Title: Sleep and other factors associated with mental health and psychological distress after intensive care for critical illness

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ACTRN: 12605000166673

Short running head: Psychological outcomes after ICU

Word count: Text 2961

Electronic supplementary material

ABSTRACT

Purpose: Some patients who survive intensive care unit (ICU) treatment report psychological sequelae during recovery. This study examined factors associated with psychological outcomes of former ICU patients up to 6 months after hospital discharge.

Methods: Participants (n=195) were adult survivors of ICU enrolled in a multicenter trial of physical rehabilitation after hospital discharge. The 36-Item Short-Form Health Survey (SF-36), the Impact of Events Scale (IES), the Depression, Anxiety and Stress Scales were completed, and sleep rated on a 5-point scale at weeks 1, 8 and 26; clinical and demographic data were obtained from patient records. Results: Participants were 41% females with mean±SD age of 57±16 years and APACHE II scores of 19±7; median lengths of mechanical ventilation and ICU stay were 89 hours and 6 days, respectively. Impaired mental health, depression, anxiety, stress and psychological distress significantly improved after week 1. Female gender, younger age and sleeping problems were associated with impaired psychological outcomes in bivariate analyses. Age; gender; week 1 anxiety, depression and stress; week 26 sleeping; and rehabilitation study group were entered into multiple linear regression analyses for week 26 IES and SF-36 Mental Component Summary (MCS) outcomes. IES scores were associated ($p<0.05$) with gender, week 1 stress and week 26 sleep but not study group; MCS scores were associated ($p<0.05$) with week 1 stress and week 26 sleep but not study group. Conclusion: Female gender, early levels of increased stress and problems sleeping are associated with worse psychological recovery for survivors of a critical illness.

Word count: ~~249~~ 248

Keywords: critical illness, intensive care, mental health, psychological distress, sleep

Introduction

Critical illness has been described as being a pandemic that will not wane in the coming decades [1]. In 2006 in the United States it was estimated that there were 55,000 patients in an intensive care unit (ICU) on any given day [2]. In Australia at that time there were approximately 82,500 adult patients admitted to public intensive/critical care units per annum [3], of a population of 21.9 million people. In the last decade there has been increasing interest in the course of recovery of survivors of an episode in an ICU, with identified problems of persisting morbidities, poor physical functioning, neurocognitive deficits, compromised health-related quality of life (HRQOL), psychological distress and impaired mental health [4]. These problems are associated with substantial burden on survivors, their families and carers, health care systems and communities in general [1, 5].

Recent rigorous reviews have summarised research on HRQOL [6] and psychological problems in survivors of critical illness that required ICU treatment [7-9]. In a systematic review of 21 studies involving 7,320 adult general ICU (medical and/or surgical) survivors followed up between 6 months and 14 years after discharge it was found that HRQOL was lowered in almost all domains assessed and was significantly lower than that of the general population; HRQOL improved by clinically meaningful amounts in most domains at 6-12 months but remained lower than matched population norms [6]. Where HRQOL prior to ICU admission was assessed by proxy or retrospective self-report it too was lower than that of the general population [6]. The point prevalence of symptoms of substantial depression, posttraumatic stress disorder (PTSD) and nonspecific anxiety in acute respiratory distress syndrome (ARDS) survivors were much higher than the general US adult population up to one year after ICU [7]. A high prevalence of

depression symptoms (28%) [8] up to one year post-illness and a point prevalence of 22% for post-ICU PTSD symptoms have also been reported in general ICU survivors [9, 10].

Thus there is persuasive evidence that decreased HRQOL and psychological morbidity are common in ICU survivors, prompting recommendations for interventions to address these and other post-ICU problems [5, 11]. However the magnitude and heterogeneity of the target population necessitate further studies to identify subgroups of the population who would most benefit from targeted interventions [11]. The purpose of the present research was to identify patient factors associated with mental health and psychological distress in survivors of an episode in general ICU 6 months after hospital discharge.

METHODS

Study Design, Participants and Data Collection

Participants in this observational study were enrolled in a randomised controlled trial (RCT) of the effects of an eight-week home-based rehabilitation program on the health status and quality of life of the survivors of critical illness (protocol described elsewhere) [12]. Briefly, participants were 18 years or older, had an ICU length of stay (LOS) 48 hours or greater, were mechanically ventilated for > 24 hours, and discharged home to self-care or a family carer within 50 kilometres of the study hospitals. Patients in another organised rehabilitation program, with dysfunction preventing physical exercise or receiving palliative care were excluded.

