Associations between sedation, delirium and post-traumatic stress disorder and their impact on quality of life and memories following discharge from an intensive care unit

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THE 3 ORIGINAL PAPERS ARE

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2. Helle Svenningsen, Ingrid Egerod, Doris Christensen, Else K. Tønnesen Morten Frydenberg, Poul B. Videbech. Delirium in the intensive care unit and the risk of post-traumatic stress disorder: a Danish cohort study. Submittet.

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INTRODUCTION

In 2004, an interview with a former patient opened my eyes to delirium. The patient stayed 78 days in the intensive care unit (ICU) without obvious signs of clinical delirium, however after discharge he told about many bizarre situations involving himself, his family and the attending staff. To me delirium was, prior to that interview, when ICU patients tried to pull out intravenous lines or to escape from the ICU bed, and I thought the condition would resolve as soon as the patient was discharged from the ICU. That was my world, but definitely not the patients' world. The current PhD study is the natural continuation of my master's study [1], which dealt with improving knowledge about prevention of delirium in the ICU, helping patients and relatives when delirium was present and understanding the impact of delirium on the patient's life after ICU discharge.

Front Figure
By Kurt Westergaard

During interviews in the PhD study, a few patients' memories of delusions were told as narratives and were an excellent basis for illustrations. One of these narratives is cited in Paper 3, and an-

other is cited in *italics* in the dissertation and illustrated on the cover. Although these illustrations were outside the main target of this dissertation, they have been an eye-opener that aroused interest among both hospital staff and other healthcare professionals. By focusing my attention on this subject the ICU care and treatment can hopefully improve delirium prevention, and improve understanding of what the patients might have been struggling with while in the ICU.

BACKGROUND FOR THE PHD PROJECT AND THE EXISTING LITERATURE

DELIRIUM

Delirium is an underestimated condition, especially in ICU patients [2], and each day of ICU delirium or coma increases the risk of mortality by 10% in the first year after discharge [3]. Delirium is classified with some variation in two systems: the International Classification of Diseases (version 10, by World Health Organisation) (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders, version four (DSM-IV).

The National Clinical Guideline Centre, United Kingdom (UK), showed that only 0.15% of ICU patients had an ICD-10 code for delirium (F05), while the median range in epidemiologic data was 48% (29.8-83.3%) [4]. Though DSM-IV diagnostic criteria are mostly used for epidemiologic data, the difference in incidence cannot be explained by DSM-IV being less restrictive than ICD-10. The differences can instead be explained by studies that show that bedside nurses and doctors fail to recognise delirium [5-10]. Another reason for the missing ICD-10 coding for delirium in hospitals could be the widespread use of synonyms for delirium such as the ICU syndrome, acute brain dysfunction, acute brain failure, psychosis, confusion or encephalopathy [11]. In Denmark "intensiv-syndrom" was used in the 90s, and sometimes "delir" turns up, but delirium must be considered as the clinical and scientifically most correct term.

My gastric tube was a kind of branch that attaches itself by its new buds. It grew onto my nose and throat, so I did what could to pull it out. I succeeded several times, and I knew the nurses were getting tired of me.

Although this study was done in Denmark where the relatively more restrictive ICD-10 is used, the American DSM-IV definition was chosen for this dissertation given that the CAM-ICU is based on it. DSM-IV diagnostic criteria for delirium:

1. A disturbance of consciousness (i.e. reduced clarity of awareness of the environment) is evident, with reduced ability to focus, sustain or shift attention
2. There is a change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a pre-existing or evolving dementia.
3. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.
4. There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition [12].

Since the fourth criterion is always met for an ICU patient, the focus in diagnosing should be on the first three criteria.

Delirium can appear as hyperactive, hypoactive or mixed delirium [13]. Symptoms of hypoactive delirium can easily be interpreted as symptoms of depression or as dementia. Because there is an association between the duration of delirium in the ICU and cognitive impairment, it is important to recognise the condition [14]. A wide range of factors contribute to the development of delirium: anaemia [15], hypo-albuminaemia [16], blood transfusions [17], genetic predisposition [18], systemic inflammation [19], high or fluctuating glucose level [20], medications [21], dementia [22], physical restraints [23]; Common denominators for all these factors are advanced age and severe illness. Beyond avoiding these risk factors, early mobilisation and occupational therapy have demonstrated a reduction in the length of ICU delirium [24].

DELIRIUM ASSESSMENT

Several instruments are available for delirium assessment. In the present study, the CAM-ICU (see appendix) was chosen to detect delirium when an acute change of mental status or a fluctuating course was combined by either disorganised thinking or an altered level of consciousness. It is easy to use after a short introduction [25,26]; it is well validated in ICU patients [27-29]; it is preferable for use in intubated patients [29,30]; and it was translated and validated in a Danish context [31], although it is not widely used nationally [32]. In case of doubt, the CAM-ICU assessments should be supplemented with clinical testing and comparison to a gold standard (e.g. DSM-IV) [33].

The Intensive Care Delirium Screening Checklist (ICDSC) [34] can be used in intubated patients as well, although the sensitivity and specificity are lower than for CAM-ICU [29], possibly due to lack of an inattention test. Several other instrument might be efficient: the Delirium Rating Scale-revised-98 (DSR-R-98) [35], the Memorial Delirium Assessment Scale (MDAS) [36], the Delirium Detection Score (DDS) [37], the Delirium Index (DI) [38], the Nursing Delirium Screening Scale (Nu-DESC) [39], the short Informant Questionnaire on Cognitive Decline in the Elderly (short IQCODE) [40], the NEECAHM Confusion Scale [41], the Delirium Symptom Interview (DSI) [42] and finally the base for the CAM-ICU: the Confusion Assessment Method (CAM)[30]. Consequently, lack of tools is not a reason for the lack of delirium assessment, but intubation, sedation and overly complex tools are given as reasons by the nurses [43], contrasting with the research showing that several tools are easy to use [34,44-46]. Nevertheless, delirium detection depends on routine assessments by educated staff [2,47] and occasionally by specialists [48].

PHARMACOLOGICAL TREATMENT OF DELIRIUM

There are no international guidelines for the medical treatment of delirium in ICU patients, nor are there Danish guidelines. Internationally, four guidelines have been published: in the United States of America [49], Australia [50], Canada [51] and the United Kingdom (UK) [52]. None of these guidelines are specifically designed for ICU patients. They focus on the elderly in general and in some also, at least in part, on acute care settings. The newest guidelines [52] recommend: "Start at the lowest clinically appropriate dose and titrate cautiously according to symptoms". These guidelines state, however, that haloperidol (Serenase®) and olanzapine (Zyprexa®) do not have marketing authorisation for delirium (in the UK). This recommendation regarding medications is based on three randomised controlled trials (RCT) [53],[35] and only one with a critical care focus [54]. Four other relevant studies are published, but not included in the guidelines, one in an ICU[55], three outside ICU [56] [36] [57], see table 1.

Studies	Participants	ICU?	Delirium assessment tool	Haloperidol	Olanzepine	Quetiapine	Amisulpride	Risperidone	Chlorpro-mazine	Lorazepam	Placebo	Results
Hu & Deng 2006 *	175	no	None (CGI-S1)	i.m. n=72	p.o. n=74						n=29	Olanzepine and haloperidol have similar effects in treating semille delirium
Lee et al 2005 *	40	no	DSR-R-98			n=15	n=16				no	Both amisulpride and quetiapine may be useful
Skrobik et al 2004 *	73	yes	Delirium Index	p.o. n=45	p.o. n=28						no	Olanzepine is a safe alternative to haloperidol
Devlin et al 2010	36	yes	ICDSC	(i.v. supll)		n=18					n=18	Quetiapine + as-needed haloperidol is better than placebo + haloperidol
Tahir et al 2010	42	no	DSR-R-98			n=21					n=21	The quetiapine group improved more rapidly than the placebo group
Breitbart et al 1996	(244) 30	no	DRS	(n=11)					n=13	n=6	no	Both haloperidol and chlorpromazine decreased delirium. Lorazepam had no effect on delirium but sedating side effects
Han & Kim 2004	28	no	MDAS	(n=12)				n=12			no	No differences
Kim et al. 2005	42	no	CAM & DSR-R-98	(n=24)				n=18			no	No differences

Table 1
RCTs on pharmacological treatment of delirium. [35,36,53-58]
* is included in the NICE guideline

Reviews conclude that further studies are needed to enable an evidence based recommendation for the treatment of delirium [59], especially in the ICU [60].
Altogether it is difficult to determine which drug is best, it appears that medical treatment is better than no treatment, and preferably with one of the newer antipsychotic drugs when oral administration is possible to reduce possible side effects. Sedation is the last resort in agitated delirious patients because of the risk of increased confusion [58]; but, sedation is still frequently used [32,61-63].

