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LETTER

Systemic glucocorticoid use during ICU admission and symptoms of posttraumatic stress disorder in intensive care unit survivors

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Dear Editor,

Intensive care unit (ICU) survivors are at risk of developing mental health problems, such as symptoms of posttraumatic stress disorder (PTSD), anxiety and depression [1–3]. Glucocorticoid use has been proposed to diminish the risk of these problems, but evidence remains conflicting [4, 5]. This study investigated the association between systemic glucocorticoid use during ICU admission and the incidence of PTSD symptoms in a large population of ICU survivors.

This is a single-center, retrospective cohort study with 1-year follow-up using prospectively collected data. The institution's Medical Research Ethics Committee waived the need for informed consent. Patients alive 1 year after ICU discharge, aged ≥ 18 years and admitted to the ICU > 48 h between January 2011 and February 2020 were included. The cumulative glucocorticoid dose during ICU stay was calculated per subject by (1) obtaining all glucocorticoid administrations (registered in the ICU's Patient Data Management System), (2) converting oral doses to intravenous equivalents, (3) converting different glucocorticoids to prednisolone equivalents and (4) summing these over the period of ICU admission. The primary outcome was PTSD symptoms 1 year after ICU discharge, defined as an Impact of Event Scale (revised) score of ≥ 35 or a mean score of > 1.6, respectively. Secondary outcomes included symptoms of anxiety and depression as measured by the Hospital Anxiety and Depression Scale (sum score of ≥ 8) and Health-Related Quality of Life (HRQoL) as measured with the EuroQol-5D 1 year after discharge. Results were adjusted for age, sex, ICU length of stay, type of admission, referral by a pulmonologist (yes/no), Simplified Acute Physiology Score (SAPS) II, mechanical ventilation, delirium during ICU stay, modified Sequential Organ Failure Assessment (mSOFA) score on day of admission, the difference between the mSOFA score on day of admission and on day 4, cumulative midazolam dosage, cumulative propofol dosage and outpatient use of glucocorticoids / antidepressants / antipsychotics / anxiolytics using a propensity score approach.

In total, 1737 subjects were included of whom 690 (40%) were systemically exposed to glucocorticoids. Subjects who received glucocorticoids were more often female, had a longer ICU length of stay, were more often admitted to the ICU after acute surgery and had a higher mean SAPS II. 187 (11%) Subjects developed PTSD symptoms, 313 (18%) developed symptoms of anxiety and 303 (17%) developed symptoms of depression. Table 1 shows the effect of glucocorticoids on the risk of symptoms of PTSD, anxiety and depression. Adjusted logistic regression analysis showed no beneficial effect on developing PTSD symptoms (adjusted odds ratio (aOR) 0.99, 95% confidence interval (CI) 0.68–1.45) with glucocorticoid use ($n = 81$; 12%) versus non-use ($n = 106$; 11%). Glucocorticoid use was not associated with a decreased incidence of symptoms of anxiety (aOR 0.89, 95% CI 0.65–1.21), symptoms of depression (aOR 0.81, 95% CI

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Table 1 Primary and secondary endpoints

	PTSD symptoms, *n* (%)[a]	Crude OR (95% CI)	Adjusted OR (95% CI)[e]
Glucocorticoid use	81 (12)	1.17 (0.86–1.60)	0.99 (0.68–1.45)
No glucocorticoid use	106 (11)		
	Symptoms of anxiety, *n* (%)[b]	**Crude OR (95% CI)**	**Adj. OR (95% CI)[e]**
Glucocorticoid use	121 (18)	0.95 (0.74–1.23)	0.89 (0.65–1.21)
No glucocorticoid use	192 (19)		
	Symptoms of depression, *n* (%)[c]	**Crude OR (95% CI)**	**Adj. OR (95% CI)[e]**
Glucocorticoid use	106 (16)	0.79 (0.61–1.03)	0.81 (0.59–1.10)
No glucocorticoid use	197 (19)		
	EQ-5D Utility score, median (IQR)[d]	**Change in utility value (crude)**	**Change in utility value (adjusted)[e]**
Glucocorticoid use	0.811 (0.687–1)	− 0.003 (− 0.028–0.022)	0.027 (− 0.003–0.057)
No glucocorticoid use	0.811 (0.687–1)		

Results after multiple imputation

PTSD posttraumatic stress disorder, *OR* odds ratio, *CI* confidence interval, *IQR* interquartile range

[a] Missing for 95 patients (5%)

[b] Missing for 49 patients (3%)

[c] Missing for 42 patients (2%)

[d] Missing for 67 patients (4%)

[e] Adjusted for age, sex, Intensive Care Unit (ICU) length of stay, type of admission, referral by a pulmonologist (yes/no), Simplified Acute Physiology Score II, mechanical ventilation, delirium during ICU stay, modified Sequential Organ Failure Assessment (mSOFA) score on day of admission, difference between mSOFA on day of admission and on day 4, cumulative midazolam dosage, cumulative propofol dosage and outpatient use of glucocorticoids / antidepressants / antipsychotics / anxiolytics

0.59–1.10) or change in HRQoL (adj. linear regression; 0.027 increase in utility value, 95% CI − 0.003–0.057).

Strengths of this study include the large sample size, in particular in the field of mental health disorders post ICU. Also, the mixed ICU population enhances generalizability of the results.

The main limitation of this study was potential confounding by indication, as certain diseases might call for treatment with glucocorticoids and may carry a greater risk of developing mental health problems. Also, no data were available on psychological support received by subjects during follow-up, which might have led to a smaller chance of finding a relationship between exposure and outcome [6].

In conclusion, this study suggests no potential protective effect of systemic exposure to glucocorticoids during ICU admission on the development of PTSD symptoms, nor on symptoms of anxiety and depression or lower HRQoL in ICU survivors. This study does not warrant a randomized controlled trial on glucocorticoids to decrease PTSD symptoms in ICU survivors.

Supplementary Information
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Declarations

Conflicts of interest
None.

