terms
	1950 to December 2007
#1	(Explode "Critical Care" in MIME, MJME, PT) or (explode " intensive care-+") in MIME, MJME, PT)
#2	((Critical Care) in ti, ab) or ((intensive care) in ti, ab)
#3	#1 or #2
#4	"Stress-Disorders-Post-Traumatic"/all SUBHEADINGS in MIME, MJME, PT
#5	((Post*traumatic stress or PTSD) in ti, ab)
#6	Explode Stress, Psychological or Psychopathology or Depression or Anxiety or Affective disorders in MIME, MJME, PT)
#7	((psycholog* or psychiatr* or psychopathology or psycho*social or anxi* or depressi* or mental or emotion*) in ti, ab)
#8	"Quality of Life"/ all SUBHEADINGS in MIME, MJME, PT)
#9	((SF-36 or NHP or SIP or EuroQol* or HRQL) in ti, ab)
#10	#4 or #5 or #6 or #7 or #8 or #9
#11	Explode "Cohort" in MIME, MJME, PT
#12	((cohort or prospective or follow-up or long-term or longitudinal) in ti, ab)
#13	#11 or #12
#14	#3 + #10 + #13
#15	(#14) and (AGE:MEDS = ADULT)

2.2.3 Quality assessment

It has been reported that 50% of systematic reviews of observational studies do not carry out any quality assessment, i.e. a systematic appraisal of the internal and external validity of the studies included (Mallen et al., 2006). Previous researchers may have overlooked the issue of quality assessment because there is no accepted method of assessing the quality of non-randomised trials. A multiplicity of methods and checklists have been used but none of the latter have been validated or tested for comparability. However without assessing the methodological rigour of each study, all would be given equal weight regardless of quality, which would lead to inaccurate conclusions.

In the absence of a gold standard for quality assessment of observational studies, the NHS Centre for Reviews and Dissemination (Khan et al., 2001) recommended that reviewers select components from available checklists that are most relevant to the topic and purpose of the systematic review. I based my quality assessment on the methodology checklists developed by the Scottish Intercollegiate Guidelines Network (SIGN, 2004) for study designs including cohort studies. Although SIGN checklists were designed for reviewing papers for the preparation of clinical guidelines rather than for systematic reviews, I chose to use them because of their

clear description of each quality criterion. For example rather than simply asking what is the "representativeness of the sample", as in other checklists, the SIGN item spells out exactly what has been assessed for representativeness: *"A clear definition of source population and clear eligibility criteria for selection of subjects are used, to ensure the sample is representative."* This guided me in making the assessment, and should also help to make the reasons for my assessment of quality more transparent.

As the systematic review had a particular focus on psycho-social *outcomes* of ICU survivors, quality criteria regarding the robustness of outcome data were used. Studies that did not use reliable validated questionnaires were not eligible for the review; However there were distinctions to be made between questionnaires that were more or less appropriate for this research question. For example a study that used the Impact of Events-Revised Scale (Weiss & Marmar, 1997) to assess PTSD scored more highly than one using the Impact of Events Scale (Horowitz, Wilner & Alvarez, 1979) as the latter only includes two of the three symptom clusters of PTSD (APA 1994). Another criterion – controlling for other factors which may be relevant to the outcomes – was considered particularly important for evaluating the quality of follow-up studies. To determine the strength of the association between risk factors and outcome, a further criterion selected was the use of an appropriate statistical analysis in a study. The quality criteria are listed in figure 2.2.

Figure 2.2 Quality criteria

The sample
1. A clear definition of source population and clear eligibility criteria for selection of subjects are used, to ensure the sample is representative.
2. Comparison is made between full participants and those lost to follow up
3. A power calculation is reported. If not, sample size is small, medium or large
Outcome
4. The likelihood that some subjects might have the outcome at baseline is accounted for.
5. The outcomes are clearly defined.
6. Evidence is used to demonstrate that measure of outcome is valid and reliable.
7. Follow-up is long enough for outcome to occur.
Risk factors-outcome analysis
8. The study addresses an appropriate and clearly focused question
9. Any measures of risk factors are reliable
10. Main potential confounders are identified and taken into account in design and analysis
11. Confidence intervals have been provided.
12. Appropriate statistical analyses have been carried out
Overall assessment
How well was study done a) to minimise risk of bias and b) to establish a causal relationship between exposure and effect.

Each separate criterion was assessed as a) poorly addressed b) adequately covered or c) well covered. As no definitions of these assessment levels were given in the guidance for using SIGN checklists, subjective judgments had to be made.

Initially,as recommended by SIGN, an overall quality assessment of the study was indicated by:

- **-** (did not meet most criteria; **poor quality**)
- **+** (met an adequate number of criteria; **medium quality**)
- **++** (met all or most criteria; **high quality**).

I assigned two quality ratings based on the above – one for the quality of the estimate of prevalence given, and one for the quality of any associations reported between predictors and outcomes. Using this system the majority of studies were judged to be of medium quality, with few that were very poor and few that were very good. It was therefore difficult to distinguish between them. In order to construct tables demonstrating the relative quality of studies (tables 2.3 and 2.7), I assigned a more detailed numerical score to each study based on the number of poor (0), adequate (1) and good (2) ratings for four key criteria: the representativeness of the sample, power of the study/sample size, the robustness of outcome assessment, and the appropriateness of analysis of size of association. The first three criteria applied to prevalence; the fourth to analysis of associations. This enabled me to make finer distinctions about the quality of the studies. The range of scores was 0-6 out of 6 for the prevalence rating, and 0-2 out of 2 for the analysis of association rating.

2.2.4 Inter-rater reliability

Three supervisors also assessed three papers each for risk of bias. There was 100% agreement between all raters in the quality assessment of the nine papers (20% of the total of 45 papers).

2.2.5 Data extraction strategy

The same data were systematically extracted for each study using a data extraction sheet (see Appendix 2).

2.2.6 Synthesis of extracted evidence

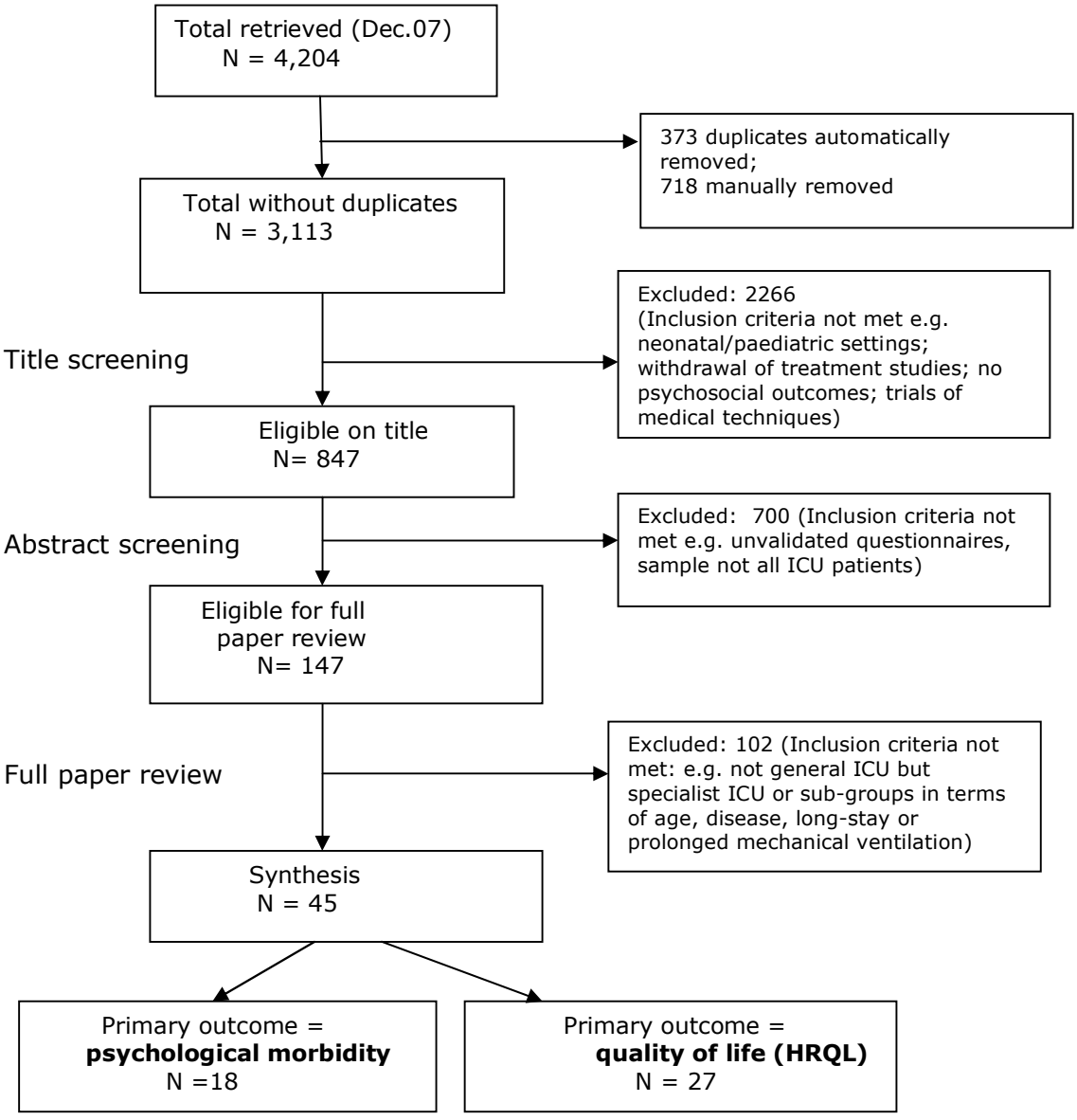
For most outcomes such as PTSD and other psychological morbidity and some measures of HRQL, it was not possible to carry out a meta-analysis due to the heterogeneity of the results and the lack of consistency in reporting results. Heterogeneity was probably due to differences in ICU populations (illness severity, length of stay, exclusions), different measures used with different diagnostic thresholds and different lengths of follow-up. Therefore I examined ranges of estimates and identified reasons for variation in results, using quality criteria. However I carried out a random effects meta-analysis for the studies that assessed the quality of life of former ICU patients using the SF-36, as results were consistent and well-reported. I excluded repeats (some studies reported multiple results at

different time-points) and outliers from the meta-analysis. Synthesis of information about risk factors was difficult as few studies reported results in a comprehensive manner. Non-significant results were rarely reported and p-values rather than effect sizes were reported. It was not clear how many tests had been carried out in most studies. Therefore I was merely able to summarise the number of times associations were found or not found across studies.

2.3 Results

A total of 4,204 papers were retrieved as a result of the search outlined above After removing duplicates, 3113 titles and then 847 abstracts were screened until 147 papers were found eligible for full paper review. Of these 45 papers were included in the review. Of these, 18 had PTSD or depression as the primary outcome, and 27 had HRQL as the primary outcome.

Figure 2.3 Flowchart of reference retrieval, exclusions and inclusions



2.3.1 Characteristics of studies of psychological morbidity

There were 16 cohorts of patients in 18 studies with a primary outcome of psychological morbidity (see table 2.2). Two cohorts were both included in two studies each with different outcomes, as indicated by asterisks in table 2.2. A total of 2087 unique patients were enrolled in these studies. They were recruited from general ICUs in 14 studies, from medical ICUs in two, from a surgical ICU in one, and from both medical and surgical in one study. Most of the studies (ten) were carried out in the UK, while three were in the USA and five in Europe (Germany, Italy and Sweden). A variety of study designs were included in the review. There were 13 prospective studies, two retrospective cohorts, two cross-sectional studies and one RCT. Follow-up rates varied from 15.6% to 100%. In total, psychological outcomes were assessed for 1351 participants out of the 2087 that were enrolled. This means that 64% of the participants across studies were followed up.

2.3.2 Patient characteristics

Inclusion. Minimum time spent in the ICU by a patient to qualify for inclusion in a study ranged from 24 hours in most studies to 72 hours in a few, to 30 days in one study. In five studies, only mechanically ventilated patients were included.

Exclusion. The most common reasons for excluding participants were previous psychiatric disorders including psychosis, neurological disease, cognitive dysfunction and attempted suicide. As it is thought that prior psychological history may be a risk factor for outcomes such as PTSD, it would be better practice to include this factor as a covariate in the final model rather than exclude participants. The prevalence estimates of such studies may be too low.

The socio-demographic composition of study cohorts varied considerably in several ways. Age differed from mean 41.7 years in one study to median 69 years in another (some studies reported means, and others reported medians). Gender composition ranged from 43% male in one study to 76% male in another. Age and gender are known risk factors for psychological morbidity and quality of life, therefore differences in prevalence estimates could be expected to occur when cohorts vary considerably in these factors. Data on ethnicity or socio economic status were rarely reported in the studies.

Illness severity of patient cohorts ranged between Apache II scores of 11.93 - 25 (mean or median scores). The Apache II score is a general measure of disease severity, based on current physiologic measurements, age and previous health condition. The range of possible scores is 0-71 and a high score is associated with an increasing risk of hospital death (Knaus et al., 1981). Mean or median length

of stay (LoS) in the ICU ranged from five to 51.9 days. As the mean LoS of UK ICU patients is five days and median two days (Icnarc 2010), it can be seen that some cohorts were atypical for this variable. Differences in Apache II and LoS results suggest a wide range in physical condition and ICU experience between cohorts.

Table 2.2 Characteristics of studies of psychological outcomes of ICU

Study reference	N at FU*	ICU Setting (Inclu-sions)	Exclusions	Design	Outcome	Age	Sex % men	LoS ICU	Apache II score
Capuzzo et al. (2005)	63	General Italy (> 3d)	Psychol-ogical history	Prospective	PTSD	69	60	5	14
Cuthbertson et al. (2004)	78	General UK	None	Prospective	PTSD	58	56	6	18
Girard et al. (2007) **	43	Medical US (MV)	Neurol-ogical disease	Prospective	PTSD	52	47	10	25
Griffiths et al.(2006a)	108	General UK (> 3d)		Cross sectional	PTSD	57	66	14	
Jackson et al.(2003)**	34	Medical USA (MV)	Neurol. Psych. disorders	Prospective	Cognitive deficits	53	53	10	25
Jones et al. (2001)	30	General UK(MV> 24h)	Psychosis, suicide, head injury	Prospective	PTSD	57	44	8	17
Jones et al. (2003)	44	General 3 in UK (MV>48h	Neuro-surgery, psychosis	RCT (controls)	PTSD	59	57	13	16
Jones et al. (2007)	238	General 6 Europe (>48h)	Psychosis, suicide	Prospective	PTSD	54-73		5-13	13-19
Nickel et al. (2004)	41	Medical Germany (>24h)		Cross sectional	PTSD	47	69	12	12
Perrins (1998)	41	General UK (>48h)	Past mental illness	Prospective	PTSD	49		6	
Rattray (2005)	80	General UK (>24h)		Prospective	PTSD				
Richter (2006)	37	Surgical Germany (> 30 d)		Retro-spective	PTSD	42	76	51.9	20
Samuelson (2007)	226	General Sweden >24h MV	Psychosis, suicide, head injury	Prospective	PTSD	63	52	5.75	18
Scragg et al.(2001)	80	General UK	Trauma	Retro-spective	PTSD	57	47		
Sukantarat (2005)***	45	General UK (>72h)		Prospective	Cognitive deficits	58	43	17	15
Sukantarat (2007)***	45	General (>72h)		Prospective	PTSD	58	43	17	15
Twigg et al. (2008)	44	General UK, 2 sites	Dementia, Confusion, Overdose	Prospective	PTSD	56	45	11 7	16 14
Weinert & Meller (2006)	153	Medical-surg.US >36hMV	Chronic cognitive deficits	Prospective	Depression	55	51	6	

* FU=follow-up **same study population *** same study population. C=controls, MV=mechanical ventilation, h=hours, d=days . Age, LoS (length of stay in ICU) and Apache II (Knaus et al., 1981) scores were means or medians, as reported in studies. If cells are empty, data were not reported in studies.

2.3.3 Outcome assessment (psychological morbidity)

The shortest time at which outcomes were assessed was two months after ICU discharge, whereas the maximum time was 35 months (see table 2.4). Clearly psychological outcomes such as PTSD might be expected to change across time and this might account for some variation. Many different PTSD measures were used in the studies, including self-report questionnaires such as the Posttraumatic Diagnostic Scale (PDS; Foa et al., 1997), the Impact of Events Scale (IES; Horowitz et al., 1979), the Impact of Events Scale-revised (IES-R; Weiss & Marmar, 1997), the Davidson Trauma Scale (DTS; Davidson et al., 1997), the Post-traumatic Stress Syndrome 10-Questions Inventory (PTSS-10; Stoll, 1999), the UK Post-traumatic Stress Syndrome 14-Questions Inventory (PTSS-14; Twigg et al., 2008), the Trauma Screening Questionnaire (TSQ; Brewin et al., 2002), a clinical interview - the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; First et al., 1998) and others. It is of concern that seven out of 18 studies in this review used the (unrevised) IES as a measure of PTSD, for although it is a good measure of distress related to life events, it is not a measure of PTSD. It includes only two of the three clusters of symptoms needed to diagnose PTSD (Weiss & Marmar, 1997). This could lead to inflation of PTSD prevalence. Only one study used the PDS (Foa et al., 1997) the only questionnaire that is diagnostic for PTSD using DSM-IV criteria (APA 1994).

Measures of depression and anxiety used, including the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983), the Center for Epidemiologic Studies Depression Scale, (CES-D; Radloff, 1977), the Geriatric Depression Scale (GDS; Yesavage et al., 1983), the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; First et al., 1998) and the State Trait Anxiety Inventory (Spielberger et al., 1983), were all valid and reliable. However there is always some doubt as to whether questionnaires measuring psychological constructs such as depression and anxiety are precisely comparable with each other. Even studies that used the same measure sometimes used different cut-points with different meanings (such as likely disorder, possible disorder, probable disorder, borderline disorder etc.) so that results are difficult to compare. For example in studies using the IES (Horowitz et al., 1979), some used a cut-point of 19, some of 26 and others of 30 or 35. Where a lower cut-point is used, higher prevalence rates will inevitably be found in those studies.

Table 2.3 Quality assessment of studies of psychological outcomes of ICU

Author	N*	F.U rate	Represen-tativeness	Sample size**	Outcome Assessment	Analysis of association	Prevalence rating (max=6)	Association rating (max=2)
Capuzzo et al. 2005	63	75%	adequate	adequate	poor	poor	2	0
Cuthbertson et al. 2004	78	70%	good	adequate	good	poor	5	0
Girard et al. 2007	43	16%	adequate	poor	adequate	good	2	2
Griffiths et al. 2006	108	67%	adequate	adequate	adequate	adequate	3	1
Jackson et al. 2003	34	12%	adequate	poor	good	adequate	3	1
Jones et al. 2001	30	66%	poor	poor	poor	poor	0	0
Jones et al. 2003	44 Cs	77%	adequate	poor	poor	poor	1	0
Jones et al. 2007	238	78%	adequate	good	good	good	5	2
Nickel et al. 2004	41	82%	adequate	poor	good	adequate	3	1
Perrins 1998	41	57%	adequate	poor	poor	poor	1	0
Rattray 2005	87	73%	good	adequate	adequate	adequate	4	1
Richter et al.2006	37	100%	good	poor	good	poor	4	0
Samuelson 2007	226	72%	good	good	good	adequate	6	1
Scragg et al.2001	80	56%	good	adequate	poor	adequate	3	1
Sukantarat 2005	45	88%	adequate	poor	good	adequate	3	1
Sukantarat 2007	45	88%	adequate	poor	adequate	poor	2	0
Twigg et al. 2008	44	79%	adequate	poor	good	n/a	3	n/a
Weinert & Meller 2006	153	55%	good	good	good	adequate	6	1

* N at follow-up **Sample size ratings: **poor**: 30-59 **adequate**:60-150 **good:**>150

2.3.4 Prevalence of post-ICU PTSD

As I was not able to carry out a quantitative synthesis of PTSD results, it was not possible to test whether variation in PTSD estimates could be explained by study and patient characteristics such as mean age of the cohort, gender, illness severity, type of ICU, country, study design or follow-up period. I carried out informal assessment by constructing tables ordering results according to each of these factors but they did not produce any meaningful patterning of results. However it appeared that results did vary according to the method of outcome assessment used. As a rating for outcome assessment was an important part of overall quality assessment, a table of results was created in order of quality assessment (table 2.4). This was used to inform the reporting of prevalence estimates for PTSD.

2.3.4(i) Quality assessment of PTSD studies

I found that out of fifteen studies whose main outcome was PTSD there were:

3 with a **high score** (5/6) for prevalence.

6 with a **medium score** (3/4) for prevalence.

6 with a **low score** (0-2) for prevalence.

2.3.4 (ii) PTSD estimates

The range of PTSD prevalence estimates found was 0 - 62% across all studies. According to the PTSD measure and cut-points used, different studies reported different categories or levels of PTSD severity or diagnosis, corresponding to "some impact of PTSD" (n=3; 23-32%) "possible PTSD" (n=5; 25–62%), "borderline/sub-syndromal PTSD" (n=5, 8.4% - 32%) or "likely PTSD" (n=4,12-28%) while others were able to confirm a diagnosis of PTSD (n=4, 9.2%-19%).

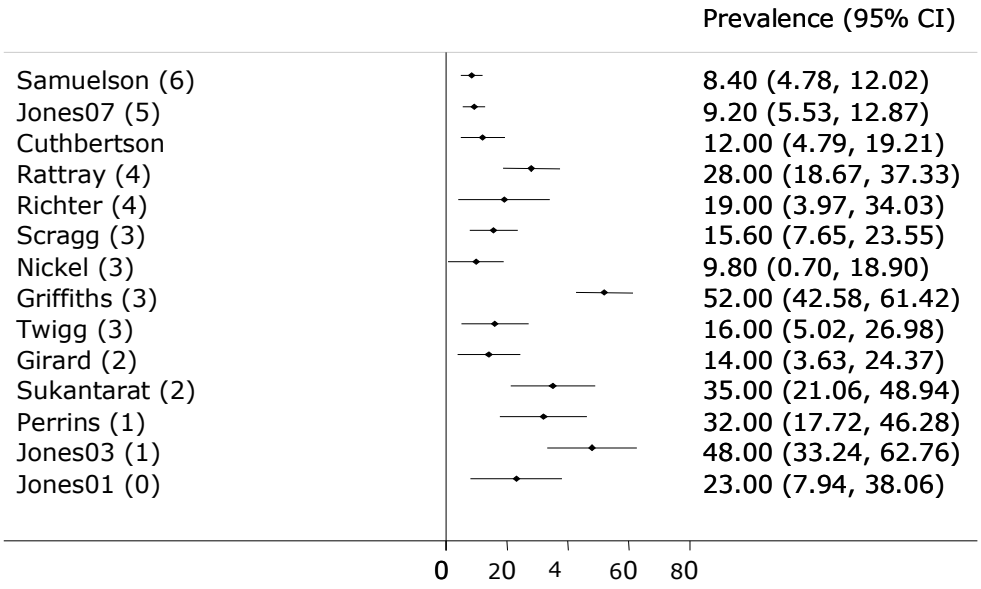
2.3.4(iii) Forest plots of PTSD estimates

The three forest plots shown on the next pages (figure 2.2) display the patterning of results when studies are arranged in order of quality (highest quality first); in order of length of follow-up (lowest to highest); and in order of publication date (most recent first). Whereas table 2.4 includes multiple results for each study (for different time-points or for different severity levels of PTSD) the forest plots include just one result for each study. I chose to show results for the first follow-up point in each study (e.g. three months rather than six months for Cuthbertson et al. (2004)) and for the most stringent definition of PTSD (i.e. a score for likely PTSD rather than possible PTSD). Therefore the range of estimates is a little narrower than seen in table 2.4.

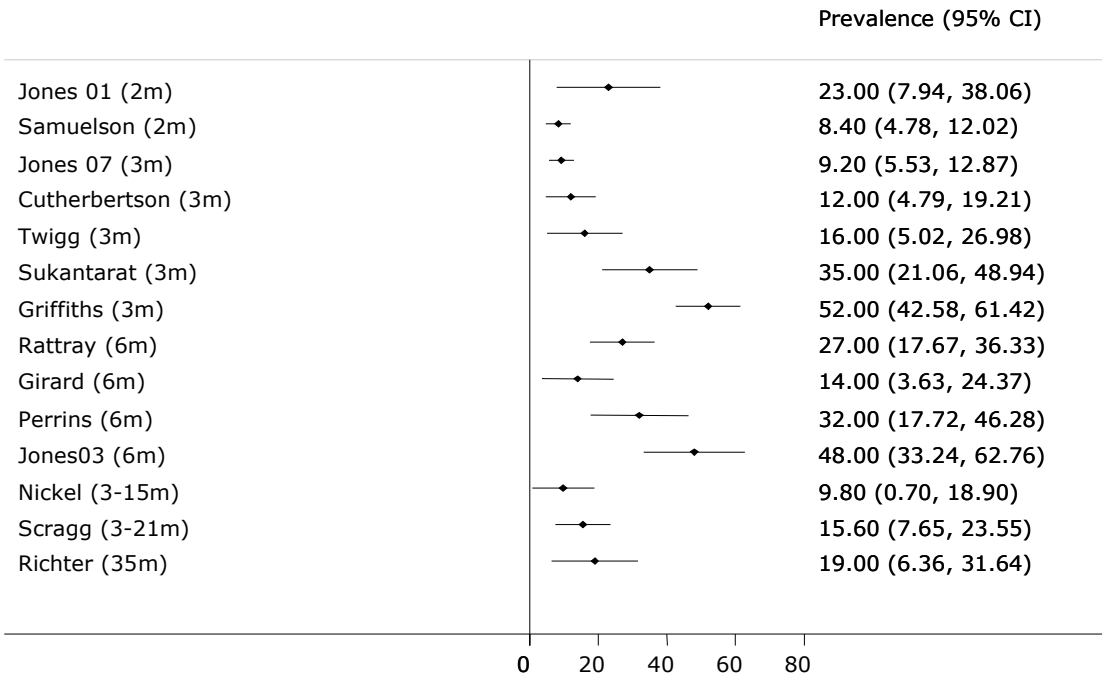
In Forest plot a) **order of quality**, it can be seen that the higher quality studies at the top cluster together without excessive variation (8-28) whereas the lower quality studies at the bottom look much more disparate, with outlying scores up to 52. Therefore it looks as if the quality of studies accounted for some of the variation in PTSD results. However no decisive pattern emerged from the plot of studies arranged in order of length of follow-up. It would be expected that the rate of PTSD might increase or decrease over time but this is not clearly seen. There may be a trend for the rate of PTSD to increase between two and six months, and then decrease over the next two years, but there is too much variation between scores at similar time-points to be certain. Ordering by date of publication might reflect changes in ICU practice over time or improvements in study design or diagnostic instruments for PTSD. However forest plot c) did not yield a clear pattern leading to this interpretation. The top four studies (2007-8) appear to cluster more than the rest around a lower range of scores (8-16) but the fifth study, Sukantarat (2007), was from the same year with a much higher score (35).

Figure 2.4 Forest plots showing estimates of PTSD prevalence

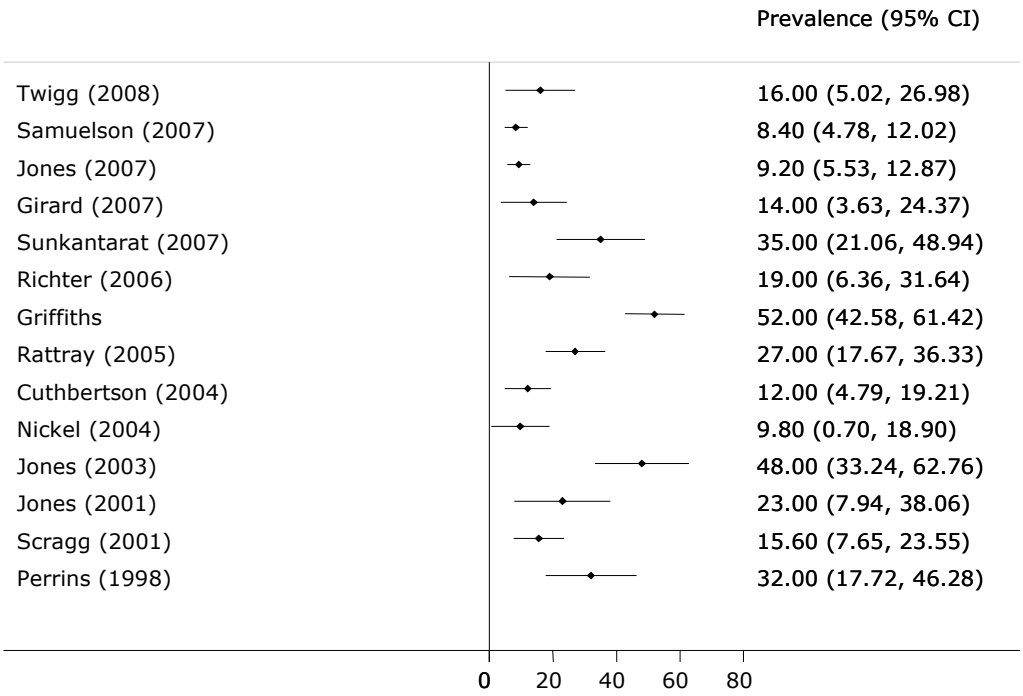
a) PTSD prevalence by quality



b) PTSD prevalence by length of follow-up



c) PTSD prevalence by date of publication



The forest plots suggest that most important source of variation for PTSD results was in the quality of studies. Therefore I arranged table 2.4 below in order of quality scores. If only high quality studies (quality score 5 or 6) were included in the assessment (n=3), the range of prevalence rate estimates was much narrower, at 8.4% - 22%. The best interpretation of this range is that 22% of patients had a high number of PTSD symptoms; between 8.4% -12% had borderline or likely PTSD, while 9.2% had a full diagnosis of PTSD. However the result must be viewed with caution as the range of estimates was based on only three high-quality studies.

Table 2.4 Prevalence rates for PTSD
(arranged in order of quality score)

Author	Time of Follow up	N at follow-up	PTSD measure	Results as reported	Interpretation of results	Quality Scores (max=6)
Samuelson 2007	2m or later	226	IES-R (0-88)	**8.4%** ≥ 30 (*95%CIs* 4.78,12.02)	**8.4%** borderline PTSD	6
Jones et al. 2007	3m	238	PTSS-14, PDS	**9.2%** had PTSD using PDS. (*95% CI*s 5.53,12.87	**9.2%** full diagnosis of PTSD	5
Cuthbert-son et al. 2004	3 m	78	DTS	**22%** > 27 *(95%CI*s12.81,31.19) **12%** > 40 (*95% CIs*0.79,19.21)	**22%** possible PTSD **12%** likely PTSD	5
Rattray 2005	6m 12m	87 80	IES (0-60)	6m**: 29%** ≥ 30 (95%CIs19.46,38.54) **27%** ≥ 30 (95%CIs17.67,36.33) 12m: **28%**≥ 35 (95%CIs18.57,37.43) **24%**≥ 35 (95%CIs15.03,32.97)	**29%** borderline at 6m **27%** likely at 6m **28%** borderline at 12m **24%** likely at 12m	4
Richter et al.2006	35m	37	Semi-structured psychiatric interview.	**32%** (5/6 criteria) (95%CIs16.97,47.03) **19%** (6 criteria) (95%CIs3.97, 34.03)	**32%** sub-syndromal PTSD **19%** full diagnosis of PTSD	4
Scragg et al. 2001	Variable: 3-21m	80	IES	**30% >** (unknown) (95%CIs19.9, 40.04) **15.6%** >30 (95%CIs7.65, 23.55)	**30%** possible PTSD **15.6%** borderline PTSD	3
Nickel et al. 2004	Variable: 3-15m	41	PTSS-10. SCID	**17%** >=35 (95%CI: 5.50, 28.50) **9.76%** with SCID (95%CI: 0.70,18.90)	**17%** likely PTSD **9.8%** full diagnosis of PTSD	3
Griffiths et al. 2006	6m/12m **chk**	108	Trauma Screening checklist	**52%** "PTSD" (95%CIs42.58,61.42)	**52%** likely PTSD	3
Twigg et al. 2008	3m	44	PDS, IES, PTSS-14	**16%** six criteria (95%CIs5.02, 26.98) **27%** five criteria PDS	**16%** full PTSD **27%** subsyndromal	3
Capuzzo et al. 2005	3 m	63	ICUM (all) IES	**0%** on IES subscales (95%CIs 0.00,0.00)	**0%** possible PTSD	2
Girard et al. 2007	6 m	43	PTSS-10	**25%** >= 27 (95%CIs12.06,37.94) **14%** >=35 (95%CIs3.63,24.37)	**25%** possible PTSD **14%** likely PTSD	2
Sukantarat 2007	3m (9m)	45	IES	3m: **35%**>26 (95%CIs21.06,48.94) 9m: **62%** >26 (95%CIs47.82,76.18)	3m **35%** possible PTSD 9m **62%** possible PTSD	2
Perrins 1998	6m	41	IES	6m**: 32%** >19 (95%CIs17.72,46.28) 12m**: 27%** >19 (95%CIs13.41,40.59)	6m **32%** some impact 12m **27%** some impact	1
Jones et al. 2003	6m	102 (44 control)	IES	**48%** > 19 (95%CIs33.24,62.76	**48%** some impact	1
Jones et al. 2001	2m	30	IES	**23%** >19 (95%CIs7.94, 38.06)	**23%** some impact	0

2.3.5 Results: Prevalence of anxiety, depression and other outcomes

2.3.5(i) Depression

Eleven studies included depression as a primary (n=1) or secondary (n=10) outcome (see table 2.6). Four of these were rated high quality and five were rated medium quality. The estimates for prevalence of depression ranged from 2.8% to 47% at times between two and 15 months. This variation may be explained by a number of factors. First, studies measured depression using different instruments, including the CES-D (Radloff, 1977), the HADS (Zigmond & Snaith, 1983), the Geriatric Depression Scale (Yesavage et al., 1983) and SCID (First et al., 1998). In addition it should be noted that two levels of depression were measured – possible depression (ranging from 7% to 47%) and probable depression (ranging from 2.8% to 35%). Even when quality criteria were taken into account, and estimates from only high quality studies were included, rates of depression still varied from between 2.8% to 32%. It is of interest that in the one study that used the gold-standard instrument for diagnosing depression, the SCID, (Weinert & Meller 2006), the overall rate of depression was high, with 16% diagnosed with major depressive disorder and 16% given a "diagnosis of depression not otherwise specified". It is also of concern that evidence from these studies suggests that depression does not appear to lessen and may even increase over time.

2.3.5 (ii) Anxiety

Six studies reported estimates for the prevalence of anxiety as a secondary outcome among former ICU patients. Two were given a high quality rating, two were medium quality and two were low quality studies. All measured anxiety using the Hospital Anxiety and Depression scale (Zigmond & Snaith, 1983) but some gave rates of *possible* anxiety while others measured *probable* anxiety. There are further discrepancies because studies variously used 8, 10 and 11 as the cut-points for clinically significant levels of anxiety. Estimates for the prevalence of anxiety in ICU survivors range from 4.9% to 43% for possible anxiety and 4.9% to 34% for probable anxiety at times between two to15 months. Variation in anxiety or depression rates did not appear to be explained by measure used, time of follow-up or quality of study.

Table 2.5 Prevalence of anxiety, depression, other outcomes
(arranged in order of quality score)

Author	**N**	**F.U.**	**Anxiety** (measure)	**Depression** (measure)	**Cognitive**	**Other psychological phenomena**	**Quality score (max 6)**
Weinert & Meller, 2006	153	2m		32% depression SCID			6
Samuelson 2007	226	2m	**4.9%** probable HADS	**7.5%** probable HADS		**69%** ICU memories	6
Chelluri et al. 2004*	231	1y		**32%**≥16(**high**) CES-D			5
Eddleston et al.2000	143	3m	**4.9%** possible **7%** probable HADS	**7%** poss **2.8%** prob HADS		**27%** flashbacks **33%** memory lapses **44%** sleep	5
Jones et al. 2007	238	3m				**57%** delusional memories	5
Chelluri et al. 2002*	232	2m		**35%**≥16(**high**) CES-D			4
Rattray 2005	87	6m 12 m	6m **19%** poss **22%** prob 12m**27%**poss **18%** prob HADS	6m **19%** poss **7%** prob 12m **17%** poss **17%** prob HADS			4
Boyle et al. 2004	53	1m 3m		1m **19.22(**high) 3m **13.79** mild CES-D		**70%** unpleasant ICU memories	3
Griffiths et al. 2006	108	6 or 12 m				Sexual problems **44%**	3
Jackson et al. 2003	34	6m		**36%** depressed (impaired) **17%** (non-impaired) GDS	**32%** impaired		3
Scragg et al. 2001	80	3-21 m	**43%** (poss) HADS	**30%** (poss) HADS			3
Sukanta-rat 2005	45	3m			**35%** impaired		3
Sukanta-rat 2007	45	3m 9m	3m **24%** 9m **24%** HADS	3m: **35%** 9m**: 47%** HADS			2
Jones et al. 2003	44 Cs	6m	**34%** (poss) HADS	**12%**(poss) HADS			1
Jones et al. 2001	30	2m				**73%** delusional memories	0

* same study population FU= follow-up

2.3.5(iii) Cognitive impairment

Only two fully reported studies were found of cognitive outcomes in former general ICU patients. Both were rated as medium quality in the quality assessment and both were based on small samples (n=34 and n=45). Using a battery of neuropsychological tests, Jackson et al. (2003) found that 32% of patients were cognitively impaired at six months in the domains of psychomotor speed, visual and working memory, verbal fluency and visuo-construction. Sukantarat (2005) found that three months after ICU 35% of patients scored at or below the level of the lowest 5% of the normal population on tests of executive function and fluid

intelligence; By nine months, only 4% were impaired to this extent, but cognitive performance remained below population norms.

2.3.5(iv) Other psychological symptoms

Studies also reported the presence of a number of other troubling psycho-social symptoms affecting former ICU patients at high levels during their first year of recovery, including sexual dysfunction (44%, n=1), unpleasant or "delusional" memories (57-73%, n=4), flashbacks (27%, n=1), memory lapses (33%, n=1), and sleep problems (44%, n=1).

2.3.6 Results: HRQL

As well as studies of psychological morbidity, the review included 28 papers that were identified as using a validated HRQL measure with intensive care survivors. One of these (Sukantarat 2005) was also included in the previous section on psychological morbidity as its outcomes were cognitive impairment and HRQL.

2.3.6(i) Characteristics of HRQL studies

Of the 28 identified studies, 18 were prospective, 9 retrospective cohorts and one was cross-sectional (see table 2.6). Five studies were carried out in the UK, three in the USA, two in Australia and one in Hong Kong. The other 17 took place in European countries including Sweden, Norway, Germany, Finland, France, Spain, Switzerland, Belgium, Portugal, Slovenia and Holland. Patients were recruited from general ICUs (n=23), medical ICUs (n=4), surgical ICUs (n=2) and medical-surgical ICUs (n=2). A total of 7924 patients were followed up from a baseline sample of 13035. From this it can be calculated that 60.79% of the total number of baseline participants from all studies were followed up. Follow-up rates within individual studies ranged from 28% - 95%. The average age of cohorts ranged from 33-65 years. Gender composition of studies was between 44%-73% male. Several disease severity scoring systems – Apache II (Knaus et al., 1981), SOFA (Vincent et al., 1996) and SAPS II (Le Gall et al., 1993) - were used so illness results are not easily comparable. The range of mean illness severity scores, according to studies that used the Apache II system, was 9.7 - 23.4, suggesting important differences in health status between cohorts. Length of stay in the ICU varied from 2 days (median) to 16.9 days (median). Exclusion factors from study cohorts included neurological, spinal, terminal, burns, tracheostomy, elective surgery, comatose or delirious, obviously brain injured, and non-coronary patients.

Table 2.6 Characteristics of studies of HRQL in former ICU patients

Author year	N at F.U.	Design	Type ICU Inclusion	Exclusion	Out-come	Age	Sex % M	LoS in ICU	Apache II/ other
Badia et al. (2001)	334	Prospective	General Spain		EQ-5D 12m	57	64	5	28 SAPS2
Bell&Turpin (1994)	60	Prospective	General UK	Transfers other unit	NHP 3m	54	51	3	12
Boyle et al. (2004)	53	Prospective	General Australia (>48h)	Neuro , spinal	SF-36 1m/6m	59	63	7	16
Chelluri et al. (2002) *	232	Prospective	General US (MV)	Trans-plants	SF-36 2m	60	54	11	68. Ap-ache 3
Chelluri et al. (2004)*	231	Prospective	General US (MV)	Trans-plants	SF-36 12m	60	54	11	68 A.3
Cuthbertson et .(2005)	201	Prospective	General UK	Terminal	SF-36 6m	61	59	7	18
Eddleston et al. (2000)	136	Prospective	General UK		SF-36 3m	49	53	4	19
Flaatten & Kvale(2001)	51	Retros-pective	General Norway	Burns	SF-36 13y	33		5	19 SAPS2
Fok et al. (2005	88	Cross-sectional	General HK	Tracheo-stomies	SF-36 4w	60	70	4	
Frick et al. (2002)	85	Retros-pective	General Swiss		SIP 6m	65		2	22 SAPS
Garcia-Lizana (2003)	96	Prospective	General Belgium	Elective surgery	EQ-5D 18m	60	61	3	3 SOFA
Gardner (2005)	51	Prospective	General Australia		SIP 6m	55.4	66	4	11
Graf et al. (2003)	153	Prospective	Medical Germany	Coma delirious	SF-36 9m	64	73	3	26 SAPS2
Granja et al. (2002)	275	Prospective	Med-surg Portugal		EQ-5D 6m	57	57	2	13
Granja et al. (2005)	464	Retros-pective	10 gen Portugal		EQ-5D 6m	58	61	4	31 SAPS2
Hurel (1997)	223	Prospective	4 general France		NHP 6m	52	56	8	12 SAPS2
Jagodic et al. (2006)	39	Prospective	Surgical Slovenia		EQ-5D 2y	45	64	11	11
Kaarlola et al. (2003)**	169	Prospective	Med-sur Finland		Rand36 1y 6y	58	65		
Kvale et al. (2003)	210 ?	Retrospec-tive	General Norway		SF-36 6m	51	?	5	38 SAPS2
Lipsett et al.(2000)	47	Prospective	Surgical US(>6d)		SIP1,3, 6,9 m	57		11	24
Niskanen (1999)	368	Retros-pective	Gen.Fin-land >4d		NHP 6 m	56	66	13	12
Orwelius (2005)	343	Retrospec-tive	2 general Sweden		SF-36 6m	57		4	16
Pettila et al.(2000)**	299	Retrospec-tive	Medsurg Finland		Rand at 12m	53		5	13
Ridley et al. (1997)	95	Prospective	General UK		SF-36 at 6 m				
Stricker et al. (2005)	150	Retrospec-tive	General Swiss	Major burns	SF-36 at 1y	59 L 67S		15L 2S	36L34S SAPS2
Sukantarat (2005)	45	prospective	General UK>72 h	Brain injury	SF-36 3m 9m	58	44	17	15
Tian (1995)	3655	Prospective	36 ICUs Holland		SIP 6m	60		3	10
Wehler et al. (2003)	171	Prospective	Medical Germany	Non-coronary	SF-36 6m	57		11	18

* or **same cohort LS/SS = long/short stay. Age, Los in ICU and Apache II or similar: means or medians, as reported in study. If cells empty, results were not reported in study. SOFA= Sepsis-related Organ Failure Assessment (Vincent & Moreno, 1996) SAPS II = simplified acute physiology score (Le Gall et al., 1993)

Four HRQL measures were used in the 28 papers; the SF-36 (Ware, Jr. & Sherbourne, 1992), the EQ-5D (Brooks et al., 2003), the Nottingham Health Profile (Hunt et al., 1980) and the Sickness Impact Profile (Gilson et al., 1975). The Rand-36, used in two studies, is the same as the SF-36.

Table 2.7 Quality assessment of HRQL studies

Author year	N*	F.U. rate %	Represe-ntative sample?	Sample size**	Outcome Assess-ment	Analysis of association	Rating: Prevalence (max=6)	Rating: Association (max=2)
Badia 2001	334	89	adequate	good	good	good	5	2
Bell & Turpin 1994	60	63	adequate	adeq-uate	adequate	n/a	3	n/a
Boyle et al. 2004	53	54	adequate	poor	good	adequate	3	1
Chelluri et al. 2002	232	28	Good	good	adequate	n/a	5	n/a
Chelluri et al.2004	231	28	good	good	good	n/a	6	n/a
Cuthbertson et al. 2005	201	67	adequate	good	good	n/a	5	1
Eddleston et al. 2000	143	95	good	adeq-uate	good	n/a	5	n/a
Flaatten & Kvale 2001	51	58	adequate	poor	good	n/a	3	n/a
Fok et al. 2005	88	93	adequate	adeq-uate	adequate	n/a	3	n/a
Frick et al. 2002	85	85	adequate	adeq-uate	good	n/a	4	n/a
Garcia-Lizana 2003	96	66	good	adeq-uate	good	Adequate	5	1
Gardner 2002	51	55	good	poor	good	adequate	4	1
Graf et al. 2003	153	62	good	good	good	adequate	6	1
Granja et al. 2002	275	77	good	good	good	adequate	6	1
Granja et al. 2005	464	51	good	good	good	adequate	6	1
Hurel 1997	223	68	adequate	good	good	n/a	5	n/a
Jagodic et al. 2006	39 (?)	50	good	poor	good	n/a	4	1
Kaarlola et al. 2003	169	58	good	good	good	n/a	6	n/a
Kvale et al. 2003	210	61	adequate	good	good	n/a	5	n/a
Lipsett et al. 2000	47	81	good	poor	good	n/a	4	1
Niskanen 1999	368	78	good	good	good	n/a	6	2
Orwelius 2005	343	61	good	good	good	good	6	2
Pettila et al. 2000	299	85	good	good	good	good	6	2
Ridley et al. 1997	95	57	adequate	adequa te	good	adequate	4	1
Stricker et al. 2005	150	63	good	good	good	n/a	6	2
Sukantarat 2005	45	88	adequate	poor	good	adequate	3	1
Tian 1995	365 5	59	good	good	good	adequate	6	2
Wehler et al. 2003	171	54	adequate	good	good	n/a	5	0

* N at follow-up **Sample size ratings - **poor**: 30-59 **adequate**: 60-150 **good**: >150

2.3.6(ii) Quality Assessment of HRQL studies

Using the same criteria to assess the risk of bias as described in section 2.2.3, 18 out of 28 studies measuring the quality of life of ICU survivors were found to be high-quality with regard to prevalence. A detailed break-down of the quality assessment can be found in Table 2.7.

2.3.7 Meta-analysis: SF-36 studies

Most of the 16 studies that used the SF-36 (Ware Jr. & Sherbourne 1992) reported results in the form of means of the eight SF-36 domains. The results of the eight domains cannot be aggregated to give one HRQL score. Scores can be calculated for two overall measures, physical and mental component scores (PCS and MCS), but most studies in the review did not report these. I decided to conduct meta-analyses to obtain pooled effect sizes for three domains of the SF-36. These were physical functioning (PF, which correlates highly with the PCS), mental health (MH, which correlates highly with the MCS) and general health perception (GH). When a meta-analysis was conducted under the random effects model for physical functioning (PF), the pooled ES was **58.83 (95% CIs: 56.23-61.42)**. I^2 was 54.7%. When a meta-analysis was conducted under the random effects model for mental health (MH), the pooled Effect Size was **65.75 (95% CIs: 64.20-67.29)**. I^2 was 15.4%. Finally a random-effects meta-analysis was performed for General Health Perception (GH). The pooled effect size was **48.20 (95% CIs: 46.45-49.94)**, and I^2 was 0%.

I^2 represents the variation in effect size attributable to between-study heterogeneity (characteristics of sample or design that vary between studies) rather than within-study variability (due to sampling error). Heterogeneity was much higher for physical functioning (I^2=54%) than for the other two domains. The results of the meta-analysis, with pooled effect sizes of 58.83 for PF, 65.75 for MH, and 48.20 for GH, demonstrate that the HRQL of ICU survivors in important SF-36 domains was much lower than general population norms. Although norms vary from country to country, between men and women and age-groups, the best-validated UK norms are 79.4 for PF, 75.9 for MH, and 68.4 for GH (Jenkinson et al., 1996). PF and GH were around 20 points and MH 10 points lower in ICU survivors than the general population.

Other trends in SF-36 scores can be observed in table 2.8. HRQL was very poor one month after leaving ICU but gradually improved over the months and years. However after a year HRQL was still impaired compared to the general population. In two studies that followed patients up after six and 13 years, there were still deficits in comparison with reference populations. It can be seen that HRQL did not

Table 2.8 Results of three SF-36 domains, in order of time of follow-up

0= worst possible health, 100 = best possible health

Author	N at FU	Result reported	Time of FU	Mental Health	Physical Function	General Health Perception	Quality Rating Max 6	Overview
Fok et al. 2005	88	SF-36 means	1m	43.7 (27.6)	53.5 (29)	43.1 (6.1)	3	Scores very low especially MH, GH
Graf et al. 2003	164	SF-36 means	1m	64.6 (22.3)	50.3 (28.9)	48.5 (18.3)	6	Low scores, esp. PF, GH
Cuthbertson et al. 2005	233	SF-36 means	3m	75.5 (20.1)	59.4 (24.1)	58.0 (23.7)	5	PF and GH below norm; MH near norm
Sukantarat 2005	51	SF-36 means	3m	63.8 (19.9)	52 (29.9)	51.8 (22.2)	3	Impaired in all domains
Boyle et al. 2004	53	SF-36 means	6m	68.9 (21.3)	52.5 (31.0)	48.0 (25.1)	3	5/8 domains improved from 1m to 6m; still below normal
Cuthbertson et al. 2005	201	SF-36 means	6 m	76.8 (19.7)	61.7 (28.7)	58.7 (25.4)	5	Little improve-ment since 3m – same pattern
Orwellius 2005	270	SF-36 means	6m	66	61.5:	55	6	Large differences in all domains
Ridley et al. 1997	95	SF -36 means	6m	62	62	61	4	Improvements in 4 domains from pre-ICU
Kvale et al. 2003	210	SF-36 domains	6m	Not well reported			5	Significantly lower than gen. population
Eddleston et al. 2000	136	SF-36 means	3m	No overall results reported	No overall results	No overall results	5	Scores in all except MH much lower than gen. pop.
Graf et al. 2003	207	SF-36 means	9m	65.7 (20.9)	55.6 (28.4)	48.0 (18.7)	6	Below norms at 9 months
Sukantarat 2005	45	SF-36 means	9m	63.1 (23.6)	57.5 (29.2)	54.4 (15.7)	3	Improvement from 3m but still well below gen. pop.
Cuthbertson 2005	173	SF-36 means	12 m	76.4 (20.1)	61.9 (31.7)	59.9 (24.9)	5	Little change since 3 months
Pettila 2000	299	RAND36 means	12m	67.3 (26.2)	61.9 (32,7)	47.7 (24.9)	6	All domains well below general population
Stricker 2005	150	SF-36 medians	1 year	L*: 76(76) S*: 80(79)	L: 65 (79) S: 80(79)	L: 62(60) S: 67(62)		No significant difference re LoS. Both less than population norms
Kaarlola 2003	169	RAND36 medians	6 y	80 (60-88.5)	70 (41.3-90)	50 (33.1-70)	6	Since 1y, marked improvement in MH, not in GH
Flaatten 2001	51	SF-36 means	13y	71.9	75.3	57.7	3	QoL significantly less than ref.pop.

*L Long stay, S short stay FU= follow up

improve evenly across domains. Mental health improved more than physical functioning and general health perception but was well below population levels in most studies. Physical functioning was much lower than population levels. The worst domain of the three was general health perception which stayed at very low levels even after several years.

2.3.8 Studies using other HRQL measures

The Euroqol or EQ-5D (Brooks et al., 2003) is a health outcome measure that expresses results as no problems, moderate problems or extreme problems in five domains. All five studies that used the EQ-5D reported the percent of patients with problems (moderate or extreme) in each of the domains. It can be seen in summary table 2.10 that the proportions of patients with problems in all domains were very high, with up to a half of patients impaired in Usual Activities, Pain and Discomfort and Anxiety/Depression. Follow-up times ranged from 6 months to 2 years. These studies were generally of high quality (see table 2.9).

Table 2.9 Studies measuring QoL with the EQ-5D
(% with moderate and extreme problems in 5 dimensions)

Author	Tool	Time of FU	Mobility	Self-Care	Usual Activities	Pain / Discomfort	Anxiety Depression	Qual score
Badia 2001	EQ-5D	12m	31%	23%	52%	47%	34%	5
Garcia-Lizana 2003	EQ-5D	18m	33%	22%	48%	63%	47%	5
Granja et al. 2002	EQ-5D	6m	37%	22%	46%	45%	54%	6
Granja et al. 2005	EQ-5D	6m	46%	33%	64%	60%	55%	6
Jagodic et al. 2006	EQ-5D	2y	56%	26%	60%	56%	40% sepsis 70%trauma	4

Table 2.10 Summary of EQ-5D results

Domain of EQ-5D	% with problems (moderate and extreme)
Mobility	31%-56%
Self-care	22%-33%
Usual activities	46%-64%
Pain	45%-63%
Anxiety/Depression	34%-55%

Few studies used the NHP (Hunt et al., 1980) or the SIP (Gilson et al, 1975) so only a short summary is given. Studies using the NHP showed severe impairment in most domains at 3-6 months, particularly Energy, Sleep and Emotion. SIP studies suggested that there was significant impairment in physical and psychological domains at three months, and moderate disability in both at six months. By 11 months there were improvements in both domains but HRQL was still not within the normal, healthy range.

Table 2.11 Studies measuring HRQL with the Nottingham Health Profile

(NB: 0= no handicap. 100= max handicap)

Author	N	Time of FU	Scores	Comparison w. population	Over-view	Quality score
Hurel 1997	223	6 months	Energy 47.8 emotion 28.9 sleep 35	Much lower scores than French population	Mean scores show severe handicap in most dimensions.	5
Niskanen 1999	368	6 months	Only given for disease/age sub-groups		Most limitations in trauma or respiratory failure patients	6
Bell & Turpin 1994	60	3 months	Energy 34 pain 13 emotion 18 sleep 22 social 9 physical 18		Worst scores for energy and sleep	3

Table 2.12 Studies measuring HRQL with the Sickness Impact Profile

(0-5: normal, healthy, 5-15 moderate disability, >15 significant impairment)

Author	N	Time of FU	Scores	Subscores	Over-view	Quality score
Frick et al. 2002	85	6 m	7.3	Physical: 6.2 Psychosocial: 6.1	57% normal 27% moderate 16% severe	4
Gardner 2002	51	6m	13.07	Physical 10.7 Psychosocial 12.5	33% normal. Problems: sleep, leisure, emotion	4
Lipsett et al. 2000	47	3m 1y	36.2(3m) 11 (1y)	Physical 33 Psychosocial 21 Physical 8 Psychosocial 5	Severe at 3m Moderate disability at one year	4
Tian 1995	3655	6m	8.5 (9.5)	6.9 (11.1) 7.1 ((10.6)	Moderate disability	6

2.3.9 Results: predictors of psycho-social outcomes of ICU

One of the aims of this systematic review was to identify a consistent set of predictors of psychological morbidity or HRQL. However the quality assessment scores for analysis of association showed that quality for this aspect was not very high (see table 2.13). Although studies collected a great deal of data on patients, many studies did not attempt to identify predictors, or reported only statistically significant results regarding one or two predictors. It was unclear how many tests had been performed regarding risk factors in most studies. Questions about predicted associations were not well-defined. When associations were reported, they were usually in the form of p-values only, as effect sizes, confidence intervals or standard errors were rarely presented.

Table 2.13 Quality Assessment: analysis of association in studies.

Analysis of Association	High Quality(2)	Medium Quality(1)	Low Quality(0)	No results reported
Psychological morbidity	2	7	7	1
Quality of Life (HRQL)	6	12	1	9

Therefore all that can be documented in tables 2.14 and 2.15 is whether studies found an association with a given factor – yes or no. The summary table 2.16 shows how consistently those associations were found or not found across studies. Looking first at studies of psychological morbidity (PTSD, anxiety, depression, cognitive impairment), age, gender and psychological history were *inconsistently* found to be risk factors. Illness severity score and length of stay were consistently found **not** to be risk factors. Clinical factors were found to be risk factors in five studies and not to be risk factors in five studies. Examining clinical factors more closely, days of mechanical ventilation was mainly found not to be a risk factor; while sedation practice was an inconsistent risk factor. Other factors of interest such as the use of physical restraint or mode of admission to the ICU were only tested in single studies.

The most consistent category of predictors of psychological morbidity was psycho-social factors, mainly ICU psychological factors. The most consistent psychological predictor, found in four out of five studies, was "unpleasant memories of the ICU" such as traumatic or delusional memories. Another predictor (found in three studies) was "recalled mood in the ICU" – including moods such as fear, depression or agitation. Delirium was found not to be a predictor in the two studies that tested it.

Predictors that were consistently identified in the HRQL studies were age, illness severity (Apache II score; Knaus et al., 1981) or presence of multiple organ dysfunction (MOD)) and prior health. Sex was not found to be a predictor of QoL. Length of stay in the ICU and diagnostic groups were inconsistent predictors. Diagnostic groups that seemed more at risk of poor HRQL were trauma, non-scheduled surgery and respiratory patients. Two psycho-social factors, education and memories of ICU, were found to be predictors of HRQL, but were tested in single studies only.

Table 2.14 Risk factors for psychological morbidity

(yes = association reported, no = no association reported)

Author **(outcome)**	**Age**	**Sex**	**Illness severity in ICU**	**Psycho-logical history**	**Clinical/ health factors**	**Psycho-logical factors**	**Diag-nosis**	**LoS**	**Qual-ity Score**
Cuthbertson et al. 2004 **(PTSD)**	Yes	No	No	Yes	Yes **Days MV**		No	No	0
Girard et al. 2007 **(PTSD)**	Yes	Yes	No		Yes **Lorazepam** No **other sedatives** No **MV**	Yes **Traumatic Memories** No **Delirium**		No	2
Jones et al. 2007 **(PTSD)**				Yes	Yes **Sedation opiates** Yes **Physical restraint**	Yes **Delusional memories (DMs)**	No		2
Nickel et al. 2004 **(PTSD)**			No	No					1
Richter et al. 2006 **(PTSD)**	No		No	No	No **Duration of MV** No **sedation**		No	No	0
Samuelson 2007 **(PTSD)**		Yes			Yes **Midazolam**	Yes **ICU Fear Agitation ICU Stress**			1
Jones et al. 2001(**PTSD)**				No		Yes **DMs**	No		0
Jones et al. 2003(**PTSD)**						Yes- **DMs**			0
Perrins 1998 **(PTSD)**					Yes - **Admission mode**	No **ICU Memories**	Yes		0
Rattray 2005 **(P/A/D)**	Yes					Yes **Recall Fear satisfaction**		Yes	1
Sukantarat 2007 **(P/A/D)**	No		No						0
Scragg et al. 2001 **(P/A/D)**	Yes	No						No	1
Weinert & Meller 2006 **Depression**				Yes	Yes **pre-ICU physical HRQL**				1
Jackson 03 **(Cognitive deficits)**	No	No	No.		No **Days MV**	Yes **ICU Depression** No **Delirium** Yes **Education**	No	No	1
Sukantarat 2005 **(Cognitive deficits)**			No					No	1

MV = mechanical ventilation DM = delusional memories P/A/D= PTSD, anxiety, depression

Table 2.15 Factors associated with any aspects or domains of HRQL

Author	**Age**	**Sex**	**Apache II** (or MOD)	**Prior health**	**LoS**	**Diagnosis (worse group)**	**Others**	**Qual-ity score**
Badia et al. 2001						Yes **Trauma vs surgical or medical**		2
Bell & Turpin 1994		No						1
Boyle et al. 2004	Yes							1
Cuthbertson 2005	No		No	Yes **chronic health**	No	No **Type of admission**		1
Garcia-Lizana 2003	Yes	Yes	Yes		Yes	Yes **Multiple trauma Nonscheduled surgery**		1
Gardner 2002			YES					1
Graf et al. 2003	Yes		No					1
Granja et al. 2002	Yes		Yes	Yes **previous health**			Yes **education**	1
Granja et al. 2005	Yes		Yes		Yes	Yes	Yes **memories**	1
Jagodic et al. 2006						No **Trauma or sepsis**		1
Lipsett et al. 2000						No		1
Niskanen 1999	Yes					Yes **Trauma respiratory**		2
Orwellius 2005	No	No	No	Yes	No			2
Pettila et al. 2000	Yes	No	Yes **(MOD vs non-MOD)**		Yes	Yes		2
Ridley et al. 1997			Yes	Yes (chronic v acute)	Yes			1
Stricker et al. 2005					Yes			2
Tian 1995			No		No			2
Wehler et al. 2003			Yes **(MOD vs non-MOD)**			Yes **Acute renal or respiratory failure**		0

MOD=multiple organ dysfunction

Table 2.16 Summary table of predictors of psychosocial outcomes

Factors Outcome	**Age**	**Sex**	**Psychol-ogical history**	**Diagnosis In ICU**	**Illness Severity**	**Days In ICU**	**Clinical Factors**	**Psycho-social**	**Prior health**
Psychological morbidity	✓ (4) × (3)	✓ (2) × (3)	✓ (3) × (3)	✓ (1) × (5)	✓ (0) × (7)	✓ (1) × (6)	✓ (5) × (5)	✓ (9) × (4)	✓ (1)
Quality of Life	✓ (7) × (2)	✓ (1) × (3)	no data	✓ (5) × (3)	✓ (7) × (4)	✓ (5) × (3)	no data	✓ (2)	✓ (4)

✓ = significant effect found for factor (x) number of times
× = no significant effect found for factor (x) number of times

2.3.9(i) Summary of risk factors

The only consistently found risk factors for psychological morbidity after the ICU were psychological symptoms - **unpleasant memories of the ICU** (traumatic or delusional) and **mood** in the ICU. Consistent risk factors for HRQL post-ICU were socio-demographic and clinical factors - **age, illness severity** and **prior illness**. These results help to suggest areas for future investigation but overall this review demonstrates a lack of systematic investigation of predictors of psycho-social outcomes after intensive care.

2.4 Discussion

Using explicit and systematic strategies to identify observational studies of psycho-social outcomes of ICU patients, I retrieved 18 studies of psychological morbidity and 28 studies of HRQL that matched my criteria.

2.4.1 Prevalence of psychological morbidity

Due to the heterogeneity of both methods (measures, interpretation and follow-up times) and results of studies of psychological morbidity after ICU, it did not make sense to aggregate results in a meta-analysis. Therefore I examined ranges of estimates and identified reasons for variation in results, using quality criteria. Based on a small number of high quality studies, the best estimate of PTSD prevalence possible is that up to 22% of former ICU patients have high levels of PTSD symptoms. Approximately half of these patients would have symptoms meriting a full diagnosis of PTSD. Rates of probable depression in ICU survivors in high quality studies range from 2.8% to 32%. Rates of probable anxiety in ICU patients are 4.9 to 34%. Additionally two small studies found that 32-35% of former ICU patients had cognitive impairments at three to six months.

These results contrast with two previous systematic reviews which presented PTSD estimates of 0-64% (Griffiths et al. 2007) and 5-63% (Jackson et al. 2007). This review's results are closer to the point prevalence rates of 19% for clinician-diagnosed PTSD and 22% for PTSD symptoms calculated by Davydow et al. (2008). The 19% rate for diagnosable PTSD is higher than my estimate of 9-12%, possibly because the review by Davydow et al. (2008) included studies of a sub-group of patients with sepsis, who may have a higher rate of PTSD. Davydow et al. (2009) found that the prevalence of depression was 28% (by questionnaire) and 33% (by clinician diagnosis), rates that were similar to the upper end of prevalence estimates in my review. However I concluded that there is not yet sufficient good-quality evidence to definitively establish the prevalence of PTSD and other types of psychological morbidity (including cognitive impairment) after intensive care.

2.4.2 Estimates of HRQL

Of the 28 HRQL studies reviewed, 18 were of high quality by this review's criteria. Four different HRQL instruments were used and results were reported in inconsistent ways. Nevertheless, in common with the findings by Dowdy et al. (2005), a clear pattern emerged that former ICU patients had much poorer quality of life in physical and mental health domains than the general population at all time points covered (from one month to thirteen years in my review). However unlike Dowdy et al. (2005), my review was able to quantify some of the effects. It is the first review in which a meta-analysis of HRQL based on mean SF-36 scores of former ICU patients (between three months and one year) has been carried out. Effect sizes found were 58.83 for Physical Functioning, 65.75 for Mental Health, and 48.20 for General Health Perception. These totals out of 100 are low compared to the UK population norms of 79.4 for Physical Function, 75.9 for Mental Health, and 68.4 for General Health (Jenkinson et al. 1996).

It is unfortunate that there were no pre-ICU HRQL levels to compare these scores to, but this is a common problem in psychological research on intensive care as most ICU stays are unplanned. However the results of the meta-analysis suggest that there is a greater deficit in physical functioning (PF) and general health perception (GH) than in mental health (MH). Several studies found that GH scores were particularly low (Cuthbertson et al. 2005; Fok et al. 2005) and that it improved less than PF and MH over time (Kaarlola et al., 2003). A study by Flaatten et al. (2001) that took place 13 years after intensive care found near-normal levels of MH at 72 and PF at 75, but GH was very low at 57.7. It is possible that the shock of undergoing life-threatening illness changes patients' perception of their health in a profound way, so that they come to think of themselves as unhealthy even when their physical and mental health has improved. This could have detrimental effects on their chances of making a full recovery, as it is known that beliefs about health and illness can have effects on a range of outcomes and recovery (Weinman & Petrie, 1997).