Patients were enrolled from 6 tertiary referral hospitals, 5 district hospitals and 1 private hospital in the metropolitan regions of Sydney, Brisbane and Perth, Australia. The study was approved by the Human Research Ethics Committees of each hospital and university. In total

5,980 patients were screened with 195 enrolled between June 2005 and August 2008 (Figure 1). Participants allocated to the intervention group (n=97) received graded, individualized endurance and strength training for 8 weeks and an exercise manual supporting the training; those in the control group (n=98) received usual care.

Blinded assessments at weeks 1, 8 and 26 after hospital discharge examined physical functioning, HRQOL and psychological well being. The primary outcome for the RCT was measured by the Physical Function (PF) scale of the SF-36 [13]. The remaining 7 scales of the SF-36 assessed HRQOL. Psychological well being was assessed using the Depression Anxiety and Stress Scales (DASS-21) [14] and the Impact of Event Scale (IES) [15]. Both instruments are valid and reliable measures of psychological distress [14, 16]. Quality of sleep was assessed using an item from the 15D HRQOL instrument with a 5-point scale, ranging from 'no problems' to 'severe sleeplessness' [17] (Electronic supplementary material). Clinical and demographic data were obtained from ICU and hospital records. Participant characteristics in the control and intervention groups of the RCT were equivalent at baseline, and no significant differences in physical or HRQOL outcomes were identified at 8 or 26 weeks [18]. Data from both groups were therefore combined for the purpose of identifying factors associated with mental health and psychological distress 6 months after hospital discharge.

Data analysis

Primary outcome measures for this analysis were the Mental Component Summary (MCS) of the SF-36 [13] and IES total score; the three subscales of the DASS, and IES intrusion and avoidance were explored. Data were assessed using histograms and described using means and medians. Scores were then tested for change over time using repeated measures analysis of

variance (RM-ANOVA) and post hoc pairwise comparisons, with Bonferroni adjustment for MCS, and the Friedman test for others, with post hoc Wilcoxon Signed Ranks Tests with Bonferroni adjustment (p=.017). Bivariate associations were assessed using one-way ANOVA or the Kruskal-Wallis test, and Pearson's or Spearman's correlation coefficients. Multiple linear regression tested the relationships of treatment group, age, gender, week 1 anxiety, depression and stress, SF-36 Physical Component Summary (PCS) and sleeping at 26 weeks to MCS and IES at 26 weeks.

RESULTS

Patients (n = 195) were mixed medical and surgical ICU admissions, approximately 40% females with an average age of 57 years (Table 1). The norm-based MCS at week 1 (38.6) was 1 standard deviation below the age-matched population mean of 50, but had improved to 48 by weeks 8 and 26. Mental health, depression, anxiety, stress and psychological distress all showed significant improvement during follow-up (Table 2). Using the recommended cut-points for moderate, severe and extremely severe depression, anxiety and stress [19], the rates of participants with probable symptoms also declined during follow-up (Table 2). At week 1, over a quarter of participants reported symptoms of depression, but this proportion reduced to 17% and 21% by weeks 8 and 26, respectively. Almost one-half had symptoms of anxiety initially, but this reduced to about one-quarter at weeks 8 and 26. Stress symptoms were evident in 17%, 16% and 12% across the three measurement points.The proportion of patients reporting moderate or worse sleep problems declined from 50% at week 1 to 31% at week 26 (Figure 2).

A number of bivariate relationships ($p \leq 0.1$) were found. Females had lower MCS at 26 weeks, higher depression and anxiety scores at weeks 1 and 8, and a higher total IES at 1, 8 and 26 weeks. Younger age was associated with higher stress on DASS and total IES at week 1 ($p \leq$

0.1). Intervention study group membership was associated ($p<.01$) with higher week 1 depression, anxiety and stress scores (Electronic supplementary material). The PCS at week 26 was positively associated ($p<0.1$) with MCS and total IES scores at week 26. Reported worse sleep was associated with worse scores on all psychological outcome measures at all time points (Electronic supplementary material). Multiple linear regression analyses showed that study group membership was not independently associated with week 26 MCS (B=2.284, 95% CI -.911 – 5.480, p=.160) or week 26 IES (B=0.131, 95% CI -4.135 – 4.397, p=.952). More stress at week 1 and poorer sleep at week 26 were independently associated with lower MCS at 26 weeks, and female gender, stress at week 1 and sleep at week 26 were independently associated with higher IES at 26 weeks as shown in Table 3.

