FACULTY OF HEALTH, AARHUS UNIVERSITY

Impact of preadmission anti-inflammatory drug use on risk of depression and anxiety after intensive care requiring mechanical ventilation

Research year report

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PREFACE

The present report is based on a study conducted during my research year at the Department of Clinical Epidemiology, Aarhus University Hospital, Denmark.

First, I would like to express my deepest appreciation to my main supervisor, Christian Fynbo Christiansen. He has motivated me, encouraged my ideas, shown me great trust and stood behind me throughout the year. He would always find time for a meeting, even on very short notice, and guide me with great questions and constructive feedback.

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ABBREVIATIONS

ATC	Anatomical Therapeutic Chemical classification system
CI	Confidence interval
ICD	International Classification of Diseases
ICU	Intensive care unit
NSAID	Non-Steroidal Anti-Inflammatory Drug
PTSD	Posttraumatic Stress Disorder
SKS	Health Care Classification system (Sundhedsvæsenets Klassifikationssystem)

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ABSTRACT

Importance: Risk of depression and anxiety is elevated after intensive care. Drugs with anti-inflammatory properties may have antidepressant and anxiolytic effects.

Objective: To investigate the association between preadmission use of drugs with anti-inflammatory effects and risk of new-onset depression and anxiety among patients admitted to an intensive care unit.

Design, setting and participants: Propensity score matched population-based cohort study of all adults who received mechanical ventilation in an intensive care unit in Denmark during 2005–2013.

Exposures: Preadmission single-agent or combined use of statins, non-steroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids.

Main outcomes and measures: Cumulative incidence and risk ratio of new-onset psychiatrist-diagnosed depression or anxiety or prescriptions for antidepressants or anxiolytics.

Results: Among 48,207 intensive care unit patients, propensity score matching yielded 6,088 statin user pairs, 2,886 NSAID user pairs, 1,440 glucocorticoid user pairs and 1,743 combination drug user pairs. The cumulative incidence of depression and anxiety during the three years following intensive care was 18.0% (95% confidence interval (CI) 17.0%-19.0%) for statin users, 21.3% (95% CI 19.8%-22.9%) for NSAID users, 17.4% (95% CI 15.4%-19.5%) for glucocorticoid users and 19.0% (95% CI 16.3%-20.2%) for combination users. The cumulative incidence was similar in non-users compared with users in all drug groups. The risk ratio of depression and anxiety three years after admission to intensive care unit was 1.04 (95% CI 0.96-1.13) for statin users, 1.00 (95% CI 0.90-1.11) for NSAID users, 0.97 (95% CI 0.82-1.14) for glucocorticoid users and 1.05 (95% CI 0.90-1.21) for combination users, compared with non-users. Results were robust across subgroups (gender, age, preadmission diseases, type of admission) and sensitivity analyses (depression and anxiety separately).

Conclusions and relevance: Approximately a fifth of mechanically ventilated patients in an intensive care unit received a diagnosis of depression or anxiety or a prescription for an anti-depressant or anxiolytic drug within three years following intensive care unit admission. We did not find that preadmission use of statins, NSAIDs, glucocorticoids or combinations of these drugs altered the risk of depression and anxiety.

DANSK RESUMÉ

Baggrund: Risikoen for depression og angst er høj efter intensivindlæggelse. Medicin med anti-inflammatoriske egenskaber har muligvis antidepressive og anxiolytiske effekter.

Formål: At undersøge associationen mellem brug af medicin med anti-inflammatoriske effekter forud for indlæggelse på en intensiv afdeling og risikoen for nyopstået depression eller angst efterfølgende.

Metode: Propensity score matched populations-baseret kohorte studie af alle voksne patienter, der blev mekanisk ventileret på en intensiv afdeling i Danmark fra 2005–2013.

Eksponeringer: Enkelt eller kombineret brug af statiner, non-steroide anti-inflammatoriske midler (NSAIDs) eller glukokortikoider.

Udfald: Kumuleret incidens og risiko ratio af incident psykiater-diagnosticeret depression eller angst eller recept på antidepressiva eller anxiolytika.

Resultater: Blandt 48.207 intensivpatienter gav propensity score matching 6.088 statinbruger par, 2.886 NSAID-bruger par, 1.440 glukokortikoidbruger par og 1.743 kombinationsbruger par. Den kumulerede incidens af depression og angst tre år efter intensivindlæggelse var 18,0 % (95 % konfidensinterval (CI) 17,0 %-19,0 %) for statinbrugere, 21,3 % (95 % CI 19,8 %-22,9 %) for NSAID-brugere, 17,4 % (95 % CI 15,4 %-19,5 %) for glukokortikoidbrugere og 19,0 % (95 % CI 16,3 %-20,2 %) for kombinationsbrugere. Den kumulerede incidens var ensartet ved sammenligning af brugere med ikke-brugere i alle grupper. Risiko ratioen for depression og angst tre år efter intensivindlæggelse var 1,04 (95 % CI 0,96-1,13) for statinbrugere, 1,00 (95 % CI 0,90-1,11) for NSAID-brugere, 0,97 (95 % CI 0,82-1,14) for glukokortikoidbrugere and 1,05 (95 % CI 0,90-1,21) for kombinationsbrugere, sammenlignet med ikke-brugere. Resultaterne var robuste på tværs af subgrupper (køn, alder, sygdomme forud for indlæggelse og indlæggelsestype) og sensitivitetsanalyser (depression og angst separat).

Konklusion og relevans: Cirka en femtedel af mekanisk ventilerede patienter på en intensivafdeling får en depressions- eller angstdiagnose eller en recept på antidepressiva eller anxiolytika inden for tre år fra indlæggelsestidspunktet. Vi fandt ikke, at brug af statin, NSAIDs, glukokortikoider eller en kombination af disse forud for indlæggelse var associeret med en ændret risiko for depression og angst.