SEDATION

Sedation is the administration of a medication that usually calms the nervous system [64]. Based on clinical experience, it appears that fluctuations in sedation are unpleasant and lead to restlessness, agitation or anxiety. The indications for the use of sedatives in ICU patients are not well defined. Sedation for uncooperative patients may expedite and simplify special procedures that require little or no movement, i.e. mechanically ventilation. Since pain can be the reason for restlessness or agitation, analgesia therapy is the first choice [65]. Sedatives are sometimes referred to as "chemical restraints"; although there is no evidence that fewer sedatives are used in countries where physical restraints are used [66].
Sedation, however, has not been used in the early days of ventilator therapy. Several pictures from the 1940s of "iron-lungs" show awake patients, and hand-ventilated intubated patients from the beginning of manual tracheal ventilator therapy under the Danish polio epidemic in 1952-53 were also conscious [67].
The history of deep sedation and curarization during mechanical ventilation most likely started in the mid-1950s as treatment of tetanus [68]. But in 1980s distressing patient narratives are reported [69,70], where patients were paralysed, but not sedated. Under the headline: "Paralysis or sedation for controlled ventilation?" a discussion took place in the Lancet in 1980 as to whether sedation is necessary. Jones found it disturbing that 96% of 50 patients who had received controlled ventilation in the UK received muscle relaxants, sometimes as the only agent used to control ventilation [71]. Green asks him not to see "this useful adjuncts in the ICU" as an "ogre" [72]. Finally, Gilston comments "it is also common to find anæsthetists1* administering a muscle relaxant, rather than a narcotic or an analgesic … during general anaesthesia" apparently started a movement towards deep sedation at the ICUs to ensure adequate controlled ventilation with less horrifying memories [73].
In the beginning of the 1990s, mechanically ventilated patients were still deeply sedated. In the past decade, attention has increasingly focused on the downside of deep sedation, such as prolonged mechanical ventilation and ICU stay, and particularly, the inability to assess the mental status of the patient. When Kress et al. in 2000 demonstrated that daily interruption of continuous intravenous infusions of sedatives decreased the duration of mechanical ventilation, length of ICU stay, and length of hospital stay, the advancement to daily sedation (and analgesia) interruption gained momentum [74]. The authors recommended that infusions of sedatives and morphine should be restarted when patients were awake and able to follow instructions, or when patients became uncomfortable or agitated, and again required sedation.
As a result Strøm et al.(2010) went further and tested a protocol of no sedation, using morphine for pain management [75]. They demonstrated the feasibility of no sedation and demonstrated that it was associated with a reduction in ventilator time and ICU stay. However, the lack of systematic delirium assessments led to new questions on the mental consequences of the daily wake-up calls or no-sedation. Both Kress and Strøm have examined patients' long-term mental status after the stay in the ICU, both without assessing for delirium in the ICU, and both with focus on post-traumatic stress disorder (PTSD) [76,77].

SEDATION ASSESSMENT

The benefit of a protocol that included sedation assessment has been shown several times [78-81], although the use of such a protocol is far from widely used [43,61,62,82]. In 2009, 96% of all Danish ICUs used a validated tool for sedation assessment [32]. Most frequently used was the Ramsay Sedation Scale [83], the Motor Activity Assessment Scale [84] and the Sedation-Agitation Scale [85]. The Glasgow Coma Scale [86] was typically used as an extra tool for patients with neurological disorders. The Richmond Agitation-Sedation Scale (RASS) [87] was used in 13% of the Danish ICUs in 2009 but has definitely gained ground the last few years and has facilitated transfer of patients between ICUs.

PHARMACOLOGICAL SEDATION THERAPY

Midazolam or propofol is traditionally used in Denmark for sedation in the ICU. Pro and cons for both agents are numerous in the literature [88-90]. Since November 2012, a new sedative agent

[1]* spelled with an "æ" in The Lancet

has been marketed in Denmark: dexmedetomidine (Dexdor®). Recent studies indicate a possible association between sedation and delirium in the ICUS: a double RCT on dexmedetomidine vs. propofol and dexmedetomidine vs. midazolam reports no differences in delirium assessed by CAM-ICU 48 hours after sedation cessation (no further delirium assessments were reported). The most adverse effect was associated with dexmedetomidine compared with both midazolam and propofol [91]. Increased delirium in the dexmedetomidine group was reported, when the CAM-ICU was used on a daily basis [92]. Dexmedetomidine has in other studies resulted in more delirium and coma free days compared with lorazepam [93] and compared with midazolam [94], and it has been used as an alternative to haloperidol in a small study with hyperactive delirious patients where it indicated decreased intubation duration [95]. See table 2.

Studies	Participants	ICUP	Delirium assessment tool	Midazolam	Propofol	Lorazepam	Sevo-flurane	Haloperidol	Dexmede-tomidine	Placebo	Results
(Weinbroum et al. 1997)	67	yes	none	36	31					30	Equal, except midazolam depressed respiration, allowed better maintenance of sedation, and yielded complete amnesia at a lower cost, while propofol caused more cardiovascular depression during induction and costed 4-5 times more
(Jakob et al. 2009)	(60)	yes	none	14	14		19			20	Sevoflurane decreased wake-up times and extubation delay.
(Hsiao et al. 2006)	102	yes	none	?	?					50	Both midazolam and propofol are effective amnestic and anxiolytic drugs. Midazolam tends to have fewer malic effects on amnesia
(Reade et al. 2009)	20	yes	ICDSC					10	10	20	Small study, only hyperactive delirious patients randomised. Dexmedetomidine entailed significantly extubation than haloperidol
(Riker et al. 2009) (Pandharipande et al. 2007)	(375) 247	yes	CAM-ICU	103					124	20	Dexmedetomidine-treated patients spent less time on the ventilator, experienced less delirium, and developed less tachycardia and hypertension. The most notable adverse effect of dexmedetomidine was bradycardia
(Pandharipande et al. 2007)	106	yes	CAM-ICU			51			52	20	Dexmedetomidine resulted in more days alive without delirium or coma than lorazepam
(Tunheim et al. 2009)	85	Yes	CAM-ICU	16	28				41	98	Delirium more frequent with dexmedetomidine, whereas sedation needed to be restarted after a sedation stop due to agitation or anxiety more frequent in midazolam/propofol
(Jakob et al. 2012)	(1001)	Yes	none	223	214				227+223	10	Dexmedetomidine reduced duration of mechanical ventilation compared with midazolam (but not propofol) and improved patients' ability to communicate pain compared with midazolam and propofol. More adverse effects were associated with dexmedetomidine

Table 2
RCTs on sedation in the ICU. 88-95

Regardless of the drug for used sedation, assessment of the sedation level is crucial to reach the sedation goal, preferably by protocol.

POST-TRAUMATIC STRESS DISORDER

The definition of Post-Traumatic Stress Disorder (PTSD) diagnosis is complex [12], and PTSD has evolved from a diagnosis for refugees or war veterans to include other types of extreme experiences [96]. "Hyperarousal", disturbed sleep, and memory impairment are symptoms of PTSD as well as delirium. Several symptoms are dissimilar between delirium and PTSD, especially the time factor, the level of consciousness, and the duration of the diagnose. Patients with delirium perceive an acute ongoing (imaginary or real) event that might be terrifying, whereas patients with PTSD have flash backs of the traumatic event. The term Acute Stress Disorder is used if symptoms occur and resolve within four weeks of the traumatic event [12]. PTSD usually begins within the first three months after the traumatic event, but can be delayed months or even years before symptoms appear [12].

To assess PTSD in post-ICU patients, several validated instruments have been used, but with very diverse results. The Post-Traumatic Stress Syndrome 10-question Inventory (PTSS10) has showed a PTSD prevalence from 0% [77] to 43% [97]; and the Revised Impact of Events Scale (IES) from 8% [77] to 37% [98]. Some of these variations could be related to the timing of the assessment, but variations are found even within the same timeframe. PTSD was found from 5% [99] to 44% [97] within 2 weeks after ICU discharge, and after 12 months from 2% [99] to 18% [100]. The reason for variation among studies is complex, but might be explained by differences in admission diagnosis, severity of illnesses, care regimes (e.g. systematic use of physical restraints in sedation practice [66]), incidence of delirium, or pre-ICU psychopathology [101]. In a systematic review, the prevalence of PTSD in ICU survivors was as high as 64%, with a mean of 29% [101], indicating that result transmission between contexts can be problematic.

The complex nature of PTSD demands attention to symptoms of both anxiety and of depression, since an overlap is inherent.

I was sure they wanted to give me a cigarette, but it was an oxygen mask, although I still fought to avoid the cigarettes.

ANXIETY

The prevalence of anxiety in the Danish background population is approximately 3%. This is only an estimate due to the difficulties of correct diagnosing [102]. The equivalent for former ICU patients is described internationally as approximately 11% [100,103,104] to 47% [105]. The choice of assessment instrument has an impact on the results: variations exist within the same instrument [103,105]. The time of assessment could be another factor, but again, variations exist within the same time span [76,106]. Nevertheless, a higher incidence of anxiety may be present in former ICU patients since most of them had or have had natural reasons to be anxious, a recurrence of the illness that made the ICU stay crucial.

DEPRESSION

Depression must be seen as another potential consequence of severe illness and the implications on everyday life after discharge from the hospital. An incidence of 69% is described for 24 former ICU patients without pre-existing depression [107], but must be considered as a separate result, because larger studies show incidences around 10% [100,103,104]. Although such incidences are lower, they still indicate a threefold increase compared with the point prevalence of major depression in the Danish background population of 3.3% [108].

MEMORIES

memories, which have been reported as a contributory cause to PTSD [109]. Recalling memories of delusion without memories of facts might contribute to the symptoms of PTSD [110].