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References

1. Parker AM, Sricharoenchai T, Raparla S, Schneck KW, Bienvenu OJ, Needham DM (2015) Posttraumatic stress disorder in critical illness survivors: a meta analysis. Crit Care Med 43(5):1121–1129
2. Nikayin S, Rabiee A, Hashem MD, Huang M, Bienvenu OJ, Turnbull AE et al (2016) Anxiety symptoms in survivors of critical illness: a systematic review and meta-analysis. Gen Hosp Psychiatry 43:23–29
3. Rabiee A, Nikayin S, Hashem MD, Huang M, Dinglas VD, Bienvenu OJ et al (2016) Depressive symptoms after critical illness: a systematic review and meta-analysis. Crit Care Med 44(9):1744–1753
4. Schelling G, Roozendaal B, Quervain DJ-F (2004) Can posttraumatic stress disorder be prevented with glucocorticoids? Ann N Y Acad Sci 1032(1):158–166
5. Kok L, Hillegers MH, Veldhuijzen DS, Cornelisse S, Nierich AP, van der Maaten JM et al (2016) The effect of dexamethasone on symptoms of posttraumatic stress disorder and depression after cardiac surgery and intensive care admission. Crit Care Med 44(3):512–520
6. Jensen JF, Thomsen T, Overgaard D, Bestle MH, Christensen D, Egerod I (2015) Impact of follow-up consultations for ICU survivors on post-ICU syndrome: a systematic review and meta-analysis. Intensive Care Med 41(5):763–775

Supplementary material to:

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Supplementary material A: Extended manuscript

Introduction

Intensive Care Unit (ICU) survivors are at risk of developing mental health problems, such as posttraumatic stress disorder (PTSD), anxiety and depression.(1–3) A recent meta-analysis showed that up to one fifth of ICU survivors suffer from clinically important PTSD symptoms at 1-year follow up.(1) PTSD symptoms have been associated with worse health-related quality of life (HRQoL).(1,4,5) In addition, one third of ICU survivors experience symptoms of anxiety and depression during their first year of recovery.(2,3) Strategies such as keeping an ICU diary, early clinical psychologist support and early rehabilitation may have a beneficial effect in reducing some of these problems.(6–8) A pharmacological intervention during ICU admission to reduce mental health problems is not available.

Glucocorticoid use has been proposed to diminish the risk of mental health problems following ICU admission.(9) The physiological mechanism behind this hypothesis is that glucocorticoid levels induced by stress may result in temporary impairment of memory retrieval.(10–14) As memories of traumatic experiences during ICU admission such as pain,

panic or respiratory distress are related to later development of PTSD, administration of stress doses of glucocorticoids could hypothetically be beneficial for reducing this risk.(5,15–17)

However, current literature on this topic remains conflicting. Some small observational studies of glucocorticoid use during ICU admission showed a potential beneficial effect on the incidence of PTSD, HRQoL and chronic stress symptoms after ICU discharge.(17–19) A recent clinical trial in cardiac surgery patients evaluated the effect of a single (high) intraoperative dose of dexamethasone on symptoms of PTSD, depression and HRQoL 1.5 years after ICU admission.(20) No overall effect was found but subgroup analyses showed that female patients may benefit from glucocorticoid administration, with a significantly lower prevalence of PTSD symptoms and depression within this group.(20) This result could be explained by a gender difference in response to stress in the hypothalamic-pituitary-adrenal (HPA) axis.(21,22) In addition to the conflicting evidence, previous studies have focused on specific subgroups of ICU survivors (i.e. cardiac surgery patients or sepsis survivors).(17–20) The generalizability of the effect of glucocorticoids on PTSD, anxiety and depression in a larger and broader population of ICU survivors remains therefore unclear.

Consequently, the hypothesis tested in this study was whether systemic glucocorticoid exposure during ICU admission could have a protective effect on the occurrence of PTSD symptoms in adult ICU survivors. Secondary outcomes included anxiety, depression and HRQoL.

Methods

Study design, setting and population

In this retrospective cohort study with one year follow-up, prospectively collected data was used. Former ICU patients alive one year after ICU discharge were included when aged 18 years or older at time of ICU admission and admitted for more than 48 hours to the 32-mixed bed medical-surgical ICU of the University Medical Center Utrecht (UMCU) between January 2011 and February 2020. Subjects were excluded if they had been transferred from another ICU, were referred to the ICU by a neurologist or a neurosurgeon, were admitted after cardiac arrest, did not return the questionnaire sent one year after ICU discharge or indicated that they were not able or did not wish to answer the questionnaire. If a patient was readmitted, only information of the first admission was used. The Medical Research Ethics Committee of the UMCU approved this study and waived the need to obtain informed consent (protocols 12/421 and 10/006).

Glucocorticoid exposure

Data on use of systemic glucocorticoids (prednisolone, hydrocortisone, dexamethasone and methylprednisolone) during ICU admission were obtained from the ICU's Patient Data Management system (PDMS). Glucocorticoids for topical use or for inhalation were not taken into account. The cumulative glucocorticoid dose during admission was expressed per subject as intravenous prednisolone equivalent (in milligrams) by taking the following steps: first, oral doses of hydrocortisone, dexamethasone and prednisolone were converted to intravenous equivalents by adjusting for oral bioavailability (0.96, 0.8 and 1 respectively).(23) Next, intravenous dosages of the different glucocorticoids were converted to prednisolone equivalents using the corresponding activity factors (0.25 for hydrocortisone, 6.67 for dexamethasone and 1.25 for methylprednisolone), and summed over the period of ICU admission.(24)

Outcome measurements

The primary outcome was PTSD symptoms one year after ICU discharge. Surviving subjects received a postal survey containing different questionnaires (process published in detail elsewhere (25)), including the Impact of Event Scale (IES or IES-R, explained below), the Hospital Anxiety and Depression Scale (HADS) and the EuroQol-5D (EQ-5D). Symptoms of PTSD during the seven days prior to questionnaire completion were measured either by the original IES with 15 items (26) (sent to subjects admitted before September 2016) or the revised 22-item version (27) (IES-R; sent to subjects admitted from August 2016 onwards). Items in the original IES, representing subscales for intrusion and avoidance, were scored on a 4-point scale as "not at all" (0) to "often" (5), giving a sum score ranging from 0 to 75. An IES sum score of 35 or higher is considered indicative for clinically significant symptoms of PTSD.(28) The IES-R includes 7 additional items on hyperarousal. Items are scored on a 5-point Likert scale as "not at all" (0) to "extremely" (4). Instead of raw sums, mean scores are calculated for the IES-R ranging from 0 – 4, with a mean score > 1.6 indicating clinically significant PTSD symptoms.(29)

Secondary outcomes included anxiety, depression and health related quality of life. The HADS was used to estimate symptoms of anxiety and depression.(30) The questionnaire comprises two subscales of 7 items each, scored on a 4-point Likert scale (0 – 3). A sum score of 8 or higher on a subscale indicates clinically relevant symptoms of anxiety or depression, respectively.(31) This cutoff value was used to define possible cases of anxiety and depression. To measure HRQoL the EQ-5D (either the 3-level or 5-level version) was used.(32,33) The EQ-5D contains five items representing the HRQoL domains mobility, self-care, usual activities, pain or discomfort and anxiety or depression. Each item has three or five levels, ranging from no problems (1) to severe problems (3 or 5), giving a so-called 'health-

state' as total score. To translate these health-states into a utility value ranging from 0 – 1 (0 meaning death and 1 meaning full health), the Dutch tariff was used.(34)