2.4.3 Risk factors for psychological morbidity and HRQL

Some of the studies investigated potential risk factors of post-ICU psychological morbidity or HRQL. However in most of these studies, results were not well or consistently presented. The only risk factors that were consistently found for psychological morbidity after the ICU were psychological symptoms such as **unpleasant memories of the ICU** (traumatic or delusional) and **mood in the ICU**. No socio-demographic or clinical factors consistently predicted psychological morbidity in the studies in my review. The reviews by Jackson et al. (2007) and Davydow et al. (2008) reported the same finding that memories of the ICU was a

consistent risk factor, but they also found socio-demographic predictors (younger age, female gender) and clinical factors. However one review found that LoS in the ICU and mechanical ventilation were risk factors (Jackson et al., 2007) the other found that they were not (Davydow et al., 2008). Both reviews concluded that sedation practice was a risk factor. Consistent risk factors for HRQL after the ICU from my review were socio-demographic and clinical factors such as **age, illness severity score** and **prior illness**. Dowdy et al. (2005) also found that older age and severity of illness were predictors of worse HRQL.

From this review it can be concluded that there may be psychological, clinical and socio-demographic risk factors for adverse psycho-social outcomes after the ICU but they have not yet been clearly identified. In chapter three I will report on a further literature review about ICU stress and the experiences of intensive care patients that I carried out after completing the systematic review. I did so in order to deepen and widen my thinking about possible causal risk factors for severe psychological distress after intensive care that I could test in a prospective study.

2.4.4 Strengths of systematic review

In conducting this review I adhered to recent recommendations (Moher et al., 1999; Moher et al., 2009) for carrying out systematic reviews by working from a protocol, and using systematic and explicit methods to identify, select and critically appraise studies. The risk of bias in studies was assessed, including the quality of outcome assessment. The review should be useful to clinicians in mixed, general ICUs because it includes studies of all known psycho-social outcomes after ICU and a comprehensive assessment of risk factors. No studies of diagnostic or demographic sub-groups of ICU patients were included, and therefore estimates of prevalence have not been inflated by patient groups with exceptionally high rates and should be applicable to mixed general ICU patients.

2.4.5 Limitations of systematic review

Although the exclusion of studies of patient sub-groups improved the generalisability of the review, it meant that much of the evidence accrued and frequently referenced in discussions of psychological morbidity in ICU patients could not be weighed to produce this overview. However, the review did include eight studies of mechanically ventilated ICU patients and these could be said to form a sub-group of ICU patients who potentially have higher prevalence rates of psychological morbidity or poorer quality of life. However I decided to include them on the basis that the majority of level 3 intensive care patients, including patients with mixed diagnoses, receive mechanical ventilation. Additionally a small number

of studies took place not in general ICUs but in medical or surgical ICUs. Although samples from these ICUs were not completely representative of all ICU patients, it was decided to include them because patients had mixed diagnoses and body systems involved and received a range of ICU interventions.

Another weakness of the review was that no statistical aggregation of most of the results was possible due to the heterogeneity of studies. Conclusions about prevalence of psychological morbidity were based on just three high quality studies of general ICU patients. While it was possible to carry out a meta-analysis of SF-36 results, it was also based on a small number of studies (n=6), after repeats and outliers were excluded. In addition to the SF-36, the review included HRQL studies using three other measures, all with different domains, making results difficult to compare.

Studies were carried out in many different countries (15 in the UK, six in the US, two in Australia, one in Hong Kong and 22 in 12 different European countries). Intensive care units are run, funded and organised in different ways, creating another source of variation that is hard to measure and control for. Studies were also carried out at different time-points after the patients' stay in the ICU – ranging from one month to thirteen years. Clearly it would be surprising if these outcomes were not influenced by the effect of time. However the majority of studies took place from three to six months after intensive care, so the results are probably most generalisable to patients at about three to six months after discharge from an ICU.

Finally I was unable to achieve an important aim of the review, to provide an adequate synthesis of information about predictors of post-ICU psychological morbidity. This was not possible because risk factors were inadequately tested and reported in many of the studies included in the reviews.

2.4.5 Clinical implications of the review

A NICE guideline applying to England, Wales and Northern Ireland (Tan et al. 2009) has stipulated that all intensive care patients should be assessed for psychological morbidity and if necessary offered rehabilitation both in and after the hospital stay. This review helps to clarify the type and prevalence of psycho-social outcomes that may be expected in former ICU patients and some of the possible risk factors for patients who may experience these outcomes. It could therefore help ICU clinicians to be aware of potential problems and plan assessment and rehabilitation services.

2.4.6 Research implications of review

Studies carried out in this area have been compromised by problems such as very small samples, inadequate outcome assessment, a lack of testable hypotheses and failure to control for confounding variables. Therefore studies with larger numbers and clear hypotheses about associations between risk factor and outcome need to be carried out. In this way more accurate prevalence rates could be established, and consistent risk factors could be identified. Previous studies have emphasised PTSD while paying little attention to other psychological outcomes such as anxiety, depression and cognitive impairment. Future studies should assess all likely psychological and cognitive outcomes and not focus solely on PTSD.

After carrying out this review, I decided that the main study for my PhD should be a prospective cohort study with a well-defined representative sample of level 3 ICU patients in order to measure the range and extent of psychological outcomes of intensive care, and to identify the strongest clinical, psychological and socio-demographic risk factors. I also believed this would help to inform future interventions to target those ICU patients most at risk of future psychological morbidity and give appropriate preventative or treatment support. Such interventions should also be evaluated in future research. As ICU memory was the most commonly identified risk factor for future psychological morbidity, but has remained a vague concept in research to date, I also decided to carry out a qualitative study to examine the nature and content of patients' memories after intensive care.

Chapter 3 Literature review: risk factors for adverse psycho-social outcomes of intensive care

3.1 Introduction

As the systematic review showed that little was known about risk factors for psychological morbidity and poor HRQL after intensive care, I decided to carry out a further literature review to identify potential predictors. This review covered qualitative and quantitative literature on patients' experiences of intensive care; accounts of stress and psychological distress in intensive care; and investigations of risk factors for delirium in intensive care. Although ICU delirium has not been decisively linked to post-ICU psychological morbidity, it will be seen that both may be triggered by similar alterations in processes in the brain.

Many factors (related to illness, treatment, socio-economic circumstances, psychological reactions, chronic health and patient vulnerability) were highlighted as potentially relevant to post ICU psychological distress in this literature review. To introduce some structure into a long list, I have tried to group variables in terms of stress processes. Although the studies of psycho-social outcomes of intensive care reviewed in chapter two did not refer to stress theories, the assumption that seemed to underlie the studies was that intensive care was a traumatic stressor or series of stressors that might lead to adverse psycho-social outcomes in the future. It seems reasonable to examine this implicit assumption by considering the relationships between potential risk factors of post-ICU psychological morbidity in terms of an ICU stress process.

A huge body of psychological research has explored the relationship between stress, health and illness (e.g. Kiecolt-Glaser et al., 2002). Psychological stress theories have borrowed the concepts of "stress" (an external force applied to a system) and "strain" (the resulting change in the system) from physics. Stress models usually include *stressors*, external or internal factors that put pressure on people; *stress responses,* the emotional, behavioural, cognitive or physiological reactions elicited by the stressors; and *stress outcomes* (or chronic strain), the negative impact of the stress process on people, usually in the form of mental or physical disorders (Steptoe & Ayers, 2004). In this chapter I have categorised some ICU factors as potential *stressors (*critical care illness, ICU interventions, ICU environment); some as *ICU stress responses* (emotional and cognitive reactions); and some as *background or vulnerability factors (*socio-demographic factors such as age, gender and SEC, and chronic factors such as prior physical or psychological

health). All may be related to the *stress outcomes* of ICU such as depression, anxiety and PTSD that were discussed in chapter one.

Finally I have depicted all the factors within an informal ICU stress model, (see figure 3.1 at the end of this chapter). This model should help to explore whether the acute stress of being a patient in intensive care may lead to outcomes such as depression and PTSD in the longer term, and whether intervening factors alter the relationship.

3.2 Stress in the ICU

Reports of extreme psychological reactions in intensive care patients began soon after the first units were set up nearly 50 years ago. Kornfeld (1969) described confused, agitated patients who would pull out catheters and drains, and whose high anxiety compromised their cardiovascular status and increased the risk to their life. Tomlin (1977) observed that beyond psychological distress known to be associated with severe illness, there were specific psychological problems related to being in intensive care; these included the apathetic depression of the prolonged stay patient and the extreme terror of ventilated patients who had to be "weaned" off the machines that helped them to breathe.

Qualitative studies appeared in the nursing literature in which former ICU patients retrospectively described their psychological state. They recalled extreme anxiety, panic, depression, withdrawal, confusion, agitation, hallucinations, and delusions (Bergbom-Engberg & Haljamae, 1989; Granberg et al., 1998). This constellation of symptoms was labelled intensive care syndrome (Kleck, 1984) or, more controversially, ICU psychosis (Sitzman, 1993). Nahum (1965) named it the "new madness of medical progress". In a much-cited paper, "Preventing ICU syndrome: How not to torture your patients" Dyer (1995) a senior ICU nurse, drew parallels between the ICU experience and the Amnesty International definition of torture – both involved pain, thirst, sleep deprivation, isolation, the administration of psychoactive drugs, physical restraint, disorientation, sensory overload and sensory deprivation. Dyer encouraged ICU staff to use psychological nursing interventions and to modify the environment and medical practices to reduce the stress on ICU patients and prevent damaging outcomes.

Below I will review evidence that possible ICU stressors, stress responses and cognitive responses may be predictors of later psycho-social outcomes. I will then consider other risk factors that could affect the long-term stress response, such as SEC, social support, age, gender, past trauma and previous psychological history.

3.2.1 ICU stressors

Several studies were carried out in which patients were asked which ICU experiences they found most stressful (Nelson et al., 2001; Nelson, 2004; Novaes et al., 1997; Rattray, 2005; Samuelson, 2007; Simini, 1999). Results of these quantitative studies were very similar and matched the conclusions of numerous qualitative studies (Stein-Parbury & McKinley, 2000). Patients reported physical, psychosocial and environmental stressors:

Physical stressors: Pain, inability to sleep, having tubes in nose/mouth, hunger, thirst, difficulty breathing, being "trapped" and "tied down" by equipment.
Psychosocial stressors: Seeing or hearing other patients suffer and die, feeling isolated, being unable to communicate.
Environmental: Loud noise, unexplained noise, the absence of windows and natural daylight, the absence of a night/day cycle.
These stressors may be seen as effects of illness; effects of interventions; and effects of the ICU social and physical environment.

3.2.1(i) Possible effects of illness

Could subsequent psychological morbidity be related directly to the serious illnesses suffered by intensive care patients? We already know that psychological morbidity is associated with some serious illness. For example, depression is known to be both a risk factor for coronary heart disease (Rumsfeld & Ho, 2005; Frasure-Smith et al., 2009) and a psychological consequence of CHD (Davidson et al., 2010). Major depressive disorder (MDD) develops in approximately 15% of cardiac patients with a further 20% experiencing minor depression or high levels of depressive symptoms. Depression has also been found to be highly prevalent in cancer patients. In a review of 350 studies, Pirl (2004) concluded that the prevalence of MDD in cancer patients was 10-25%. This compares to an estimated point prevalence of MDD in the general population of 2.2%.

Anxiety is also associated with serious illness, although it has often been overlooked. It is known that depression in CHD is often accompanied by symptoms of anxiety (Denollet et al., 2006). But as with depression, it is unclear whether anxiety should be regarded as a predictor or consequence of medical illness. A recent study by Szekely et al. (2007) in which 180 patients who underwent cardiac surgery were followed up until four years post discharge, found that 42% of the sample had clinically significant anxiety symptoms before surgery. In this study anxiety and depression were strongly correlated, but only anxiety was significantly associated with increased mortality and morbidity. There is also strong evidence of high prevalence of anxiety in patients with respiratory disease. A review by

Mikkelsen et al. (2004) of anxiety and depression in patients with chronic obstructive pulmonary disease (COPD) found that the prevalence of anxiety symptoms in COPD patients was as high as 50%. Similarly high rates of depression were also detected. Patients with COPD and other pulmonary dysfunction also have particularly high rates of panic attacks and panic disorder (Smoller et al., 1996). There may be a pathophysiological relationship between dyspnea, hyper-ventilation and panic anxiety with physical and psychological symptoms fuelling each other.

Medical illness may also be a risk factor for developing PTSD. A review of PTSD and cancer found that prevalence of current PTSD among adult survivors of cancer (all breast cancer patients) was between 1.9–14% (Smith et al., 1999). In a review of studies investigating PTSD and medical illness and treatment, Tedstone & Tarrier (2003) reported PTSD prevalence for myocardial infarction (0%-16%), cardiac surgery (10.8-18%), haemorrhage (32%) stroke (9.8%) and miscarriage (7-25%). Tedstone & Tarrier (2003) found that the highest prevalence rates of PTSD were reported in studies of intensive care (0-59%) and HIV patients (30 and 35%).

How relevant are these studies of medical illness and psychological morbidity to ICU patients? The examples suggest that being seriously ill, as most ICU patients are, can lead to psychological outcomes such as MDD, an anxiety disorder or PTSD (although there is a question about the direction of the effect). However the strongest evidence is for depression and anxiety being linked to *chronic* illness such as coronary heart disease, cancer and COPD. Some ICU patients may of course have chronic underlying illness of this type, but it is not known how many. The Intensive Care National Audit and Research Centre (Icnarc), the main source of information about UK ICU patients, mainly publishes data about acute events (primary reasons for admission to a critical care unit) such as pneumonia, septic shock, or ruptured aortic aneurysm (Icnarc, 2010). Their data includes only extremely serious co-morbidities such as biopsy proven cirrhosis and metastatic cancer. Thus little is known about the chronic health status of ICU patients in the UK. Few studies have tested associations between *acute* medical illness and later psychological morbidity. However some studies have demonstrate high levels of depression and PTSD after myocardial infarction (Roberge et al., 2010) and haemorrhage (Sheldrick et al., 2006) and this suggests that acute medical illness may also be associated with psychological morbidity.

Furthermore having a life-threatening illness (and all ICU patients are critically ill, whatever the cause) is now officially recognised as a precipitating trauma for post-traumatic stress disorder (American Psychiatric Association,1994). There has been

controversy about whether a life-threatening illness is really comparable to other traumatic stressors such as war, rape or natural disaster. However it is argued that the onset of physical illnesses (e.g. myocardial infarction or haemorrhage) can be sudden and unexpected. Similarly a diagnosis of cancer can be a serious shock that comes out of the blue for many people (Smith et al. 1999). Patients may react to such events with extreme fear, helplessness and loss of control, as in other traumatic incidents.

A specific pathway by which critical illness may trigger psychological morbidity may be related to the effects of extreme physiological disturbances on the brain. Critical illness often affects the functioning of the brain as well as other organs of the body, so that the patient suffers both physical stress and possible alterations to cerebral processes or even brain damage. Many pathophysiological mechanisms occurring as a result of critical illness such as sepsis or respiratory failure may lead to cerebral dysfunction (Milbrandt & Angus, 2005). Reductions or increases of neurotransmitters such as acetylcholine, dopamine or gamma-aminobutyric acid (GABA) may occur. Occult diffuse brain injury may be inflicted as the result of local and systemic hypoxia, hypoperfusion, hyperglycemia, cytokine-mediated inflammation and microvascular thrombosis, all of which may occur due to critical illness. Metabolic derangements such as hypernatraemia and hypercalcemia, endocrine effects on cortisol or thyroid hormone and the effects of sedatives and analgaesics (see section 3.3.1.iii) should also be considered.

It is thought that any of the above abnormalities may precipitate delirium in the ICU, and potentially also lead to longer-term cognitive dysfunction (Hopkins & Brett 2005). It can also be hypothesised that neurotransmitter abnormalities could lead to other psychological conditions such as depression or PTSD. It has been suggested that the effects of inflammatory stress on neurotrophins (proteins that induce the survival, development and function of neurons), neurotransmitters and their receptors could lead to problems with memory consolidation and retrieval processes (Weinert & Meller, 2007) providing a possible biological basis for ICU-related PTSD and other disorders.

Some patients become critically ill not as a result of disease but as a consequence of events such as road traffic accidents, poisoning or burns. It is known that patients who have suffered injuries and trauma may have poor psycho-social outcomes. For example, after a major injury patients had low scores on the quality of well being scale (QWB) at 12 and 18 months after a major injury (Holbrook et

al., 1999). There is known to be a high prevalence of psychological morbidity, including PTSD, among patients who have suffered burns (e.g. Baur et al., 1998).

In the systematic review (chapter two) illness-related factors were found to be associated with quality of life but mainly not with psychological morbidity. HRQL was predicted by illness severity, by the existence of prior or chronic illness and by diagnostic group (for example, trauma, respiratory illness, neurological illness and renal illness) However the systematic review did not provide conclusive evidence for any of these associations and further research is needed to establish the most important illness-related risk factors for post-ICU psychological morbidity.

3.2.1(ii) Effects of intensive care interventions and healthcare

A small number of studies have found that ICU interventions may be predictors of psycho-social outcome after intensive care. As we saw in the systematic review in chapter two these include duration of mechanical ventilation (Cuthbertson et al., 2004), aspects of sedation practice (Girard et al., 2007; Jones et al., 2007, Samuleson, 2007); and the use of paralysis or physical restraint for mechanically ventilated patients (Jones et al., 2007). Other health care factors that have been studied include length of stay in the ICU (LoS) and in the hospital, and type of admission. LoS in the ICU was negatively associated with HRQL in a number of studies in the systematic review. This suggests that greater "exposure" to intensive care results in more serious outcomes. Uncertain results have been obtained for type of admission or diagnostic groups – see systematic review.

Several of the possible risk factors described above are related to mechanical ventilation. This is undoubtedly a stressful treatment. During positive-pressure ventilation (now the most common form of mechanical ventilation), air is forced into the lungs by an external overpressure. The pressure causes oxygen to flow in via an endotracheal tube inserted into the trachea through the mouth or nose, or via a tracheostomy tube surgically inserted into the trachea. When a ventilator breath is terminated, airway pressure drops and the chest passively pushes the air out. Mechanical ventilation is thought to be particularly burdensome for patients (Rotondi et al., 2002). Most patients have to be sedated in order to tolerate the endo-tracheal tube. Procedures such as "suctioning" to clear secretions from the lungs, can be uncomfortable, distressing and painful for some patients. For many the weaning period brings fear of suffocation, panic and a feeling of dependency on the ventilator (MacIntyre, 1995). Some patients have said that in retrospect they would choose not to undergo ventilation again (Mendelsohn, 2002).

Many early qualitative studies highlighted the distressing nature of mechanical ventilation for patients (Bergbom-Engberg & Haljamae, 1989; Gries & Fernsler, 1988; Johnson & Sexton, 1990). Patients reported that the endotracheal tube was uncomfortable and remembered having their hands restrained to stop them touching the tube, or being threatened with restraint. They felt they were going to suffocate during suctioning of secretions from the trachea and could not synchronise their breathing with the ventilator after suctioning. Patients frequently found the procedures of extubation and decannulation, following weaning from the ventilator, to be unpleasant and problematic (Bergbom-Engberg & Haljamae, 1989).

Communication difficulties were often highlighted by patients as the worst part of the experience of ventilation. Patients on ventilators are usually unable to talk when endo-tracheal or tracheostomy tubes are *in situ* as they generally have a cuff around the distal end of the tube inflated to prevent air flow so effective ventilation can occur. A qualitative study by Russell (1999) highlighted the need for improved communication in the ICU. In this and other qualitative studies patients said they were unable to express their wishes, ask questions, seek advice or reassurance or just hold a simple conversation. They felt that nurses did not always try to enable them to communicate by other means. This led to feelings of extreme isolation and affected the quality of care. Patients found good communication therapeutic and reassuring, and a lack of communication distressing. Poor communication led to increased anxiety and slower recovery.

Mechanical ventilation is one of the nine types of organ support that occur in intensive care (see table 1.3 in chapter one). The possible psychological effects of the other forms of organ support – basic respiratory, cardiovascular (advanced and basic), renal, neurological, gastro-intestinal, liver and dermatological have not been considered in the literature. However it can be hypothesised that most of them are also highly stressful for patients. Basic respiratory support does not involve invasive ventilation, yet many patients have subsequent nightmares of claustrophobia and suffocation due to tight-fitting oxygen masks that may be used (see chapter seven). It also involves the suctioning of secretions, a procedure that has already been documented above as stressful for some patients. Cardiovascular support involves the use of inotropic drugs that may have unpleasant side effects (see section 3.3.1.iii on drugs below) and invasive monitoring that often necessitates the insertion of arterial lines, central venous pressure (CVP), and rarely, pulmonary artery catheters.

Renal support involves highly invasive procedures such as blood purification techniques to control hyperkalaemia and uraemia. Blood may be purified using dialysis or, more commonly in ICUs, haemofiltration methods. Haemofiltration in ICU usually involves percutaneous cannulation of a large central vein so that continuous veno-venous haemofiltration (CVVH) can be commenced. Some ICUs have the facilty to perform haemodialysis, either via a central venous catheter or a pre-existing arteriovenous shunt. Rarely, peritoneal dialysis is performed.

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The most common form of gastro-intestinal support is enteral nutrition, involving feeding with a naso-gastric tube, which may be another source of discomfort for patients. Many patients are already malnourished on entry to hospital and undergo periods of starvation during their treatment, so enteral feeding is often instituted early during an ICU stay. A complication of enteral feeding is that most patients remain under-fed (De Jonghe et al., 2001), due to maladministration or to upper gastro-intestinal intolerance (Mentec et al., 2001). Abdominal distention and diarrhoea are also common discomforts during this type of nutrition. Parenteral nutrition is also commonly used in ICU. Total parenteral nutrition (TPN) is routinely administered via a large central vein as it can be uncomfortable to deliver via a peripheral cannula. Insertion of central venous lines to facilitate this feeding regimen can also be an unpleasant patient experience.

Neurological support in ICU usually encompasses ventilation as patients often have a reduced level of consciousness. Assessment of intracranial and cerebral perfusion pressure (Grant & Andrews, 1999) may require a highly invasive form of monitoring using intracranial pressure devices that are placed into the right frontal region through a small burr hole. Neurological patients are often heavily sedated and may also require neuromuscular paralysis and anticonvulsant agents. The experience of patients receiving dermatological support has rarely been written about, yet it is likely that such treatment is stressful or traumatic. These patients may have serious burns, multiple trauma dressings or complex dressings, for an open abdominal wound for example. Patients being managed with an open abdomen (usually for scheduled re-laparotomies for bacterial peritonitis and infected necrotising pancreatitis) can be the most distressed patients on an ICU unit (personal communication with clinicians). Patients who survived this aggressive surgical treatment had Sickness Impact Profile scores indicating that they suffered from depression (Bosscha, 2001). It is not known if receiving any of these forms of organ support are risk factors for adverse psychological outcomes, although descriptions of the invasive methods involved suggest plausible reasons why some of them might be. It can be hypothesised that the longer intensive care treatment

continues, and the greater the number of interventions received, the more serious the psychological outcomes may be.

Although little research has been done about the longer-term psychological outcomes of ICU interventions, parallels may be drawn from literature on psychological morbidity following other medical procedures. PTSD has been identified after procedures such as heart catheterisation, craniotomy and haemorrhage following tonsillectomy (Shalev et al., 1993), and following abortion and gynaecological procedures (Tedstone & Tarrier, 2003). There is also evidence of adverse psycho-social outcomes such as depression following surgery, a procedure that at least 40% of ICU patients are known to have undergone (Icnarc, 2010). In one study (Burker et al., 1995) 50% of patients reported clinically meaningful depression after a coronary artery bypass grafting (CABG). Depression may stem from poor recovery and poor quality of life after surgery. Gundle et al (1980) reported that patients who had undergone coronary artery bypass surgery one to two years previously were functioning poorly; 83% were unemployed, and 57% had sexual dysfunction.

There is also good evidence that cognitive outcomes after major surgery can be poor. Neuro-cognitive impairments have been reported at six weeks and five years in patients who have undergone cardiopulmonary bypass surgery and percutaneous angioplasty (Newman et al., 2001; Wahrborg et al., 2004). Furthermore, in a study of 1218 patients after major non-cardiac surgery, cognitive impairments were found in 26% at one week and 10% at three months (Moller et al., 1998). Hopkins & Brett (2005) hypothesise that the process of surgery, including hospitalisation, surgical procedures, removal from a familiar environment, and inability to control decision-making, are partly responsible for post-surgical cognitive impairment. These factors are also relevant to critically ill patients. As intensive care patients undergo multiple medical procedures and operations, it is likely that they are highly at risk of poor outcomes. Fairly routine ICU procedures such as bladder catheterisation and restraints are already known to lead to delirium in the short-term (Weinhouse et al., 2009); It is important to discover if there are also longer-term effects of ICU procedures.

3.2.1(iii) Drug effects

An important aspect of ICU treatment, which merits specific attention, is the administration of drugs. ICU patients are often given multiple drugs with possible psychoactive effects that may cause emotional and cognitive symptoms as well as possible withdrawal syndromes and sleep deprivation. Drugs that are commonly given in ICUs which may cause psychological side-effects include benzodiazepines,

opiates, anti-cholinergics and corticosteroids. For a list of drugs that are frequently used in intensive care units and that may have psychoactive effects, see table 3.1. Simply scanning the lists of side effects from the British National Formulary (BNF, 2008) makes it clear that ICU patients receive a cocktail of drugs that all have possible side effects such as hallucinations, confusion, disorientation, anxiety, depression, insomnia and aggression. All these mental states have been documented in ICU patients.

Table 3.1 ICU drugs with possible psychoactive effects

Class of Drugs	**Use in ICU**	**Possible 'psychological' side effects** *(British National Formulary 2008)*	**Examples used in ICU**
Benzodiazepines	Anxiety reduction, Sedation for ventilated patient	Hallucinations, confusion, amnesia, dependence, aggression, delirium	Midazolam, Lorazepam
Anaesthetics	Sedation	Memory impairment	Propofol
Hypnotics	Inducing Sleep	*Rarely* – aggression, confusion, depression, hallucinations, amnesia	Zopiclone
Sympatho-mimetics	Raising blood pressure and cardiac output	Anxiety, restlessness, sweating	Noradrenaline Adrenaline
Anticholinergic drugs	Oliguria Heart failure, arrhythmias	Memory impairment, confusion, delirium, hallucinations, depression.	Furosemide, Digoxin
Antipsychotics	Treat delirium		Haloperidol
Opioids	Analgesia	Restlessness, mood change, disorientation, agitation, delirium, hallucinations, euphoria, mental detachment, anxiety, confusion, sleep disturbances.	Morphine, Tramadol, Fentanyl
Gabapentin	Neuropathic pain	Confusion, depression, hostility, insomnia, anxiety, amnesia.	
Glucocorticoids	Anti-inflammatory effects	Extreme psychiatric reactions – psychosis, insomnia, mood lability, suicidal thoughts, memory impairment.	Prednisolone
Anti-epileptics	Convulsions	Insomnia, nervousness, confusion, agitation, aggression, amnesia, depression, hallucinations	Phenytoin, Levetiracetam
Anti-depressants	Depression	Confusion, impaired concentration, abnormal dreams. Withdrawal – anxiety, sleep problems.	Citalopram

Sedation and analgesia are key elements of ICU care. They are given to help patients tolerate mechanical ventilation, and other diagnostic and therapeutic procedures routinely carried out in ICUs. The aim is to suppress tachycardia, hypertension, hyperventilation or respiratory efforts against mechanical ventilation (Behne, 1995). However, although sedatives and analgesics relieve anxiety and pain, they may be associated with delirium. In one study (Pandharipande et al., 2006) it was found that lorazepam was an independent risk factor for daily transition to delirium (OR: 1.2; 95% CI 1.1 – 1.4, p=0.003). Fentanyl, morphine and propofol were associated with higher but not statistically significant odds ratios for delirium. Jones et al. (2007) found that high doses of benzodiazepines increased the risk of delirium (median dose 24 mg vs 13 mg, p = 0.03), although no

individual benzodiazepine was identified. Patients receiving high daily doses of opiates (median dose 88 mg vs 43 mg, p=0.039) were also more likely to be delirious. Patients with withdrawal symptoms from sedation and analgesia were also more likely to be delirious (25 out of 30 patients, p<0.0001).

There has been little research to examine prospective associations between ICU drugs and psychological outcome. In a trial of the practice of daily interruption of sedatives to allow patients to awaken to a conscious state, Kress (2003) found that intervention patients had a lower Impact of Events (Horowitz et al., 1979) score for PTSD-related symptoms, (11.2% v 27.3%, p=0.02) and a trend towards lower incidence of PTSD (0% vs 32%, p=0.06). Daily interruption of sedatives was also associated with shorter duration of mechanical ventilation and shorter ICU stay (Kress et al., 2000). In an analysis of data using structural equation modelling Jones et al. (2007) found that prolonged treatment with sedation and opiates was a predictor of PTSD, along with previous psychological problems and physical restraint. Sedation and opiates had both a direct effect on outcome, and an indirect effect mediated by delusional memories. In Girard et al. (2007) the total dose of lorazepam received during the ICU stay was associated with PTSD symptoms six months after discharge.

3.2.1 (iv) Cumulative Stress

In addition to considering the specific stresses and strains due to illness and interventions in intensive care, both may lead to an overload of the type of experiences that patients say they find stressful. These include pain, discomfort from procedures and invasive monitoring, hunger, thirst, fatigue, sleep deprivation, and perceived difficulty in breathing (Simini, 1999). There may be a cumulative effect of having several of these individual stressors, that adds up to an overwhelmingly stressful experience for some patients leading to extreme stress responses in ICU and to psychological morbidity following discharge.

The presence of hunger may be explained by a post-operative period of starvation and inadequate enteral or parenteral nutrition. The thirst complained of by many patients may be due to dehydration caused by diarrhoea, pyrexia, sweating, drainage, unnecessary fluid restriction or inadequate fluid replacement (Hinds & Watson, 2008). Pain may result from the illness or operation the patient has been admitted for, from ICU procedures and interventions, or from immobility, uncomfortable positioning, restraint, constipation or endo-tracheal suction (Dyer, 1995). Although pain should be well-controlled in ICU, many studies have found that patients reported severe pain and that nurses were not aware of it, particularly in sedated patients. For example in a study of 50 critical care patients with

tracheostomies by Nelson et al. (2004), 44% rated their pain as being at the "highest levels". In another study of mechanically ventilated patients, 13 out of 43 had suffered "intolerable" pain (Pochard, 1995). In a study of post-surgical patients, 25% reported severe pain while in the ICU (Bohrer et al., 2002).

An important function of intensive care is to monitor patient's vital signs and this frequently involves invasive monitoring. Patients in intensive care tend to be connected to a variety of machines and to have their bodies punctured with lines in the arteries and veins, catheters, cannulae, drains, drips, nasal and oral tubes and infusion pumps. This can be an alienating and frightening experience for many people who recall feelings of being trapped and tied down by equipment (Stein-Parbury & McKinley 2000). Insertion of cannulae and catheters can also be difficult and painful for patients.

Sleep deprivation has long been known to occur in intensive care patients, and has recently been considered as a risk factor for ICU delirium (Weinhouse et al. 2009). ICU patients tend to be wakeful and to sleep lightly. They are typically deprived of the all-important REM (rapid eye movement) and delta (deep) stages of sleep (Cooper et al., 2000). There has been a debate over the degree to which practices and environment in the ICU contribute to sleep deprivation. It has been argued that patients are deprived of sleep because of environmental noise, unnatural lighting which does not allow them to establish a natural sleep/wake cycle or being woken up in the night for checks and observations (Freedman et al., 2001). Sleep disruption and delirium share many physiologic similarities such as inattention, fluctuating mental status and impaired cognition in the domains of memory, planning, creative thinking and judgment (Weinhouse et al. 2009). If sleep disturbances continue untreated for a long time, including after intensive care, they also constitute a risk for psychiatric disorders (especially major depression), memory impairment and compromised quality of life (Roth, 2001).

3.2.1 (v) Effects of ICU environment

Many studies have considered aspects of the ICU social and physical environment as a source of stress for patients. The following quotation from a qualitative study of ventilated patients outlines an impression of one ICU that is mirrored by patients quoted in other studies, "It was cramped, you couldn't move. And they had all the machinery there. And the alarms were going off all night long. There was no peace, there was no peace at all. Everything was a hundred mile an hour. Patients in and out, in and out." (Wade, 2006, p.38).

Physical aspects of the ICU environment that may be stressful include unnatural lighting, loud noise, a lack of distinction between day and night and the presence of machines and equipment, that may look disturbing to patients (Brullmann, 1997). Patients whose bed is placed with a view of a window may be more oriented than patients who have no window. In one study (Wilson, 1972) it was found that patients with a view of a window had half the rate of delirium of patients with no window. If there is no window or if lighting is left on at night to enable procedures to take place, patients may become disorientated and sleep deprived, as they are unable to establish a normal day/night sleep cycle.

Noise has also been highlighted as a disruptive environmental factor. The noise level in one ICU was measured at more than 70dB, equivalent to the noise of heavy traffic in one study (Bentley et al., 1977). The recommended maximum noise level for a hospital ward is 45 dB. In most interview studies patients talked about noise comes from machinery, alarms, telephones ringing (often unanswered, in the middle of the night) other patients groaning or shouting, and from staff conversations(Green, 1996). Some patients reported that they found staff having normal conversations comforting (Green, 1996), while others said that staff talking over them while carrying out procedures was demeaning. A patient quoted by Russell (1999, p.787) criticised staff for "laughing, joking, talking about social life, what pub they were going to, where they were going for holidays – Bali etc".

Similarly the considerable amount of technology and equipment found in ICUs (see chapter one) may elicit a sense of safety and comfort in some patients, or be a source of fear and alienation to others. For example a patient interviewed by Russell (1999) p788 said, "Guess I wouldn't be here if it wasn't for it. The machinery is there for a purpose. I wouldn't know what it was, but I'm sure glad it saved me." However a patient interviewed in Granberg et al. (1998, p.304) described, "tubes and lines all over me, in my arms and legs, forcing me to lie still, they also had lines in my stomach so it was impossible for me lie on my side. I felt bound and controlled by the equipment, which was both alien and noisy."

Efforts have been made in some ICUs to manage and improve environmental aspects such as lighting and noise levels in order to regularise day-night cycles and improve patients' psychological states (Bennun, 2001). However it may be more difficult to manage the social environmental aspects of the ICU. These social environmental aspects are mainly related to the perception of other patients. Many patients feel isolated because they are unable to talk to their fellow patients, yet they are aware of each others' suffering and are quite likely to see or be aware of

another patient dying. In Granberg et al., (1998) patients reported being highly aware of other patients. One patient described another as "a very confused person who was noisy and who fought and was disorderly and wanted to get out of bed….who could not speak, only scream and who just kept on hitting the nursing staff" (p 301). Another patient felt great fear and unease when he realised the person in the next bed had died. He was "afraid of what was happening on the other side of the curtain" (p 301). These environmental social problems are not easily solvable. Staffing levels and space constraints dictate that it is often easier for staff to manage patients in small units with several bed spaces rather than in individual rooms (Hinds & Watson, 2008).

Another social stressor is the difficulty involved in communication between staff and patients, particularly ventilated patients. Reviews of ICU communication studies have found that communication between staff and patients in ICU is generally poor (Llenore & Ogle, 1999). Nurses typically receive no or little training in non-vocal communication methods, or in the assessment and application of augmentative communication methods (Happ, 2001). These communication methods could enhance the experience of ICU patients and potentially lessen the stressfulness of being in intensive care, but they are rarely used in ICUs. However strategies should be adopted to train staff in better communication methods and make low-tech communication aids easily available in ICUs (Magnus & Turkington, 2006).

3.3 Stress responses

It is clear that a great many potential stressors are present in intensive care units. However according to psychological theories of stress, psychological outcome may be determined more by patients' responses to the stressors, rather than the mere presence of stressors (Lazarus & Folkman, 1984). Stress responses include emotional, cognitive, behavioural and physiological effects (Steptoe & Ayers, 2004). Physiological stress responses involve activation of the autonomic nervous system, producing changes to breathing and heart rate, and of the neuro-endocrine system, leading to the release of stress hormones such as adrenaline, noradrenaline and cortisol (Axelrod & Reisine, 1984). The immune response to stress, which includes changes to natural killer cell and cytotoxic activity (Kiecolt-Glaser et al., 2002) could be extremely relevant to the outcome of seriously ill patients as a decrease in immunity could impede their recovery.

Physiological stress responses have rarely been measured in intensive care, probably because patients are already undergoing a high burden of testing, monitoring and intervention. However ICU patients are frequently treated with the

stress hormones adrenaline and noradrenaline to restore blood pressure and cardiac output, and cortisol, to reduce inflammation. Schelling et al. (2008) reported on studies investigating the effects of exogenously administered stress hormones on ICU patient outcomes such as PTSD and traumatic memories. Administration of catecholamines was associated with an increased number of traumatic memories held by ICU patients, but cortisol was associated with fewer PTSD symptoms in the recovery period (Schelling, 2002). As little has been published about physiological or behavioural responses to stress in the ICU, I will focus on emotional and cognitive responses to ICU stressors, and evidence that these responses may be risk factors for psychological outcome or possibly factors that mediate between clinical stressors and outcome.

3.3.1 Emotional responses

Several studies have quantified ICU patients' emotional responses. As might be expected there is a combination of anxiety and depression in many cases. Pochard (1995) assessed 43 patients 48 hours after weaning from the mechanical ventilator. He found that 38 patients (88%) had "subjective physical depression" with 70% intensity, 33 patients (77%) were delirious or confused, 25 (58%) felt unable to communicate and 22 (51%) had a diffuse anxiety disorder, with 16 describing an intense fear of dying. Of 50 tracheostomy patients studied by Nelson (2004), more than 80% were anxious or depressed, with 60% reporting anxiety and depression at the highest levels (frequently or almost constantly); while 90% suffered severe distress due to inability to communicate. A study by Menzel (1998) reported that fear and anger were the predominant emotional responses in ventilated patients, mainly associated with communication difficulties. A study of ICU patients with cancer (Nelson et al., 2001) found that severe or moderate levels of depression were reported by 40% of patients, and anxiety symptoms by 55%-75% of patients.

Anxiety

The overwhelming response to being in intensive care is usually said to be extreme fear and anxiety (Bennun, 2001). Granberg et al. (1998) described patients as being in a state of emotional chaos on regaining consciousness in intensive care, and being vulnerable to extreme fear reactions such as anxiety, panic and agitation. Fear of dying, fear of ICU equipment, fear of suffocating and fear of the future were all common manifestations of this anxiety (Wade, 2006). Anxiety rates of 55% and 62% were found in questionnaire studies of 114 medical ICU patients (Brullmann et al., 1997). In 20% of cases, nurses underestimated patients' anxiety. In a study by Chlan (2003) the mean Stait-Trait Anxiety Inventory (STAI) score for state anxiety among ICU patients receiving mechanical ventilatory support was in

the clinically significant range (49.2). Those who received mechanical ventilation for more than 22 days had a higher mean score (54.2). Anxiety can be severe enough to prevent patients from being weaning off mechanical ventilation (Gimenez et al., 2003). Anxiety may interfere with the patients' ability to breathe by increasing sympathetic nervous system activity. This could lead to increasing heart rate and contraction, a faster breathing rate increasing the work of breathing, and muscle tension leading to fatigue. Any of these symptoms might help to sabotage the weaning process (Johnson & Sexton, 1990).

Depression

Bennun (2001) argued that an absence of fear and anxiety in ICU patients may indicate a potential withdrawn or depressed state. Some patients, rather than become anxious or panicky, simply stop responding, and refuse to communicate with staff and families, or to comply with treatment or even simple care such as washing. In a questionnaire study of 100 general surgical ICU patients (Bohrer et al., 2002) it was found that the main psychological symptom, experienced by 29% of patients, was helplessness, a symptom of depression. In a 1998 study of patients receiving mechanical ventilation for more than seven days, Higgins (1998) found that patients had Profile of Mood State (McNair, 1984) scores suggesting a "moderate" depressed mood state as well as suffering from fatigue, lack of nutrition and disruption of their sleep-rest patterns. Mendel & Khan (1980) observed that depression impaired motivation to return to spontaneous breathing in mechanically ventilated patients. The type of depression observed in these studies is reminiscent of the helplessness-depressions often associated with lack of control. The concept of learned helplessness in response to uncontrollable events (Miller & Seligman, 1975) may be extremely relevant to understanding ICU patients' emotional and behavioural responses in the ICU. A series of experiments showed that both animals and humans acted helplessly when faced with uncontrollable events (e.g. electric shocks or loud noise). On learning that stressful events were completely out of their control, people displayed motivational, cognitive and emotional deficits of passivity, slow learning and depressed affect. This has become known as the depression sub-type of "helplessness depression" (Abramson et al., 1978).

The experience of being in intensive care could almost be defined by lack of control. Patients are subject to a cascade of physiological events, and to control by medical staff, who must intervene with a succession of invasive treatments to save their lives. Another useful concept is the idea of external locus of control (Rotter, 1966) which has often been associated with the "helplessness" concept of learning that outcomes are uncontrollable. Being an intensive care patient is all about handing over control to medical staff so locus of control must by definition be external.

However interventions to improve patients' self-efficacy (Bandura, 1977) by giving them a sense of control over small matters such as when they should be washed have been discussed, particularly in the nursing literature (Dyer, 1995).
Other emotional reactions documented in research studies included agony and insecurity (Bergbom-Engberg & Haljamae 1989), mainly among ventilated patients who were unable to talk. However in a small number of studies more positive responses were documented. A few studies found a positive effect of the psychological attribute of "mastery" or "personal control" (Moody et al., 1997). In their review of patients' experiences in the ICU, Stein-Parbury et al. (2000) found that patients gained feelings of comfort and security from the emotional support and attention of nurses, whose care helped to reduce their anxiety. However the focus of research has been on negative emotional responses to the ICU, and there is little evidence about the protective effect that positive factors might have on ICU patients. A recent review of positive affect (PA) and general health (Pressman & Cohen, 2005) concluded that there was evidence to suggest an association between PA and lower morbidity, decreased symptoms and pain.

Although many studies have documented extreme psychological reactions in ICU patients, few have tested whether these reactions predicted subsequent psychological outcomes. Samuelson et al. (2007) found that several psychological factors were predictors of high levels of PTSD symptoms at 2 months, including fear of the ICU (OR 6.95, 95%CIs: 2.22, 21.7, p=0.0002) and agitation in ICU (OR 1.77, 95% CI: 1.21, 2.59, p=0.005). A higher depression score (using the GDS-SF) at hospital discharge was significantly associated with cognitive impairment at 6 months (mean 6.2 v 3.7, p=.04) in a study by Jackson et al. (2003). Another psychological factor, ICU recall or memory, was reported to be a risk factor in five studies in the systematic review. Memory is best considered within the category of cognitive response, to be discussed in the next section.

3.3.2 Cognitive responses

Having described studies dealing with the acute emotional response to being in intensive care, I shall now look at the cognitive responses of ICU patients. Cognitive responses to stress include changes in perception, attention and memory processes (Sapolsky, 2000). Attentional processes are particularly vulnerable to stress, and failure to notice important stimuli under stressful conditions is often the cause of accidents. Stress also has many effects on memory. After a trauma people often have incomplete memories of the stressful event as well as emotionally charged memories that may lead to long-term stress disorders such as PTSD (Brewin et al., 1996). There is now a considerable amount of evidence that

cognitive processes may become severely distorted in the ICU (Ely et al., 2001c; Granberg et al., 1999) and this may be partly due to psychological and physical stress. Here we need to distinguish between cognitions and beliefs (see section 3.3.2 (iv)) and cognitive function.

A uniform picture of extreme cognitive dysfunction in many cases can be built up from early descriptions by clinical staff, subsequent qualitative studies where patients described their experiences, and more recent quantitative data that gives more precise statistics about the prevalence and nature of such responses. An early psychiatric report by Kornfeld (1969) referred to agitated, aggressive patients, as well as a high incidence of "psychosis" among another group of intensive care patients. The psychosis was said to begin with perceptual distortions, to progress to auditory and visual hallucinations and from there to frank paranoid delusions. All this was accompanied by disorientation to time and place. Kornfeld and colleagues believed these to be the effects of sleep and sensory deprivation on patients whose capacity to handle stress was already impaired by the effects of illness and surgery.

Interview studies confirmed that many ICU patients could remember and describe being in acute confusional states. Granberg et al. (1999) categorised these states as unreal experiences; disorientation (the distortion of day, time and place perception) and cognitive impairment (the inability to talk, think, remember and understand). The unreal experiences appeared to be triggered by conditions of extreme fear; when a patient felt a degree of self-control or trust and confidence in nurses, unreal experiences occurred less often. In many studies a combination of these emotional and cognitive reactions was described and labelled as "ICU syndrome" or "ICU psychosis".

An insider account of "ICU psychosis" was provided by a medical sociologist who spent seven weeks in intensive care with peritonitis and septicaemia, in an article entitled "Coming out of intensive care crazy: dreams of affliction" (Richman, 2000). He described his disturbed mental state as he regained consciousness. "I displayed psychotic and paranoiac symptoms. I believed firmly that the reason for my hospitalisation was that I was shot in the university car park. I believed that the $5 million I carried for a foreign agency was stolen and that their agents were set on assassinating me. I told my youngest son to camp out on the flat roof of the hospital building and if anyone came on the roof….he was not to ask questions but throw that person off the roof" (p87).

Richman also had constant nightmares that began when he was in a coma in the ICU and continued after his transfer to the HDU. He was so terrified of the nightmares that he tried to avoid them by not sleeping at night. "It was like existing in a gigantic kaleidoscope that was constantly shaken. Colours were heightened. Impending danger was constant. I was in continuous motion flying through the sky, above the sea, and over ragged, barren mountains. Space and time seemed eternal……I had no notion of body and self, yet, I felt my invisible body being shredded." (Richman, 2000, p.94) Richman wrote that these experiences left him with severe depression and guilt that persisted several years after the events.

Delirium

It is now recognised that symptoms such as disorientation, agitation, confusion, inattention, aggression, hallucinations, delusions and nightmares occur commonly in ICU patients. In the medical literature these are commonly identified as a syndrome known as delirium (Ely et al, 2001a). The DSM-IV (APA 1994) describes delirium as featuring a disturbance of consciousness and attention and a change in cognition or perceptual disturbances, such as hallucinations, with rapid onset. Delirium may not always present with agitation or hallucinations. Some patients have hypoactive delirium, characterised by decreased mental and physical activity and inattention. At the other extreme are agitated and combative patients, with hyperactive delirium. Mixed delirium has features of both (Marcantonio et al., 2002). In addition many patients only exhibit some cognitive responses (for example hallucinations) and not the whole range of delirium features. This may be explained by the existence of a sub-syndromal form of delirium (Ouimet et al., 2007); alternatively it can be argued that cognitive responses to ICU treatment may occur independently, not always in the specific cluster of symptoms that is needed to satisfy the diagnostic criteria for delirium.

The prevalence of delirium has been reported as 20%, 70% or 80% of patients in ICU cohort studies (Bergeron, 2001; Ely et al, 2001; McNicoll et al., 2003), but goes unrecognised by physicians and nurses in 32% to 66% of cases. It is often misdiagnosed as dementia, depression or simply regarded as an expected occurrence in the critically ill, especially the elderly (Inouye, 1994). However delirium should not be disregarded, as it has been shown to be a strong risk factor for mortality in both non-ICU and ICU samples, entailing a 3-fold higher risk of death, after pre-existing co-morbidities, illness severity, coma and the use of sedative and analgesics have been controlled for (Ely et al., 2004). It is often regarded as a transition state between coma and a normal state, but in fact it

occurs as frequently in those who have not been in a coma, as in those who have. It persists in 11% of patients at the time of hospital discharge (Ely et al. 2004).

There is often the assumption of an underlying medical cause for delirium, such as metabolic disturbances, electrolyte imbalances, withdrawal syndromes, acute infection, seizures, head trauma or brain lesions (McGuire et al., 2000). However other studies and reviews provide evidence that environmental or psycho-social factors such as social isolation, stress, circadian disruption, light, noise and sleep deprivation also contribute to delirium (e.g. Weinhouse et al., 2009).

Drug-induced delirium is of particular interest in the ICU context. With enough oxygen and nutrition, consciousness is generally very resistant to disruption by drugs, according to Ashton (2002). However drugs can disrupt consciousness leading to hallucinations and delirium in adverse conditions. For example the risk of drug-induced delirium is increased by hepatic encephalopathy, head injury, viral encephalitis and hypoxia. Drug-induced delirium may result from direct toxic effects of drugs on cerebral function or indirect effects on metabolism such as hypoglycaemia or electrolyte disturbance. More than 90 medications have been identified as having an association with delirium (Murray et al., 1993). Drugs that have been known to cause delirium include anticholinergic drugs (Perry & Perry, 1995); drugs with anti-muscarinic actions including antipsychotics and antihistamines; noradrenergic drugs including adrenaline and monoamine oxidase inhibitors (MAOIs); selective serotonin reuptake inhibitors (SSRIs; Sternbach, 1991); and barbiturates, benzodiazepines, zopiclone, anticonvulsants and ketamine.

The neurophysiological changes that may underlie delirium are not yet well understood. One current theory is that two connected neural circuits that are important for attention and working memory are compromised in cases of delirium (Trzepacz, 1999). One circuit involves the prefrontal cortex, anterior cingulate and basal ganglia; the other involves the parietal lobes, superior colliculus and thalamic pulvinar. The malfunction may be due to the vulnerability of these circuits to a variety of insults, leading to cellular dysfunction. The malfunction causes an imbalance of neurotransmitter systems leading to a deficiency of cholinergic innervation and excess of dopaminergic stimulation, thought to be a common pathway for the development of symptoms of delirium. Evidence for this theory has come from studies that found a higher prevalence of delirium in patients who received many anti-cholinergic drugs (Tune, 2000).

However other authorities argue there is no common pathway but that delirium is the final common symptom that can result from aberrations in many different neurotransmitter pathways and pathological processes (Flacker & Lipsitz, 1999). For example van der Mast & Fekkes (2000) stressed the importance of serotonin and its precursor tryptophan in delirium. Both an excess of serotonin (serotonin syndrome) and diminished serotonin (as in alcohol withdrawal) are associated with delirium.

Whether the "ICU syndrome" is seen to be a well-defined medical psychiatric condition, or a multi-factorial psycho-physiological one, it predicts adverse ICU outcomes including increased risk of death, cognitive impairment, longer hospital stay and higher costs (Ely et al., 2004, Ouimet et al., 2007). It is not yet known whether delirium or indeed individual symptoms of delirium such as disorientation, hallucinations or nightmares predict psychological outcomes in the months after discharge from ICU. In the systematic review (chapter two) two studies included delirium as a potential risk factor. In Girard et al. (2007) no significant correlation was found between duration of delirium (days) and PTSD symptoms. Jackson et al. (2003) found no association between days of delirium and cognitive impairment at six months. This is an issue that will be examined further in this PhD.

3.3.3 Memory

A specific aspect of cognition that may be of particular relevance to psychological outcomes after intensive care is memory. As mentioned above, several studies found that the nature of memories of ICU was associated with outcomes, particularly PTSD (e.g. Jones et al. 2001). This is perhaps not surprising, as it has been argued that a key feature of PTSD is the distortion of normal memory processes (Brewin 2001). The experience of intensive care is known to have several effects on memory. Some patients suffer total or partial amnesia for both admission to an ICU and for the duration of their stay. This amnesia may be explained by loss of consciousness or the effect of sedative drugs while in the ICU (Ghoneim, 2004b), yet this may not be a complete explanation, as it is also common for people undergoing other types of trauma that do not involve unconsciousness or drugs, to forget important parts of the experience (Brewin & Holmes, 2003). Some patients report that they remember events that happened before regaining consciousness in the ICU. For example in a study by Rundshagen et al. (2002), 17% of patients remembered the endotracheal tube or being on the ventilator while unconscious, 21% reported dreams or dream-like sensations, 9.3% reported nightmares and 6.6% recalled nightmares from that pre-conscious time.

For some ICU patients the most disturbing memories are of real experiences they had in intensive care, especially those involving pain and discomfort, such as extubation or endo-tracheal suctioning (Rotondi et al., 2002). Others are troubled by so-called "delusional" memories of "unreal" phenomena experienced in intensive care. Memories of hallucinations, paranoid delusions or nightmares appear to be particularly frightening for ICU patients (Griffiths & Jones, 2001). The experiences remembered are often persecutory; for example patients "remember" ICU staff trying to harm or kill them, or aliens taking the place of their relatives (Jones et al., 1994).

Some patients have both factual and delusional memories. Both types of memory have been found to predict psychological outcome, although there are conflicting findings about which type is the strongest predictor. My systematic review (chapter two) included five studies that reported some form of ICU memory to be a predictor of psychological outcome. Rattray (2005) found that greater recall of ICU experiences was associated with higher anxiety and depression at 6 months. Similarly, Girard et al. (2007) found that the presence of "traumatic" memories (of pain, suffocation, panic and nightmares) was highly associated with PTSD. A study by Schelling (1998) of ICU patients with ARDS (excluded from the systematic review) suggested that the number of adverse memories a patient could recall from ICU was associated with PTSD. Since the systematic review was completed, Myhren et al. (2010) found that factual recall was a predictor of PTSD (OR:6.6, 95%CIs: 1.4, 31.0)

However Perrins et al. (1998) reported a trend for higher levels of PTSD symptoms to be experienced by those who had no memories of ICU. Jones et al. (2001) found that the presence of "delusional" memories two weeks after discharge, was predictive of PTSD symptoms while "factual memories", however unpleasant, were protective against PTSD. This finding was repeated in three further studies (Jones et al. 2003; Jones et al. 2007; Weinert & Sprenkle, 2008). The authors of Jones et al. (2001) hypothesised that two processes contribute to memory problems experienced by former ICU patients. First, effects of illness and treatment such as delirium and sleep deprivation may cause confusion and amnesia, while drugs including benzodiazepines and opiates have known distorting effects on memory. Second, the physical and social effects of undergoing ICU treatment such as restraint and isolation, cause patients to focus on internally generated images at the expense of external ICU events. Therefore they clearly recall memories of hallucinations and nightmares, and have poor recall for the factual events that occurred in the ICU.

Another possibility is that, regardless of the content (factual or delusional), having early post-ICU memories that are intrusive and hard to control will predict future psychological morbidity. It is known from the wider literature on (non-ICU) PTSD that intrusive thoughts and memories often begin immediately after a traumatic experience (Brewin et al. 1996) and are an early predictor of PTSD. To my knowledge no studies have been carried out in the ICU setting to investigate whether early intrusive memories are potential risk factors for post-ICU psychological morbidity.

3.3.4 Illness Perceptions

As well as effects on cognitive function, ICU stress may alter patients' illness beliefs or perceptions. Almost nothing is known about this because patients are rarely in a good condition to answer questions about beliefs while in intensive care (it is somewhat easier to detect their moods with simple one word items such as those used in the Profile of Moods States (McNair et al., 1984)). The illness perception approach is based on patients' experience of illness and their own model of their condition (Weinman & Petrie, 1997). Illness perceptions are defined as idiosyncratic beliefs about illness based on the patients' cognitive representations of their symptoms or condition. These core beliefs concern the identity of the illness (what is it?); the causes of the illness, the suspected consequences of the illness, time-line (how long will it last?) and cure/control (what will make it better?). Illness perceptions have previously been found to predict recovery, disability and health behaviours of diverse groups such as women with breast cancer, chronic fatigue sufferers and myocardial infarction patients (Weinman & Petrie, 1997). To my knowledge ICU patients' illness perceptions have not been assessed in previous research. However a study by Sheldrick et al. (2006) that assessed illness perceptions after acute medical trauma may be relevant to intensive care. It found that certain illness perceptions (identity, timeline, consequences and emotional representation) predicted post-traumatic stress in survivors of acute medical trauma such as myocardial infarction or subarachnoid haemorrhage.

It can be hypothesised that the severe nature of critical illness in addition to receiving highly intrusive medical treatment and the loss of psychological control is likely to profoundly alter patients' illness perceptions. Additionally illness perceptions may be distorted by the effects that ICU has on cognitive function and memory described in previous paragraphs. More negative and possibly catastrophic illness perceptions about control or timeline may also have a negative effect on patients' mental and physical recovery and HRQL.

3.4 Intervening variables

As well as stimuli and responses, most current stress models include a number of intervening variables that have some effect on the stimulus-response relationship (Jones & Bright, 2001) and determine the way an individual will react to a stressor. However there is little agreement about which are the most important intervening variables, and different models focus on different types of variable. A group of intervening variables that have attracted particular interest are "psychosocial resources", resources that are available to people to help them cope with demands made on them. In some models these are environmental factors such as social support or economic resources; other models emphasise personal factors such as previous experience, negative or positive affect, type A personality, pessimism, self-efficacy or coping strategies. Individual vulnerability is also indicated by experience of past traumas or past psychiatric history (Brewin et al., 2000).

In the studies reviewed in chapter 2, three out of six studies that included psychological history in their models found that it was a risk factor for PTSD or depression after intensive care (Cuthbertson et al., 2004; Jones et al., 2007; Weinert & Meller, 2006;). Cuthbertson et al. (2004) found that subjects who reported visiting a GP or mental health professional for psychological distress prior to their ICU admission had higher levels of PTSD three months after ICU. Jones et al. (2007) found that receiving prolonged sedation in the ICU and recalling more delusional memories from the ICU were possible mediators of the relationship between prior psychological history and PTSD. It is possible that small samples or methodological problems prevented other studies from detecting the effect of previous psychological history. Certainly it is well known that previous episodes of depression make a future episode of depression more likely (Lewinsohn et al., 1988). Alternatively it could be argued that the ICU may be a stressor of such magnitude that previous history has a weaker effect than might usually be expected. Few studies have included personality factors, although Myhren et al. (2010) found that optimism predicted fewer symptoms of PTSD, depression and anxiety one year after ICU.

Important differences have also been found in the risk of developing mental or physical ill-health after exposure to adverse experiences, because of socio-demographic factors including age and sex. Sex and age differences have been documented in both physical and mental health outcomes such as heart disease (Jousilahti et al., 1999) or depression (Bebbington et al., 2003). The different vulnerability due to age and sex may be explained by social, genetic or biological approaches. For example, as people age, biological changes occur that modify stress responses and an individual's capacity to adapt homeostatically (Seeman &

Robbins, 1994). Age and sex are also established predictors of health-related quality of life in the general population. In the systematic review (chapter 2), age predicted post-ICU psychological morbidity in four out of seven studies that reported it, while sex was a risk factor for post-ICU psychological outcomes in only two out of five studies. The trend was for younger age and female sex to be associated with PTSD. Several studies found that older age was a consistent predictor of HRQL after intensive care while sex was not. Sex was found to be associated with clinical outcomes of intensive care such as duration of intubation and length of stay after coronary artery surgery (Butterworth et al., 2000). However sex was not associated with outcomes of mechanical ventilation including duration of intubation or success of weaning trials (Epstein & Vuong, 1999).

No studies of psychological outcomes of ICU included data on ethnicity. However it has been found that higher rates of disease and poorer general health are more prevalent in some ethnic groups than others. For example, there is higher prevalence of hypertension and diabetes in Caribbean- and South Asian-born adults than representative samples of the general population. Higher risk factors for cardiovascular disease such as obesity and raised waist-hip circumference ratios have also been found in South Asian, African-Caribbean and some Irish-born adults (Landman & Cruickshank, 2001). However there are fewer coronary heart disease deaths among Caribbean-born adults and fewer cancer deaths among Caribbean, South Asian and East African-born adults in the UK. Irish- and Scottish-born adults have higher mortality from all causes. However it has been argued that social and economic inequalities are the fundamental causes of ethnic inequalities in health rather than cultural or genetic factors (Nazroo, 2001).

"Psycho-social resources" also include social factors such as social support. There are two main theories of social support. In the "main effect model" it is hypothesised that social integration and participation in multiple social roles is associated with lower mortality and morbidity, regardless of the level of life stress (Berkman, 1997). In the "stress-buffering" model, social ties are viewed as protective against life stress. Emotional support, practical support and information have been shown to mitigate the effect of adverse experiences such as serious illness (Cohen & Wills, 1985). There is also some evidence that social support may be helpful in recovery after surgery. In a study of post-operative recovery (Neuling & Winefield, 1988), recovery was associated with satisfaction with support from family, the surgeon or with both at different time points.

3.4.1. Socio-economic circumstances

People with more deprived socio-economic circumstances may be more at risk of intensive care stress. Therefore it is important to discover if SEC predicts worse psychological outcomes or quality of life after intensive care. In general terms, SEC, whether defined by occupation, income or educational attainment, is a particularly powerful predictor of health outcomes. A social gradient in health has been demonstrated for both morbidity and mortality from common illnesses throughout the developed world (Adler & Ostrove, 1999). A social gradient has been found for cardiovascular disease, metabolic syndrome, diabetes, chronic respiratory disease, gastrointestinal disease, lung cancer and accidental and violent deaths.

Mixed results have been found for SEC and mental health. Social gradients have been demonstrated for the more severe mental disorders such as schizophrenia or bipolar disorder (Dohrenwend et al., 1992; Lorant et al., 2003). However findings have been inconsistent for less severe "common mental disorders" such as depressive symptoms and anxiety. While several studies showed an association between poor socioeconomic circumstances and more symptoms of general mental ill-health, other studies showed no association and some showed the reverse association, between higher SEC and more mental ill-health (Lahelma et al., 2006). However a systematic review by Fryers et al., (2003) found that results varied according to the indicator of socioeconomic circumstances used in studies. Occupational social class was found to be the least consistent marker, but consistent associations were found with mental ill-health when SEC markers such as unemployment, education and low income or standard of living were used.

Some of the difference in health outcomes according to SEC is due to direct effects of poverty such as worse living and working conditions and exposure to pollutants and dangerous environments (Evans & Kantrowitz, 2002). Health behaviours such as smoking, poor nutrition and alcohol use contribute to the effect. It is also hypothesised that the effect of SEC on health outcomes may be due to stress-related factors. Lower socioeconomic groups are likely to be subject to several forms of chronic stress such as low job control, financial problems, and living in neighbourhoods with increased crime and other social problems. Laboratory studies suggest that people from more deprived backgrounds show more prolonged cardiovascular reactions after exposure to a standardised mental stressor (Steptoe, 2002). Impaired post-stress recovery is associated with heightened risk for cardiovascular disease (Schuler & O'Brien, 1997) and mortality in patients with existing CHD (Cole et al., 1999). This is an example of one of the pathways by which adverse socioeconomic circumstances may lead to worse health.

Mortality is the only outcome that has been studied in relation to SEC with intensive care patients. Mixed results have been found for SEC as a predictor of ICU mortality. Findlay et al., (2000) found that social deprivation (measured by the Carstairs score) did not influence outcome in 774 patients admitted to an intensive care unit in Glasgow. A study of 51,572 admissions to 99 ICUs between 1995 and 2000 by Hutchings et al. (2004), demonstrated a social gradient in mortality among one category of ICU patients, elective surgical patients, with lower SEC patients having a higher mortality rate. The SEC gradient for mortality was not explained by differences in case mix. The authors argued that the SEC gradient might be the result of unmeasured differences in health status at admission to an ICU. They also considered the possibility that patients received different care according to their SEC.

Another study (Latour et al., 1991) of 847 patients in three Spanish ICUs found higher mortality among patients of lower SEC (OR=1.61, p=0.020). However the mortality excess in lower SEC patients was largely accounted for by higher age and illness severity at admission (measured by the Simplified Acute Physiology Score, SAPS, Le Gall et al., 1993). The authors also concluded that there was no difference in care received according to SEC, because the ratio of therapeutic effort (measured with TISS) to illness severity (the TISS/SAPS ratio) was the same for the high and low SEC groups.

Welch et al. (2010) found an association between increasing deprivation, and an increased risk of mortality for all types of admission (medical, elective surgical and emergency surgical) to general ICUs in England. The sample consisted of 78,631 patients admitted to English ICUs between April 2000 and April 2002. The association remained after adjusting for age, sex, acute severity, medical history, source of admission and reason for admission (adjusted OR for most vs least deprived quintile, 1.19; 95% confidence interval, 1.10-1.28).

There has been no previous research on SEC in relation to psycho-social outcomes of intensive care. However, as associations have been found between both severe and common mental disorders and several indicators of SEC, a similar pattern could be expected for psychological morbidity occurring after intensive care. Worse socioeconomic circumstances have also been demonstrated to be a risk factor for post-traumatic stress disorder, with evidence from responses to traumatic situations including assault, air disaster and treatment for breast cancer (Brewin et al., 2000). Therefore SEC is likely to be a risk factor for post-ICU PTSD.

In the absence of studies examining associations between SEC and psycho-social outcomes of intensive care, are there parallels to be found in studies of other types of serious illness? The psychological response to cancer has been reported to vary according to SEC. Lower SEC patients with breast, prostate or colorectal cancer were more likely to have depression [OR:2.16, 95%CIs: 1.01-4.61, $p<0.05$], anxiety [OR: 2.59, 95%CIs: 1.49-4.51, $p<0.001$) and worse quality of life two months after diagnosis than patients with higher SEC (Simon & Wardle, 2008). Several other studies reported lower well-being in patients with cancer (including gynaecological and colorectal cancers) from lower SEC backgrounds (Dunkel-Schetter et al., 1992; Ramsey et al., 2000). In the area of heart disease, Clarke et al. (2000) found that SEC was an independent predictor of an important domain of HRQL (severe limitations of activities of daily living) at 1 year for patients with left ventricular dysfunction (odds ratios in the 1.5-2.0 range).