HEALTH RELATED QUALITY OF LIFE

For human and socio-economic reasons, ICU care should result in the best possible health related quality of life (HRQoL) after discharge. Due to the heterogeneity of the discharged patients, any measurement of HRQoL presents a challenge. Several studies have estimated HRQoL in the post-intensive care population [111-

113] and found that comorbidity and social isolation are key factors in the HRQoL and that both psychosocial and physical aspects play an important role long after discharge [109,114,115]. On the other hand, the severity of the illness at admission might not influence HRQoL [116]. More knowledge is needed regarding the associations between delirium, memories and HRQoL.

HEALTHCARE DEPENDENCY

Healthcare dependency and need for assistance in activities of daily living (ADL) might be affected by ICU delirium in patients recovering from critical illness [117], and delirium is show to be a strong and independent factor for discharge to a place other than home [118].

DIARY AND FOLLOW-UP VISITS

ICU staff in Denmark have launched two new projects to improve patients' HRQoL after discharge: diaries written by staff, relatives or a combination while patients were in the ICU and follow-up visits in which patients (and relatives) have the opportunity to talk to the staff (ICU nurses and occasionally doctors) about the ICU stay and the challenges they have met after discharge. In some set-ups, delivery of the diary is part of a ICU follow-up visit [119,120] (as in Hillerød), in others the diary follows the patients from the ICU to the ward and home. Some follow-up programs do not use a patient diary. In these the focus is on memories from the ICU, and the patient is encouraged to revisit the ICU and especially to hear the sounds of e.g. the suctions system, the mechanical ventilator or whatever is relevant to the patient (as in Aarhus).

Diaries are useful tools in the debriefing process following intensive care; the detailed narratives of the patient's stay are read by both patients and relatives [121]. The provision of a diary has shown improved HRQoL using the SF-36 in some of the domains for a selected group of the most severely ill patients for up to 3 years after discharge[111]. A review [101] suggested that future studies should comprehensively address how patient-specific factors, e.g. pre-ICU psychopathology, administration of sedatives, ICU delirium, relate to one another and HRQoL/PTSD. This is what this dissertation attempts to do, which leads to the following hypotheses and aims:

HYPOTHESES

1: Delirium is more often in sedated than in non-sedated patients
2: Delirious patients are more likely to develop post-traumatic stress disorder (PTSD)
3: Delirium decreases health related quality of life (HRQoL) after discharge

AIMS

Aim1:
The aim was to investigate whether sedatives or fluctuations in sedation levels were associated with delirium estimated by the Confusion Assessment Method for the ICU (CAM-ICU) in critically ill patients

Aim 2:
The aims were to estimate the prevalence of PTSD 2 and 6 months after discharge from the ICU, and the association between PTSD and ICU delirium. In addition:

1. We wished to estimate whether ICU delirium had an influence on the degree of anxiety and depression
2. We examined whether prior mental illness – assessed by redeemed prescriptions – were associated with ICU delirium.
3. We wished to estimate associations between ICU memories of facts, feelings or delusions and PTSD/anxiety/depression after ICU stay.

Aim 3:
The aim was to investigate the effect of delirium in the intensive care unit on HRQoL, healthcare dependency, and memory after discharge. Furthermore, we wished to investigate the impact of memories, patient diaries, and follow-up on HRQoL.

METHODOLOGIES OF THE PHD PROJECT

PATIENTS, SITES AND SETTINGS

The study was performed as a prospective cohort study with interview follow-up. Patients were included from three multidisciplinary ICUs at two university hospitals in Denmark, from September 2009 to June 2011 at Aarhus University Hospital Nørrebrogade (ITA) and Tage Hansens Gade ("600"/OVITA), and from November 2010 to July 2011 at Hillerød Hospital (ITA). All adult patients (> 17 years) were included. Exclusion criteria were ICU shorter than 48 hours, non-Danish speaking, and brain damage making communication impossible. Readmissions to the ICU were regarded as one admission if the patient had a
< 24 hour stay at the hospital ward in between the ICU stays. If patients were transferred to other hospitals, institutions or home, readmission was a reason for exclusion from the rest of the study. Patients were interviewed at three points in time following the ICU stay. After information was given and consent was obtained, the first interview was performed at the bedside as a structured interview using the ICU memory tool. Follow-up interviews were performed by telephone 2 and 6 months after the discharge (from the ICU) using six questionnaires, in total 116 questions. Although some of the questionnaires were also diagnostic tools, we only used them to assess the aftermath of delirium. Patients were excluded from the follow-up interview if they were readmitted to an ICU.

The number of participants included in each study was based on sample size calculations as established in a pilot study conducted in July 2009, and on patient characteristics in 2008. Our primary outcomes were delirium and PTSD. Assuming PTSD to have a prevalence of 22% [101] and delirium an incidence of 40% [122], an estimated relative risk of 1.5 had a power at 0.90 when 250 patients were included.

In the first part (aim 1) of the study, the primary endpoint was the presence of delirium. Secondary endpoints were ventilator days, length of ICU stay, and ICU mortality. Exposure variables were sedation level (RASS), medication status (sedated vs. non-sedated), and medication administration (bolus vs. continuous infusions).

In the second part (aims 2 and 3) six different assessments tools were used. The primary endpoints were prevalence of PTSD (aim 2) and HRQoL, healthcare dependency, and memory (aim 3). Secondary endpoints were other forms of anxiety and depression. Exposure variables were delirium, age, gender, severity of illness, time in mechanical ventilator, and length of ICU stay. Other secondary endpoints were ICU memories of facts, feelings or delusions, and mental illness prior to ICU (aim 2), with delirium, memories, and redeemed prescriptions as exposure variables,

and HRQoL (aim 3), with memories, patient diaries, and follow-up as exposure variables.
For each patient data on gender, age, severity of illness (simplified acute physiology score; SAPS II [123]), and length of ICU stay were obtained from the hospital records. If SAPSII was unavailable, it was omitted. Visual problems were defined as the need for glasses other than reading glasses, and hearing problems were defined as use hearing aids. Tobacco consumption was registered if any kind of tobacco was regularly used 6 weeks before admission to the ICU [124], and alcohol abuse was registered if the average daily consumption was above minimum three drinks for men and two drinks for women, which was maintained even though the recommendations changed during the study [125]. Patients were asked (at first interview) if they prior to admission were medicated for hypertension or psychosis within the past three months. Some patients were uncertain of their medications and were unable to distinguish between the various drugs. To ensure accuracy, data on redeemed prescriptions were obtained from Statistics Denmark's closed database for all 942 patients eligible for inclusion and used to record pre-hospitalisation medications.

DURING ICU STAY
All patients admitted to the three ICUs were scored by RASS 87 and CAM-ICU 25 by the ICU nurses as soon as possible – predominantly in the first 12 hours. Patients were scored a minimum of twice a day until discharge from the ICU and were supplemented with extra scores if mental status changed. This could, however, not always be achieved because of the heavy work load in the ICUs, and if included patients had less than two scores/day, they were grouped as "unable to assess" (UTA). I gave ongoing support to caregivers during the entire study period, either in person or by phone. If results of CAM-ICU were missing on an observation sheet, the medical chart or nursing papers were reviewed for CAM-ICU results. If delirium status was still unknown, "UTA" was noted in the database. The fluctuation in sedation and agitation level sometimes caused the staff to record an ambiguous RASS (e.g. -1/+2). In this case, the worst score was noted in the database.
Prescription of relevant medications was organised differently at the three ICUs, and changed over time. At the beginning of the study, ICU "600" recorded administered medicine on the observation sheet (see figure 1), which that made it possible to find the exact dose given to the patients. Staff at ITA and NBG only recorded PRN medications on the observation sheet, and the routine prescriptions on the medicine sheet. The hospitals computerised system was consulted in case of lost paper-documentation. During the last 8 months, routine medications were documented in the computerised chart"EPJ", and data had to be found both places.
Sedatives and analgesics and their administration form (continuous or bolus) were noted but not the exact dose, since this study focused on individual effects of sedatives/analgesics and antipsychotics.

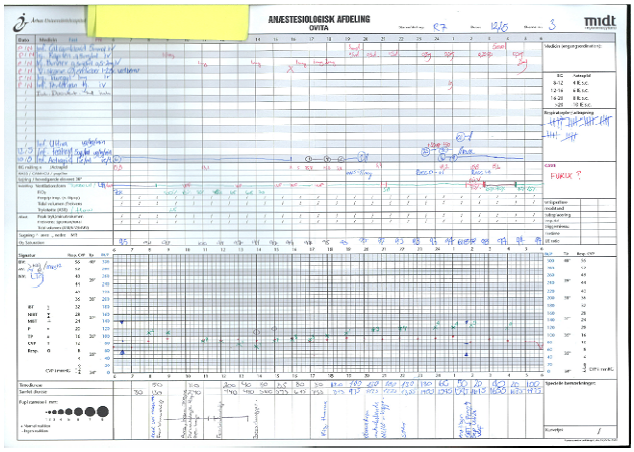

Figure 1
Scan of a random observation sheet

Days of mechanical ventilation or intubation were noted if any kind of tracheal intubation was ongoing, whereas non-invasive ventilation was not recorded.
Mobilisation was noted for any type of activity during which patients were out of bed, although this might have involved being lifted into a wheel chair. "Sitting" in the bed was not recorded as mobilisation.

AFTER ICU DISCHARGE
All patients from Hillerød Hospital were contacted on the ward by one nurse for informed consent and the first interview. Patients in Aarhus were contacted by my self, expect for 2 weeks during the summer 2009 when another nurse served as stand-in.