DISCUSSION

This study showed that survivors of an episode of critical illness who were hospitalized in intensive care had impaired mental health and symptoms of depression, anxiety, stress and psychological distress in the form of intrusive and avoidance post-traumatic stress symptoms 1 week after discharge home from hospital. All of these outcomes had improved by week 8 and remained approximately at the same level at week 26. Importantly, anxiety symptoms persisted for approximately a quarter of participants at 8 and 26 weeks. Over 20% of participants also had persistent depression, and over 10% had persistent symptoms of stress. Self-reported sleep problems were common early and moderate to severe for half of the respondents; sleep disturbances progressively decreased in frequency and severity over time, but remained a problem for almost one-third of participants at week 26. Six months after return home, mental health and psychological distress were independently associated with higher stress early after

discharge and self-reported sleeping problems at 26 weeks. Physical function measured by SF-36 was not independently associated with mental health or psychological distress in the multiple regression analyses. Neither were age, severity of illness, reason for ICU admission, length of mechanical ventilation, or length of stay in ICU or hospital associated with psychological outcomes.

Many of these findings are consistent with others reported in survivors of critical illness. The MCS is based predominately on the Mental Health, Vitality, Social Functioning and Role-Emotional subscales of the SF-36 and correlates most highly with them [20]. Authors investigating general ICU and ARDS survivors reported scores on these 4 SF-36 subscales early after discharge that were lower than population norms matched for age and gender, and which improved at 6 and 12 months [6, 21]. Other reports of the MCS in general ICU patients show scores similar to those in this study at 3 months or later after discharge [22-24], although the scores we report in week 1 are lower (38.6) than those reported from a similar patient sample (49.1) at hospital discharge in a single ICU in the Netherlands (n=280) [23]. The rates of depressive symptoms we report for ICU survivors are similar to others reported in ICU survivors [8], as are the rates of anxiety [25] and, where studied, similarly decreased over time [8, 22, 26]. Where a measure of stress on the DASS has been reported in former ICU patients, the proportions with moderate to extremely severe symptoms at 3 and 9 months was lower than we found at 2 and 6 months, though in a relatively small sample (n=51) [27]. The mean intrusion and avoidance IES scores we found at week 1 were in the lower ranges of those reported after illness and injury [28] and intensive care [9, 22], and reduced to levels in the range for reference comparison by 8 weeks [28].

Given the limitations of self-report measures, the continued debate about the construct and diagnostic criteria for PTSD [16], absence of questions about hyperarousal symptoms and the uncertainty in the current body of literature about the prevalence of posttraumatic stress in survivors of intensive care [9, 10, 29], it is not possible to make inferences about the rate in this study or comparisons with other reported rates. Other studies have also shown that female gender is a risk factor for posttraumatic stress symptoms in ICU survivors, though not consistently [9]. A large meta-analysis of risk factors for PTSD noted that women are at higher risk than men in the event of civilian traumas, though the authors warn that the effect may not be related to gender *per se* but to other characteristics, such as reporting symptoms more readily or greater exposure to prior trauma [30]. In this study we did not attempt to diagnose PTSD and did not screen for hyperarousal symptoms. Nevertheless the independent association of female gender with greater psychological distress should be noted and investigated further in this population.

The finding that stress in the first week after hospital discharge was associated with poorer scores on both the MCS and the IES is a unique finding in ICU survivors. Many authors report anxiety and depression [25] but a specific measure of stress is not often used [27]. Although stress is highly correlated with both depression and anxiety [27] it is notable that neither of those emotions was independently associated with 6-month psychological outcomes in this study. It may be that efforts to avoid and specifically alleviate stress in the early weeks after hospital discharge would be beneficial to longer term psychological health. Follow-up services for former patients by ICU personnel [31], have tended to be offered 2 to 3 months after discharge. A recent randomized trial of clinic-based follow-up programs commencing at 3 months found no benefit in HRQOL or psychological outcomes [24]. If our findings are

confirmed by others, stress-relieving interventions very early after discharge may be of benefit and warrant investigation.