MANUSCRIPT

Introduction

Critical illness requiring intensive care unit (ICU) admission is associated with 3-year mortality ranging from 21.3% to 63.2%, depending on morbidity level.[1,2] Advances in intensive care and associated improvements in patient prognosis require increased attention to patient mental health after discharge.[3] Depression and anxiety are common psychiatric sequelae after intensive care, with prevalence of symptoms ranging from 19% to 31% and a higher risk of these conditions compared with matched cohorts of other hospital patients.[4–6]

Inflammation is one mechanism that may link critical and mental illness, as ICU patients often have high levels of inflammation and several studies have documented the role of inflammation in conditions such as depression.[7] For instance, autoimmune diseases and infections were risk factors for mood disorders in a Danish nationwide prospective cohort study.[8] As well, a meta-analysis of 29 studies found that patients with depression had elevated inflammatory markers, even in the absence of other medical illnesses.[9] Finally, in a study of patients treated with pro-inflammatory cytokines, such as interferon-alpha, 17.2% developed depression within 8 weeks of treatment initiation.[10] Targeting inflammation in critical illness thus may decrease the risk of mental illness.

Drugs with anti-inflammatory effects, such as statins, non-steroidal anti-inflammatory drugs (NSAIDS) and glucocorticoids, reduced the risk of psychiatric disorders in some studies.[11–18] In a nested case-control study, statin use was associated with lower risk of depression in patients in general practice.[11] This was also found in a study of use of statins combined with selective serotonin reuptake inhibitors.[12] Study findings are conflicting concerning the possible role of statins in reducing symptoms of anxiety.[13] NSAIDs decreased depressive symptoms in a meta-analysis of randomized controlled trials.[14] In a Danish nationwide cohort study, however, only ibuprofen was associated with a lower risk of depression.[15] NSAIDs as a group were associated with an increased risk of depression.[15]

The effect of anti-inflammatory drugs on risk of mental illness specifically in critically ill patients has only been assessed in a few studies focusing on selected patient subgroups, and results have been conflicting.[16–24] In three observational studies of patients with acute coronary syndrome,

stroke or need for surgical cardiac intervention, respectively, the odds ratio for development of depression was lower among statin users compared with non-users.[16–18] Conversely, Kang *et al*. found the hazard ratio of depression among patients with stroke to be higher among statin users than among non-users.[19] Five randomized controlled trials have examined the impact of glucocorticoids on mental illness after cardiac surgery or septic shock.[20–24] Three found that stress doses (glucocorticoid administration equivalent to the endocrine secretion rate of the adrenal gland under maximal stimulation[25]) of hydrocortisone reduced posttraumatic stress disorder (PTSD) and stress symptoms,[20–22] but one found no effect.[23] A study assessing a single intra-operative dose of dexamethasone during cardiac surgery also found no effect.[24] The effect of NSAIDs on risk of depression and anxiety after critical illness has not been examined previously.

A recent review called for treatment strategies to lessen the burden of mental illness among survivors of critical illness.[3] Attenuating the inflammatory response in the early phase of critical illness may reduce the risk of subsequent mental illness. Thus it might represent an early intervention for patients at high risk of critical illness. This study investigated the association between preadmission use of drugs with anti-inflammatory effects among ICU patients and risk of depression and anxiety during the three years following admission.

Methods

Design and study population

This nationwide cohort study included all adult patients (≥18 years) who underwent mechanical ventilation in a Danish ICU between January 1, 2005 and December 31, 2013. We chose ICU patients who had received mechanical ventilation to ensure comparable severity of illness among patients. The study period began in 2005 when data on ICU admissions were complete. Patients were excluded if, within a year prior to ICU admission, they had a psychiatric hospital contact with a diagnosis of depression, anxiety disorder, bipolar disorder, schizophrenia or schizoaffective disorder, or a filled prescription for an antidepressant, anxiolytic, or antipsychotic medication.

Data were obtained through linkage among national registries using the unique personal identification number assigned to all Danish residents. Patients who received mechanical

ventilation in an ICU (all departments defined as an ICU in the Danish Intensive Care Database[27]) were identified using the Danish National Patient Register.[26] This registry has recorded all non-psychiatric inpatient contacts since 1977, with complete coverage of public hospitals.[26] The code for mechanical ventilation has been validated, yielding a positive predictive value of 100%.[27] The Health Care Classification system (SKS) procedure codes, *International Classification of Diseases, Tenth Revision* (ICD-10) codes and Anatomical Therapeutic Chemical Classification System (ATC) codes used in the study are provided in **Supplemental Table 1**.

Exposures

The exposure was preadmission use of a single or combination use of drugs with anti-inflammatory effects, including statins, NSAIDs and/or systemic glucocorticoids. Users were defined as patients with at least one filled prescription for statin within 125 days prior to ICU admission or one prescription for NSAID or glucocorticoid within 60 days prior to ICU admission. These periods were chosen based on drug types and package sizes available in Denmark.[28–32] A combination user of a statin, NSAID or glucocorticoid had two or more current prescriptions in any combination. Patients with no filled prescriptions for the medications of interest were classified as non-users. All prescriptions filled more than 125 days prior to ICU admission for statins and 60 days prior to ICU admission for NSAIDs and glucocorticoids were considered prior use for both users and non-users. We calculated prior use for all patients as a cumulative dose using the defined daily dose described by the World Health Organization.[33] Filled prescriptions were identified from the Danish National Prescription Registry.[34] The ATC codes used to define exposure variables are provided in **Supplemental Table 2**.