ICU Memory tool (ICUMT)
At all three interviews, the ICU Memory Tool (ICUMT) was used [126,127]. It contains eight questions plus sub-questions. Question 7: "Have you had any intrusive memories from your time in hospital or of the event that lead up to your admission?" often produced questions and astonishment from the patients and after a few months this question was omitted, since it was not part of the analysis in the present study in which any intrusive memories were explored in HTQ.
In ICUMT, memories are categorised as sums in subscales of factual memories scoring 0-11 (family, alarms, voices, lights, faces, breathing tube, suctioning, darkness, clock, tube in nose, and ward rounds), memories of feelings scoring 0-6 (being uncomfortable, feeling confused, feeling down, feeling anxious/frightened, panic, and pain), and memories of delusion scoring 0-4 (hallucinations, nightmares, dreams, "feeling that someone was trying to hurt you") [127].

Harvard Trauma Questionnaire (HTQ)
The Harvard Trauma Questionnaire (HTQ) was originally developed to assess PTSD in Indochinese refugees [128], but since has been translated and validated in several cultures including the Danish [129-133]. Original HTQ consisted of three sections, 1) description of traumatic events, 2) open-ended question and 3) a symptom item list. Part 3 had 30 symptoms listed, 14 symptoms associated with the refugees traumatic life events and 16 that met the DSM-IV's criterion for PTSD: re-experiencing (4 items), avoidance (7 items) and arousal (5 items). The current study used these 16 questions to screen for PTSD, and patients were asked to state how much of the last week the feelings had been present.

There are four categories of response ranging from “Not at all” (score=1) “A little” (score=2), “Quite a bit” (score=3) to “extremely” (score= 4). The total score is calculated as score of items divided by the numbers of items answered, < 2 indicates no PTSD, 2-2.4 probable PTSD, and >2.4 positive PTSD [134].

Major Depression Inventory (MDI)

In the present study Major Depression Inventory (MDI) was used as a rating scale to assess the degree of depression, but it can also be used for diagnostic purposes [135]. On the MDI, patients rate how much of the past 2 weeks they have felt sad/ lacking energy and strength/ that life wasn’t worth living/ difficulty in concentration etc. on a six point Likert scale from “At no time” (score=0) to “All the time” (score=5) [136]. A sum less than 20 indicates no depression, 20-24 minor depression, 25-29 moderate depression, and 30 or more a severe depression. The sensitivity of the MDI algorithms for major (moderate to severe) depression varied between 0.86 and 0.92, and the specificity varied between 0.82 and 0.86 [135]. Symptom scores from the Danish background population are available [137,138].

State-Trait Anxiety Inventory (STAI)

The State-Trait Anxiety Inventory (STAI) consists of 20 statements that evaluate how respondents feel "right now, at this moment" (state anxiety or anxiety about an event) and 20 statements that assess how respondents feel "generally" (trait anxiety) [138,139]. In the present study, a short-form was used using the 10 symptom-orientated state anxiety questions: “Right now I fell… tense/ nervous/ restless/ anxious/ guilty/ etc.“. Answers were given on the Likert scale “Not at all” (score= 1), “Somewhat”, “Moderately so”, “Very much so” (score= 4). A sum score of 20 or more was a cut-point indication of clinical anxiety.

Short-Form 36 (SF-36)

Health related quality of life was assed using the SF-36 that generates information in eight specific domains: physical function (PF), role physical (RP), bodily pain (BP), general health perceptions (GH), vitality (VT), social function (SF), role emotional (RE), and mental health (MH) [140,141]. All answers are transformed to a scale from 0 (worst score) to 100 (best score).
In the case of severe dyspnoea, severe hearing defects or severe concentration difficulty, the SF-36 was deselected.

Barthel Index of Disability (BI)

To assess healthcare dependency, the Barthel Index of Disability (BI) was used [142]. It consists of 10 activities of daily living. Participants were asked to rate their level of dependency on relatives or healthcare professionals on a scale from “fully independent” to “unable to perform task”. A high sum score is associated with better functioning (max 100).

Supplemental

In all questionnaires, the issues were discussed with the patients until they decided which response was most correct. Finally, patients were asked if an ICU-diary had been provided for them [143] (kept by relatives or staff) and if they had read it, if they have seen photos from their stay or if they have participated in any follow-up [144] concerning the ICU stay.

STATISTICAL CONSIDERATIONS

All data from the ICU and the interviews were entered in EPI-DATA, and transferred to STATA12 for statistical analysis. Delirium determination is fully described in Paper 1.
All psychometric measurements were analysed using descriptive statistics. Only completed questionnaires were used in the analyses; no imputation was done. The internal validity of the data was determined by consistency between the instruments when the same items were assessed, e.g. the ability to climb stairs.
Results were considered significant if the p-value was less than 0.05.
Continuous data were presented by mean and standard deviation (SD) if normally distributed, otherwise as median and 10% and 90% percentiles or by proportions. Populations were compared using Chi-square test (categorical data) or Kruskal-Wallis test (numerical data).

PAPER 1

Primary focus was on assessing the impact of sedation on delirium in the ICU. Data were analysed using multiple logistic regression. Adjustments were made for gender, age (in quartiles), SAPS-II (in quartiles), ICU site, and ICU setting (medical/surgical). To illustrate the effect of sedation level, choice of sedative or analgesic agent, and administration method (bolus vs. continuous), we estimated odds ratio (OR) for each score based on the previous scores up to the first positive delirium score. Estimates for the total ICU stay were calculated as well.

PAPER 2

Primary focus was on assessing the impact of delirium on PTSD, anxiety, and depression. The PTSD, anxiety, and depression outcomes were tested using multiple regression analysis, adjusting for delirium, age, gender, SAPS II score, hospital, number of ICU days, and type of admission (medical/surgical) to address potential confounding. To test for confounding by indication, regressions were done with and without control for antipsychotic medications. The associations between HTQ, STAI, MDI scores, and number of memories were estimated by linear regressions.

PAPER 3

Primary focus was on assessing the impact of delirium on HRQoL, health dependency, and memories at 2 and 6 months after ICU. See Paper 3, supplemental material, figure 3 for illustration of analysis.
HRQoL was determined by the mean SF-36 score and estimated using multiple regression models. The impact of memories, patient diaries, and follow-up on HRQoL were estimated. Healthcare dependency data were obtained from the Barthel Index and were analysed as the means of continuous variables.
Memories were treated both as effect modification, and as categorical variables: Factual memories; Factual and memories of delusion; Memories of delusion and No memories. Memories of feelings were not included in this analysis because feelings such as anxiety might be caused by factual or memories of delusion. Factual memories were compared to the other three categories by differences with 95% CI.

ETHICAL CONSIDERATIONS

The study was conducted in accordance with The International Council of Nurses code of ethics [145], and was approved by the Danish Data Protections Agency (journal number 2007-58-0010)

and the National Health Service of Denmark (journal number 7-604-04-2/226/KWH). The study was registered at ClinicalTrials.gov Protocol Registration System; Protocol Record NCT01291368. The study protocol was approved by the Danish Data Protection Agency According to the Regional Research Ethics Committee; the study required no approval because no interventions were performed.

National Health Service of Denmark gave permission to use ICU data from deceased patients, and Statistics Denmark provided anonymous data on the prescribed medications.

The departments of Århus Sygehus were informed by letter to the head nurse and the leading consultant, and requested to contact the author if any problems arose due to the inclusion of patients from the departments. The departments at Hillerød Hospital had Doris Christensen as contact person. A contract was written for collaboration between Copenhagen University (Hillerød Hospital) and Aarhus University (Århus Sygehus).

When patients were approached and invited to participate in studies II and III, staff at the ward were asked if it would be ethically acceptable to ask the patients about participation. Patients were advised of the voluntary nature of the study and their right to withdraw at any time. This procedure was renewed at any contact, since critical illness often leads to memory loss.

I knew my name when they asked, but I only knew my old addresses. They reoriented me many times.

Patients who demonstrated symptoms of depression or PTSD were offered a letter to their GP as a call for treatment. A copy of the letter was sent to the patient.

RESULTS

Among the 3,066 admissions in less than two years, 641 patients were included, representing 6,427 days in the ICU and more than 18,000 delirium assessments; for details on diagnostic groups see Paper 1. Included patients differed from not included in age, SAPSII, ICU stay, mortality and ICU site (table 3).

	Not-included n = 302 (32%)	Included n = 640 (68%)	*p-value*
Age, mean (sd)	60.4 (16.5)	63.5 (14.6)	<0.01
Men, n (%)	164 (54%)	379 (59%)	0.15
SAPS II mean (sd)	46.3 (18.9) *	40.9 (16.9)	<0.01
Medical, n (%)	156 (52%)	285 (45%)	0.04
ICU stay, median (10;90 % percentil)	5 (2;16)	6 (2;25)	<0.01
ICU Mortality, n (%)	93 (31 %)	60 (9%)	<0.01
ICU, n			
ITA, Aarhus	177	313	
OVITA, Aarhus	72	152	<0.01
transfered ITA/OVITA	9	41	**
Hillerød	44	134	

* n = 91, due to missing SAPSII data
** differences between the ICUs, Kruskal Wallis

Table 3
Demographics of not-included and included patients

More than 90% of the invited patients accepted participation in the interviews, giving 870 interviews (1-3/participant) (table 4). The interviewed were significantly younger, had a lower SAPSII, were mostly surgical patients, and fewer were delirious than were patients that were not interviewed. More females than males were interviewed, but this was not significant, nor was length of ICU stay (Paper 2, table 1).