Approximately half our participants reported moderate (e.g. disturbed sleep, or feeling I have not slept enough) to severe sleeping problems (e.g. sleep is almost impossible even with full use of sleeping pills, or staying awake most of the night) one week after hospital discharge; this declined to about one third at week 8. However approximately 30% continued to report moderate or great sleeping disturbances (e.g. having to use sleeping pills often or routinely, or usually waking at night and/or too early in the morning) 26 weeks after discharge and poorer sleep was associated with poorer psychological outcomes at each time point. Sleep quality at 26 weeks was independently associated in multivariable analyses with poorer mental health and worse psychological distress at 26 weeks. Two studies reported quality of life in former long-term ICU patients using the Nottingham Health Profile [32, 33], which includes a section on sleep, and noted that sleep disturbances were more frequent 6 months after ICU than in the general Finnish population [32] and 8-62 months after ICU (average 3 years) compared to the general French population [33]. Another study that specifically examined relationships with sleep disturbances found that poorer sleep at 6 and 12 months after hospital discharge was associated with lower scores for the mental health, vitality, general health, bodily pain and role-physical domains of SF-36 [34]. Up to 38% of former ICU patients in that study reported sleep disturbances, but the quality of sleep was similar to patients' retrospective reports of pre-ICU sleep and ICU factors such as severity of illness and length of stay were not related to sleep; the strongest association with poor sleep was concurrent disease (e.g. cancer, diabetes, cardiovascular) prior to ICU [34]. In a study investigating relationships between former patients' recollections of experiences in ICU and quality of life 6 months afterwards, 44% of patients

remembered ‘noisy and bad sleeping nights’ and 41% reported current sleep disturbances; this was independently associated with poorer quality of life, as were difficulties in concentrating and difficulties in remembering recent events [35].

In long term follow up of ARDS survivors, 7 patients who reported changes in sleep quality 6 months or longer after hospital discharge were investigated with overnight polysomnography (PSG) in a sleep laboratory; all were found to have sleep abnormalities, identified in most as a conditioned insomnia related to their critical illness [36]. No patients had histories of sleeping difficulties prior to their ICU stays nor evidence of clinical depression during their sleep assessments [36]. Insomnia is typically accompanied by changes including cognitive arousal/stress, dysphoria, depression or anxiety, fatigue and physiological changes [37], so the direction of the relationship between sleeping problems and poorer psychological states in the present study is unclear. Nevertheless the finding is noteworthy; the possibility cannot be ruled out that sleeping problems reported 6 months after hospital discharge are a legacy of sleep disruption which begins during the ICU stay, a problem that has been objectively demonstrated over many decades [38-40]. There is an urgent need for longitudinal studies using valid instruments to capture patients’ self-reports of sleep from the time they are in ICU, on the hospital wards and after hospital discharge to investigate if later sleep problems commence in ICU and continue afterwards.

This study has limitations other than those referred to above**.** As the patients we studied were enrolled in a trial of a physical exercise intervention, the explanatory and outcome variables available to address the aims of this paper were limited to those selected for the trial. Other patient factors potentially related to the outcomes we studied, for example quality of life, sleep quality and exposure to other traumatic events prior to the critical illness necessitating intensive

care, and some factors in the ICU were not included in the analysis. Notably, in-ICU factors of current interest in the investigation of post-ICU outcomes, such as pain, sedation regimens and delirium were not available for the analyses and need to be investigated in further prospective studies. The attrition of 18% of participants over the 6-month study period is not unexpected in a longitudinal study in this population. Nevertheless it meant that not all participants who had provided data could be included in the longitudinal and multivariate analyses. The reported exclusions should also be noted as limitations to the generalisability of the study. In particular, almost one fifth of excluded patients had neurological or spinal dysfunction precluding participation in the intervention tested in the study and may have been at higher risk for the psychological and mental health outcomes reported.