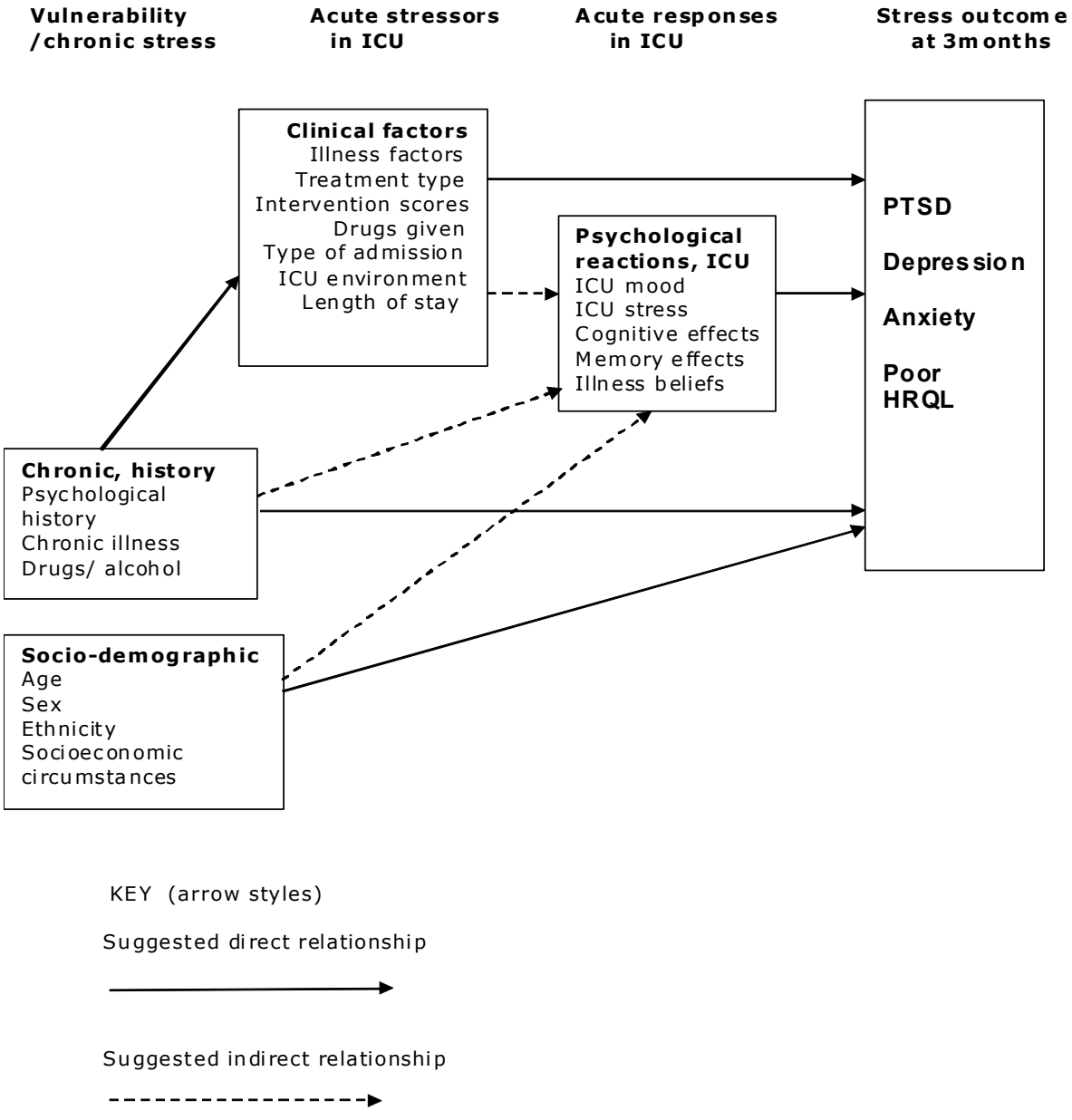
3.5 Conclusion

It is proposed that the development of psychological morbidity and poor HRQL after intensive care can be seen as a stress process in which stressors including illness, treatments and ICU environment elicit acute cognitive and emotional stress responses in patients, which may in turn trigger the development of stress outcomes such as PTSD and depression. The development of adverse psycho-social outcomes will be also be affected by individual vulnerability to stress, and socio-demographic factors. No consistent risk factors for psychological morbidity or poor HRQL after intensive care have been established by research so far. In this chapter I have reviewed the literature on the experience of ICU patients to help me identify the most likely potential predictors of ICU psychological outcomes. Clinical factors, healthcare factors, psychological factors and socio-demographic factors have all been identified as likely risk factors.

Figure 3.1 (see next page) is a diagrammatic representation of ways in which clinical, psychological, socio-demographic and chronic factors could be related and result in adverse psychosocial outcomes after intensive care. Figure 3.1 is not intended to suggest a statistical model, and not all possible variables, arrows and directions are included, due to the number of possible interrelationships. Potential stressors include clinical variables. Psychological factors include acute emotional and cognitive responses in the ICU and illness perceptions. Background vulnerability factors such as chronic health and socio-economic circumstances are also included. Possible outcomes are PTSD, depression, anxiety and poor health-related quality of life. As the discussion in this chapter suggests, there may be direct relationships between clinical, psychological and socio-demographic risk

factors and psycho-social outcomes, and indirect relationships between risk factors and outcome, possibly mediated by ICU psychological factors.

Figure 3.1: ICU stress processes



Chapter 4 Methods, cohort study

4.1 Aims, objectives and hypotheses

4.1.1 Aims

The aims of the cohort study were first, to achieve accurate estimates of the prevalence and extent of psychological morbidity and poor health-related quality of life of patients three months after discharge from intensive care. The second aim was to identify clinical, socio-demographic and psychological risk factors for adverse psycho-social outcomes three months after intensive care. The final aim was to identify how risk factors work together in the development of post-ICU psychological outcomes

4.1.2 Objectives

The objectives of undertaking this prospective cohort study were to:

1. Investigate clinical reasons for patients' admission to intensive care and interventions received in intensive care.
2. Identify the age, sex, ethnicity and socio-economic circumstances of the study cohort.
3. Assess patients' acute psychological responses in intensive care.
4. Find out how much patients remember from intensive care.
5. Detect the presence of intrusive memories of intensive care.
6. Follow up patients for presence and severity of PTSD, anxiety and depression three months after intensive care.
7. Assess health-related quality of life three months after intensive care.
8. Identify the strongest risk factors in each group – clinical, psychological and socio-demographic.
9. Examine whether the strongest risk factors were independent of each other.
10. Find out if a relationship between clinical factors and psycho-social outcomes was mediated by psychological factors.

4.1.3 Hypotheses

Based on the literature about psychological outcomes of intensive care reviewed in chapters one to three, the study had four broad hypotheses that encompassed a number of more specific hypotheses.

H1. More negative psycho-social outcomes will be associated with these clinical factors

a) Higher TISS (therapeutic intervention score, (Keene AR, 1983)
b) Higher number of organs supported
c) More days as a Level 3 patient
d) More days of sedation
e) More specified drug groups administered
f) More days of each type of organ support
g) Receiving a specified drug group (e.g. benzodiazepines)
h) Sepsis

H2. More negative psycho-social outcomes will be associated with these psychological factors

a) Higher ICU stress
b) Higher ICU mood
c) Little memory of the ICU stay
d) Early intrusive memories of the ICU
e) Higher delirium
f) Higher physical stress
h) Lower control
i) More negative illness perceptions

H3. More negative psycho-social outcomes will be associated with these socio-demographic factors

a) Socioeconomic groups with less control and fewer resources
b) Younger age
c) Female gender
d) Ethnic minorities

H4. The relationship between clinical risk factors and psycho-social outcomes will be partially mediated by ICU psychological factors

4.2 Study Design

I carried out a prospective cohort study of level 3 intensive care patients who were admitted to the critical care unit at University College Hospital, London. Assessment of psychological responses and collection of clinical and socio-demographic data took place before patients were discharged from the unit (time one). A follow-up assessment of psychological outcomes and HRQL was carried out three months after patients were discharged from the Unit (time two).

Risk Factors Clinical, psychological, socio-demographic risk factors

Outcome Variables PTSD, Anxiety, Depression, HRQL

The primary outcome PTSD. Other outcomes were secondary

Possible confounding factors Chronic illness, pre-ICU psychological problems

Possible mediating factors Acute psychological factors (also risk factors)

4.2.1 Justification for study design

After carrying out a systematic review and a wider but more informal literature review, I concluded that psychological morbidity and poor HRQL were serious problems after intensive care, but their prevalence had not been established. In designing the study I wanted to ensure there would be adequate participants, a highly representative sample and good quality outcome assessment so that an accurate estimate of the prevalence of PTSD and other post-ICU outcomes could be made. I decided to follow up patients at three months as this was an adequate time period to allow for the development of PTSD symptoms. A longer time period would lead to more uncertainty that the outcome was related to ICU risk factors.

I also concluded that little was known about the risk factors for intensive care. However the literature suggested that many aspects of critical illness and intensive care could be seen as potential stressors leading to stress outcomes. I therefore decided to test whether clinical factors that captured critical illness and ICU treatments, including drugs received, were predictors of poor psycho-social outcomes. It was also clear from the literature that patients experienced extreme emotional reactions and cognitive dysfunction in the ICU. I wanted to test whether these acute psychological responses were also risk factors for poor psycho-social outcomes. The literature also suggested that post-ICU psycho-social outcomes might vary according to age, sex or socio-economic circumstances. An alternative hypothesis to all the above was that post-ICU psycho-social outcomes were primarily related to chronic physical or mental health problems of ICU patients. Therefore I decided to include chronic ill health and previous psychological history

as possible confounding factors. It was important to use a prospective design to achieve the key aim of identifying these potential groups of risk factors for post-ICU psychosocial outcomes.

The study was designed to test multiple risk factors in three clusters – clinical, psychological and socio-demographic factors. After univariable analysis, all significant predictors were entered into multivariable linear regression models to identify the strongest risk factors. As this was an observational study, no causality could be assumed, but as outcomes were assessed three months after likely risk factors were measured, there was a greater likelihood of finding possible causal links than in a cross-sectional study. If a retrospective design had been chosen, measurement of some risk factors would be subject to recall bias, and there would be a risk of the cohort being less representative than in a prospective study. Chronic factors were also entered into the multivariable regressions as potential confounding variables.

The ICU stress model (chapter three, figure 3.1) suggested that as well as direct relationships between clinical variables and outcomes, there could be indirect relationships mediated by ICU psychological factors. Therefore I decided to carry out analysis to test if psychological factors mediated the relationship between clinical variables and outcomes. Kraemer et al. (2001) noted that medical disorders, particularly in psychiatry, may often have multiple causal chains rather than a single cause. Often the effect of one risk factor may only be understood in relation to all the others. There are still many questions about which methodological tools should be used to tease out relationships between risk factors. Moreover terminology in risk factor research is confused and in need of clarifying. Risk factors may variously be described as intervening variables, mediating variables, confounding variables and effect modifiers (among other commonly used terms). A full consideration of this vexed issue is beyond the scope of this PhD, but it is important to clarify the definitions I have used of mediating and confounding variables. I have used the definition of a mediator as a variable that accounts or partially accounts for the relation between the predictor and outcome and may be on the causal pathway between predictor and outcome (Baron & Kenny, 1986). A confounder is defined as "a variable that can cause or prevent the outcome of interest, is not an intermediate variable, and is associated with the factor under investigation" (Last, 1995, p.35).

4.3 Ethics

I applied to the Joint UCL/UCLH Committees on the Ethics of Human Research (Committee Alpha) for ethical approval to carry out this study. The Ethics Committee had concerns that either the baseline psychological questionnaire or the follow-up questionnaire could be upsetting for some patients and wanted to know if an internal referral to a psychologist would be possible. This was my response:

"In response to the committee's judgement that the assessments may be upsetting for some patients, I have met the clinicians at the Critical Care Unit to discuss what further psychological provision could be provided. Unfortunately the CCU has no resources to provide long-term psychological support for any of their patients but the following is what we propose:

At Time 1 (in the ICU): If a patient gets distressed while answering the questionnaire given around the time of discharge from the CCU, the researcher will alert the local collaborator, Dr David Howell, or another CCU consultant. He will arrange for the patient to be seen by the unit's part-time clinical psychologist, Dr Anthony Hazzard. If Dr Hazzard is not immediately available and the problem is acute, the patient could be seen by the acute on-call liaison psychiatry team, who are available to see patients immediately.

At Time 2 (three months follow up): If I detect adverse psychological outcomes in a patient's responses to the follow-up questionnaires, the patient will be offered an urgent appointment at the intensive care follow-up clinic with Dr Howell and Dr Hazzard, where all concerns and issues can be raised. However the follow-up clinic cannot offer any former CCU patients continuing psychological treatment, due to a lack of resources. Their usual practice is to write to the GP if they believe further psychological support is appropriate, and they would do so in these cases.

In the unlikely event that an acute incident is triggered by the follow-up assessment, the researcher will contact Dr Howell. In addition to being one of the Critical Care Consultants, Dr Howell is also one of the Acute Medical Physicians at UCLH and works closely with acute psychiatry services. If a patient assessed at home requires urgent review for an acute psychological deterioration, Dr Howell will be able to arrange for the patient to be seen by the on-call liaison psychiatry team in the emergency department at the hospital."

The Ethics Committee was satisfied with these arrangements and gave approval for the study to continue on September 10, 2008. The letter of approval is in Appendix

3. They also approved an amendment to the study based on changes made after the pilot stage on June 8, 2009 (Appendix 5).

4.4 Setting

The Critical Care Unit at University College Hospital is a 27-bedded unit providing both general adult intensive care and high dependency care. The hospital is sited in central London and serves a large and diverse local population. The CCU is a tertiary referral unit (accepting patients requiring intensive care over and above what can be offered to them locally). Its admission policy is based on the principle that "patients requiring our services are generally better off with us, accepting that nurse and doctor to patient ratio may not be as high as desired" and the declared aim is "the greatest good for the greatest number" (UCLH intensive care, 2006, p.1). There were 1292 admissions to the unit in 2005, the most recently reported year (Icnarc, 2007). Mean age of patients was 54.9(19.6) and 43.3% of patients were male (Icnarc, 2007).

In July-December 2005, admissions were 55.7% non-surgical, 35.5% elective surgical and 8.9% emergency surgical (Icnarc, 2007). Mean Apache II score on admission was 17.5 (7.3). The top five reasons for admission to the Critical Care Unit in July-December 2005 were septic shock, pneumonia, head or neck tumour (not intra-oral or intra-cranial), intro-oral or pharyngeal tumour, and large bowel tumour. Mortality was 13.7% within the Unit and 21.3% at ultimate hospital discharge. The critical care unit has an outreach team of nurses with critical care training and experience that visit patients on other wards after they leave critical care. All patients receive an after-care booklet after discharge from the ICU explaining about physical and psychological symptoms they may experience during their recovery period. All patients who were in critical care for three days or more are offered an appointment to attend a follow-up clinic run by a medical consultant, a nurse consultant and clinical psychologist three months after discharge from hospital. Of 352 patients offered a follow-up appointment, 100 accepted and 247 declined. The other five had died. The clinical psychologist is also available to see patients in the unit one afternoon per week

4.5 Participants

Participants were all consecutive, eligible "level 3" patients who spent more than 24 hours in the University College London Hospital critical care unit (CCU) between November 2008 and September 2009. Level 3 is defined as

a) Patients needing advanced respiratory monitoring and support (excluding patients needing short term i.e. less than 24 hour routine postoperative ventilation with no other organ dysfunction).
b) Patients needing monitoring and support for two or more organs (one of which may be basic or advanced respiratory support)
c) Patients with chronic impairment of one or more organ systems sufficient to restrict daily activities and who require support for an acute reversible failure of another organ system.

This definition of level 3 (The Intensive Care Society, 2002) was revised towards the end of the data collection period (The Intensive Care Society, 2009) to clarify some aspects of the original version. The main revision was that "basic respiratory" and "basic cardiovascular" should not count as two type of organ support if they occur simultaneously. As this had not been clarified when I was recruiting patients, there may be patients in this study who would not be classified as Level 3 patients under the revised criteria.

Complete inclusion and exclusion criteria were as follows:

Inclusion criteria:

- All patients who were "level 3" for more than 24 hours.
- Ready for discharge from the CCU or just been discharged.
- Awake, alert and orientated.
- Able to communicate.

Exclusion criteria:

- Not English-speaking/no translator available.
- Chronic or continuing acute confusion (prior diagnosis or nurse assessment).
- Communication problems or sensory impairment due to e.g. deafness; inability to speak, read or write. Absence of hearing aid or reading glasses.
- Receiving palliative or terminal care.
- Reduced consciousness e.g. Glasgow Coma score<15 (Teasdale & Jennett, 1976).
- Patient less than 18 years of age.

4.6. Procedure

4.6.1 Baseline assessment at discharge from the ICU (time one)

During the recruitment period I visited the critical care unit every week-day (apart from annual leave) to identify eligible patients by checking the daily lists of patients in the Unit. It was also possible to track patients who were admitted at weekends by using the patient lists. It was necessary to consult the electronic patient notes to double-check that patients met Level 3 criteria, as the Unit's system of categorising patients on the electronic record did not exactly fit with the ICS criteria (2002). If patients who were identified as Level 3 for more than 24 hours improved and were stepped down to level 2 or level 1 care, they were approached by a research nurse

who explained to them about the study, using the script written by me and reproduced in appendix 9. The research nurses also gave patients a patient information sheet (PIS) describing the study and a consent form to take part in the study (appendix 7). If patients felt unable to read the PIS the research nurse read them a shortened version of the PIS (appendix 8).

Unless the patient told the research nurses immediately that they did not wish to participate, I visited them after 24 hours or at a time specified by the patient. I would ask if they had read and understood the PIS. Often, understandably, they had not read it, so I would go through it with them, and answer any questions they had about the study. I explained the consent procedure and emphasised that they could withdraw from the study at any time without giving a reason. If the patient gave their consent to take part in the study, I would ask them to sign the consent form (appendix 10). I asked if they wanted to answer the questionnaire now or later.

Usually the assessment using the ICU baseline psychological questionnaire (appendix 12) took place soon before their discharge from the ICU, or occasionally soon after their discharge to another ward. Usually, due to patients' ill-health and fatigue, I read the questionnaire to patients and wrote down their answers, but on some occasions patients preferred to complete the questionnaire alone and I waited with them in case of queries or misunderstandings, or collected it from them later. It usually took about fifteen minutes to complete the questionnaire. I told patients that I would be sending them a postal questionnaire about their ICU experiences after three months.

Some Level 3 patients unfortunately deteriorated and died in the Unit; some others were transferred to another hospital such as the Heart Hospital (a sister hospital to UCH) before it was possible to approach them about the study. On some occasions when patients had expressed willingness to take part, I visited them and found that they were too confused to take part or were unable to communicate easily for a number of reasons. For example some patients who had had maxillofacial surgery (a specialism offered by UCH) were unable to talk, either temporarily or permanently. This combined with sight or hearing problems and an absence of their usual hearing aids or spectacles made communication too effortful for these patients. In some cases confused patients became more lucid as they began to recover and the effects of sedation and opiates wore off, and I was able to assess them on subsequent visits. In some cases I visited patients several times before

their discharge but was unable to carry out the assessment because on each occasion they were receiving clinical care or sleeping.

If patients appeared tired or upset during the ICU assessment, I would ask them if they would prefer not to finish the questionnaire, or to finish it at another time. I would visit them at a time convenient to them to complete the questionnaire, if that was requested. If any patients appeared at all upset or anxious after finishing the questionnaire I stayed on to talk with them until they said that they felt calm or "okay". Some patients were not upset but were very interested in talking about issues raised by the questionnaire, such as the experience of hallucinating in the intensive care unit, as nobody had told them that this was a fairly common experience. Only one patient appeared to be very upset by the questionnaire. This was an eighteen-year-old cancer patient and I fetched her father at her request, and talked to him afterwards to check that she was not in need of any further psychological support. As this was during the pilot period I also removed one item from the questionnaire – about "fear of dying" and changed the wording of another item – in response to this patient's reactions. On a few occasions where I thought a patient was possibly in need of general psychological support (for example they were having very troubling intrusive memories about ICU after transferring to the ward) I would mention them to a member of the critical care outreach or follow-up team.

4.6.2 Follow-up assessment three months after ICU discharge (T2)

Three months after patients were discharged from the intensive care unit, I checked with hospital databases to find out if patients were still alive and where they had gone after leaving hospital. I then posted them a follow-up questionnaire about symptoms of PTSD, anxiety, depression and HRQL, and socio-economic circumstances (see Section 4.7.2 and Appendix 13) along with a letter (Appendix 13) reminding them about their participation in the study while in the ICU, and a stamped addressed envelope. After ten days I sent reminder post-cards to patients if they had not sent back the questionnaire. If they had not returned the questionnaire after a further week, I phoned patients once to check that they had received the questionnaire and to find out if they wanted any help in answering the questions. This proved to be worthwhile as some patients had not received questionnaires due to the hospital holding the wrong address for them in their records, or to postal strikes which took place during this period. I was able to post new questionnaires to these patients and thus increase the follow-up rate.

4.6.3 Clinical data

I collected most of these data after patients had given consent and completed the ICU baseline questionnaire, from electronic records held in the critical care unit. I recorded them on a patient data form (see Appendix 11). Data that were not accessible in electronic records were provided to me by the unit data manager from other databases. Some additional data were collected but were not eventually analysed in the study, to reduce the number of variables and for other specific reasons.

Table 4.1 Clinical data collected for cohort study (excluding drugs)

Variable	Categories or scoring	Further notes/references
Type of admission	Elective surgical (elective/scheduled); Emergency surgical (emergency /urgent); Non-surgical	Data collected by the CCU as part of ICNARC case mix programme (www.icnarc.org)
Admitted to ICU from….	Theatre/recovery; Ward; A&E; other	**Other** other ICU, other hospital(non-ICU), or other.
Post-hospital discharge	Discharged home; Transferred to other hospital; Residential care or rehab; Readmission(s);Not discharged from hospital. Died after ICU discharge.	**Readmissions** to hospital since discharge home **Not discharged** still in UCH at 3m **Died after ICU discharge–**in ward or at home
Illness severity – Apache II score (Knaus et al., 1981)	Acute Physiology and Chronic Health Evaluation, scored from 0-71, used as measure of disease severity and predictor of mortality in ICU.	Point score calculated from 12 physiological measurements during first 24 hours, and prior health information
Primary body system -reason for admission (www.icnarc.org)	**1** Respiratory **2** CV **3** GI **4** Neurological **5** Trauma **6** Poisoning **7** GU **8** Endocrine **9** Haematological **10** Musculoskeletal **11** Dermatological	Each patient coded for primary reason admission, by ICU using Icnarc coding method with body system as 1 of 5 coding levels
Hospital length of stay	Number of days - this admission.	
ICU Length of stay	Total number of days patient spent in Critical Care Unit.	Includes days spent as level 1, 2 or 3 patient in ICU
"Level 3" days	Number of days in Critical Care Unit that patient received level 3 care.	Number of level 3 days is recorded by the CCU for the DoH
TISS score (Keene et al., 1983)	Therapeutic intervention scoring system. The TISS patient classification: Class **1**<10 points, **2** 10-19 points **3** 20-39 points **4** >40 points	Points for each ICU activity e.g. monitoring, dressing changes, drugs and major interventions (e.g. ventilation, haemodialysis)
Days advanced respiratory support (ARS)	Number of days received (definition of ARS chapter one, Section 1.2.5)	Number days organ support recorded by the CCU for the DoH
Days basic respiratory support	As for ARS	
Days advanced CV support (ACVS)	As for ARS	
Days basic CV support	As for ARS	
Days renal support	As for ARS	
Days neuro support	As for ARS	
Days GI support	As for ARS	
Days dermatological support	As for ARS	
Days liver support	As for ARS	
Number types organ support	Number organs supported	Maximum = 9 (including advanced/basic ARS and ACVS)
Number drug groups	Number of drug groups received in ICU	Maximum number – seven
Sepsis (Dellinger et al., 2008)	Sepsis diagnosed (1) not diagnosed (0) using biomarkers including CRP, WCC	CRP=C-reactive protein, WCC=white cell count

Table 4.2 Drug data collected for cohort study

Variable	Categories/Scoring	Notes/details
Days of Sedation	Number of days patients were sedated with either benzodiazepines or anaesthetics as in rows below	Staff record in electronic notes
Hypnotics	Coded 1 (received)or 0 (did not)	Zopiclone, temazepam
Benzodiazepines for sedation	Coded 1 (received) or 0 (did not)	e.g.midazolam, diazepam, lorazepam
Anaesthetics for sedation	As above	Propofol, ketamine, isoflurane, remifentanil, clonidine,
Antipsychotics	As above	Haloperidol, chlorpromazine
Inotropes or vasopressors	As above	e.g.Adrenaline, noradrenaline, dobutamine, vasopressin
Steroids received	As above	Methylprednisolone, prednisolone, hydrocortisone, dexamethazone
Opioids received	As above	Fentanyl, methadone, morphine sulphate, tramadol, diamorphine hydrochloride, dihydrocodeine,
Number drug groups	Number of drug groups with potential psychoactive effects received in ICU	Maximum number – seven (as in rows above)

Three drug groups had too few participants who received them in the CCU to make analysis meaningful. These were non-opioid analgesics (gabapentin), anti-epileptics and anti-depressants. A variable about patients' destinations after discharge from the CCU was not used, as 95% of patients were discharged to a ward, so other categories of the variable were too small. Comorbidities were intended to be used in the study as a variable that would capture important information about patient's chronic health status. However the only data initially available for this (Icnarc 2007) included only extremely severe conditions such as biopsy-proven cirrhosis and very severe respiratory disease. Therefore it was not a sensitive measure of chronic health problems; 17% of patients were recorded as having co-morbidities with this measure. Later another source of data on chronic health was used (see 4.6.6) Data about reasons for admission to the critical care unit were entered, but it was not possible to code them in a meaningful way because of the large number of different conditions. Another intended variable, "consultants' speciality" had too many categories and did not contribute helpful information to the clinical picture.

4.6.4 Socio demographic factors

During data collection I recorded patients' age, date of birth, gender, and address including postcode from electronic notes held in the CCU. Postcode was later used to derive Index of Multiple Deprivation 2007 (Communities and Local Government, 2010) quintiles. The ICU baseline questionnaire included questions about occupation, ethnicity (Office of National Statistics, 2010a) and education level (no qualifications, GCSE or equivalent, A' level or equivalent, college or equivalent, degree or above). The follow-up questionnaire included questions pertaining to the National Statistics Socio-economic Classification (NS-SEC; Office of National Statistics, 2010b).

Contact details: During baseline assessment patients were asked to give a home number, mobile number and relatives' numbers to increase the chances of being able to contact them for the follow-up assessment. If they could not remember them, any available phone numbers were noted from the electronic database in the CCU. It was not possible to contact some participants at the follow-up stage as they were homeless, moving between addresses, or all contact details given to the hospital were incorrect.

4.6.5 Socio-economic circumstances

4.6.5(i) The National Statistics Socio-economic Classification (NS-SEC)

Two socio-economic classifications have been widely used in the UK for official statistics and academic research: Social Class based on Occupation (SC, formerly Registrar General's Social Class) and Socio-Economic Groups (SEG). However it has been recommended by the Economic and Social Research Council that a new occupationally-based classification, NS-SEC (Office of National Statistics, 2010) should replace both SC and SG. NS-SEC was developed from the Goldthorpe Schema (NS-SEC User Manual, ONS, 2010) a sociological classification that has been widely used in research because it is conceptually clear and accepted internationally. NS-SEC was constructed to measure employment relations and conditions of occupations. It is argued that these are central to showing the structure of socio-economic positions in modern societies and helping to explain variations in social behaviour. NS-SEC categories distinguish different ways by which employees are regulated by employers through employment contracts. There are three main forms of employment regulation.

1. Service relationship. The employee's service is compensated by immediate rewards (eg salary) and long-term, prospective benefits. This is typified by Class 1 of the full eight-class version of NS-SEC; higher managerial and professional occupations.

2. Labour Contract. Employee gives discrete amounts of labour in return for a wage calculated on amount of work or time. This is typical of Class 7, routine occupations.

3. Intermediate. Aspects of both forms of employment regulation, typical in Class 3 (intermediate occupations e.g. intermediate clerical and administrative jobs).

The information required to create the full NS-SEC is a) occupation, coded to 353 unit groups (OUGs) from the Standard Occupational Classification 2000 (Office of National Statistics, 2010c) and b) details of employment status: whether an employer, self-employed or employee; whether a supervisor; and the number of employees at a workplace. For this study it was necessary to use the self-coded, self-completion version of NS-SEC (Office of National Statistics, 2010) as it was part of a postal questionnaire. The self-coded version of NS-SEC has five classes: 1.

Managerial and professional occupations 2. Intermediate occupations. 3. Small employers and own account workers. 4. Lower supervisory and technical occupations. 5. Semi-routine and routine occupations. In the self-coded version, occupational class is derived using a matrix including occupation (the respondent ticks one of eight categories of occupation), employment status and size of organisation.

The self-completion questionnaire was included in the follow-up questionnaire sent out to patients at three months (appendix 13). For complete coverage, I wrote and added further questions pertaining to students, retirement, spouse's income and unemployment. Retired and unemployed people were asked to answer the questionnaire in reference to their last main job, or their spouse's job if relevant, but many did not do so. A sixth category "not classified" was created to include students, those who gave inadequate employment details, and retired or unemployed people who did not answer questions about their previous job. A further problem using the self-employment questionnaire was that several participants self-classified their occupation incorrectly on the self-report questionnaire. This was discovered when checking their occupational self-classification against the occupation they gave when answering the ICU baseline questionnaire. Where I had sufficient information about a person's occupation from their baseline questionnaire I corrected the self-classification. It was initially decided that for the purposes of comparison and to strengthen conclusions drawn about the effect of socio-economic circumstances, another socio-economic indicator would also be used in the study. As I had already recorded patients' postcodes during data collection it was possible to derive an area-level measure of deprivation using the Index of Multiple Deprivation, 2007.

4.6.5(ii) Index of Multiple Deprivation, 2007

The Index of Multiple Deprivation (IMD) 2007 is part of the UK government's official measure of multiple deprivation at small area level (Communities and Local Government, 2010). It is based on Lower Super Output Areas (LSOAs); in most cases LSOAs are smaller than wards, with an average population of 1500 people. There are 32,482 LSOAs in England. The IMD is composed of 37 different indicators covering seven domains of deprivation; Income; Employment; Health and disability; Education; Skills and training; Barriers to housing and services, and Living environment and crime. These have been weighted and combined to create the overall IMD 2007. LSOAs are ranked by the IMD 2007 so that the LSOA ranked 1 is the most deprived and that ranked 32,482 is the least deprived. For this study participants were categorised according to IMD 2007 quintiles, with quintile one as the least deprived quintile and five the most deprived quintile.

However, although I used the IMD measure when reporting descriptive data, ultimately I decided to use the NS-SEC (ONS, 2010) rather than the IMD (Communities and Local Government, 2010) to represent patients' socio-economic circumstances in the statistical analysis. My reasons for this decision were that the majority of the cohort came from two London boroughs in which most areas are classified as being deprived. But area-level deprivation is not always an indicator of individual SEC. In Camden, according to the 2009 Camden health profile (The Association of Public Health Observatories, 2010a) 69% of residents live in areas of high deprivation (fourth and fifth quintiles) and none live in an area of least deprivation (first quintile). In Islington (The Association of Public Health Observatories, 2010b) 97.3% of people live in areas of high deprivation (fourth and fifthe quintiles). This could give rise to the ecological fallacy (Schwartz, 1994) that occurs when relationships between variables that hold at an area level are assumed to hold at the individual level. For example this cohort included five people from Camden or Islington whose occupations were correctly classified as managerial/professional (class 1), but who also lived in one of the most deprived postcodes (fifth IMD quintile).

4.6.6. Chronic factors and patient history.

As data on these factors were not easily available from the electronic records in the critical care unit, they were not initially collected by me. However assistance became available later from a young medical researcher. She carried out a meticulous search through medical and nursing records to identify details of the participants' chronic physical diseases, cancer, alcohol and recreational drug use, and prior psychological problems.

4.7 Psychological measures

4.7.1 ICU baseline questionnaire

This questionnaire was constructed by me to measure mood in the ICU, stress in the ICU, illness perceptions, memory and some socio-demographic data (appendix 12). The sections on mood and illness perceptions were adapted from validated questionnaires; the section on ICU stress was created by me for this study and based on literature about patient experience in the ICU; and questions in the memory section were based on literature about the effects of the ICU on memory, with guidance from Professor Chris Brewin, an expert on intrusive memories and PTSD at University College London. I wanted to use a questionnaire that would cover a range of key psychological responses in intensive care (anxiety, depression,

positive emotion, anger, delirium, control, physical stress, support, memory of ICU and intrusions about ICU) but that would not be too long or difficult for seriously ill patients. No existing questionnaire covered all these areas or was sufficiently brief and simple. Variables extracted from the baseline questionnaire were ICU mood, ICU stress, amnesia for ICU, intrusive memories of ICU and illness perceptions. I used three criteria to construct the baseline questionnaire:

a) questionnaire items or scales had good construct validity
b) where possible, questionnaire items or sub-scales had been widely used and validated in this patient group or similar patient groups
c) the questionnaire was short and simple to administer to seriously ill patients in the ICU

4.7.1(i) Mood states in ICU

These were detected using fifteen items from POMS, the Profile of Mood States (McNair, 1984). The full POMS has 67 items and six sub-scales. I chose to use POMS because of the range of mood states it encompasses and the brevity of its one-word items. POMS has achieved wide acceptance as a measure of psychological distress in a variety of healthy, physically ill and psychiatric populations (Curran et al., 1995). However, physically ill patients may take up to 20 minutes to complete the full POMS (Shacham, 1983). Therefore the full POMS would have been too time-consuming and tiring for ICU patients to complete, along with other items it was necessary to include in the questionnaire. Several short forms of POMS have been validated for use in patient groups, including breast cancer patients, bone marrow transplant patients and renal transplant patients (Cella et al., 1987; Curran et al., 1995; Shacham, 1983). However the items selected in these versions did not exactly fit the purpose of this study. Therefore I adapted the original POMS by taking three items (symptoms) each from five of the POMS scales – Tension-Anxiety, Depression-Dejection, Vigour-Activity, Anger-Hostility and Confusion-Bewilderment. The original sub-scales were of varying length, of between seven and 15 items each. I intended to use this, not to "diagnose" depressive or anxiety disorders, but to give a brief snapshot of a patient's transient moods during the days before their discharge from the ICU. I did not take items from the sixth POMS scale of Fatigue-Inertia as I expected that all patients would be very fatigued and therefore there would be little variance in this factor.

I selected some POMS items because they had high loadings on the relevant factor in the original confirmatory factor analysis (McNair, 1971). Six independent factor analytic studies were conducted in the development and validation of the POMS. A correlation of 0.30 or higher between item and factor was considered significant. For example the item "helplessness" had the following loadings on the Depression

scale in six studies: 47, 54, 51, 43, 33, 39. The item "nervous" loaded highly on the Anxiety scale: 61, 58, 56, 73, 56, 57 and was therefore used. I also selected some items because they reflected symptoms that might be particularly relevant for ICU patients, based on previous literature. For example panic is a common state in ICU (Granberg et al., 1998) and therefore "panicky" was selected from the POMS Anxiety Scale. I included "terrified" and "helpless" from the POMS Depression scale as they are important components of a subsequent diagnosis of PTSD: Criterion A2 for a PTSD diagnosis is that "the person's response [to a trauma] involved intense fear, helplessness or horror" (American Psychiatric Association, 1994).

The scoring for each item was 0-4 for responses ranging from **not at all** to **extremely**. Scoring was reversed for positively worded items, e.g. "cheerful". Sub-scale scores were obtained by adding the three items together to give a total from 0-12. A total mood disturbance score (TMDS) can also be obtained from POMS (McNair 1984). TMDS scores for my shortened version ranged from 0-60.

Reliability Cronbach's α for the total mood scale used in this study was 0.904 based on 151 cases (baseline sample) and 0.906 based on 95 cases (follow-up sample). Therefore the total scale had very good reliability, and it was reasonable to use the total mood disturbance scale as a variable in the analysis.

Factor analysis When I carried out a confirmatory factor analysis of this version of POMS, there were three factors rather than the expected five. Variance explained was 63%. One factor was comprised of all the negative mood words (terrified, nervous, panicky, tense, unhappy, forgetful, confused, helpless; Cronbach α = 0.886), one was all the positive terms (alert, cheerful, lively, able to concentrate, Cronbach α = 0.812) and one was anger (angry, bad-tempered, resentful, Cronbach α = 0.803). It has previously been found in factor analysis of psychological questionnaires that negative and positive items may cluster together and form two separate factors. These may not reflect true factors but a response bias introduced by negative or positive wording (Hankins, 2008). As I was interested to find out if there were specific effects related to specific ICU mood states I decided to use the original five factor structure for POMS in my analysis. Cronbach's α was 0.809 for Anxiety, 0.722 for Depression, 0.803 for Anger, 0.786 for Positive Emotion and 0.684 for Mental Confusion. As Cronbach's α over 0.7 is regarded as acceptable, I decided it was reasonable to use these sub-scales in the analysis, although mental confusion was clearly less reliable than other sub-scales. (In fact as part of the data reduction process, most statistical analyses were calculated using total mood disturbance scores rather than subscale scores.

However I carried out sub-group analysis to look at the effects of specific ICU mood states as predictors of outcome).

4.7.1(ii) Perceived stress in ICU

I created the 18-item ICU Stress scale (ICUSS) specifically for this study to detect which stressful ICU experiences a participant had experienced and how stressful they perceived them to be. The ICUSS also included positive, protective factors reported in the psychological literature on intensive care, such as feeling in control and receiving emotional support. Other published questionnaires on ICU stress (e.g. Granja et al., 2005; Novaes et al., 1997; Rattray, 2005) were either too long for participants to complete in this context, or did not encompass the primary stressful ICU experiences highlighted in the literature. However I noted their content and used it to inform the selection of items for the ICUSS. When designing the scale I envisaged four sub-scales – one for **physical stress** with items on pain, discomfort from tubes, difficulty breathing and being unable to sleep; one for **disorientation** with items on hallucinations, nightmares, disorientation, isolation, agitation and feeling unreal; one for **self-efficacy** with items on feeling in control, confidence in getting better and ability to communicate and one for **emotional support** in the ICU, including support from staff and family and respect for one's dignity.

Response options for each item ranged from **not at all** to **extremely** (0-4) and scores were summed for each sub-scale. A total ICU stress score was obtained by reverse-scoring the positive items and summing all items to produce a score ranging from 0 to 72, with 72 as the worst possible stress. Cronbach's α was 0.818 based on 145 cases (whole sample), and 0.831 based on 94 cases (follow-up sample). As reliability of the total scale was acceptable, total ICU stress was used as a variable in the analysis. As this was a new scale, as well as piloting it with ICU patients (see **4.7.1 (vi)**), it was important to carry out factor analysis, to check if the original envisaged structure was evident. Using the Promax method of principal components analysis, four factors were detected; Physical stress (dyspnea, anxiety about breathing, pain, discomfort from tubes), "Delirium" (disorientation, nightmares, hallucinations, isolation, agitation), control (communication, control, confidence, information and sense of unreality) and support (dignity, staff support, family and friends support, sleep). The sleep item had a much lower loading of 0.393 on the "support" factor than other items. The structure matrix of the four factors of ICUSS can be seen in Table 4.2. Cronbach's α alpha was acceptable for three of four scales; 0.777 for Control; 0.751 for Physical Stress; 0.741 for Disorientation. Cronbach's α for the support scale was 0.493 and was therefore not acceptable. When the sleep item was dropped from the support scale there was no improvement as α was reduced to 0.453. It will be necessary to work on the

support sub-scale to improve reliability if it is to be retained in future studies. The "delirium" sub-scale was not intended to represent the DSM-IV (American Psychiatric Association, 1994) diagnosis of delirium, but consisted of features frequently detected in ICU patients who are delirious or sub-delirious, such as hallucinations, disorientation and agitation.

Table 4.3 Factor Analysis of the ICUSS showing four factors

Kaiser-Meyer-Olkin Measure of Sampling Adequacy.		.792
Bartlett's Test of Sphericity	Approx. Chi-Square	813.841
	df	153
	Sig.	.000

	Component			
	1	2	3	4
Control (r)	.777	.285	.222	.141
Communication(r)	.728	-.040	.269	.336
Confidence (r)	.673	.296	.232	.306
Information (r)	.649	-.062	.359	.596
Feeling unreal	.623	.314	.575	.038
dyspnea	.259	.836	.272	.003
Anxiety breathing	.356	.807	.400	-.034
Pain	.048	.647	.113	.038
Discomfort – tubes	.131	.630	.440	-.009
Disorientation	.559	.366	.780	.172
Nightmares	.031	.242	.730	.132
Hallucinations	.262	.163	.686	-.113
Isolation	.409	.290	.590	.534
Agitation	.466	.485	.582	.155
Dignity (r)	.275	-.023	.202	.722
Emotional support-staff (r)	.374	.013	-.032	.623
Emotional support-family (r)	-.012	-.048	-.080	.570
Sleep (r)	.377	.332	.220	.393

Rotation Method: Promax with Kaiser Normalization. (r) = reversed scoring

4.7.1(iii) Patients' illness perceptions

The eight items of The Illness Perceptions Questionnaire-Brief (Broadbent et al., 2006; Broadbent et al., 2006) were included in the questionnaire to tap into patients' subjective cognitions about the nature of their medical condition. These cognitions have been shown to be predictive of many health outcomes (Weinman & Petrie, 1997; Weinman et al., 1996). After the piloting of the ICU baseline questionnaire, three items were dropped to shorten the questionnaire. Items included in the final version were

1. **Timeline** (how long does patient thinks their condition will last?)
2. **Control** (how much control does patient feel they have over the condition?)
3. **Concern** (how concerned is the patient about the condition?)

4. **Understanding** (does the patient understand their condition?)
5. **Emotional representation** (does the condition affect patient emotionally?).

Each item was scored separately on a Likert scale of 0-10. Scales were anchored at both ends with phrases such as *not at all concerned* (0) or *extremely concerned* (10).

4.7.1(iv) ICU memories

Six items on ICU memory were included in the questionnaire. Existing ICU memory scales were too long and did not include a key factor in my study, early intrusive memories of ICU. The memory items used in the questionnaire were based on the literature concerning the effects on memory of being in ICU (e.g. Jones et al., 2001) and on discussions with Professor Chris Brewin, a clinical psychologist and expert on intrusive memories. The items were designed to detect how much patients could remember of their ICU experience, and the presence and nature of early intrusive memories about the ICU (before discharge from the ICU). If intrusive thoughts were present they could be categorised as factual or unreal. Previous studies referred to "delusional" memories but I preferred the term "unreal" as a more accurate reflection of ICU memory content (see chapter 7).
Memory items were:

a) Memory of admission to ICU.
   Scores: **0** (no) **1** (yes)
b) Memory of ICU stay.
   Scores: **0** (very little) **1** (some) **2** (most)
c) Intrusive memories of ICU? - if yes, content described.
   Scores: **0** (none) **1** (yes, factual) **2** (yes, unreal)
d) Frequency of intrusive memories
   Scores: **1** (less than once a day) to **3** (many times a day)
e) How distressing are ICU memories?
   Scores on Likert scale from **0** not at all distressing
   to **7** extremely distressing.

4.7.1(v) Cognitive function

At the beginning of the study, the baseline questionnaire included the Mini Mental State Exam (MMSE; Folstein et al., 1975) as I hoped to get a baseline measurement of patient's cognitive state. However after the pilot stage, I dropped the MMSE from the questionnaire for reasons to be explained in the next section.

4.7.1(vi) Piloting the ICU baseline questionnaire

The questionnaires used at both time points were piloted among ICU patients. As the ICUSS was a new measure designed specifically for this study it was particularly important to pilot it for acceptability and face validity. Although most other measures had been widely used and validated, they had been shortened by me and

it was also important to find out if the package of measures was acceptable to respondents.

The ICU baseline questionnaire was piloted among the first ten participants in the study (pilot questionnaire in appendix 4). Piloting was not carried out in a separate group of patients because of the difficulty in enrolling sufficient ICU patients for a fully powered study within the allotted time period. All ten patients said they found the questionnaire acceptable, clear and not too burdensome. They did not object to answering any of the questions. The average time taken to complete the questionnaire was 25 minutes, including the time taken to complete the MMSE. However two among the next ten patients I assessed had problems with the questionnaire. One patient found two of the questions upsetting, and another found it too tiring to complete the questionnaire. My own instinct when helping patients complete the questionnaire was that it was somewhat long and that patients were becoming tired during the last part of the questionnaire.

I therefore amended the questionnaire with guidance from my supervisor John Weinman, professor of health psychology at Kings College, London. I removed two items from the ICU Stress Scale (ICUSS), three mood items, and three illness perception items. I had noticed that some very fatigued patients found it difficult to understand and answer the IPQ questions. The removal of these items and other minor changes did not jeopardize the measurement of the mood and stress constructs, as there remained sufficient items to generate reliable measures and assess scale reliability. However there was an unfortunate loss of information about patients' illness perceptions. The items that caused potential upset (to a very young patient) were Q14 from the ICU Stress scale (Have you felt frightened of dying?) and Q2 from the IPQ:

Q: How long do you think your medical condition will continue?

A: **A very short time** 0 1 2 3 4 5 6 7 8 9 10 **forever**

I removed ICUSS 14, and amended IPQ2 from "forever" to "a very long time".

I also decided during the pilot stage that administering the mini mental state exam (MMSE) was not worth the extra time it was taking. Some elderly patients were unable to complete it because of current difficulties with reading or writing, or physical weakness (the MMSE involves writing, spelling and drawing). Those patients who were able to complete it all gained very similar scores (in the normal range). Leaving out the MMSE reduced the time taken to complete the

questionnaire to 15 minutes on average. The ten patients who participated in the pilot of the baseline questionnaire remained in the study cohort.

4.7.2 ICU follow-up questionnaire

The questionnaire that was posted to patients three months after discharge from the ICU comprised scales to detect PTSD, anxiety and depression, a brief quality of life measure, questions about pre-ICU mental health and questions about socio-economic circumstances. Each section of the questionnaire is described in greater depth below. For full questionnaire, see appendix 13.

4.7.2(i) PTSD measure

As the primary outcome of this study was PTSD, I chose to use a questionnaire that could be used to diagnose PTSD according to DSM-IV criteria (American Psychiatric Association, 1994).The PDS, Posttraumatic diagnostic scale, (Foa et al., 1997) is regarded as the gold-standard for questionnaires that detect symptoms of post-traumatic stress disorder. It is a validated questionnaire that provides both formal diagnosis of PTSD and a 17-item measure of symptom severity. The PDS has been shown to have high internal consistency and test-retest reliability, high diagnostic agreement with the PTSD module of the Structured Clinical Interview (SCID; First et al., 1998), and good sensitivity and specificity. I adapted the symptom severity items to detect responses specifically related to the ICU, as recommended by the authors (Foa et al. 1997) and as advised by Professor Brewin (personal communication).

The symptom severity scale (Part 3 of the PDS) consists of the cardinal symptoms of PTSD, including five re-experiencing or intrusive symptoms; seven avoidance symptoms and five hyper-arousal symptoms. Each item was scored from 0-3 with a total possible PTSD score of 51. Response options were *not at all, once per week or less, 2-4 times per week* and *5 or more times per week*. Scores of 1-10 are considered to be mild, 11-20 are moderate; 21-35 are moderate-severe, and >36 are severe (McCarthy, 2008). Other parts of the PDS used in the study were Part 1, a checklist of traumas (scoring was 1= life-threatening illness only, 2= illness plus one other trauma, 3=illness plus two other traumas, 4= illness plus three or more traumas) and Part 4, the level of impairment caused by symptoms across nine areas of life functioning. Part 2 was not used. Part 2 was designed to cover DSM IV's Criterion A1 – 'the person experienced, witnessed or was confronted with an event or events that involved actual or threatened death or serious injury, or a threat to the physical integrity of self or others' – and A2 – 'the person's response involved intense, fear, helplessness or horror'. I assumed that all level 3 ICU

patients fulfilled A1, and questions on helplessness and terror had been included in the Mood questionnaire at baseline.

PDS scoring

To qualify as having PTSD according to Foa (1997) there should be

1. A trauma to be identified (Part 1)
2. Fulfilment of Criterion A1 and A2 (Part 2)
3. One or more positive re-experiencing symptoms; positive score=1,2 or 3
   Three or more positive avoidance symptoms
   Two or more positive hyper-arousal symptoms
4. One or more positive responses in Part 4 (level of impairment)

However as Brewin et al. (1999) pointed out, this method could lead to an over-diagnosis of PTSD as people with scores as low as nine, or who had no individual item scores higher than one would receive a diagnosis. I decided to use a method based on a study (Ehring et al., 2007) in which 18 scoring rules for the detection of current chronic PTSD were tested. Three of these were found to lead to overall diagnostic efficiency of 80% and sensitivity and specificity of at least 0.75. Two of the three methods were a) using a PDS total scale cut-point of 18 and b) symptom cluster scoring (described above) plus a total scale cut-point of 18. As both methods were rated as highly efficient, I opted to use the total PDS scale cut-point of 18. Therefore everyone who scored more than 18 on the PDS scale was considered to have PTSD and everyone who scored 18 or under was not.

Reliability and factor analysis

Cronbach's alpha for the PDS in this study was 0.934, which is acceptable. When the PDS was factor analysed, the Kaiser-Meyer-Olkin measure of sampling adequacy (KMO) was 0.885 and three factors were identified, explaining 67% of variance. However the factor structure reported by Foa et al. (1997) was not replicated. In this study one factor was most of the re-experiencing symptoms, one factor included most of the avoidance and hyperarousal symptoms together, and a third factor consisted of a single item about not being able to remember time in the ICU. This third factor was probably related more to loss of memory due to sedation or coma in the ICU than to PTSD. The factor structure of PDS was not highly relevant in this study as my intention was to use the total PDS score in analysis, and not sub-scale scores.

4.7.2(ii) Depression measure

Clinical depression at three months was assessed using the 20-item Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977). The CES-D is the most widely used measure of depression in epidemiological and community studies and has been validated for both general and psychiatric populations. Responses are scored 0 to 3, with higher scores indicating higher frequency giving a possible range of total scores from 0 to 60. Scores above 16 are considered high by the authors and an indication that the patient is likely to be clinically depressed (Radloff, 1977). Severity categories are mild (10-15), moderate (16-24) and severe (>24).

In validation studies internal consistency has been found to be high for both general (Cronbach's alpha =0.85) and psychiatric patients (Cronbach's alpha= 0.90). The CES-D showed criterion group validity, discriminating between general population and psychiatric patients; 70% of patients and only 21% of the general population scored above the suggested cut-point of 16. Subsequent studies (Radloff & Locke, 1986) confirmed the screening value of the CES-D in detecting depressive disorder.

Other authors have suggested that the recommended cut-point of 16 is too low. For example a cut-point of 19 was suggested for rheumatoid arthritis patients because of the effect of somatic symptoms (Covic et al., 2007). For example a positive response to "I felt everything I did was an effort" could be due to disease rather than depression. A similar argument could apply to recovering ICU patients who may be suffering from physical weakness rather than depression. Other studies suggested that the cut-point should be raised to 24 or higher to achieve appropriate diagnostic characteristics (Gotlib et al., 1995; Roberts et al., 1991). However Cheung et al. (2007) found that sensitivity and NPV were compromised by increasing the cut-point from 16. It was concluded there was no optimal cut-point but researchers should choose one that was fit for their purpose. I decided not to depart too much from the scale authors' recommendation, but to take into account the effect of somatic symptoms and use the cut-point of 19 recommended by Covic et al. (2007).

Reliability and factor analysis

In my cohort study, Cronbach's alpha for the CES-D was 0.911. In a confirmatory factor analysis, four factors were found explaining 68% of the variance. A four-factor structure was also found by the original factor analytic validation among three different population samples. The factors were depressed affect, positive

affect, somatic and retarded activity, and interpersonal. However in my study analysis was carried out using the total depression score.

4.7.2(iii) Anxiety

Clinical anxiety at three months was measured using a short version of the State Trait Anxiety Inventory (Spielberger et al., 1983), a widely used questionnaire that has been used with many different populations and different health conditions. It has well-established criteria and construct validity and internal consistency reliability coefficients. In this study Cronbach's alpha was 0.878. After factor analysis KMO was 0.820, and one factor was found, as expected, explaining 63% of variance.

The full version of STAI includes 20 items to detect state anxiety and 20 items to detect trait anxiety. The short form of STAI used in this study consisted of six items (calm, secure, tense, at ease, upset, worried) to measure state anxiety only. Responses were "not at all, somewhat, moderately, and very much". Scores per item were from 1-4. The total score was divided by six and multiplied by 20 to give a range of scores that was consistent with the full STAI of 0-80.

No definitive cut-point has been established for the STAI to determine clinical levels of anxiety. The authors, Spielberger et al. (1983) suggested a cut-point of 32. Cut-points of 37 and 39 (Addolorato et al., 1999) have also been used. In surgical patients the cut-point was set at 44/45 (Kindler et al., 2000). Finally 54/55 was recommended as a cut-point for geriatric patients in their 80s with chronic ill health (Kvaal et al., 2005). I chose to use the cut-point of 44/45 as ICU patients probably have more similarities with surgical patients than other populations assessed with STAI, and I wanted a conservative cut-point that would not yield an unrealistically high prevalence rate.

4.7.2(iv) Quality of life

The SF-36 (Ware, Jr. & Sherbourne, 1992) is a generic, multipurpose health survey that produces a profile of function and well-being in eight domains, as well as two summary measures for physical and mental health. Extensive evaluation has taken place to establish its reliability and validity, and it has been used in articles describing more than 200 diseases and conditions. In this study I used its short version, the SF-12 health survey (Ware, Jr. et al., 1996). Its 12 questions cover four physical domains – physical functioning, role-physical, bodily pain, general health and four mental domains – vitality, social functioning, role-emotional, and mental health. The four physical domains are summed into a physical health

summary measure (PCS) and the mental domains in a mental health summary measure (MCS).

I obtained the PCS and MCS results for each patient by using the SF-12 algorithm recommended by the SF-12 manual (Ware, Jr et al., 1996).They are scored using norm-based methods based on the general US population. Both the PCS-12 and MCS-12 scales are transformed to have a mean of 50 and a standard deviation of 10 in the general U.S. population. A one-point difference is one-tenth of a standard deviation. Therefore results can be meaningfully compared with one another. Although no cut-points are recommended for poor HRQL by the SF-12 manual, a number of recent studies defined poor PCS or MCS by scores lower than or equal to 40 (e.g. Casso et al., 2004; Myint et al., 2005). Poor PCS has been defined as substantial limitations in self-care, physical, social, and role activities; severe bodily pain; or frequent tiredness. Poor MCS was defined as frequent psychological distress and substantial social and role disability due to emotional problems (Rumsfeld et al., 2004).

4.7.2(v) Past psychological history

There was a short section in the follow-up questionnaire about past mental health problems. Patients were asked if they had ever been to see a GP, therapist, counsellor or psychiatrist for a mental health problem. If yes, they were asked what the problem was, what treatment they received for it, and if it occurred before intensive care, since intensive care or both. Finally they were asked if they were currently taking medication for depression or another mental health problem. However few patients answered this section (and some answered incorrectly) so the data were not used. Subsequently a medical researcher collected data on prior mental health problems from the electronic records at the UCH CCU. She noted any current or previous mental health diagnoses or current medications prescribed for psychological problems that were recorded by ICU staff.

4.7.2(vi) Social support

A nine-item social support scale about "support you get from other people" was also used in the follow-up questionnaire. It included six items about emotional support, and three about instrumental support (support for health behaviours including taking medication, having a healthy diet and taking exercise). There were five responses ranging from not at all (0) to all of the time (4) resulting in a possible range of scores from 0 to 36. The six emotional support items came from the ENRICHD Social Support Inventory created for a study of patients recovering from myocardial infarction (Mitchell et al., 2003). It was found to have concurrent and predictive validity, and acceptable reliability when used with cardiac patients

(Vaglio, Jr. et al., 2004). The three items on instrumental support were added to the original six items for the TRACE study on tracking recovery after coronary events (Wikman et al, in press).

4.7.2(vii) Socio-economic circumstances

Finally the follow-up questionnaire included questions pertaining to the NS-SEC (Office for National Statistics, 2010). This classification, that is now used in all official statistics and surveys in the UK, was used to derive patient SEC. Further details were given in Section 4.6.5.

4.7.2(viii) Piloting the follow-up questionnaire

I piloted the follow-up questionnaire by sending out questionnaires to patients who had been discharged from the ICU three months previously and had been invited to attend the ICU follow-up clinic. I sent out 17 questionnaires and 11 were returned (response rate: 65%). Of the six non-responses, two patients had been readmitted to the ICU, one was going in for new surgery, and three did not respond, for unknown reasons. The piloted follow-up questionnaires were not used in the final study as these patients had not taken part in the baseline assessment.

Mean time taken to complete the follow-up questionnaire was 21 minutes. Eight of the eleven patients completed it in 15 minutes or less. Seven patients had no problems with the questionnaire. One patient objected to some questions, "I thought the questions were meaningless. My answers relate to other problems in my life, not ICU". (This patient scored highly on the CES-D, a validated depression questionnaire (Radloff, 1977). The study did not make the assumption that depression was caused by the ICU as confounding variables were considered, so I did not alter the questionnaire). Two patients found some of the response options to the validated questionnaires confusing. One patient found the layout was unclear. None found any questions unclear or ambiguous. The "results" were that six patients had no psychological symptoms, and five patients had high levels of depression or ICU-related PTSD. In response to patient comments I amended the layout of the questionnaire to make it as clear and easy to complete as possible. It was not necessary to shorten the questionnaire or make any major changes to it.

4.8 Power and statistical analysis

4.8.1 A priori power calculation

The primary outcome was PTSD symptomatology measured on a continuous scale on the PDS which has a range of 0-51 and a standard deviation of 14.68 (Foa et al., 1997). It was determined that a clinically significant difference in PTSD between two groups (as defined by a median split on the ICUSS or any other risk factor)

would be ten points on the PDS (personal communication with Professor Brewin), approximately two thirds of a standard deviation (Foa et al., 1997). For this effect size, 80% power and 5% significance, 34 patients were required in each group. With this sample size, the detection of a correlation coefficient of 0.3 between a continuous risk factor and outcome would be possible. In order to carry out multiple linear regression, the sample size should be inflated. In order to detect the same correlation coefficient (0.3) between a risk factor and outcome in a multiple regression model where all other variables in the model explained 30% of the total variation in outcome, the sample size needed to be inflated by 40%. This yielded a total sample size of 95 patients. Based on previous studies I estimated that the drop-out rate would be around 30% by the time of follow-up. Therefore I aimed to recruit a minimum of 140 patients at baseline. As the study progressed it became clear that the drop-out rate was around 35% rather than 30% so I carried on recruiting until I had 157 patients at baseline. When I closed the study 100 patients (64%) had completed both baseline and follow-up assessment. Therefore the study was fully powered according to the a priori calculation.

4.8.2 Preparation of data for statistical analysis

All data was double-checked as data entry proceeded, to achieve a high level of accuracy. Before data analysis, the steps involved in data cleaning were conducted as recommended by a standard text book (Kirkwood & Sterne, 2003). The accuracy of data entry was assessed by conducting range checks and inspecting histograms of continuous variables to identify out of range values and outliers. For categorical variables I checked that all observations related to allowed categories and that the frequencies in each category made sense. Any errors were corrected by referring back to original questionnaires and data record forms. Outliers that were not errors were not removed from the dataset as is sometimes recommended, because high scores, for example on one of the psychological questionnaires, were highly relevant data to inform one of the main aims of this study, to assess the extent and prevalence of psychological morbidity after ICU. The level and location of missing data were assessed, followed by an assessment of the extent to which continuous data met the assumptions required by statistical tests.

4.8.3 Missing data

There are no accepted guidelines indicating the amount of missing data which can be "allowed" in a sample (Tabachnick & Fidell, 2007) nor are there accepted strategies for how to ameliorate the problem (Graham, 2009). In this study there were no missing clinical or health-care data, as they were collected directly from the electronic records of the patient's stay in the ICU. Data on age and sex were also collected from patient records and were complete, but there were missing data

on NS-SEC classification as they were collected via a self-report questionnaire. Therefore some cases had to be excluded from analyses using the SEC variable. There were missing data from the psychological questionnaires, but only to a limited extent, although the amount of missing data from the follow-up questionnaires was greater than from the baseline questionnaires. For example, the range of missing data for items in the ICU stress scale was 0-2% but for PDS items the range of missing data was 2-8%.

I decided that for most of the individual scales used in the questionnaires, cases with over 20% of items missing would be excluded. However the manual for the SF-12 (Ware et al., 1996) specifies that that all cases with even a single missing value should be excluded, and this was adhered to. For the remaining scales it was decided to replace missing values in questionnaires by individual means (the participant's mean score for that scale or sub-scale). An article comparing imputation methods for dealing with missing data in a depression scale concluded that while multiple imputation was the most accurate method for dealing with missing data, imputing the mean of an individual's complete responses to other questions, was also an appropriate method that would be interpretable to the majority of medical readers (Shrive et al., 2006).

4.8.4 Distribution of data

The distribution of continuous variables was assessed by examining frequency histograms and using a statistical test for normality, the KS Lilliefors test. When data were identified by this method as having a skewed distribution, further investigation of the level of skew was carried out, by standardising scores and dividing by standard error (Field, 2005). For data to be treated as normally distributed, skew should be within +2 and -2. If distribution was outside the recommended skewness levels, transformation options were considered. If tranformation did not result in the variable being normally distributed, non-parametric statistical tests were used.

4.8.5 Descriptive Statistics

Means, standard deviations and ranges or medians and ranges were calculated for all continuous variables. Prevalence rates of psychological outcomes were calculated as percentages with confidence intervals. Numbers and percentages of cases in each category were calculated for binary and categorical variables.

4.8.6 Re-coding categorical variables

After examining the descriptive statistics some categorical variables were re-coded. In some cases this was because there were very few cases in some of the

categories. For example variables representing drug groups such as "benzodiazepines" had several categories for each specific drug or combination of drugs e.g. midazolam, diazepam etc. However this led to so many possible categories that analysis was not possible in a sample of this size (100 patients). Therefore drug group variables were re-coded so that 1= yes, received a drug from this group and 0= no, did not receive a drug from this group. Other categorical variables were re-coded for entry into multivariable regression, after univariable analysis showed that there were no differences between certain categories. For example, intrusive memories was originally coded to have three categories: no, yes/factual and yes/delusional. This was because the literature suggests that delusional memories of ICU were a predictor of psychological outcome, but factual memories were not (e.g. Jones et al. 2001). However as there were no significant differences between the factual memory and delusional memory groups at the univariable stage, the variable was re-coded as 0=no intrusive memories, and 1= yes, intrusive memories present. Similarly memory of ICU was re-coded from three categories (little or some or most) to two categories (very little or some/most).

4.8.7 Outline of statistical analysis

All statistical analyses were conducted using SPSS for Windows (version 14). Normal regression models were used with the primary outcome (PTSD) treated as a continuous variable.

(i) Each risk factor was related to the outcome in a univariable model to estimate the unadjusted associations. Correlations, T-tests and one-way analysis of variance (Anovas) were used with, respectively, continuous, binary and categorical predictor variables.

(ii) The strongest independent predictor variable or variables within each of the four pre-defined risk factor groups (1. clinical 2. socio-demographic 3. psychological and 4. chronic) were then identified using a series of multivariable regression models.

(iii) A final regression model was developed to assess whether identified risk factors were independent of each other. Each step is described in more detail below. The same procedure was carried out with all other outcomes. Appropriate tests for multivariable model assumptions were carried out (see 4.8.8).

4.8.7(i) Univariable analysis

Correlations, T-tests and Anovas were carried out to look for associations between clinical, socio-demographic, psychological and chronic risk factors and psycho-social outcomes. Associations between risk factors were also examined, e.g. between clinical and psychological factors, as this would suggest a potential role of some risk factors as mediators or confounders (definitions were given earlier in the chapter). Many tests were carried out as part of the univariable analysis, increasing the risk

of type 1 errors. This approach was justified as the study was an exploratory one to identify risk factors that should be investigated further, in an area in which few risk factors have been identified to date. Furthermore in assessing the most important risk factors I considered effect sizes, direction of results and patterns of results that pointed to similar conclusions rather than relying on significance alone. This approach makes it less likely that results were mere statistical artefacts.

4.8.7(ii) Separate multivariable models

In recognition of the number of potential variables being tested in these analyses and the associated implications for sample size, a two-stage analysis process was implemented. If several predictors within each of the 4 risk factor groups were identified during the univariable analysis, all statistically significant ($p<0.05$) predictors were entered into a multiple regression. (However, in the case of PTSD, there were too many statistically significant clinical predictors to enter into a regression, so I selected the variables with largest effect sizes and dropped some variables that overlapped with others.) The strongest predictors from these regressions, based on effect size and an adjusted significance level ($p<0.1$), would then be entered into the final multivariable model. If only one or two statistically significant clinical predictors were identified in univariable analysis, the second stage was missed out and predictors were directly entered into a final multivariable model.

4.8.7(iii) Final multivariable model

The strongest predictors, based on effect size and significance, from each group of risk factors (clinical, socio-demographic, psychological and chronic) were entered in separate blocks into final regression analyses for each outcome, to enable the variance in outcomes explained by each group of variables (socio-demographic, clinical, psychological risk factors, chronic) to be assessed. Socio-demographic variables were entered first, clinical variables and chronic health second, psychological variables third and psychological history last. Thus the effects of clinical variables on outcomes were adjusted for socio-demographic variables, and the effects of adding acute and chronic psychological factors to the model could be seen. The final regression models were carefully examined to detect which were the strongest risk factors (largest effect sizes and smallest p-values, which were independent risk factors (not confounded by other variables) and which risk factors were confounded or mediated by others.

4.8.8 Tests of multivariable assumptions

4.8.8.(i) Linearity, normality and homoscedasticity

In order to have confidence in the results of the multiple regressions, it is important to check that they do not violate multivariable assumptions (Tabachnick & Fidell,

2007). These assumptions include a) a straight line relationship between residuals and predicted scores b) that residuals are normally distributed c) that error is random and d) that there is homoscedasticity (constant variance of residuals at each level of the predictor variable), (Field, 2005). If these assumptions are met there is more likelihood that the model that we get for a sample can be applied to the population of interest. For each of the final regressions for each outcome, I examined histograms of residuals, normal probability plots and scatterplots of residuals and predicted values for evidence of linearity, normality and homoscedasticity.

4.8.8(ii) No perfect multicollinearity

Multicollinearity poses a number of problems in multiple regression. If there is perfect collinearity between predictors it is impossible to obtain unique estimates of the regression coefficients. As collinearity increases, so do the standard errors of the regression coefficients, increasing the risk of type II errors. Collinearity also makes it difficult to assess the individual importance of predictors. For all multiple regressions I looked at collinearity diagnostics produced by SPSS such as variance inflation factors (VIFs indicate if a predictor has a strong linear relationship with another) and tolerance factors. It has been argued that if the average variance inflation factor is greater than one, multicollinearity may be biasing the model (Bowerman & O'Connell, 1990). The reciprocal of the VIF (1/VIF), the tolerance statistic, is another useful diagnostic. It has been suggested that tolerance values lower than <0.2 (Menard, 1995) are of concern. If there had been multicollinearity I would have deleted one of the variables based on reliability or tolerance value.