	1 week	2 months	6 months
ICUMT	325	295	246
HTQ		296	247
STAI		296	248
MDI		296	248
BI		294	243
SF-36		279	240

Table 4
Fulfilled questionnaires at the three time points

The flow diagram in figure 2 provides details on exclusion and inclusion of patients and on patients lost to follow-up.

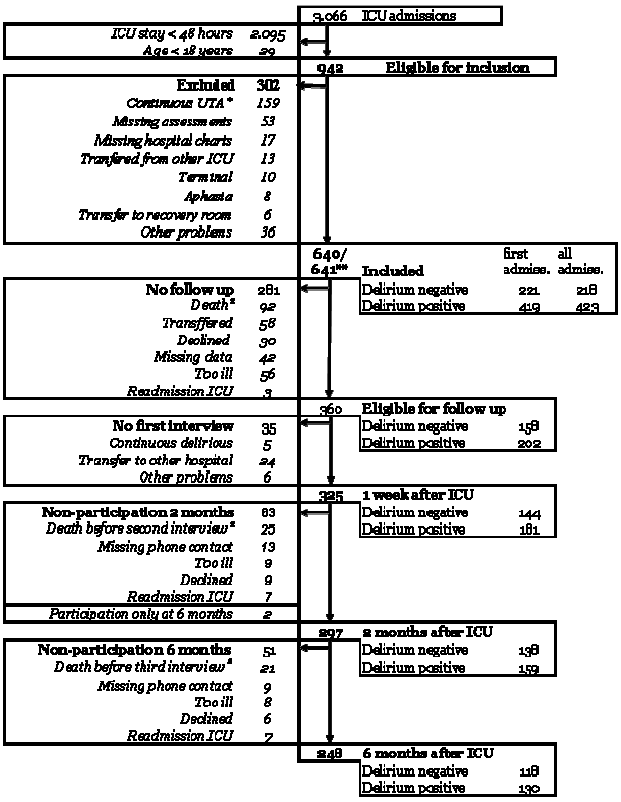

Figure 2
Flow chart
* UTA: Unable to assess with the CAM-ICU.
** one UTA patient became delirium positive at ICU readmission
2 If patients were too ill and then died, only the first reason for non-participation is shown

DELIRIUM

Delirium was detected in 65% of the patients during their first ICU stay; 35% were delirium negative (figure 2). Statistically significant variations characterise the delirious patients: they were older, had a higher SAPSII, were intubated longer, stayed longer in the ICU and ICU mortality was threefold that of the non-delirious patients (Paper 1, table 1).

Delirium was detected more frequently in males than females, but this finding was not significant. ICU patients were comatose 35% of the time, delirious 20% of the time and without delirium or coma 45% of the time during their stay in the ICU.

In 69% of the time the delirious patients had a RASS less than or equal to zero (Paper 1, Figure 2). Hypoactive delirium was detected in 40% of the patients, hyperactive delirium in 12%, and the remaining 48% were identified with mixed delirium.

Days with delirium (one to four positive assessments/day) calculated per patient had a median of 3 days (IQR 1 - 10), see figure 3.

Only 20% had more than 10 CAM-ICU POS assessments; 45% had fewer than four CAM-ICU POS, and 18% had only one CAM-ICU POS.

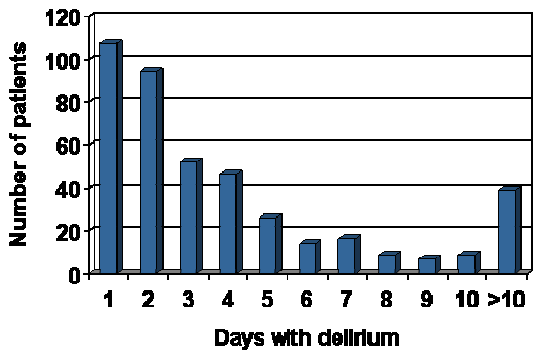

Figure 3
Duration of delirium in the 419 delirious patients

On admission to the ICU, 41 patients were already delirious. If readmissions are included in the calculations, one former UTA patient and three delirium-negative patients became delirious, modifying the percentage of delirious to 66%.
Prior to ICU admission, delirious patients more often than non-delirious patients used antidepressants (11% vs. 7%), anxiolytics (22% vs. 18%), hypnotics (28% vs. 23%) and antipsychotics (11% vs. 7%). Although these findings were consistent, they were not statistically significant.
Treatment with intravenous haloperidol was used in 36% of the 641 patients during the ICU stay. Eight patients had haloperidol though they were CAM-ICU UTA (n=2) or NEG (n=6); all were either wailing or bothered by hallucinations. In 22% of the 641 patients oral antipsychotics, mainly olanzapine, were used.

SEDATION
Patients were not sedated during 71% of their ICU stay. The impact of sedation on the development of delirium was estimated with regard to 1) sedatives, 2) administration form of the sedatives (both also estimated in relation to time to first positive delirium score and the total ICU stay), and 3) fluctuations in sedation level priory to first positive delirium score.

1: sedatives
In the time period until first positive delirium score, propofol and delirium were positively associated (OR 1.41), whereas midazolam had a decreasing association with delirium (OR 0.61). Both were, however, not significant after adjusting for gender, age, SAPSII, ICU site and setting (Paper 1, table 2).
For the total ICU stay, propofol increased odds ratio (OR) for delirium significantly (OR 1.39; p = 0.003 adjusted), whereas midazolam did not affect the rate of delirium (OR 0.98).

2: administration form
In the time period until first positive delirium score, patients received no sedation 56% of the time, continuous infusions 38% of the time, and bolus 6% of the time. The administration of continuous infusions of midazolam appeared to decrease the incidence of delirium significantly (OR 0.41, p<0.003) compared to propofol or compared to no sedatives (Paper 1, table 2).
For the total ICU stay: Patients received no sedation 71% of the time, continuous infusions 23%, and bolus 6% of the time. We found a positive association between bolus propofol administration and delirium, which, however, was not statistically significant after adjustment. This is in contrast to continuous administration of propofol, which was significantly negatively associated with delirium, as was continuous administration of midazolam.
3: fluctuations in sedation
The OR for development of delirium from a stable RASS to a RASS with changes of more than two levels (major fluctuations in sedation level) was 5.98 (unadjusted) and 5.19 (adjusted) (p<0.001) (Paper 1, table 2). We found that any change in RASS significantly affected delirium status. The OR was 1.32 (1.26–1.40) (unadjusted) and 1.36 (1.29–1.44) (adjusted) for each RASS level change (p<0.001). The OR was exponentially multiplied for every change, e.g. a patient sedated to RASS -4 that was awakened to RASS 0, and then re-sedated to -4, had an OR of 1.328 = 9.22 for delirium.

MEMORIES AT THE ICU MEMORY TOOL

I was in a large hall with 1000 beds. At the end of a brick wall was a huge clock. I walked around in there as a healthy person. Each bed had a small computer disc that I pulled out. There were social security numbers on them, and one was mine. Then I knew it was my bed in case of an emergency.

In all 360 participants were assessed with the ICU memory tool (ICUMT) at least once, 214 of these three times. See table 5. Of the 35 participants without a 1-week ICUMT, five were not interviewed due to delirium at the CAM-ICU.

	ICUMT at 1 week	ICUMT at 2 months	ICUMT at 6 months
ICUMT 1 week	63	46	214
ICUMT 2 months		5	30
ICUMT 6 months	2		0

Table 5
Overview of interviews with use of ICU memory tool (ICUMT).

Some kind of memories from the ICU were recalled in at least one of the three interviews by 99% of the non-delirious participants and by 89% of the delirious patients.
Non-delirious patients had significantly more factual recall and fewer memories of delusions than did delirious patients at all three interviews; memories of feelings did not vary significantly between non-delirious and delirious at any time (Paper 3, table 2).
The feeling that “someone is trying to hurt me” was present in both non-delirious and delirious at some time point (table 6).

	After 1 week		After 2 months		After 6 months	
	no	yes	no	yes	no	yes
non-delirious	134	10	123	14	58	4
	93%	7%	90%	10%	94%	6%
delirious	144	36	121	37	49	10
	80%	20%	77%	23%	83%	17%
p value	0.001		0.003		0.071	

Table 6
Memories of the feeling that “someone was trying to hurt me”

See Paper 3 figure 2 and the matching narrative for additional examples of memories.
Among patients reporting no recall of the ICU (n= 25), there were significantly more that had been delirious (n = 23) than had been non-delirious (n = 2) (p < 0.001).

PSYCHOMETRICS

The prevalence of PTSD, anxiety, and depression was significantly higher than in the general population, and correlated with the type of ICU memories. Presence of more than one of the assessed mental conditions was seen but not exclusively; i.e. PTSD was found in five participants without signs of depression or anxiety, see figure 4.