Patient characteristics

A number of chronic diseases associated with use of anti-inflammatory drugs are also associated with depression and anxiety.[35,36] To adjust for potential confounding, we obtained data on diagnoses associated with earlier hospital contacts or use of drugs 10 years prior to ICU admission from the Danish National Patient Register and Danish National Prescription Registry.[26,34] Relevant diagnoses included myocardial infarction, congestive heart failure, hypertension, atrial fibrillation/atrial flutter, chronic pulmonary disease, cancer, diabetes, connective tissue disease,

gastrointestinal and liver disease, renal disease, dementia, osteoporosis and alcoholism. We also characterized patients by age, sex, education level, gross income and job position using data from the Integrated Database for Labour Market Research and the Danish Civil Registration System.[37,38] We included all socioeconomic variables and preadmission diseases in our analyses as they were potential confounders. The ICD-10 codes and ATC codes used to define preadmission diseases and prior drug use are provided in **Supplemental Table 3**.

Outcomes

The main study outcome was depression or anxiety disorder, defined as a diagnosis at a psychiatric hospital in- or outpatient clinic, including visits to emergency departments, or a filled prescription for an antidepressant or anxiolytic. Anxiety disorders were broadly defined as neurotic, stress-related and somatoform disorders. Patients were followed from day of ICU admission until a diagnosis of depression or anxiety, death, three years following ICU admission, or censoring as appropriate if full follow-up time was unavailable (applicable to patients admitted to ICUs later than 2010), whichever came first. Information on diagnoses of psychiatric disorders was obtained from the Danish Psychiatric Central Research Register, which contains data on all psychiatric inpatient and outpatient contacts since 1995.[39,40] The diagnosis of a single depressive episode, schizophrenia and posttraumatic stress disorder have been validated with positive predictive values of 75.4%, 97.5% and 83% respectively.[41–43] Information on filled prescriptions was obtained from the Danish National Prescription Registry, which contains individual-level information on all prescriptions dispensed since 1995.[34] The ICD-10 codes and ATC codes used to define the study outcomes are provided in **Supplemental Table 4**.

Statistical methods

We summarized patient characteristics according to user status (non-users, statin users, NSAID users, glucocorticoid users and combination users). Given the observational nature of this study, important differences were observed in the baseline characteristics of users and non-users of anti-inflammatory drugs. We therefore created a propensity score matched cohort for each of the anti-inflammatory drug categories (statins, NSAIDs, glucocorticoids and combinations). Propensity scores were computed using multivariable logistic regression. Covariates included in the

regressions were sex, age, education level (basic education, youth education, higher education or unknown), income (< 100,000, 100,000 – 199,999, 200,000 – 299,999, ≥ 300,000 Danish kroner or unknown), job status (employed, retired early, pensioner, unemployed or unknown), comorbid illnesses, preadmission use of cardiovascular drugs (y/n), respiratory drugs (y/n), immunosuppressant drugs (y/n) and opioids (y/n), as well as prior cumulative use of statins, NSAIDs and glucocorticoids. We matched statin users, NSAID users, glucocorticoid users and combination users, respectively, with non-users who had the nearest propensity score within a caliper range of ±0.025 without replacement. We assessed covariate balance, considering an absolute standardized difference below 0.1 adequate.[44]

After propensity score matching, we computed the 6-month, 1-year and 3-year cumulative incidence (risk) of depression and anxiety following the date of ICU admission according to anti-inflammatory drug use, accounting for the competing risk of death.[45]

We compared the risk in users with that in non-users within each matched cohort accounting for the competing risk of death using the pseudovalue method.[46] For each observation a pseudovalue was calculated based on the difference between the pseudovalue for the entire cohort and that for the cohort without the given observation. After all pseudovalues were obtained, the risk ratio was calculated with a generalized linear regression model using a log-link function. In a sensitivity analysis, we assessed depression and anxiety separately. Finally, we conducted subgroup analyses focusing on gender, age, preadmission diseases and type of admission.

All analyses were performed using STATA 14 (Stata Corp LP, College Station, TX). All data were anonymized and accessed via remote access at Statistics Denmark. The study was approved by the Danish Data Protection Agency (journal number: 2014-41-3658), Statistics Denmark (project number: 702770) and the National Board of Health (journal number: 7-505-29-1405/1). As the study relied on existing data with no intervention, it did not require ethics committee approval according to Danish law.

Results

Baseline characteristics

A total of 48,207 patients were mechanically ventilated and had no prior mental illness (see flowchart in **Supplemental Figure 1**). Before propensity score matching, their clinical and socio-demographic characteristics varied according to use of anti-inflammatory drugs (**Table 1**). Non-users were generally younger, had a higher education and income and fewer preadmission diseases compared with users of any of the drugs. Propensity score matching produced 6,088 pairs of statin users, 2,886 pairs of NSAID users, 1,440 pairs of glucocorticoid users and 1,743 pairs of combination users (**Table 2**). The standardized differences were below 10% in the propensity score matched cohorts with few exceptions (**Table 2**).

Risk of depression and anxiety following intensive care

The cumulative incidence of anxiety and depression was 18.0% (95% CI 17.0%-19.0%) for statin users, 21.3% (95% CI 19.8%-22.9%) for NSAID users, 17.4% (95% CI 15.4%-19.5%) for glucocorticoid users and 19.0% (95% CI 16.3%-20.2%) for combination users during the three years following intensive care (**Figure 1** and **Table 3**). Cumulative incidence was similar among users and non-users in all groups.

The association between anti-inflammatory drug use and depression and anxiety

None of the anti-inflammatory drugs were associated with altered risk of depression and anxiety (**Table 3**). The risk ratio at six months and three years following ICU admission was 0.94 (95% CI 0.84-1.05) and 1.04 (95% CI 0.96-1.13) for statin users, 0.98 (95% CI 0.85-1.14) and 1.00 (95% CI 0.90-1.11) for NSAID users, 1.00 (95% CI 0.79-1.26) and 0.97 (95% CI 0.82-1.14) for glucocorticoid users and 1.07 (95% CI 0.88-1.31) and 1.05 (95% CI 0.90-1.21) for combination users during the study period.