Covariates

Baseline characteristics and clinical data were obtained from the PDMS. A recent systematic review and meta-analysis was used to identify risk factors for developing mental health problems after ICU discharge.(35) Selected potential confounders included age, sex, ICU length of stay, type of admission (medical, acute surgical or elective surgical), medical specialism by which the patient was referred to the ICU, Simplified Acute Physiology Score second edition (SAPS II) (36) score, the modified Sequential Organ Failure Assessment (mSOFA) (37) score (excluding the central nervous system component due to high interference with delirium) on the day of admission as well as the difference between the mSOFA score on the day of admission and on day 4 of admission (or if the admission was <4 days, the last day of admission; this parameterization of the SOFA score shows high predictive performance in prediction models for ICU outcomes) (38), receiving mechanical ventilation at any time during ICU admission (dichotomous) and cumulative dose of midazolam and propofol during ICU admission. Having delirium at any time during ICU admission (dichotomous) was determined with mental status classification on a daily basis as "coma", "delirium" or an "awake without delirium" state, using a validated multistep algorithm.(39) In summary, this algorithm is based upon the Confusion Assessment Method for the ICU (CAM-ICU) (40) scores from bedside nurses, start of haloperidol as part of delirium treatment, review of medical and nursing charts and additional CAM-ICU, which showed superior sensitivity when compared to CAM-ICU in daily practice only.(39,41)

Information on home medication was collected by the hospital pharmacy either prior to an elective admission or at time of admission by retrieving the community pharmacy dispensing list through the electronic Nationwide Medication Record System.(42) If possible, this information was verified with the patient. This information was used to assess additional potential confounders (outpatient use of antidepressants [ATC N06A], antipsychotics [ATC N05A excluding lithium], anxiolytics [N05BA] or glucocorticoids [dexamethasone, hydrocortisone, methylprednisolone, prednisolone or prednisone]).

Missing Data

If a patient had missing answers to one of items of the IES, IES-R or HADS, the difference between the cutoff score to be defined as a case (sum score of 35, mean score of 1.6 and a subscale score of 8, respectively) and the subjects' score without missing answers was calculated. If the difference was zero or if it had a negative value (i.e. the cutoff score was already reached, even with some answers missing), the patient was defined as a case. If this difference was greater than the maximum score the patient could potentially score if answers were not missing (i.e. 5 per missing answer for the IES, 4 per missing answer for the IES-R and 3 per missing answer for the HADS), the patient was defined as not being a case. For remaining subjects with missing answers, the dichotomous variable defining a patient as a case (or not) was imputed through multiple imputation by chained equations, using the 'mice' package (version 3.13.0, Van Buuren 2021) in R. All variables mentioned under section covariates were included in the multiple imputation model. Multiple imputation by chained equations was also used to impute missing values for the EQ-5D utility score as well as all other covariates, effectively retaining all subjects in the analysis. A complete-case analysis was performed as sensitivity analysis to investigate the impact of multiple imputation of missing data on the results.

Statistical analysis

Logistic regression analysis was used to calculate adjusted odds ratios for developing PTSD symptoms, anxiety or depression if being exposed to systemic glucocorticoids during ICU admission as opposed to not being exposed. Linear regression analysis was used to assess the association between systemic glucocorticoid use and EQ-5D utility scores. Correlation between potential confounders was calculated by a Spearman test for continuous variables and Cramer's V test for categorical variables. If two variables had a correlation coefficient with a value >0.7, one of the variables was omitted in the regression model. Propensity scores for being exposed to systemic glucocorticoids were estimated for each subject through logistic regression, using all the other variables, after which results were adjusted by these propensity scores. With this approach, more covariates could be added in the final regression model. (43)

To explore a possible dose-effect relationship, subjects who were exposed to glucocorticoids during ICU admission were stratified based on the 10^{th} percentiles of the cumulative prednisolone equivalent dose into ten categories. Each category was compared to subjects who did not use glucocorticoids by calculating adjusted odds ratios for developing PTSD symptoms, which were then plotted and further analyzed with a 2-knot linear spline regression for testing a non-linear relationship between dose and adjusted odds ratio. Additionally, to explore effect modification, analyses on glucocorticoids were stratified based on sex and on outpatient use (versus no outpatient use) of glucocorticoids. Sensitivity analysis was carried out by stratifying on year of admission to explore change in ICU practice over time and the impact of changing from the IES to IES-R tool. Lastly, in additional sensitivity analysis, two linear regressions were carried out with the IES and IES-R score respectively as dependent variable.

All statistical analyses were 2-sided using a level of significance of 0.05. Data cleaning as well as statistical analyses were performed in R version 4.0.3 (The R Foundation for Statistical Computing, 2020; including 'base', 'stats', 'dplyr', 'mice' and 'splines' packages).

Results

A flow-chart of eligible subjects is shown in Figure 1. During the study period, 3642 former ICU patients were sent a questionnaire, of whom 2411 responded (response rate 66%). Non-responders were younger (non-responders, mean age 54 (SD 17); responders 59 (16), $p<0.001$) and were more often admitted to the ICU for medical reasons (non-responders 51% of admissions, responders 37% of admissions; Table 1). Of the responders, 473 (20%) were excluded because they were referred to the ICU by a neurologist or a neurosurgeon and 201 (8%) were excluded because they were admitted after cardiac arrest.

A total of 1737 subjects were included in this study of whom 690 (40%) were systemically exposed to glucocorticoids during ICU admission (Table 2). Subjects who received glucocorticoids were more often female, had a longer ICU length of stay, were more often admitted to the ICU after acute surgery and had a higher mean SAPS II score. Of the referred medical disciplines, pulmonology showed the most obvious difference (19% of patients who received glucocorticoids versus 3% of who did not).

187 (11%) subjects had symptoms of PTSD at one year follow-up. Table 3 shows the effect of glucocorticoids on the risk of PTSD symptoms, anxiety and depression. Logistic regression analyses showed no association with PTSD symptoms (adj. OR 0.99, 95% CI 0.68-1.45) with

glucocorticoid use (n = 81; 12%) versus non-use (n = 106; 11%). Glucocorticoid use was not associated with anxiety (adj. OR 0.89, 95% CI 0.65-1.21) or depression (adj. OR 0.81, 95% CI 0.59-1.10). Linear regression showed a non-significant increase in EQ-5D utility value of 0.027 (95% CI -0.003-0.057) when being exposed to systemic glucocorticoids.

Figure 2 shows the adjusted odds ratios for developing PTSD symptoms per 10^{th} percentile of cumulative prednisolone equivalent versus no glucocorticoid use. A 2-knot linear spline regression (knots at the 25^{th} and 75^{th} percentile) visualized no apparent dose-effect relationship. Stratification by sex, year of admission and use of glucocorticoids as home medication showed no significant difference between groups (Tables 4 – 6). Linear regression analyses with the IES and IES-R score as dependent variable showed no significant effect of exposure to glucocorticoids (Table 7).