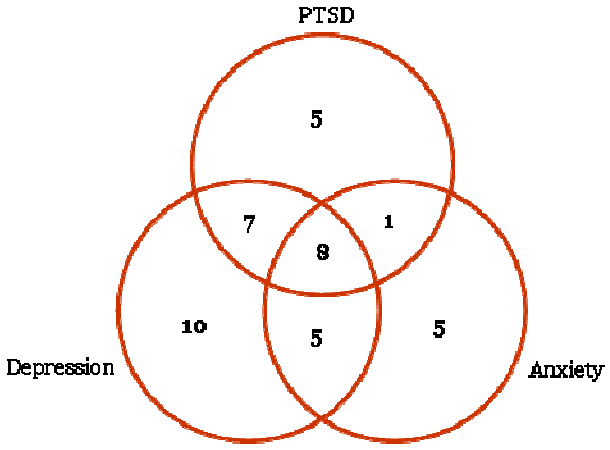

Figure 4

Number of patients with any degree of symptoms of PTSD, anxiety, or depression – and combinations. Results of the 2-month screenings. Similar results were found after 6 months.

PTSD

Symptoms of severe PTSD were found in four patients (1.4%) after 2 months, three of which had experienced delirium, and 17 (6%) patients had probable PTSD, half of whom were delirious. At 6 months follow-up, PTSD was found in seven patients (3%) (of whom four were previously delirious), and five (2%) had probable PTSD (four were formerly delirious) (Paper 2, table 2). PTSD was significantly more frequent in younger age groups at both time points. In females though, it was seen after 6 months only (p = 0.01).

Once it felt like four people were changing my diaper. The last one was a man who groped me which infuriated me.

Time on mechanical ventilator was never associated with symptoms of PTSD (nor depression or anxiety) (paper 2). Neither haloperidol, nor sedatives, nor other psychotropic drugs given in the ICU significantly affected the prevalence of PTSD, anxiety, and depression after discharge.

DEPRESSION

After 2 months, 30 patients (11%) suffered from depression according to the MDI: 12 (4%) had mild, 10 (4%) had moderate, and 8 (3%) had severe depression. In the severely depressed group, we found twice as many previously delirious than non-delirious patients (Paper 2, table 2), though this was not statistically significant. After 6 months, symptoms of depression were found in 18 patients (9%). Depression was more prevalent in younger age groups after 2 months (p = 0.002), but this was borderline significant after 6 months (p = 0.08). Females had more symptoms of depression at 6 months than did men (p=0.002 at the multiple regression analysis)

I was particularly sad the day I was discharged. They wanted to conduct a response measurement. This woman wheeled in a table with a computer and speakers. I had to press a button and started to cry. I kept crying because it was too overwhelming.

ANXIETY

Previously delirious patients were more anxious according to the STAI after 2 months versus not delirious (12 vs. 7), but after 6 months this changed, and five vs. four had symptoms of anxiety (Paper 2, table 2). Again anxiety was more prevalent in younger age groups at both interviews, and for females at 6 months (p=0.02)

HRQOL AND HEALTH CARE DEPENDENCY

Based on answers from the 279 patients at the interview after 2 months and 240 patients after 6 months, there was a significant decrease in four domains of the SF-36 (vitality, social function, role emotional, and mental health) if patients had PTSD, anxiety, or depression. Bodily pain and general health (from SF-36) were reduced in patients with PTSD, anxiety or depression compared to patients without PTSD, anxiety or depression. This was, however, not significant regarding PTSD at 6 months (Paper 2, table 4). Delirium was not found to affect HRQoL on any of the SF-36 scores (Paper 3, table 3). Also, the type of memories was not associated with HRQoL (Paper 3, supplemental material, table 4a and 4b).

Health care dependency (ADL) measured at BI was not affected by delirium, age, nor SAPSII after 2 or 6 months. After 2 months "days of intubation" had statistically significant association with ADL in the regression analysis (p = 0.002), but this effect was absent at 6 months (p = 0.87). The only statistically persisting differences in ADL from 2 to 6 months were seen regarding gender. Mean BI was 95 (CI 93;97) for males, whereas it was 91 (CI 88;94) females, regression coefficient -3.68 (p=0.02) after adjustment for SAPS II, age, ICU site, and medical/surgical.

In our study, mobilisation was recorded, but kept out of the analysis since mobilisation and occupational therapy became a solution to help patients out of delirium, and not an equal priority for all patients.

DISCUSSION

Our three major findings were that fluctuations in sedation level increased delirium, that delirium was not associated with PTSD, anxiety, or depression, and that delirium did not affect quality of life, although it did have an impact on the patient memories from ICU.

METHODOLOGICAL CONSIDERATIONS

A A cohort study, like the present, where a group of individuals (patients admitted to the three ICUs) is followed over time (from admission to 6 months after ICU discharge, dropout, or death), gave excellent opportunities to analyse a binary outcome (delirium), not only as to whether or not the outcome occurs, but also the time at which it occurs (e.g. after sedation fluctuation) [146]. By using censuring, we can express the causal association, i.e. the influence from sedation fluctuations or sedatives, on the incidence of delirium, instead of the reverse causation: that sedation is given because of delirium. A disadvantage of the cohort study is the lack of randomisation that excludes the researchers' oppor-

tunity to match the participants. This disadvantage should, however, be eliminated by the size of the present study.
Overall, our included cohort is a sample of less ill patients, more surgical patients, and patients that stayed longer in the ICU (see table 1 in the dissertation, Paper 2, and Paper 3) than in other studies [147-149]. Surprisingly, included patients in Paper 1 were older than those not included, although the age difference evened out on follow-up (Papers 2 and 3). A study of older participants than non-participants is, however, not unique [149].
Sedation can be interpreted in several ways [150]. We choose a priory to analyse RASS fluctuations larger than 2. Mean RASS, days with RASS other than 0, days in coma, or any other cut-point might have been interesting as well. However the decision was made based on clinical observations of patients experiencing discomfort because of the daily wake-up call.
Implementation of the CAM-ICU has been a gradual process at the ICUs at Aarhus University Hospital, although 53 patients had to be excluded from the study due to missing assessments. This can be due to understaffing or other reasons. By recording positive (POS) on the sheet (Figure 1), the nurse can get the feeling that she/he "marks" the patient and shortens the way to antipsychotics. A positive CAM-ICU is however never a shortcut to medication. It is by now well known in the involved ICUs that delirium treatment is a package and that it is first and foremost about communication with the patients and relatives and optimising the environment around the patient. Only if this does not help, medical treatment will be considered.
The ICU Memory Tool (ICUMT) begins with a few overall questions, coming across as a gentle opening before the questions regarding ICU memories [127]. These questions have apparently never been used in an analysis [110,147,148,150-154]; nevertheless they represent a good icebreaker. A few patients were affected deeply by the recall caused by question 4. By starting all telephone interviews with the ICUMT and ending up with the SF-36, we attempted to ensure that participants' attention was directed towards present life at the end of the interview. Question 5 about transferring to the general ward quite often led to narratives from the ward, and not always positive ones. By asking patients this question they could get the feeling that the interviewer would pass the potential complains to the relevant ward. Since this was not the case, I had to be very specific in directions to patients that wanted to complain. Patient satisfaction surveys can be very relevant–but were not the aim here–and the focus of the interview was temporarily changed.
Although only the third part of the Harvard Trauma Questionnaire (HTQ) was used in the study (see method page 17), the first two parts (describing traumatic events, and open-ended questions) were dealt with in the ICUMT. For diagnosing PTSD this would not be enough, but still the ICUMT led the patients' minds through the experiences from the ICU, and it probably influenced the HTQ answers. Patients answering "not at all" to this first question found questions 2, 11, 12, 15, and 16 irrelevant, since a non-exciting event could not have influence on their minds. A few patients were unsure of how to answer "you are uncommitted towards or isolated from other humans" because of geographical distance to relatives or isolation due to immunosuppressant therapy. They were asked to answer "not at all" if they did not feel uncommitted or isolated.
In most interviews with the State-Trait Anxiety Inventory (STAI), I had to explain the sentence "I feel anxious" (in Danish: "Jeg føler mig ængstelig") and some times I had to add the word "angst" or "bange" ("scarred") to guide the patients towards an answer. This could indicate a linguistic problem, but presumably caused no bias in the data since the remaining questions in the STAI were clear to the participants.
Although anxiety is one of the symptoms of PTSD, few had anxiety as measured on the STAI. This could suggest a problem with at least one of the scales.
The time span from "less than half of the time" to "some of the time" in the Major Depression Inventory (MDI) was too big for a few patients who would have preferred a more detailed scale, although that would not have had any influence on how many depressed we found.
Answering "Have you felt lacking in energy and strength?" many participants stated that they had a lot of energy but too little strength. Lack of strength (in the muscles) must be considered as very normal after a long illness. Since both conditions are in the same question, the MDI did not give the opportunity to distinguish between them and participants had to choose.
Although the Short Form-36 (SF-36) is often used to assess HRQoL in former ICU patients [109,111-115,154-159], it has potential sources of error. Question 2 "compared to 1 year ago, would you say your health is…" is missing in the cumulative analysis, though it could have been very relevant in our cohort. A questionnaire should only contain questions that can be answered unambiguously. Sill the SF-36 has several complicated questions. In answering question 4 or 5 "During the past 4 weeks… how much of the time … did you have to cut down on the amount of time you spent on work or other activities?", patients often answered "none of the time" since they had been more active in the preceding 4 weeks than they had been during the first 4 weeks after the ICU – although they still were on sick leave. The Danish translation of question 9a ("…did you feel full of life" translated to "har du følt dig veloplagt og fuld af liv", and question 9h ("… have you been happy" translated to "har du været glad og tilfreds") were difficult for a few patients to answer. As one stated:
"I haven't been happy for many years, but I'm satisfied…".
One question (9d) kept the double combination of feelings from the original ("… calm and peaceful") but in question (9f) "have you felt downhearted and depressed" the translation ("har du følt dig trist til mode") solved the problem. In questions 11a and b, participants are asked to state whether they appeared more sick or healthy than other people. Several participants pointed out that that very much depended on who the other people were (e.g. those in the nursing home or rehabilitation centres) and "sick"… is that a cold or critical illness? These participants have a wider range of contacts than do most other people due to the ICU stay.
The documentation of medication raised the possibility that some doses might be prescribed (and noted in my database) but not given due to special circumstances, but the opposite could occur as well. However, the influence of this on our results/conclusions must be considered as minimal.
With one telephone interviewer, a high consistency should be ensured at the 2- and 6-month interviews. One patient stated that the nurse was so very kind at the first (ward) interview, so he said "yes" to a lot of memories from the ICU, but at the 6-month interview, he stated that this was probably wrong. Due to the nature of bias, this was either a recall bias (that he after 6 months had forgotten what he recalled earlier) or bias due to patients' effort to please. Although 45 patients declined to be interviewed, the kindness of the interviewers might have caused other patients to answer more than necessary. The main reason for declining participation in the final interview was "nothing new" to add.