Sensitivity and stratified analyses

The sensitivity analyses conducted for depression and anxiety separately yielded results similar to those for our main analyses (**Supplemental Table 5** and **Supplemental Table 6**). Our results were robust across subgroups (**Figure 2**). Due to the low number of patients in some subgroups, associated estimates were imprecise and could not be calculated in all subgroups.

Discussion

In this nationwide cohort study, approximately a fifth of mechanically ventilated patients in intensive care units received a diagnosis of depression or anxiety or a prescription for an antidepressant or anxiolytic within three years following ICU admission. The rate of depression and anxiety after intensive care found in the current study is consistent with results of prior studies.[4–6]

Our main finding was that preadmission use of drugs with anti-inflammatory effects – statins, NSAIDs, glucocorticoids or combinations – was not associated with depression and anxiety in the three years following intensive care. This is contrary to results of studies conducted among non-critically ill patients,[11,12,14] as well as other studies of critically ill patients treated with statins or glucocorticoids.[16–18,20–22] Differences between the results of the current work and previous studies may be due to our high degree of control of confounding. Differences may also be associated with timing and dosage, as the studies that found an association between glucocorticoid use and lower risk of depression assessed stress doses of glucocorticoids during intensive care, not continuous everyday preadmission use as in our study. Thus, glucocorticoids may have a beneficial effect when administered in high doses around the time of illness, but not as a continuous lower dose over a longer period prior to illness. Our study does support the lack of association between use of glucocorticoids and depression and anxiety found in other studies.[23,24]

Strengths of the current study include its use of nationwide registry-based data, which alleviates concerns about selection bias. Another strength is its access to information on several types of anti-inflammatory drugs, as well as on combination use and prior use. Most prior studies have assessed single anti-inflammatory drugs without accounting for use of other drugs. We also had extensive and detailed patient data, including both socioeconomic variables and preadmission diseases, which permitted strict confounder control and decreased the risk of confounding by indication in our propensity score matched cohorts.

A number of limitations should also be considered when interpreting our results. Anti-inflammatory drug use was assessed in terms of prescriptions only. Some patients may have been misclassified as users if they filled a prescription, but never actually used the drug, or misclassified as non-users if they bought an NSAID over-the-counter. In our study period the percentage of total

NSAID sold on prescription ranged between 75–83%.[47] Such non-differential misclassification would usually bias the association towards the null, potentially obscuring an actual association.

If a patient was hospitalized during the 125 days or 60 days, respectively, prior to the ICU admission this could lead to a misclassification of exposure as this would shorten the observation period defining the exposure. This immeasurable time bias would lead to a bias away from the null.[48] Further, some patients who were not exposed prior to admission may be exposed during admission. The probability of being exposed during admission is probably higher among users compared with non-users leading to a differential misclassification, which should bias the estimates away from the null. Yet, we did not find an association rendering little concern of these biases. Depression or anxiety was defined by hospital diagnoses or by filled prescriptions for antidepressants or anxiolytics. These drugs can, however, be prescribed for indications other than depression and anxiety, leading to non-differential misclassification, which would also usually bias the association towards the null. Also, we did not randomize patients to an anti-inflammatory treatment and some unmeasured confounding may have occurred, despite our use of carefully constructed propensity scores. As well, ICU patients are heterogeneous and subgroup analyses were limited by the number of patients in each subgroup. Our main results were, however, robust across subgroups. Still, some patients may have benefited while others did not, as we lacked information on the level of inflammation on an individual level before and after intensive care. If a patient had no inflammation, he/she would presumably not benefit from anti-inflammatory treatment. Similarly, these drugs may have been inadequate in decreasing the inflammatory response. Finally, an anti-inflammatory drug might affect the severity of depression or anxiety rather than completely prevent it. We did, however, not have information on severity.

In conclusion, anxiety and depression are important concerns following intensive care. Our results do not support that preadmission anti-inflammatory drugs are associated with an altered risk of depression and anxiety in the intensive care setting.

SUPPLEMENTARY

Methodological and statistical considerations

Study design

The study was a nationwide historical cohort study of all adult patients receiving mechanical ventilation in an intensive care unit (ICU) between January 1, 2005, and December 31, 2013. Our study was observational. Information on use of anti-inflammatory drugs (exposure), socioeconomic status and preadmission diseases (covariates) and depression or anxiety (outcome) was obtained from the national registers.

A randomized controlled trial is considered the golden standard study design to investigate the effect of a drug.[49] Yet, we found a cohort study more suitable in this case. Our exposure of interest was anti-inflammatory drug use *prior to* ICU admission. Randomizing patients prior to ICU admission – which is a rare event – would require an immense sample as the majority of patients would not be admitted to an ICU and among those admitted even fever would develop depression or anxiety. Further, to randomize patients to use drugs with potential harmful side effects in a cohort where only a minor percentage would potentially benefit would be unethical. A register-based cohort study allowed us to test our hypothesis in a large cohort in an economical and ethical way. Had we found an association this could warrant further investigations in the form of randomized controlled trials of selected high-risk patient groups (e.g. prior to major surgery). Further, in randomized controlled trials inclusion and exclusion criteria are often very strict rendering a high degree of internal validity but a low external validity (generalizability).[50] We included all adult patients regardless of characteristics, however, we must be cautious making inferences in patients younger than 18 years. Finally, a register-based study usually allows for longer follow up than randomized controlled studies.[50]