Complete case analysis showed that complete cases (n = 1627, 94%) had no differences in patient characteristics compared to incomplete cases (n = 110, 6%) and gave similar results for the main analysis as well as the stratification analyses compared to the results after multiple imputation (Tables 8 – 11).

Discussion

This study investigated the effect of systemic glucocorticoid exposure during ICU admission on PTSD symptoms one year after ICU discharge, as well as on anxiety, depression and HRQoL in a general Dutch adult mixed ICU population. We found no difference in the proportion of PTSD symptoms, anxiety or depression between subjects who had

glucocorticoids and those who never had glucocorticoids during ICU admission. In addition, no dose-effect relationship was found.

The current literature on the effect of corticosteroids on long term mental outcomes in ICU patients is conflicting. The present study confirms the findings of Kok et al. (2016) where no overall effect of glucocorticoids was found.(20) However, the results could not confirm the findings of the studies by Schelling et al. (1999 & 2001) and Weis et al. (2006), where a lower incidence of PTSD and a decrease in chronic stress symptoms were found in the group of subjects receiving glucocorticoids.(17–19) One of the important differences between the current study and earlier research is the dosing regimen of glucocorticoids, as well as the timing of glucocorticoid administration. In the primary analysis of this study, any use of glucocorticoids at any time during ICU admission would classify a subject as being exposed. To explore the hypothesized physiological mechanism of memory retrieval impairment in stress dose steroids during the traumatic event, the cumulative prednisolone equivalent was stratified in an additional analysis. No dose-effect relationship was found.

Strengths of this study are the large sample size, in particular in the field of mental health disorders post ICU.(17–20) Also, a robust method for multiple imputation was used, so all subjects could be included in the analysis, decreasing the risk of bias. Lastly, the mixed ICU population ensures generalizability of the results.

This study had several limitations. First, questionnaires were used to assess PTSD symptoms, anxiety and depression. These measures are not used to actually diagnose these mental health disorders. This may have led to over- or underdiagnosis, but is likely to be non-differential and may therefore only underestimate our study findings (rather than inflate). In addition, the

used cut-off scores for the IES, IES-R and HADS to define cases are strongly associated with the results of validated interviews by psychiatrists for diagnosing PTSD, anxiety and depression respectively.(28,29,31,44) Because mental health disorders were assessed one year after ICU discharge, other events possibly causing these disorders may have occurred, although again this is expected to be non-differential. The study might have suffered from confounding by indication, as certain diseases might call for treatment with glucocorticoids and carry a greater risk of developing mental health problems. This was however adjusted for by adding referring specialism and different disease severity parameters to the multivariate models. No data were available on previous mental health disorders, which is a known risk factor for developing PTSD post-ICU discharge.(35) However, outpatient use of antidepressants, antipsychotics or anxiolytics before ICU admission was introduced as a variable to serve as a proxy. Because of the observational nature of the study there might have been residual confounding. Lastly, this was a single-center study, which may limit the generalizability.

Conclusion

This study found no protective effect of systemic glucocorticoid use during ICU admission on the development of PTSD symptoms one year after ICU discharge. Furthermore, no effect was found on the development of anxiety and depression, nor had glucocorticoid use impact on HRQoL. In additional analysis, no dose-effect relationship was found. This study does not warrant a randomized controlled trial on glucocorticoids to decrease PTSD in ICU survivors.

References

1. Parker AM, Sricharoenchai T, Raparla S, Schneck KW, Bienvenu OJ, Needham DM. Posttraumatic stress disorder in critical illness survivors: a metaanalysis. Crit Care Med [Internet]. 2015 May;43(5):1121–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25654178
2. Nikayin S, Rabiee A, Hashem MD, Huang M, Bienvenu OJ, Turnbull AE, et al. Anxiety symptoms in survivors of critical illness: a systematic review and meta-analysis. Gen Hosp Psychiatry [Internet]. 43:23–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27796253
3. Rabiee A, Nikayin S, Hashem MD, Huang M, Dinglas VD, Bienvenu OJ, et al. Depressive Symptoms After Critical Illness: A Systematic Review and Meta-Analysis. Crit Care Med [Internet]. 2016 Sep;44(9):1744–53. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27153046
4. Davydow DS, Gifford JM, Desai S V., Needham DM, Bienvenu OJ. Posttraumatic stress disorder in general intensive care unit survivors: a systematic review. Gen Hosp Psychiatry [Internet]. 2008 Sep;30(5):421–34. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0163834308000807
5. Schelling G, Stoll C, Haller M, Briegel J, Manert W, Hummel T, et al. Health-related quality of life and posttraumatic stress disorder in survivors of the acute respiratory distress syndrome. Crit Care Med [Internet]. 1998 Apr;26(4):651–9. Available from: http://journals.lww.com/00003246-199804000-00011
6. McIlroy PA, King RS, Garrouste-Orgeas M, Tabah A, Ramanan M. The Effect of ICU Diaries on Psychological Outcomes and Quality of Life of Survivors of Critical Illness and Their Relatives. Crit Care Med [Internet]. 2019 Feb;47(2):273–9. Available from: http://journals.lww.com/00003246-201902000-00017
7. Peris A, Bonizzoli M, Iozzelli D, Migliaccio ML, Zagli G, Bacchereti A, et al. Early intra-intensive care unit psychological intervention promotes recovery from post traumatic stress disorders, anxiety and depression symptoms in critically ill patients. Crit Care [Internet]. 2011;15(1):R41. Available from: http://ccforum.biomedcentral.com/articles/10.1186/cc10003
8. Fuke R, Hifumi T, Kondo Y, Hatakeyama J, Takei T, Yamakawa K, et al. Early rehabilitation to prevent postintensive care syndrome in patients with critical illness: a systematic review and meta-analysis. BMJ Open [Internet]. 2018 May 5;8(5):e019998. Available from: https://bmjopen.bmj.com/lookup/doi/10.1136/bmjopen-2017-019998
9. Schelling G, Roozendaal B, Quervain DJ-F. Can Posttraumatic Stress Disorder Be Prevented with Glucocorticoids? Ann N Y Acad Sci [Internet]. 2004 Dec;1032(1):158–66. Available from: http://doi.wiley.com/10.1196/annals.1314.013
10. de Quervain DJ-F, Roozendaal B, Nitsch RM, McGaugh JL, Hock C. Acute cortisone administration impairs retrieval of long-term declarative memory in humans. Nat Neurosci [Internet]. 2000 Apr;3(4):313–4. Available from: http://www.nature.com/articles/nn0400_313
11. de Quervain DJ-F, Roozendaal B, McGaugh JL. Stress and glucocorticoids impair retrieval of long-term spatial memory. Nature [Internet]. 1998 Aug;394(6695):787–90. Available from: http://www.nature.com/articles/29542
12. Roozendaal B, Griffith QK, Buranday J, de Quervain DJ-F, McGaugh JL. The hippocampus mediates glucocorticoid-induced impairment of spatial memory retrieval: Dependence on the basolateral amygdala. Proc Natl Acad Sci [Internet]. 2003 Feb 4;100(3):1328–33. Available from: http://www.pnas.org/cgi/doi/10.1073/pnas.0337480100
13. Roozendaal B, de Quervain DJ-F, Schelling G, McGaugh JL. A systemically