4.8.9 Mediational analysis

Finally, if associations between risk factors from different groups were found at the univariable stage of analysis, for example between ICU clinical factors and psychological factors, and assumptions for a mediational relationship were met, then a mediational relationship was tested in a further stage of analysis (Baron & Kenny, 1986). This analysis was designed to test whether acute psychological factors partially accounted for the relationship between clinical predictors and psycho-social outcomes and if those factors might be on the causal pathway between clinical effects and outcomes (as predicted by hypothesis four).

This method involves first regressing the "mediating variable" on the predictor variable; second, regressing the outcome on the predictor variable; and third, regressing the outcome on both the predictor variable and the mediating variable. The assumptions of mediation are that the predictor must affect the mediator in the first equation, the predictor must affect the outcome in the second equation and the mediator must affect the outcome in the third equation. If these conditions all

hold, then the effect of the predictor on the outcome must be less in the third equation than in the second. Perfect mediation would occur if the predictor had no effect on the outcome when the mediator was controlled. However when treating phenomena that have multiple causes, it is more realistic to seek mediators that significantly decrease the predictor-outcome relationship rather than eliminate it (Baron & Kenny, 1986).

Chapter 5 Results of cohort study

In this chapter I have reported the results from the prospective cohort study of 157 level 3 intensive care patients that I carried out at UCLH in 2008-2009. The results include the prevalence of psychological morbidity after intensive care, specifically PTSD, anxiety and depression, and the extent of poor mental and physical HRQL. The results of univariable and multivariable statistical analyses to detect strong indendependent risk factors for post-ICU psycho-social outcomes, and mediational analysis to identify possible mediating variables, are also reported.

5.1 Recruitment of sample

5.1.1 Baseline recruitment

A total of 157 "Level 3" intensive care patients were recruited for this study in the UCH critical care unit during a period of approximately 10 months from November 19, 2008 to September 30, 2009, excluding times when I was on annual leave (see figure 5.1). The total number of level 3 patients admitted to the Unit during that time was 375. Of these, 104 (28%) died in the CCU, 22 were transferred to other hospitals from the CCU, four discharged themselves and 62 were excluded according to study criteria. This left 183 patients who were eligible to participate. Of these, nine were unable to complete the assessment for miscellaneous reasons, and 17 declined to participate. Overall 86% of level 3 patients who were eligible to participate in the study were recruited and took part in the baseline assessment at time of discharge from the ICU. There were no significant differences in age, sex or illness severity between recruits and non-recruits. However it can be seen from Table 5.1 below that non-recruits were more likely to be men, were a little younger than recruits and a little less sick on admission to the ICU.

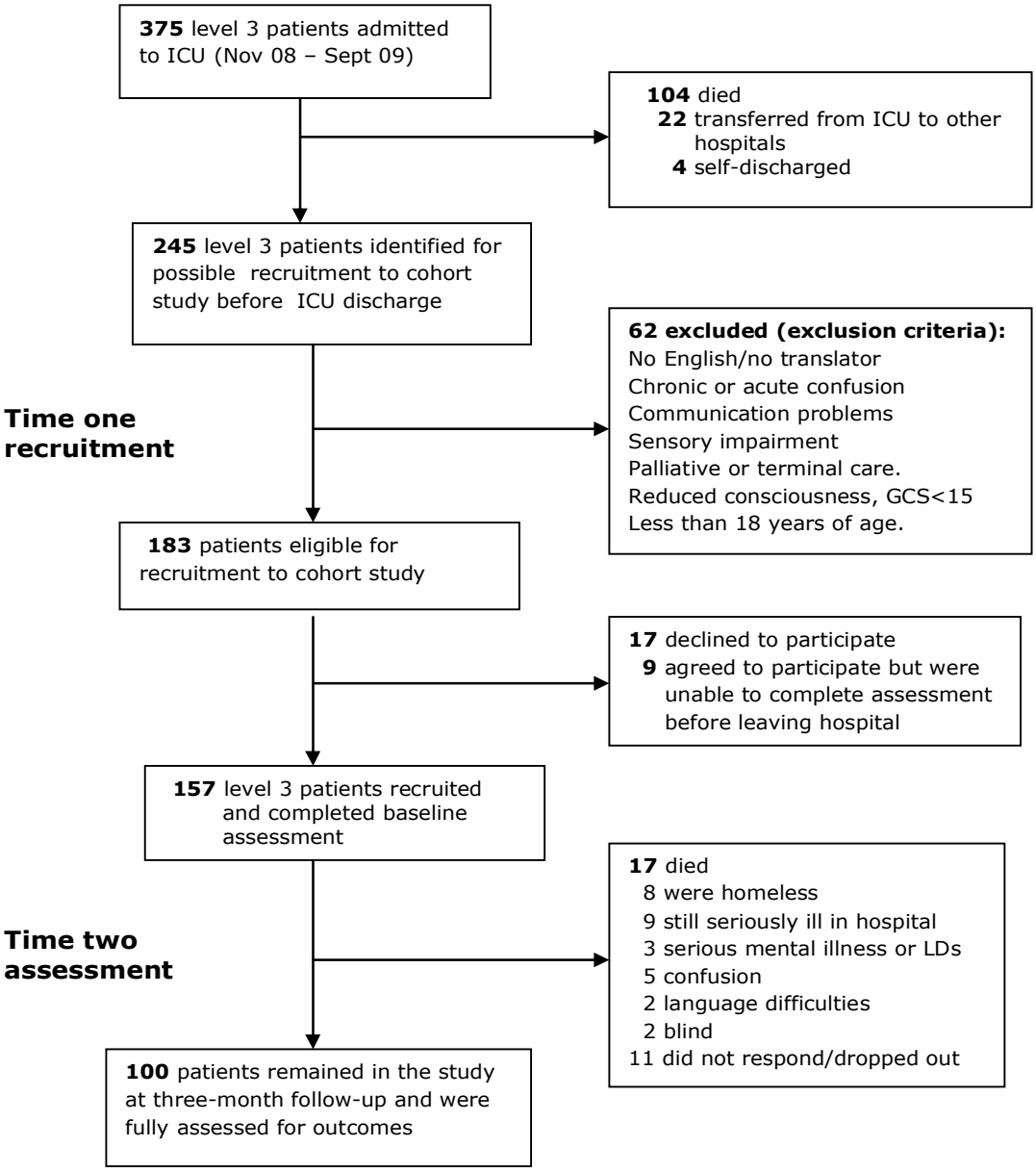
Table 5.1 Comparison of baseline characteristics, recruits and non-recruits

	N	Age Mean (SD)	Sex % men/women	Illness severity Mean (SD)
Recruits	157	57.24 (16.83)	57.3% vs 42.7%	22.17
Non-recruits	17	55.53 (13.46)	64.7% vs 35.3%	20.41
Mean difference, 95% CIs, p-value		1.71 (-6.63, 10.04) p=0.687	p=0.558	1.75 (-0.71,4.22) p=0.157

5.1.2 Follow up sample

A total of 57 patients were lost to follow-up. Of these, 46 could not be contacted or were unable to complete an assessment for the following reasons: 17 had died after leaving intensive care, nine were homeless, eight were still seriously ill in hospital, three were mentally ill or had learning disabilities, five were confused,

Figure 5.1 Recruitment, participation and follow-up of patients



two had language difficulties and two were blind. Eleven further patients declined to take part or did not respond to successive efforts to contact them. This left 100 patients who took part in both baseline (time one) and follow-up (time two) assessments. Overall follow-up rate was 64%. However 90% of patients who were alive, contactable and capable, participated in the follow-up assessment.

5.2 Characteristics of the sample

5.2.1 Socio-demographic characteristics

Table 5.2 contains socio-demographic data about the full sample of participants at time one, the 100 participants who were followed up at time two and the 57 who

were not. The mean age of participants was approximately 57 years old. There were more men than women at time one (57.3%/42.7%) but the final sex balance (52% men /48% women) was an almost even split. Most participants at both time points (85.5%) were white. Participants were predominantly from the most deprived areas (4th and 5th quintiles). At time one 43.4% of participants were from the most deprived areas (5th) while 8.6% lived in the least deprived areas (1). At time two 37.1% of participants were from the most deprived (5th) and 12.4% from the least deprived (1st). However a somewhat different picture of the socio-economic circumstances of the follow-up group emerged from the classification by occupational groups using NS-SEC (see Figure 5.2). This measure, which was completed at time two, indicated that 33% of the sample belonged to class 1 (professional, managerial classes) while 20% belonged to class 5 (routine and semi-routine occupations). For reasons explained in chapter four (methods) I decided that NS-SEC (Office of National Statistics, 2010) was a better indicator of SEC in this cohort, and so used NS-SEC rather than IMD 2007 (Communities and Local Government, 2010) in the statistical analyses.

Table 5.2 Patients' socio-demographic characteristics

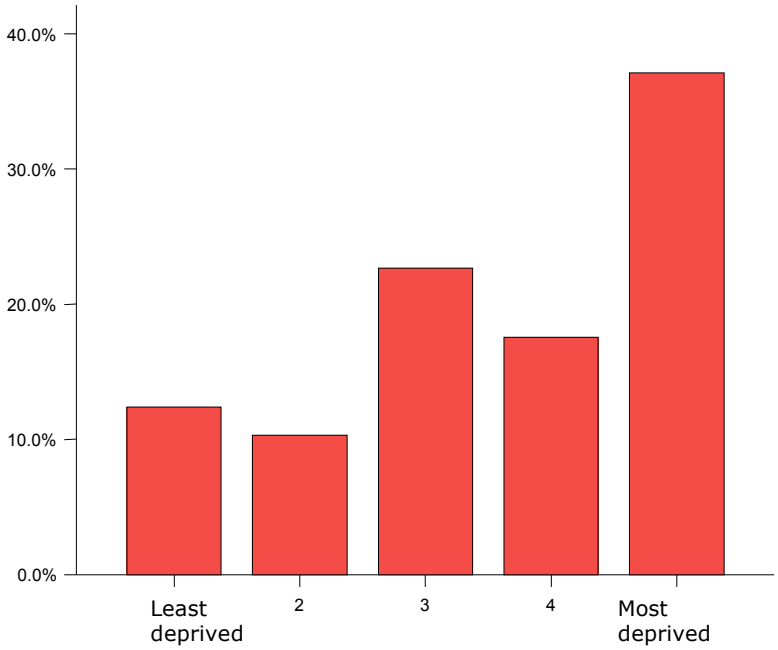
Means, SDs for continuous variables; N (%) for categorical variables

	Total Sample (n=157)	**Not followed up (group 1)** (n=57)	**Followed up (group 2)** (n=100)	**Difference between groups 1 and 2**
Age (years)	57.24 (16.8) median 59 (79) min 18y max 97y	57.19 (15.62)	57.26 (17.40)	p=0.981
Sex men	90 (57.3%)	38 (66.7%)	52 (52%)	
women	67 (42.7%)	19 (33.3%)	48 (48%)	**p=0.074**
Education				
Degree	39 (26.5%)	12 (22.2%)	27 (29%)	
College	20 (13.6%)	8 (14.8%)	12 (12.6%)	p=0.220
A'level	19 (12.9%)	5 (9.3%)	14 (14.7%)	
GCSE	25 (17.0%)	7 (13.0%)	18 (18.9%)	
No qualification	44 (29.9%)	22 (40.7%)	22 (23.2%)	
Ethnicity				
white	132 (85.5%)	49 (86%)	83 (85.6%)	p=0.625
other ethnicity	22 (14.5%)	8 (14%)	14 (14.4%)	
Deprivation*				
1.Least	13 (8.6%)	1 (1.8%)	12 (12.4%)	
2.	13 (8.6%)	3 (5.5%)	10 (10.3%)	**p=0.001**
3.	25 (16.4%)	3 (5.5%)	22 (22.7%)	
4.	35 (23%)	18 (32.7%)	17 (17.5%)	
5. Most	66 (43.4%)	30 (54.5%)	36 (37.1%)	
Occupation ** 1. Professional 2. Intermediate 3. Own account 4. Technical 5. Routine 6. Unclassified	*No data – data collected at time two (follow up)*		33 (33%) 10 (10%) 21 (21%) 7 (7%) 20 (20%) 9 (9%)	

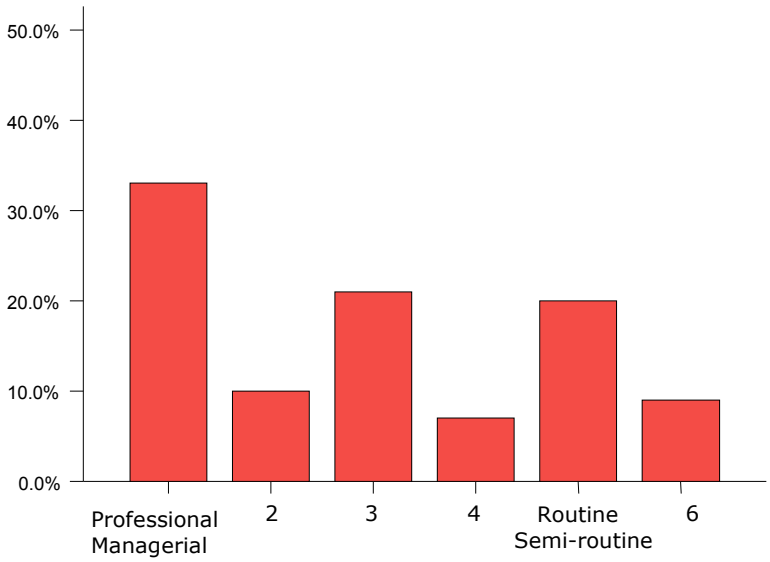
*IMD 2007 (Communities and Local Government, 2010)** NS-SEC (Office of National Statistics, 2010)

Figure 5.2 Bar charts showing socio-economic circumstances
(follow-up sample, with a)IMD 2007 and b)NS-SEC)

a) Percent of sample in Index of Multiple Deprivation 2007 quintiles



b) Percent of sample in NS-SEC categories



5.2.2 Comparison of followed up/not followed up groups

Participants in the follow-up group did not significantly differ from the non-follow-up group in terms of age, education or ethnicity. There was however a difference in the sex composition of the two groups which approached significance, caused by more men (42%) than women (28%) "dropping out" between times one and two. There was a significant difference in level of deprivation between the follow-up and non-follow-up groups, as a smaller percentage of participants from 4th and 5th IMD

quintiles (most deprived) took part in the follow-up compared to participants from less deprived quintiles. From table 5.2, it can be seen that 44 out of 51 (85%) participants from the three least deprived quintiles responded at time two, whereas only 53 out of 101 participants (52%) from the two most deprived quintiles took part in the follow-up assessment. Although there was no significant difference in Education, it was noticeable that people with no qualifications were almost twice as likely to be in the not followed up group (40.7% vs 23.2%). Those with a degree were more highly represented in the follow up group (29% vs 22.2%).

5.2.3 Clinical indicators and interventions received

To summarise the main points emerging from the large amount of acute clinical and healthcare data that was collected for patients (see table 5.3), I have mainly referred to the statistics for the follow-up sample of 100 patients. I will report first on admission and healthcare pathways. Most patients were admitted to the CCU from theatre/recovery (34.7%) or from a UCH ward (28.6%), with the rest coming from A&E, or other hospitals' ICUs or wards. Patients in this study spent 13.55 days on average in the CCU, including a mean 8.53 days receiving "level 3" intensive care. After discharge from the CCU, most patients went to UCH wards (93%). After an average stay in hospital of 39.67 days, 69% of patients went home and were still there at three months. Of the rest, six per cent went to residential care or rehabilitation, and 11% had one or more re-admissions to hospital. Four were still in hospital at three months. However 18 (11.5%) of the original sample died – 17 died before time two and one died after time two. Illness severity scores were high, with a mean Apache II score (Knaus et al., 1981) of 22.

The primary body system most commonly affected was the respiratory system (30% of patients), followed by the gastro-intestinal (GI) system (29%) and the cardiovascular (CV) system (17%). Most patients were non-surgical patients (63%), with emergency surgical patients forming the smallest group (14%). A total of 81 (81%) of patients had sepsis (based on C-reactive protein scores, white cell count and lactate levels). The level of intervention received was measured by the TISS (therapeutic intervention scoring system) score (Keene et al., 1983). Mean score was 24.61. Patients received up to nine types of organ support, with mean 4.40 (1.70) types of organ support received. The most common forms of organ support received were GI support (mean 9.38 days, 73% of participants), advanced respiratory support (mean 7.92 days, 79% participants) and advanced CV support (mean 2.13 days, 52% of patients). The most common combination of organ support received was respiratory, CV and GI support (29.9% of patients). The

second most common combination was respiratory, CV, GI and dermatological support (11.5%).

Table 5.3 Clinical data (excluding drugs received)

Means (SD) continuous variables (+median if skewed) or N(%) for categorical variables				
	Total sample (n=157)	**Not followed up group (n=57)**	**Followed up group (n=100)**	**p-value of difference**
Type Admission				
Elective surgical	37 (23.6%)	14 (24.6%)	23 (23%)	p=0.627
Emergency surgical	19 (12.1%)	5 (8.8%)	14 (14%)	
Non-surgical	101 (64.3%)	38 (66.7%)	63 (63 %)	
Admitted from				
Theatre	50 (32.1%)	16(28.1%)	34 (**34.7%**)	
Ward	45 (28.8%)	16(28.1%)	28 (28.6%)	p=0.725
A&E	31 (19.7%)	14(**24.6%**)	17 (17.3%)	
Other	32 (19.2%)	11(19.4%)	19 (19.4%)	
Post-hospital to:				
Home	96 (61.1%)	27(47.4%)	69 (69%)	**p=0.000**
Other hospital	17 (10.8%)	8 (14%)	9 (9%)	
Care/rehab	8 (5.1%)	2 (3.5%)	6 (6%)	
Died*	18 (11.5%)	**17 (30.1%)**	1 (1 %)	
Readmission/s	13 (8.3%)	2(3.5%)	11(11%)	
Still in hospital	5 (3.2%)	1(1.8%)	4(4%)	
Illness severity on admission	22.17 (7.90) Range (7-48)	22.44 (9.07)	22.01(7.19)	p=0.760
Primary system				
Respiratory	48 (30.6%)	18(31.6%)	30 (30%)	
CV	28 (17.8%)	11(19.3%)	17 (17%)	
GI	43 (27.4%)	14(24.6%)	29 (29%)	p=0.625
Neuro	11 (7%)	5 (8.8%)	6 (6%)	
Hospital LoS (days)	40.32 (39.15) median 27(239)	41.44 (41.06)	39.67(38.18) median 27(239)	p=0.788
ICU LoS	13.10(13.24) median 9 (85)	12.31(9.25)	13.55(15.10) median 8(85)	p=0.575
Level 3 days	8.07(12.11) median 4 (80)	7.26(7.775)	8.53(14.02) median 3 (80)	p=0.530
TISS score	24.52(5.34) Range (0-36)	24.37 (5.86)	24.61(5.05)	p=0.786
Number of organs supported	4.6 (1.69) Range (1-8)	4.97(1.61)	4.40(1.70)	**p=0.040**
Advanced respiratory support	7.41(11.95)days median 3 (80) N:128 (81.5%)	6.53(7.41)	7.92(13.89) median 3 (80) N: 79 (79%)	p=0.484
Advanced cardiovascular support	2.29(3.53) days median 1(20) N: 88 (56.05%)	2.58(3.81)	2.13(3.37) median 1(16) N: 52 (52%)	p=0.446
Renal support	1.69 (4.99) days median 0 (40): 37 (23.57%)	1.72(1.67)	1.67(5.56)) median 0(40) N: 21 (21%)	p=0.953
Neuro support	0.48(1.04) days median 0 (5) N: 38 (24.20%)	0.54(1.09)	0.44(1.02) median 0(5) N: 22 (22%)	p=0.550
Gastro-intestinal support	8.93(13.09)days median 4 (89) N: 73 (89%)	8.14(9.54)	9.38(14.76) median 4(89) N: 73 (73%)	p=0.570
Dermatological support	1.43(4.48) days median 0 (39) N: 46 (29.3%)	1.35(2.82)	1.48(5.21)) median 0(39) N: 24 (24%)	p=0.863
Liver support	0.05(0.464) days median 0 (5) N: 2 (1.3%)	0.09(0.662)	0.03(0.300) median 0 (3) N: 1 (1%)	p=0.455

Level 3 patients are often administered a number of drugs with potential psycho-active effects during the ICU stay. Patients were sedated for an average 3.13 days, up to 24 days; with 60% of patients receiving benzodiazepines (e.g.

midazolam) and 66% receiving anaesthetics agents (mainly propofol) for sedation. Other drugs received were opioids such as morphine sulphate or fentanyl (93%), inotropes and vasopressors, including adrenaline and noradrenaline (47%), antipsychotics, primarily haloperidol for delirium (39%), hypnotics, mainly zopiclone, for insomnia (31%), and steroids such as hydrocortisone or dexamethazone (33%). The mean number of "psychoactive" drug groups received was 3.67(1.68) of a possible seven.

Table 5.4 Drugs received by the cohort

Variable	Total sample n=157	Not followed up group n=57	Followed up group n=100	p-value for difference
Days of Sedation	3.48 (4.41) days median 2 (24)	4.12 (4.66)	3.13(4.24) median 2(24)	p=0.184
Number drug groups received	Not calculated for total sample		3.67 (1.68) Range 0-7	
Hypnotics	47 (29.9%)	16 (28.1%)	31 (31%)	0.700
Benzodiazepines	100 (63.7%)	40(70.2%)	60 (60%)	0.186
Anaesthetics	105 (66.9%)	39 (68.4%)	66 (66%)	0.757
Antipsychotics	66 (42%)	27 (47.4%)	39 (39%)	0.700
Inotropes and vasopressors	82 (52.2%)	35 (61.4%)	47 (47%)	**0.082**
Steroids	53 (33.8%)	20 (35.1%)	33 (33%)	0.790
Opioids	146 (93%)	53(93%)	93 (93%)	0.997
Sepsis	not calculated for total sample		81 (81%)	

It can be seen from table 5.3 above that there were few significant differences in clinical (illness and treatment) factors between the followed-up and not followed-up groups. This suggests that the follow-up sample was representative of the total sample in terms of illness and healthcare received**.** There was a significant difference for the post-hospital variable, but this was accounted for by the fact the non-follow-up group included the 17 patients who died before time two. There was a genuine difference for "numbers of organ supported"; with a lower score in the follow-up group (4.97 vs 4.40, p=0.040). Although not significant findings, there appeared to be real differences in the amounts of drugs received between the two groups (table 5.4). The group who were not followed up were more likely to have had benzodiazepines (70.2% vs 60%, p=0.186) for sedation, or inotropes or vasopressors (61.4% vs 47%, p=0.082). They also had more days of sedation (4.12 vs 3.13) and more time in intensive care (13.55 vs 12.1 days) than the follow-up group. Follow-up patients were more likely to have come from theatre (34.7% vs 28% of sample) than non follow-up patients whereas non-follow-up patients were more likely to come from Accident & Emergency (24.6% vs 17.3%) than follow-up patients. It would not be surprising if the non-follow-up group had more organ failure and intensive care, as it included those who died or were too ill to take part in follow-up. However as these differences were non-significant, they are not of great concern.

5.2.4 Psychological response of ICU patients

Table 5.5 Acute psychological responses in the ICU

Means(SD) for continuous variables or Ns(%)for categorical variables

		Total sample n=157	**Group1 – not followed up** n=57	**Group 2 – followed up** n=100	**difference between groups 1+2**
(i)Total mood disturbance		28.34 (13.57) Range 3-59 Poss Range 0-60	27.18(13.58)	29.00 (13.60) Range 3-59	p=0.421
Anxiety		5.10 (3.69) Range 0-12 Possible 0-12	4.90(3.84)	5.18 (3.610) Range 0-12	p=0.606
Depression		5.46 (3.38) Range 0-12	5.28(3.39)	5.51 (3.410) Range 0-12	p=0.613
Positive emotion		3.49 (3.04) Range 0-11 Possible 0-12	3.73(3.10)	3.36(3.02) Range 1-12	p=0.464
Anger		2.91 (3.39) Range 0-12	2.63(3.03)	3.08 (3.58) Range 0-12	p=0.427
Mental confusion		6.45 (3.47) Range 0-12	6.21(3.62)	6.58 (3.368) Range 0-12	p=0. 511
ii) ICU Stress Total		32.42 (12.49) Range 3-61 Possible 0-72	31.62(11.98)	32.89 (12.81) Range 3-61	p=0.541
Physical stress		8.22 (4.43) Range 0-16 Possible 0-16	7.57(4.34)	8.61 (4.46) Range 0-16	p=0.721
Delirium		8.06 (5.19) Range 0-20 Possible 0-20	7.86(5.49)	8.17 (5.04) Range 0-18	p=0.162
Sense of personal control		9.57 (4.86) Range 0-19 Possible 0-20	9.51(4.59)	9.61 (5.03) Range 0-19	p=0.902
Emotional Support in ICU		10.31 (2.95) Range 2-16 Possible 0-16	10.36(2.65)	10.28 (3.13) Range 2-16	p=0.874
iii) Illness perceptions					
Timeline of condition		6.56 (2.82) Range 0-10	6.44(2.93)	6.64 (2.77) Range 0-10	p=0.692
Control over condition		4.22 (3.09) Range 0-10	4.62(3.31)	4.00 (2.97) 0-10	p=0.248
Concern about condition		7.25 (2.94) Range 0-10	7.09(3.20)	7.34 (2.80) Range 0-10	p=0.612
Understanding of condition		7.19 (3.06) Range 0-10	7.41(3.23)	7.06 (2.97) Range 0-10	p=0.498
Emotional effect of condition		6.04 (3.40) Range 0-10	6.24(3.75)	Mean 5.92 (3.40) Range 0-10	p=0.592
iv) Memory					
Memory of admission to ICU	**Yes**	55 (35.5%)	21 (37.5%)	34 (34.3%)	
	No	100 (64.5%)	35(62.5%)	65 (65.7%)	p=0.693
Memory for whole ICU stay	**Little**	66 (43%)	21(37.5%)	45 (45.5%)	p=0.188
	Some	42 (27%)	13 (23.2%)	29 (29.3%)	
	Most	47 (30%)	22(39.3%)	25 (25.3%)	
Early intrusive memories re-ICU	**Yes**	73 (47.1%)	24(42.8%)	49 (49.5%)	p=0.727
	No	82 (52.9%)	32(57.1%)	50 (50.5%)	

(i) based on POMS items (ii) ICUSS items (iii) Brief IPQ (iv) memory items

5.2.4 (i) Mood and stress (mean scores**)**

I have also mainly referred to the scores of the 100 follow-up participants in this section on psychological response (see table 5.5). Patients' mean total mood disturbance score was 29.00 (on a scale of 0 to 60). Sub-scale scores were 5.18 for anxiety (0-12), 5.51 for depression (0 to 12), 3.08 for anger (0-12), 3.49 for

positive mood (0-12) and 6.58 for mental confusion (0-12). The mean score for total ICU stress was 32.89 (0-72). Mean ICUSS sub-scale scores were 8.61 for perceived physical stress (0-16), and 8.17 for "delirium" (0-20). Mean score for sense of control was 9.61 (0-20) and for emotional support from family and staff was 10.28 (0-16).

5.2.4 (ii) Mood and stress (severity levels)

In table 5.6 it can be seen that 78% of patients had mood disturbance (with 47% of scores at the higher levels). Furthermore 35% were in the two higher ranges for anxiety, 37% for depression, 51% for "mental confusion" and 21% for anger. ICU stress was experienced by 88% of patients, with 36% of patients at the higher levels. As many as 77% had physical stress (pain, dyspnea, discomfort from tubes) with 56% at higher levels, and 66% had "delirium" with 34% at higher levels. Within positive factors, 77% had high scores for emotional support received from staff and family but positive emotion was lacking, with 81% of scores in the lower ranges. A low sense of personal control while in the ICU was prevalent in 58% of participants. As no severity cut-points have been set for POMS (McNair, 1984), I set low-mild scores for total mood disturbance as 0-15, mild-moderate were 16-30, moderate-high were 31-45 and high-very high were 46-60. This was based on the meaning of response options. I carried out a similar process for ICU stress. These ranges should be validated in further studies.

Table 5.6 Levels of mood disturbance and stress in ICU

(based on follow-up sample; n=100)

	Low-mild	**Mild-moderate**	**Moderate-high**	**High- v. high**
Total mood disturbance	22%	31%	36%	11%
Total ICU Stress	12%	52%	32%	4%
Negative factors				
Anxiety	38%	27%	21%	14%
Depression	34%	29%	22%	15%
Anger	67%	12%	13%	8%
Mental Confusion	23%	26%	28%	23%
Delirium	34%	32%	25%	9%
Physical Stress	23%	21%	36%	20%
Positive factors				
Sense of Control	24%	34%	28%	14%
Support	6%	17%	54%	23%
Positive Emotion	51%	30%	16%	3%

Looking in more detail at the ICU stress questionnaire, delirium results showed that 64.6% of patients had hallucinations (43.4% at highest levels); 47.5% had nightmares; 73.7% were disorientated (43.4% at highest levels); 68% had confusion (42% highest) and 75% were agitated (37% at highest levels). In terms of physical stress, it was found that pain affected 73% of patients (43.4% at highest levels) while 75.8% endured difficult breathing (46.5% highest levels) and 79.8% were sleep deprived (55.6% highest levels). Socially, 52% felt isolated (31% very much so); 56.8% had problems communicating in the ICU (40% very

much so); and 86% felt they had little personal control in the ICU (67.3% very much so).

5.2.4 (iii) Illness perceptions

Mean scores for illness perceptions (0-10) suggested that patients believed their condition would last for a long time (6.64), that their control over their condition was limited (4.00), that they were concerned about their condition (7.34), they believed they understood their condition (7.06) and that they were emotionally affected by their condition (5.92).

5.2.4 (iv) Memory

Two thirds of patients had no memory of their admission to the ICU while a third were able to remember being admitted. For the rest of their ICU stay, 45.9% said they remembered little; 29.6% remembered a moderate amount of the time and 24.5% remembered most of the time. Almost half of all patients (49.5%) said they had intrusive thoughts or "memories" about the ICU by the time of discharge from the ICU. For 22.6% of patients, their intrusive memories were "factual" – apparently pertaining to real events and experiences in the ICU. But for 20% of patients, the intrusions were "unreal" memories of dreams, hallucinations or delusional states experienced in the ICU. Another five patients described their memories as both factual and unreal, and two patients chose not to describe the content of the memories.

5.2.5. Summary of psychological state of ICU patients

To summarise the psychological state of a sample of 157 level 3 patients who were on the point of discharge from the ICU, there were considerable levels of mood disturbance such as anxiety and depression, and of cognitive dysfunction such as confusion and delirious symptoms. High levels of physical stress including pain, discomfort and difficulty breathing were reported. Personal control and positive emotion were low, but emotional support from staff and family was rated as high. Memory was distorted, as nearly half of the patients remembered little of their ICU stay, and many patients experienced intrusive thoughts about the ICU.

5.2.6 Comparison of psychological factors: follow-up/non follow-up groups

There were no significant differences of mean scores for mood and stress between the follow-up and non-follow-up groups, but it is of interest that all the follow-up group's scores were somewhat more negative than the non-follow-up group's. Although there were also no significant differences between groups for memory factors, it can be seen that the patients who remembered least about the ICU and patients who had intrusive memories were more likely to have responded to the follow-up survey.

5.2.7 Chronic health-related factors

Other background factors that could have an impact of psychological outcomes after intensive care were chronic physical illness, psychological history, and history of alcohol abuse. Data on these outcomes were collected only for the 100 patients who were followed up, due to difficulties in getting access to data, and limitations of time (see chapter four). Although these factors could be broken down into more detailed categories (see table 5.7), they were used as binary variables in analysis because of small numbers within categories. Mean social support at 3 months (emotional and practical support from loved ones) was good (26.29 (8.68)).

Table 5.7 Chronic health-related factors

		n/% or mean(SD)	Description/detailed coding/frequencies
chronic physical illness	**yes**	49	Included respiratory (5 patients), cardiovascular (5), endocrine(6), neurological(4), GI/obesity (10), HIV(2), renal (1), 2 conditions(9), 3 or more(6)
	no	51	
cancer	**yes**	24	Included lung (2), breast(1), gastrointestinal(3), head and neck(7), urological(2), gynaecological(2), sarcoma(2), haematological(4), neuroendocrine(2)
	no	76	
history of depression	**yes**	16	Includes previous or current psychological history. Depression (14), depression with psychosis (1) anxiety, OCD, depression(1)
	no	84	
alcohol use	**yes**	12	Includes previous or current heavy alcohol use. Amounts recorded vary from one bottle wine/day to 20 pints a day.
	no	88	
Social support		26.29 (8.68) Range 0-36	Measure of emotional support and practical support at three months

5.3 Prevalence of psycho-social outcomes

Mean scores, prevalence rates and symptom severity ranges for PTSD, anxiety depression, and HRQL at three months follow in table 5.8 below.

Table 5.8 Outcomes and prevalence of psychological morbidity at three months**.**

	PTSD	Depression	Anxiety	Mental HRQL	Physical HRQL
Mean	14.3 (11.81)	20.55 (14.00)	43.71 (14.78)	**43.93(10.82)** (95%CIs: 32.26, 36.58)	**34.42(10.07)** (95%CIs: 41.62, 46.26)
Range	0-51	0-54	20-80	18.92-64.19	17.44- 55.91
Possible range	0-51	0-60	20-80	0-100	0-100
Cut-off	18	19	45		
Prevalence 95%CIs	**27.1%** (18.3, 35.9%)	**46.3%** (36.5, 56.1%)	**44.4%** (34.6, 54.2%)		
no symptoms	6%	3%	5%		
mild symptoms	41%	38%	24%		
moderate symptoms	32%	24%	17%		
severe symptoms	21%	35%	54%		
Subscale mean(SD)	*Intrusion* 3.24 (3.94) Max: 15				
Subscale mean(SD)	*Avoidance* 6.03(5.32) Max: 21				
Subscale mean (SD)	*Arousal* 4.83 (4.26) Max: 15				

5.3.1 Primary outcome: PTSD at 3 months

The mean score on the PDS scale (Foa et al., 1997) was 14.13 (11.81). Mean sub-scale scores were 3.24 (3.94) for *intrusive* symptoms (maximum 15), 6.03 (5.32) for *avoidance* symptoms (maximum 21), and 4.83 (4.26) for *hyper-arousal* symptoms (maximum 15). Using a method for diagnosing PTSD recommended by the author of the PDS (Foa et al., 1997), the prevalence of cases was 45.8% (95% CIs: 35.8%, 55.79%). However a number of different methods have been suggested for using the PDS to establish a diagnosis of PTSD (Foa et al., 1997). In a study that tested 18 different scoring rules, it was found that using a cut-point of 18 on the PDS severity scale was a highly efficient method of diagnosing PTSD (Ehrings et al., 2007). Using this method, the prevalence of PTSD cases was **27.1% (95%CIs: 18.3, 35.9%).** Only six% of patients had no PTSD symptoms, 41% had mild symptoms (1-10); 32% had moderate symptoms (11-20), 15% had moderate/severe symptoms (21-35) and 6% had most severe symptoms (36-51).

5.3.2 Outcome: Depression

The authors of the CES-D (Radloff, 1977) recommend a cut-point of 16 for likely clinical depression, but I used a more conservative cut-point of 19 recommended for patients with somatic symptoms, as explained in chapter four. Using the original cut-point, prevalence of depression in this sample would be 55.8%, but using the more conservative cut-point the prevalence of depression was **46.3%** (95% CIs: 36.5, 56.1%).

5.3.3 Outcome: Anxiety

Cut-points of 32 and 39 have been recommended for the STAI, but 44-45 was suggested for hospital patients (see chapter four). The latter seemed more appropriate for this sample, and prevalence for anxiety was found to be **44.4%** (95% CIs: 34.6, 54.2%).

5.3.4 Outcome: HRQL

Results are given for the physical component summary (PCS) and the mental component summary (MCS) of the SF-12 (Ware et al., 1996). These two scales were transformed to have a mean of 50 and a standard deviation of 10 (in the American population). Mean PCS in this sample was **34.42** (95%CIs: 32.26, 36.58). The minimum score was 17.44 and the maximum was 55.91. Mean MCS was **43.93** (95%CIs: 41.62, 46.26). Minimum score for MCS was 18.92 and maximum was 64.19. Therefore mean PCS at 3 months was 16 points below average in the population and MCS seven points below average. Therefore physical health of former ICU patients was **1.6 SDs** below the mean of the normal population and mental health was **0.6 SDs** below. Further examination of the frequency of scores showed that **43%** of the patients had MCS scores of between

18 and 40 and therefore had poor mental HRQL. For PCS 50% of patients had scores ranging from 17.5 to 34, suggesting their physical HRQL was extremely poor. Up to **75%** of patients had scores under 40, the cut-point for poor HRQL (Casso et al., 2004).

5.3.5 Associations between outcomes

Associations between psycho-social outcomes were measured because of the issue of co-morbidity. The correlation between PTSD and depression was 0.796 ($p<0.001$); between PTSD and anxiety it was 0.653, ($p<0.001$) and between depression and anxiety it was 0.809 ($p< 0.001$). Depression was associated with worse mental and physical HRQL (with MCS -0.770, $p<0.001$; with PCS -0.250, $p=0.022$). Post-ICU anxiety was highly associated with both aspects of HRQL (with MCS -0.808, $p<0.001$; with PCS -0.323, $p=0.002$). Finally
PTSD was associated with MCS (0.590, $p<0.001$) but not with PCS (-0.115, $p=0.293$). The physical and mental aspects of HRQL, PCS and MCS, were not significantly associated with each other ($r=0.174$, $p=1.09$).

5.3.6 Prevalence of adverse psycho-social outcomes after ICU

As the aim of my study was to present the extent of adverse psycho-social outcomes affecting ICU patients after 3 months, I am also reporting combined rates. Looking first at psychological morbidity alone, **55%** of patients had either PTSD or depression or anxiety after 3 months. Of these 23% had all three syndromes, 17% had two syndromes and 15% had one. If poor mental HRQL (MCS<40) is included, then **60%** of patients had an adverse psycho-social outcome. If poor physical HRQL is included (PCS<40) then **86%** of patients had an adverse psycho-social outcome. Fifteen percent of patients had all five adverse psycho-social outcomes.

5.4 Statistical Analysis

To test hypotheses one to four, univariable, multivariable and mediational analyses of data were carried out.

5.4.1 Distribution of continuous data

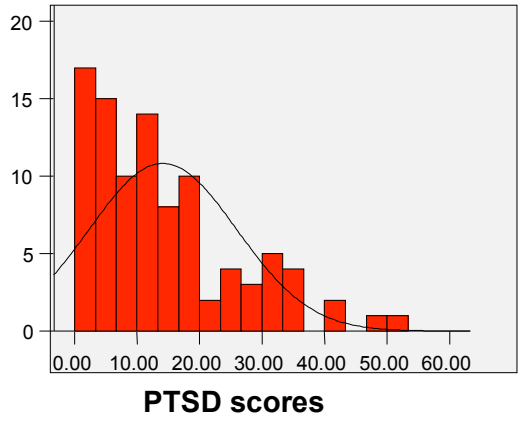
Before testing for associations, distributions were examined and tests carried out to check whether continuous variables had normal distributions. Looking first at the results of KS Lilliefors normality tests (table 5.9) and histograms for outcomes figure 5.3), it was clear that anxiety, physical HRQL and mental HRQL had close to normal distribution. However both PTSD and depression scores were skewed to the left, with a long right-hand tail. For data to be treated as normally distributed, skew should be approximately within +2 and -2 (Field, 2005). Therefore it was acceptable to treat depression as a normally distributed variable as the skew was <2. As the skew of PTSD was 4.38, I tried log-transforming PTSD data but the skew

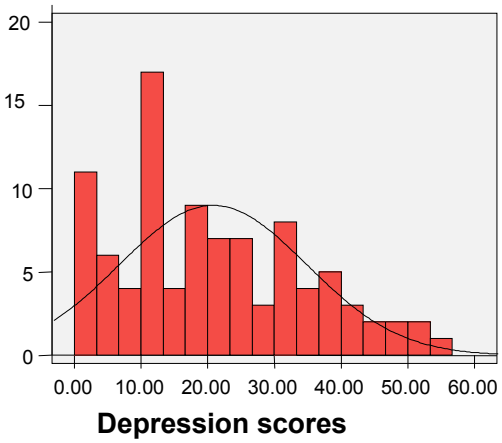
was still 2.96. However when PTSD was regressed on individual risk factors, residuals were normally distributed (see Figure 5.4 for scatterplot and normal probability plot for PTSD and one risk factor, TISS). As PTSD was an outcome variable, I decided it was acceptable to treat it as a normally distributed variable for carrying out regressions. Therefore parametric tests were used for associations between normally distributed risk factors and all outcomes including PTSD.

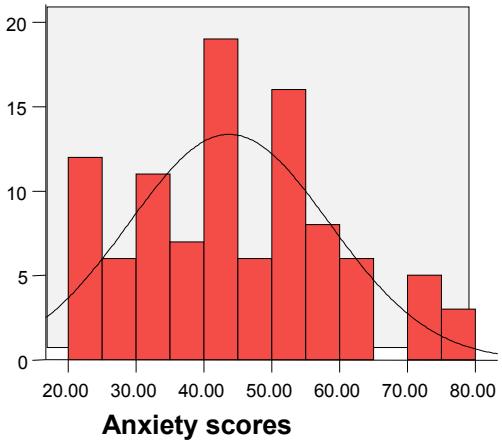
Table 5.9 Tests of normality and skewness statistics for outcomes

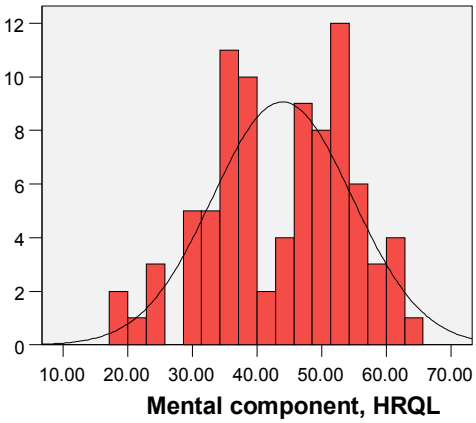
	KS-Lilliefors Test of Normality	Skewness	SE of skewness	Skewness÷ SE
PTSD scores	.121, df=96, p = .001	1.077	.246	4.38
Depression	.105, df=95, p= .012	.473	.247	1.91
Anxiety	.070, df=95, p= .200	.393	.243	1.62
Phys HRQL	.088, df=86, p= .097	.456	.261	1.75
Mental HRQL	.085, df=86, p= .173	-.262	.261	-1.00
Transformed PTSD scores		-.722	.244	2.96

Figure 5.3 Histograms for outcomes






20
15
10
5
0
20.00
30.00
40.00
50.00
60.00
70.00
80.00
Anxiety scores


12
10
8
6
4
2
0
10.00
20.00
30.00
40.00
50.00
60.00
70.00
Mental component, HRQL

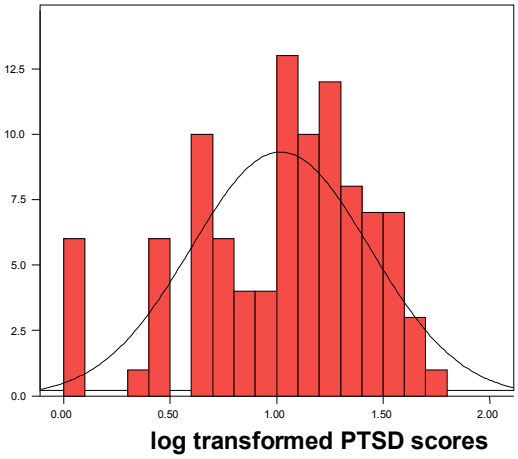
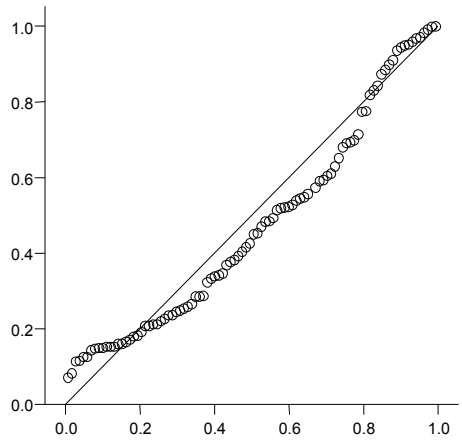

12.5
10.0
7.5
5.0
2.5
0.0
0.00
0.50
1.00
1.50
2.00
log transformed PTSD scores

Figure 5.4 Plots showing distribution of residuals in PTSD regressions.

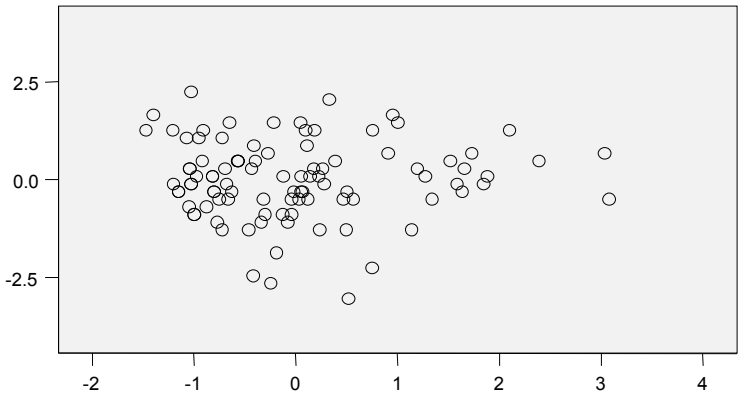
Normal Probability plot (TISS and PTSD)

(Dependent Variable: PTSD)



Scatterplot (TISS and PTSD)

(Y-axis=Regression Standardised Predicted Values
X-axis =Regression Standardized Residual?)



5.4.2 Distribution of continuous variables ("risk" factors)

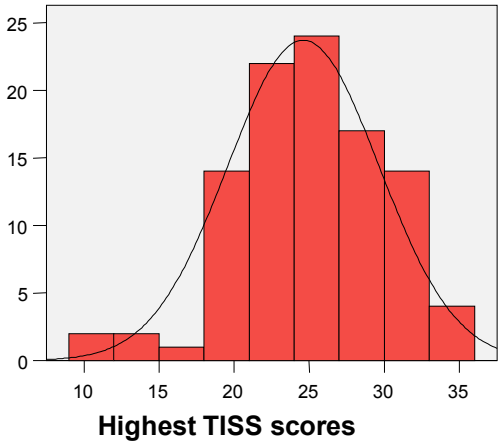
Because there were many variables in the study, most histograms of risk factors are not shown. However all continuous variables were examined for normality.

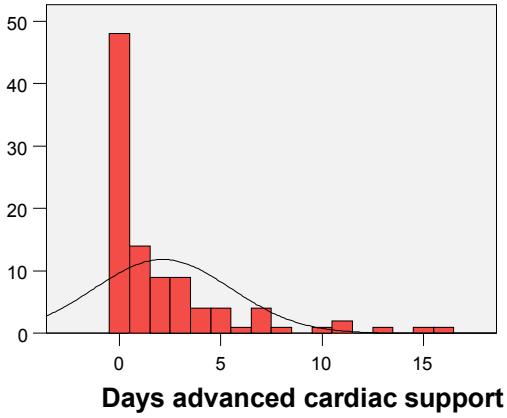
5.4.3 Clinical continuous variables

Apache II scores, TISS scores, number of organs supported and number of drug groups received all had a skew of <2 and were treated as normally distributed variables. However hospital, ICU and Level 3 days, sedation days and all days of organ support variables were skewed to the left, with a long right-hand tail, reflecting the fact that most patients were admitted and treated for a few days

while a few patients stayed for many days. Figure 5.5 shows the histograms for TISS (nearly normally distributed) and days of advanced cardiac support (very skewed to the left) to illustrate the difference. I decided to use parametric tests for associations of outcomes with normally distributed clinical variables, and non-parametric tests for associations of outcomes with very skewed variables such as days of sedation or days in ICU.

Figure 5.5 Distribution of predictors





5.4.4 Distribution of psychological and socio-demographic variables

The variable for age was slightly skewed to the right, due to the older age of patients in the ICU, but the skew was <2, so age was treated as a normally distributed variable. Total ICU stress score and total mood disturbance score were normally distributed variables. All ICU stress sub-scales (delirium, physical stress, control and support) and almost all POMS subscales (depression, anxiety, confusion, positive mood) were normally distributed. Some IPQ variables were

skewed. I used parametric tests for associations with most psychological and socio-demographic variables, and non-parametric tests with IPQ variables.

5.5 Univariable associations

In the tables in this section I have presented associations between all groups of explanatory factors and each outcome. I have then reported on associations between the four groups of risk factors.

5.5.1 Socio-demographic risk factors of psycho-social outcomes

As shown in table 5.10 age and sex did not have statistically significant associations with any of the outcomes, but there were trends for those with higher PTSD scores to be younger (r=0.184, p=0.073) and female (p=0.075).The effect of sex was a difference in mean PTSD scores of 4.3 points. Ethnicity was a significant predictor of depression but no other outcome; Mean depression score for "other ethnic groups" was 6.41 points higher than the score for "white" ethnic groups. Socio-economic circumstances were significant predictors of depression, anxiety and mental HRQL (MCS), but not of PTSD or physical HRQL (PCS). Education was not a significant risk factor for any outcome.

Table 5.10 Associations between socio-demographic variables and outcomes.

	PTSD	Depression	Anxiety	Mental HRQL	Physical HRQL
Age	-0.184 **p=0.073**	0.166 p=0.107	-0.027 p=0.789	0.096 p=0.381	-0.095 p=0.382
Sex	4.30 (-9.04,0.44) **p=0.075**	4.01 (-9.69,1.68) p=0.165	-3.39 (-9.69,1.68) p=0.257	4.20 (-0.39,8.79) **p=0.072**	-0.81(-5.16,3.54) p=0.712
Ethnicity white other	p=0.604	-6.41 (-12.69,-0.13) **p=0.046**	p=0.493	p=0.200	p=0.153
NS-SEC	p=0.246	**p=0.008**	**p=0.041**	**p=0.016**	p=0.691
1. professional	11.77(9.10)	14.46(10.68)	39.27(11.69)	48.47 (9.53)	35.86(9.66)
2. intermediate	15.61(7.25)	30.33(12.51)	53.00(13.19)	39.58(10.73)	31.16(6.95)
3.own account	13.12(12.46)	22.71(14.21)	43.33(13.89)	45.55(10.79)	34.13(10.81)
4. technical/	8.04(4.79)	13.64(8.59)	36.19(11.45)	43.53(8.75)	38.21(10.77)
5. routine/semi	18.19(13.77)	24.75(15.65)	46.33(16.11)	38.43 (9.48)	35.40(11.32)
6. unclassified	18.56(18.66)	24.98(21.30)	50.52(21.30)	37.98(12.97)	34.57(11.45)
Education	p=0.261	p=0.585	p=0.735	p=0.921	p=0.184

†There were significant differences in depression scores between NS-SEC classes 1 and 2. There were no significant differences in anxiety between classes. There was a significant difference of mean MCS between NS-SEC classes 1 and 5.

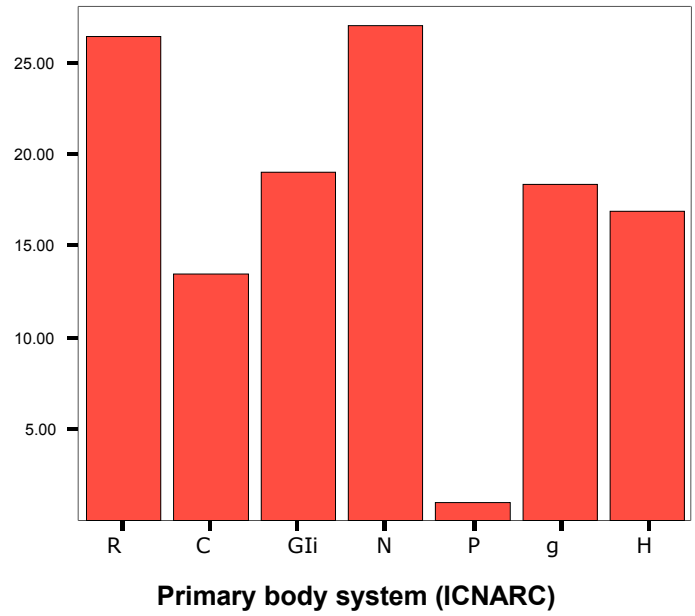
For NS-SEC, a significant mean difference of 15.88 points (95%CIs: 0.67,31.08) was found for depression between class 1 (professional/managerial) and class 2 (intermediate professions). Class 2 was more depressed. A significant mean difference of 10.04 points (95% CIs: 0.79, 19.29) was found for mental HRQL between class 1(professional/managerial) and class 5(routine/semi-routine occupations). The latter had worse mental HRQL. There were no significant differences in anxiety scores between NS-SEC groups. Although

relationships between SEC and PTSD were non-significant in this analysis, differences between groups could be seen. For example there was a seven point difference between NSSEC classes 1 (professional) and 5 (routine).

5.5.2 Clinical risk factors and 3-month outcomes

Looking first at illness-related factors, it can be seen from Table 5.11 that there were no associations between **illness severity** on admission (Apache II scores) and any of the outcomes, although there was an association of 0.179 with three-month anxiety that approached significance (p=0.077). There were also no associations between **primary body system** involved at ICU admission and PTSD, anxiety and HRQL.

Figure 5.6 Depression scores at 3 months for different diagnostic groups



R=respiratory, C=cardiovascular G=gastrointestinal, N=neuro, P=poison, g=genitourinary, H=haematological

However there was a significant relationship between primary body system and depression at three months (see Figure 5.6). Specifically there was a significant difference of 13 points between respiratory and CV for depression, as well as large non-significant differences between other groups. There were few significant relationships between outcomes and factors representing health care pathways. However three-month depression was predicted by hospital length of stay and destination after hospital discharge. Otherwise, psychosocial outcomes were not associated with type of admission (non-surgical, elective or emergency surgical),

source of admission, ICU length of stay or days as level 3 patient in ICU. Many significant relationships were found between intervention and treatment-related

Table 5.11 Associations between clinical factors and outcomes

(Effect sizes: "r" for normally distributed continuous variables, rho for skewed variables, mean difference with 95%CIs for binary variables. P-values only are reported for categorical variables)

	PTSD	Depression	Anxiety	Mental HRQL	Physical HRQL
Illness severity score	0.059 p=0.569	0.123 p=0.236	0.179 ***p=0.077***	-0.143 p=0.190	-0.040 p=0.712
Primary body system	p=0.201	**p=0.028**	0.139	p=0.304	p=0.169
TISS score	0.253 **p=0.013**	0.080 p=0.438	0.066 p=0.517	-0.055 p=0.618	0.036 p=0.742
No. of organs	0.264 **p=0.009**	0.124 p=0.232	0.058 p=0.571	-0.079 p=0.467	0.075 p=0.491
Days respiratory	0.204 **p=0.046**	0.089 p=0.390	0.058 p=0.568	-.013 p=0.909	-.014 p=0.899
Days adv Circulatory	0.246 **p=0.016**	0.142 p=0.169	0.125 p=0.218	-0.201 ***p=0.063***	-0.030 p=0.787
Days gastro-Intestinal	0.221 **p=0.031**	0.122 p=0.238	0.007 p=0.948	-0.072 p=0.509	0.000 p=0.999
Days of sedation	0.268 **p=0.008**	0.189 ***p=0.066***	0.171 ***p=0.090***	-0.203 ***p=0.061***	0.025 p=0.820
No. of drug Groups	0.280 **p=0.006**	0.102 p=0.323	0.103 p=0.311	-0.099 p=0.467	-0.197 ***p=0.070***
Hypnotics *	-4.11 (-9.13,0.91) p=0.108	-2.24 (-8.39,3.91) p=0.471	-0.67 (-7.06,5.71) p=0.835	0.23 (-4.67,5.12) p=0.927	-1.38 (-5.93,3.16) p=0.546
Benzo-diazepines	-6.96 (-11.57,-2.36) **p=0.002**	-7.44 (-13.07,-1.81) **p=0.010**	-5.95(-11.87,-0.03) **p=0.049**	4.08 (-0.56,8.73) ***p=0.084***	0.27 (-4.12,4.67) p=0.902
Anaesthestics	-1.64 (-6.65,3.35) p=0.514	2.35 (-3.80,8.50) p=0.449	2.61 (-3.65,8.88) p=0.409	-2.02 (-6.93,2.9) p=0.416	-4.45(-8.94,0.04) **p=0.052**
Inotropes and vasopressors	-4.84 (-9.57,-0.1) **p=0.046**	-3.70 (-9.40,1.99) p=0.200	-7.63(-13.37,-1.89) **p=0.010**	4.51 (-.06,9.08) **p=0.053**	-0.06 (-4.41,4.29) p=0.978
Antipsychotics	-5.81(-10.81,-0.8) **p=0.024**	-1.59 (-7.39,4.31) p=0.594	-1.18 (-7.25,4.87) p=0.699	1.58(-3.12,6.28) p=0.507	-4.14 (-8.43,0.15) ***p=0.059***
Opioids	0.55(-9.32,10.42) p=0.912	**7.12** (-3.77,18) p=0.197	**7.79**(-3.66,19.25) p=0.180	**-7.42**(-15,80,0.96) ***p=0.082***	-0.29 -8.23,7.65 p=0.943
Steroids	0.28 (-4.77,5.33) p=0.913	1.08 (-5.08,7.25) p=0.728	1.57 (-4.71,7.85) p=0.622	0.59 (-4.31,5.48) p=0.813	**-5.57** (-9.96,-1.18 **p=0.029**
Type admission	p=0.806	p=0.502	p=0.232	0.812	0.531
Source of Admission	p=0.828	p=0.531	p=0.975	p=0.217	p=0.507
Days as level 3 patient in ICU	0.163 p=0.114	0.083 p=0.425	0.043 p=0.670	-0.075 p=0.493	0.041 p=0.710
Days in ICU	0.109 p=0.292	-0.046 p=0.656	-0.056 p=0.581	-0.018 p=0.869	0.018 p=0.868
Days in hospital	0.149 p=0.152	0.206 **p=0.049**	0.089 p=0.388	-.179 p=0.105	-0.065 p=0.561
Post-hospital destination	p=0.377	**p=0.048**	p=0.249	p=0.220	p=0.903
C-reactive protein on admission**	0.248 **p=0.014**	0.163 p=0.114	0.098 p=0.336		
C-reactive protein (highest)	0.219 **p=0.030**	0.104 p=0.315	0.079 p=0.439		

*For all drug groups, the mean for patients who had the drug was subtracted from the mean of patients who did not have the drug. Therefore negative mean differences indicated higher outcome scores for those who the drug (meaning worse psychological morbidity or better HRQL).

**C-reactive protein is a sepsis diagnostic marker ***Significant p-values are in bold, almost significant p-values (trend) are in bold italic.

variables (including drugs) and PTSD. The variables that predicted PTSD were TISS (Keene et al., 1983), a sepsis marker (CRP), number of organs supported, number of drug groups given, days of sedation, days of respiratory support, days advanced CV support, days of GI support, benzodiazepines, inotropes and antipsychotics. Use of benzodiazepines predicted depression at three months in addition to the healthcare factors mentioned above. Anxiety at three months was predicted by the the use of benzodiazepines and inotropes. The administration of inotropes predicted mental HRQL, and steroids and anaesthetics predicted better physical HRQL. Other trends seen in table 5.11 are of interest. The associations between days of sedation and depression, anxiety and mental HRQL at three months were all approaching significance at the 0.05 level. Although not significant, participants who received opiates had substantially better depression, anxiety and mental HRQL scores (around seven points lower) than participants who did not. This was in contrast to those receiving benzodiazepines, hypnotics and inotropes who generally had worse psychological outcomes than patients who did not receive these drugs.

5.5.2 Acute psychological factors and outcomes

Mood and Stress in the ICU

It is clear from table 5.12 that there were many highly significant relationships between acute psychological responses, both emotional and cognitive, in the ICU, and psycho-social outcomes at three months. Total ICU mood disturbance and total ICU stress were both significantly correlated with all outcomes except physical HRQL. All ICU mood subscales (symptoms of anxiety and depression, positive emotion, anger and mental confusion) were associated with most outcomes. Three of the four ICU Stress sub-scales – physical stress, delirium and ICU control were associated with all outcomes except physical HRQL. However the fourth sub-scale, ICU support, was not related to any outcomes. This may be explained because most patients rated support received from staff and family in the ICU highly and there was little variation in this factor. Most effect sizes between ICU mood and stress and outcomes were medium and large.

Cognitive factors

It was seen in the previous section that the cognitive factors – mental confusion and "delirium" from the ICU mood and ICU stress scales were associated with PTSD, depression, and to a lesser extent, with anxiety at three months. A similar pattern was found with two further cognitive variables, memory for ICU and early intrusive memories of ICU. Patients with very little memory of their ICU experience had significantly higher levels of PTSD and depression at three months

Table 5.12 Associations between ICU psychological factors and outcomes

	PTSD	Depression	Anxiety	Mental HRQL	Physical HRQL
Total ICU mood disturbance	0.495 **p=0.000**	0.420 **p=0.000**	0.376 **p=0.000**	-0.473 **p=0.000**	-0.011 p=0.923
Anxiety	0.421 **p=0.000**	0.344 **p=0.001**	0.377 **p=0.000**	-.399 **p=0.000**	-0.007 p=0.950
Depression	0.380 **p=0.000**	0.340 **p=0.001**	0.369 **p=0.000**	-0.421 **p=0.000**	-0.113 p=0.301
Positive	-0.386 **p=0.000**	-0.298 **p=0.003**	-0.238 **p=0.018**	0.334 **p=0.002**	0.128 p=0.241
Anger	0.362 **p=0.000**	0.356 **p=0.000**	0.280 **p=0.005**	-0.402 **p=0.000**	0.100 p=0.359
Mental confusion	0.377 **p=0.000**	0.287 **p=0.005**	0.196 **p=0.052**	-0.296 **p=0.006**	0.079 p=0.471
ICU stress Total	0.463 **p=0.000**	0.361 p**=0.000**	0.316 **p=0.002**	-0.373 **p=0.000**	-0.90 p=0.413
Physical stress	0.394 **p=0.000**	0.357 **p=0.000**	0.316 **p=0.002**	-0.329 **p=0.002**	-0.034 p=0.759
"Delirium"	0.402 **p=0.000**	0.252 **p=0.014**	0.196 **p=0.052**	-0.270 **p=0.012**	0.002 p=0.987
Personal control	-0.360 **p=0.000**	-0.285 **p=0.005**	-0.262 **p=0.009**	0.304 **p=0.005**	0.122 p=0.265
Support in ICU	-0.050 p=0.634	-0.023 p=0.823	-0.004 p=0.965	0.048 p=0.659	0.068 p=0.537
Illness Perceptions	0.275	.217	0.228	-0.157	-0.393
Timeline	**p=0.008**	**p=0.038**	**p=0.027**	p=0.157	**p=0.000**
Control of condition	-0.038 p=0.716	-0.066 p=0.531	-0.049 p=0.635	-0.056 p=0.613	0.129 p=0.242
Concern	0.277 **p=0.007**	0.323 **p=0.002**	0.219 **p=0.032**	-0.197 p=0.073	-0.264 **p=0.015**
Under-standing	-0.083 p=0.426	0.040 p=0.702	-0.006 p=0.955	0.019 p=0.861	-0.074 p=0.499
Emotional Representation	0.289 **p=0.005**	0.315 **p=0.002**	0.290 **p=0.004**	-0.281 **p=0.009**	-0.175 p=0.109
Memory admission	1.72 (-3.34,6.78) p=0.501	-0.33 (-5.84,6.50) p=0.917	0.57 (-5.72,6.85) p=0.858	-3.00(-7.88,1.88) p=0.225	0.66(-3.93,5.26) p=0.774
ICU memory	-6.30 (-10.98,-1.56) **p=0.010**	-6.05 (-11.73,-0.37) **p=0.037**	-3.06 (-9.-4,2.91) p=0.311	2.01 (-2.68,6.71) p=0.396	-0.54(-4.95,3.85) p=0.806
ICU Intrusions	-9.39 (-13.85,-4.92) **p=0.000**	-7.10 (-12.71, -1.47) **p=0.014**	-5.85 (-11.72,0.02 **p=0.051**	3.38 (-1.27,8.03) p=0.152	-1.86 (-6.23,2.52) p=0.401

(Effect sizes: 'r' or 'rho' for continuous variables; mean differences+ 95%CIs for categorical)
Significant p-values are in bold.

than patients who could remember what happened to them in the ICU, but there was no significant association with anxiety at three months. Patients who had intrusive memories about ICU experiences at the point of ICU discharge had significantly higher levels of PTSD, depression and, to a lesser extent, anxiety at three months. Memory of ICU and ICU Intrusions were associated with each other (χ^2=5.346, df=1, p=0.021). The association was that patients with very little memory of ICU were more likely to have early intrusive ICU memories than patients who remembered the ICU (62.2% vs 38.8%). The finding that cognitive and memory disturbances in the ICU had strongest associations with PTSD and depression at three months will be discussed in chapter six.

Illness perceptions (patients' beliefs about their medical condition while in ICU) were associated with all outcomes including physical HRQL. Timeline and concern predicted PTSD, Depression, Anxiety and PCS, while emotional representation predicted psychological morbidity and MCS. Timeline and concern were the only psychological factors that predicted PCS.

5.5.3 Chronic health-related factors and outcomes

Several chronic health-related factors were associated with outcomes. Chronic disease was associated with depression, anxiety and health-related HRQL. Cancer patients had better psychological outcomes than non-cancer patients but the differences were not significant. Psychological history was a significant predictor of all outcomes except PCS. Alcohol use predicted only PTSD. The existence of past traumas (prior to having a life-threatening illness or condition) had no significant effect on psychological morbidity at 3 months but there was a trend that it predicted PTSD (p=0.080). Social support at three months was not associated with any outcomes (see table 5.12).