Propensity score matching

Our baseline covariates were not equally distributed across exposure groups (**Table 1**). This was expected given the observational nature of our study in which treatment selection is influenced by indication based on patient characteristics, not randomly allocated. Non-users were generally younger, had higher education level and fewer preadmission diseases. This corresponds well with prescription of the drug being indicated, e.g. glucocorticoids are prescribed for patients with

inflammatory diseases, who also tend to be older, have a lower education level and higher disease burden. Direct comparison between users and non-users would be associated with high risk of confounding, especially confounding by indication (see the section *Confounding*). We therefore created a propensity score matched cohort (**Table 2**). The propensity score is the probability that a patient is exposed to a drug based on his/her baseline covariates.[44] Propensity score matching renders the observational study to mimic a randomized controlled trial by balancing covariates. First, we predicted the probability of receiving statin, NSAID and glucocorticoid, respectively, based on a multivariable logistic regression including both risk factors for depression and anxiety as well as confounders for the association between use of anti-inflammatory drugs and depression and anxiety. Risk factors and confounders chosen were based on existing literature and clinical knowledge (see the section *Confounding*). We then matched each user to a non-user with a similar propensity of receiving the drug. That meant that the two patients based on their baseline covariates had the same probability of receiving treatment, e.g. statin. We then assessed whether covariates were well-balanced in the propensity score matched cohort and considered an absolute standardized difference below 0.1 adequate.[44] This was fulfilled for the majority of covariates and we thus had four cohorts of users and non-users for our analysis (a statin cohort, NSAID cohort, glucocorticoid cohort and combination cohort). This came at the cost of exclusion of patients, who could not be matched. This was especially patients with a very low propensity (probability) or a very high propensity (probability) of receiving treatment.

Definition of exposure: Use of anti-inflammatory drugs

Defining who is exposed to a drug at the time of interest in a register-based study implies assumptions. In our study we assumed that a filled prescription equaled taking the drug and that a patient was a user if he/she had a filled prescription within 125 days prior to ICU admission for statin use and 60 days prior to ICU admission for NSAID and glucocorticoid use. These exposure windows were chosen based on the most common types and package sizes available in Denmark and for comparability with prior studies.[29–32,51] The choice of exposure window affects sensitivity and specificity of drug use identification. The sensitivity is our ability to correctly identify all those who were taking the drug at the time of admission. The specificity is our ability to correctly identify those who were not taking the drug at the time of admission. We would like a high

sensitivity without losing specificity. A wider time frame, e.g. a filled prescription within 150 days of admission for statin, would increase sensitivity. This would be at the expense of specificity as some prescriptions might not last until the time of admission and these patients would be classified as users without actually taking the drug (false positive). A narrower time frame, e.g. 90 days, would increase specificity. This would be at the expense of sensitivity as some users with long-lasting prescriptions would be classified as non-users though actually taking the drug (false negative).

We then challenged our original exposure definition – denoted *version 1* – in a sensitivity analyses with the following two exposure definitions.

Exposure definition version 2

We calculated how long each prescription lasted based on total dose. A patient was a user if a filled prescription could last up until admission. We used the Defined Daily Dose by the World Health Organization to calculate the expected duration of each prescription and added this duration to the date of dispense to obtain the end date of each prescription.[33] If the end date of a given prescription was on or later than the date of admission the patient was a user.

This version relies on the assumption that all patients need the same dose which is not the case for any of the drugs we assessed. Further, national prescription recommendations may vary from international guidelines. The defined daily dose by the World Health Organization and Danish prescription recommendations, however, were quite similar (**Supplemental Table 7**).[28,33]

Exposure definition version 3

A patient was a user if deemed so according to both version 1 and version 2. In version 3 patients had filled a prescription within 125 days prior to admission for statin and 60 days prior to admission for NSAID and glucocorticoid and the given prescription lasted till the day of admission. This, however, lead to exclusion of all patients with discordance between version 1 and version 2.

We cross-tabulated version 1 and version 2 to assess the agreement (**Supplemental Table 8**). More patients were users according to version 1 compared with version 2 across all drugs. We then created propensity score matched cohorts for each exposure version and estimated the risk

ratio of depression and anxiety comparing users with non-users (**Supplemental Table 9**). The estimates were strikingly similar across all three definitions.

Finally, we had to choose which anti-inflammatory drugs to include. This study was a proof-of-concept study so we included broad categories of anti-inflammatory drugs, e.g. NSAID, rather than single drugs, e.g. Ibuprofen. This approach renders an overall estimate, however, may be flawed if drugs within a category has opposite effects. For instance, Köhler et al found that Ibuprofen concomitant with selective serotonin reuptake inhibitors decreased the risk of psychiatric contacts whereas NSAID as a group increased the risk of psychiatric contacts in a nationwide cohort study.[15] The authors, however, indicate that the results may be confounded by indication as choice of type of NSAID is affected by patient characteristics.

Definition of outcome: Depression and anxiety

The primary outcome was a diagnosis of depression or anxiety or use of antidepressant or anxiolytic. Though depression and anxiety are highly comorbid we also did a sensitivity analysis of depression (diagnosis or use of antidepressant) and anxiety (diagnosis or use of anxiolytics) separately (**Supplemental Table 5** and **Supplemental Table 6**).[52]

We did not have information on the severity of depression or anxiety. Usually the more severe cases are referred to psychiatric in- or outpatient care and an admission could be a proxy for severity of illness. Unfortunately, we were restricted from analyzing diagnosis of depression separate from use of antidepressants and diagnosis of anxiety separate from use of anxiolytics by a low number of patients in each group.

Time-to-event and competing risk

Patients entered our study at time of admission to the ICU. Each patient was followed until diagnosis of depression or anxiety, use of antidepressants or anxiolytics, death, three years after admission or censoring if full follow-up time was unavailable, whichever came first (**Supplemental Figure 2**). We analyzed our data as time-to-event for each patient.[49]

We also accounted for competing risk in our analyses. Competing risk occurs when a patient is in risk of another event that would prevent the outcome of interest in happening: E.g. if a patient

died he/she was no longer at risk of depression or anxiety.[49] All analyzes applied included competing risk by death.[45] Approximately 25% of our study population died within the first 30 days after ICU admission which potentially introduces selection bias due to death by censoring (see the section *Selection bias*).