Other patients expressed that the questions had had a therapeutic effect on them. Probably, the opportunity to have an experienced nurse to oneself on the phone as long as desired had a positive effect on some patients. Since this possibility was the same for patients notwithstanding whether they had suffered from delirium or not, it may not have had any influence on the consequences of delirium in the follow-up scores. It might though have led to a slightly better outcome for a few patients. This effect was probably the same for patients with and without delirium. The effect might have improved the outcome for patients who suffered from severe depression and/or PTSD at 2 months, when a referral to their GP was given. Despite the potential for inaccurate responses, the overarching purpose of the study was hardly compromised since the results were far from significant (delirium vs. PTSD/anxiety/depression) or highly significant. Informed consent must never be a pretext for inaction. In an implementation study nurses reported that some patients were unexpectedly found to be overtly delirious a time when they just had signed a consent form [44]. To avoid this, our participants were assessed with the CAM-ICU before the first interview, revealing five delirious patients.

COMPARISON WITH THE EXISTING LITERATURE

In the present study, we tried to explore the complete multifactorial coherence in the "cobweb" between sedation, delirium, memories, PTSD (anxiety and depression), and HRQoL. No other studies have shown complete results for this, but several studies have explored parts of it. To simplify this discussion of a comparison of our findings with those in the literature, the letters in figure V will be used, and further discussion regarding anxiety, depression, and drugs will be minimised.

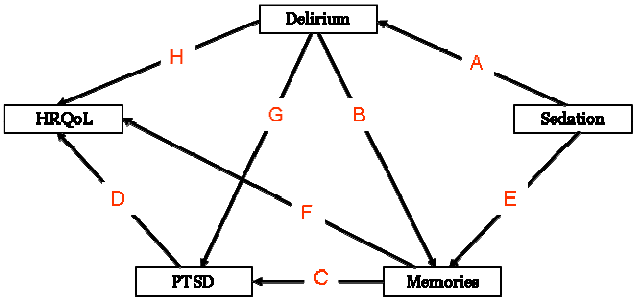

Figure 5
The multifactorial coherence of the literature, the "cobweb".

A. SEDATION AND DELIRIUM

Documentation of the influence of sedation on delirium as we analysed it is very limited, although it seems an obvious consequence of daily awaking trials. One RCT found that daily interruption of sedatives and analgesics used for sedation (analgesics for pain continued) did not affect the incidence of delirium, and for every seven patients in whom interruption of sedation was practised, one life was saved [80]. The study [80] had a strong design being a RCT, but the Danish context is perhaps different. As patients in Denmark are sedated less (more awake), perhaps daily awakening would cause fluctuations in RASS, which could lead to delirium. Our recommendation is less or no sedation, rather than daily awakenings. This should, of course, be integrated with improved pain management.

The medications used for sedation (and pain relief) make the "cobweb" even more complicated. Comparison to other studies dealing with delirium and medication is difficult because data in cohort studies are often pooled, which leaves the question "what was first?" – the delirium or the medication. RCTs should be the answer, but are still limited in number and the conclusions are ambiguous [60]: still our method of analysis is not comparable to a RCT. We recommend a large RCT of ICU patients to clear up the cobwebs. Reading these results regarding delirium and medication, one should furthermore be aware that withdrawal symptoms of the medications used for sedation are highly associated with delirium.

B. DELIRIUM AND MEMORIES

Memories of delusion are considered to reflect a previous delirious state [110,160], and the absence of memories of being transferred out of the ICU was significantly associated with delirium in 41 patients, but any recall of factual memories was not significant [161]. In cancer patients (outside the ICUs) meeting DSM-IV criteria for delirium, a reduced level of consciousness caused a decreased ability to recall delirium. None of these patients were deeply sedated since they had to breathe on their own [162]. Among these patients, 46% had no recall of being delirious, but those who did remember the delirium found it distressing regardless of the subtype of delirium [162]. The more severe the delirium the less likely the patients were to recall their delirium episode. In the ICUMT recall of (ICU) hallucinations is one of the "memories of delusion" [110], but when severe hallucinations induce less recall of delirium[162], the ICUMT can hardly be used as marker for ICU delirium. The strength of our study was that a high number of factual memories and a low number of memories of delusion correlated with ICU delirium (Paper 3, table 2), but the absence of memories of delusion does not preclude delirium with absolute certainty.

Different methods for delirium detection probably contribute to the variation in the incidence of ICU delirium. Incidences vary from 20 to 89%, as illustrated in figure V, where CAM-ICU is green and ICDSC is yellow, and although both are considered as valid tools[29,163,164], the variation is large.

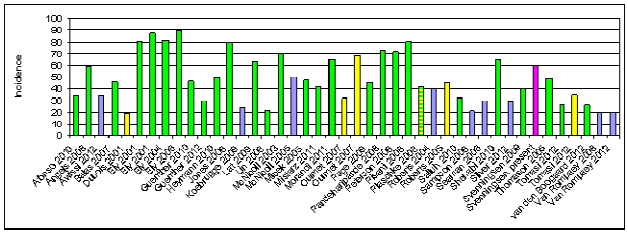

Figure 6
Incidence of delirium at ICUs since 2001. [2,16-18,21,22,27,30,42,45,47,117,163-191]

Because loss of factual memory from the ICU was present in 11% of the participants, it was necessary to reinform and assure that there was a wish to take part at the beginning of any new contact. In daily clinical practice, the staff must assess delirium status at the beginning of ward rounds. A CAM-ICU positive/delirious patient must be considered as unable to decide whether respiratory therapy should be initiated if an exacerbation of breathing problems should occur or able to make any other important decisions.

C. MEMORIES AND PTSD

Memories of delusions were found associated with PTSD after both 2 and 6 months in our study, and in two studies by Jones [156]. The assessment method for memories and PTSD vary so

much that comparisons are difficult [106,109,192,193]. Furthermore, patient recalls can change over time [147]. Perhaps we helped to stabilise the patients' memories by asking them to recall the memories three times within half a year. We do not know the answers to this. Likewise it is not known whether the non-delirious with memories of "someone trying to hurt me" in our data were CAM-ICU false negative or whether patients did indeed have occasion to be concerned, e.g. by sharing a room with an aggressive patient. Symptoms of PTSD have been seen more frequently in females in other studies, but not in association with memories of delusions with or without factual recall[44].

D. PTSD AND HRQOL

Our results confirmed other studies that symptoms of PTSD are more common in younger patients [105,106,194,195] and in females [103,105,195]. The association between symptoms of PTSD and decreased HRQoL has also been described before [192], [109].

E. SEDATION AND MEMORIES

Studies have suggested that lighter sedation is associated with more ICU memories [77,104,150]. Although some patients have recounted horrifying memories of their ICU stay, we still recommend keeping patients more awake (less sedated).
Patients who were conscious during mechanical ventilation describe in a qualitative study [196] that caring actions, e.g. holding the patients' hand, physical contact in general, eye contact, and proper analgesics, helped them cope with the situation. By keeping patients more awake, the opportunity to communicate improves [91], and also the opportunity to optimise care.

F. MEMORIES AND HRQOL

Numerous qualitative studies describe how memories from ICU influence patients lives [197-200], but only a few have measured HRQoL 74. In our data no pivotal differences were seen on memories and HRQoL. The question remains unanswered whether qualitative or quantitative methods are best for the determination of the "real" influence on the quality of life. A mixed-methods approach combining qualitative and quantitative data might increase our understanding of how ICU memories impact quality of life.

G. DELIRIUM AND PTSD

We failed to find an association between delirium and PTSD corresponding to other studies [195], but the prevalence of PTSD was higher than in the general Danish population [138]. We found some overlap in symptoms of PTSD, anxiety and depression. Considering the definition of PTSD, it is surprising that not all our patients with PTSD had anxiety as well. This has, however, been described by others, who note that PTSD overlaps with major depression in 48% of patients and that 34-70% of patients with anxiety have depression [201]. The only comparable Danish study found one patient (3%) with PTSD, although another questionnaire was used, and this can explain some of the differences [202].