Table 5.13 Chronic and previous illness and outcomes

(Effect sizes: 'r' or 'rho' for continuous variables; mean differences+ CIs for categorical

	PTSD	Depression	Anxiety	MCS	PCS
Chronic illness	3.55 (1.14, 8.23) p=0.136	5.94 (0.33,11.54) **p=0.038**	7.31 (1.57,13.05) **p=0.013**	7.25 (2.86,11.65) **p=0.001**	4.41 (0.17,8.64) **p=.042**
Cancer	-1.38 (-4.12, 6.88) p=0.620	-2.80 (-3.88, 9.46) p=0.407	-0.48 (-6.42, 7.41) p=0.887	1.01 (-6.28,4.26) P=0.704	1.47 (-6.37,3.43) P=0.552
Psychological history	10.48 (16.52,4.43) **p=0.001**	11.42 (4.12,18.71) **p=0.002**	12.92 (5.30,20.54) **p=0.001**	7.25 (1.47,13.03) **p=0.015**	3.12 (-2.42,8.66) p=0.119
Alcohol use	9.17 (2.20,16.15) **p=0.011**	6.36 (2.17,14.89) p=0.142	3.62 (5.44,12.67) p=0.430	0.38 (-6.35,7.11) P=0.911	-0.19 (-6.45-6.10) P=0.953
Social support	-0.050 p=0.658	0.004 p=0.970	0.025 p=0.820	0.013 p=0.913	-0.063 p=0.586
Past trauma	4.41 (-9.36,0.53) ***p=0.080***	3.52 (-9.5,2.46) p=0.286	2.07 (-8.26,4.12) p=0.509	-0.71 (-5.26,3.85) p=0.758	-0.61 (-5.50,4.28) p=0.805

5.5.4 Relationship of clinical factors and ICU psychological response

In table 5.12 we saw that there were large correlations between acute psychological responses in ICU and psycho-social outcomes at three months. As the first step in testing hypothesis H4, that acute psychological risk factors could be mediators between acute clinical factors and outcomes, I looked at correlations between acute clinical risk factors and acute psychological responses in the ICU The overall pattern (see table 5.13) was that increased numbers of interventions or drugs were associated with worse psychological responses, i.e. more negative mood, more stress, more intrusive thoughts and less memory for the ICU.

Table 5.14 Clinical factors and ICU psychological responses

(Effect sizes: 'r' or 'rho' for continuous variables; mean differences+ 95%CIs for categorical)

	Total mood	Total ICU stress	ICU Intrusions	Memory of ICU	Illness reps1-5
TISS	0.339 **p=0.001**	0.315 **p=0.002**	-1.427 (-3.44,0.59) p=0.163	-2.76 (-4.73, -.8) **p=0.006**	0.214 *timeline* **p=0.037**
Number organs	0.270 **p=0.007**	0.290 **p=0.004**	-0.55 (-1.23,0.12) p=0.107	-0.99 (-1.65,-.33) **p=0.004**	all n.s.
Number drugs	0.278 **p=0.005**	0.294 **p=0.003**	-0.76 (-1.41, -.10) **p=0.024**	-0.76 (-1.41, -0.10) **p=0.025**	0.174 *timeline* ***p=0.091***
Days sedation	0=.305 **p=0.005**	0.299 **p=0.003**	-2.13 (-3.80,-.46) **p=0.013**	-2.78 (-4.51,1.04) **p=0.002**	0.230 *timeline* **p=0.024**
Days respira-tory support	0.143 p=0.156	0.300 **p=0.003**	-5.40 (-11.85,1.05) ***p=0.099***	-1.46 (-7.81,4.89) p=0.656	0 .184 *timeline* **p=0.073**
Days Advanced CV support	0 .287 **p=0.004**	0.308 **p=0.002**	-1.05 (-2.40,0.30) p=0.125	-1.33 (-2.67,0.014) **p=0.052**	0 .228 *timeline* **p=0.025**
Days GI support	0.158 p=0.116	0.284 **p=0.004**	-3.75 (-9.64,2,15) p=0.210	-1.00 (-6.96,4.96) p=0.740	all n.s.
Primary body system	p=0.483	p=0.378	p=0.751	p=0.132	*emotional rep* **p=0.012**
Hospital days	0.174 ***p=0.089***	0.147 p=0.154	p=0.187	-3.88 (-19.58,11.82) p=0.625	all n.s.
Post hospital	p=0.399	p=0.396	***p=0.097***	p=0.661	all n.s.
Benzodi-azepines	-5.10 (-0.50,0.27) ***p=0.063***	-7.19 (-12.2,-2.18) **p=0.005**	benzodiazepines =more IMs **p=.018**	benzodiazepines =less memory **p=.003**	*concern* **p=0.054**
Antipsy-chotics	-5.25 (-0.68,0.18) ***p=0.058***	-4.50 (-9.70,0.71) ***p=0.089***	antipsychotics-more IMs **p=0.053**	antipsychotics =less memory **p=.029**	all n.s.
Iono-tropes	-5.78 (-11.11,-0.44) **p=0.035**	-5.21 (-10.24,-0.17) **p=0.043**	p=0.368	p=0.659	*timeline* **p=0.016**
Anaes-thetics	p=0.446	p=0.235	p=0.320	anaesthetics =less memory **p=0.010**	all n.s.
Steroids	p=0.414	p=0.645	p=0.069	p=0.477	*control* **p=0.041** *under-standing* ***p=0.084***

Factors that indicated increased amount of intensive care (e.g. TISS) were associated with ICU amnesia. Intrusive memories of ICU were mainly related with drug variables. Other relationships between clinical factors and acute psychological response were approaching significance.

5.5.5 Relationship between clinical and socio-demographic factors

As can be seen in table 5.15 there were very few associations between clinical factors and socio-demographic factors. Interventions and drugs received did not appear to vary according to age, sex, or socio-economic circumstances. The only

significant results obtained were that illness severity increased with age, and women had an average 1.43 days more of advanced CV support than men.

Table 5.15 Clinical and Socio-Demographic factors

	age	sex	NS-SEC
TISS	p=0.292	p=0.791	p=0.709
Number organs	p=0.734	p=0.933	p=0.631
Number drugs	p=0.670	p=0.566	p=0.733
Days sedation	p=0.293	p=0.519	p=0.302
Days Respiratory	p=0.245	p=0.192	p=0.597
Days advanced CV	p=0.399	1.43 (2.79, -0.08) **p=0.039** more women	p=0.992
Days GIS	p=0.172	p=0.460	p=0.713
Primary system	***p=0.099***	p=0.132	p=0.419
Hospital days	0.193 ***p=0.058***	p=0.230	p=0.750
hypnotics	-6.45 (-13.84,0.94) ***p=0.086*** *older more*	p=0.359	p=0.340
Benzodiazepines	p=0.841	p=0.896	p=0.598
Antipsychotics	p=0.127	p=0.264	p=0.458
Inotropes	p=0.253	***p=0.075*** *more women*	p=0.527
steroids	p=0.512	p=0.621	p=0.867
Illness severity score	0.221 **p=0.027**	p=0.967	p=0.876

5.5.6 Socio-demographic and psychological factors

Patients with intrusive thoughts about the ICU were on average 6.73 years younger than patients who had no intrusions (p=0.054). There was also a trend that patients with amnesia about ICU were younger (see table 5.15). Women had more negative mood than men (mean difference = 5.35 points) and were

Table 5.16 Psychological and socio-demographic factors

	age	sex	NS-SEC
ICU mood total	p=0.261	-5.35 (-10.65,-.06) **p=0.047** Women have worse mood	1. 27.89 (14.83) 2. 41.61 (8.16) 3. 28.23 (11.98) 4. 29.00 (18.35) 5. 24.80 (12.53) 6. 30.44 (8.53) **p=0.046***
ICU stress total	p=0.998	p=0.234	p=0.325
Intrusions in ICU	6.73 (-0.12,13.57) **p=0.054** Intrusions group younger	**p=0.021** Intrusions group more women	p=0.966
Amnesia in ICU	5.83 (-1.08,12.74) ***p=0.097*** Amnesia group younger	p=0.508	p=0.265
Illness perceptions	p=0.622 timeline	**p=0.052** Women timeline	p=0.080 timeline

*Differences between NS-SEC classes 2 and 1, and classes 2 and 5

more likely to have intrusions (62% women vs 38% men). There was a significant association between NS-SEC and ICU total mood score. NS-SEC class 2 (intermediate occupations) had worse average total mood scores than both classes 1 (professional/managerial occupations) and 5 (semi-routine/routine occupations).

5.5.7 Relationships between chronic factors and others

Finally I examined relationships between chronic factors – psychological history, chronic physical illness and alcohol use – and the socio-demographic, clinical and acute psychological factors. Table 5.17 shows that psychological history was associated mainly with clinical factors while chronic physical illness was associated mainly with psychological and social factors. Psychological history was associated with TISS (trend), number of organs supported in ICU, and benzodiazepines and inotropes (trend). It was also associated with acute psychological factors mood in ICU and timeline. Chronic physical illness was associated with deprivation and with ICU mood, ICU stress, ICU amnesia and timeline. It was also associated with steroids. Alcohol use was associated with more days of sedation, benzodiazepines (a trend) and ICU amnesia.

Table 5.17 Associations between chronic factors and other groups of factors

		Psychological history (PH)	chronic physical illness (CPI)	alcohol use (AU)
i) S.D.	**age**	p=0.688	p=0.115	p=0.306
	sex	p=0.205	p=0.313	p=0.278
	SEC	p=0.724	p=0.532	p=0.365
ii) Clinical	**TISS score**	-2.55 (-5.25,0.151) (PH higher score) ***p=0.064***	p=0.691	p=0.342
	Apache	p=0.311	p=0.368	p=0.836
	Number of organs	-0.95 (-1.85,-0.05) (PH higher score) **p=0.040**	p=0.917	p=0.133
	Days of sedation	p=0.485	p=0.247	-2.88 (-5.42,-0.34) (AU more days) **p=0.026**
	Number of drugs	p=0.132	p=0.922	p=0.203
	Benzodia-zepines	81.8% HoD vs 53.6% no HoD **p=0.040**	p=0.814	83.3% AU vs 54.5% no AU ***p=0.058***
	Antipsy-chotics	p=0.123	p=0.111	p=0.143
	Inotropes	68.6% HoD vs 42.9% no HoD ***p=0.057***	p=0.430	p=0.693
	Anaesthetics	p=0.747	p=0.571	p=0.177
	Steroids	p=0.186	22% CPI vs 43.1% no CPI **p=0.028**	p=0.979
iii) Acute psychological	**ICU mood total**	-8.89 (-16.03,-1.75) (PH higher score) **p=0.004**	-6.23 (-11.48,-0.98) (CPI higher score) **p=0.020**	p=0.154
	ICU stress total	p=0.253	-7.87 (-12.76,-2.98) (CD higher score) **p=0.002**	p=0.145
	ICU amnesia	p=0.344	54.2% CPI v little memory vs 37.3% no CPI **p=0.091**	83.3% AU vs 40.2% no AU **p=0.005**
	ICU Intrusions	p=0.965	p=0.267	p=0.204
	Timeline	-1.41(-2.90,0.08) (PH higher score) **p=0.062**	-1.13 (-2.37,-0.03) (CPI higher score) **p=0.045**	p=0.629

5.5.8 Summary of univariable analysis

Most clinical factors relating to interventions, sedation and administration of psychoactive drugs in the ICU were associated with PTSD at three months. Some clinical factors, notably administration of benzodiazepines and inotropes, were associated with depression and anxiety at three months. Almost no healthcare factors such as type of admission or LoS were associated with outcomes (except hospital days and hospital destination with depression). Acute psychological factors such as ICU mood, ICU stress and memory of ICU were associated with all outcomes at three months except PCS. Of the socio-demographic factors measured, ethnicity was associated with depression, and socio-economic circumstances were associated with anxiety, depression and MCS. Other notable results were that most clinical factors were associated with most ICU psychological responses. There were few associations between socio-demographic factors and clinical factors, but some findings related to socio-demographic factors and acute psychological response. Psychological history was related to several clinical factors while chronic physical illness was mainly related to psychological factors and deprivation. Alcohol use was related to days of sedation and benzodiazepines.

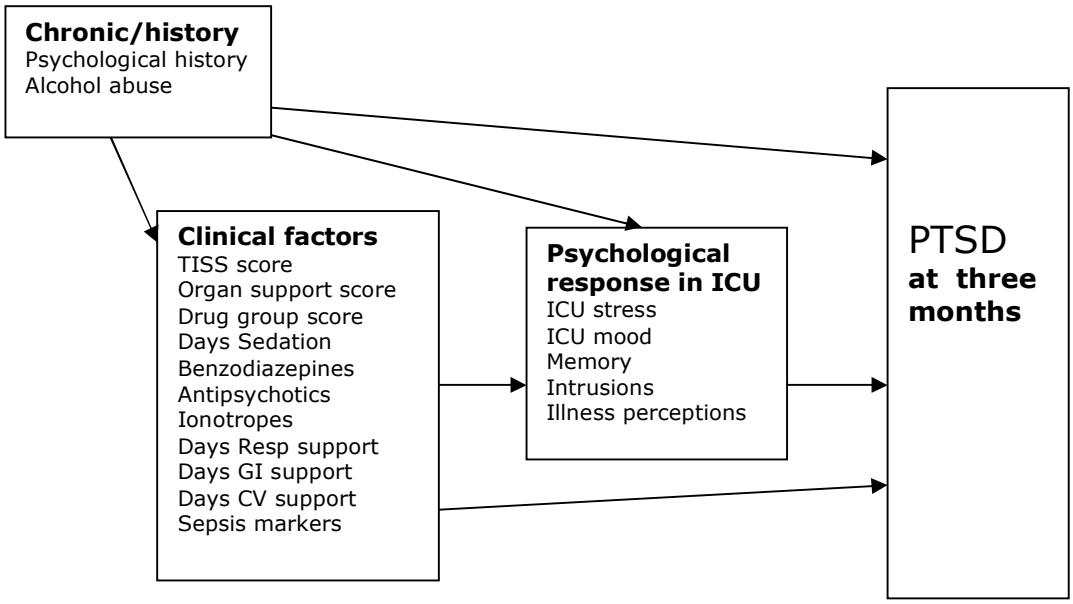
5.6 Multivariable analysis

In this section I have presented the analysis carried out to identify independent risk factors of post-ICU psychosocial outcomes as well as possible mediating variables. This was done as a two-stage process in order to reduce the number of predictors that would be entered in the final multiple regressions for each outcome. First if there were many statistically significant predictors ($p<0.05$) in a category (socio-demographic, clinical, psychological or chronic) I identified the strongest predictors by entering them in a multiple regression. I then entered only the strongest predictors (based on effect size and significance level $p<0.1$) from each group in a final regression for each outcome.

5.6.1 Risk factors for post-ICU PTSD

Figure 5.7 is a model showing all factors that had significant associations with PTSD ($p<0.05$) in the univariable analysis. All listed clinical factors were associated with PTSD, and most of them were associated with most factors in the psychological response box.

Figure 5.7 Predictors of PTSD and possible relationships



Data patterns in the above model would suggest that relationships between ICU clinical factors and PTSD were mediated by acute psychological responses. However before proceeding to test for mediational relationships, I decided it was necessary to carry out further data reduction on the clinical and psychological factors, to find out which were the strongest predictors and most important relationships.

5.6.2 Analysis of clinical factors

I tried several approaches to identifying the variables that captured the most important clinical information. As a number of ICU interventions, practices and drugs were predictors of PTSD, one approach would be to use the TISS variable (Keene et al., 1983) as it is a global indicator that summarises the amount or intensity of intervention that a patient received in the ICU. This is in line with the advice of Kraemer, Stice, Kadzin et al. (2001) that where there are multiple risk factors of an outcome, all may be proxy risk factors for one global factor and may be aggregated to gain clearer understanding of what the causal processes might be. Other arguments in favour of this approach included the finding that TISS was highly correlated with a number of other clinical variables (see table 5.16).

Table 5.18 Correlations between TISS and other clinical variables

	Number of organs supported	Number of drug groups given	Days of Sedation
TISS	r=.748**	r=.552**	r=.632**

When TISS was entered into a regression and adjusted for socio-demographic factors and the Apache II illness severity score (as it is common practice in ICU research to adjust for these variables), the model was significant (p=0.018) and

explained 12.2% of variance. It can be seen in table 5.19 that TISS had a significant medium-size effect on PTSD (β =0.261, p=0.012) when adjusted for age, sex, and illness severity.

Table 5.19 Multiple regression of PTSD on TISS and other factors

Model		Unstandardized Coefficients	Standardized Coefficients	p-value
		B	Beta	
1	(Constant)	3.335		.641
	Highest TISS score in ICU	**.603**	**.261**	**.012**
	Apache II score	.058	.036	.731
	Age	-.116	-.173	.115
	Sex	2.831	.120	.259

Similarly the variable "number of types of organ support received" could be argued to capture the totality of ICU interventions experienced by a patient. Identified predictors such as "days of cardiovascular support" were probably proxy risk factors for this more global variable (Kraemer et al., 2001). When "number of organs" was entered into a regression with socio-demographic factors and illness severity, a similar result was obtained as for TISS (table 5.20). The model explained 12.5% of variance and was significant, (p=0.015). "Number of organs" had a significant medium size effect on PTSD (β=0.270, p=0.010) after adjusting for age, sex and illness severity.

Table 5.20 Multiple regression of PTSD on "number of organs" and other factors

Model		Unstandardized Coefficients	Standardized Coefficients	p-value
		B	Beta	
1	(Constant)	9.058		.126
	Age	-.095	-.142	.194
	Sex	3.389	.144	.177
	Number of organs	**1.897**	**.270**	**.010**

5.6.3 Multiple regression: clinical factors and PTSD

To examine further the relationship between global risk factors such as TISS, number of organs supported and their possible proxies, another approach was to enter significant clinical predictors (p<0.05) into a regression to identify the strongest predictors of PTSD. In this case all significant predictors were not entered because of the large number of variables and the fact that many were overlapping. I did not include days of respiratory support, CV support or GI support on the grounds that they were most likely covered by the organ support variable and they had smaller effect sizes than other variables. Only one sepsis indicator was included, highest C-reactive protein during admission. In table 5.21, it can be seen

that the model was highly significant (p=0.005) and explained **21.6%** of variance in the sample.

Table 5.21 Multiple regression of PTSD on all clinical variables

Model		Unstandardized Coefficients		Standardized Coefficients	p-value
		B	Std. Error	Beta	
1	(Constant)	10.062	6.337		.116
	Highest TISS score	.027	.347	.011	.939
	Number of types of organ support received	-.640	1.303	-.091	.624
	Days of sedation	**.703**	**.340**	**.256**	**.042**
	Benzodiazepines	**7.348**	**3.027**	**.308**	**.017**
	Inotropes	**5.904**	**3.168**	**.251**	**.066**
	Antipsychotics	**6.074**	**3.145**	**.254**	**.057**
	Number of drug groups	-2.223	1.553	-.316	.156
	Sepsis	.013	.010	.144	.197

The most important clinical predictors of PTSD in this regression based on the size of standardised coefficients and p-values were **"days of sedation"** (β =0.256, p=0.042), **inotropes** (β =0.251, p=0.066), **benzodiazepines** (β=.308, p=0.017) and **antipsychotics** (β =0.254, p=0.057). It can be seen that the effect size (standardized coefficient) of TISS/PTSD had reduced from 0.253 (p=0.013) in the univariable analysis to 0.011 (p=0.939) in this multiple regression with other clinical factors. This analysis suggested it was likely that TISS was a significant predictor for PTSD in large part because it was a global score that included the effects of days of sedation and drugs such as benzodiazepines, inotropes and antipsychotics. Kraemer et al. (2001) argue that sometimes a complex global measure such as TISS needs to be disaggregated to improve understanding of the causal process. I decided that **days of sedation**, **benzodiazepines**, **and antipsychotics** would be the best clinical variables to include in a final model for PTSD as they had the largest standardised coefficients and lowest p-values.

5.6.4 Acute psychological response and PTSD

To reduce the number of psychological variables in the final analysis, first I decided to use total mood scores and total ICU stress scores rather than all sub-scale scores. This was acceptable from a psychometric point of view as Cronbach α was 0.818 for the ICU stress scale and 0.904 for the mood scale. When all psychological response factors that were significant in the univariable analysis (ICU stress, mood, memory, intrusions and three illness perceptions) were entered into a multiple regression on PTSD (table 5.22) they explained **37.6%** of variance in the sample, and the model was highly significant, (p<.001). Most important

psychological predictors of PTSD were **mood** (β=.252, p=.083), **intrusions** (β=.228, p=.018) and **timeline** (β=.185, p=.042).

Table 5.22 Regression of PTSD on ICU psychological factors

Model		Unstandardized Coefficients		Standardized Coefficients	p-value
		B	Std. Error	Beta	
1	(Constant)	-8.676	4.060		.036
	Mood total	.220	.125	.252	**.083**
	ICU stress total	.117	.128	.127	.361
	ICU amnesia	1.130	2.219	.048	.612
	ICU Intrusions	5.361	2.216	.228	**.018**
	IPQ Timeline	.789	.382	.185	**.042**
	IPQ concern	.482	.410	.114	.243
	IPQ emotional rep	.104	.396	.028	.793

It looked from this analysis as if ICU stress and ICU mood were "overlapping" risk factors, that were tapping into the same construct (Kraemer et al., 2001). Univariable analysis showed that the two factors were highly correlated (r=.729**). Although mood, intrusions and IPQ timeline were all entered in the final regression model for PTSD, I also carried out parallel regressions on PTSD using ICU stress as a variable because ICU stress encompassed elements of interest such as physical stress and delirious phenomena, that were not aspects of the "mood" variable. When mood was not entered, ICU stress was a strong significant risk factor for PTSD (β=.322, p=.002) along with ICU intrusions and IPQ timeline, and variance explained was **35.5%.** When stress was not entered, mood was a significant predictor of PTSD (β=0.344, p=0.001) and variance explained was **36.9%.** I carried out all multiple regressions in different versions with both ICU stress and ICU mood (although I have not presented the ICU stress versions as tables here) and found that results were almost always the same.

5.6.5 Chronic health factors and PTSD

Finally psychological history, alcohol use, and past traumas were entered into a regression model for PTSD. Variance explained was **17.3%** in a highly significant model (p<0.001) in which psychological history and alcohol use were more important predictors than past trauma.

Table 5.23 Regression of PTSD on chronic health factors

Model		Unstandardized Coefficients		Standardized Coefficients	p-value
		B	Std. Error	Beta	
1	(Constant)	10.598	1.471		.000
	Psychological history	**9.415**	3.100	**.291**	**.003**
	Alcohol use	**7.755**	3.526	**.210**	**.030**
	Any past traumas	3.300	2.344	.134	.163

5.6.6 Multiple regression model with strongest predictors of PTSD

I carried out a final regression using the most important clinical, acute psychological and chronic health predictors identified in the first round of regressions. Factors were entered using the hierarchical method with clinical factors in block one, psychological factors in block two and chronic factors in block three. I found that:

Model 1(clinical factors) was significant, p=0.001, accounting for **17.5%** variance
Model 2(clin/psych) was significant, p<0.001, accounting for **39.1%** of variance
Model 3(clin/psych/chronic) was significant, p<0.001, accounting for **44.7%** of variance.

In table 5.24 model one showed that **days of sedation** was the strongest clinical predictor of PTSD with a medium effect size (r=0.256, p=0.019). The PTSD score increased by 0.692 points with each extra day of sedation. When acute psychological factors were entered into the model, **mood, intrusions** and **IPQ timeline** were all shown to be significant and independent predictors of PTSD. Days of sedation was not a significant risk factor in model two and its effect size was halved by the introduction of the acute psychological factors (the unstandardised coefficient was reduced from 0.692 to 0.349). The effect sizes of benzodiazepines and antipsychotics were also greatly reduced. This suggested that acute psychological responses acted as partial mediators of the relationships between clinical variables such as days of sedation and PTSD. When I entered **psychological history** and **alcohol use** into model 3, psychological history was shown to be an independent predictor of PTSD. The acute psychological factors **mood total** and **intrusions** were also independent predictors of PTSD in this model. Therefore the strongest independent predictors of PTSD found in this model were t**otal mood** (0.284, p=0.000), **intrusions** (0.248, p=0.007) and **psychological history** (0.207, p=0.021) after controlling for clinical factors.

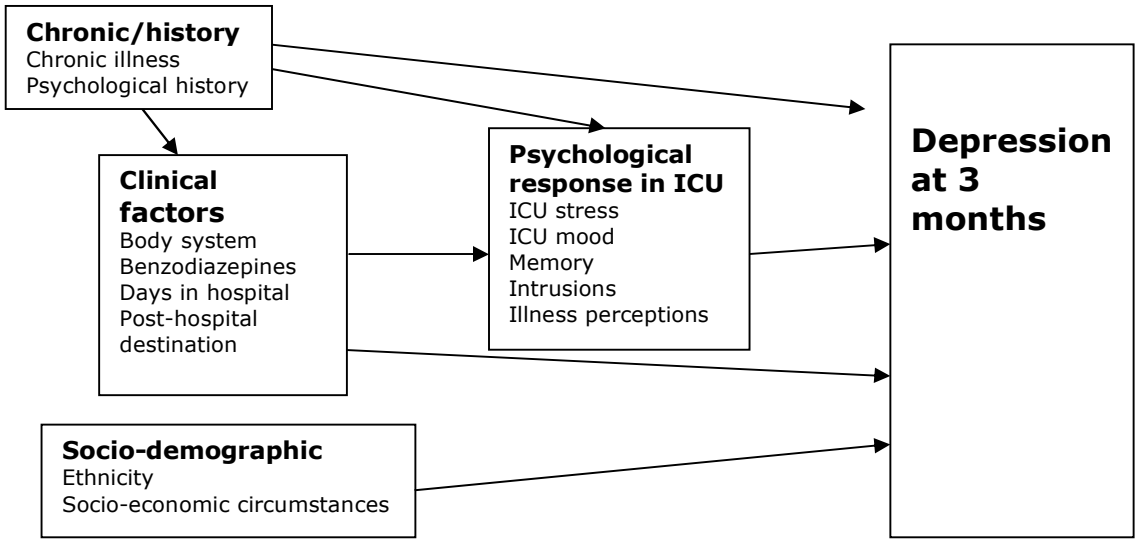
Table 5.24 "Final" regression for post-ICU PTSD

Model		Unstandardized Coefficients		Standardized Coefficients	p-value
		B	Std. Error	Beta	
1	(Constant)	8.292	1.926		.000
	Days of sedation	**.692**	**.288**	**.256**	**.019**
	Benzodiazepines	3.980	2.508	.166	.116
	Antipsychotics	3.315	2.477	.139	.184
2	(Constant)	-4.845	3.248		.140
	Days of sedation	.349	.260	.129	.184
	Benzodiazepines	1.259	2.250	.053	.577
	Antipsychotics	1.883	2.189	.079	.392
	Mood total	**.306**	**.083**	**.343**	**.000**
	IPQ timeline	**.786**	**.369**	**.187**	**.036**
	Intrusions	**5.208**	**2.161**	**.221**	**.018**
3	(Constant)	-3.884	3.166		.223
	Days of sedation	.332	.255	.123	.197
	Benzodiazepines	.352	2.193	.015	.873
	Antipsychotics	1.055	2.131	.044	.622
	Mood total	**.254**	**.083**	**.284**	**.003**
	IPQ timeline	**.711**	**.359**	**.169**	**.051**
	Intrusions	**5.833**	**2.104**	**.248**	**.007**
	Psychological history	**6.549**	**2.790**	**.207**	**.021**
	Alcohol use	4.629	3.088	.128	.138

5.6.7 Independent risk factors for post-ICU depression

It was seen in the univariable analysis that there were fewer clinical risk factors for depression at three months than for PTSD. All acute psychological factors were associated with depression at three months. Socio-economic circumstances (NS-SEC), and ethnicity were also associated with depression. Chronic physical illness and psychological history were also associated with depression at three months. Figure 5.8 depicts how these factors might be inter-related.

Figure 5.8 Possible relationships between predictors and depression



5.6.8 Regression of clinical factors and depression

When I entered significant clinical factors into a regression on depression (table 5.25 below), **10.5%** of variance was accounted for and the model was significant, (p=0.044). The strongest clinical predictor was **benzodiazepines** (B=5.685, β=.201, p=0.065). Patients given benzodiazepines for sedation in the ICU were nearly six points higher on the depression scale than patients who were not given benzodiazepines, after adjusting for other important clinical factors for depression.

Table 5.25 Regressing depression on clinical factors

Model		Unstandardized Coefficients		Standardized Coefficients	p-value
		B	Std. Error	Beta	
1	(Constant)	17.381	3.358		.000
	Primary body system (ICNARC)	-.558	.595	-.099	.351
	Length of stay in hospital	.066	.042	.180	.120
	Hospital discharge to..	-.573	1.227	-.053	.642
	Benzodiazepines	**5.685**	3.044	**.201**	**.065**

5.6.9 Regression of psychological factors on depression

Next I entered the psychological predictors into a regression for depression (table 5.26). The model was highly significant (p<0.001) and accounted for **24.6%** of variance. The strongest predictor was **ICU mood score** (β =0.292, p=0.011).

Table 5.26 Regression of depression on acute psychological factors

Model		Unstandardized Coefficients		Standardized Coefficients	p-value
		B	Std. Error	Beta	
1	(Constant)	-1.223	4.924		.804
	IPQ Timeline	.552	.494	.109	.267
	IPQ Concern	.668	.529	.133	.210
	IPQ Emotional rep	.370	.499	.084	.461
	Mood total	**.302**	.117	**.292**	**.011**
	Intrusions	3.105	2.826	.111	.275
	ICU Amnesia	1.572	2.816	.056	.578

5.6.10 Final regression model with strongest predictors of depression

Finally I built a model for post-ICU depression including SEC, ethnicity, benzodiazepines, chronic physical illness, ICU mood, and psychological history (table 5.27). As a discrete categorical variable, NS-SEC had to be entered into the model as dummy variables NSSEC 2,3,4,5, 6. These compared the numbered group with all other groups. As there were six groups in NS-SEC, five dummy variables were needed. The three models were highly significant and accounted for 18%, 27% and 39% respectively of variance in the sample. SEC was found to be a risk

factor for depression with significantly higher depression among groups 2 (intermediate professions), 3 (self-employed) and 5 (routine/semi-routine jobs) than the other groups. Ethnicity was no longer significant when adjusted for SEC. When adjusted for socio-demographic variables, **benzodiazepines** was an independent predictor of three-month depression accounting for a difference of 6.73 depression points (p=0.014). Chronic physical illness accounted for 5.1 depression points (p=0.059). When ICU mood and psychological history were added to the model, **mood**, **psychological history** and **SEC** variables were the only significant factors. Therefore the strongest independent predictors of post-ICU depression in this model were **SEC, ICU mood** (0.268, p=0.01) and **psychological history** (0.206, p=0.030). Total mood score appeared to mediate the effect of benzodiazepines on depression as B (the unstandardised coefficient for benzodiazepines) was reduced from 6.73 (p=0.014) to 4.54 (p=0.085) when mood was entered into the model.

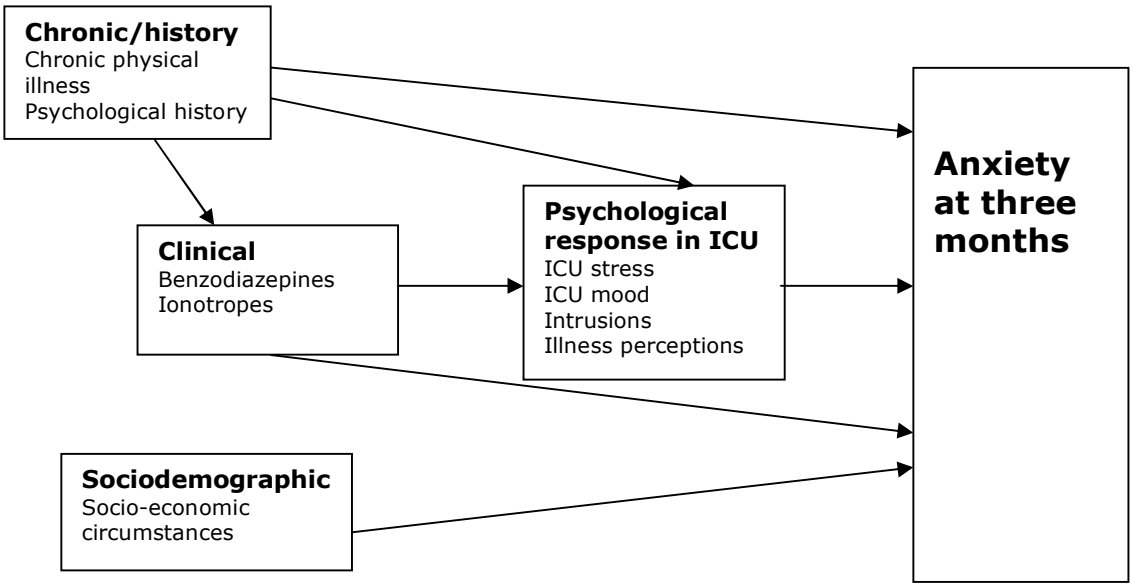
Table 5.27 Final regression model for post-ICU Depression

Model		Unstandardized Coefficients		Standardized Coefficients	p-values
		B	Std. Error	Beta	
1	(Constant)	8.116	4.710		.088
	Ethnicity	5.485	3.547	.151	.126
	NSSEC2	15.362	5.191	.306	.004
	NSSEC3	8.241	3.796	.237	.033
	NSSEC4	-.745	5.469	-.014	.892
	NSSEC5	10.331	3.736	.302	.007
	NSSEC6	9.548	4.985	.201	.059
2	(Constant)	2.553	4.805		.597
	Ethnicity	5.336	3.388	.147	.119
	NSSEC2	14.587	4.968	.291	.004
	NSSEC 3	7.862	3.650	.226	.034
	NSSEC4	-1.747	5.227	-.033	.739
	NSSEC5	9.078	3.597	.266	.013
	NSSEC6	7.639	4.890	.161	.122
	Benzodiazepines	**6.734**	**2.674**	**.239**	**.014**
	Chronic physical illness	**5.052**	**2.643**	**.181**	**.059**
3	(Constant)	-3.878	4.760		.417
	Ethnicity	5.153	3.226	.142	.114
	NSSEC2	**11.394**	**4.772**	**.227**	**.019**
	NSSEC3	**7.609**	**3.396**	**.218**	**.028**
	NSSEC4	-.381	4.868	-.007	.938
	NSSEC5	**10.553**	**3.361**	**.309**	**.002**
	NSSEC6	7.399	4.522	.156	.106
	Benzodiazepines	3.803	2.575	.135	.143
	Chronic physical illness	3.100	2.531	.111	.224
	Mood total	**.278**	**.105**	**.268**	**.010**
	Psychological history	**7.671**	**3.475**	**.206**	**.030**

5.6.11 Independent risk factors for anxiety

In the univariable analysis, the factors depicted in figure 5.9 were found to be significant predictors of post-ICU anxiety.

Figure 5.9 Possible relationships between risk factors and anxiety



5.6.12 Regression: psychological responses and anxiety

When acute psychological predictors were entered in a regression with anxiety (table 5.28), the model was significant and variance accounted for was 20.2%. The most important psychological predictors were ICU mood and IPQ timeline.

Table 5.28: Psychological factors and anxiety outcome

Model		Unstandardized Coefficients		Standardized Coefficients	p-value
		B	Std. Error	Beta	
1	(Constant)	22.664	5.289		.000
	Total mood	.287	.122	.261	**.021**
	Intrusions	2.025	2.990	.068	.500
	IPQ timeline	.961	.529	.181	**.073**
	IPQ concern	.084	.570	.016	.883
	IPQ emotional reps	.719	.558	.151	.201

In a final regression containing all the strongest risk factors for anxiety, the five models were all significant and variance accounted for was 12%, 21%, 26%, 31% and 34% respectively. **Inotropes** was the strongest clinical risk factor when entered with SEC (β=7.06, p=0.023). When **chronic illness** was entered it was significant (6.573, p=0.023) and **inotropes** remained significant.

Table 5.29 "Final" regression model for post-ICU anxiety

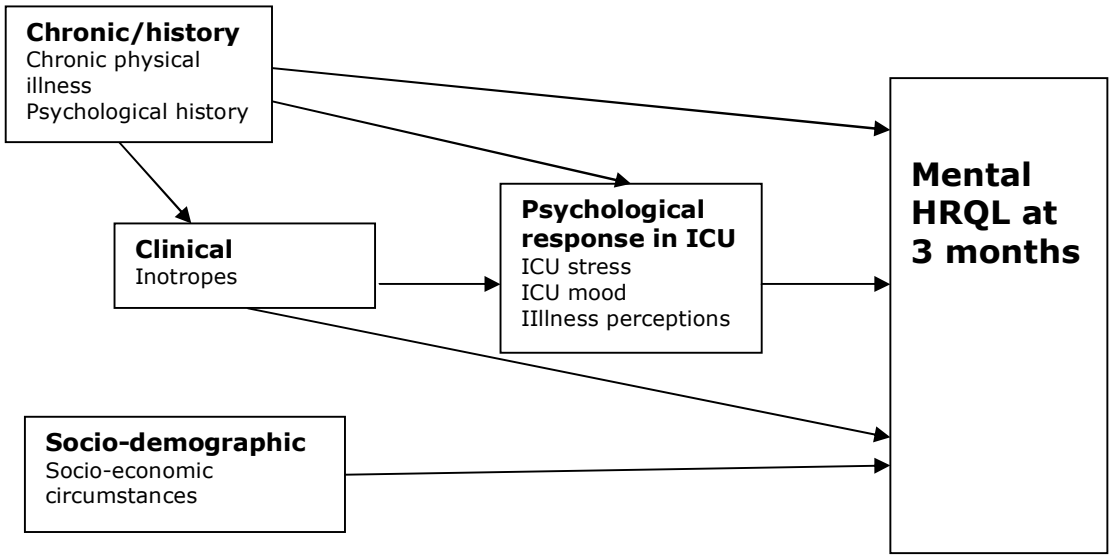
Model		Unstandardized Coefficients		Standardized coeff.s	p-values
		B	Std. Error	Beta	
1	(Constant)	39.273	2.495		.000
	NSSEC2	12.949	5.389	.257	.018
	NSSEC3	3.710	4.127	.101	.371
	NSSEC4	-3.082	5.963	-.055	.607
	NSSEC5	8.505	4.199	.226	.046
	NSSEC6	11.246	5.389	.223	.040
2	(Constant)	33.098	3.074		.000
	NSSEC2	11.912	5.166	.236	.023
	NSSEC3	5.176	4.076	.140	.208
	NSSEC4	-1.503	5.767	-.027	.795
	NSSEC5	9.036	4.032	.240	.028
	NSSEC6	9.488	5.277	.188	.076
	Benzodiazepines	4.513	3.051	.150	.143
	Inotropes	**7.057**	**3.049**	**.238**	**.023**
3	(Constant)	30.394	3.217		.000
	NSSEC2	11.521	5.043	.229	.025
	NSSEC3	5.865	3.988	.159	.145
	NSSEC4	-2.166	5.634	-.038	.702
	NSSEC5	7.812	3.969	.207	.052
	NSSEC6	10.657	5.173	.211	.042
	Benzodiazepines	4.061	2.983	.135	.177
	Inotropes	**6.600**	**2.981**	**.223**	**.029**
	Chronic physical illness	**6.573**	**2.830**	**.223**	**.023**
4	(Constant)	23.158	4.705		.000
	NSSEC2	7.818	5.171	.155	.134
	NSSEC3	5.923	3.901	.161	.133
	NSSEC4	-2.453	5.512	-.043	.657
	NSSEC5	8.138	3.980	.216	.044
	NSSEC6	9.568	5.156	.190	.067
	Benzodiazepines	2.589	2.981	.086	.387
	Inotropes	**5.478**	**2.987**	**.185**	**.070**
	Chronic physical illness	4.616	2.893	.156	.114
	ICU mood	**.263**	**.113**	**.238**	**.023**
	IPQ timeline	.363	.535	.068	.499
5	(Constant)	25.208	4.702		.000
	NSSEC2	**9.352**	**5.111**	**.186**	**.071**
	NSSEC3	4.734	3.858	.128	.223
	NSSEC4	-1.373	5.418	-.024	.801
	NSSEC5	**7.985**	**3.896**	**.212**	**.044**
	NSSEC6	**9.756**	**5.048**	**.194**	**.057**
	Benzodiazepines	2.080	2.927	.069	.479
	Inotropes	4.635	2.950	.157	.120
	Chronic physical illness	**5.159**	**2.843**	**.175**	**.073**
	ICU mood	**.200**	**.115**	**.181**	**.085**
	IPQ timeline	.184	.530	.034	.730
	Psychological history	**8.373**	**3.874**	**.212**	**.034**

Inotropes also remained significant when **ICU mood** (0.263, p=0.023) was entered. In the final model the independent risk factors for Anxiety were **SEC** (groups 2 (intermediate), 5(routine) and 6 (unclassified) had higher anxiety than other groups), **chronic physical illness, ICU mood** and **psychological history.** Inotropes appeared to be partially mediated by ICU mood.

5.6.13 Risk factors for mental HRQL after intensive care

In univariable analysis, associations were found between psychological factors (stress, mood, illness perceptions: emotional representations), socio-demographic factors (SEC) and one clinical factor (inotropes) and MCS (mental HRQL). MCS was also associated with chronic physical illness and psychological history (figure 5.10)

Figure 5.10 Relationships between predictors and mental HRQL



5.6.14 Final multiple regression of risk factors for mental HRQL

When all predictors were entered into a regression for Mental HRQL (table 5.30), **42.8%** of variance was accounted for in a significant model, (p<0.001). **Inotropes** (-0.194, p=0.05) and **chronic physical illness** (-0.301, p=0.003) were both independent risk factors after adjusting for SEC. In the final model, **ICU mood** and **socio-economic circumstances** (with group 5 (routine) and group 6 (unclassified) having worse MCS (9-10 points lower) than other groups) were the strongest independent predictors of Mental HRQL score at three months.

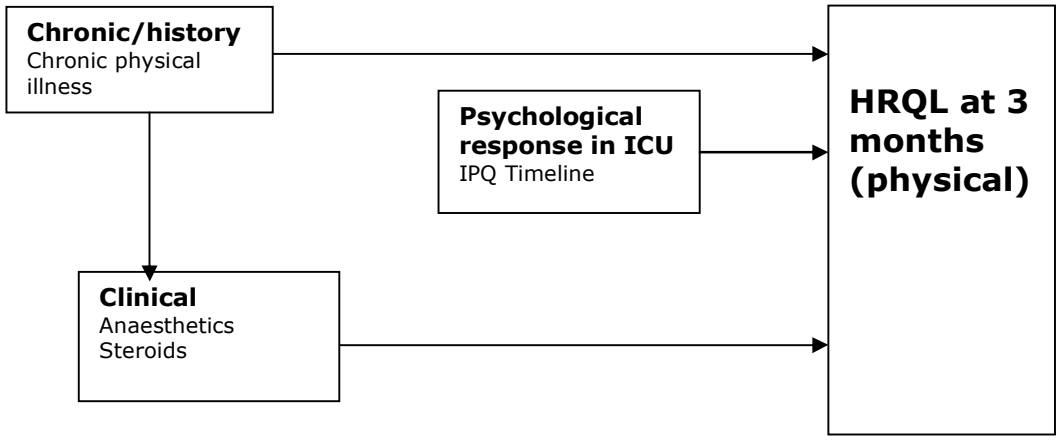
Table 5.30 Risk factors for mental HRQL after ICU

Model		Unstandardized Coefficients		Standardized Coefficients	p-values
		B	Std. Error	Beta	
1	(Constant)	48.470	1.879		.000
	NSSEC2	-8.888	4.321	-.226	.043
	NSSEC3	-2.875	3.018	-.111	.344
	NSSEC4	-4.937	4.973	-.107	.324
	NSSEC5	-10.039	3.187	-.363	.002
	NSSEC6	-10.487	4.096	-.283	.012
2	(Constant)	53.755	2.306		.000
	NSSEC2	-7.444	4.060	-.189	.071
	NSSEC3	-4.430	2.865	-.171	.126
	NSSEC4	-5.471	4.711	-.119	.249
	NSSEC5	-8.740	3.016	-.316	.005
	NSSEC6	-11.225	3.832	-.303	.004
	Inotropes	**-4.208**	**2.163**	**-.194**	**.055**
	Chronic physical illness	**-6.516**	**2.146**	**-.301**	**.003**
3	(Constant)	60.828	2.891		.000
	NSSEC2	-3.453	3.849	-.088	.373
	nssec3	-3.310	2.642	-.127	.214
	NSSEC4	-3.451	4.715	-.075	.467
	NSSEC5	-10.179	2.816	-.368	.001
	NSSEC6	-9.819	3.561	-.265	.007
	Inotropes	-2.281	2.038	-.105	.267
	Chronic physical illness	-3.480	2.103	-.161	.102
	ICU mood	**-.324**	**.091**	**-.405**	**.001**
	IPQ emotional reps	-.094	.379	-.027	.805
4	(Constant)	60.269	2.907		.000
	NSSEC2	-4.110	3.862	-.104	.291
	NSSEC3	-3.129	2.633	-.121	.238
	NSSEC4	-3.986	4.708	-.087	.400
	NSSEC5	**-9.915**	**2.809**	**-.358**	**.001**
	NSSEC6	**-9.640**	**3.546**	**-.260**	**.008**
	Inotropes	-1.783	2.062	-.082	.390
	Chronic physical illness	**-3.84**	**2.115**	**-.180**	**.070**
	ICU mood	**-.289**	**.095**	**-.361**	**.003**
	IPQ emotional reps	-.073	.378	-.021	.848
	Psychological history	-3.650	2.753	-.129	.189

5.6.15 Possible relationships between risk factors and physical health

As depicted in figure 5.11 steroids, anaesthetics, illness perceptions and chronic physical illness were the only risk factors for Physical HRQL identified by the univariable analysis.

Figure 5.11: Risk factors for physical HRQL



When a regression model was built for physical HRQL using these predictors, it explained 27.5% of variance in physical HRQL and was significant, p<0.001 (table 5.31). **Anaesthetics** and **steroids** in the ICU predicted physical HRQL more strongly than chronic physical illness. The illness perception "IPQ timeline" was also a highly significant predictor of physical HRQL.

Table 5.31 Risk factors for physical HRQL after ICU

Model		Unstandardized Coefficients		Standardized Coefficients	p-value
		B	Std. Error	Beta	
1	(Constant)	31.440	2.344		.000
	Anesthetics	4.373	2.243	.206	**.055**
	Steroids	4.809	2.278	.227	**.038**
	Chronic physical illness	-2.678	2.165	-.133	.220
2	(Constant)	42.063	3.829		.000
	Anesthetics	4.345	2.082	.205	**.040**
	Steroids	4.690	2.165	.221	**.033**
	Chronic physical illness	-.339	2.100	-.017	.872
	IPQ timeline	-1.282	.362	-.360	**.001**
	IPQ concern	-.446	.379	-.123	.243

To summarise all the models described in this section, Table 5.32 contains the variables that could be considered strong independent risk factors for psycho-social outcomes after ICU. All the clinical risk factors were drug-related: number of days during which a patient was sedated; and the administration or not of benzodiazepines, inotropes or steroids. The over-riding acute psychological risk factors for worse psycho-social outcomes were total mood disturbance in the ICU and ICU stress (physical stress, delirium and loss of control). Additionally "intrusions" (early intrusive memories of ICU) was an independent risk factor for PTSD, and IPQ timeline (a patient's belief about how long their condition would last)

was an independent risk factor for physical HRQL. Socio-economic circumstances were strong risk factors for worse depression, anxiety and mental health. Groups 2 (intermediate), 5 (routine jobs) 6 (unclassified, retired, unemployed etc) were worse off for at least two outcomes each. Chronic physical illness was an independent risk factor for depression, anxiety and MCS. Psychological history was an independent risk factor for PTSD, depression and anxiety. Acute psychological responses were independent of psychological history.

Table 5.32 Summary of strongest risk factors

Risk factors	PTSD	Depression	Anxiety	Mental HRQL	Physical HRQL
Acute clinical	Days of sedation	Benzodiazepines	Inotropes	Inotropes	Steroids Anaesthetics
Acute psychological response	ICU mood ICU stress ICU Intrusions	ICU mood ICU stress	ICU mood ICU stress	ICU mood ICU stress	IPQTimeline
Socio-demog		NS-SEC (groups 2,3,5 worse)	NS-SEC (groups 2,5,6 worse)	NS-SEC (groups 5,6)	
Chronic health	psychological history	Chronic illness Psych history	Chronic illness Psych history	Chronic illness	

5.6.16 Assumptions of the models

It is recommended to check that multiple regressions do not violate multivariable assumptions (Field, 2005; Tabachnick & Fidell 2007). For each of the final regressions for each outcome, I examined histograms of residuals, normal probability plots and scatterplots of residuals and predicted values. In each case the histogram suggested that residuals were normally distributed, as did the normal probability plots of expected and observed values. The shape of the scatterplots (a random array of dots evenly dispersed around zero) suggested that errors were random and that there was homoscedasticity (that the variance of residuals was constant at each level of the predictor variable).

I also looked at tolerance values and variance inflation factors to assess multicollinearity – when predictors within a multiple regression are too highly correlated (Field 2005). As the average variance inflation factor in each case was around one (Boweman & Connell, 1990) and tolerance values were not <0.2 (Menard, 1995), there was no evidence of collinearity. However I also inspected the eigenvalues given in the SPSS collinearity diagnostics table and again found no evidence of collinearity.

5.7 Mediation

In the final regression models presented in section 5.6, it was seen that while the strongest clinical factors were significant after controlling for socio-demographic factors, they became non-significant and weaker when acute psychological factors

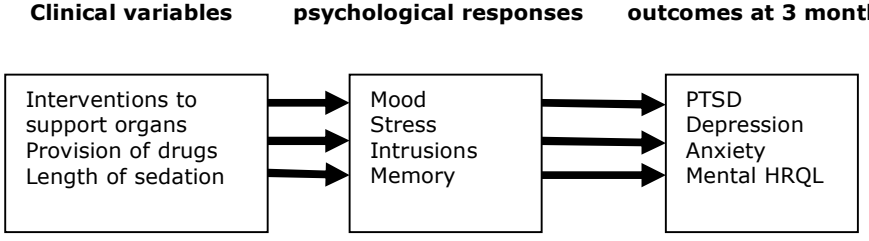
were added to the models. This suggests that acute psychological factors partially mediated relationships between clinical risk factors and adverse psycho-social outcomes. Therefore as an alternative approach I decided to carry out further mediation analyses as these could lead to a better understanding of possible causal pathways than the multiple regressions carried out above.

To explore further whether psychological factors mediated between clinical factors and psychosocial outcomes, I carried out mediation analyses using a method recommended by Baron & Kenny (1986). This method involves first regressing the "mediating variable" (MV) on the clinical variable (IV); second, regressing the outcome (DV) on the IV; and third, regressing the DV on both the IV and the MV. To establish mediation, the IV must affect the mediator in the first equation, the IV must affect the DV in the second equation and the mediator must affect the DV in the third equation. If these conditions all hold, then the effect of the IV on the DV must be less in the third equation than in the second. Perfect mediation would occur if the IV had no effect on the DV when the mediator was controlled. However when treating phenomena that have multiple causes, it is more realistic to seek mediators that significantly decrease the IV-DV relationship rather than eliminate it (Baron & Kenny, 1986).

5.7.1 Mediators between clinical factors and psychological outcomes

I looked at whether psychological responses in the ICU such as stress, mood, intrusions and memory mediated the relationships between clinical factors and PTSD, depression, anxiety and mental HRQL (figure 5.12). First I looked at mediational relationships using the strongest independent risk factors identified in the multiple regressions in Section 5.7. However, this approach meant that important predictors and mediators could be over-looked. Therefore I subsequently looked at other hypothesised predictors that could be involved in mediational pathways. Not all mediational processes were reported in full here due to the large number of possible combinations. However all results are summarised in table 5.32.

Figure 5.12 Potential mediational pathways



M1. *Did 'mood in ICU' mediate the effect of 'days of sedation' on PTSD?*

Step 1. Regress MV (Mood) on IV (days of sedation) B=0.785 β = 0.246 p=0.014

Step 2. Regress DV (PTSD) on IV (days of sedation) **B=0.926** β =0 .338 p=0.001

Step 3. Regress DV (PTSD) on IV (days of sedation) **B=0.596** β = 0.217 p=0.019

and MV (Mood). B=0.385 β=0.435 p=0.000

Because the MV (Mood) had an effect on the DV (PTSD) in the third equation, and the effect of the IV (days of sedation) on the DV was substantially less in the third equation, ICU mood can be said to partially mediate the effect of days of Sedation on PTSD. The unstandardised coefficient of "days of sedation" was reduced by 35.64% when "mood" was added.

M2. *Did 'ICU intrusions' mediate the effect of 'days of sedation' on PTSD?*

Step 1. Regress MV (Intrusions) on IV (days sedation) B=.030 β = 0.251 p=0.012

Step 2. Regress DV (PTSD) on IV (days of sedation) **B=0.926** β =0.338 p=0.001

Step 3. Regress DV (PTSD) on IV (days of sedation) **B=0.695** β =0.253 p=0.009

and MV (Intrusions) B= 7.859 β=0.333 p=0.001

The MV (Intrusions) had an effect on the DV (PTSD) in the third equation, and the effect of the IV (days of sedation) on the DV was less in the third equation. Therefore ICU intrusions partially mediated the effect of days of Sedation on PTSD. The unstandardised coefficient of "days of sedation" was reduced by 24.95% when "intrusions" was added.

M3. *Did ICU stress mediate the effects of TISS on PTSD?*

Step 1. Regress MV (ICU stress) on IV (TISS) B=0.795 β =0 .315 p=0.002

Step 2. Regress DV (PTSD) on IV (TISS) **B=0.575** β = 0.248 p=0.014

Step 3. Regress DV (PTSD) on IV (TISS) **B=0.253** β =0.109 p=0259

and MV (ICU stress) B=.399 β=.428 p=0.000

The MV (ICU stress) had an effect on the DV (PTSD) in the third equation, and the effect of the IV (TISS) on the DV was less in the third equation and became non-significant. Therefore the ICU stress variable partially mediated the effect of TISS on PTSD. The unstandardised coefficient (B) of TISS was reduced by 56% when ICU Stress was added.

M4. *Did ICU stress mediate the effects of benzodiazepines on depression?*

Step 1. Regress MV (stress) on IV (benzodiazepines) B=7.186 β = 0.278 p=0.005

Step 2. Regress DV (Depression) on IV (benzodiazepines) **B=7.439** β =0 .263 p=0.010

Step 3. Regress DV (Depression) on IV (benzodiazepines) **B=5.071** β =0.179 p=0.079

And MV (stress) B=0.331 β=0.306 p=0.003

The MV (ICU stress) had an effect on the DV (depression) in the third equation, and the effect of the IV (benzodiazepines) on the DV (depression) was less in the third equation and became non-significant. Therefore the ICU stress variable mediated the effect of benzodiazepines on depression. The unstandardised coefficient of benzodiazepines was reduced by 31.85% when stress was added to the equation.

M5. *Did ICU mood mediate the effect of inotropes on anxiety?*

Step 1. Regress MV (mood) on IV (inotropes) B=5.686 $\beta = 0.211$ p=0.035

Step 2. Regress DV (Anxiety) on IV (inotropes) **B=7.634** $\beta = 0.259$ p=0.010

Step 3. Regress DV (Anxiety) on IV (inotropes) **B=5.553** $\beta = 0.188$ p=0.050

And MV (mood) B=0.366 β=0.336 p=0.001

The unstandardised coefficient for inotropes was reduced by 27.26% when mood was added to the regression for anxiety. Therefore it appears that "mood" partially mediated the effect of inotropes on anxiety.

M6. *Did ICU mood mediate the effect of inotropes on MCS (mental HRQL)?*

Step 1. Regress MV (mood) on IV (inotropes) B=5.686 $\beta = 0.211$ p=0.035

Step 2. Regress DV (MCS) on IV (inotropes) **B= –4.511** $\beta = 0.209$ p=0.053

Step 3. Regress DV (MCS) on IV (inotropes) **B= –2.186** $\beta = 0.101$ p=0.309

And MV (mood) B= –0.355 β=0.448 p=0.000

The unstandardised coefficient for the effect of inotropes on the outcome mental HRQL was more than halved and the effect of inotropes became non-significant. Therefore there was clear evidence that "ICU mood" mediated the relationship between inotropes in the ICU and mental health-related HRQL.

To summarise the results of all mediation analyses carried out, it can be seen in table 5.33 that mood, stress and intrusions in ICU were found to mediate pathways between a number of clinical risk factors and psycho-social outcomes. In addition, ICU memory was a mediator between TISS and PTSD.

Table 5.33 Mediators of clinical factors and psychological outcome

	Mediators for PTSD	Mediators for Depression	Mediators for Anxiety	Mediators for MCS (HRQL)
Days sedation	**Mood in ICU** **Intrusions in ICU** **ICU Stress**			
TISS	**ICU Stress** **ICU Mood** **ICU Memory**			
Benzodiazepines	**Intrusions** **Mood** **Stress**	**ICU Stress** **ICU Mood**		
Inotropes			**ICU Mood** **ICU Stress**	**ICU Mood**

5.7.2 Sub-analysis of mediating (psychological) factors

Three of the four subscales of the ICU stress questionnaire represent variables of considerable interest in the ICU literature and in the clinical setting. They are also potentially modifiable risk factors. They are a) delirium, symptoms such as disorientation and hallucinations in the ICU b) control, the patient's sense of being in control of their situation in the ICU and c) physical Stress – the patient's perception of how much pain and discomfort they have had in intensive care. I decided to look at the relationships in which ICU stress was identified as a mediator to explore if any of these three factors were particularly important. I also looked at mood subscales – depression, anxiety, positive emotion, and mental confusion. It would be important in the development of tools to assess whether patients are at risk of poor psychological outcomes, and the development of interventions to reduce post-ICU psychological distress, to know if specific psychological symptoms that can be detected and recorded in the ICU are predictive of psycho-social outcomes.

Unadjusted correlations between the three factors of ICU stress and clinical factors. are in table 5.34. Delirium was associated with global indicators of the amount of ICU intervention received such as TISS, "number of organs supported" and days of sedation. The more intervention received, the higher the rates of delirium. As it was not associated with most specific drugs or interventions, "delirium" may be a response to some sort of overload of multiple failing organs, drugs and treatments. Its association with anti-psychotics was expected as they are a treatment for delirium in ICU. Almost all of the clinical factors, specific or global, were associated with Control; the more intervention received, the lower the perception of control. Perceived physical stress was associated with days of sedation, but no other clinical factors. Of the ICU mood factors (table 5.35), most were associated with most clinical factors.

I then carried out an analysis to explore if delirium could be a mediating factor between TISS and PTSD. All conditions for mediation held, and the association between TISS and PTSD was reduced by 42% and became non-significant when delirium was added to the regression. Therefore there is a strong case that delirium was a powerful partial mediator between TISS (amount of intervention) and PTSD. Control reduced the effects of benzodiazepines on 3-month depression by 27.5%, and on PTSD by 36%. It reduced the effect of inotropes on 3-month anxiety by 22%. In all cases the effect of the clinical factor on the outcome became non-significant when mediated by control. Therefore ICU delirium and ICU control look like variables that may lie on the causal pathway between intensive care treatment and adverse psychological outcomes at three months.

Table 5.34 Correlations of ICU stress sub-scales with clinical factors

	TISS	Number organs	Days Sedation	Days ACVS	Benzodiaz-epines	Antipsy-chotics	Inotropes
Delirium	0.286	0.268	0.233	0.172			
p-value	**0.004**	**0.007**	**0.020**	0.087	0.176	**0.008**	0.258
Control	0.393	0.271	0.267	0.279			
p-value	**0.000**	**0.007**	**0.008**	**0.005**	**0.000**	**0.030**	**0.004**
Physical stress	0.170	0.152	0.197	0.063			
p-value	0.093	0.134	**0.050**	0.533	0.196	0.853	0.252

ACVS=advanced CV support

Table 5.35 Correlations of ICU mood subscales with clinical factors

	TISS	No of organs supported	Days sedation	Days of advanced CV support
Anxiety in ICU	0.239	0.196	0.289	0.201
p-value	**0.017**	**0.050**	**0.004**	**0.045**
Depression in ICU	0.327	0.253	0.274	.252
p-value	**0.001**	**0.011**	**0.006**	**0.011**
Positive Emotion	0.364	0.250	0.183	.288
p-value	**0.000**	**0.012**	0.069	**0.004**
Mental confusion	0.341	0.318	0.206	.323
p-value	**0.001**	**0.001**	**0.039**	**0.001**

5.7.3 Summary of multivariable and mediational analysis

When multiple regressions were carried out, it was found that the strongest clinical predictors were **days of sedation** for PTSD, **benzodiazepines** for depression, **inotropes** for anxiety and **steroids** and **anaesthetics** for physical HRQL. Strongest psychological predictors were **ICU mood, ICU stress, ICU intrusions and IPQ timeline** for PTSD, **ICU mood and stress** for depression, anxiety and mental HRQL and IPQ **timeline** for physical HRQL. The strongest socio-demographic factor was **SEC** predicting depression, anxiety and mental HRQL. Chronic physical illness was an independent risk factor for depression, anxiety and poor mental HRQL but did not confound the effects of acute ICU clinical factors (treatment and illness). Psychological history was an independent risk factor for PTSD, depression and anxiety. However acute ICU psychological response had an independent effect from psychological history in all models except anxiety.

The clinical predictors remained significant after controlling for SEC; however when ICU psychological factors were entered into the models, effect sizes of clinical predictors were greatly reduced. Therefore as psychological factors appeared to be mediating the relationship between clinical predictors and psycho-social outcome, mediational analysis was carried out. The factors of ICU mood, stress, intrusions and memory were found to be mediators between clinical factors such as TISS, days of sedation, benzodiazepines and inotropes, and psychosocial outcomes.

Chapter 6 Discussion: cohort study

In this chapter I will discuss whether the findings of the cohort study answered the original research questions and furthered existing knowledge. The first research aim was to establish the prevalence and severity of PTSD, depression, anxiety and HRQL three months after intensive care. The second aim was to identify key clinical, psychological and socio-demographic risk factors driving poor psychosocial outcomes. The third was to explore how risk factors worked together, as independent predictors or as mediators explaining the effect of other variables. Finally I discuss potential biological and psychological mechanisms underlying the association between intensive care and psychological morbidity.

6.1 Prevalence of psycho-social outcomes 3 months after ICU

This is the only fully-powered prospective study to date that has assessed the full range of psychosocial outcomes after intensive care including PTSD (using DSM-IV criteria), depression, anxiety, and mental and physical health-related HRQL. It is debatable whether there can ever be a "true" prevalence rate of psychological morbidity as different rates will be obtained depending on methods of assessment used and decisions made about thresholds for clinical disorder. Nevertheless I believe that the conservative and sensible methods of estimating prevalence used in this study lend credibility to the findings.

6.1.1 Prevalence of post-ICU PTSD

This study found that **27.1%** (95% CIs: 18.3%, 35.9%) of patients had PTSD at three months using Foa et al.'s PTSD Diagnostic scale (1997). The prevalence rate was arrived at using a more conservative method than the method recommended by Foa et al. (1997) which yielded a higher rate of 44%. Nevertheless a rate of 27.1% was higher than the prevalence rates established by the systematic review (see chapter two). Initial results of the systematic review were that prevalence of post-ICU PTSD ranged from 0 to 62%. When only high quality studies were included, a narrower range of estimates was obtained, from 8.4% - 22%. However these were based on only three high quality studies (Cuthbertson et al., 2004; Jones et al., 2007; Samuelson, 2007). While some of the lower quality studies used assessment tools that were not true measures of PTSD, these three studies used good instruments – the PDS (Foa et al., 1997), the IES-R (Weiss & Marmar, 1997) and the DTS (Davidson et al., 1997). The difference in prevalence rates between those and my cohort study is therefore not likely to be due to using different questionnaires. Time to follow-up was also around three months in the three other studies, so would not account for the differences in prevalence.

Perhaps the difference between prevalence rates could be attributed to differences in the populations; For example patients in my cohort study had higher illness severity scores on admission to ICU (mean Apache II score 22) than the other studies (means or medians from 13-19) and spent longer in the ICU (mean 13.55 days vs means or medians ranging from 5-13). My sample contained a higher percentage of non-surgical patients than the other three studies (63% vs 50-54%). It should also be noted that one of the other three studies was conducted in Sweden and one was a multi-centre European centre. There are undoubtedly differences between intensive care in the UK and other countries. However it is hard to make good comparisons between the three studies and mine as some reported different statistics (e.g. medians instead of means) or different clinical details. I would argue that the prevalence rate of 27.1% arrived at in my cohort study is credible as I used a gold-standard questionnaire for diagnosis of PTSD. The rate also accords with the common finding that 25-30% of people exposed to a trauma are likely to develop PTSD (Green, 2003). Furthermore I chose a cut-point of 18 for the PDS because in a comparison of 18 scoring rules for detecting PTSD (Ehring et al., 2007) it was one of the three rules that had the highest diagnostic efficiency, with a sensitivity of 0.88, specificity of 0.87 and overall efficiency of 0.87. Since the completion of my systematic review, another study (Myhren et al., 2010) reported the same prevalence rate (27%) for PTSD in ICU patients after one year, using the Impact of Events Scale (IES, Horowitz, 1976).

6.1.2 Prevalence of depression three months after ICU

The prevalence rate for depression estimated in my study, **46%** (95%CIs: 36.5, 56.1) was also somewhat higher than the estimates of studies in the systematic review. My estimate was calculated using the CES-D scale (Radloff, 1977), which is the most widely used measure of depression in epidemiological and community studies and is validated for both psychiatric and general populations. According to the author, a cut-point of 16 represents likely clinical depression, but I used a cut-point of 19. The slightly higher cut-point was previously used in a study of rheumatoid arthritis patients (Covic et al., 2007) and recommended as a better predictor of depression in patients with somatic symptoms. In the systematic review, studies that included depression as a primary or secondary outcome post-ICU yielded estimates for the prevalence of depression ranged from 2.8% to 47% at times between two months and fifteen months. Taking only rates of probable depression from high quality studies the range of estimates was still wide, from 2.8% to 32%. Comparing my study to the four high quality studies with depression as an outcome (Chelluri et al., 2004; Eddleston et al., 2000; Samuelson, 2007;

Weinert & Meller, 2006), three had a similar follow-up time-point (two-three months) and one was carried out at one year. From other study characteristics where sufficient information was reported by the other studies, the only aspect that stands out is that my cohort had a longer mean LoS in ICU (13.55 days vs 5.57-11). However LoS does not appear be a risk factor for post-ICU depression. A high estimate of prevalence (32%) came from the study by Weinert & Meller (2006) using the SCID (First et al., 1998), arguably the most reliable method of diagnosis to establish depressive disorders. Therefore a high estimate seems realistic.