Cumulative incidence

We computed the cumulative incidence of a diagnosis of depression or anxiety or use of anti-depressant or anxiolytic. The cumulative incidence is the probability that an event has occurred by a given time.[49] The cumulative incidence function incorporates competing risk of death without removing it.[45] For instance 18.0% of statin users will have had a depression or anxiety after 3 years (**Table 3**). If more patients had died, fewer would have had a depression or anxiety disorder and the cumulative incidence would have been lower. The cumulative incidence is thus a real-world probability useful for the clinician and planning purposes.

Pseudovalue method

A common method for analyzing time-to-event data is Cox regression. This requires proportional hazards, which our data did not fulfill. Thus we applied the pseudovalue method.[46] This method allows for estimation of risk ratios and risk differences in right-censored time-to-event data, incorporates competing risk and does not require proportional hazards. Further, the pseudovalue methods allows comparison of cumulative incidence (risk ratio) of depression and anxiety at a given time rather comparison of the rate (hazard ratio) of depression and anxiety.

We calculated a pseudovalue for each patient in our study at 6 months, 1 year and 3 years. The pseudovalue for a given patient is the estimator, e.g. cumulative incidence function, of the entire sample minus the estimator of the sample without the given patient. This was repeated for each patient in the sample. The pseudovalue was then used in a generalized linear model as our incomplete observations had been replaced with complete pseudovalue observations and thus it represented non-censored time-to-event data.

Strengths and limitations

Selection bias

Selection bias occurs if patients included in the study differ systematically from patients not included in the study in determinates of the study outcome.[49] Our study cohort is assembled on nationwide register-based data covering all hospital contacts which minimizes the risk of selection bias. The positive predictive value of an ICU admission in the Danish National Patient Register was 95.9%.[27] In our cohort of ICU patients many died, which can lead to selection bias due to censoring by death. If depletion of patients susceptible to getting a depression or anxiety is differential depending on user status this may introduce a bias.

Information bias

Information bias occurs if patients are wrongly classified with respect to either exposure or outcome.[49] The misclassification can be non-differential or differential. If the misclassification is random (neither related to exposure or outcome) it is non-differential. If the misclassification is related to either exposure or outcome it is differential.

In our study it is very likely that some patients were misclassified as users because they filled a prescription, but did not actually take the drug (false positive). The magnitude of this has not been studied in our cohort, however, prior studies have estimated an adherence of 93% for statin users,[53] 84.1 % of short-term NSAID users[54] and 78% of long-term glucocorticoid users.[55] Adherence will differ according to method of assessment, cohort, indication and duration of treatment. It is also likely that some patients were misclassified as non-users though they bought an over-the-counter NSAID (false negative). In our study period the percentage of total NSAID sold on prescription ranged between 75–83%.[47] Thus 17–25% could be misclassified, however, patients with prescriptions might buy over-the-counter as well and thus still be correctly classified. We assume both instances of misclassification to be unrelated to the risk of depression and anxiety resulting in a non-differential misclassification of the exposure. This would dilute the association leading to a bias towards the null. We did not consider prior hospitalizations which may lead to misclassification. If a patient is hospitalized within the exposure window – 125 days for statins, 60 days for NSAIDs and glucocorticoids - he/she cannot collect a prescription. This leads to a shorter period of exposure decreasing the probability of being exposed. This is termed immeasurable time

bias.[48] Further, we do not have information on exposure during admission which may also affect the risk of depression and anxiety. The probability of being exposed during recent admission is probably higher among users compared with non-users leading to a differential misclassification. Both of these misclassifications, however, would bias the estimates away from the null, so given our lack of association this is theoretical issue.

We also risk misclassification of our outcome. Antidepressants and anxiolytics are prescribed for other indications than depression or anxiety, e.g. neuropathic pain or sleeping disorders.[51] Petty et al found that in general practice 83% of selective serotonin reuptake inhibitors were prescribed for depression and/or anxiety and 17% for other indications.[56] Also, the general practitioner may wrongly diagnose and treat a patient despite a specificity of 81.3% for depression in a meta-analysis of 19 general practitioner studies.[57] Yet, a study found that initiation of antidepressant therapy was rather conservative.[58] Thus, some patients may be categorized with depression or anxiety though not suffering from any of these (false positive). Opposite, some patients with a mild depression may not receive medication or see a psychiatrist. The odds ratio for prescription of an antidepressant was reported to be 17.04 (95% CI 7.97-36.43) if the depression was moderate to severe compared with minimal in 38 UK general practices.[59] Finally, the general practitioner may miss a patient who has a depression with a sensitivity of 50.1% in the meta-analysis of 19 general practitioner studies.[57] Thus, some patients may be categorized as healthy when having a depression or anxiety (false negative). We assume this to be unrelated to use of anti-inflammatory drugs resulting in a non-differential misclassification of the outcome resulting in bias towards the null.

Confounding

Confounding occurs when the effect of the factor investigated is confused with the effect of another factor associated with both the exposure and the outcome but not part of the causal chain (**Supplemental Figure 3**).[49] An example from our study could be gender: females have a higher risk of depression and anxiety than males, the proportion of females was higher among non-users compared with users of statin, but statin use does not cause a change in gender.[60] Thus it would seem that patients using statins were at lower risk of depression and anxiety, though it would actually be an effect of fewer females in this group. A major concern in

pharmacoepidemiology is confounding by indication.[61] Confounding by indication occurs when patients who are treated are inherently different from patients not treated. This arises because treatment is given for a reason, that is assignment of treatment depends on baseline characteristics of each patient: e.g. a person with no diseases should not be prescribed glucocorticoids whereas patient with rheumatoid arthritis and chronic obstructive pulmonary disease probably should be. Usually the two will differ on other baseline characteristics than just preadmission diseases, e.g. age and income. This corresponds well with the observed differences in our baseline covariates. The use of glucocorticoids may thus be associated with a higher risk of depression and anxiety, however, this is actually confounded by the increased risk of depression and anxiety by rheumatoid arthritis and chronic obstructive pulmonary disease, the indication for treatment.