administered β-adrenoceptor antagonist blocks corticosterone-induced impairment of contextual memory retrieval in rats. Neurobiol Learn Mem [Internet]. 2004 Mar;81(2):150–4. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1074742703001151
14. Wolf OT, Convit A, McHugh PF, Kandil E, Thorn EL, De Santi S, et al. Cortisol differentially affects memory in young and elderly men. Behav Neurosci [Internet]. 2001;115(5):1002–11. Available from: http://doi.apa.org/getdoi.cfm?doi=10.1037/0735-7044.115.5.1002
15. Schelling G, Richter M, Roozendaal B, Rothenhäusler H-B, Krauseneck T, Stoll C, et al. Exposure to high stress in the intensive care unit may have negative effects on health-related quality-of-life outcomes after cardiac surgery. Crit Care Med [Internet]. 2003 Jul;31(7):1971–80. Available from: http://journals.lww.com/00003246-200307000-00012
16. Stoll C, Kapfhammer HP, Rothenhäusler HB, Haller M, Briegel J, Schmidt M, et al. Sensitivity and specificity of a screening test to document traumatic experiences and to diagnose post-traumatic stress disorder in ARDS patients after intensive care treatment. Intensive Care Med [Internet]. 1999 Jul 22;25(7):697–704. Available from: http://link.springer.com/10.1007/s001340050932
17. Schelling G, Stoll C, Kapfhammer H-P, Rothenhäusler H-B, Krauseneck T, Durst K, et al. The effect of stress doses of hydrocortisone during septic shock on posttraumatic stress disorder and health-related quality of life in survivors. Crit Care Med [Internet]. 1999 Dec;27(12):2678–83. Available from: http://journals.lww.com/00003246-199912000-00012
18. Schelling G, Briegel J, Roozendaal B, Stoll C, Rothenhäusler H-B, Kapfhammer H-P. The effect of stress doses of hydrocortisone during septic shock on posttraumatic stress disorder in survivors. Biol Psychiatry [Internet]. 2001 Dec;50(12):978–85. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0006322301012707
19. Weis F, Kilger E, Roozendaal B, de Quervain DJ-F, Lamm P, Schmidt M, et al. Stress doses of hydrocortisone reduce chronic stress symptoms and improve health-related quality of life in high-risk patients after cardiac surgery: A randomized study. J Thorac Cardiovasc Surg [Internet]. 2006 Feb;131(2):277-282.e1. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0022522305016417
20. Kok L, Hillegers MH, Veldhuijzen DS, Cornelisse S, Nierich AP, van der Maaten JM, et al. The Effect of Dexamethasone on Symptoms of Posttraumatic Stress Disorder and Depression After Cardiac Surgery and Intensive Care Admission. Crit Care Med [Internet]. 2016 Mar;44(3):512–20. Available from: http://journals.lww.com/00003246-201603000-00008
21. Osuch EA, Cora-Locatelli G, Frye MA, Huggins T, Kimbrell TA, Ketter TA, et al. Post-dexamethasone cortisol correlates with severity of depression before and during carbamazepine treatment in women but not men. Acta Psychiatr Scand [Internet]. 2001 Nov;104(5):397–401. Available from: http://doi.wiley.com/10.1034/j.1600-0447.2001.00395.x
22. Rohleder N, Schommer NC, Hellhammer DH, Engel R, Kirschbaum C. Sex Differences in Glucocorticoid Sensitivity of Proinflammatory Cytokine Production After Psychosocial Stress. Psychosom Med [Internet]. 2001 Nov;63(6):966–72. Available from: http://journals.lww.com/00006842-200111000-00016
23. Royal Duth Pharmacists Association. KNMP Kennisbank.
24. Meikle AW, Tyler FH. Potency and duration of action of glucocorticoids. Effects of hydrocortisone, prednisone and dexamethasone on human pituitary-adrenal function. Am J Med [Internet]. 1977 Aug;63(2):200–7. Available from:

http://www.ncbi.nlm.nih.gov/pubmed/888843
25. Dijkstra-Kersten SMA, Kok L, Kerckhoffs MC, Cremer OL, de Lange DW, van Dijk D, et al. Neuropsychiatric outcome in subgroups of Intensive Care Unit survivors: Implications for after-care. J Crit Care [Internet]. 2020 Feb;55:171–6. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0883944119312523
26. Horowitz M, Wilner N, Alvarez W. Impact of Event Scale: a measure of subjective stress. Psychosom Med [Internet]. 1979 May;41(3):209–18. Available from: http://www.ncbi.nlm.nih.gov/pubmed/472086
27. Weiss DS, Marmar CR. The Impact of Event Scale - Revised. In: Wilson J, Keane TM, editors. Assessing psychological trauma and PTSD. New York: Guilford; 1996. p. 399–411.
28. Neal LA, Busuttil W, Rollins J, Herepath R, Strike P, Turnbull G. Convergent validity of measures of post-traumatic stress disorder in a mixed military and civilian population. J Trauma Stress [Internet]. 1994 Jul;7(3):447–55. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8087405
29. Bienvenu OJ, Williams JB, Yang A, Hopkins RO, Needham DM. Posttraumatic stress disorder in survivors of acute lung injury: evaluating the Impact of Event Scale-Revised. Chest [Internet]. 2013 Jul;144(1):24–31. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23699588
30. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand [Internet]. 1983 Jun;67(6):361–70. Available from: https://onlinelibrary.wiley.com/doi/10.1111/j.1600-0447.1983.tb09716.x
31. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res [Internet]. 2002 Feb;52(2):69–77. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11832252
32. EuroQol Group. EuroQol - a new facility for the measurement of health-related quality of life. Health Policy (New York) [Internet]. 1990 Dec;16(3):199–208. Available from: https://linkinghub.elsevier.com/retrieve/pii/0168851090904219
33. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res [Internet]. 2011 Dec 9;20(10):1727–36. Available from: http://link.springer.com/10.1007/s11136-011-9903-x
34. Lamers LM, McDonnell J, Stalmeier PFM, Krabbe PFM, Busschbach JJ V. The Dutch tariff: results and arguments for an effective design for national EQ-5D valuation studies. Health Econ [Internet]. 2006 Oct;15(10):1121–32. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16786549
35. Lee M, Kang J, Jeong YJ. Risk factors for post-intensive care syndrome: A systematic review and meta-analysis. Aust Crit Care [Internet]. 2020;33(3):287–94. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31839375
36. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA [Internet]. 1993;270(24):2957–63. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8254858
37. Ferreira FL. Serial Evaluation of the SOFA Score to Predict Outcome in Critically Ill Patients. JAMA [Internet]. 2001 Oct 10;286(14):1754. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.286.14.1754
38. Soliman IW, Van Dijk D, De Lange DW, Slooter AJC, Cremer OL, Van Delden JJM, et al. Incorporating repeatedly measured predictor data in prediction models for intensive care unit outcome. Universiteit Utrecht; 2018.
39. Zaal IJ, Tekatli H, van der Kooi AW, Klijn FAM, Koek HL, van Dijk D, et al.