In conclusion, during the first week after hospital discharge survivors of an episode in ICU had impaired mental health and symptoms of depression, anxiety, stress, intrusion and avoidance; median scores improved by 8 weeks and remained at similar levels at 6 months, although a significant proportion reported persistent symptoms, particularly for anxiety. Sleeping problems were common early and reduced with time, but also remained for a substantial proportion of participants. Female gender, stress early after hospital discharge and sleep disturbances are related to poorer mental health at 6 months, and early stress and sleeping problems are related to worse psychological distress. Further observational studies of these relationships are warranted.

Funding: National Health and Medical Research Council Project Grant No. 352407

Acknowledgements

Penny Taylor for study coordination, screening and enrolment of patients and data collection; Rachel Foley, Selina Hole, David Wastell, Mary Fien, Anne Limpic, Mary Maxwell, Eleanor Rose, Jacelle Lang, Lydia Gawa and Teresa Williams for screening and enrolment of patients and data collection; Dena Hogben, Marianne O'Reilly, Kylie Leach, Ashley Job, Nicohle Kenney, Jennie King, Jacquie Hyslop, Sheridan Hatter, Leonie Weisbrodt Debbie Carney, Leanne Jack, Renae Deans, Claire Bertenshaw, Janine Stuart, Melissa Lassig-Smith, Mary Nolan, Leeona Smith for screening and enrolment of patients; Jill Dent, Monika Fluckiger, Elizabeth Robertson, Sally Cumming, Renee Subacius and Belinda Green for data collection; Linda Parker, Ann Tully, Shane Patman, Meagan Jerome, Tenille Ricketts and Amanda Simmonds for provision of the study intervention; Phillip Johnson for assistance with database construction.

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Table 1. Participant characteristics (n = 195)

Demographic	
Age, years – Mean (SD)	57 (16.0)
Female – N (%)	79 (40.9)
Clinical	
Day 1 APACHE[a] II score – Mean (SD)	18.8 (6.9)
Operative admissions N (%)	105 (55.0)
Reason for admission to ICU[b] (APACHE[a] III categories)	
Cardiovascular N (%)	38 (19.9)
Respiratory N (%)	46 (24.1)
Gastrointestinal N (%)	57 (29.8)
Other N (%)	50 (26.2)
Hours of mechanical ventilation - Median (IQR)	89 (46-185)
Length of stay in ICU, days - Median (IQR)	6 (4-11)
Length of stay in hospital, days - Median (IQR)	18 (12-29)

a Acute Physiology and Chronic Health Evaluation

b Intensive care unit.

Table 2. Psychological outcome scores over time

Measure	Week 1	Week 8	Week 26	P
Mental Component Summary of SF-36 – Mean (SD)	38.6 (14.2)	47.7 (11.2)	47.6 (11.6)	.0005 *
Depression, Anxiety and Stress Scales – Median (IQR)				
Depression	8 (2-12)	4 (0-10)	4 (0.5-10)	.0005 †
Anxiety	8 (4-14)	4 (0-8)	4 (2-10)	.0005 †
Stress	8 (2-14)	6 (2-14)	6 (0-10)	.0005 †
Depression, Anxiety and Stress symptoms – N (%)				
Depression				
- Moderate (14-20)	24 (13.2)	13 (7.7)	19 (11.9)	
- Severe (21-27) - Extremely severe (28-42)	25 (13.7)	15 (8.9)	15 (9.4)	
Anxiety				
- Moderate (10-14)	35 (19.2)	19 (11.2)	23 (14.4)	
- Severe (15-19) - Extremely severe (20-42)	47 (25.8)	21 (11.4)	18 (11.3)	
Stress				
- Moderate (19-25)	17 (9.3)	14 (8.3)	10 (6.3)	
- Severe (26-33) - Extremely severe (34-42)	14 (7.7)	13 (7.7)	9 (5.7)	
Psychological distress – Median (IQR)				
Impact of Events Scale total	18.5 (3-31)	9 (0-24)	8 (1-22)	.0005 †
Impact of Events Scale intrusion	8 (1-15)	4 (0-12)	4 (0-12)	.0005 †
Impact of Events Scale avoidance	9 (1-18)	3.5 (0-14)	3 (0-12)	.0005 †

* Week 1 vs week 8 and 26 – RM-ANOVA with post hoc comparisons with Bonferroni adjustment (n=152)