Several approaches can be applied in deciding which factors are potential confounders.[49] We went through prior literature identifying all the variables known to be associated with either the use of anti-inflammatory drugs or risk of depression and anxiety. Another approach is to calculate the change in estimate: if the regression estimate changes by more than 10% by taking the variable, e.g. age, into account, the variable is considered a confounder. [49] In our case none of the potential confounders changed the estimate by more than 10%. Finally, one can show that the variable is associated with both the exposure and the outcome.[49] We chose confounders based on prior literature and clinical sense.

Confounding can be handled in the design phase by randomization, restriction and matching or in the analysis phase by matching, stratification and adjustment.[49] We chose propensity score matching. We could not randomize patients to an anti-inflammatory treatment so unmeasured confounding may exist, despite our use of thoroughly constructed propensity scores.

Implications

This nationwide register-based study underlined the importance of considering mental health after intensive care. Our findings did not support a beneficial effect of preadmission anti-inflammatory drug use.

The cohort, ICU patients, is a heterogeneous group. We did subgroup analyses, however, our findings were robust across subgroups (**Figure 2**). Yet, from a mechanistic point of view it would be interesting to repeat the analysis according to inflammation level: In the ideal world both preadmission and during admission inflammation level. Maybe, there is an effect in patients who were actually inflamed, but not in those who were not. Unfortunately, we did not have information on inflammation, changes in inflammation levels or use of anti-inflammatory drugs during admission. During admission inflammation level might be available for a subset of patients through the Clinical Laboratory Information System (LABKA) research database.[62]

Depression and anxiety are both complex multifactorial diseases.[63] We did not have information on the severity of the depression or anxiety. In a clinical trial it would be feasible to measure the severity. It could be of interest as anti-inflammatory drug use might just alter the severity, not prevent the illness entirely. Anti-inflammatory drugs are, however, not without side-effects and the benefits need to be weighed against the harms: a possible alleviation of severity needs to be clinically meaningful to outweigh the side effects.

Our results do not support that anti-inflammatory drugs reduce the risk of depression and anxiety in an intensive care cohort. We cannot rule out effects in subgroups not assessed here, e.g. by type of cancer. It could be interesting to re-examine the association with a mechanistic focus, such as changes in level of inflammation or severity of the underlying disease.

TABLES

Table 1. Preadmission patient characteristics by anti-inflammatory drug use in the overall cohort.

	No use N=28,053	Statin use N=13,636		NSAID use N=2,887		Glucocorticoid use N=1,454		Combination use N=2,177	
	N (%)	N (%)	Standard. Diff., %	N (%)	Standard. Diff., %	N (%)	Standard. Diff., %	N (%)	Standard. Diff., %
Sex									
Female	9,439 (33.6)	3,587 (26.3)	16.1	1,095 (37.9)	-8.9	673 (46.3)	-26.0	753 (34.6)	-2.0
Male	18,614 (66.4)	10,049 (73.7)		1,792 (62.1)		781 (53.7)		1,424 (65.4)	
Age, years									
18-39	3,414 (12.2)	66 (0.5)	-49.4	240 (8.3)	-12.7	62 (4.3)	-29.1	18 (0.8)	-47.3
40-64	11,096 (39.6)	4,167 (30.6)	-18.9	1,207 (41.8)	4.6	430 (29.6)	-21.1	604 (27.7)	-25.2
65-79	9,990 (35.6)	7,699 (56.5)	42.8	1,068 (37.0)	2.9	700 (48.1)	25.6	1,246 (57.2)	44.4
80+	3,553 (12.7)	1,704 (12.5)	-0.5	372 (12.9)	0.7	262 (18.0)	14.9	309 (14.2)	4.5
Educational level									
Primary School	11,468 (40.9)	5,657 (41.5)	1.2	1,288 (44.6)	7.6	704 (48.4)	15.2	999 (45.9)	10.1
High School	10,472 (37.3)	5,431 (39.8)	5.1	1,064 (36.9)	-1.0	495 (34.0)	-6.9	824 (37.9)	1.1
Higher Education	4,485 (16.0)	2,139 (15.7)	-0.8	378 (13.1)	-8.2	192 (13.2)	-7.9	279 (12.8)	-9.0
Unknown	1,628 (5.8)	409 (3.0)	-13.7	157 (5.4)	-1.6	63 (4.3)	-6.7	75 (3.4)	-11.2
Gross income, DKK									
< 100,000	3,243 (11.6)	1,305 (9.6)	-6.5	<325 (<11.3)	-1.4	<180 (<12.4)	1.9	<250 (<11.5)	-0.5
100,000-199,999	12,818 (45.7)	6,758 (49.6)	7.8	1,455 (50.4)	9.4	827 (56.9)	22.5	1,219 (56.0)	20.7
200,000-299,999	5,457 (19.5)	2,665 (19.5)	0.2	572 (19.8)	0.9	269 (18.5)	-2.4	368 (16.9)	-6.6
>300,000	6,296 (22.4)	2,893 (21.2)	-3.0	535 (18.5)	-9.7	180 (12.4)	-26.8	340 (15.6)	-17.5
Unknown	239 (0.9)	15 (0.1)	-10.7	<5 (<0.2)	-10.2	<5 (<0.3)	-11.6	<5 (<0.2)	-11.1
Employment status									
Employed or self-employed	9,790 (34.9)	3,568 (26.2)	-19.0	932 (32.3)	-5.5	286 (19.7)	-34.7	453 (20.8)	-31.8
Retired early	1,431 (5.1)	258 (1.9)	-17.5	<150 (<5.2)	-0.4	<50 (<3.4)	-10.1	<40 (<1.8)	-18.8
Unemployed, receiving benefits or student	4,956 (17.7)	1,798 (13.2)	-12.4	556 (19.3)	4.1	244 (16.8)	-2.3	325 (14.9)	-7.4