Classification of daily mental status in critically ill patients for research purposes. J Crit Care [Internet]. 2015 Apr;30(2):375–80. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0883944114004390
40. Ely EW, Margolin R, Francis J, May L, Truman B, Dittus R, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med [Internet]. 2001 Jul;29(7):1370–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11445689
41. van Eijk MM, van den Boogaard M, van Marum RJ, Benner P, Eikelenboom P, Honing ML, et al. Routine use of the confusion assessment method for the intensive care unit: a multicenter study. Am J Respir Crit Care Med [Internet]. 2011 Aug 1;184(3):340–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21562131
42. Uitvlugt EB, van den Bemt BJF, Chung WL, Dik J, van den Bemt PMLA, Karapinar-Çarkit F. Validity of a nationwide medication record system in the Netherlands. Int J Clin Pharm [Internet]. 2019 Jun;41(3):687–90. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31028600
43. Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart MA. High-dimensional Propensity Score Adjustment in Studies of Treatment Effects Using Health Care Claims Data. Epidemiology [Internet]. 2009 Jul;20(4):512–22. Available from: https://journals.lww.com/00001648-200907000-00008
44. Brennan C, Worrall-Davies A, McMillan D, Gilbody S, House A. The Hospital Anxiety and Depression Scale: A diagnostic meta-analysis of case-finding ability. J Psychosom Res [Internet]. 2010 Oct;69(4):371–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0022399910001698

Supplementary material B: Figures and Tables

Figure 1

Inclusion of eligible subjects flow-chart.

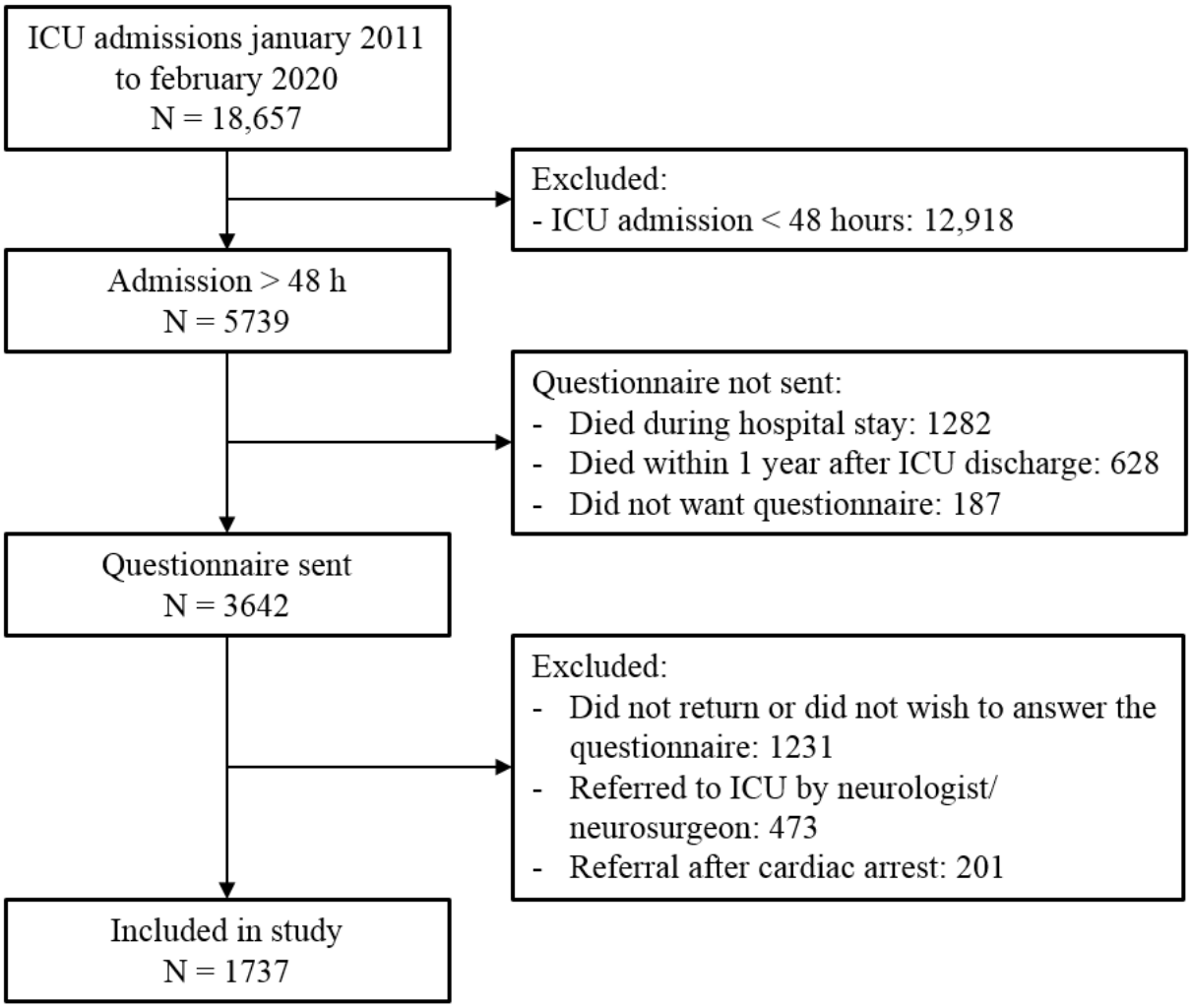
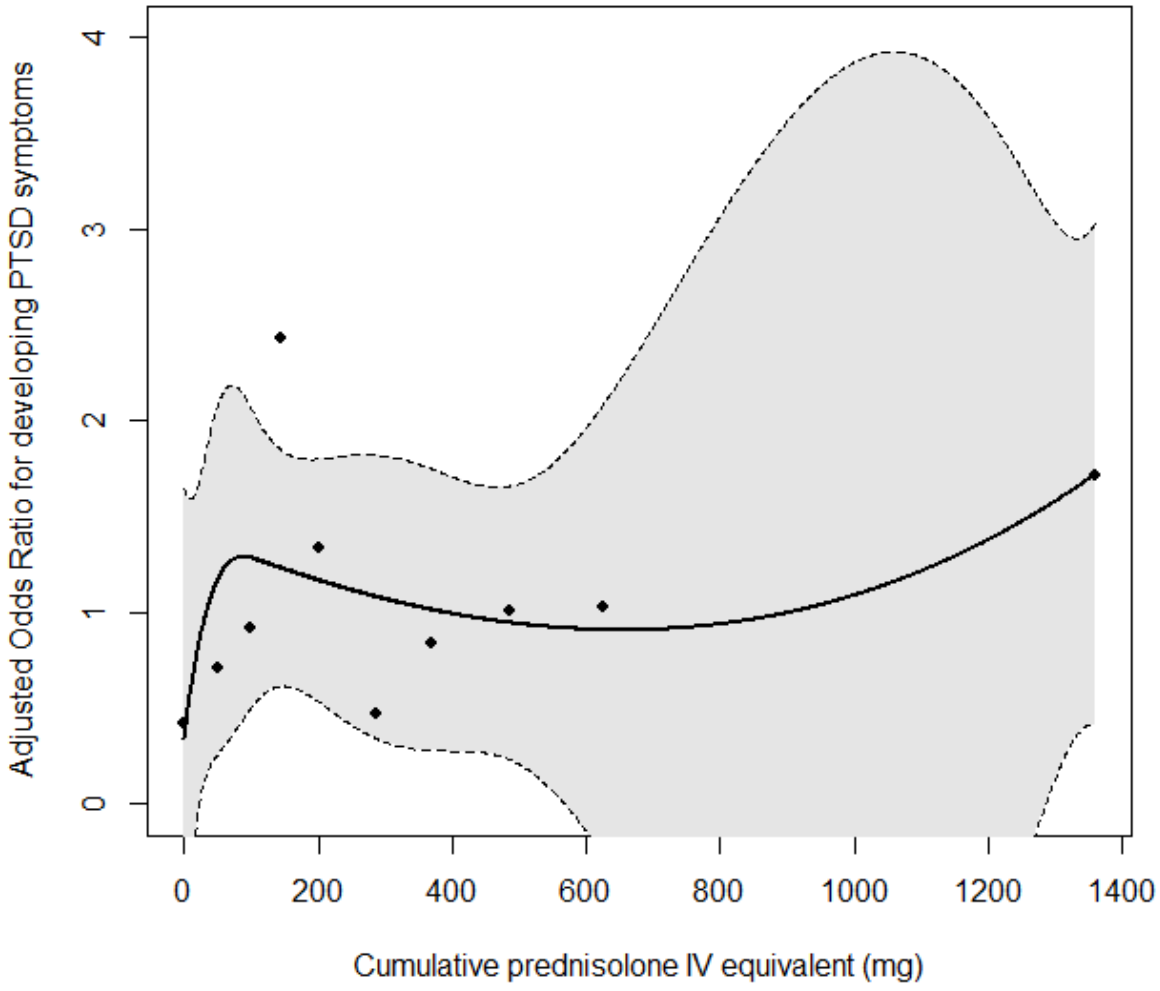