† Week 1 vs week 8 and 26 – Friedman test with post hoc signed ranks test and Bonferroni adjustment (n=156)

Table 3. Multiple linear regression analyses of factors associatied with week 26 SF-36 Mental Component Summary and Impact of Events Scale scores *

3A. Mental Component Summary of SF-36

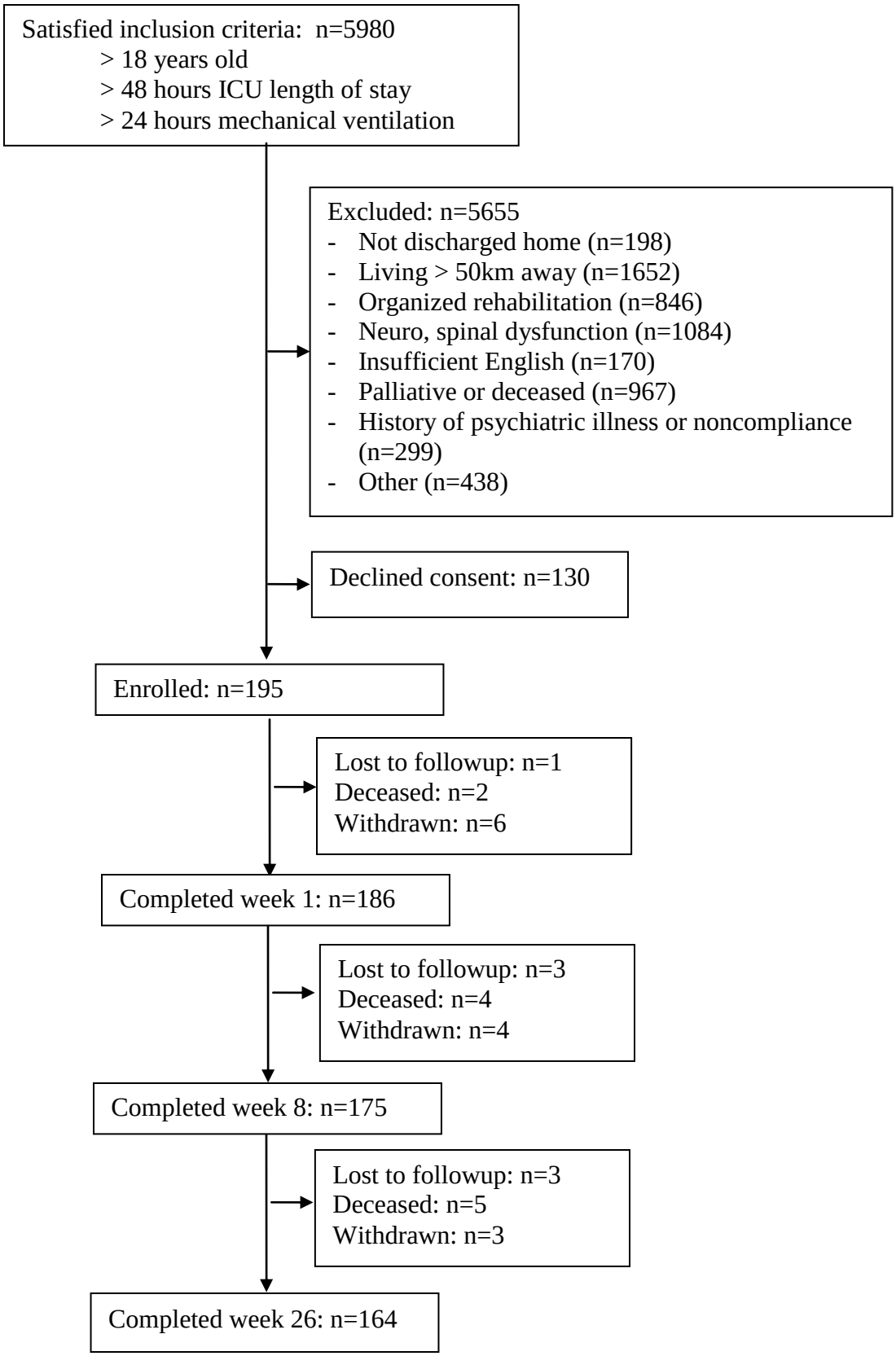
	B	SE of B	Beta[a]	p	95% CI for B	
Stress week 1	-.349	.162	-.262	.032	-.668	-.030
Sleeping week 26	-3.738	-.857	-.331	.0005	-5.432	-2.044
Adjusted R^2 = .283, p = .0005 for model						