6.1.3 Prevalence of anxiety at 3 months

The prevalence of anxiety found in my cohort study was **44.4%** (95%CIs: 34.6%, 54.2%) based on a cut-point of 44/45 for the Stait Trait Anxiety Inventory (Kindler et al., 2000). This compared to prevalence found in the systematic review of up to 43% possible anxiety and up to 34% probable anxiety. The results of the cohort study and systematic review were similar, and suggested that post-ICU patients experienced clinically significant levels of anxiety symptoms.

6.1.4 HRQL

The mean score for the mental health component of the SF-12 (Ware et al., 1996) for patients in my cohort study was **43.93 (10.06).** This compares to a mean of 50 and standard deviation of 10 in the general population. Therefore the average mental HRQL of former ICU patients was 6.07 points or 0.6 of a standard deviation lower than the general population. However the range of scores was 18.92 - 64.19, suggesting that some participants had extremely poor mental health. Indeed examination of the frequency of scores shows that **43%** of the patients had MCS scores of between 18 and 40 and therefore had very poor mental HRQL. This percentage is in line with the rates of psychological morbidity found in the cohort study. In the meta-analysis of previous studies that measured HRQL in post-ICU patients using the SF-36 (see chapter two), mean mental HRQL was found to be ten points below the UK population norm (65.75 vs 75.9, based on scores for the MH domain rather than MCS aggregate scores, as the latter were not reported in most of the reviewed studies).

The mean score for the physical health component of the SF-12 (Ware et al., 1996) for patients in the cohort study was 34.43 (10.06) compared to the population mean of 50 (10). In fact 50% of patients had scores ranging from as low as 17.5% to 34%, suggesting that the physical component of HRQL was extremely poor for many patients in the cohort. Up to **75%** of patients had scores under 40. In the meta-analysis of previous studies from my systematic review, I found that mean

scores for the physical functioning domain were 58.82 for ICU patients compared to 79.4 in the general population. Therefore results from the cohort study and meta-analysis led to the conclusion that both mental and physical HRQL were greatly compromised for many former ICU patients at three months. Physical health scores were generally lower than mental health scores.

6.1.5 Prevalence of adverse psycho-social outcomes after ICU

Part of the first aim of the study was to discover the extent of adverse psycho-social outcomes. For psychological morbidity alone, **55%** of patients had either PTSD or depression or anxiety after 3 months. Of these 23% had all three syndromes, 17% had two syndromes and 15% had one. If poor mental HRQL (MCS<40) is included, then **60%** of patients had an adverse psycho-social outcome. If poor physical HRQL is included (PCS<40) then **86%** of patients had an adverse psycho-social outcome. Fifteen percent of patients had all five adverse psycho-social outcomes. No previous study has looked at the extent of psychological morbidity or HRQL in this way. It is a truly troubling picture.

6.1.6 Prevalence of pre-ICU psychological morbidity

Before admission to ICU, 16(16%) of the cohort of patients had past psychological problems. All 16 patients had a past or current history of depression. One of the 16 was diagnosed with depression with psychosis and one had been diagnosed with depression and OCD since being diagnosed with cancer. No patients were recorded as having PTSD or an anxiety disorder before admission to ICU. Since the prevalence of psychological problems including PTSD, depression and anxiety post-ICU was estimated as 55% it can be assumed that around 39% of cases were new post-ICU cases.

6.1.7 Relationship between psychological morbidity and HRQL

Post-ICU depression was associated with worse mental and physical HRQL (with MCS -0.770, $p<0.001$; with PCS -0.250, $p=0.022$). Post-ICU anxiety was also highly associated with both aspects of HRQL (with MCS -0.808, $p<0.001$; with PCS -0.323, $p=0.002$). PTSD was associated with MCS (0.590, $p<0.001$) but not with PCS (-0.115, $p=0.293$). MCS and PCS were not significantly associated with each other ($r=0.174$, $p=1.09$). This is curious, because depression and anxiety were associated with PCS. The associations between outcomes should be regarded cautiously as they were measured simultaneously at three months and are therefore cross-sectional data. It is unclear whether psychological morbidity affects HRQL, or vice versa, or whether both are measures of closely related constructs.

6.1.8 Co-morbidity of psychological outcomes

In this study all three psychological outcomes were highly correlated. The correlation between PTSD and depression was 0.796 (p=0.000); between PTSD and anxiety it was 0.653 (p=0.000) and between depression and anxiety it was 0.809 (p= 0.000). For patients, severe distress is severe distress, however it is labelled; However from a clinical point of view, it is important to have an accurate idea of the nature of post-ICU distress to inform likely interventions. It is well- known that depression and anxiety frequently co-exist, and it has been argued that a diagnosis of mixed anxiety-depression should be recognised (Gorwood, 2004). The link between PTSD and anxiety is clear; PTSD is an anxiety disorder and one of the main symptom clusters is of hyperarousal symptoms (DSM-IV, APA, 1994). Indeed PTSD is almost always found with other disorders. In one survey, 88% of men and 79% of women with PTSD were also diagnosed with another psychological disorder (Davidson et al., 1991). The most frequent co-diagnoses are depression, general anxiety disorder and substance abuse. It has been observed that many depressive symptoms also appear in the DSM-IV criteria for PTSD. However Brewin et al. (1996) argued that symptom overlap is not the explanation for co-morbidity and that distinctive features of PTSD are the exaggerated startle, the re-experiencing symptoms and physiological reactivity to trauma-related cues. In this study it was found that different outcomes were most strongly predicted by different risk factors, suggesting that distinct syndromes had occurred.

6.2 Risk factors for psychological morbidity after ICU

After establishing the likely prevalence of psychological morbidity three months after ICU, the second aim of the PhD was to identify consistent risk factors for psychological morbidity and poor HRQL. The systematic review (chapter two) showed that few risk factors had been investigated and identified in a systematic way in previous studies. As so little was known, I decided to explore a comprehensive set of risk factors divided into three groups;

1. Clinical factors (illness and healthcare)
2. Psychological factors (emotional and cognitive reactions in the ICU)
3. Socio-demographic factors (age, sex, SEC, ethnicity)

Chronic physical illness, previous psychological history and alcohol use were investigated as possible confounding variables.

6.2.1 Psychological risk factors: Prevalence of distress, delirium and memory problems in ICU

The study showed that there was a high prevalence of emotional distress, and cognitive problems such as delirium and memory distortions, while patients were in the ICU. The severe nature of the emotional, physical and social stress experienced by patients in ICU may help to explain how psychological morbidity could develop as a consequence. Of the 100 follow-up patients (results for the 157 baseline sample were very similar), 78% had mood disturbance (anxiety, depression, confusion, anger) with 47% at the highest levels; while 88% experienced ICU stress (delirium, physical stress, loss of control, emotional support) with 36% at highest levels.

Delirium results showed that 64.6% of patients had hallucinations (43.4% at highest levels); 47.5% had nightmares; 73.7% were disorientated (43.4% at highest levels); 68% had confusion (42% highest) and 75% were agitated (37% at highest levels). The fact that results were so similar for hallucinations, disorientation, confusion and agitation suggests that it is correct to see them as a delirium syndrome, with about **43%** experiencing severe delirium and a further **25-30%** moderate delirium. This was also consistent with memory results as 45.5% of patients remembered very little of their ICU stay and 49.5% had experienced intrusive memories of ICU by the time of discharge.

Physical stress results showed that pain affected 73% of patients (43.4% at highest levels) while 75.8% endured difficult breathing (46.5% at highest levels) and 79.8% were sleep deprived (55.6% at highest levels). Socially, 52% felt isolated (31% very much) and 57% had communication problems (40% very much); However 83% gave high ratings for emotional support from family and 65% for emotional support from staff. Respect for dignity was highly rated by 73% and provision of information by 59%. Less positively, 86% felt they had no personal control in the ICU (67.3% felt this very much).

6.2.2 Prevalence of ICU distress in other studies

These results suggest that 70-80% of patients had a difficult time in the ICU and that **40-45%** of patients were particularly badly affected by their experiences. There is little previous research to provide a comparison with these rates. Much research about the psychological condition of patients in ICU was based on a few case histories (Tomlin, 1977) or interviews (Laitinen, 1996). Interviews often took place several months after ICU (Stein-Parbury & McKinley, 2000) and therefore depended on memories that may not have been reliable. Much of the research is

now more than twenty years old and cannot be assumed to represent the experiences of ICU patients today. However a few studies (Bohrer et al., 2002; Brullmann et al., 1997; Nelson et al., 2001; Nelson, 2004; Pochard, 1995; Simini, 1999) reported quantitative data about psychological symptoms and stressors assessed within a few days of weaning (coming off a mechanical ventilator) or at discharge from the ICU. The most common issues were insomnia (62-68% prevalence), pain (43-56%), discomfort from tubes (75%), anxiety (51-69%) and depression (29-60%). Hunger, unsatisfied thirst and distress at inability to communicate were also common. The growing literature on ICU delirium (e.g. Pandharipande et al., 2005) suggests that the prevalence of delirium in the ICU is up to 80%. Prevalence rates of ICU psychological distress may vary according to methods of measurement, but this cohort study and others suggest there is clear evidence that pain, insomnia, discomfort from tubes, anxiety, depression and delirium are serious problems in intensive care for the majority of patients.

It is striking that the prevalence of most severe distress in the ICU (mood and delirium) was **40-45%,** and prevalence of anxiety and distress at three months post-ICU was **44-46%.** Prevalence of PTSD was 27.1% but there were many more patients with significant levels of PTSD symptoms; and prevalence would have been **44-45%** using the Foa et al. (1997) scoring method. It may be that distress in the ICU persisted after discharge, and had developed into clinical disorders at three months, although the truth of this is not known. The proportion of patients who had suffered psychological problems (mainly depression) at any time before admission to the ICU was 16%. Therefore it appears that many people developed acute emotional and cognitive problems for the first time in ICU, and that this might have triggered processes leading to psychological morbidity at three months. Therefore it should not be assumed (as currently it often is) that psychological reactions commonly seen in the ICU are transient and do not require intervention.

6.2.3 Psychological predictors of post-ICU psychological morbidity

The cohort study showed that total mood disturbance in the ICU strongly predicted all psychological outcomes at three months (e.g. correlation with PTSD; $r= 0.495$, $p<0.001$). "ICU stress", (physical stress, delirium, control and support) was also a potent risk factor (e.g correlation with PTSD; $r=0.463$, $p<0.001$). Within these broader categories of mood and stress, it is of particular interest that delirium, physical stress such as pain and loss of control predicted all psychological outcomes. The association of delirium with PTSD ($r=0.402$, $p<0.001$) and depression ($r=0.252$, $p=0.014$) was much larger than with anxiety ($r=0.196$, $p=0.05$). The same pattern was seen with the predictor confusion. This might

suggest that PTSD and depression are more strongly predicted by more cognitive ICU factors while anxiety is more strongly predicted by emotional ICU factors. This fits with increasing evidence that PTSD and depression are accompanied by structural changes in the brain as well as emotional reactions (Bremner, 1999; Marazziti et al., 2010)

Two memory variables were strongly correlated with three month psychological outcomes. Amnesia for the ICU was correlated with PTSD (mean difference=-6.30, 95%CIs: -10.998,-1.56, p=0.01) and with depression (mean difference=-6.05, 95%CIs:-11.73, -0.37; p=0.037). Again amnesia is a cognitive risk factor, while PTSD and depression involve cognitive as well as emotional changes (Brewin, 2001; Kizilbash et al., 2002). Early intrusive thoughts about ICU (at discharge from ICU) strongly predicted later PTSD (mean difference= -9.39, 95% CIs: -13.85,-4.92, p<0.001), depression (-7.10, 95% CIs: -12.71, -1.47, p=0.014) and anxiety (-5.85, 95%CIs: -11.72, 0.02, p=0.05). Patients' beliefs about their condition (particularly IPQ timeline, the belief that their condition would continue for a very long time; Broadbent et al., 2006) were also associated with psychological outcomes and physical HRQL.

These results are consistent with the hypothesis that critical illness and intensive care give rise to extreme acute stress reactions which if untreated or unmodified, may trigger longer term psychological morbidity. Furthermore they suggest that the effects of ICU on memory systems may be important processes in the development of psychological morbidity, particularly PTSD and depression. Memory deficits are known to be associated with clinical depression (Bremner et al., 2000) as well as PTSD (Brewin et al., 2010). The combination of amnesia for real ICU events and early intrusive memories either of fragments of reality (such as pain) or of hallucinations and delusions, may be fertile ground for the development of post-ICU PTSD.

6.2.4 Psychological risk factors from other studies

Previous studies had identified a number of psychological risk factors for post-ICU psychological morbidity. A study by Samuelson (2007) identified **extreme fear of ICU** (OR: 6.95, 95%CIs: 2.22-21.7, p=0.002), **number of stressful events in ICU** (OR: 1.13, 95%CIs:1.03-1.24), p=0.008) and **agitation in ICU** (OR:1.77 CIs: 1.21-2.59, p=0.005) as predictors of PTSD at two months. **Satisfaction with care** was a risk factor for anxiety (standardised β= -0.188, p=0.046) at 12 months (Rattray, 2005). **Depression at ICU discharge** was a predictor of cognitive impairment at six months (Jackson et al., 2003). These factors are similar to the

emotional reactions measured in my study (total ICU mood disturbance and ICU stress).

A number of studies (Jones et al., 2001; Jones et al.; 2003, Jones et al., 2007) identified unreal (delusional) memories as a risk factor for PTSD. In my study intrusive memories (IMs), both factual and unreal, at discharge from ICU predicted post-ICU psychological morbidity but there were no significant differences between factual or unreal IMs. My study suggested that it was the intrusiveness of memories (breaking into consciousness when unwanted) that predicted outcome rather than the content (factual vs unreal) of memories. However the qualitative memory study I carried out (see chapter seven) did suggest that unreal intrusive memories at three months were more prevalent in post-ICU PTSD than factual memories. Other studies investigated different types of memory variables such as "traumatic" memories (Schelling, 1998) or just ICU recall (Rattray, 2005) at various times. A lack of clarity about the type of memory investigated and the appropriate time to assess memory has hampered investigation of this risk factor.

When psychological factors were entered into multiple regressions with other types of factor in my cohort study the strongest risk factors for all psychological outcomes were ICU mood and ICU stress. However when they were entered together, ICU mood suppressed the effect of ICU stress. There was some overlap between mood items (anxiety, depression, anger, positive emotion and confusion) and stress (physical stress, delirium, control, support) and this could have been improved in the design phase of the study. However I reported some results for ICU stress as it included items such as pain and delirium that are of great interest in the ICU. Additionally "ICU intrusions at time one (ICU discharge)" was a strong independent predictor of PTSD at three months after controlling for other risk factors. This is in line with PTSD studies that found that high levels of intrusion immediately after a trauma were predictive of a worse outcome (McFarlane, 1989). However others such as Creamer et al. (1992) found that initial intrusions were a predictor of successful recovery. ICU amnesia was not an independent risk factor and was confounded by ICU mood and ICU stress. This was possibly due to ICU mood and stress including sub-scales for delirium and confusion that helped to explain the presence of ICU amnesia. Finally IPQ timeline was the strongest psychological predictor for physical HRQL; Patients who believed at ICU discharge that their condition would continue for a long time, had worse physical HRQL at three months.

6.3 Clinical risk factors

This cohort of level 3 ICU patients consisted of 36% surgical and 64% non-surgical patients with mixed diagnoses. The respiratory system was the primary system involved for 30% of patients, the gastro-intestinal system for 27% and the cardiovascular for 18%. On average each patient received more than four types of organ support. Up to 79% received advanced respiratory support, 73% GI support, 52% CV support, 24% dermatological support and 24% renal support. They spent an average of 13.5 days in the ICU and 40 days in the hospital. The prevalence of sepsis was 81%. Mean number of drug groups of interest administered was 3.67 per patient; Opioids were administered to 93% of the cohort, 64% received benzodiazepines, 52% inotropes, 42% anti-psychotics and 34% steroids.

Many clinical risk factors were found to predict PTSD in this study. They included TISS (Therapeutic Intervention Scoring System, Keene et al., 1983), number of organs supported, days of respiratory, GI and CV support, sepsis biomarkers, days of sedation, benzodiazepines, inotropes, antipsychotics and number of drug groups administered. Many of these factors had not been investigated before. Of those that had been investigated in other studies, **duration of respiratory support** was found to have an association with PTSD in one study (Cuthbertson et al., 2004) but not in two others. However these two studies (Richter et al., 2006; Girard et al., 2007), had only 37 and 43 participants respectively and may not have been powered to detect an association between duration of respiratory support and PTSD.

The only other clinical predictor of PTSD to receive much previous attention was **sedation.** Jones et al. (2007) found that duration of sedative and opiate medication was a predictor of PTSD, while Girard et al. (2007) reported that total lorazepam dose (in 10mg intervals) predicted PTSD symptoms (rho=0.300, p=0.05). In Samuelson (2007) patients with high level PTSD symptoms at 2 months were more likely to have received midazolam (p=0.020). A study by Kress et al. (2003), that was not included in my systematic review because of small numbers, found that patients whose sedation was interrupted on a daily basis had a lower number of PTSD-type symptoms (using the Impact of Events Scale, Horowitz, 1979) than a control group (11.2 vs 27.3, p=0.02). Richter et al. (2006) found that sedation did not predict PTSD, but this was tested in a sub-group of only sixteen patients.

Sedation and the administration of particular drug groups proved to be the most important clinical predictors of PTSD in my cohort study. When all clinical factors

were entered into a multiple regression for PTSD, the strongest predictor was **duration of sedation (days)** (β=0.294, p=0.062). Other important predictors of PTSD were **benzodiazepines** (β=0.277, p=0.036), **inotropes** (β=0.292, p=0.059) and **antipsychotics** (β=0.248, p=0.072).

In my systematic review no clinical risk factors were reported for anxiety and depression. In the cohort study clinical risk factors for depression included primary body system involved (respiratory patients had higher depression scores than cardiovascular patients), longer stay in hospital and post-hospital destination, but the strongest risk factor was **benzodiazepines**. Those who received benzodiazepines in the ICU had higher three-month depression scores than those who did not receive benzodiazepines (mean difference 7.44 points, 95% CIs: 1.81,13.07, p=0.01). **Duration of sedation** was also approaching significance (rho=0.189, p=0.066). Benzodiazepines (mean daily ICU dose of ≥75mg of midazolam-equivalent) were also found to predict depression (RR:2.1, 95%CIs: 1.1-3.5) in a study of acute lung injury (ALI) patients 6 months after ICU (Dowdy et al., 2009). Other risk factors identified in this study were surgical admission (RR 2.2, CIs: 1.1,4.2) and maximum daily SOFA (Vincent et al., 1996) score >10 (RR 2.1, 95% CIs: 1.1,3.5). Hypoglycemia in the ICU was associated with increased depression at three months (mean difference = 2 points, 95%CIs: 0.5,3.5) in a study of ALI patients by Dowdy et al. (2008). These studies were not considered for inclusion in my systematic review because they appeared after the review was completed, but would not have been eligible as the cohorts consisted of an ICU sub-group (ALI patients) and not general patients.

Clinical predictors of three-month anxiety in my cohort study were **inotrope** usage (-7.63, 95% CIs:-13.37,-1.89, p=0.01) and **benzodiazepines** (-5.95, 95%CIs: -11.87,-0.03, p=0.049). **Days of sedation** was also approaching significance as a predictor of anxiety. Mental HRQL was predicted by **inotropes** (4.51, 95% CIs: -.06, 9.08, p=0.05). Other factors that also approached significance as predictors of mental HRQL were days of sedation, benzodiazepines and days of CV support. There was a big effect size for **opioids** (7.42, 95%CIs:-15.80, 0.96, p=0.08) as a predictor of better mental HRQL. A similar effect in the same direction was found for opioids and depression (7.12 points) and anxiety (7.79 points), although the results were not significant. Finally physical HRQL (PCS) at three months was predicted by **steroids** (-5.57, 95%CIs: -9.96,-1.18, p=0.029) and **anaesthetics** (-4.45, 95%CIs:-8.94, 0.04, p=0.05). The association between antipsychotic drugs and physical HRQL (-4.14, 95% CIs: -8.43, 0.15) was nearing significance

(p=0.059). Those administered steroids, anaesthetics or antipsychotics had better physical HRQL than those who were not.

A different set of clinical predictors was identified for HRQL in my systematic review. Illness severity, assessed by Apache II score (Knaus et al., 1981), SOFA score (Vincent & Moreno, 1996) or presence of MOD (multiple organ dysfunction) was a predictor in seven out of eleven studies that investigated it (see chapter two). However in my cohort study Apache II score had no association with HRQL. Length of stay (LoS) in the ICU predicted HRQL in five out of eight studies in the systematic review. But LoS in ICU was not a risk factor for HRQL in my cohort study. Finally HRQL was predicted by diagnostic group or admission type in five studies reviewed, but not in my cohort study. Trauma or multiple trauma patients had worse HRQL than other groups in four studies (Badia et al., 2001; Garcia-Lizana, 2003; Granja et al. 2002; Niskanen, 1999). Others found to be at risk of poor HRQL were neurological patients (Garcia-Lizana, 2003), emergency surgical patients (Granja et al., 2002), respiratory patients (Niskanen, 1999; Wehler et al., 2003) and acute renal failure patients (Wehler et al., 2003). The reasons for the differences between results of my cohort study and other studies regarding clinical risk factors were not clear. Studies used different measures of HRQL at different time-points and reported different domains. Furthermore studies took place in different countries in a variety of types of ICU. Additionally my cohort study measured several clinical factors that were not measured by other studies and therefore cannot be compared.

The results of the cohort study suggest two distinct types of relationship between clinical risk factors and psychological outcomes. First there is a clear message that PTSD is associated with an accumulation of clinical factors. PTSD score increased with a higher TISS score (Keene et al., 1983), a greater number of organs supported and a greater number of drug groups given as well as with specific interventions such as advanced respiratory support. In other words, the more intensive care a patient received the greater their risk of PTSD at three months. However these aggregated risk factors did not put them at greater risk of depression, anxiety or poor HRQL at three months. Secondly there were quite specific risk factors for each psychological outcome. These were all related to sedation or other types of drugs given in the ICU, highlighting a possible central role for drugs in the development of psychological morbidity after intensive care. Thus the strongest clinical risk factor for PTSD was duration of sedation (rho=0.268, p=0.008), for depression it was benzodiazepines (7.44 depression points, p=0.01), and for anxiety it was inotropes (7.63 anxiety points, p=0.01).

Inotropes also predicted worse mental HRQL, and steroids and anaesthetics predicted better physical HRQL.

6.3.1 Possible psychological mechanisms explaining the effect of clinical risk factors

I would argue that there are different biological and psychological mechanisms underlying these two types of relationship. First it could be argued that one of the underlying causes of post-ICU PTSD is an accumulation of factors (captured by variables such as TISS score and number of organs) putting the patient under significant levels of physiological, psychological and social stress. The TISS score (Keene et al., 1983) encompasses all interventions received by an ICU patient including drugs, treatments and invasive monitoring. Similarly an increasing "number of organs supported" entails a greater number of potentially stressful treatments and procedures such as oxygen delivered by tight-fitting face mask, mechanical ventilation, endo-tracheal tubes, naso-gastric tubes, dialysis and haemofiltration, open abdomen procedures, and cardiac, abdominal, neurological and pulmonary monitoring.

As level 3 ICU patients undergo multiple treatments, generally know that their life is threatened and stay in an environment that is thought to be extremely frightening (Dyer, 1995), it is not surprising that they exhibit severe stress responses as described earlier in the thesis. Theories of psychological stress suggest that repeated acute stress responses may become chronic and lead to outcomes such as a mental or physical illness (Steptoe & Ayers, 2004). PTSD is defined as an anxiety disorder that often follows exposure to an extreme stressor that causes injury, threatens life or physical integrity (American Psychiatric Association, 1994). To meet diagnostic criteria for PTSD, the person's response to the event or series of events must involve intense fear, helplessness or horror at the time of the trauma. Critical illness was added as an example of a traumatic stressor that could cause PTSD in the last version of the DSM (APA, 1994) and section 6.2.1 quantified the high levels of fear, helplessness and horror suffered by many patients in intensive care.

The appraisal of continued threat is thought to be central to the development of post-traumatic stress disorder. Patients with PTSD continue to detect and react to threats in the environment even when a traumatic event is over (Ehlers & Clark, 2000). ICU patients are subject not just to one stressor but to repeated or even continuous stressors and emotional and physical shocks over a period of days or weeks. Furthermore ICU experiences are unpredictable, uncontrollable by patients and may be of long duration, which are characteristic of stressors that produce

pronounced physiological stress responses (Steptoe & Ayers, 2004). All this, along with a state of heightened arousal, confusion and cognitive dysfunction, might trigger in patients a tendency to react strongly to real or imagined threats to their well-being after leaving intensive care.

In support of this argument, mediational analysis carried out in the cohort study showed that emotional and cognitive risk factors partially mediated the relationships between clinical risk factors and psychological outcomes. A mediator is a variable (B) that explains how or why another variable (A), which must precede (B) affects the outcome (O), and may be on the causal pathway between predictor (A) and outcome (Baron & Kenny, 1986; Rothman & Greenland, 1998). Of course causality cannot be inferred from non-experimental data; the most that can be said is that what is observed would be expected if there were a causal path leading from A to B to O (Kraemer et al., 2001).

When acute psychological risk factors such as mood, stress or intrusions were entered into regressions with clinical risk factors, the effect size of clinical risk factors was greatly reduced and often became non-significant. So for example, the effect size of the TISS score on PTSD (B=.575, p=0.014) was more than halved (B=0.253, p=0.259) when ICU stress was entered into the regression. This suggests that the relationship between TISS and PTSD at three months was partly explained by the stress experienced in ICU. The remaining effect of TISS may be due to other psychological mediators or to physiological mechanisms involved in PTSD (to be discussed in 6.3.3 below).

As depicted in the possible mediation model from chapter five (figure 6.1), the hypothesised causal pathways were that interventions, sedation and drugs administered might trigger mood and stress responses and memory changes in ICU which might in turn lead to adverse psychological outcomes at three months. More specifically, intrusive memories at T1 (ICU discharge) partially mediated the pathway between benzodiazepines and PTSD, and ICU amnesia partially mediated the pathway between TISS and PTSD. Mood and stress mediated pathways between several clinical factors and outcomes (see Table 6.1)

Figure 6.1 Potential causal pathways

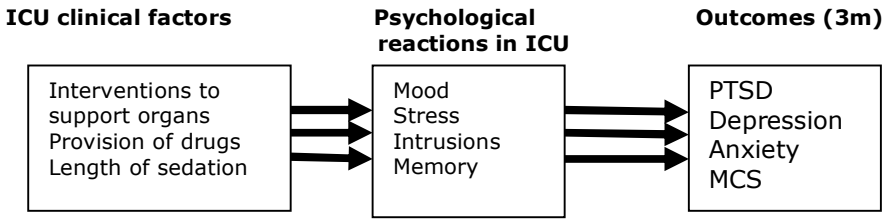


Table 6.1 Mediators identified in analysis

	Mediators (PTSD)	Mediators (Depression)	Mediators (Anxiety)	Mediators (mental HRQL)
Days sedation	**ICU Mood** **ICU Stress** **ICU Intrusions**			
TISS	**ICU Mood** **ICU Stress** **ICU Amnesia**			
Benzodiazepines	**ICU Mood** **ICU Stress** **ICU Intrusions**	**ICU Mood** **ICU Stress**		
Ionotropes			**ICU Mood** **ICU Stress**	**ICU Mood**

6.3.2 Possible psychobiological mechanisms explaining the effect of clinical risk factors

As well as psychological explanations for the way stress leads to outcomes such as PTSD, other theories centre on biological aspects of the stress response and their long-term effect. It is thought that extreme fear activates the amygdala, part of the brain that initiates autonomic responses to stress including the release of stress hormones such as adrenaline, noradrenaline, and cortisol (LeDoux, 1996). Prolonged, intense stress may lead to over-production of cortisol, which is thought to impair hippocampal function and to enhance functioning of the amygdala. The hippocampus has been shown to be smaller in PTSD sufferers in a number of studies (Bremner et al., 1995). As the hippocampal formation is necessary for establishing long-term explicit or declarative memory (Zola et al., 2000), intense stress can be expected to have a profound effect on memory processes. A similar pattern of high levels of cortisol, reduced hippocampal volume and declarative memory deficits has also been found in depression (Bremner et al., 2000). Thus prolonged intense fear, which is frequently experienced in the ICU, could in principle trigger a series of events leading to PTSD or depression. This theory would also suggest that extreme ICU stress could also be associated with physical outcomes such as heart disease but this was not investigated in the study.

6.3.3 Possible physiological mechanisms explaining the effect of clinical risk factors

Mechanisms relating PTSD (and depression) to psychological stress caused by multiple stressors in the intensive care environment have been outlined. However there are also plausible mechanisms that could link the physiological stress of critical illness and intensive care to damaging effects on the brain and subsequent psychological morbidity. The exact mechanisms are unknown but might be related to characteristics of critical illness such as sepsis, hypoxia, hypoperfusion, hypotension, cytokine-mediated inflammation and microvascular thrombosis, as well as abnormalities in neurotransmitter systems involving acetylcholine, dopamine, GABA, serotonin, glutamate and noradrenaline (Milbrandt & Angus, 2005). The cohort study showed that a number of sepsis markers (C-reactive protein, white cell count, lactate and noradrenaline administration) were related to PTSD and anxiety, though not to depression. This is the first study to show this link, which merits further research.

C-reactive protein is a marker of acute inflammation and it has been hypothesised that acute inflammation may lead to diffuse brain damage and thus to the development of delirium (Sharshar et al., 2005). It is well known that sepsis commonly induces secondary encephalopathy, often in the form of delirium. Although the pathophysiology behind septic encephalopathy is not well understood (Flierl et al., 2010), it is thought that the blood-brain barrier is broken down by cytokines, activation of the complement cascade and bacterial products. An inflammatory response is then triggered in the subarachnoid space. A study by Sharshar et al. (2002), which found white matter lesions in the brains of sepsis patients, suggested that diffuse occult brain injury was associated with high levels of pro-inflammatory cytokines. It is not known if these patients had delirium, but acute inflammation was shown to be associated with delirium in a study of 41 elderly post-operative hip-fracture patients (Beloosesky et al., 2007).

It is not yet known if there is a further link from sepsis-related brain inflammation and delirium to psychological morbidity such as PTSD or depression. Although it has not previously been tested in research, there are fragments of evidence. First, cognitive deficits in attention, executive function, memory and learning are known to be associated with PTSD in general (Vasterling et al., 2002; Bustamante et al., 2001). In the post-ICU context, depression has been associated with cognitive impairment at 6 months (36% impaired vs 17% non-impaired, Jackson et al., 2003). It is also known that longer hospital stay is a consequence of delirium (Ely et al., 2001a) and in my study longer hospital stay was a risk factor for 3-month depression. My cohort study found, for the first time, that ICU delirium was a risk factor for all psychological outcomes. Effect sizes were large in the case of delirium

and PTSD (r=0.402, p<0.001), medium for delirium and depression (r=0.252, p=0.014) and small for anxiety (r=0.196, p=0.05). Almost identical results were obtained for associations between a similar variable (the confusion subscale of mood) and outcomes.

Furthermore it is known the activation of pro-inflammatory cytokines and impaired immune function can also be triggered by psychosocial stress. Repeated activation of the hypothalamic-pituitary-adrenal axis (due to chronic psychosocial stress) made people more susceptible to infection and led to inflammatory processes (Zhou et al., 1993). Therefore it can be argued that the psychological stress of being in ICU combined with the physiological stress of critical illness would be a potent milieu for the development of inflammation-related brain dysfunction, delirium and subsequent psychological morbidity.

6.3.4 Effects of ICU on neurotransmitters

A further related physiological hypothesis is that long-term psychological outcomes of ICU are related to imbalances in neurotransmitters (Meyer & Hall, 2006; Milbrandt & Angus, 2005; Weinert, 2005). Likely affected neurotransmitter systems could include acetylcholine, GABA, dopamine, serotonin, glutamate and noradrenaline, although detailed evidence is lacking. Neurotransmitter dysregulation is probably caused both by critical illness itself, and by the effects of ICU drugs. Acetylcholine is thought to inhibit the synthesis of pro-inflammatory cytokines (Czura et al., 2003), a process that could be disrupted by many drugs commonly used in the ICU that have high anticholinergic effects. These include opiates, glucocorticoids and benzodiazepines. The reduction in cholinergic activity is thought to result in overproduction of dopamine, an excitatory neurotransmitter which may contribute to the development of delirium (Sommer et al., 2002). Other potential neurotransmitter systems worth investigating would be abnormalities in serotonin, excess GABA activity after benzodiazepine withdrawal causing delirium, excessive noradrenergic function that might be associated with panic attacks and delusions and the role of glutamate in causing confusion (Milbrandt & Angus, 2005). It is thought that the inflammatory stress of critical illness could also have effects on a network of neurotrophins, neurotransmitters and receptors leading to problems with memory consolidation and retrieval (Weinert & Mellor, 2007).

Having discussed the general mechanisms that could link the overall burden of critical care illness and treatment to psychological morbidity, I would now like to consider the more specific links that were found. All the strongest clinical predictors of psycho-social outcomes were drug-related. Days of sedation, benzodiazepines

and inotropes all had a detectable effect on PTSD, depression, anxiety and outcomes, but each had a stronger effect on one specific outcome. Steroids had a positive effect on physical HRQL, while there was a trend that opioids were associated with better psychological outcomes.

6.3.5 Days of sedation and PTSD

Duration of sedation was a stronger predictor of PTSD than any specific drug, and sedation may involve a number of benzodiazepines or anaesthetic agents such as propofol. Therefore I would suggest that any mechanisms involved would be linked to shared properties of sedative drugs rather than specific structures of specific drugs. According to Ghoneim (2004a) most drugs that cause sedation also cause amnesia. These drugs may have different molecular structures and involve different neurotransmitters and binding areas in the brain but they produce similar patterns of memory impairment. Amnesic drugs, with the exception of general anaesthetics, tend to spare short-term memory and impair long-term memory. They have most effect on explicit and episodic memory by impairing the encoding and consolidation of new information (Ghoneim & Mewaldt, 1990). Implicit memory, associative memory, procedural learning and semantic memory are generally less affected.

Having impaired explicit memories of a trauma along with heightened associative, emotional memories has been linked with the development of PTSD (Brewin & Holmes, 2003). A similar memory pattern was arguably seen in studies such as Jones et al., (2001) where patients with delusional memories and few factual memories were more likely to develop PTSD. My cohort study also showed that having little "real" memory for the ICU was a risk factor for PTSD. It is likely that the longer a patient spends sedated, the less they will remember about real ICU events and the more they will have fragmentary emotional memories or unreal memories of hallucinations. It has been assumed that the effects of sedative drugs on memory result from disruption of the medial temporal lobe system, including the hippocampal formation (Longo, 1966; Ghoneim, 2004) but few investigations have been carried out to my knowledge. It may be hypothesised that the longer the patient is sedated, the more hippocampal structures are impaired, resulting in worse effects on memory and a greater likelihood of developing intrusive memories and PTSD. However this may be a simplistic picture as recent research suggests that damage occurring to different regions of the hippocampus results in different effects. It is thought that damage to the dorsal hippocampus affects learning and memory, whereas damage to the ventral hippocampus results in behavioural disinhibition and reduced anxiety (Bannerman et al., 2004). It might be fruitful to investigate whether the disinhibited behaviour exhibited by sedated, delirious, ICU

patients involves ventral hippocampal structures. It is also now believed that fear and anxiety may be separate processes with fear mediated by the amygdala and anxiety behaviours by the ventral hippocampus.

6.3.6 Benzodiazepines and depression

This is the first study to find that benzodiazepines were a risk factor for depression in general ICU patients. However Dowdy et al., (2009) reported that benzodiazepines (mean daily ICU benzodiazepine dose of ≥75mg of midazolam-equivalent) predicted 6-month depression in a subgroup of ICU patients with acute lung injury (ALI). In the wider literature the link between benzodiazepines and depression is controversial. The DSM-IV (APA, 1994) includes a diagnosis of drug-induced depression called substance-induced mood disorder and lists benzodiazepines as one of the potential causes. Depression is listed as a possible adverse reaction to benzodiazepines by American manufacturers. Finally a number of studies have reported depression to be a long-term effect of benzodiazepine use (Patten et al., 1996). However Patten (2008) concluded that there is a lack of evidence to substantiate the link. The mechanism by which benzodiazepines might cause depression is unknown but one theory is that they cause a reduction in central monoamine activity (Longo & Johnson, 2000). It is thought that depression is caused by deficiencies in three monoamines; serotonin, noradrenaline and dopamine (Stahl, 2000).

Benzodiazepines are sedative drugs that primarily bind to receptors for GABA, the most prominent inhibitory neurotransmitter in the CNS. As well as therapeutic effects (anxiolysis) they are known to have adverse effects (Ashton, 1989; Ashton, 1991; Ashton, 1997) including psychomotor retardation (with poor concentration and mental confusion), short and long term withdrawal effects (insomnia, anxiety, delirium) and paradoxical disinhibition and aggression. The elderly are particularly at risk of some adverse effects such as psychomotor retardation, cognitive dysfunction and paradoxical disinhibition (Longo & Johnson, 2000). Symptoms similar to these adverse effects have been well documented in the short-term in ICU patients, many of whom are elderly. It is feasible that psychomotor retardation, delirium and cognitive dysfunction in the ICU, if left untreated, could trigger serious depression in the longer term.

6.3.7 Inotropes and anxiety

No previous prospective study has highlighted inotropes as a risk factor for future psychological morbidity. But in this cohort study it was the most important predictor both of three-month anxiety and of three-month mental HRQL with a

substantial effect size of nearly eight points for anxiety. No mechanism has been proposed for this effect as it has not been seen before, but it intuitively makes sense as the inotropes used in ICU are primarily noradrenaline and adrenaline, the stress hormones. Often known as the "fight or flight hormones" adrenaline and noradrenaline prepare the body for strenuous activity or life-threatening situations (Axelrod & Reisine, 1984; Sapolsky, 2000). They produce effects such as increased heart rate, increased blood pressure, and production of glucose to prepare the body for action. These effects are helpful in response to one-off threats, but can become maladaptive if constantly reactivated. When given as medication, adrenaline and noradrenaline are known to cause anxiety symptoms or iatrogenic anxiety in the short term (House & Stark, 2002). Side effects include tachycardia, palpitations, anxiety, tremor, restlessness, sweating and other autonomic symptoms. These symptoms would not be expected to persist after short periods of medication, but it may be that the physical sensation of autonomic symptoms along with the intense fear experienced by many ICU patients, leads to a vicious circle of ever-increasing anxiety. If acute anxiety symptoms are not treated, persistent forms of anxiety may develop, such as generalised anxiety disorder (involving muscle tension, inability to relax, feeling on edge and irritability) or panic disorder (in which anxiety symptoms such as a pounding heart are mistaken for serious illness such as a heart attack; NICE, 2004).

Furthermore, it is known that inotropes have many effects distant from their cardiovascular actions. They have metabolic effects, both pro- and anti-inflammatory effects, and they can alter both immunity and mitochondrial function, which drives the body's metabolic processes (Singer & Glynne, 2005). Thus, along with other drugs used in the ICU, such as sedatives and antibiotics, inotropes may cause harm by inhibiting mitochondrial function. Mitochondrial shut-down is believed to be part of the process leading to sepsis and multiple organ failure. This in turn increases the risk of septic encephalopathy or delirium and cerebral insults that may be lead to the development of later psychological morbidity in survivors.

Another potential effect of the drugs noradrenaline and adrenaline is that unlike most ICU drugs that tend to cause amnesia, the catchecholamines are thought to enhance memory, particularly emotional memory (McGaugh et al., 1993). If they enhance traumatic memories at the time when a patient is most seriously ill, this would be likely to contribute to increased anxiety in the future. A series of studies were carried out to examine the effect of stress hormones on memory formation and PTSD in ICU patients (Schelling, 2002). It was found that the total number of traumatic memories recalled increased and that memory consolidation was better

with increasing numbers of stress hormones (adrenaline, noradrenaline and cortisol) administered exogenously in the ICU.

6.3.8 Steroids and physical HRQL

It is of interest that patients who received corticosteroids had much better physical HRQL at three months than those who did not, in my cohort study. ICU patients are given steroids such as hydrocortisone to modify the inflammatory reaction which often occurs in patients with critical illness such as sepsis (Schelling, 2001). In one study patients given hydrocortisone in the ICU had significantly lower levels of the pro-inflammatory cytokines interleukin-6 and interleukin-8 (Briegel et al., 2001). One explanation for the physical HRQL result in my cohort study is that steroids protected patients against the most harmful effects of inflammation and so they were less physically impaired at three months.

Patients in Schelling et al. (2001) who received steroids in the ICU had a lower rate of PTSD in spite of having enhanced and better consolidated trauma memories. This might suggest that because the inflammatory response was reduced by steroids, the brain, in particular the hippocampus (interleukin-6 and its receptors are expressed on hippocampal neurons) was protected, and the risks of developing disorders such as PTSD was reduced. It could also suggest that having better consolidation of trauma memories (probably involving hippocampal structures) is protective against PTSD, as would be predicted by the dual representation theory of PTSD (Brewin et al., 1996). However no association between steroids and PTSD was found in my cohort study

6.3.9 Opioids

There was a trend for opioids to have a positive effect on all psychological outcomes except for PTSD in my cohort study. Although results were not significant, effect sizes for the associations with depression, anxiety and mental HRQL were large, of the order of 7-8 points. Although some studies found that sedation and opiates combined were a risk factor for psychological morbidity (e.g. Jones et al., 2007), studies where the effects of sedatives and opioids were looked at individually suggested different effects of the two drug groups. No studies were found that tested whether opiates were an independent risk factor for psychiatric morbidity, but a possible association between opiates and delirium has been investigated. Ouimet et al. (2007) found that patients without delirium had higher daily doses of opioids than patients with delirium. Morrison et al. (2003b) found that hip-fracture patients treated with larger doses of opioid analgesics

(>10mg/day parenteral morphine sulphate equivalent) were less likely to develop delirium than those who received less opioid analgesia.

These studies and the effects of opioids in my cohort study point to possible protective psychological effects of adequate analgesia. Although pain has not previously been established as a risk factor for post-ICU psychological morbidity, my cohort study found that pain affected 73% of patients (43.4% at highest levels) and that physical stress (including pain, discomfort and difficult breathing) was a highly significant risk factor for PTSD, depression, anxiety and mental HRQL. Pain was consistently found to be one of the three main stressors (prevalence 43-56%) in studies that assessed ICU distress (see 6.2.2 above). Inadequate pain relief would be expected to lead to emotional reactions in the ICU such as fear and helplessness. If pain is also a risk factor for delirium as suggested by Girard et al. (2008), a combination of pain, fear, helplessness and delirium in the ICU might be a precursor for subsequent psychological morbidity.

Nevertheless further research is needed into the effects of opioids on the psychological outcomes of ICU patients. Opioids are known to inhibit the release of acetylcholine in the brain (Michaelson et al., 1984) and to interfere with sleep patterns (Arankowsky-Sandoval & Gold, 1995). So arguably opioids could increase other risk factors for delirium and poor memory. Opioids have also been associated with hallucinations and delirium in a number of non-ICU studies (Bruera et al., 1992; Williams-Russo et al., 1992). However associations were often weak and results contradictory. A systematic review (Wheeler et al., 2002) found that CNS effects of post-operative opioid analgesia were idiosyncratic rather than dose-related. One study (Saxe et al., 2001) found a significant association between dose of morphine and PTSD at six months with a greater reduction in PTSD symptoms in children who had higher doses of opioids. The authors hypothesised that opioids reduced consolidation of traumatic memories by inhibiting the production of noradrenaline at the level of the amygdala thus reducing fear conditioning and PTSD. Thus the evidence of the effects of opioid analgesia on psychological outcomes need to be carefully weighed.

6.4 Socio-demographic risk factors

Age and sex did not predict psychosocial outcomes of intensive care although there was a trend for younger age (p=0.184, p=0.073) and female gender (p=0.075) to predict PTSD. This was a surprising result as age and gender are well-established risk factors for psychological morbidity and HRQL. It is possible that the psychological effects of ICU are so prevalent that they override individual

differences. The only socio-demographic risk factor found to predict post-ICU psychological outcomes was socio-economic circumstances. SEC was measured using NS-SEC (ONS, 2010), a self-coded occupational variable with six classes:

1. professional/managerial occupations
2. intermediate occupations
3. small employers and own account workers
4. lower supervisory and technical occupations
5. semi-routine and routine occupations
6. unclassified (including some retired/unemployed/students/spouse working).

SEC was found to predict depression (p=0.008), anxiety (p=0.041) and mental HRQL (p=0.016) at three months. It did not predict PTSD, which is inconsistent with the finding by Brewin (2001) that SEC was a risk factor for PTSD, albeit a weak one. A significant difference of 15 points was found between group one (professional/managerial) and group two (intermediate occupations e.g. clerical) for post-ICU depression, with depression higher in **group two**. No significant differences in post ICU anxiety were found between NS-SEC groups but **group two**'s anxiety score was 13 points higher than group one's and group six's score was 11 points higher than group one. For mental HRQL a significant difference was found between groups **one** and **five** (one had better HRQL by 10 points).

This was the first study to find that SEC was a predictor of post-ICU psychological morbidity or HRQL. Previously no studies have investigated this risk factor although two studies investigated the effect of educational level; Jackson et al. (2003) found that mean years of education was associated with post-ICU cognitive impairment (11.3 years of education if impaired vs 14.1 years if non-impaired) and Granja et al. (2002) found that education predicted HRQL six months after ICU. Patients who did not continue education after minimum schooling (48% of the sample) had significantly more problems after ICU with mobility, self-care, usual activities and pain/discomfort.

SEC has previously been found to be associated with non-psychological ICU outcomes such as mortality. Hutchings et al., (2004) demonstrated a social gradient for mortality among elective surgical patients, with lower SEC patients having a higher mortality, in a study of more than 51,000 admissions to 99 ICUs from 1995-2000. The authors speculated that the SEC gradient might result from unmeasured health differences at admission to the ICU mediated by factors such as stress and quality of social support. They also considered the possibility that

patients received different care according to SEC. An association was found by Welch et al. (2010) between increasing deprivation and increased risk of mortality for all types of admission in a sample of 78,631 patients admitted to English ICUs from 2000-2002. Welch et al. (2010) found that indicators of illness severity such as physiology scores, levels of mechanical ventilation and severe sepsis were similar across quintiles of IMD, suggesting that severity of illness did not vary according to deprivation. Thresholds of admission were also found not to vary. No conclusion was reached about the reasons for the association found between SEC and ICU mortality.

Similarly it was difficult to identify the reasons for differences in depression, anxiety and mental HRQL between NS-SEC groups in my study. Population-based studies have reported a social gradient in psychological disorders, with people with lower SEC having worse mental health problems. This has been demonstrated in psychotic illnesses and more common mental disorders such as anxiety and depression (Fryers et al., 2003). Therefore it would be expected that patients of lower SEC would be more likely to have anxiety or depression. However as the prevalence of post-ICU anxiety and depression was approximately 45%, compared to 16% pre-ICU, the issue here is not background mental health issues, but recent psychological morbidity occurring after intensive care. It could be argued that people with poorer SEC are more vulnerable to mental health problems. They may be more likely to react badly to stressors such as ICU and to develop subsequent problems with mental health. Few studies have looked at an SEC effect on psychological morbidity as a reaction to medical illness, but Simon & Wardle (2008) found that lower SEC patients with breast, prostate or colorectal cancer were more anxious and depressed and had worse HRQL two months after diagnosis. In a study of oral cancer surgical patients those with a lower annual family income had significantly worse physical and mental HRQL. SEC was also found by Clarke et al. (2000) to predict severe limitations of daily living in cardiac patients (with left ventricular dysfunction).

There was no association between SEC and clinical (illness and treatment) factors in this study. No significant differences were found between SEC groups for illness severity, primary body system involved, sepsis markers, amount of intervention received, number of organs supported, days of mechanical ventilation or categories of drugs received. Mean group scores showed that group one patients (professional/managerial) had higher scores for illness severity, number of organs supported, intervention intensity and sepsis than all other groups (possibly because of the higher rate of attrition of more deprived patients between times one and

two). However the lack of significant results suggests that the SEC association with post-ICU psychological distress is not likely to be related to how ill a patient was or what type of intervention they received.

There was an SEC association with ICU mood (p=0.046), with a much higher mean score (41.61 (8.16)) for **group two** (intermediate occupations) compared to group one (28.89 (14.83) and group five (24.8(8.53)). Additionally, although it was not a significant result, group two had higher ICU stress (40.68) compared to other groups (e.g. group one, 32.38). ICU memory and intrusions were not associated with NS-SEC in this study. Nor were any chronic factors including psychological history, chronic illness or alcohol use. The finding that NS-SEC was associated with total mood disturbance in the ICU suggested that there was more vulnerability to stress among some NS-SEC groups than others. This might help to explain the difference in three month outcomes. In this case patients with intermediate occupations (e.g. PAs, clerical officers and lower grade civil servants) had worse mood disturbance in the ICU and more depression and anxiety three months after the ICU than other groups. It is unclear why this should be. One possibility is that their jobs have characteristics thought to cause chronic stress or job strain; characteristics such as high demands with low control (Karasek, 1979), or an imbalance between effort put in and rewards received (Siegrist & Marmot, 2004) together with employment insecurity. Previous studies have shown that surgical patients with more life stress before coming in to hospital had worse post-operative recovery in terms of pain, drowsiness, and a number of indicators of post-operative morbidity (Liu et al., 1994). It is arguable that higher levels of work-related chronic stress could explain group two's vulnerability to disturbed mood in the ICU and psychological morbidity at three months. However it is not clear why group two should have more chronic stress than other vulnerable groups such as group five (routine and semi-routine occupations).

Another level of explanation is that three month psychological outcomes would be determined not just by experiences in the ICU, but by factors affecting patients after discharge from hospital. Some patients return to more difficult environments in which to recuperate – for example those with less money for food, heat and medicines, or less social support or more family conflict. Post-ICU factors were not measured in this study, with the exception of social support at three months which was not found to be associated with psychological outcomes. There were differences in levels of social support within NS-SEC groups (p=0.05). Social support was high in groups one (28) and five (29), and low in group four (14.67). However this result does not shed light on the prevalence of anxiety and depression in groups two and five.

Table 6.2 Social support mean scores by NS-SEC

1. (professional/managerial)	28.17
2. intermediate	25.13
3. small employers, own account workers	23.28
4. lower supervisory and technical	14.67
5. semi-routine and routine	29.00
6. student, unemployed, retired, unclassified	26.00

6.4.1 Summary of SEC results

SEC was associated with three outcomes; depression, anxiety and HRQL. **Group two** (intermediate occupations) was the most distressed group with higher rates of anxiety and depression at three months post-ICU in comparison with other occupational groups. **Group five** (routine, semi-routine occupations) had worse mental HRQL than other groups and **group six** had highest scores for anxiety. **Groups one** (professional/managerial) and **four** (technical/supervisory) had the best mean scores for both depression and anxiety. A significant association between ICU Mood and NS-SEC (and other trends) suggested that **group two** had worse emotional reactions to being in the ICU than other groups. This may have been exacerbated by chronic stress relating to their occupations, resulting in anxiety and depression at three months. Perhaps higher levels of control and autonomy in their occupations made patients from groups **one** and **four** more resilient in coping with the stressful ICU environment.

6.5 Chronic factors

Data on chronic physical illness, psychological history and alcohol use were collected. It was believed that these could be important confounding variables. A recent NICE guideline (Pilling et al., 2009) presented strong evidence that there was a high prevalence of depression in patients with chronic health conditions. In my systematic review five out of five studies that included chronic or pre-existing physical illness as a risk factor found it predicted depression (Weinert & Meller, 2006) or HRQL (Cuthbertson et al., 2005; Granja et al., 2002; Orwellius, 2005; Ridley et al., 1997). There has been much debate about the causal role of previous mental health problems in PTSD after critical illness. In the systematic review three studies (Cuthbertson et al., 2004; Nickel et al., 2004; Weinert & Meller, 2006) found that psychological history was a predictor of PTSD or depression and two (Richter et al., 2006; Jones et al., 2001) found that it was not a predictor of PTSD or were inconclusive. Previous non-ICU studies have found that an existing or past mental health problem is a risk factor for PTSD (Ozer et al., 2003).

In this study chronic physical illness was found to predict depression, anxiety and HRQL. Psychological illness predicted PTSD, depression, anxiety and MCS. Past trauma did not predict psychological morbidity three months after ICU but there was a trend for it to predict PTSD (mean difference 4.41; 95%CIs: 0.53,9.36, p=0.080). Alcohol use was also a predictor of PTSD (mean difference 9.17; 95% CIs: 2.20, 16.15, p=0.011). When multiple regression was carried out with clinical, psychological and socio-demographic variables, chronic physical illness was found to be an independent predictor of depression, anxiety and mental HRQL. It did not confound the effects of days of sedation on PTSD; of benzodiazepines on depression; or the effects of inotropes on anxiety. It was of interest that chronic physical illness was correlated with psychological outcomes but not physical HRQL. Psychological history was associated with PTSD, depression and anxiety. It did not confound the effects of ICU mood, intrusions or timeline on PTSD or of ICU mood on Depression; but did reduce the effect of ICU mood on Anxiety. It was not an independent risk factor for mental HRQL.

6.6 Evaluation of study

6.6.1 Strengths of the study

With 157 patients assessed at baseline and 100 who completed followed-up, the cohort study was fully powered to detect a correlation coefficient of 0.3 between a continuous risk factor and an outcome, according to an a priori power calculation that the minimum sample size was 95. This sample size had been inflated by 40% to allow for the detection of the same size of correlation coefficient in a multiple regression where all other variables explain 30% of the total variation in outcome. An adequate sample size was achieved by approaching every consecutive eligible level 3 patient admitted to ICU for a period of ten months. All ICU patients' charts were checked every morning to identify patients who were receiving level 3 care by Intensive Care Society criteria regarding number of organs supported and other factors (Intensive Care Society, 2002), therefore the sample consisted of a very tightly defined group of intensive care patients. With an 86% participation rate, very few eligible patients declined to participate, and comparisons between recruits and non-recruits suggested the sample was representative.

A rigorous system for following up patients was in place ensuring a 64% follow-up rate, although 90% of patients who were contactable and capable of answering the questionnaires took part in the follow-up. The follow-up sample did not differ significantly from the baseline sample for psychological and clinical factors, but the rate of attrition between T1 (ICU discharge) and T2 (three months) was greater among men and among people living in the most deprived IMD quintiles. Sex was

not associated with post-ICU psychological morbidity in this study, therefore the change in the sample's male-female ratio should not have affected results. As SEC was a risk factor for anxiety, depression and mental HRQL, the higher rate of attrition from the most deprived IMD quintiles could suggest that the prevalence of depression and anxiety at three months could have been higher if the whole sample had been followed up. However this cannot be argued with any certainty because it was decided that the IMD 2007 (Communities and Local Government, 2010) was not a useful measure of SEC in this study.

Another strength was the prospective nature of the cohort study. All psychological and clinical risk factors were assessed at the time of patients' discharge from the ICU. This was the first prospective study to assess patient's psychological state in ICU and then follow it up at three months. I designed an ICU baseline questionnaire that covered all likely psychological risk factors but was not too long or burdensome for patients to complete. I visited all patients and read them the questionnaire as many were too sick to tackle it alone. All patients were then contacted by post after three months. The methods used for outcome assessment were robust. The PDS (Foa et al., 1997) is regarded as the gold-standard self-report measure for PTSD as it is based on specific and exact DSM-IV criteria (APA, 1994). The CES-D (Radloff, 1977) is the mostly widely used questionnaire in community and epidemiological studies to detect likely clinical depression. As anxiety was a less important outcome than PTSD and depression, a short version of STAI (Spielberger et al., 1983) was used. This may be less reliable than the full version but it was used to reduce the length of the questionnaire and to make it more likely that patients would complete it in full. A short version of the SF-36, the SF-12 (Ware et al., 1996) was used for the same reason.

A further strength is that prevalence rates, which are notoriously variable in psychiatric epidemiology and will vary according to methods used and other factors, were calculated using sensible and conservative methods so as not to under- or over- estimate the likely prevalence. I chose a three-month follow-up period because it was long enough for PTSD to be detected, but not so distant from the ICU experience that too many other factors had intervened. Three months was also a reasonable time by which patients might expect to be making a good recovery. Finally, a comprehensive set of risk factors was studied in this cohort study. Few risk factors had been identified to date, so I decided to examine three groups of likely risk factors and used appropriate statistical methods to identify the strongest independent risk factors. Another strength was that potential confounding

variables were carefully considered and measured. These were chronic ill-health, previous psychological history, cancer, heavy alcohol use and recreational drug use.

6.6.2 Limitations of the study

The sample size may not have been large enough to detect all important associations. As a result of the number of potential risk factors investigated, many statistical associations were found in the study, introducing the risk of type one errors. In this situation it is important to differentiate between statistical artefacts and true associations. It is necessary to consider plausible biological or other types of mechanism by which associations might be explained, as I have outlined in this discussion. As a result of limited concentration and time for seriously ill ICU patients to complete the baseline questionnaire, I had to adapt and shorten existing questionnaires or create new ones. Thus I had to balance the potential loss of reliability and validity if full questionnaires were used, with the feasibility of the patients being able to complete questionnaires. I was also concerned not to exhaust seriously ill patients.

Additionally I found that existing ICU stress or memory questionnaires were too long or did not address the specific risk factors I considered most important. Therefore I created my own ICU stress questionnaire and took advice from Professor Christopher Brewin from UCL, an expert on intrusive memories, to devise questions to elicit information on intrusive memories. After piloting the questionnaire I found that it was marginally too long and I reduced the number of items further. I cut some questions from the brief Illness Perception Questionnaire (Broadbent et al., 2006) that patients seemed to find confusing and thus lost information on some of the core illness perceptions. I also dropped the Mini-mental state exam (Folstein et al., 1975) as it made the baseline assessment too arduous, and therefore lost the opportunity to get more information about the patients' cognitive function post-ICU.

Another limitation was the possible inaccuracy in the measurement of socio-economic circumstances. As patients filled in the NS-SEC (Office for National Statistics, 2008) questionnaire at home as the final part of the follow-up questionnaire, many people did not fill it in or did so incorrectly. In particular people who were retired or unemployed did not follow the instructions to answer the questions with reference to their last job. Also some people misclassified themselves as group one (professional/managerial). As a result of this, I decided to use postcodes to classify people's SEC according to IMD (2007) areas of deprivation. However ultimately I decided that NS-SEC was a better indicator of

SEC in this cohort, and so used NS-SEC rather than IMD in the statistical analyses of the cohort study. My reasons for this decision were that the majority of the cohort came from two London boroughs, Camden and Islington, in which most areas are classified as being deprived. But area-level deprivation is not always an indicator of individual SEC. In Camden , according to the Association of Public Health Observatories (2010a) 69% of people live in areas of high deprivation (fourth and fifth quintiles) and none live in an area of least deprivation (first quintile). In Islington 97.3% of people live in areas of high deprivation (The Association of Public Health Observatories, 2010b). This could give rise to the ecological fallacy (Schwartz, 1994) that occurs when relationships between variables that hold at an area level are assumed to hold at the individual level. To improve the NS-SEC (Office of National Statistics, 2010) results I used information about patients' occupation from the baseline questionnaire to reclassify some participants. However sometimes there was insufficient information to do so.

6.7 Clinical and research implications

Clinical: This study suggested that modifications could be made in clinical practice to reduce the intensity of ICU interventions, to use inotropes and sedatives judiciously and to prescribe appropriate opiate analgesia and steroids, and that these may improve psychological outcome. In the meantime, patients should be routinely assessed for psychological distress and offered support in ICU and post-discharge, as has now been recommended by the NICE guideline on rehabilitation for intensive care patients (Tan et al., 2009). At present few ICUs have access to a psychologist, so psychological assessment and support would have to be provided by nursing staff. Nursing staff may feel they do not have adequate time or training for this role, and consideration should be given to a possible need for health psychology input in ICUs to provide support to patients as well as training and research consultancy for staff.

Research: Ideally a much larger prospective study should be carried out to confirm the strongest clinical, psychological and socio-economic risk factors identified in this study. Data collection could include biological and physiological markers in order to assess possible biological mechanisms underlying the associations observed (i.e. between TISS and PTSD; benzodiazepines and depression; inotropes and anxiety; steroids and PCS and the suspected role of opioids). Follow-up should take place at three months, as in this study, but be repeated again at nine months or a year to detect the prevalence of long-term psychological morbidity or possible late-onset PTSD (occurring after six months; APA, 1994). It would be desirable to include physical as well as psychological outcomes. Studies of ICU survivors involving

functional imaging of the brain using PET (positron emission tomography) scans would be of particular interest.

As the cohort study showed that level 3 ICU patients have considerable psychological morbidity both during and after intensive care, interventions to reduce levels of morbidity should be evaluated. Two types of intervention would be possible. A psychological intervention would involve assessment of all patients by a health psychologist in the ICU (using a tailored, validated version of the ICU baseline questionnaire from this study) followed up with psychological support in the ICU, on the ward after ICU discharge and after discharge from hospital for those in need. Examples of psychological support might include anxiety management in the ICU, reassurance about unexpected ICU symptoms such as hallucinations after transfer to the general wards, and management of intrusive memories or depression during the recovery period at home. Patients with poor psychosocial outcomes at three months are likely to make a worse physical as well as psychological recovery (Ballenger et al., 2000; Stansfeld et al., 1993). This could lead to increased hospital re-admissions as well as GP visits to access mental health services. Therefore preventative psychological interventions could prove cost-effective as well as beneficial for patients. After piloting and testing the feasibility of such an intervention, it should be tested by a randomised controlled trial. Two strategies would be possible. Either patients could be psychologically assessed in ICU and those affected could be randomised to the new intervention or to usual care; or a cluster randomised controlled trial would be designed in which some ICUs delivered the psychological intervention and others did not.

A second type of intervention would be a medical and pharmaceutical trial involving comparisons of different drug regimes. Psychological outcomes of patients receiving an "optimal" drug regime would be compared with those from patients receiving usual care. An optimal drug regime might involve adequate opioid analgesia combined with the judicious use of benzodiazepines and ionotropes, and steroid use where indicated. It would be designed with the help of pharmacists and clinicians and be informed by existing knowledge of the effects of different sedatives and analgesics.

6.8 Conclusion

Previous research suggested that intensive care patients suffered from considerable psychological morbidity and poor HRQL in the months after ICU. However accurate rates of prevalence had not been established. Furthermore very few risk factors for post-ICU morbidity had been properly tested or identified. Building on a systematic

review of 45 previous studies, my study was the first prospective cohort study that tested for associations between a comprehensive set of clinical, psychological and socio-demographic risk factors and a full range of relevant psycho-social outcomes. Using sensible and appropriate methods I estimated that **44%** of consecutive level 3 ICU patients had clinical anxiety, **46%** had clinical depression, and that **27%** had PTSD (with a further 17% who had significant symptoms of PTSD) three months after ICU. In total, **55%** of patients suffered from either PTSD, anxiety or depression after leaving intensive care. This compared to 16% of patients who had a history of psychological problems before admission to ICU.

This is the first study to identify a group of clinical factors that were strongly associated with post-ICU distress. They included TISS score, sepsis biomarker scores, number of organs supported and increasing number of drug groups given. As well as finding a strong association between amount of intensive care received and outcomes, I identified specific risk factors such as duration of sedation for PTSD, benzodiazepines for depression, inotropes for anxiety and mental HRQL, and steroids and anaesthetics for better physical HRQL. Another new finding was that patients' socio-economic circumstances were found to predict anxiety, depression and mental HRQL in ICU survivors. Adverse outcomes were also strongly predicted by patients' acute reactions during ICU, including mood disturbance, extreme physical stress, delirium, control, illness beliefs, amnesia and intrusive memories. More sophisticated analysis showed that clinical factors had both a direct effect on three-month outcomes and an indirect effect as they were partially mediated by acute psychological reactions in the ICU. It is of particular interest that sepsis and delirium were found to be risk factors for post-ICU PTSD and other psychological outcomes as this had not been shown before. These findings have important clinical and research implications and point to a need for interventions to reduce the harmful psychological impact of intensive care and to help patients who suffer extreme psychological distress.

Chapter 7 Memory study

7.1 Introduction

Admission to ICU may have bizarre effects on memory. A number of alterations and distortions to memory processes have been reported in the psychological literature on intensive care. As many patients are sedated or unconscious when admitted to intensive care, few remember their admission to the unit, which adds to their disorientation when they wake up to find themselves immobilised in a strange environment (Capuzzo, 2001). Subsequently many patients say they remember little about the time they spent in intensive care (Compton, 1991). As they begin to recover and leave the ICU, patients often puzzle over frustrating gaps in their memory (Griffiths & Jones, 2001), while they try to recreate a meaningful narrative of what happened to them in intensive care. At the same time some patients start to be troubled by insistent thoughts or memories about intensive care. Even though the patient believes they remember little of intensive care, memories of experiences, some that occurred while they were unconscious, start coming back to them (Rundshagen et al., 2002).

As well as "factual" memories of realistic events that could have occurred in intensive care, they may also have "unreal" memories of hallucinations or bizarre dreams that they had in intensive care (Jones et al., 2001). Both types of memories are known to occur at two and eight weeks after discharge (Jones et al., 2001) and even several years later (Schelling et al., 1998). As discussed in earlier chapters, PTSD and other psychological morbidity are highly prevalent in post-ICU patients. My cohort study found high levels of PTSD symptoms in 27% of patients as well as depression in 46% and anxiety in 44% three months after leaving intensive care. The prevalence of PTSD is consistent with a review (Green, 1994) that found that around 30% of people get PTSD after a trauma. Green (1994) also found that half of the 30% are likely to have PTSD for a long time.