Figure 2

Adjusted [a] odds ratios for developing PTSD symptoms per 10th percentile of cumulative prednisolone equivalent versus no glucocorticoid use, analyzed with a 2-knot linear spline regression (knots at 25th and 75th percentile). Dotted lines represent the 95% confidence intervals of the regression fit.



[a] Adjusted for age, sex, ICU length of stay, type of admission, referral by a pulmonologist (yes/no), SAPS II, mechanical ventilation, delirium during ICU stay, mSOFA on day of admission, difference between mSOFA on day of admission and on day 4, cumulative midazolam dosage, cumulative propofol dosage and outpatient use of glucocorticoids / antidepressants / antipsychotics / anxiolytics

Table 1

Responders versus non-responders.

Variable	**Responders n = 1737**	**Non-responders n = 1489**	**p-value**
Age in years, mean (SD)	59 (16)	54 (17)	<0.001
Sex			0.44
Male, n (%)	1119 (64)	939 (63)	
Female, n (%)	618 (36)	550 (37)	
ICU length of stay in days (median, IQR)	5.1 (3.0 – 9.8)	5.1 (3.1 – 9.9)	0.99
Type of admission			<0.001
Medical (n, %)	641 (37)	761 (51)	
Planned surgical (n, %)	614 (35)	325 (22)	
Acute surgical (n, %)	477 (28)	401 (27)	
Missing, n	5	2	

ICU = Intensive Care Unit, SD = standard deviation, IQR = interquartile range

Table 2

Patient characteristics.

Variable	**Glucocorticoid use n = 690**	**No glucocorticoid use n = 1047**
Age in years, mean (SD)*	58 (14)	59 (17)
Male, n (%)***	405 (59)	714 (68)
ICU length of stay in days, median (IQR)***	6.8 (3.8 – 13.9)	4.4 (2.9 – 7.8)
Type of admission***, [a]		
Medical, n (%)	260 (38)	381 (36)
Planned surgical, n (%)	180 (26)	434 (41)
Acute surgical, n (%)	246 (36)	231 (22)
Referral by a pulmonologist, n (%)***	130 (19)	36 (3)
SAPS II, mean (SD)***	40.2 (13.7)	36.0 (11.1)
Mechanically ventilated, n (%) [b]	672 (98)	1001 (97)
Delirium during ICU stay, n (%)**	352 (51)	450 (43)
mSOFA at day of admission, mean (SD)***, [c]	6.0 (2.9)	4.7 (2.7)
Difference between mSOFA on day of admission and on day 4, mean (SD) [d]	-0.6 (3.1)	-0.3 (2.7)
Midazolam use, n (%)***	415 (60%)	503 (48%)
Propofol use, n (%)***	498 (72%)	660 (63%)
Cumulative midazolam dosage in milligrams within users, median (IQR)***	164 (19 – 450)	50 (10 – 242)
Cumulative propofol dosage in milligrams within users, median (IQR)	3438 (860 – 11171)	3869 (1072 – 9902)
Outpatient use of		
Glucocorticoids, n (%)***	189 (27)	16 (2)
Antidepressants, n (%)	59 (9)	84 (8)
Antipsychotics, n (%)	16 (2)	25 (2)
Anxiolytics, n (%)	85 (12)	105 (10)

*p-value <0.05, **p-value <0.01, ***p-value <0.001

ICU = Intensive Care Unit, SD = standard deviation, IQR = interquartile range, SAPS II = Simplified Acute Physiology Score second edition, mSOFA = modified Sequential Organ Failure Assessment score

[a] Missing for 5 patients (0.3%)
[b] Missing for 13 patients (0.7%)
[c] Missing for 13 patients (0.7%)
[d] Missing for 14 patients (0.8%)

Table 3

Primary and secondary endpoints.