H. DELIRIUM AND HRQOL

A general decrease in HRQoL is understandable after critical illness, and an association with delirium has been reported [149,203]. Our findings were inconclusive, and the significance disappeared after adjustments in the study by van den Boogaard [149], whereas van Rompaey deselect adjustments [203] giving less opportunity to compare results.

DEPRESSION AND ANXIETY

In a recent Danish study Strøm et al. [77] found depression in one of the non-sedated vs. four2* of the sedated patients. In total 5/26 = 19%, which is twice as many as we found.
On request, Strøm informed us that anxiety (STAI > 50) was found in five of the non-sedated and eight of the sedated patients in total 13/26, giving 50% with symptoms of anxiety. This disagree with our results, with 4% showing symptoms of anxiety after 6 months – using similar questionnaires. The main reason for the differences can be in the study size, as stated by Strøm.
Preoperative anxiety and depression was found not to associate wit postoperative delirium in planned surgery [204].

PSYCHOTROPIC DRUG

Our results showed a higher although not significant use of psychotropic drugs in delirious patients. It could be that the delirious patients had more symptoms of anxiety and depression prior to ICU stay. Because admissions were acute, we can not assess patients prior to admission, but in studies of patients admitted for planned surgery, no associations were found between postoperative delirium and preoperative anxiety or depression even though the prevalences of these conditions were high [77] .

OVERALL

Delirium is not only seen in the ICU but is also very common on general wards, and even in patients being cared for at home, and the economic and social consequences are massive [205]. Although we failed to show a significant decrease in HRQoL after delirium, no one can imagine that the experience of delirium could be positive for the patient – just look at the mortality rate which increased three-fold when delirium occurred (Paper 1, table 1). In a cohort study like ours, it is not possible to say whether delirium occurs because death is imminent or whether death occurs as a result of one more organ failure: delirium. Notwithstanding, preventing delirium is essential, and rethinking sedation procedures seems reasonable.

CONCLUSION

In this dissertation, we found that fluctuations in sedation increases delirium in the ICU.
We also found a correlation between ICU delirium and memories at least 6 months after ICU discharge, although the impact on health-related quality of life and healthcare dependency was insignificant.
We cannot reject the notion that there is a correlation between memories and PTSD, nor that PTSD (anxiety or depression) decreases HRQoL.
We can reject the notion that there is a direct correlation between ICU delirium and decreased HRQoL, and that there is a direct correlation between ICU delirium and PTSD, anxiety, and depression, even though the prevalences were high.
No statistically significant correlation was found between ICU delirium and use of psychoactive drugs prior to admission.
The use of patient diaries and follow-up was limited, but the results showed neither harm nor benefit from the initiatives.

[2]* The abstract says three, but four is correct cf. T.Strøm (as seen in the table of the study).

PERSPECTIVES

The study produced far more data than the dissertation could encompass. Analyses regarding alcohol or tobacco dependency prior to ICU admission, hearing or visual deficits, comorbidity, mobilisation, trips outside the ICU, and qualitative interpretation of the patients narratives from ICU memory tool are planned. Due to the use of haloperidol in doses over 30 mg/day, a handwriting test was given to the first 180 participants in 2-month follow-up. Preliminary analyses of these showed no significant variation in fine motor control between patients that received or did not received haloperidol. Further analyses, presumably including graphology, are crucial before any conclusion can be published. Despite the amount of data, information in four additional areas would have been preferable:

Firstly, a registration of which room patients were in, presence of any fellow patients, and the educational level of the bedside nurse should be undertaken. Several patients were uncomfortable sharing a hospital room. After the data collection was completed, the ITA was converted from a layout with only two-bed rooms to one with one-, two-, and three-bed rooms. Further research on the impact on delirium incidence, time in delirium, and advantages and disadvantages as experienced by patients and relatives in relation to room conditions could be a guideline for coming ICUs. Regarding the ICU room[206], when external circumstances, e.g. fellow patients or ICU lay-out, are unalterable, a temporary solution could be an eye mask and/or earplugs. Studies regarding these initiative are seen[207], but the subject needs more research. For instance, will a delirious patient benefit from this, or will the lack of visual and hearing impulses increase the delirium? Despite Hillerød having the oldest patients with the highest SAPS, they had significantly less delirium. Hillerød had mostly single rooms (at the time of the data collection), whereas the ICUs in Aarhus mainly had two-bed rooms. Hillerød had 95% ICU certified nurses, whereas Aarhus had approximately 50%. Further studies should try to take this into account.

Secondly, sleep assessments would have been interesting, though difficult to measure. Intervention study of earplugs and eye masks have been preformed previously[208,209], but have excluded delirious patients, leaving the question unanswered whether delirious patients could benefit from these simple utensils. Other sleep promoting care must be considered as well[210].

Thirdly, a registration of non-invasive-ventilation (NIV) should be done. Sedation of patients in non-invasive-ventilation seems to be ongoing, but the impact on the stress and delirium it might cost the patient remains unknown until further research surfaces.

And finally, an assessment should be made of cognitive function after discharge to see whether delirium increases dementia and whether this is dependent on age. In a post-operative setting, delirium seems to decrease cognitive function long after surgery[211]. Further investigation in this area is important because patients' social lives can be devastated as a consequence of the cognitive decreased seen after delirium.

Based on the spin-off benefit of the collaboration between bedside staff and researchers in the present study, a "manual" on how to take best care of the delirious patient will have great perspectives for the economy, the staff, and last but absolutely not least the patients.

SUMMARY

In the intensive care units (ICUs) sedation strategies have changed in the past decade towards less sedation and daily wake-up calls. Recent studies indicate that no sedation (after intubation) is most beneficial for patients. A smaller number of these patients have been assessed for post-traumatic-stress disorder (PTSD) after ICU discharge, but none of them were assessed for delirium while in the ICU. In other studies, delirium in the ICU is described as distressing for the patients and increasing morbidity, i.e. dementia after discharge and mortality. The associations between sedation, delirium, and PTSD have not previous been described.

The aim of this PhD study was to investigate 1) how sedation is associated with delirium in the ICU, 2) the consequences of delirium in relation to PTSD, anxiety, and depression, 3) the consequences of delirium for the patients' memories from ICU and the health-related quality of life after discharge.

In a prospective observation study with patients admitted a minimum of 48 hours to the ICUs in Aarhus or Hillerød, we included all patients aged > 17 years. Non-Danish speakers, patients transferred from other ICUs and patients with brain injury that made delirium-assessment impossible were excluded. Patients were interviewed face-to-face after 1 week, and at 2 months and 6 months by telephone using six different questionnaires.

Among 3,066 patients admitted to the ICUs, 942 fulfilled the inclusion criteria. Primarily due to the inability to test for delirium, 302 patients were later excluded. Of the remaining 640 patients, 65% were delirious on 1 or more days. Fluctuations in sedation levels increased the risk of delirium statistically significantly with or without adjustments for age, gender, severity of illness, surgical/medical patient, or ICU site.

After 2 months vs. 6 months, 297 patients vs. 248 patients were interviewed. PTSD was found in 7% vs. 5%, anxiety in 6% vs. 4%, and depression in 10% at both interviews. Delirium had no association with any of the psychometric results. Memories of delusion and memories of feelings were statistically significantly associated with delirium and with the psychometric outcomes, whereas memories of facts had no association with the psychometric outcomes. Health-related quality of life (SF-36) was statistically significantly decreased in most of the domains if patients had PTSD, anxiety, or depression but was not associated with delirium or the type of memories.

Conclusion: Fluctuations in the level of sedation of patients in the ICU increased the incidence of delirium, but the delirium did not affect the risk of PTSD, anxiety, or depression. These were, however, affected by the type of memories the patients had. Health-related quality of life (SF-36) was decreased if patients had PTSD, anxiety, or depression but was unaffected by memories of the ICU and the presence of delirium while in the ICU.

LIST OF ABBREVIATIONS

ADL	Activities of Daily Living
BI	the Barthel Index of Disability
CAM-ICU	the Confusion Assessment Method for the Intensive Care Unit
DI	the Delirium Index
DSM-IV	the Diagnostic and Statistical Manual of Mental Disorders (version 4, by the American Psychiatric Association)
DSR-R-98	the Delirium Rating Scale-revised-98
HRQoL	Health related quality of life

HTQ	Harvard Trauma Questionnaire
ICD-10	International Classification of Diseases (version 10, by World Health Organisation)
ICDSC	Intensive Care Delirium Screening Checklist
ICU	Intensive Care Unit
IES	(Revised) Impact of Events Scale
ICUMT	ICU Memory Tool
i.m.	intramuscular (injection)
i.v.	intravenous (injection)
ITA	Intensiv Terapi Afsnit
MDAS	Memorial Delirium Assessment Scale
MDI	Major Depression Inventory
NEG	Negative on the CAM-ICU (indicating no delirium)
OR	Odds ratio
p.o.	per os (orally or sublingually administration)
POS	Positive on the CAM-ICU (indicating delirium)
PRN	Pro re nata
PTSD	Post-Traumatic Stress Disorder
RASS	Richmond Agitation and Sedation Scale
RCT	Randomised Controlled Trials
SAPS II	Simplified Acute Physiology Score version 2
SF-36	Short-Form 36 (health related quality of life)
STAI	State-Trait Anxiety Inventory
UK	United Kingdom
UTA	Unable To Assess (with the CAM-ICU)

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