The question arises whether the high prevalence of psychological morbidity after intensive care is related to the memory effects that appear to occur within intensive care due to a variety of illness and treatment factors. It is well known that alterations to memory processes are found in several psychological disorders. A significant stable association between memory impairment and depression was found by a meta-analysis of 147 studies of recall or recognition in depressed and non-depressed samples (Burt et al., 1995). Evidence has also been found of hippocampal volume reduction in major depression (Bremner et al., 2000b). As the hippocampus is believed to play an important role in the laying down of coherent

memories, hippocampal dysfunction could contribute to the well-known deficits in declarative memory found in depression.

A range of unusual memory phenomena are thought to be the most characteristic symptoms of PTSD (Brewin & Holmes, 2003). Findings from my cohort study (reported in chapter five) suggested that two types of ICU memory effect - a) having very little memory for ICU and b) experiencing intrusive memories of the ICU around the time of ICU discharge - were significant predictors of PTSD, depression and anxiety. There were highly significant differences of seven points on the PTSD scale and 6.05 points on the depression scale between patients with and without memory of the ICU. Patients who had early intrusive memories of the ICU were 9.5 points higher on the PTSD scale and 7.10 points higher for depression. Mediational analysis suggested that both memory variables partially mediated the relationships between clinical factors such as intensity of treatment and number of days of sedation, and PTSD at three months. It is already known that amnesia for details of a traumatic event is a symptom of PTSD (American Psychiatric Association, 1994). Furthermore, an initial period of intrusive thoughts/memories immediately after a trauma was described as a sign that a fear network (a network of memories linking details about the trauma with cognitive, behavioural and physiological responses) was being activated (Creamer et al., 1992). Creamer et al. (1992) suggested that initial intrusions would be a predictor of successful recovery, whereas other studies found that prior levels of high intrusion were predictive of a worse outcome (McFarlane, 1989).

In my third study, I wanted to explore further the effects of ICU on memory, and the memory processes that may underlie the development of ICU-related PTSD. I decided to interview patients who were troubled by intrusive ICU-related memories at three months about the nature and content of these memories. Before reporting this study, I will summarise previous findings about the effects of intensive care on memory, possible causes for the memory effects, and existing knowledge about memory effects in PTSD after other sorts of trauma.

7.1.1 Memory of intensive care

Studies of memory in intensive care fall into two categories; those that tried to find out to what extent patients could recall the ICU and what ICU experiences they recalled; and those that were interested in categorising types of memory such as "traumatic", "factual" or "delusional" (based on hallucinations or other unreal experiences) memories. Many of the latter studies were designed to find out which types of memory were predictors of PTSD. In line with anecdotal accounts and clinical beliefs, a number of early studies showed that patients had little or no

memory for actual events during the intensive care stay (Compton, 1991; Jones et al., 1979). In my cohort study, 45.9% of patients said that they remembered very little of their stay in the ICU while 29.6% remembered some of the time, and only 24.5% remembered most of the time. Only 34% of the cohort could remember being admitted to the ICU.

However, although patients often believe they remember little about their ICU experience, when they are questioned about specific memories they appear to have some recall. A number of studies assessed patients' recall around the time of discharge from the ICU. In Rotondi et al. (2002) 67% of a cohort of 150 patients who received mechanical ventilation for more than 48 hours remembered either the endo-tracheal tube or other aspects of being in intensive care. When interviewed in the hospital shortly after their discharge from ICU, they remembered the ICU experiences which had bothered them most, such as pain, anxiety, lack of sleep, nightmares and loneliness. In a qualitative study by Green (1996) only around eight per cent of patients who were interviewed 48 hours after ICU discharge had no recollection of the ICU at all. Others had quite vivid recollections, mainly of pain, the presence of tubes, panic or fear, and of not knowing where they were.

Other studies examined patients' long-term recall months or years after leaving ICU. In a study of patient's recall two years after the ICU (Roberts et al., 2007) 83% of them still had factual memories of the ICU. The factual memories were predominantly about procedures (including "breathing pipe", CPAP mask, catheters, dialysis, dressing changes) comfort (including pain, thirst, fear, security) and staff (lovely nurse, hand-holding, snappy answers). Schelling et al. (1998) looked specifically at recall of "traumatic" memories. They found that 43% of patients recalled no or one traumatic experience (anxiety, respiratory distress, pain or nightmares) whereas 57% remembered multiple traumatic experiences. This study took place at varying times from six months to up to ten years after the ICU.

In a study of 289 ICU patients, Rundshagen et al. (2002) discovered that 35% of patients had memories from the time before they regained consciousness in the ICU. Around 17% remembered "real" events such as having an endo-tracheal tube or being on the ventilator. A further 21.1% of patients remembered dreams, nightmares and hallucinations from this time. Jones et al., (2001) was the first study to focus particularly on the distinction between factual and delusional memories, the latter being defined as memories of vivid nightmares, hallucinations or paranoid delusions. They assessed memory at two weeks after ICU discharge and found that 20% of patients had delusional memories alone; 18% had factual memories alone; 55.5% had both types of memory; and only 6.5% had no

memories. Furthermore delusional memories were retained over time, whereas factual recall of ICU events declined (16% of patients at two weeks failed to recall any factual event, which increased to 37% of patients at eight weeks). Having delusional memories without recall of factual events at two weeks was found to be a predictor of possible PTSD symptoms at eight weeks ($p<.0001$).

Jones et al., (2001) hypothesised that there were two processes leading to delusional memories. The first was a general dampening of memory along with confusional state, caused by treatment and illness effects such as delirium, sleep deprivation and drugs known to affect memory such as opiates, benzodiazepines and corticosteroids administered in the ICU. Secondly they proposed that physical constraints and social isolation experienced by ICU patients caused an attentional shift away from external events and enhanced memory for internal events (such as hypnagogic hallucinations).

Jones et al., (2001) was a small study of 30 fully followed-up patients. Two further studies found that early delusional memories of the ICU were a risk factor for PTSD (Jones et al., 2003; Jones et al., 2007) Additionally Rattray (2005) found that a lack of factual recall of ICU was a predictor for emotional distress at six or 12 months. Roberts & Richard (2007) found that factual memories were significantly less common in delirious patients than non-delirious patients (66% vs 96%; OR 0.09, 95% CI: 0.01-0.85, $p=0.035$). These findings began to suggest a hypothetical pathway leading from delirious symptoms such as hallucinations in the ICU to an absence of factual memories along with the presence of delusional memories post-discharge, to the later development of PTSD.

However other studies did not support this hypothesis. A high quality study of 226 intubated patients by Samuelson (2007), found that psychological distress two months after the ICU was not predicted by delusional memories or by amnesia for the ICU. In Schelling (1998), patients with multiple traumatic memories were more likely to have PTSD symptoms than patients with one or none ($p=0.007$). The traumatic memory scale used by Schelling (1998) and Stoll et al. (2000), included three types of factual memory (pain, respiratory distress, anxiety) and one type of delusional memory (nightmares). In my cohort study, although I found a difference in outcome between those with and without intrusive memories at discharge from the ICU, there was no difference in outcome between those whose intrusive memories were "unreal" (or delusional) or "factual" (mean difference in PTSD scores = 0.85; 95% CIs: -6.98, 8.68, $p=1.00$). There should also be a degree of scepticism about whether patients' "factual" memories genuinely were real or were

partly imagined, as there was no way of validating the reality of memories in mine or other studies.

The results of cross-tabulating the two memory variables in my cohort study (memory for ICU and early intrusions about ICU) could shed light on the question of how and why PTSD develops in ICU patients. As can be seen in table 1.1, of the 45 patients who said they had very little memory of the ICU, 62.2% of them had intrusive memories about intensive care on the point of discharge from the unit. Among the 54 patients who remembered some or most of the ICU, only 38.9% of patients experienced intrusive thoughts. The chi square test was significant (p=0.021). This would suggest that having some conscious memory for real events in the ICU was to an extent protective against intrusive memories whereas having little conscious memory of the ICU was associated with the presence of intrusions. Research in several areas of cognitive psychology supports the view that information processing takes place at both conscious and non-conscious levels (Epstein, 1994). Memories from two different types of processing (perceptual and conceptual) is thought to be stored in different locations or by different codes (Tulving & Schacter, 1990). It may be that these distinctions (which may underlie normal and intrusive memories) are more important than the distinction between unreal and real memories in predicting psychological outcome after ICU

Table 7.1: cross tabulation of ICU memory and ICU intrusive memory variables

			Intrusions - yes or no		Total
			No	Yes	
ICU memory	some or most memory of ICU	Count	33	21	54
		% within ICU memory	61.1%	**38.9%**	100.0%
	v little memory of ICU	Count	17	28	45
		% within ICU memory	37.8%	**62.2%**	100.0%
Total		Count	50	49	99
		% within ICU memory	50.5%	49.5%	100.0%

7.1.2 PTSD and memory systems

These results suggest dual pathways for post-ICU memory and are consistent with the dual representation theory of PTSD (Brewin & Holmes, 2003) that was outlined in chapter three. According to this theory, two different types of memory system work in parallel using different pathways in the brain. At its most basic the theory posits that normal autobiographical memories are processed by the hippocampus which is responsible for laying down integrated, coherent representations of experience that are registered by the conscious brain (Brewin, 2001). However another type of more detailed, emotional memory may occur which bypasses the hippocampus, taking a direct route to the amygdala, an emotional centre of the

brain that has an important role in activating fear responses (LeDoux, 1996). These emotional memories may come from a lower level processing of sights, sounds and physical sensations that were not consciously registered when the event occurred. Memories like this, such as intrusive memories, including flash-backs, may be triggered automatically by perceptual reminders of events. There is increasing evidence that intense stress accompanied by high levels of cortisol can impair the hippocampus and encourage processing by the amygdala (e.g. Elzinga & Bremner, 2002). The narrowing of attention brought about by extreme stress as well as loss of hippocampal function means that less information about a traumatic event is stored in a consciously available form (Brewin & Holmes, 2003).

This theory has recently been updated to incorporate the latest neuroscience relating to memory (Brewin et al., 2010). Key distinctions between types of memory that are relevant to the dual theory have been refined. One of these is the distinction between voluntary and involuntary memory (Berntsen & Rubin, 2008). In contrast to voluntary memory, which is a strategic effortful process, involuntary memory is seen as an associative process that is prompted by cues in the environment. A new distinction has also been made between autobiographical and episodic memory, two types of memory that were traditionally seen as one system. However Conway (2005) has proposed that they are separate. Episodic memory is seen as an image-based system retaining sensory and perceptual knowledge in the posterior temporo-occipital areas for fairly brief periods. To be retained for longer, it needs to be integrated with longer-term autobiographical memory, a conceptually organised system located in pre-frontal areas. Other key findings concern the neural mechanisms behind fearful memories. Involuntary fearful responses, such as freezing in rodents or the "startle" response in humans, depend on molecular processes in the amygdala (Monfils et al., 2009). These processes connect low-level sensory representations to internal representations of emotional states, probably supported by the insula.

In the revised dual representation theory, (Brewin et al., 2010) episodic memory is equated with low-level sensation-based memory and is renamed as S-memory, with its representations known as S-reps. Flashbacks in PTSD are examples of involuntarily recalled S-reps. In a healthy individual, S-reps for an event are associated with abstract contextual memories (C-reps in C-memory) in the medial-temporal lobe (MTL). This connection prevents memories from being re-experienced and provides top-down control of S-memories (such as deliberate suppression if required) from the pre-frontal cortex. But in PTSD this connection is weakened, so that strong sensation-bound memories (S-reps) occur without top-down control

from the C-system to provide contextualisation. Therefore vivid visual representations are activated and re-experienced as if happening in the present.

It is currently believed that PTSD involves two different types of memory deficit. The first relates to impaired or fragmentary recall of the trauma (which may be explained by the dual representation theory, as above). However deficits in general memory functioning have also been found in PTSD patients. Deficits have been found in verbal and nonverbal memory and learning (Bremner et al., 2000), attention (Vasterling et al., 2002), and executive function (Beckham et al., 1998).

7.1.3 Cognitive deficits after intensive care

As we saw in earlier chapters, three studies found that cognitive deficits including memory impairment were present in more than 30% of general ICU patients six months after ICU discharge. In one of these, a neuropsychological study of 34 mechanically ventilated patients in a medical intensive care unit (Jackson et al., 2003), 32% of patients were found to have significant cognitive impairment 6 months after intensive care. Deficits were found in several domains including psychomotor speed, visual and working memory, verbal fluency and visuo-construction. The rate of neuropsychological deficits in the ICU population was higher than population norms for mild dementia. A neuro-cognitive evaluation of 32 critically ill medical patients who underwent mechanical ventilation for five days or more, found that 91% of patients at hospital discharge and 41% at 6 months, had cognitive impairments. The cognitive functions primarily affected were attention, memory, mental processing speed and executive function (Hopkins et al., 2005). In a study of 45 general ICU patients, Sukantarat (2005) found that three months after ICU 35% of the cohort scored at or below the level of the lowest 5% of the normal population on tests of executive function and fluid intelligence. At nine months, cognitive performance remained below normal but there had been improvements since three months. In an informal review of the evidence from nine cohorts of ICU patients (mainly with ARDS), Hopkins & Brett (2005) concluded that neuro-cognitive impairments were extremely common at hospital discharge, and that despite improvement between six and 12 months, many patients had significant cognitive impairment at time-points between six months and six years. Domains most commonly affected were memory, attention and executive function.

Deficits in general memory functioning, in addition to other cognitive problems, are therefore not uncommon after the ICU. A case could be made that the formation of intrusive memories under conditions of extreme stress, along with general deficits in memory functioning, combine to make former ICU patients highly vulnerable to developing PTSD. Memory impairments that have been found in ICU patients such

as problems with psychomotor speed, attention and verbal memory, may also contribute to the high prevalence of depression after intensive care (Marazziti et al., 2010).

Jones et al., (2000) discussed many ICU factors that could contribute to fragmented memory and amnesia including delirium and sleep disturbance; physical restraint, visual deprivation and social isolation; and therapeutic drugs including anaesthetics such as propofol, benzodiazepines such as midazolam, opiates, adrenaline and corticosteroids. Many of these factors and their effects on the brain were considered in chapter three; However it is worth considering further the effects that many ICU drugs might have on memory.

According to Ghoneim (2004b) a wide variety of drugs, including benzodiazepines, anticholinergic agents, anaesthetics and others impair memory. Many of these amnesic drugs are used in the ICU. Although the drugs have a wide diversity of chemical structures, they seem to produce similar profiles of memory impairment. Some general characteristics of amnesic drugs listed by Ghoneim (2004b) are:

- Acquisition of new information is impeded – anterograde amnesia
- Episodic but not semantic memory is impaired
- Explicit memory is much more impaired than implicit memory
- Learning of skills or procedures usually remains intact
- The degree of amnesia is related to dosage, additive effects of other drugs and ageing

These effects fit in with the evidence discussed above that conscious contextualised memory processing may be impaired in the ICU, while unconscious emotional memories are unaffected. This phenomenon may encourage the production of fragmentary, intrusive memories that break through into normal consciousness. But are there also any features of the action of ICU drugs that would contribute to the persistence of unreal (delusional) as opposed to real (factual) memories? Little is known about this area but in some studies it was noticed that when patients who had taken benzodiazepines (as with marijuana) were given memory tests they were more likely than others to falsely recall words that were not on the original list (Gorissen et al., 1998; Mewaldt & Ghoneim, 1979). It is possible that the action of benzodiazepines increased irrelevant associations from semantic memory or led to disinhibition in recall. Could this be linked to the memory distortions that occur in post-ICU patients, including the production of delusional memories?

7.1.4 Parallels with post-psychosis PTSD

The experience of unreal (delusional) intrusive memories after intensive care has a parallel in the literature on post-psychotic PTSD. Acute psychosis is defined as the presence of delusions, hallucinations or marked formal thought disorder (World Health Organisation, 1990). Although the reasons for experiencing hallucinations and delusions are different for intensive care and psychotic patients, the distress they cause and subsequent mental impact may be similar. Shaner & Eth (1989) reported a PTSD-like reaction in a patient with schizophrenia and McGorry et al. (1989) found that the prevalence of PTSD after admission for an acute psychotic episode was 46% at four months and 35% at 11 months. Hypotheses for the aetiology of post-psychosis PTSD were that persecutory delusions would be associated with post-traumatic reactions because they were particularly frightening (Shaw et al., 2002), and that hospitalisation experiences (Shaw et al., 1997) such as seclusion, receiving involuntary treatment and ECT would be potentially traumatic. A study by Meyer et al. (1999) found that delusional symptoms were more traumatic than the coercive measures used to control them, as 69% of traumatic symptoms were related to psychosis and 24% to hospitalisation. In Shaw et al. (2002) memories of persecutory delusions and visual hallucinations were among the intrusions found with greatest frequency in a post-psychotic PTSD group compared to a non-PTSD group.

The brief review of the literature on memory in intensive care above (section 7.1.1) showed that findings were sparse and inconsistent. Most of the studies tended to define memories in different ways, to measure memories in different ways and at different times. It was not always clear whether memories were predictors or outcomes. Different authors focussed on traumatic memories, general recall, factual memories or delusional memories. As my cohort study found the most important distinction to be between those who had intrusive memories of the ICU (probably linked to emotional, involuntary, sensation-based memory systems) at the point of discharge from the ICU, and those who had no intrusive memories, I decided to carry out a further study to discover more about intrusive memories of the ICU. I wanted to look at the persistence and content of these memories at three months. As there has been little success to date in analysing the effect of patients' memories on ICU outcomes using questionnaires, I decided to carry out a small interview study. The study was developed with guidance from a leading expert on psychological processes in PTSD, Christopher Brewin, professor of clinical psychology at UCL. A structured interview that has been used with other PTSD populations (Patel et al., 2007) was used for the first time to examine the content, vividness, frequency and emotions associated with patients' memories of intensive care.

7.2 Methods

7.2.1 Aims

(i) To investigate the nature and content of intrusive memories of intensive care that patients experienced in the months after discharge from intensive care.
(ii) To quantify levels of distress and impairment associated with post-ICU intrusive memories.
(iii) To find out if patients require support in managing intrusive memories after intensive care, and what types of support would be helpful.

7.2.2 Participants

A sub-group from the main cohort of ICU patients and from the pilot of the follow-up study was interviewed for this study. Patients were invited to participate in this study if they had positive scores (2 or 3 out of 3) on the first or second items of the PDS (Foa et al., 1997):

1. Have you had upsetting thoughts or images about your time in intensive care that came into your head when you didn't want them to?

2. *Have you had bad dreams or nightmares about your time in intensive care?*

A total of 26 participants from the cohort study had these scores. Three patients from the pilot follow-up study were also eligible for the interview study. Of the 29 patients who were therefore eligible to participate in the study, 12 were not recruited. Five of them declined, either because they were physically ill around the time of the interviews, or because they found it upsetting to talk about the memories and were trying to put the experience behind them. Three patients did not reply to messages about the study, and one patient did not turn up for a pre-arranged meeting. One further patient agreed to participate but when we spoke told me that he was no longer bothered by the memories at all. I did not manage to contact the last two patients before closing the study. However I already had a sample of 17, well within my projected sample size of 10-20 patients.

7.2.3 Procedure

When I received the postal follow-up questionnaires for the cohort study about three months after discharge from ICU, I phoned participants who gave a positive response to items 1 or 2 on the PDS, explained the memory study to them and asked them if they would be willing to do a phone interview with me about the nature of their memories of the ICU. This study had been described in the PIS they received in intensive care, although it is unlikely that any of them remembered it. If they agreed, I wrote them a letter enclosing a copy of the interview (appendix 14) and reminding them of the date and time that I would phone them. I then phoned, asked them to have their copy of the interview in front of them and carried out the

interview. I began by asking them to focus on two main memories of the ICU (if they had any). I took notes on their description of the memories, and marked their ratings scales with them. Conversations were tape recorded after seeking their permission. The length of time taken for interviews ranged from 30 minutes (as expected) to one and a half hours (as some patients found they had a lot to say about their memories). Two patients filled the interview form in on receipt and sent it back to me. This was a less successful method than carrying out an interview over the phone, and I phoned them in order to clarify their answers. The average time between ICU discharge and the interview was five months (range four to eight months). I will call the time at which interviews were carried out time three.

7.2.4 Measure

The Intrusions Interview (Patel et al., 2007). This is a structured interview designed to elicit the presence and content of intrusive memories, images and thoughts about a trauma. For simplicity I asked only about intrusive memories. I also adapted the interview to refer specifically to memories of intensive care (see appendix 14 for my version of the Full Intrusions Interview). It should take about 30 minutes to administer. I asked patients if they had any spontaneous memories of their time in intensive care that came to mind repeatedly over the past week. If the last week was exceptional they were asked about a typical recent week. Only the two most frequent and distressing memories were explored further in the interview. Patients were asked to describe the content of their memories in as much detail as possible. Memories were defined as visual pictures of events that happened to the participant. Ratings scales were completed to assess the frequency and duration of each memory, vividness of the memory, emotions accompanying the memory, sense of "nowness" and re-experiencing of physical sensations and emotions that were present in the ICU. The impact of the memory was assessed by rating interference with daily activities, uncontrollability of the memory and distress caused by the memory in the past week. I made some further adaptations to the interview. First in order to simplify ratings that were being done over the phone, patients were given a choice of responses (e.g. not at all, a little, somewhat, very much so) rather than rating their experience from 0 to 100. Items were scored from 0-2 where three response options were given, or 0-3 if four response options were given.

I also added a section on "help" with intrusive memories of the ICU as I was interested to find out if patients recovering at home had wanted or been able to get help with these memories if they found them distressing. I asked:

1. Do you feel you need some help with these memories?

2. Have you been to the ICU follow-up clinic? Did it help with the memories?
2. Have you tried to get any other type of help? If so, give details.
4. What kind of help would you ideally like?

7.2.5 Ethics

Several patients felt they were becoming quite upset during the interview because it reminded them of memories or activated memories. I found that having the "help" section at the end of the interview was useful because it distracted their attention from the memories and brought us back to a more normal type of conversation. I would check with them several times that they were feeling "OK" and chat to them about lighter subjects before drawing the conversation to a close. If they felt they needed help with their intrusive memories I would offer to put them in touch with the follow-up clinic to get an appointment, or discuss other ways of getting help such as contacting their GPs if that was their preference.

7.2.6 Analysis

i) Content of memories The results of the qualitative section of the intrusions interview were analysed using a simple type of content analysis as recommended by Patel et al. (2007) in which all memories were assigned to particular categories. In the present study categories were not pre-decided. As little is known about the type of intrusive memories experienced by patients in the months after intensive care, it was important that categories should emerge from, rather than be imposed on patients' interviews. Therefore I carefully scrutinised all seventeen interviews and extracted the most common categories. This initial analysis revealed a clear distinction between intrusive memories of hallucinations and delusions experienced in the ICU (which I labelled unreal memories rather than delusional memories) and memories of real events in the ICU (labelled factual memories). Results of the content analysis are seen in table 6.4. First, the number of memories or images described and the types of memories (**factual, unreal, both/unsure**) were recorded. Second, content was categorised in the following ways:

1. Memories of medical or care procedures
2. Memories of pain or physical horror
3. Memories of ICU environment
4. Memories of visual hallucinations or delusions
5. Memories concerning inter-personal relationships
6. Memories involving shame or guilt
7. Memories relating to control and information
8. Memories concerning death and the afterlife.

ii) Characteristics of memories

Results for characteristics of memories such as vividness, associated emotions, "nowness", duration, frequency, distress, uncontrollability and interference in daily life were calculated as mean scores out of three with standard deviations, and then multiplied by 100 to give percentages, to aid comprehension.

iii) Help

Content analysis was used to interpret the four questions about patients' perceived need for help with intrusive memories and help-seeking.

7.2.7 Statistical analysis

Although this was a small interview study designed to generate rather than test hypotheses, a limited amount of statistical analysis was carried out to look for possible associations between memory data from the interviews, and previously collected data such as delirium at time one, intrusive memories at time one and PTSD at time two. However I recognised that the study was not powered to detect these associations.

7.3 Results

7.3.1 Socio demographic and clinical characteristics of participants

In table 6.2 it can be seen that the 17 participants in the memory study were younger than the rest of the original ICU cohort (53 vs 58 years), more likely to be women (53% vs 47%) and more likely to be in the most deprived quintile of the population (60% vs 33%). Their average illness severity score at admission to the ICU (19.27) was approximately three points lower than the rest of the cohort, but the intensity of intervention score was the same (24.60). A much larger proportion of memory study participants were **surgical** admissions than the original cohort (53.4% v 34.2%). The respiratory system was the primary body system affected in 40% of the memory patients compared to 28.2%. Memory study participants spent fewer days in the ICU than the rest (11.40 vs 13.94) but had more days of sedation (3.80 v 3.13 days). More had received anxiolytics (73.3% vs 56.5%), inotropes (53.3% vs 45.9%) and opiates (100% vs 91.8%) than the original cohort. None of these comparisons were statistically significant, but the sample size was small.

Summary: The 17 participants in the memory study were younger, female and more likely to come from the most deprived quintile than the rest of the cohort. They were more likely to be surgical patients with the respiratory system as the primary body system involved. They were less sick on admission to the ICU but received as much therapeutic intervention and were sedated for longer than the rest of the cohort. More of them received anxiolytics, opiates and ionotropes.

7.3.2 Psychological scores of participants in ICU and at 3-month follow-up

In table 7.3 it can be seen that memory study participants had worse total mood disturbance in the ICU (32.13 vs 28.48), worse total ICU stress (36.6 vs 32.23) and a higher mean delirium score (8.53 vs 8.10) than the original cohort. The mean differences were not significant, probably due to the small sample size. The proportion who remembered very little of their ICU experience was about the same in both groups (46.7% vs 45.2%). Many more of the memory study participants had had intrusions while still in intensive care than the rest of the cohort (73.4% vs 45.2%). More memory study participants had also had "unreal" intrusions in ICU than the rest (33.4% vs 22.6%). Furthermore memory participants were significantly more distressed by the intrusive memories they experienced in intensive care than others (4.18 vs 1.89, p=0.004). At time two their PTSD scores were significantly higher than the rest (23.07 v 12.47) and their depression (25.70 vs 19.58) and anxiety scores were also higher (48.36 vs 42.88). The prevalence of PTSD (46.7% vs 23.5%), depression (60% vs 43.7%) and anxiety (66.7% vs 43.5%) was higher among these participants than the rest of the cohort.

Summary: The participants in this study had more psychological distress and problems with intrusive memories than the rest of the cohort at both time one and time two.

Table 7.2 Sociodemographic and clinical characteristics of interviewees

	age	Deprivation (IMD) a	Sex	Admission type b	Primary body system c	Apache II	TISS	LoS in ICU	Drugs	Days sedation
Mean - interviewees	**53.1**					**19.27**	**24.60**	**11.40**		**3.87**
SD	15.96					6.39	3.66	8.19		6.28
Minimum	29.00					12.00	18.00	2.00		0.00
Maximum	89.00					31.00	32.00	31.00		24.00
Mean – rest of cohort	**58**					**22.49**	**24.61**	**13.94**		**3.00**
p-significance of mean difference	0.314					0.109	0.993	0.551		0.468
N (%) - interviewees		**1** 2(13.3%) **2** 2(13.3%) **3** 2(13.3%) **5** 9(60%)	**Men** 7(46.7) **Women** 8(53.3)	**0** 4(26.7%) **1** 4(26.7%) **2** 7(46.7%)	**1** 6(40%) **2** 2(13.3%) **3** 5(33.3%)				**Anxiolytics** 11 (73.3) **Opiates** 15 (100%) **Ionotropes** 8 (53.3)	
N(%) - rest of cohort		**1** 10(12.2%) **2** 8(9.8%) **3** 20(24.4%) **4**17(20.7%) **5** 27(32.9%)	**Men** 45 (52.9%) **Women** 40 (47.1%)	**0** 19(22.4%) **1** 10(11.8%) **2** 56(65.9%)	**1** 24(28.2%) **2** 15(17.6%) **3** 24(28.2%)				**Anxiolytics** 48 (56.5%) **Opiates** 78(91.8%) **Ionotropes** 39 (45.9%)	
p-significance of mean difference		0.167	0.654	0.238	0.937				0.221,0.249 0.594	

a) Index Multiple Deprivation (Communities and Local Government, 2010). Quintile 1= least deprived, quintile 5=most deprived
b) Type of admission 0=elective surgical, 1=emergency surgical, 2=non surgical
c) Primary body system, 1=respiratory, 2=cardiovascular, 3=gastro-intestinal

Table 7.3: Interviewees' psychological scores at time one (discharge from ICU) and time two (3 months)

	Mood ICU	Stress ICU	Delirium ICU	Memory of ICU at discharge	ICU Intrusive memories (IMs) at discharge	Distress re IMs in ICU	PTSD 3m	Depression 3m	Anxiety 3m
Mean this study	**32.13**	**36.60**	**8.53**			**4.18**	**23.07**	**25.70**	**48.36**
SD	10.30	12.70	3.80			1.78	10.70	16.39	15.03
Poss min	0.00	00.00	0			0	0.00	0.00	0.00
Poss max	60.00	72.00	20			7	51.00	60.00	80.00
Mean rest of cohort	**28.48**	**32.23**	**8.10**			**1.89**	**12.47**	**19.58**	**42.88**
p-values	0.366	0.225	0.762			**0.004**	**0.001**	0.121	0.188
N(%)				**Very little** 7 (46.7%) **Some/most** 8 (53.3%)	**None** 4 (26.7%) **Factual** 6 (40%) **Unreal** 5 (33.4%)		Prevalence 46.7%	Prevalence 60%	Prevalence 66.7%
% Cohort				**Very little** 38 (45.2%) **Some/most** 46 (54.8%)	**None** 46 (54.8%) **Factual** 19(22.6%) **Unreal** 19(22.6%)		Prevalence 23.5%	Prevalence 43.7%	Prevalence 40.5%
p-values				0.918	0.128				

7.3.4. Content Analysis of Intrusive Memories

(i) Number of patients with factual or unreal intrusive memories at time of interview

Seven patients had only unreal intrusive memories.
Two patients had only factual intrusive memories.
Eight patients had both factual and unreal memories.

(ii) Number of types of memory

The total number of unreal memories recorded was **21.**
The total number of factual memories recorded was **15.**
The total number of mixed unreal/factual memories was **five**.

(iii) Content of Intrusive Memories

a) <u>memories of ICU procedures.</u>

Ten people had memories relating to ICU procedures.
Four memories concerned feelings of panic and suffocation when wearing ICU face masks. Patients remember fighting the masks and having them forced on them.
Three memories were related to tubes that were inserted in the ICU, either breathing tubes connected to the ventilator or feeding tubes.
Other memories about ICU procedures included choking during suctioning, having injections, having a stoma bag fitted, being constantly tested.

b) <u>memories of physical horror or pain</u>

Four people had memories or images of physical horror or pain.
Three memories were about being covered with blood or coughing up blood.
Two were about cannulae: Fear of having them inserted, or being covered in them.
Three memories were of extreme pain.

c) <u>memories about the ICU environment</u>

Five people had memories concerning the ICU environment.
In **four** of these memories, ordinary aspects of the ICU environment including noises, lights, machines or curtains kept turning into shapes, faces or animals. One memory was of the belief that the air conditioning unit was pumping out poison.
One environmental memory was a view from the window of the ICU that triggered a fear of the outside world.

Table 7.4: Nature and content of patients' intrusive memories at time of interview(T3) (see next three pages)

Name (Not real name)	**Number/ type memories: F=factual U=unreal B=both**	**Content: ICU Proced-ures**	**Content: Physical horror/ pain**	**Content: Environ-ment**	**Content: Hallucinations /delusions**	**Content: Inter-personal**	**Content: Shame Guilt**	**Content : Control/ Informed**	**Content: Death/ afterlife**
Anna	1. Money laundering **U** 2. Poisoned air-con **U** 3. Man with nurses harem **U** 4. Same man in her bed **U**			Air-con is morphine poisoning me. Refusing to drink or clean teeth.	Nurses after organs; doctors operating and taking patients' money. If you pay more you get more anesthetic.	Nurses dressing up, getting in bed with patient. Same man in my bed behind me.			
Franco	1.About to die **B** 2.Procedures **F**	Daily events in intensive care, pleasant or unpleasant							Ready to meet the Lord and souls of relatives. Mysteries of life.
Sally	1. Noise, lights, smells **B** 2. people saying "she is dying" **B**			Lights on/off all the time. Machines + alarms. Smells					Nurses, doctors saying I'm going to die
Colin	1. Coughing up blood **F** 2. Tube in neck **F** 3. Universal logo **U**	Coming round on the respirator. Feeling of choking during suctioning.	Having to cough up blood. Pain wakes me from coma when tube sticks in ambulance man's coat		Keep seeing psychedelic sign like Universal film logo– orange, yellow, blue,				
Karen	1. Dead, in purgatory **U** 2. Warning patient about a trial **U**				Am a prisoner tied down by tubes. Going to be killed. Nurses using a bay as mock courtroom to put patient on trial.		Embarra-ssment - shouting to patient to escape from trial		Already dead in purgatory

Name	Number/type memories	Proced-ures	Physical horror	Environ-ment	Hallucinations	Inter-personal	Shame Guilt	Control/ Informed	Death/ afterlife
John	1. Very detailed hallucination - nurses being paid to turn patients into zombies and kill them. **U**	Trigger: Nurses giving an injection to put me to sleep.			Pushed in trolley to basement of dying people. Family in abbot cloaks taking souls. Jumped out but ended back in ward.	Shaking feet at nurses to repel them.			In coffin; tell wife-she can remarry but she asks me to stay
Paul	1. Nurse shaving Indian boy **U** 2. Was paid assassin **U**				Going on bus in dressing gown to post office. Want nurse shaving Indian boy to shave me too. Fly to Brazil, shoot 3 people on roof then fly back		"I am guilty" – an assassin		
Dora	1. Hallucinations – several **U** 2. Endless procedures. 3. Isolation **F**	Refusing refit of feeding tube that punctured lung. Fighting mask. Pulling tubes.			Tropical beach bar. On a train at Checkpoint Charlie in Eastern bloc during WW2.	Feeling apart from visitors, unable to communic-ate and irritated.		Sense of dependen-cy. Having to ask for bedpans etc	Can't sleep or breathe, temper-ature up, down, think I'm dying
Aysha	1.Distress at nasal breathing tube **F**	Pain from tube	Pain from tube					Nurse making me keep tube but doctor removes it	
Raj	1. Row with wife **F** 2. Being attacked by religious cult **U** 3. Stomas bags **F**	Waking up to see nurse cutting up stoma bags. Nurse making me wear mask			Bahai cultists attacking me. Friend of mine ordering staff to sell NHS drugs to fund religion, lifestyle. I have to endorse it.	Re-stoma, nurse not nice or caring. Unsympa-thetic.	Tell wife to drive me home from UCH or "me and you are finished"	Didn't know I had a stoma bag.	

Name	Number/type memories	Proce-dures	Physical horror	Environ-ment	Hallucinations	Inter-personal	Shame Guilt	Control/ Informed	Death/ afterlife
Laura	1. Windows fear of life outside **F** 2. Told off by nurses **B** 3. Covered in cannulae **F**	Walking to window - v. weak. Prodded and poked	Covered in cannulae leaking. Swollen feet, felt removed from body	Seeing buildings - scared at life going on outside.		Calling for help.Told off, buzzer taken away			
Isaac	1. Square mask **F** 2. Hallucinatory visions **U**	Panicking about mask- had to be forced on.		Lights noise mixed up with unreal imagery	Lots of vivid shapes and colours. Ward looks like seaside posters.	Nurses' banter – finding it funny.			
Owen	1. In America, felt threat **U** 2. Violent fighting in Denmark **U**				1920s USA-kind people yet feel a threat. Also in Danish village avoiding fights	Youngest son in the dreams-makes me feel happy.			
Kate	1. Heard mum outside sobbing **U** 2. Puffins firing blood with plastic guns **U**				Puffins jumping out of curtains firing blood at me. Crazy birds jumping on bed laughing	Hearing voices from past, mum sobbing			Nurse between curtains saying "she's gone"
Nora	1. Face mask **F** 2. Having a tube inserted **F**	Suffocating with mask - air forced in fast	Fear /pain of tube going deep into artery				Double inconti-nence. Burden		
Magda	1 Begging to go to toilet **B** 2 V. pain **F** 3 Blood leak **F** 4 Nurse alien **U**	Extreme pain clean-ing "nappy rash" every few minutes	Screaming in extreme pain. Wake up covered in blood.		Nurse alien with staring eyes, head pecking up and down like chicken.	Nurses torturing me, putting knives in my bottom	Having to go to toilet in bed. Lack of dignity	Desperate to walk to toilet.Don't realise I can't walk.	
Terry	1 Killing Amy Winehouse **U** 2.Body parts **U** 3 Scary faces **U**			Bottle racks in turn into figures. Faces in curtains Animals running across floor	See Amy Wine-house and baby - car sliding into water. Staff stealing family's body parts. Porters take me to gas chamber.		I am respons-ible for death of AW - police are after me.		

(iii) Content of intensive memories continued….

d) memories of hallucinations and delusions

Twelve patients had memories of hallucinations or delusions.
Five were memories of persecutory delusions involving hospital staff. They were detailed, terrifying narratives about doctors and nurses stealing organs and money, and trying to kill patients or turn them into zombies. Imagery of emprisonment, trials, religious cults, poisoning and torture recurred.
Three memories were exotic foreign adventures. Two were frightening and violent.
Two memories were bizarre as well as frightening – one about Amy Winehouse and her baby drowning; one about puffins firing blood at the patient from plastic guns.
Two memories were simple sensory hallucinations of colours and shapes.
One memory was a frightening image of a nurse turning into an alien.

e) memories involving interpersonal relationships

Eleven memories involved interpersonal encounters or relationships.
Seven memories were about nurses: **three** were sexual or persecutory delusions, **three** were negative memories of nurses being unsympathetic, and **one** was a positive memory of hearing nurses bantering and finding it funny and enjoyable.
Three memories were about family members; **two** sad ones in which the patient felt distant from their family; **one** happy one in which they felt safe and close.
One memory was a sexual/persecutory delusion about another patient.

f) memories involving shame or guilt

Six memories were coloured by a sense of shame or guilt.
Two related to incontinence, **two** were about behaviour the patients felt had been inappropriate such as shouting, and **two** featured guilt as part of delusions.

g) memories about loss of control or information

Four memories related to loss of control or lack of information.
Two were about feeling dependent on staff for toileting. **One** was about a lack of information about stoma bags. **One** was about feeling in control, after persuading a doctor to remove an uncomfortable tube against the nurse's wishes.

h) death/afterlife

Six memories featured death. In **two** memories, people saw themselves as dead – one was in his coffin, one was in purgatory.
Three memories were snapshot images of doctors or nurses saying the patient was going to die (patients were unsure if this was real or imagined)
One memory was mystical; about many people preparing for the after-life.

7.3.5 Summary of content analysis of memories

Unreal intrusive memories of hallucinations or delusions were predominant among this group of patients. These included persecutory delusions, bizarre delusions and visual hallucinations. Most of the memories were extremely frightening and some were also coloured by a sense of shame, guilt or loss. Memories concerning interpersonal relationships were mainly persecutory or sad (due to a lack of sympathy or understanding from others). Factual memories were much less common than unreal memories. They were concerned with pain, fear of face-masks or tubes, or horror at blood and needles. In some memories real and unreal experiences were confused, as when features of the intensive care unit changed into unusual sights and sounds.

7.3.6 Ratings of features of intrusive memories

In this section ratings are given as mean scores out of 3 (except frequency, rated 1-4) and also as a percentage of 100. For other descriptive statistics see table 7.5. First memory was the one that patients chose to discuss first in the interview.

First memory: The first memory that patients chose to describe was very vivid and clear (mean =2.12, equivalent to **69%**). The most intense accompanying emotions were anxiety (1.65, equivalent to **55%**) and helplessness (1.89, **63%**). Sadness and anger were also present (1.18 or **39.3%** each). The extent to which the memory was felt to be re-experienced was scored 1.00 **(33%)**. Emotional re-experiencing was rated at 1.18 **(39.3%);** reliving physical sensations at 0.47 (**15.6%)**. The average duration of the memory was **5.86 minutes**. The frequency of experiencing memories was 1.75 **(44%)**. Interference with daily life was rated quite low at 0.65 **(22%)**. Memories were rated as 1.25 (**42%)** uncontrollable and caused much distress **(**1.75**, 58.3%).** Finally 47% of first memories were of hallucinatory or delusional experiences, 35% were of factual events, and 17% were a mixture of both. Therefore **64%** of first intrusive memories were wholly or partly unreal.

Second memory: Again the memory was very vivid **(**0.64**, 65%).** Most notable emotions accompanying the memory were anxiety **(**1.65, **55%)** and helplessness **(**1.93, **64.3%)**. The extent to which the memory was felt to be re-experienced (0.64, **21%**) was less than the first memory. Emotional re-living was rated as 0.93 **(31%)** and physical re-experiencing was 0.54 **(18%)**. The second memory was shorter than the first and lasted **2.32 minutes** on average. It was also less frequent (1.23,

33%). Interference was higher (0.71, **23%**), but memories were less uncontrollable (0.93, **31%**) and distressing (1.29, **43%**). Compared to first memories recalled, a higher proportion of second memories recalled were of factual events (40%). Therefore 60% of second memories recalled were wholly or partly unreal.

Prevalence of re-experiencing memories

Six out of 17 patients had a high rating (scores of either 2 or 3) for re-experiencing the first ICU memory as if it were happening to them now. **Nine** patients said the feeling of re-experiencing their memories had been much stronger in previous weeks, before the week of the interview. But this included two patients who rated re-experiencing at 2 out of 3 at the time of the interview. Therefore 13 (**76.4%)** of the 17 patients interviewed for the memory study had a strong sense of re-experiencing their main memory during the week of their interview or in the weeks before the interview.

Table 7.5 Ratings for characteristics of post-ICU intrusive memories at time of interview

	Vivid -ness	**Emotions associated with Intrusive Memories**	**Extent of reliving**	**Reliving emotion**	**Reliving physical**	**Duration of IMs now**	**Frequency of IMs now**	**Interf-erence**	**Control-lability**	**Distr-ess**	**Unreal Factual or both N %)**
Memory one Mean	2.12	Sad 1.18 Guilty 0.65 Ashamed 1.06 Angry 1.18 Anxious 1.65 Helpless 1.89	1.00	1.18	0.47	5.86	1.75	0.65	1.25	1.75	8 (47%) **U** 6 (35.%) **F** 3 (18%)**B**
SD	0.781		1.23	1.05	0.94	6.24	0.93	0.93	1.24	1.18	
Minimum	0	0	0	0	0	0.25	1 – once or twice weekly	0	0	0	
Max-imum	3	3	3	3	3	20	4 - many times a day	3	3	3	
Memory two Mean	1.93	Sad: 0.79 Guilt: 0.57 Shame: 0.64 Anger: 1.29 Anxious:1.65 Helpless:1.93	0.64	0.93	0.54	2.32	1.23	0.71	0.93	1.29	7 (46%) **U** 6(40%) **F** 2 (13%) **B**
SD	0.917		1.15	0.99	0.78	3.27	0.60	0.73	1.21	0.99	
Minimum		0	0	0	0	0.25	1	0	0	0	
Max-imum		3	3	3	3	10	4	3	3	3	

Table 7.6 Memory, delirium and intrusions in ICU, and intrusions and outcomes in the months after ICU

(U=Unreal, F=factual, B=both)

Name	Delirium at T1 (0-20)	Memory of ICU at T1	Intrusive memories of ICU at T1	Content of IMs at T1	Frequency of IMs at T1	Distress at IMs at T1	Number/Content of IMs at T3	PTSD score at 3m	Depression score at 3m	Anxiety score at 3m
Anna (4)	5.00	Some /most	None				1. Money laundering **U** 2. Poisoned air-con **U** 3/4. Man with harem **U**	9.00	5.00	40.00
Franco(10)	12.00	Some/ most	None				1. About to die **B** 2. Meaning of life **B**	18.00	37.78	73.33
Sally (9)	9.00	Some /most	Yes, **U**	Unreal voices no sense	2.00	5.00	1. Noise lights smells **B** 2. "She is dying" **B**	34.00	48.00	63.33
Colin (34)	5.00	V.little	Yes **F**	Tubes, shock, suctioning	2.00	3.00	1. Coughing up blood **F** 2. Tube in neck **F**	11.00	.00	30.00
Karen(39)	17.00	Some /most	Yes**, B**	CT scan, hallucinations	3.00	3.00	1. Being a prisoner **U** 2. Patient on trial **U**	32.00	26.00	56.67
John (44)	6.00	Some /most	Yes **U**	Dream noises	1.00	5.00	1. Nurses turning patients into zombies **U**	14.00	5.00	36.67
Paul (61)	5.00	V. little	Yes, **U**	Assassin, opium dens	1.00	5.00	1. Nurse shaving boy **U** 2. Was paid assassin **U**	36.00	28.00	30.00
Dora (48)	12.00	Some/ most	Yes **F**	Struggling to breathe. Fear	1.00	5.00	1. Hallucinations **U** 2. Endless procedures **F**	35.00	52.00	56.67
Aysha (57)	3.00	Some/ most	Yes **F**	Tubes, hard to breathe.	1.00	3.00	1. Pain from nasal Tube **F**	10.00	15.79	52.00
Raj (31)	10.00	V. little	Yes **U**	Trying to escape home in car	3.00	6.00	1. Row with wife **F** 2. Religious cults **U** 3. Stomas bags **F**	30.00	31.00	46.67
Laura (82)	7.00	V.little	Yes **F**	Procedures Conversations	4.00	5.00	1. Trying to walk. **F** 2. Told off by nurses **B** 3. Multiple cannulae **F**	16.00	13.00	30.00
Isaac(88)	11.00	Some/ most	None		.	.	1. Square mask **F** 2. Visual hallucination**U**	36.00	27.00	50.00
Owen (93)	11.00	V.little	Yes **F**	Operation went wrong	.	.	1 In US,felt threats **U** 2.Violence in Denmark	33.00	33.00	50.00
Kate (100)	5.00	V. little	None		.	.	1. Mum sobbing **U** 2. Puffins firing blood with plastic guns **U**	14.00	13.00	20.00
Nora (96)	10.00	V. little	Yes **F**	Mask pressure suffocation	3.00	6.00	1. Face mask **F** 2. Tubes inserted **F**	18.00	36.00	70.00
Magda	No data	No data	No data	No data	No data	No data	1. Begging for toilet **B** 2. pain **F** 3. Blood **F** 4. Nurse alien **U**	No data??		
Terry	No data	No data					1. Amy Winehouse **U** 2. Body parts **U** 3. Scary faces **U**			

7.3.7 Delirium, persistence of intrusive memories and psychological morbidity

Table 7.6 summarises data about delirium at T1, intrusive memories at T1 and T3 and psychological morbidity scores at T2. The presentation of the table suggested possible connections between these phenomena and prompted further analyses that I report in this section. The sample was too small to detect significant associations, and analyses were carried out with the sole purpose of identifying interesting trends that could suggest hypotheses to be tested in future.

a) Delirium and nature of memories

Looking across table 7.6 patients with higher rates of delirium at T1 appeared to have higher rates of psychological morbidity in T2. This fits in with results of the cohort study. Table 7.7 shows that patients with mixed unreal and factual memories at T3 had higher delirium scores at T1 (9.83) than patients with unreal memories only (8.17) or factual memories only (6.67).

Table 7.7 Nature of memories and delirium

Delirium score in ICU (0-20)	nature of memories after ICU
9.83 (2.64)	unreal and factual memories at T3
8.17 (3.51)	unreal memories only at T3
6.67 (4.92)	factual memories only at T3
p-value (Anova) =0.510	

b) Persistence of unreal memories/loss of factual memories

Table 7.8 shows that more patients had intrusive memories (of any type) at T3 than at T1 (15 vs 11). It also shows that by T3 the number of patients with factual memories only declined while patients with unreal memories (alone or mixed with factual memories) increased. Four patients who had no IMs at T1 had unreal memories at T3. Three of the six people who had factual memories at T1 had unreal memories at T3. The five patients with unreal memories at T1 still had unreal memories at T3.

Table 7.8 Change in memories over time

Number of patients with IMs at T1		Factual IMs only at T3	Unreal IMs only at T3	Unreal and factual IMs at T3
None	4	0	2	2
Factual IMs only	6	3	1	2
Unreal IMs only	4	0	2	2
Both unreal/factual	1	0	1	0
Total	15	3	6	6

c) Nature of memories and psychological morbidity

Patients with mixed unreal and factual memories at T3 had the worst mean scores for PTSD, depression and anxiety at 3 months (table 7.9). Patients with factual memories had the best (lowest) mean PTSD score. However patients with unreal memories only had the best (lowest) depression and anxiety scores.

Table 7.9 Types of memory and psychological morbidity

	PTSD Mean(SD)	Depression Mean(SD)	Anxiety Mean(SD)
Unreal memories only at T3	23.00(11.90)	18.33 (12.26)	38.89 (13.28)
Factual memories at T3	14.67 (4.16)	21.60 (12.55)	50.67(20.03)
unreal and factual at T3	27.33 (10.39)	32.63 (18.64)	53.33 (14.91)
p-value	0.262	0.286	0.273

d) Re-experiencing and psychological morbidity

Patients with high levels of re-experiencing an intrusive memory (scores of 2/3 at T3 or in previous weeks) had considerably higher PTSD, depression and anxiety scores (table 7.10) than patients who had low levels of re-experiencing (scores 0/1).

Table 7.10 Re-experiencing and psychological morbidity

	PTSD (mean, SDs)	Depression (mean,SD)	Anxiety (mean, SD)
High re-experiencing	26.73(10.02)	28.62(13.95)	49.27(12.86)
Low re-experiencing	13.00(3.92)	13.95(16.77)	40.83(23.15)
p-value	**0.002**	0.112	0.378

e) Characteristics of unreal v factual memories

In an analysis of characteristics of both types of memories (see table 7.11), unreal memories were more vivid than factual memories, lasted nearly four times longer, were associated with more guilt and shame, were more uncontrollable and interfered more with daily life. Factual memories involved more sense of re-experiencing, were shorter, were accompanied by more anxiety and caused more distress than unreal memories. (None of these differences were significant, probably due to the very small sample size). In some respects (re-experiencing, duration) the factual memories were more like typical PTSD flashbacks than the unreal memories. Yet, as seen above, those with unreal memories had higher PTSD scores.

Table 7.11: Characteristics of unreal v factual intrusive memories

	Unreal memory	Factual memory
vividness	2.33 (0.71)	1.88 (0.84)
anxiety	1.55 (0.88)	1.75 (1.16)
helplessness	1.89 ((1.05)	1.88 (1.25)
guilt	0.67 (1.32)	0.63 (0.92)
Shame	1.22 (1.30)	0.88 (1.36)
Re-experiencing	0.89 (0.93)	1.13 (1.44)
frequency	1.88 (0.99)	1.62 (0.92)
duration	8.26 (6.84) minutes	2.66 (3.77) minutes
Interference	0.78(0.97)	0.50(0.93)
uncontrollability	1.63(1.30)	0.88(1.13)
distress	1.63(1.06)	1.88(1.36)

f) ICU drugs and nature of IMs

A trend was found for a relationship between receiving benzodiazepines in the ICU and the nature of IMs at T3 (χ^2=5.25, 0.072). Of the benzodiazepine group 90% (nine) had unreal memories (with or without factual memories) compared to 60% (three) of the non-benzodiazepine group. Factual memories only were found in 10% (one) of the benzodiazepine group and 40% (two) of the non-benzodiazepine group. All patients (six) who had both unreal and factual memories were in the benzodiazepine group. No possible relationship was observed between opiates or inotropes at T1 and type of IM at T3.

7.3.8 Summary: Nature of memories and outcome

The patients who were most delirious in the ICU were most likely to have "unreal" memories at T3. Additionally patients who received benzodiazepines in ICU were more likely to have unreal IMs at T3. The number of total IMs increased between T1 and T3. Patients developed more unreal memories and fewer factual memories over time. Patients' factual memories at T3 often had the same memory content as at T1 (see table 7.6). The content of unreal memories was usually vague at T1 and more specific at T3. Patients with mixed unreal and factual memories had the worst scores for PTSD, anxiety and depression. Patients with unreal IMs only had lower depression and anxiety scores than patients with factual IMs, but patients with factual IMs had lower PTSD scores. However factual memories seemed to have more characteristics of PTSD flashbacks, as they were shorter with more sense of re-experiencing and more association with anxiety and distress. The unreal memories were longer, more vivid, associated with shame and were uncontrollable. Overall it seemed that patients with both unreal and factual intrusive memories at T3 had the worst outcomes.

7.4 Results: Help with management of intrusive memories after intensive care

The following is the content analysis of the answers patients gave to four questions about the need for help. Table 7.12 contains fuller quotations from patients.

1. Do you need help managing your intrusive memories of ICU?

Five wanted help now because they were still troubled by emotions, memories and nightmares.

Three did not want help right now but thought they had needed it during the first three months at home, or were likely to need it in future.

Nine did not want outside help with intrusive memories. **Two** of these said they could help themselves.

2. **Did you attend the ICU follow-up clinic and was it helpful for dealing with intrusive memories?**

Eight attended follow-up clinic. **Four** found it helpful. **Four** either did not talk about their memories at the clinic or did not find it helpful.

Nine did not attend the clinic. Of these, **two** would like to attend.

3. Have you tried to get help with intrusive memories from any other source?

Six have tried to get another form of professional help including seeing their GP, being referred to a counsellor by their GP, getting access to medical records via the GP, trauma counselling, occupational therapy or seeing the UCH psychologist. One patient had counselling and did not find it helpful; others had not yet seen their counsellor.

Four patients have been able to rely on help from their family or self-help.

Seven have had no other help: of these **one** would like to get help but did not know if any was available, and **one** now believes that he should have got help.

4. What kind of help would you like/would you have liked?

Four patients said none. **Three** said that talking to family or self-help was enough.

Nine people suggested forms of help and **one** woman thought there should be help but was unsure what it could be. The help suggested was specialist intensive care counselling when you get home; phone counselling when you get home; counselling arranged through the GP, help from the follow-up clinic, help from the medical team who treated you and seeing a psychiatrist. **Three** patients suggested that counselling about the effects of hallucinations and treatments would be most useful after transfer from the ICU to the ward.

In summary, eight patients tried to get help for intrusive memories. Three were fairly or very satisfied with the help they received. Five thought they still needed help with intrusive memories. Ten people thought help should be available for distressing post-ICU memories. Some patients said the most useful time for psychological support would be after intensive care discharge, either on the general or surgical wards, or soon after arriving home. The emphasis of support immediately after ICU discharge should be receiving information and reassurance about unusual ICU symptoms such as hallucinations; After hospital discharge, support should focus on intrusive memories and aspects of physical recovery. One patient who did not need help said she had been helped enormously by her interaction with nurses in the ICU, "They were lovely. It was chat, chat, chat all day long". Several patients mentioned that the help available from the follow-up clinic three or four months after discharge was too late for them.

Table 7.12 Content analysis: Patients' answers to help questions

Name	Do you need help for intrusive memories?	Did you attend ICU follow-up clinic? Was it helpful?	Have you tried to get other help for intrusive memories?	What kind of help would you like/have liked for this problem?
Magda	"Yes. This has changed my life. My personality has changed. I'm OK but go through periods when I'm very emotional. I would love to erase the memories."	Yes. "I found the leaflet useful, but the follow up clinic did not help. They just asked more questions."	She had trauma counselling at home and occupational therapy at work. She did not find them helpful.	"Specialist intensive care counselling when you first get home. That's when the impact hits you. I had severe insomnia, saw needles coming at me. Eight months on I still can't deal with it"
Terry	"Not at present. I'm getting my mind round it and beginning to cope.	Yes. "They tried to organise support locally but I went back into hospital so it didn't happen."	He tried to get help with hallucinations after ICU discharge. Left hospital before seeing psychologist.	"I would have liked anything available. Somebody over the phone would have been ideal. I don't like going back to UCH, it brings back memories"
Anna	"No. But if I get worse I might. The memories are not getting less. As I recover I'm thinking about them more and feeling more upset."	No.	No.	Her GP and her vascular surgeon would get her help if necessary. She feels adequately supported.
Franco	No. "Any problem can be solved with a positive approach."	No.	"No. I have to find the trouble with me and apply the right remedy."	"If one learns to control instinct and emotions one can be one's own master and help oneself in every situation."
Sally	No.	No.	Yes. Talking to family.	"Just talking to the family."
Colin	No	No	No	No
Karen	Yes.	"Yes. It was really helpful. I have a second appointment with them. That is sufficient.	She talked to her GP about it once. He was very supportive.	"Seeing the whole team at the FU clinic was very helpful. Hearing other people felt the same way helped."
Dora	"Yes. The memories are not far from my mind all the time."	Yes, twice. "I found it very useful and reassuring to see some of the doctors again. They recommended counselling for PTSD".	She talked to her GP and asked to see a counsellor. Now unsure - thinks counselling may be too general, too far removed from the specific experience.	"Help from someone who treated you. Help from the doctors who wrote the notes. Help with the fear of dying."
Paul	"I'm not sure. Will the memories just disappear? I don't get them as much as I did at first."	Yes. "I went to the clinic but didn't tell them about the memories. They said I was depressed."	Going to GP re-depression on advice of follow up clinic. Will tell GP about the memories.	"I'd like to speak to a psychiatrist to find out why the memories keep coming back. People should get help if memories are affecting them."
Isaac	No. "The memories are fading but I still panic about breathing".	Yes. Went to the clinic but didn't discuss the memories.	No	"Not really. I've just got to get on with it. I practise self cognitive therapy."

Raj	"I would have liked help. When I came home I kept the lights on for two months. I thought I'd be dragged back to ICU".	No. He has not heard from the follow up clinic but thinks it would have helped him.	No. But he thinks he needed counselling for the first two or three months.	"You need a therapist on the wards. I was anxious and angry but nobody asked." He needed help to cope with emotions and explanations about the effects of drugs
John	No.	No	No. He is "stern-minded and self-disciplined"	"Someone to talk to in hospital about the hallucinations. It would help to get it off your chest and explain to your family what you really went through.
Laura	No.	Follow up booklet was helpful. Went to follow up clinic. "It was helpful, but it came a bit too late. It would be more helpful to see the person who treated me.	Her GP has given her a photocopy of her medical records in ICU so she can fill in the memory gaps. This has helped a bit.	"The transfer to the ward was very distressing, I felt "dumped". I would have liked a visit from someone from ICU to chat about psychological effects. It is useful to have a timeline of what happened".
Kate	No	No	No	Doesn't need anything now. She says she was helped by the nurses in ICU who were "very nice, caring, what a team. I got talking to the nurse, it was chat, chat all day long."
Nora	Yes. "I didn't think I'd remember so much detail." She has nightmares about ICU and wakes up panicking and sweating.	No. Would like to go.	No. Not sure what could help her.	Thinks there should be help but she's not sure what it would be – she has too many physical problems including disability to focus on psychological help right now.
Owen	"No. I feel quite comfortable. I'm in my environment, I can do what I want."	Yes. "I was quite settled and I didn't need help. They asked me about memories and dreams and I said they weren't bothering me".	No	None
Aysha	No	No	No	None needed.

7.5 Discussion

7.5.1 Summary of findings

I interviewed 17 patients (15 from the cohort study; two from the pilot) who had intrusive memories about intensive care at three months. Interviewees were more likely to be young, female and from the most deprived areas, than others in the cohort study. During intensive care they were more likely to have received benzodiazepines, ionotropes and opiates, and had worse stress, mood and delirium scores than the rest of the cohort. None of these results were significant. Of the 15 cohort participants, eleven had already experienced intrusive memories of intensive care by the time of discharge from the ICU. Content analysis revealed a clear distinction between intrusive memories of hallucinations and delusions experienced in intensive care ("unreal memories"), and intrusive memories of real events that take place in intensive care ("factual memories"). However although "factual" memories were of real procedures that might happen in intensive care, we cannot be sure that the patients' memories are accurate. Early intrusive memories (at T1) were more likely to be factual; by T3 patients had fewer factual memories and more unreal or mixed unreal/factual memories.

Eight categories emerged from the content analysis of intrusive memories:

- Medical and care procedures
- Physical horror/pain
- ICU environment
- Visual hallucinations and delusions
- Inter-personal
- Shame and guilt
- Control and information
- Death and afterlife.

Ten people had factual memories concerning procedures or physical horror. Memories of **medical and care procedures** were mainly related to tight-fitting oxygen masks (CPAP masks) and endo-tracheal or naso-gastric tubes. Some remembered (or believed they remembered) resisting a mask being fitted and having it forced on them and associated it with feelings of panic and suffocation. Tubes were associated with discomfort and choking sensations. Memories of **physical horror** were of extreme pain, blood or being punctured all over by cannulae. The largest category (12 people) was of IMs of **delusions and hallucinations**. These were memories of persecutory and bizarre delusions or visual hallucinations of colours and shapes. The content of

delusions included medical staff as torturers or kidnappers, with patients as victims turned into zombies. Another category, **ICU environment**, also included mainly hallucinatory memories of real items such as curtains or bottles turning into faces, insects or animals. Lesser categories were memories focusing on interpersonal relationships (mainly negative) with nurses or family; memories intensely suffused with shame or guilt; memories about lack of control and information; and memories concerning thoughts or visions of death and the afterlife.

Patients also rated characteristics of their memories. Overall, memories were rated as very vivid and clear, frequent and long-lasting. They were uncontrollable, distressing and evoked feelings of anxiety and helplessness. Most patients said the memories had a strong sense of "nowness" either around the time of interview or in previous weeks. Factual and unreal memories had some different characteristics. Factual memories were more like classic PTSD intrusive memories (APA, 1994); They were shorter, with more "nowness" and anxiety, and caused more distress. Unreal memories were more vivid, longer, more associated with guilt and shame, more uncontrollable and interfered more with daily life. However patients with factual memories only had the lowest PTSD scores of the group.

Patients who had a mixture of both unreal and factual memories of intensive care had the worst outcomes, with highest mean scores for PTSD, depression and anxiety. Perhaps having both type of intrusive memories made it difficult to tell real events and hallucinations/delusions apart and caused greater distress and confusion. Patients with both types of memory had been more delirious in the ICU and were more likely to have been given benzodiazepines in the ICU. This is in line with the results of the cohort study suggesting a link between sedation and delirium in intensive care and worse psychological morbidity at three months. Alternatively, having both unreal and factual memories could mean just having a greater number of memories altogether and therefore be a marker of severity of PTSD.

7.5.2 Discussion of the nature of memories

Several studies have reported long lists of stressors in the ICU (Novaes et al., 1997) or experiences which patients recalled most frequently (Green, 1996; Roberts & Richard, 2007; Rotondi et al., 2002;). However this is the first study to show that patients had intrusive memories that recurred months after ICU discharge consistently featuring the same aspects of intensive care (primarily tight-fitting face-masks, endo-tracheal or

naso-gastric tubes, pain and blood). These PTSD-like memories were characterised by fear, panic, suffocation and physical horror.

Unreal memories have also been reported in several studies, notably Jones et al. (2001) and Jones et al. (2007). As in Jones et al. (2001), my study found that realistic memories of intensive care tended to decline over time while unreal memories increased. This study was the first to report that unreal memories recurred several months after intensive care as intrusive memories. Jones et al. (2001) found that patients with "factual" memories of ICU as well as unreal memories at two weeks had lower PTSD scores at eight weeks and hypothesised that factual memory of ICU was protective against psychological morbidity. However the present study found that patients with both realistic and unreal memories at four months had worse outcomes for both PTSD, depression and anxiety. Having both types of memory might be a marker for PTSD severity, or might increase patients' difficulty in distinguishing between real events and hallucinations in intensive care, leading to even more confusion and distress.

Where does the content of ICU survivors' unreal memories come from? Patients in this study said their memories were of hallucinations, delusions or nightmares they had in intensive care. Indeed some patients reported similar content when I talked to them in intensive care as they reported in their interview with me four or five months later (see table 7.6). For example "Paul" said in ICU that he'd had hallucinations about opium dens and being an assassin; Four months later he recounted a long narrative about flying into Brazil to shoot three people on a roof. Often patients gave a vague description of their hallucinations in intensive care, and a more detailed account of similar visions and stories months later. For example "Raj" told me in intensive care that he'd been threatening to leave his wife because she would not bring the car to the front of the hospital to allow him to escape: five months later he explained that he wanted to escape from Bahai cultists whom he believed were trying to attack him and steal NHS drugs to fund their lifestyle.

The main themes of the "dreams" included being poisoned (by the air conditioning, refusing to drink water or brush teeth); being tortured, being threatened with death or being put on trial in hospital court-rooms. Patients believed in conspiracies by nurses and doctors to harvest organs through operations, to steal patients' money or to sell drugs to fund religious cults. They thought porters were wheeling patients to gas chambers or basements to turn them into zombies or give them to cloaked abbots who

would steal their souls. Others saw themselves as the guilty ones; the man who drowned Amy Winehouse and her baby, or the assassin swooping into Brazil. Some dreams involved travel in space and time to Denmark, 1920s USA or the Eastern bloc during world war two. Some were simply bizarre visions such as puffins jumping crazily on beds and firing blood from plastic revolvers, or a harem of nurses in gauzy outfits slipping in and out of bed with a large man. The patients seemed to be elaborating on the real material of their ICU experience - beds, nurses, doctors, surgery, needles, blood – with the iconography of popular culture such as thrillers, gothic horror or war-time films.