	PTSD, n (%) [a]	**Crude OR (95% CI)**	**Adj. OR (95% CI)** [e]
Glucocorticoid use	81 (12)	1.17 (0.86 – 1.60)	0.99 (0.68 – 1.45)
No glucocorticoid use	106 (11)		
	Anxiety, n (%) [b]	**Crude OR (95% CI)**	**Adj. OR (95% CI)** [e]
Glucocorticoid use	121 (18)	0.95 (0.74 – 1.23)	0.89 (0.65 – 1.21)
No glucocorticoid use	192 (19)		
	Depression, n (%) [c]	**Crude OR (95% CI)**	**Adj. OR (95% CI)** [e]
Glucocorticoid use	106 (16)	0.79 (0.61 – 1.03)	0.81 (0.59 – 1.10)
No glucocorticoid use	197 (19)		
	EQ-5D Utility score, median (IQR) [d]	**Change in utility value (crude)**	**Change in utility value (adjusted)** [e]
Glucocorticoid use	0.811 (0.687 – 1)	-0.003 (-0.028 – 0.022)	0.027 (-0.003 – 0.057)
No glucocorticoid use	0.811 (0.687 – 1)		

Results after multiple imputation
[a] Missing for 95 patients (5%)
[b] Missing for 49 patients (3%)
[c] Missing for 42 patients (2%)
[d] Missing for 67 patients (4%)
[e] Adjusted for age, sex, ICU length of stay, type of admission, referral by a pulmonologist (yes/no), SAPS II, mechanical ventilation, delirium during ICU stay, mSOFA on day of admission, difference between mSOFA on day of admission and on day 4, cumulative midazolam dosage, cumulative propofol dosage and outpatient use of glucocorticoids / antidepressants / antipsychotics / anxiolytics

Table 4 – 6

Stratification analyses.

Sex

Sex	**Male**				**Female**			
	PTSD	**No PTSD**	**Missing**	**p-value***	**PTSD**	**No PTSD**	**Missing**	**p-value***
Glucocorticoid use	40 (10%)	353 (90%)	12	0.640	41 (15%)	225 (85%)	19	0.816
No glucocorticoid use	61 (9%)	609 (91%)	44		45 (14%)	268 (86%)	20	
Adjusted odds ratio	0.88 (0.53 – 1.47) (p=0.63)				1.12 (0.64 – 1.96) (p=0.70)			

Year of admission

	Year of admission											
	2011 – 2013				**2014 – 2016**				**2016 – 2020**			
	PTSD	**No PTSD**	**M**	**p***	**PTSD**	**No PTSD**	**M**	**p***	**PTSD**	**No PTSD**	**M**	**p***
Gluc. use	30 (13%)	209 (87%)	14	0.898	27 (12%)	206 (88%)	7	0.975	24 (13%)	163 (87%)	10	0.079
No gluc. use	45 (13%)	294 (87%)	26		38 (11%)	303 (89%)	16		23 (8%)	280 (92%)	22	
Adj. odds ratio	0.73 (0.39 – 1.36) (p=0.32)				1.21 (0.66 – 2.23) (p=0.54)				1.17 (0.55 – 2.50) (p=0.68)			

M = missing

Glucocorticoids in home medication

	Glucocorticoids in home medication				**No glucocorticoids in home medication**			
	PTSD	**No PTSD**	**M**	**p***	**PTSD**	**No PTSD**	**M**	**p***
Glucocorticoid use	23 (13%)	156 (87%)	10	1	58 (12%)	422 (88%)	21	0.501
No glucocorticoid use	2 (13%)	13 (87%)	1		104 (11%)	864 (89%)	63	
Adjusted odds ratio	1.02 (0.20 – 5.18) (p=0.97)				0.95 (0.66 – 1.41) (p=0.84)			

M = missing

**Chi-squared test*

Table 7

Adjusted linear regression results with IES and IES-R score as dependent variable

IES score (range 0 – 75)	**IES-R mean score (range 0 – 4)**
Change in IES score (glucocorticoid use versus non-use): - 0.6950 (95% CI -2.99 – 1.67)	Change in IES score (glucocorticoid use versus non-use): 0.01373 (95% CI -0.15 – 0.18)

Table 8 – 12

Complete case analyses.

Complete cases versus incomplete cases

Variable	**Complete cases n = 1627**	**Incomplete cases n = 110**	**p-value**
Glucocorticoid use, n (%)	653 (40)	37 (34)	0.21
Age in years, mean (SD)	58.5 (15.7)	61.2 (16.6)	0.09
Sex			0.49
Male, n (%)	1052 (65)	67 (61)	
Female, n (%)	575 (35)	43 (39)	
ICU length of stay in days (median, IQR)	5.1 (3.1 – 9.7)	5.4 (3.1 – 10.5)	0.68
Type of admission			0.16
Medical (n, %)	605 (37)	36 (34)	
Planned surgical (n, %)	568 (35)	46 (44)	
Acute surgical (n, %)	454 (28)	23 (22)	
Missing, n	0	5	
SAPS II score, mean (SD)	37.7 (12.3)	37.4 (12.6)	0.81
mSOFA at day of admission, mean (SD)	5.3 (2.9)	4.8 (2.8)	0.10
Missing, n	0	13	
Difference between mSOFA on day of admission and on day 4, mean (SD)	-0.4 (2.9)	-0.2 (3.0)	0.47
Missing, n	0	14	

Main analyses: complete cases only

PTSD

	Odds Ratio (95% CI)	
	Crude	**Adjusted**
Glucocorticoid use	1.16 (0.85 – 1.58)	0.98 (0.67 – 1.42)

HADS Anxiety

	Odds Ratio (95% CI)	
	Crude	**Adjusted**
Glucocorticoid exposure	0.94 (0.73 – 1.21)	0.88 (0.65 – 1.20)

HADS Depression

	Odds Ratio (95% CI)	
	Crude	**Adjusted**
Glucocorticoid exposure	0.78 (0.60 – 1.01)	0.81 (0.59 – 1.10)

EQ-5D (Linear regression)

	Increase in utility value	
	Crude	**Adjusted**
Glucocorticoid exposure	0.00029 (-0.024 – 0.025)	0.029 (-0.0007 – 0.059)