3B. Impact of Events Scale total score

Female gender	5.222	2.328	.167	.026	.621	9.823
Stress week 1	.444	.216	.253	.041	.018	.871
Sleeping week 26	4.978	1.144	.335	.0005	2.716	7.239
Adjusted R^2 = .261, p = .0005 for model						

[a] Standardised coefficient

* The analyses for each outcome were adjusted for study group, age, gender, week 1 depression, anxiety and stress, week 26 SF-36 Physical Component Summary score and week 26 sleep.


Satisfied inclusion criteria: n=5980
> 18 years old
> 48 hours ICU length of stay
> 24 hours mechanical ventilation
Excluded: n=5655
- Not discharged home (n=198)
- Living > 50km away (n=1652)
- Organized rehabilitation (n=846)
- Neuro, spinal dysfunction (n=1084)
- Insufficient English (n=170)
- Palliative or deceased (n=967)
- History of psychiatric illness or noncompliance (n=299)
- Other (n=438)
Declined consent: n=130
Enrolled: n=195
Lost to followup: n=1
Deceased: n=2
Withdrawn: n=6
Completed week 1: n=186
Lost to followup: n=3
Deceased: n=4
Withdrawn: n=4
Completed week 8: n=175
Lost to followup: n=3
Deceased: n=5
Withdrawn: n=3
Completed week 26: n=164