It is difficult to know where to place the unreal experiences that led to intrusive memories. They have similarities to psychotic experiences, yet there are certain differences. Acute psychosis is defined by hallucinations, delusions and marked formal thought disorder (World Health Organisation, 1990). Hallucinations are disorders of perception that have a compelling sense of reality. Some patients' IMs were clearly of simple visual hallucinations – a psychedelic film logo, faces appearing in the ICU curtains, spiders crawling up the walls or the ward decked out as a seaside poster. Delusions are defined as false unshakeable ideas or beliefs (Sims, 1995). There are many sub-types of delusions; for example persecutory, grandiose, guilty, sexual or bizarre delusions. Persecutory delusions are about others causing the individual physical, social or psychological harm (Freeman & Garety, 2000). The delusional experiences reported in the paragraph above were mainly persecutory although other sub-types can also be identified. Compare them with a clinical account of patients with persecutory delusions written in 1913 (Jaspers, 1979): "He is persecuted…for crimes of which he is falsely accused by gangs, Jesuits, Freemasons etc. There are also delusions of physical persecution on the bases of bodily influences (false perceptions) and … querulant delusions about injustices, plots and treacherous manipulations."

However whereas people with psychotic disorders such as schizophrenia tend to hold delusional beliefs over a period of time, ICU patients seemed to experience the delusions only in a delirious state as dreams, hallucinations and nightmares, and began to understand after leaving intensive care, that the experiences were unreal. The delusions were less like persecutory beliefs and more like dreams or hallucinations with a persecutory theme. As discussed in more detail in chapter three, these dream-like experiences in ICU may be caused by drugs such as benzodiazepines, opiates, sensory deprivation, sleep deprivation or by drug- or illness-induced delirium or encephalopathy. The role of dopamine has been highlighted in the development of

delirium (Meyer & Hall, 2006) and it may be that dopamine dysregulation contributes to the bizarre dreams and delusions of intensive care patients. It is believed that critical illness such as sepsis and respiratory failure, and intensive care treatment can lead to an imbalance of neurotransmitters with a depletion of acetylcholine and an excess of dopamine (Trzepacz, 1999). Furthermore the intense stress of an ICU admission could give rise to hippocampal dysfunction which also favours overproduction of dopamine (Gray et al., 1991). Dopamine is thought to provide special significance or salience to stimuli that would otherwise be neutral, and to create meaningful connections between coincident events (Hemsley, 1993). This would provide a possible explanation for patients noticing real events such as nurses taking blood or giving injections and weaving them into paranoid fantasies.

The dopamine hypothesis could also help to explain why such delusions become embedded in long-term memory. First, because dopamine lends salience to events, these events will naturally be more memorable. Second, it is known that dopamine is a modulator of emotional memory in animals, mediated via the amygdala (Greba et al., 2001). An experimental study using 33 healthy male volunteers suggested that dopamine also plays a significant role in biasing memory toward emotionally salient information in humans (Gibbs et al., 2007). Drugs and other ICU phenomena may also favour long-term memory of psychotic dreams by causing amnesia for much of ICU along with enhanced memory for the most traumatic aspects (Jones et al., 2000). The amnesia may be due to benzodiazepines, opiates, anaesthetics or sleep deprivation, while enhanced memory may be attributed to IV glucose infusions (Korol & Gold, 1998), to the administration of stress hormones in the ICU (Roozendaal et al., 2006) or actual stress responses releasing endogenous stress hormones while in the ICU.

Alternatively patients' unreal memories from intensive care may be something like the drug "flashbacks" that can occur after taking any hallucinogenic drug. They are particularly well-known in relation to LSD, particularly if users had a "bad trip" (Ashton, 2002). Drug flashbacks may occur spontaneously or may be triggered by fatigue, stress or taking other drugs. They may be very disturbing and are more common after taking multiple rather than single hallucinogenic drugs. They may last for several months or continue episodically for years (Halpern & Pope, 2003). Flashbacks known to occur after taking MDMA (ecstasy) include contorted and menacing faces as well as visual illusions. The neurochemical causes of drug flash-backs are not well understood, but one mechanism is thought to be the failure of inhibition in the visual pathways, related to serotonin deficits (Abraham et al., 1996),

1996. It has also been suggested that flashbacks after a bad LSTD trip are a form of PTSD (Ashton, 2002), thus bringing us back full circle.

Another parallel with the unreal memories of intensive care patients is suggested by the small but growing literature on post-psychosis PTSD. Several studies have found that patients develop PTSD months after a psychotic episode. A review (Morrison et al., 2003a) reported on a number of studies that had found prevalence rates of between 11%- 67% for PTSD in patients who suffered a psychotic episode months before. It is argued that hallucinatory and delusional disturbances can shatter the person's experience of themselves, the world and others in a similar way to non-psychotic trauma (Morrison et al., 2003). The experience of psychosis may have a similar capacity as other trauma to confront a person with horror, fear and helplessness. A counter-argument has been that PTSD in post-psychotic patients was due to other distressing experiences such as enforced hospitalisation or treatment, but most studies have found that psychosis itself was the most important stressor. For example a study by (Meyer et al., 1999) found that 69% of traumatic symptoms were related to psychosis, while 24% were related to hospitalisation.

Psychotic episodes, drug flash-backs or an ICU patient's unreal memories, do not fulfil the classic PTSD criterion that the traumatic event must include the threat of death, serious injury or physical integrity. These criteria do apply to the ICU patient's real situation (they suffered life-threatening illness) but their intrusive memories are frequently of the delirious dreams caused by their medical experiences rather than of the actual medical experiences. Does this then constitute PTSD? DiMartini et al.,(2007) presented four cases of transplant patients who experienced delusions and hallucinations during delirium who later re-experienced them as memories and met all the criteria for PTSD diagnosis. DiMartini argued that PTSD criteria should be expanded to include psychically induced experiences such as those that stem from a medical event.

7.5.3 Strengths and limitations of the study

Strengths This is the first study to investigate former ICU patients' intrusive memories of intensive care. No other study has provided such a rich description of the categories and nature of memories that patients had of intensive care. A sample size of 17 was a large number for a qualitative study. It has been recommended that six to eight participants may be sufficient for a qualitative study (Smith, 2010). The sample was a purposeful sample in that the best participants were selected to answer the

research question, a superior strategy to that of the convenience sample (Marshall, 1996). The study was designed to generate rather than test hypotheses.

Limitations This study shares the limitations of all qualitative studies in that they entail the risk of subjectivity, interviewer bias, and a lack of generalisability. Although the interview included ratings scales as well as qualitative content, the sample size was too small to detect statistical associations between different factors. Therefore any quantitative results should only be used to suggest future hypotheses that could be tested using robust quantitative methods. It may be that interviews were carried out too late, as for some patients the period of worst intrusive memories had already passed.

Clinical and research implications

This study would be of interest to clinicians who are interested in understanding the psycho-social outcomes of intensive care patients. Former ICU patients' experiences of disturbing intrusive memories occurring months after intensive care have not previously been described in the literature. The survey of patients' ideas about help needed after intensive care could help to guide planning for supportive interventions for patients in the ICU, after transfer to other wards and after hospital discharge. Future research in this area could include the evaluation of medical, pharmacological or psychological interventions to reduce intrusive memories after intensive care. It would also be of interest to administer cognitive psychological tests in conjunction with the intrusive memories interview to discover more about the neuro-psychological mechanisms underlying the observed memory dysfunction. Studies could also be carried out to test some of the hypothesised relationships between drugs and delirium in intensive care and intrusive memories after intensive care.

Conclusions of thesis

As each study had a separate discussion, and chapter six provided a full discussion of the main themes of this PhD, I will conclude the thesis with some reflections about future directions for clinical practice and research. The results of the thesis suggest that a high proportion of patients suffer considerable mood disturbance, cognitive dysfunction and physical stress in intensive care, and a significant burden of poor mental health and HRQL three months after leaving the ICU. A large epidemiological study is needed to find out if the prevalence rates found in my study – 27% PTSD, 46% depression, 44% anxiety, and 55% with at least one of these disorders – would be found in a wider level 3 ICU population. If similar prevalence was found in the wider population, this would represent 55,000 people with mental health problems, out of the estimated 100,000 admissions to ICUs in the UK every year. As well as being highly distressing and stressful for patients and their families, PTSD, depression and anxiety are likely to impede physical recovery and even to increase risk of further illness such as heart disease (Frasure-Smith & Lesperance, 2006). This has considerable cost implications for the health service as it could lead to hospital re-admissions and extra GP visits to get access to mental health services.

It is worth considering if preventative measures can be taken to reduce the high prevalence of serious psychological disorders after intensive care. Any preventative interventions would need to take into account identified risk factors to find out who is most likely to be affected and which risk factors can be modified. After establishing accurate prevalence estimates of post-ICU distress, the other major aim of my PhD was to identify risk factors for these outcomes, as my systematic review found that consistent risk factors had not previously been found. It was of great interest that in my cohort study a number of clinical risk factors were found to predict PTSD. The finding that global ICU factors such as "TISS" (a score that sums up the totality of intensive care received, from dressings to mechanical ventilation) and "numbers of organs supported" predicted PTSD, but not anxiety and depression, suggested that intensive care was a traumatic stressor for some patients (and not just a source of general distress). The more intensive care received, the more a patient was at risk of PTSD. It was also of considerable interest that sepsis biomarkers were found to predict PTSD in this study, as this was not previously known.

Additionally very specific predictor-outcome relationships were found, many for the first time; between days of sedation and PTSD; benzodiazepine usage and depression

at three months; inotropes and vasopressors and anxiety at three months; and steroids and anaesthetics and better physical HRQL. These clinical risk factors remained significant after controlling for socio-demographic factors and chronic physical ill health. There was also an interesting trend for opioid usage to improve all anxiety, depression and mental HRQL outcomes, with large effect sizes. These results point to an important role for drugs in the development of post-ICU psychological morbidity, as the global variable "number of drug groups given" was also found to predict PTSD.

These findings should be carefully considered by clinicians as they suggest possible modifications to clinical practice in intensive care. Although intensive care interventions are undertaken to save lives, likely psychosocial outcomes for patients should be taken into account during clinical decision-making and the conservative "doing less" approach that has already been recommended (Singer, 2006), could be warranted. Invasive monitors, catheters and other equipment should be removed in a timely fashion and weaning from mechanical ventilation should be attempted at the earliest opportunity. Perhaps the key area for clinical change to be considered is in administration of drugs. It is increasingly realised that benzodiazepines may have harmful effects on patients and this study suggests that inotropes and vasopressors should also be used judiciously. This study also confirms findings from other studies that opiates and steroids may have a beneficial effect on patient's eventual well-being. The total numbers of drugs being used, particularly those with known psychoactive side-effects, should also be monitored as increasing numbers of drugs used predicted worse outcomes.

Further research should be carried out to compare the relative effects on psychosocial outcomes of treating ICU patients with different drugs and drug regimes. However recent studies have been inconclusive. Sackey et al. (2008) followed up patients randomised to isoflurane (a non-GABA agonist sedative agent) or midazolam at six months and found a non-significant decrease in hallucinations and delusional memory in the isoflurane group. A study of an alternative strategy, 'light' versus 'deep' midazolam sedation strategy by Treggiari et al. (2009) found that the light group had reduced length of mechanical ventilation and LoS in the ICU but no difference in anxiety, depression and PTSD after four weeks. Further investigation should also take place into the biological and psychobiological mechanisms that are hypothesised to be causal processes in post-ICU psychological morbidity. These include the long-term effects of sepsis and septic encephalopathy or delirium on the brain, the effects of

neurotransmitter imbalances caused by drugs and critical illness, the effects of a range of ICU drugs on memory, and the processes by which extreme stress, triggering the release of stress hormones, may impair hippocampal function, leading to a range of emotional and memory problems.

This PhD also suggests the need for enhanced psychosocial support to be offered to current and former ICU patients. This has already been recommended in the 2009 NICE guideline: Rehabilitation after critical care illness. The cohort study demonstrated that there were extremely high rates in the ICU for mood disturbance (78%), delirium (66%) and physical stress such as pain, dyspnea and discomfort from tubes (77%). Patients also suffered from sleep deprivation (80%), hallucinations (65%), nightmares (48%), agitation (75%), inability to communicate (57%) and loss of personal control (86%). There was a group of around 40-45% of patients who suffered particularly badly from these symptoms. As well as being highly unpleasant states, most of these variables were also risk factors for worse outcome at three months. Some psychological factors (ICU mood, ICU stress, and ICU intrusive memories) were also found to be variables that mediated the clinical effects on outcome. This would suggest that if psychological reactions in the ICU were addressed it might be possible to mitigate the effects caused by intensive care interventions and improve outcomes. Therefore acute psychological reactions in the ICU should not simply be treated as transient, irrelevant or a nuisance, as is often the case. Furthermore, as delirium was also a mediating risk factor for psychological morbidity, all efforts should be made to assess for delirium in ICUs using the Confusion Assessment Method for the ICU (CAM-ICU; Ely et al., 2001b). A new NICE guideline on delirium advises on the prevention and management of delirium (Young et al., 2010).

Another important result, seen for the first time in this PhD, was that socio-economic circumstances of patients were a strong independent predictor of anxiety, depression and mental HRQL, but not of PTSD, after ICU. There was no variation in interventions received or illness severity linked to socio-economic circumstances. However it was found that total mood disturbance in the ICU varied by SEC. The group who had worst mood disturbance in the ICU and worse psychological outcomes at three months, in comparison with other occupational groups, was NSSEC group two (intermediate occupations) which consists of people with clerical, secretarial or administrative occupations. It is unclear why this should be. Perhaps this group has more chronic background stress than others, making them more vulnerable when faced with a highly stressful experience such as intensive care. Further research is needed with other

indicators of socio-economic circumstances to find out if particular social groups are more likely to have poor psycho-social outcomes and may need extra access to support.

My third study, a qualitative study of 17 patients with intrusive memories of ICU at three months, revealed that an important manifestation of post-ICU psychological morbidity was the presence of highly disturbing hallucinatory flash-backs or distressing snap-shot memories of bleeding, choking on tubes and pain. This study also suggested a possible pathway between ICU drugs, delirium, delusional intrusive memories and higher rates of all adverse psychological outcomes. The study also found that intrusive memories caused considerable distress and impairment, and that patients had not known where to seek help.

The NICE guideline on ICU rehabilitation (Tan et al., 2009) requires that patients should be assessed for the risk of future psychological morbidity and if necessary offered support at several time-points including a) in the ICU b) shortly after discharge from the ICU, c) before leaving the hospital and d) three months after leaving hospital. No assessment tool is currently available to assess the key risk factors for future psychological outcomes, However the ICU baseline questionnaire that I developed for this study (appendix 12) covers all the key items recommended by NICE and has been designed to be administered to level 3 ICU patients. It could potentially be shortened for daily ICU use and validated for this purpose among level 3 ICU patients.
Further work is needed to develop, pilot and evaluate psychological interventions for the ICU. Helpful interventions in the ICU would include giving information about treatment and progress; increasing patient control and self-efficacy; and giving explanations and reassurance about unexpected symptoms such as hallucinations in the ICU.

Training to enhance key skills such as anxiety management and communication should be given to all ICU staff. Access to physical exercise programmes may also help ICU patients psychologically. When a recent structured exercise and mobility package was compared to standard care in a study of 104 medical ICU patients in the USA (Schweickert et al., 2009), the intervention group had lower rates of delirium as well as less time spent on the ventilator and better physical HRQL at hospital discharge. Access to a psychologist or therapist may be necessary if a patient is particularly anxious or depressed. Anti-depressants should be used with care as they may affect

neurotransmitter systems and so increase the risk of delirium or subsequent psychological morbidity.

After transfer from the ICU to other wards, patients may need to be given additional support by relatives, nurses or a psychologist as this is often a stressful time. After hospital discharge some patients may need the opportunity to speak to someone by telephone about managing emotional distress and intrusive memories or flash-backs. They may also need follow-up appointments with a psychologist for evidence-based treatment of depression, anxiety, hallucinatory intrusive memories or PTSD, if they should occur. When this model of stepped care has been designed and piloted it should be evaluated in randomised controlled trials. If these new services can be generally introduced in intensive care units, there is hope that current levels of post-ICU psychological morbidity could be greatly reduced and the quality of patients' recovery would be much improved.

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APPENDICES

Appendix 1 Systematic review: Draft protocol

Protocol for a systematic review of studies of psychosocial outcomes after ICU

Introduction/Background

Psychological disturbances have been reported in patients in intensive care in many studies since the 1960s (e.g. Kornfeld 1969; Wilson, 1972; Tomlin; 1977). Psychological symptoms commonly experienced by ICU patients include anxiety, panic, depression, withdrawal, confusion, agitation, and distress caused by poor communication (e.g. Russell et al., 1999). This constellation of symptoms has become known in the literature as Intensive care syndrome or ICU psychosis. The syndrome is believed to occur in response to multiple stressors that affect patients in the Intensive care Unit. (Dyer, 1995).

It has also been reported that a large proportion of survivors of Intensive care suffer from psychological morbidity and impaired quality of life after leaving the Intensive care Unit. According to a review by (Weinert, 2005), psychiatric symptoms and disorders including depression and PTSD, affect 15-35% of patients in the months after intensive care unit discharge. A systematic review (Dowdy et al., 2005) found that QoL in ICU survivors is lower than in the general population. However over 1-12 months of follow-up, QoL tends to improve in ICU patients in most domains except mental health.

A number of studies have investigated whether there is an association between these two phenomena. Do psychological reactions and difficult experiences in Intensive care predict the development of psychological morbidity and poor quality of life in the months after Intensive care? If this relationship exists, is it moderated by social differences such as class, gender or ethnicity?

Socioeconomic status has been shown to be a determinant of outcome in various types of severe illness such as myocardial infarction (Shen et al., 2001) and cancer (Kogevinas et al., 1997). Furthermore a social gradient for mortality has been demonstrated within some ICU patient groups such as those who had elective surgery (Hutchings et al., 2004). Gender differences have been found in some studies of ICU outcomes such as length of stay and length of mechanical ventilation but not in others.

It seems likely that psychological outcomes of ICU treatment are also affected by social inequality.

To investigate these questions, a systematic review will be carried out assessing the proportion of ICU patients who suffer from poor psycho-social outcomes in the months after Intensive care, and the nature of relationships between different risk factors and psycho-social outcomes. Possible risk factors include psychological distress in the ICU, ICU treatment-related factors, ICU environmental factors, communication risk, age, gender and SES. Psycho-social outcome is a broad category including psychological morbidity such as anxiety and depression, PTSD and health-related quality of life.

Two previous systematic reviews; (Jackson et al., 2007) and (Griffiths et al., 2007) focused on the prevalence of PTSD in survivors of critical care treatment. Both concluded that the true prevalence of PTSD after critical care illness or ICU treatment has not been established due to the poor quality of studies. In the studies reviewed, some but not all investigated risk factors of post-ICU PTSD, including younger age, female gender, delusional memories of ICU, anxiety while in the ICU, stressful experiences in the ICU, increased LOS in the ICU, longer time on a ventilator, and greater levels of sedation while in the ICU.

The present systematic review will build on this earlier work. There were methodological weaknesses in the review by Jackson et al. (2007), for example in the search strategies and quality assessment used. There have been recent guidelines to improve the methodological rigour of systematic reviews of observational studies (e.g. Khan et al., 2001). Griffiths et al. (2007) used appropriate methods, but the review examined outcome only and not association with risk factors.

While both reviews estimated the prevalence of PTSD, a more complete assessment is needed to determine the full extent of adverse psychological outcomes affecting ICU patients after discharge. Several prospective studies suggest that survivors of Intensive care may suffer from a range of psychological symptoms and disorders, and lower quality of life after leaving hospital. Finally the effect of social inequality on psychological outcomes of Intensive care has not been looked at in a systematic review.

In conclusion, our proposed systematic review will draw on recent recommendations to improve the quality of reviews of observational studies, to assess a range of adverse

psychological outcomes and quality of life in the months after Intensive care. The ideal follow-up period to detect the presence of outcomes such as PTSD and to allow for some physical recovery, would be three months (REF) but studies may have followed patients up at different time-points. The review will also examine whether these outcomes are related to risk factors such as psychological reactions to the Intensive care environment, and social differences such as SES, age and gender.

Review questions

1. What proportion of ICU survivors suffer to what extent from adverse psycho-social outcomes (including PTSD symptoms, anxiety, depression and low health-related quality of life) in the months after Intensive care?
2. What are the risk factors (within 3 categories – psychological, socio-demographic and health-care use) for adverse psychosocial outcomes three months after ICU treatment?
3. Is there evidence of social variation in psychological outcomes following treatment in Intensive care?

Criteria for study selection

Type of studies: Cohort studies (prospective and retrospective prospective). Cross-sectional studies. Experimental studies (control groups).
Types of participants: General ICU patients who receive Intensive care >24 hours. Includes studies of mechanically ventilated patients in ICU, but not other sub-groups.
Types of outcome measures: Inventories or interviews for PTSD, anxiety and depression questionnaires or clinical interviews, other reliable, validated measures of psychological morbidity or well-being. Reliable and validated health-related quality of life instruments.

Methods

The search strategy for identification of studies is based on MOOSE guidelines (Stroup et al., 2000). Studies will be identified using the following databases:

Medline,	(Ovid, 1950-2007)
Embase,	(Ovid, 1980-2007)
Psycinfo,	(Ovid, 1806- 2007)
Cinahl	(EBSCO Host, 1982 – 2007)
Web of Science.	(ISI Web of Knowledge, 1981-2007)

The initial search will be carried out on Medline using the following strategy. Similar searches will be carried out on the other four databases. However thesaurus terms

may differ from database to database. For example, Psycinfo has a wider range of thesaurus terms to describe psychological morbidity than Medline or Embase .

1.	**MEDLINE**
	Search terms
	1950 to December 2007
#1	(Explode "Critical Care" in MIME, MJME, PT) or (explode "Intensive care-+") in MIME, MJME, PT)
#2	((Critical Care) in ti, ab) or ((Intensive care) in ti, ab)
#3	#1 or #2
#4	"Stress-Disorders-Post-Traumatic"/all SUBHEADINGS in MIME, MJME, PT
#5	((Post*traumatic stress or PTSD) in ti, ab)
#6	Explode Stress, Psychological or Psychopathology or Depression or Anxiety or Affective disorders in MIME, MJME, PT)
#7	((psycholog* or psychiatr* or psychopathology or psycho*social or anxi* or depressi* or mental or emotion*) in ti, ab)
#8	"Quality of Life"/ all SUBHEADINGS in MIME, MJME, PT)
#9	((SF-36 or NIP or EuroQol* or HRQL) in ti, ab)
#10	#4 or #5 or #6 or #7 or #8 or #9
#11	Explode "Cohort" in MIME, MJME, PT
#12	((cohort or prospective or follow-up or long-term or longitudinal) in ti, ab)
#13	#11 or #12
#14	#3 + #10 + #13
#15	(#14) and (AGE:MEDS = ADULT)

Reference lists of selected papers and personal files will also be scanned for additional papers not retrieved through searching electronic databases.

Study quality assessment

It has been reported that 50% of systematic reviews of observational studies do not carry out a quality assessment, i.e. a systematic appraisal of the internal and external validity, of the studies included (Mallen et al., 2006). Researchers may have ignored this issue because there is no accepted method of assessing the quality of non-randomised trials. A multiplicity of methods and checklists have been used but none of the latter have been validated or tested for comparability. However without assessing

the methodological rigour of each study, all are given equal weight regardless of quality, which may lead to inaccurate conclusions.

In the absence of a gold standard for quality assessment of observational studies, the Centre for Reviews and Dissemination (Khan et al., 2001) recommend that reviewers select components from available checklists that are most relevant to the topic and purpose of the systematic review. The CRD also recommends that numerical values are not given to checklist items to comprise a summary score. Instead each component may be assessed in a qualitative manner e.g. "well covered, adequately addressed or poorly addressed."

As the proposed systematic review will focus particularly on psycho-social outcomes of ICU survivors, quality criteria regarding the robustness of outcome data will be used. Another criterion - controlling for other factors which may be relevant to the outcomes - is particularly important in assessing follow-up studies. To determine the strength of the association between risk factors and outcome, another criterion will be the use of an appropriate statistical analysis. After reviewing several commonly-used check-lists I have decided to use the Scottish Intercollegiate Guidelines Network checklists for study designs including cohort studies (SIGN, 2004). Although SIGN checklists were designed for reviewing papers for the preparation of clinical guidelines rather than for systematic reviews, I chose them because of their clear description of each quality criterion. For example rather than simply asking what is the "representativeness of the sample", as in other checklists, SIGN spells out exactly what has been assessed for representativeness: *"A clear definition of source population and clear eligibility criteria for selection of subjects are used, to ensure the sample is representative."* This will guide me in making the assessment and should also help to make the assessment of quality I have made more transparent to readers

Data extraction strategy

I will extract data from each study using the attached form.

Synthesis of extracted evidence

Methods for synthesising extracted data will be determined on the basis of the quality of studies retrieved. If possible a meta-analysis will be performed to combine data from the highest quality studies.

Selected References

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Appendix 2 Systematic review data extraction form

Systematic review: Psychological outcomes after Intensive care

ID no:	
Author/date	
Title	
Source	
Aim	
Methods	
Study design	
Demographic data collected	
Clinical data	
Health care use data collected	
Risk factors/measures used 1. 2. 3. 4.	
Timing of assessment of risk factors	
Timing of follow-up(s)	
Psychological outcomes/ measures	
Quality of life outcome/measure	
Other outcomes/measure	
Statistical analysis	
Has power been calculated?	
Confounding factors considered for each risk factor	
Adjustment for confounding?	
Participants	
Number of participants	
Socio-demographics: Age	
Ethnicity	
Gender	
SES	
Inclusion criteria	
Exclusion criteria	
Setting	
Time spent in ICU	
Apache score (or similar)	
How participants recruited	
Participation rate	
Drop outs/attrition rate	
Details of control group, if included	
Incidence/prevalence rates	

Results:

Quality assessment: Adapted from SIGN methodology checklist

The sample	
1. A clear definition of source population and clear eligibility criteria for selection of subjects are used, to ensure the sample is representative.	
2. Comparison is made between full participants and those lost to follow up	
3. A power calculation is reported. If not, sample size is small, medium or large	
Outcome	
4. The likelihood that some subjects might have the outcome at baseline is accounted for.	
5. The outcomes are clearly defined.	
6. Evidence is used to demonstrate that measure of outcome is valid and reliable.	
7. Follow-up is long enough for outcome to occur.	
Risk factors-outcome analysis	
8. The study addresses an appropriate and clearly focused question (in terms of riskfactor/outcome).	
9. Any measures of risk factors are reliable	
10. Main potential confounders are identified and taken into account in design and analysis.	
11. Confidence intervals have been provided.	
12. Appropriate statistical analyses have been carried out.	
Overall assessment	
How well was study done to a) minimise risk of bias and b) to establish a causal relationship between exposure and effect. Code ++ All or most of the criteria fulfilled + Some of the criteria fulfilled - Few or no criteria fulfilled	a) Rating for prevalence estimate: b) Rating for association **-**

Dorothy Wade, April 2008

Rating quality criteria:
Good, adequate, poor. Not addressed, Not reported, Not applicable

Appendix 3 First page of ethics approval letter for ICU studies

NHS
National Research Ethics Service

The Joint UCL/UCLH Committees on the Ethics of Human Research Committee Alpha
Institute of Child Health
30 Guilford Street
London, WC1N 1EH
Tel: 020 7599 4130
Fax: 020 7599 4138
Email: t.lucas@ich.ucl.ac.uk

Our Ref: 08AL 286
10 September 2008

Dorothy ML Wade
MRC-funded PhD student
University College London
1-19 Torrington Place,
London
WC1E 6BT

Dear Ms Wade

Full title of study: **Why do survivors of Intensive Care suffer from adverse psychological outcomes, including posttraumatic stress disorder, in the months following hospital discharge?**

REC reference number: **08/H0715/75**

Thank you for your letter of 01 September 2008, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to the research sites listed on the attached form.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission at NHS sites ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

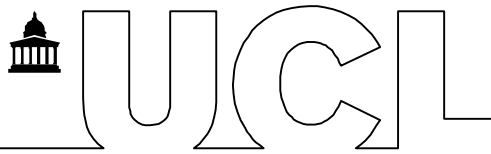
Appendix 4 Questions used to pilot the baseline questionnaire

PILOT Questions for ICU Baseline questionnaire/Dorothy Wade/ 11.11.08.

1. How long did it take to complete?
2. Were the instructions clear?
3. Were any questions unclear or ambiguous?
4. Did you object to answering any questions?
5. Was the layout clear and attractive?
6. Any other comments?
7. Is there anything else you think should be in the questionnaire?

Appendix 5 Letter to ethics committee requesting amendments after pilot study

HEALTH CARE EVALUATION GROUP
DEPARTMENT OF EPIDEMIOLOGY AND
PUBLIC HEALTH



April 8, 2009

T: 0207 679 1702
07734544512
Dorothy.Wade@ucl.ac.uk

Tom Lucas
The Joint UCL/UCLH Committees on the Ethics of Human Research
Committee Alpha
Institute of Child Health
Guildford Street
London, WC1N 1EH.

Dear Mr Lucas,

Piloting baseline and follow-up questionnaires
Ref: 08/H0715/75

As set out in the protocol for the above study, I have now piloted both questionnaires. I am writing to inform you of the results of the pilot and of subsequent minor changes I have made to the questionnaires.

ICU BASELINE QUESTIONNAIRE PILOT
I piloted the baseline questionnaire with the first ten patients in the study. All 10 patients said they found the questionnaire acceptable, clear and not too burdensome. They did not object to answering any of the questions. The average time taken to complete the questionnaire was 25 minutes, within the maximum time set out in the protocol. This included the time taken to complete the mini mental state exam (MMSE).

However two patients among the next ten patients I interviewed had comments about the questionnaire. One patient found two of the questions upsetting, and another found it tiring to complete the questionnaire. My own instinct when helping patients

complete the questionnaire was that it was a little too long and that patients were becoming tired during the last part of the questionnaire.

I have therefore amended the questionnaire slightly with guidance from my supervisor John Weinman, professor of health psychology at Kings College London. I have removed two items from the EICUQ, three items from the POMS and four items from the BIPQ. The removal of these items and other minor changes do not jeopardize the measurement of constructs, as there remain sufficient items to generate reliable measures and assess scale reliability.

The items that potentially cause upset seemed to be Q14 of the EICUQ (below) and Q2 of the BIPQ. I have removed the former item, and amended one of the responses to the latter from "forever" to "a very long time".

Q14 of the EICUQ: Have you felt frightened of dying?

Not at all	A little	Moderately	Quite a bit	Extremely

Q2 of the BIPQ How long do you think your medical condition will continue?

0 1 2 3 4 5 6 7 8 9 10
A very short time — forever

I also decided after the pilot stage that administering the mini mental state exam (MMSE) was not worth the extra time it was taking. Some elderly patients were unable to complete it because of current difficulties with reading or writing, or physical weakness (the MMSE involves writing, spelling and drawing). Those patients who were able to complete it, all gained very similar scores (in the normal range). Leaving out the MMSE reduces the time taken to complete the questionnaire to 15 minutes on average.

After the Viva exam for my PhD upgrade, it was suggested that I should include questions in the baseline questionnaire on patient's recall of the ICU as a potential mediating variable. I have added three questions (and three optional questions) as a result of this.

FOLLOW-UP QUESTIONNAIRE PILOT

After the Viva exam for my PhD upgrade, it was also suggested that I should include questions in the follow-up questionnaire on social support as an important confounding variable. In order to accommodate these questions, I shortened the questionnaire overall by using the SF-12 instead of the SF-36, and the brief six-item STAI rather than the longer 20-item version.

Having piloted the follow-up questionnaire, the results were as follows:

1. Response Rate: 65%

Questionnaires sent out: 17

Questionnaires sent back: 11

6 non-responses: 2 patients back in ICU, 1 going for surgery, 3 did not respond.

2. Time taken to complete questionnaire (median 15 mins, mean 21 mins).

10 minutes – 3 patients

15 minutes – 5 patients

30 minutes – 1 patient

40 minutes – 1 patient

> 1 hour – 1 patient

3. Issues raised about the content of the questionnaire

7 patients – no issues with questionnaire.

1 patient objected to some questions. "I thought the questions were meaningless. My answers relate to other problems in my life, not ICU"

2 patients found some of the response options of the validated questionnaires confusing.

1 patient found the layout was unclear.

Nobody found the questions unclear or ambiguous.

4. "Results"

6 patients – no psychological symptoms

4 patients – depression and post-traumatic stress related to ICU

1 patient – depression unrelated to ICU

In response to patient comments, I have slightly amended the layout of the questionnaire to make it as clear and easy to fill in as possible.

I have attached the amended questionnaires for your records.

Yours sincerely,

Dorothy Wade
MRC-funded PhD student

Appendix 6 Letter from ethics committee approving amendments

NHS
National Research Ethics Service

The Joint UCL/UCLH Committees on the Ethics of Human Research (Committee Alpha)
ICH R&D office, 1st Floor
3 Long Yard
London
Tel: 020 7599 4130
Fax: 020 7599 4138
Website: http://www.nres.npsa.nhs.uk/index.htm
WC1N 3LU

Tel: 020 7599 4130
Fax: 020 7599 4138

08 June 2009

Dorothy ML Wade
MRC-funded PhD student
University College London
MRC-funded PhD student
1-19 Torrington Place,
London
WC1E 6BT

Dear Wade

Study title: **Why do survivors of Intensive Care suffer from adverse psychological outcomes, including posttraumatic stress disorder, in the months following hospital discharge?**
REC reference: **08/H0715/75**
Amendment number: **1**
Amendment date: **29 April 2009**

The above amendment was reviewed at the meeting of the Sub-Committee held on 28 May 2009.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
ICU baseline Questionnaire	revised	29 April 2009
Follow-up Questionnaire	revised	29 April 2009
Letter regarding pilot study		08 April 2009
Notice of Substantial Amendment (non-CTIMPs)	1	29 April 2009

Appendix 7 Patient information sheet (full version/cohort study)

University College London Hospitals NHS
NHS Foundation Trust

PARTICIPANT INFORMATION Version 3. September 1, 2008

1. Subject of research: The psychological recovery of Intensive care patients.

2. Invitation

You are being invited to take part in research by a doctoral health psychology student. First I should explain why the study is being done and what will happen.

3. Why am I doing the study?

I am interested in finding out about people's recovery after they leave the intensive care unit. I am particularly interested in their emotional health and psychological well-being after they go home from hospital. I am trying to find out if there are social and medical factors that affect their psychological recovery.

4. Do you have to take part?

No, you do not have to take part in this research. If you decide not to take part, your health care will not be affected in any way. If you want to be in the study, you will be asked for written consent. Nurses and family members will be told that you are taking part in the study.

5. If you take part, what would be involved?

a) I will come to see you in the unit, to give you a questionnaire to fill in. The questionnaire is about feelings and experiences you've had in Intensive care and will take about 30 minutes. If you are tired, we can stop and complete it at another time.

b) Three months later I will phone to see how you are getting on, and send a follow-up questionnaire about your psychological recovery and your quality of life since leaving hospital. You can fill it in at home and send it back to me. If you have questions about filling in the questionnaire I may be able to help on the phone or, if you prefer, at your home. If you no longer wish to participate, you can let me know.

c) Finally, I am interested in talking to a few patients about the way they remember the Intensive care Unit. If you agree, we may also talk about this.

6. What information will be held about participants?

As well as the questionnaires, I will write down some details from medical notes including age, gender, address and diagnosis. I will also ask for a mobile phone

number and a relative's number so that we can contact you to arrange further follow-up. All of these will be kept confidential and never given out. I will store the questionnaires and other data in a locked filing cabinet and your name will be removed from all documents so it will not be possible to identify you. It is possible that inspectors from the NHS and other authorities could look at the data to check that I have done my research properly.

7. What will happen to the results of the study?

I will write a report about the findings so that healthcare staff can learn about the experiences and feelings of intensive care patients in hospital and after discharge.

8. Can you change your mind later about taking part in the project?

Yes, of course. If you feel unhappy with any aspect of the research, you can pull out of the study at any time without having to explain your reasons.

9. What to do if you wish to make a complaint about the research.

If you wish to complain about any aspect of the research, you should contact me, Dorothy Wade (see below). If you still feel you have not received a satisfactory response and you wish to take the matter further you should contact the UCLH Complaints Manager (see below) giving the project title and the researcher's contact details.

10. Extra support If you became upset when filling in a questionnaire, it would be possible to inform an Intensive care doctor who could arrange for you to talk to a psychologist. If your answers to the follow-up questionnaire showed that you might benefit from psychological support, the psychologist might contact your GP to arrange this. If any illegal behaviour is detected in the course of research, the researcher has a professional duty to report it to relevant authorities.

11. Researchers' contact details

You can keep this information and think about whether you want to take part in the study. If you have questions, I'll be happy to answer them.

Researcher
Dorothy Wade
Department of Epidemiology & Public Health
1-19 Torrington Place
London WC1E 6BT
Email: Dorothy.Wade@ucl.ac.uk
544512

Complaints Manager UCLH:
Complaints Department
2nd floor West, 50 Euston Rd
London NW1 2PQ
☏ 0845 1555 000 ext. 3413
☏ 020 7380 9655☏ 07734
Fax: 020 7380 9595

Thank you for reading about my research project, Dorothy Wade

Appendix 8 Verbal version of patient information sheet

University College London Hospitals NHS
NHS Foundation Trust

PARTICIPANT INFORMATION (short verbal version) January 12, 2009

1. Subject of research: The psychological recovery of Intensive care patients.

2. Invitation

You are being invited to take part in research by a health psychologist. We are interested in finding out about patients' experiences and feelings during their treatment in Intensive care. We will also be following their progress after they leave this Unit.

3. Do you have to take part?

No, you do not have to take part in this research. If you decide not to take part, your health care will not be affected in any way.

4. If you take part, what would be involved?

a) The researcher will help you fill in a questionnaire about feelings and experiences you've had in Intensive care. It takes about 15 minutes.

b) After three months you will be sent a follow-up survey about your quality of life and emotional well-being since leaving hospital. This will take about 30 minutes to complete.

5. Medical notes The researcher will also write down a few details from your medical notes. These will be kept confidential and never given out.

6. What will happen to the results of the study?

The researcher will write a report about the findings so that Intensive care staff can learn more about the experiences and feelings of patients. Your name will not be used.

7. If you want to make a complaint.

If you wish to complain about the research, you can contact the researcher Dorothy Wade or the UCH complaints manager. The phone numbers are on the information sheet we are giving you to keep.

Thank you for listening

Appendix 9 Script used during recruitment for cohort study

Script to use when approaching patients for recruitment into ICU psychology study

Dorothy Wade, 12/09/08

We are inviting all intensive care patients to take part in a study about people's emotional health and well-being during their stay in intensive care and later, when they are recovering at home. This will give us valuable information about the care we give patients in the Unit and the follow-up care we provide after patients are discharged from the Unit.

Appendix 10 Consent form for cohort study

University College London Hospitals NHS
NHS Foundation Trust

CONSENT FORM

Version 2. July 30, 2008

Title of Project: The psychological recovery of Intensive care Unit patients.
Researcher: Dorothy Wade T: 07734 544512(m)

	Please tick each box:
1. I confirm that I have read and understood the patient information sheet	☐
2. I have had time to think about the research project and ask questions. The researcher has answered any questions.	☐
3. I know that I do not have to take part in the study. I can decide to leave the study at any time without giving a reason.	☐
4. I understand that you may publish results from this study but you will not give out my name and identification.	☐
5. I know that some information from my medical notes will be written down. Inspectors from the NHS or other authorities could ask to look at this to check the researcher's work.	☐
6. I agree to take part in this research project.	☐
7. I agree that you can keep my name, address and phone numbers on file to send me the follow-up questionnaires.	☐
8. I understand that a member of hospital staff may contact my GP to arrange further support.	☐

	Please tick:
9. I would like you to send me a summary of the findings when they are ready.	☐ Yes / ☐ No

Continued over the page ➡

Once you have ticked the boxes on page 1, please sign below:

_____	_____	_____
Name of participant	Signature	Date
_____	_____	_____
Name of researcher	Signature	Date

Comments or concerns about this study
If you have any comments or concerns you may discuss these with the researcher (see below). If you wish to go further and complain about any aspect of the way you have been approached or treated during the course of the study, you should write or get in touch with the Complaints Manager, UCL hospitals (see below) giving the project title and the name of the Principal Investigator.

Researcher:
Dorothy Wade
Department of Epidemiology & Public Health
1-19 Torrington Place
London WC1E 6BT
Tel: 020 7679 1704
E-mail: dorothy.wade@ucl.ac.uk

Complaints Manager:
Complaints Department
2nd Floor West,
250 Euston Road,
London
NW1 2PQ
Tel: 0845 1555 000 ext. 3413 **or** 020 7380 9655
Fax: 020 7380 9595

Appendix 11 Patient data form (cohort study)

PATIENT DATA FORM/ ICU PSYCHOLOGY STUDY/ DOROTHY WADE

Patient Details

Patient ID | | | | **No**.

Name _____

Hospital Number | | | | | | | | |

Home Address _____

_____

Post Code | | | | | | | |

Home phone _____

Mobile phone _____

Next of Kin _____

NoK phone _____

GP's name _____

GP's phone _____

Age _____

Date of birth | | | | | | |

Sex Male = 0
Female = 1 | |

Admission details

Consultant's speciality _____

Admission from Theatre and Recovery 0

Ward	1
A&E	2
Other ICU	3
Other hospital/non-ICU	4
Other _____	5

[ ]

Date of CCU admission [ ][ ][ ][ ][ ][ ]

Date of CCU discharge [ ][ ][ ][ ][ ][ ]

Days in Critical Care Unit _____

Critical Care Discharge Location

0 = ward
1 = home
2 = another hospital
3= other _____

[ ]

No. of days during which sedated _____

Drugs No = 0 for each category.

Hypnotics

Temazepam = 1

Zopiclone = 2

[ ]

Other = 3 _____

Anxiolytics

Midazolam = 1

Diazepam = 2

[ ]

Lorazepam = 3

Chlordiazepoxide = 4

Propanolol = 5

Other = 7 _____

Other sedatives (anaesthetics)

Propofol = 1

Ketamine = 2

[ ]

Isoflurane = 3

Remifentanil = 4

Clonidine = 5

Anti-psychotics

Haloperidol = 1 ☐

Chlorpromazine hydrochloride = 2

Other = 3 _____

Opioids

Fentanyl = 1

Methadone hydrochloride = 2 ☐

Morphine sulphate = 3

Tramadol = 4

Diamorphine hydrochloride = 5

Dihydrocodeine = 6

Other = 7 _____

Non-opioid analgesic

Gabapentin = 1 ☐

Antidepressants

Tricyclics = 1 ☐

MAOIs = 2

SSRIs = 3 (Fluoxetine, Paroxetine, Citalopram)

Other = 4 (eg Velafaxine)

Ionotropes/vasopressors

Adrenaline = 1

Noradrenaline = 2

Dobutamine = 3 ☐

Enoximone = 4

Vasopressin/Argipressin = 5

Terlipressin = 6

Other = 7 _____

Steroids

Meythyl Prednisolone = 1 ☐

Prednisolone = 2

Hydrocortisone = 3

Dexamethazone = 4

Antiepileptics

Phenytoin = 1

Leviracetam = 2 ☐

Carbamazepine = 3

Phenobarbitone = 4

Sodium Valproate = 5

Psycho-social issues (including confusion) recorded in CCU

0= none
1 = confusion
2 = depression, low mood
3= anxiety
4 = agitation ☐
5 = sleep problems
6 = hallucinations or delusions
7 = other

Appendix 12 ICU baseline questionnaire (cohort study)

University College London Hospitals NHS
NHS Foundation Trust

Patient…… Date……..Identifying number…….

Intensive care questionnaire

Study: The psychological recovery of Critical care patients

Researcher: Dorothy Wade, 07734 544512

1. This questionnaire is you about the way you have been feeling in Critical care and the experiences that you have had here.

2. You can complete this questionnaire on your own, or we will help you. Please do whatever suits you best.

3. When answering the questions, try to think how you have been thinking or feeling during the time that you've been in the Intensive care Unit.

4. Your answers to this questionnaire will be kept confidential. The answers will be turned into numbers that will go into the study statistics. They will not be attached to your name.

Experience of intensive care

Below are questions about experiences or feelings people sometimes have in intensive care. Please circle the answer that is closest to your own experience.

1. Have you felt it was difficult to breathe?

Not at all	A little	Moderately	Quite a bit	Extremely

2. Have you felt able to communicate?

Not at all	A little	Moderately	Quite a bit	Extremely

3. Have you had much pain?

Not at all	A little	Moderately	Quite a bit	Extremely

4. Have you felt in control?

Not at all	A little	Moderately	Quite a bit	Extremely

5. Have you had hallucinations?

Not at all	A little	Moderately	Quite a bit	Extremely

6. Have you had emotional support from staff?

Not at all	A little	Moderately	Quite a bit	Extremely

7. Have you had nightmares?

Not at all	A little	Moderately	Quite a bit	Extremely

8. Have you felt confident that you would get better?

Not at all	A little	Moderately	Quite a bit	Extremely

9. Have you had a feeling of unreality?

Not at all	A little	Moderately	Quite a bit	Extremely

10. Have you been able to sleep?

Not at all	A little	Moderately	Quite a bit	Extremely

11. Have you felt isolated?

Not at all	A little	Moderately	Quite a bit	Extremely

12. Have you felt your dignity was respected?

Not at all	A little	Moderately	Quite a bit	Extremely

13. Have you felt agitated?

Not at all	A little	Moderately	Quite a bit	Extremely

14. Have you felt well-informed by staff?

Not at all	A little	Moderately	Quite a bit	Extremely

15. Have you felt anxious about your breathing?

Not at all	A little	Moderately	Quite a bit	Extremely

16. Have you felt discomfort from tubes or procedures?

Not at all	A little	Moderately	Quite a bit	Extremely

17. Have you had emotional support from family or friends?

Not at all	A little	Moderately	Quite a bit	Extremely

18. Have you felt disorientated?

Not at all	A little	Moderately	Quite a bit	Extremely

Mood

Below is a list of words that describe the way people sometimes feel in hospital. Please circle ONE answer for each question - that is nearest to the way you have been feeling while you've been in intensive care.

1. **Tense**

Not at all	A little	Moderately	Quite a bit	Extremely

2. **Cheerful**

Not at all	A little	Moderately	Quite a bit	Extremely

3. **Unhappy**

Not at all	A little	Moderately	Quite a bit	Extremely

4. **Angry**

Not at all	A little	Moderately	Quite a bit	Extremely

5. **Able to concentrate**

Not at all	A little	Moderately	Quite a bit	Extremely

6. **Resentful**

Not at all	A little	Moderately	Quite a bit	Extremely

7. **Lively**

Not at all	A little	Moderately	Quite a bit	Extremely

8. **Bad-tempered**

Not at all	A little	Moderately	Quite a bit	Extremely

9. **Nervous**

Not at all	A little	Moderately	Quite a bit	Extremely

10. **Confused**

Not at all	A little	Moderately	Quite a bit	Extremely

11. **Helpless**

Not at all	A little	Moderately	Quite a bit	Extremely

12. **Alert**

Not at all	A little	Moderately	Quite a bit	Extremely

13. **Terrified**

Not at all	A little	Moderately	Quite a bit	Extremely

14. **Panicky**

Not at all	A little	Moderately	Quite a bit	Extremely

15. **Forgetful**

Not at all	A little	Moderately	Quite a bit	Extremely

Memory of intensive care

1. Do you remember being admitted to intensive care? **Yes/No**

2. How much of the time you've spent in the ICU do you remember?

a) most of the time?
b) a moderate amount of the time?
c) very little of the time?

3. Do you have any memories, images or thoughts that come back repeatedly about anything that happened just before or while you have been in intensive care? **Yes/ No**.

If you answered Yes to question 3, please answer the following questions:

4. What's the content of the memory or image? (Prompt: is there anything else you can tell me? Any other details?)

5. How often do you get the memory or image?
a) Less than once a day.
b) Once or twice a day.
c) Several times a day.
d) Many times a day.

6. How distressing is the memory or image?

Not at all distressing 1 2 3 4 5 6 7 **very distressing**

ILLNESS PERCEPTIONS

We are interested in your own personal views about your medical condition and its effects. For the following questions, please circle the number that is nearest to your view.

1. How long do you think your condition will continue?

0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
A very short time										a very long time

2. How much control do you feel you have over your condition?

0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Absolutely No control										complete control

3. How concerned are you about your condition?

0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Not at all concerned										extremely concerned

4. How well do you feel you understand your condition?

0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Don't understand at all										understand very clearly

5. How much does your condition affect you emotionally? (e.g. does it make you angry, scared, upset or depressed?

0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Not at all affected emotionally										Extremely affected emotionally

BACKGROUND

1. What was your most recent occupation or job?

2. If you don't (or did not) work, what was your spouse's most recent occupation or job?

3. What is your highest educational qualification? Please circle 1 answer.
1. Degree or equivalent
2. Higher education (below degree level)
3. A-levels or equivalent
4. GCSEs or equivalent
5. No qualifications

3. What is your ethnic group? Please circle 1 letter (A to E), then circle a number below it.

A. White
1. British
2. Irish
3. Any Other White background, *please write in*

B. Mixed
4. White and Black Caribbean
5. White and Black African
6. White and Asian
7. Any Other Mixed background, *please write in*

C. Asian or Asian British
8. Indian
9. Pakistani
10. Bangladeshi
11. Any Other Asian background, *please write in*

D. Black or British Black
12. Caribbean
13. African
14. Any Other African background, *please write in*

E. Chinese or other ethnic group
15. Chinese
16. Any other, please write in

Contact Details
Mobile phone:_____ Relative's phone _____

THANK YOU FOR COMPLETING THE QUESTIONNAIRE!

Appendix 13 Follow up (letter and questionnaire)

University College London Hospitals NHS
NHS Foundation Trust

The Critical Care Unit,
University College Hospital,
253 Euston Rd,
London, NW1 2BU,
United Kingdom.
E-mail: dorothy.wade@ucl.ac.uk

January 21, 2010

Dear ,

Re: The intensive care patient well-being and psychology study

You may remember that I visited you in hospital. You answered a questionnaire about your experience of being in the Intensive Care Unit.

I am now sending you a follow-up questionnaire to find out how you have been getting on since leaving intensive care. It is about the reactions and emotions people sometimes have during their recovery after Intensive care treatment.

Please complete this questionnaire and send it back as soon as you can. Please try to fill in every question as well as you can, even if you are not completely sure of the answer.

If you would like any further information, please ring me on 07734 544512 or 020 7679 1702

I'd like to thank you again for your help with this project and to wish you all the best. Your contribution is very important for the success of this research,

Yours sincerely,
Dorothy Wade, Medical Research Council-funded health psychology researcher

INTENSIVE CARE FOLLOW-UP QUESTIONNAIRE

Study: The psychological recovery of critical care patients

Researcher: Dorothy Wade,
07734 544512 (m)
0207 679 1702 (w)
Email: Dorothy.Wade@ucl.ac.uk

1. The following questionnaire is about your well-being since you left the Intensive Care Unit, particularly in this past week. You can complete the questionnaire on your own. If you prefer me to help you, just phone me and I will phone you back.
2. I'd be very grateful if you could try to answer all the questions. If you are not sure of the answer, please mark the answer that is nearest to the way you feel.
3. Your answers to this questionnaire will be kept confidential. The answers will be turned into numbers that will go into the study statistics. They will not be attached to your name.
4. Answering this questionnaire will not affect any future medical care and treatment in any way.

YOUR NAME: _____

YOUR HEALTH AND ACTIVITIES

The first set of questions are about your health and daily activities. Read each item and circle one answer in the box for each.

1. In general would you say your health is:

Excellent	**Very good**	**Good**	**Fair**	**Poor**

2. The following two questions are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so how much?

- Moderate activities – such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.

Yes, limited a lot	Yes, limited a little	No, not limited at all

- Climbing **several** flights of stairs.

Yes, limited a lot	Yes, limited a little	No, not limited at all

3. Have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

- You **accomplished less** than you would like.

Yes	No

- You were limited in the **kind** of work or other activities.

Yes	No

4. Have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

- You **accomplished less** than you would like:

Yes	No

- You did work or other activities less carefully than usual

Yes	No

5. How much did **pain** interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely

6. These questions are about how you feel and how things have been with you **since you left hospital**. How much of the **time since you left hospital**:

- Have you felt calm and peaceful?

All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time

- Did you have a lot of energy?

All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time

- Have you felt downhearted and low?

All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time

7. Since you left hospital, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time

Emotional well-being (PART 1)

Please read the statements below and circle the one that is closest to how you feel right now, at this moment.

1. I feel calm

Not at all	somewhat	moderately	Very much

2. I feel secure

Not at all	somewhat	moderately	Very much

3. I am tense

Not at all	somewhat	moderately	Very much

4. I feel at ease

Not at all	somewhat	moderately	Very much

5. I feel upset

Not at all	somewhat	moderately	Very much

6. I am worried

Not at all	somewhat	moderately	Very much

Emotional well-being (PART 2)

How often you have felt any of the following during the past week: please circle one answer for each item.

1. I was bothered by things that usually don't bother me

Less than 1 day	1- 2 days	3-4 days	5-7 days

2. I did not feel like eating; my appetite was poor

Less than 1 day	1- 2 days	3-4 days	5-7 days

3. I could not shake off the blues even with help from my family

Less than 1 day	1- 2 days	3-4 days	5-7 days

4. I felt that I was just as good as other people

Less than 1 day	1- 2 days	3-4 days	5-7 days

5. I had trouble keeping my mind on what I was doing

Less than 1 day	1- 2 days	3-4 days	5-7 days

6. I felt depressed

Less than 1 day	1- 2 days	3-4 days	5-7 days

7. I felt that everything I did was an effort

Less than 1 day	1- 2 days	3-4 days	5-7 days

8. I felt hopeful about the future

Less than 1 day	1- 2 days	3-4 days	5-7 days

9. I thought my life had been a failure

Less than 1 day	1- 2 days	3-4 days	5-7 days

10. I felt fearful

Less than 1 day	1- 2 days	3-4 days	5-7 days

11. My sleep was restless

Less than 1 day	1- 2 days	3-4 days	5-7 days

12. I was happy

Less than 1 day	1- 2 days	3-4 days	5-7 days

13. I talked less than usual

Less than 1 day	1- 2 days	3-4 days	5-7 days

14. I felt lonely

Less than 1 day	1- 2 days	3-4 days	5-7 days

15. People were unfriendly

Less than 1 day	1- 2 days	3-4 days	5-7 days

16. I enjoyed life

Less than 1 day	1- 2 days	3-4 days	5-7 days

17. I had crying spells

Less than 1 day	1- 2 days	3-4 days	5-7 days

18. I felt sad

Less than 1 day	1- 2 days	3-4 days	5-7 days

19. I felt that people disliked me

Less than 1 day	1- 2 days	3-4 days	5-7 days

20. I could not "get going"

Less than 1 day	1- 2 days	3-4 days	5-7 days

PAST MEDICAL HISTORY

(your answers to these questions will be kept strictly confidential**)**

1. Have you ever been to see a GP, therapist, counsellor or psychiatrist for **mental health** problems?

Yes	**No**

2. If you answered **Yes**, please answer these further questions:

a) What kind of mental health problem(s) did (do) you have?

b) Did you have mental health problems before or after being patient in intensive care (or both)?

Before being in intensive care	**Since being in intensive care**	**Both before and after intensive care**

c) If you received any treatments for your mental health problems, what were they?

d) Please list any medication(s) you are currently taking for depression or any other *mental health* problem?

INTENSIVE CARE MEMORIES AND REACTIONS, PART A

Below are some reactions that people sometimes have after leaving Intensive care. Please circle the answer that describes how often that problem has bothered you IN THE PAST MONTH**.**

1. Have you had upsetting thoughts or images about your time in intensive care that came into your head when you didn't want them to ?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

2. Have you had bad dreams or nightmares about your time in intensive care?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

3. Have you relived your time in intensive care, acting or feeling as if it were happening again?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

4. Have you felt emotionally upset when you were reminded of your time in intensive care (e.g. feeling scared, angry, sad, guilty)?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

5. Have you experienced physical reactions when you were Reminded of your time in intensive care (e.g. breaking into a sweat, heart beating fast?)

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

6. Have you tried not to think about, talk about, or have feelings about your time in intensive care?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

7. Have you tried to avoid activities, people or places that remind you of your time in intensive care?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

8. Have you found that you were not able to remember an important part of your time in intensive care?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

9. Have you had much less interest or participated much less often in important activities?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

10. Have you felt distant or cut off from people around you?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

11. Have you felt emotionally numb (for example being unable to cry or unable to have loving feelings)?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

12. Have you felt as if your future plans or hopes will not come true?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

13. Have you had trouble falling or staying asleep?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

14. Have you felt irritable or had fits of anger?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

15. Have you had trouble concentrating (e.g. forgetting what you read, losing track of a storyontelevision)?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

16. Have you been overly alert (for example, checking to see who is around you, not being comfortable with your back to a door)?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

17. Have you been jumpy or easily startled (for example, when someone walks up behind you)?

Not at all	Once per week or less	2 – 4 times per week	5 or more times per week

MEMORIES AND REACTIONS,PART B

Have any of the problems you rated in **Qs 1-17** (on **pp7 and 8**) interfered with any of the following areas of your life DURING THE PAST MONTH? (Not all areas may be applicable to you).

1.	**Work**	Yes	No
2.	**Household chores or duties**	Yes	No
3.	**Relationships with friends**	Yes	No
4.	**Fun and leisure activities**	Yes	No
5.	**Relationships with family**	Yes	No
6.	**Sex life**	Yes	No
7.	**General satisfaction with life**	Yes	No
8.	**Overall level of functioning in all areas of your life**	Yes	No

MEMORIES AND REACTIONS, PART C

Many people have lived through traumatic events at some point in their lives. This can affect the way they react to new challenges.

Please tick the box next to ALL events that have happened to you or you have witnessed.

(1) ☐ Life-threatening illness

(2) ☐ Natural disaster (for example, flood, tornado, hurricane, or major eathquake)

(3) ☐ Non-sexual assault by a family member or someone you know (for example, being mugged, physically attacked, shot, stabbed or held at gunpoint)

(4) ☐ Non-sexual assault by a stranger (for example, being mugged, physically attacked, shot, stabbed or held at gunpoint)

(5) ☐ Sexual assault by a family member or someone you know (for example, rape or attempted rape).

(6) ☐ Sexual assault by a stranger (for example, rape or attempted rape)

(7) ☐ Military combat or war zone

(8) ☐ Sexual contact when you were younger than 18 with someone who was Five or more years older than you (e.g., contact with genitals, breasts)

(9) ☐ Imprisonment (for example, prison inmate, prisoner of war, hostage)

(10) ☐ Torture

(11) ☐ Serious accident, fire, or explosion (for example, an industrial, farm, car, plane or boat accident)

SOCIAL SUPPORT

These questions are about the support you get from other people. Please circle one answer to each question.

1. Is there someone you can count on to listen to you when you need to talk?

None of the time	A little of the time	Some of the time	Most of the time	All of the time

2. Is there someone who can give you good advice about a problem?

None of the time	A little of the time	Some of the time	Most of the time	All of the time

3. Is there someone who shows you love and affection?

None of the time	A little of the time	Some of the time	Most of the time	All of the time

4. Is there someone available to help with daily chores?

None of the time	A little of the time	Some of the time	Most of the time	All of the time

5. Can you count on anyone to provide you with emotional support (talking over problems or helping you make a difficult decision)?

None of the time	A little of the time	Some of the time	Most of the time	All of the time

6. Do you have as much contact as you would like with someone you feel close to, someone you can trust and confide in?

None of the time	A little of the time	Some of the time	Most of the time	All of the time

7. Is there someone who reminds you to take your medication?

None of the time	A little of the time	Some of the time	Most of the time	All of the time

8. Is there someone who reminds you or helps you to eat a healthy diet?

None of the time	A little of the time	Some of the time	Most of the time	All of the time

9. Is there someone who reminds you or helps you to take some exercise?

None of the time	A little of the time	Some of the time	Most of the time	All of the time

EMPLOYMENT QUESTIONNAIRE

Please read the first four questions and tick the box if a question applies to you. Then answer the remaining questions.

1. If you are retired, please tick this box. ☐
Please answer all questions in reference to your last main job (or spouse's job if you did not work).

2. If you do not work, but your spouse works, please tick this box. ☐
Please answer all questions with reference to your spouse's job.

3. If you are unemployed, please tick this box ☐
and answer all questions in reference to your last main job.

4. If you are a student, please tick this box. ☐

The following questions refer to your current main job, or to your last main job. Please tick one box only per question

5. Do (did) you work as an employee or are (were) you self-employed?

Employee ☐

Self-employed with employees ☐

Self-employed / freelance without employees (go to q. **8**.) ☐

6. Number of employees
For employees: indicate below how many people work (worked) for your employer at the place where you work (worked).
For self-employed: indicate below how many people you employ (employed). Go to Q. 8 when you have completed this question.

1 to 24 ☐

25 or more ☐

7. Supervisory Status

Do (did) you supervise any other employees? Yes ☐

No ☐

8. Occupation

Please tick one box ONLY to show which **best** describes the sort of work you do. (If you are not working now, please tick a box to show what you did in your last job).

1. Modern professions
such as: teacher - nurse - physiotherapist - social worker – welfare officer - artist - musician - police officer (sergeant or above) - software designer ☐ 1

2. Clerical and intermediate occupations
such as: secretary - personal assistant - clerical work office clerk - call centre agent - nursing auxiliary - nursery nurse ☐ 2

3. Senior managers or administrators
(usually responsible for planning, organising and co-ordinating work and for finance) *such as:* finance manager - chief executive ☐ 3

4. Technical and craft occupations
such as: motor mechanic - fitter - inspector - plumber - printer - tool maker - electrician - gardener - train driver ☐ 4

5. Semi-routine manual and service occupations
such as: postal worker - machine operative - security guard - caretaker - farm worker - catering assistant - receptionist – sales assistant ☐ 5

6. Routine manual and service occupations
such as: HGV driver - van driver - cleaner - porter - packer - sewing machinist - messenger - labourer - waiter / waitress – bar staff ☐ 6

7. Middle or junior managers
such as: office manager - retail manager - bank manager – restaurant manager - warehouse manager – publican ☐ 7

8. Traditional professional occupations
such as: accountant - solicitor - medical practitioner – scientist - civil/mechanical engineer ☐ 8

THANK YOU FOR COMPLETING THE QUESTIONNAIRE!
If you are interested in hearing about the results of this study, please tick the box ☐

Appendix 14 Letter and interview for intrusive memory study

,

Dear ,

Research project

Thanks for agreeing to take part in this research project. The interview I mentioned to you on the phone is about the nature of patient memories of intensive care. I'm sending you a copy of the interview questions to make it easier when we talk on the phone. There is no need to write any answers down, it is just for your reference.

I will ring you at a time of your convenience on . The best number to be sure of reaching me is my mobile number, 07734 544512.

Thanks so much for your help at all stages of this research. I look forward to talking to you,

Yours sincerely,

Dorothy Wade
PhD psychology researcher

ICU memories interview

Section A: memories

1. Have you had any particular memories from your time in intensive care that keep coming into your mind?
YES/NO

2. Are there TWO memories from intensive care that stand out most?
Memory 1
Memory 2

Memory One

1. Can you briefly describe the memory that you have from intensive care?

2. Please rate the vividness of this memory of intensive care:

Hazy memory	Normal memory	Very clear and vivid memory	Most clear & vivid memory

3. What are the emotions that you associate with this memory?

a)Sad:

Not at all	A little	somewhat	Very much so

b)Guilty:

Not at all	A little	Somewhat	Very much so

c)Ashamed:

Not at all	A little	Somewhat	Very much so

d)Angry:

Not at all	A little	Somewhat	Very much so

e)Anxious:

Not at all	A little	Somewhat	Very much so

f)Helpless:

Not at all	A little	Somewhat	Very much so

g) If there is another emotion you associate with the memory please write it down here: _____ How much do you associate this emotion with the memory?

A little	Somewhat	Very much so

4. When you have this memory, does it feel like it is not just a past event but is happening all over again?

Not at all	A little	somewhat	Very much so

5. When you have this memory, do you have emotions that are the same or similar to how you felt when you were really in Intensive care?

Not at all	A little	somewhat	Very much so

6. When you have this memory, do you have physical feelings that are the same or similar to how you felt when you were in Intensive care?

Not at all	A little	somewhat	Very much so

7. How many times did you experience this memory in the last week?

Once or twice a week	Several times a week	Every day	Many times a day

8. When you remember this memory how long does it last? (write in the number below and circle the amount of time)

____ seconds / minutes / hours

9. How much does the memory interfere with your daily life?

Not at all	A little	somewhat	Very much

10. How uncontrollable was this memory in the last week?

Not at all	A little	somewhat	Very much

11. How distressing was this memory?

Not at all	A little	somewhat	Very much

Memory 2

1. Can you briefly describe the second memory that you have from intensive care?

2. Please rate the vividness of this memory of intensive care?

Hazy memory	Normal memory	Very clear and vivid memory	Most clear & vivid memory

3. What are the emotions that you associate with this memory?

a) Sad:

Not at all	A little	somewhat	Very much so

b) Guilty:

Not at all	A little	Somewhat	Very much so

c) Ashamed:

Not at all	A little	Somewhat	Very much so

d) Angry:

Not at all	A little	Somewhat	Very much so

e) Anxious:

Not at all	A little	Somewhat	Very much so

f) Helpless:

Not at all	A little	Somewhat	Very much so

g) If there is another emotion you associate with the memory please write it down here: _____ How much do you associate this emotion with the intensive care memory?

A little	Somewhat	Very much so

4. When you have this memory, does it feel like it is not just a past event but is happening all over again?

Not at all	A little	somewhat	Very much so

5. When you have this memory, do you have emotions that are the same or similar to how you felt when you were really in Intensive care?

Not at all	A little	somewhat	Very much so

6. When you have this memory, do you have physical feelings the same or similar to feelings that you had in Intensive care?

Not at all	A little	somewhat	Very much so

7. How many times did you experience this memory in the last week?

Once or twice a week	Several times a week	Every day	Many times a day

8. When you remember this memory how long does it last? (write in the number below and circle the amount of time)

_____ seconds / minutes / hours

9. How much does the memory interfere with your daily life?

Not at all	A little	somewhat	Very much

10. How uncontrollable was this memory in the last week?

Not at all	A little	somewhat	Very much

11. How distressing was this memory?

Not at all	A little	somewhat	Very much

Section B: Help

1. Do you feel that you need some help with this problem?

YES	NO

2. Did you attend the ICU follow-up clinic? Did you find it helpful? Did you discuss your memories with them?

3. Have you tried to get help? (if so, give details)

4. What kind of help would you like?