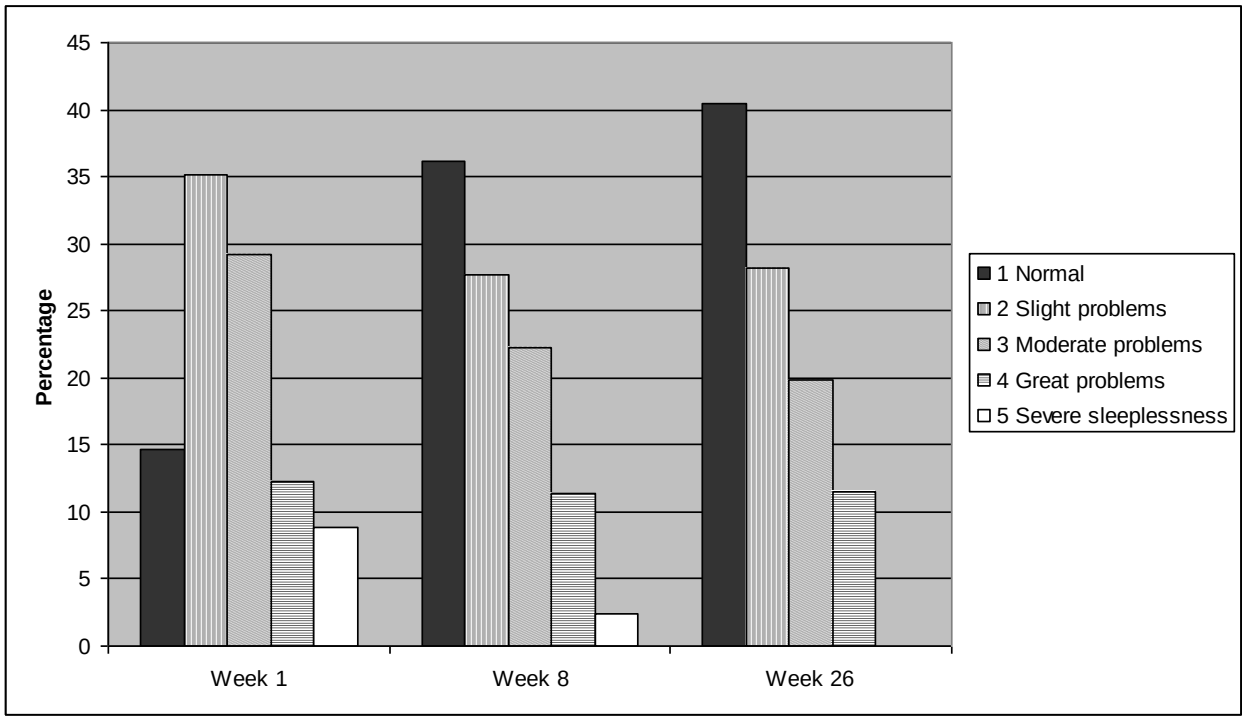


Figure legends

Figure 1 Flow diagram of patient recruitment and retention in the study

Figure 2 Sleep problems reported at weeks 1, 8 and 26 after hospital discharge

Electronic Supplementary Material

Title: Sleep and other factors associated with mental health and psychological distress after intensive care for critical illness

Table ESM 1. Scores on psychological outcome measures according to study group.

	Control	Intervention	P * †
SF-36 MCS – Mean			
- Week 1	39.95	36.57	.110
- Week 8	47.48	49.90	.749
- Week 26	42.94	42.77	.815
Depression – Mean			
- Week 1	8.54	11.80	.095
- Week 8	7.13	7.59	.164
- Week 26	7.95	6.68	.543
Anxiety – Mean			
- Week 1	9.33	11.47	.058
- Week 8	5.79	6.63	.143
- Week 26	6.21	6.39	.630
Stress – Mean			
- Week 1	8.61	11.91	.018
- Week 8	8.48	9.63	.612
- Week 26	7.52	8.08	.287
Impact of Event Scale – Mean			
- Week 1	18.64	21.21	.517
- Week 8	13.59	15.83	.208
- Week 26	13.02	15.78	.329

* Independent t-test for SF-36 MCS; † Mann-Whitney U test for all others

Table ESM 2. Question on quality of sleep from 15D (Sintonen. 2001)

During the past 4 weeks, how have you been sleeping?	(circle one)
I am able to sleep normally, i.e. I have no problems sleeping.	1
I have slight problems with sleeping, e.g. difficulty in falling asleep, or sometimes waking at night.	2
I have moderate problems with sleeping, e.g. disturbed sleep, or feeling I have not slept enough.	3
I have great problems with sleeping, e.g. having to use sleeping pills often or routinely, or usually waking at night and/or too early in the morning.	4
I suffer severe sleeplessness, e.g. sleep is almost impossible even with full use of sleeping pills, or staying awake most of the night.	5

Table ESM 3. Sleep problems reported – N (%)

	Week 1	Week 8	Week 26
None	25 (14.6)	60 (36.1)	63 (40.4)
Slight	60 (35.1)	46 (27.7)	44 (28.2)
Moderate	50 (29.2)	37 (22.3)	31 (19.9)
Great	21 (12.3)	19 (11.4)	18 (11.5)
Severe	15 (8.8)	4 (2.4)	-

Table ESM 4. Scores on psychological outcome measures according to sleep problems at 1, 8 and 26 weeks.

	None	Slight	Moderate	Great	Severe	P *
SF-36 MCS – Mean						
- Week 1	44.39	41.83	37.40	35.64	25.18	.0005
- Week 8	52.70	45.47	42.78	43.88	37.29	.001
- Week 26	52.91	47.44	43.23	38.89	-	.0005
Depression – Mean						
- Week 1	6.40	7.17	10.88	11.24	17.47	.002
- Week 8	2.13	8.74	9.35	14.63	16.00	.0005
- Week 26	3.97	5.91	9.87	17.11	-	.0005
Anxiety – Mean						
- Week 1	7.60	8.77	10.88	12.19	14.93	.027
- Week 8	2.90	6.78	7.24	12.84	11.00	.0005
- Week 26	4.22	5.50	7.74	12.22	-	.0005
Stress – Mean						
- Week 1	6.08	8.00	10.12	14.67	17.47	.0005
- Week 8	4.23	9.61	10.32	19.58	18.00	.0005
- Week 26	4.29	7.09	9.55	16.56	-	.0005
Impact of Event Scale – Mean						
- Week 1	12.48	17.75	19.52	22.71	38.33	.0005
- Week 8	14.51	19.15	25.43	27.58	21.50	.001
- Week 26	16.69	17.75	21.29	33.39	-	.003

* Kruskal-Wallis ANOVA by ranks