Pensioner	11,634 (41.5)	7,997 (58.6)	34.9	1,250 (43.3)	3.7	877 (60.3)	38.4	1,360 (62.5)	43.0
Unknown	242 (0.9)	15 (0.1)	-10.8	<5 (<0.2)	-10.3	<5 (<0.3)	-10.3	<5 (<0.2)	-11.2
Preadmission diseases									
Myocardial infarction	2,845 (10.1)	3,402 (24.9)	39.7	259 (9.0)	-4.0	111 (7.6)	-8.8	448 (20.6)	29.3
Congestive heart failure	1,463 (5.2)	1,487 (10.9)	21.0	128 (4.4)	-3.6	101 (6.9)	7.2	183 (8.4)	12.7
Hypertension	1,345 (4.8)	1,280 (9.4)	18.0	132 (4.6)	-1.1	85 (5.8)	4.7	204 (9.4)	17.9
Atrial fibrillation/atrial flutter	1,974 (7.0)	1,332 (9.8)	9.9	177 (6.1)	-3.7	150 (10.3)	11.7	197 (9.0)	7.4
Chronic pulmonary disease	7,101 (25.3)	3,551 (26.0)	1.7	803 (27.8)	5.7	949 (65.3)	87.6	948 (43.5)	39.1
Cancer	4,169 (14.9)	1,479 (10.8)	-12.0	495 (17.1)	6.2	262 (18.0)	8.5	308 (14.1)	-2.0
Diabetes	2,485 (8.9)	3,613 (26.5)	47.5	285 (9.9)	3.5	148 (10.2)	4.5	601 (27.6)	50.0
Connective tissue disease	672 (2.4)	296 (2.2)	-1.5	128 (4.4)	11.2	246 (16.9)	50.7	272 (12.5)	39.2
Gastrointestinal and liver disease	2,368 (8.4)	646 (4.7)	-15.0	423 (14.7)	19.5	142 (9.8)	4.6	216 (9.9)	5.1
Renal disease	738 (2.6)	497 (3.6)	5.8	46 (1.6)	-7.2	81 (5.6)	14.9	92 (4.2)	8.8
Dementia	170 (0.6)	79 (0.6)	-0.3	18 (0.6)	0.2	7 (0.5)	-1.7	15 (0.7)	1.0
Osteoporosis	628 (2.2)	273 (2.0)	-1.6	84 (2.9)	4.2	136 (9.4)	30.8	131 (6.0)	19.1
Alcoholism	1,989 (7.1)	356 (2.6)	-21.0	253 (8.8)	6.2	57 (3.9)	-13.9	59 (2.7)	-20.4
Preadmission drug use									
Cardiovascular drugs	11,239 (40.1)	11,870 (87.0)	111.9	1,295 (44.9)	9.7	843 (58.0)	36.4	1,798 (82.6)	97.1
Inhaled respiratory drugs	2,557 (9.1)	1,172 (8.6)	-1.8	343 (11.9)	9.0	700 (48.1)	95.7	515 (23.7)	40.1
Immunosuppressants	178 (0.6)	86 (0.6)	0.0	41 (1.4)	7.8	96 (6.6)	32.4	81 (3.7)	21.3
Opioids	2,635 (9.4)	1,273 (9.3)	-0.2	856 (29.7)	52.9	320 (22.0)	35.2	624 (28.7)	50.6
Prior cumulative use of statins									
No prior use	24,668 (87.9)	2,957 (21.7)	-178.4	2,552 (88.4)	1.4	1,253 (86.2)	-5.2	537 (24.7)	-165.6
0-25% quartile	1,406 (5.0)	2,120 (15.5)	35.2	142 (4.9)	-0.4	84 (5.8)	3.4	271 (12.4)	26.6
25%-50% quartile	888 (3.2)	2,657 (19.5)	53.3	91 (3.2)	-0.1	46 (3.2)	0.0	413 (19.0)	52.0
50%-75% quartile	625 (2.2)	2,885 (21.2)	61.6	60 (2.1)	-1.0	49 (3.4)	6.9	443 (20.3)	59.8
75%-100% quartile	466 (1.7)	3,017 (22.1)	66.6	42 (1.5)	-1.7	22 (1.5)	-1.2	513 (23.6)	69.9
Prior cumulative use of NSAIDs									
No prior use	11,339 (40.4)	4,517 (33.1)	-15.2	415 (14.4)	-61.1	461 (31.7)	-18.2	281 (12.9)	-65.5
0-25% quartile	4,290 (15.3)	1,991 (14.6)	-1.9	248 (8.6)	-20.8	200 (13.8)	-4.4	169 (7.8)	-23.7
25%-50% quartile	4,992 (17.8)	2,559 (18.8)	2.5	404 (14.0)	-10.4	248 (17.1)	-1.9	259 (11.9)	-16.6

50%-75% quartile	4,314 (15.4)	2,476 (18.2)	7.4	540 (18.7)	8.9	285 (19.6)	11.1	420 (19.3)	10.4
75%-100% quartile	3,118 (11.1)	2,093 (15.3)	12.5	1,280 (44.3)	79.9	260 (17.9)	19.3	1,048 (48.1)	88.7
Prior cumulative use of glucocorticoids									
No prior use	22,662 (80.8)	10,668 (78.2)	-6.3	2,139 (74.1)	-16.1	320 (22.0)	-145.4	1,085 (49.8)	-68.7
0-25% quartile	1,321 (4.7)	906 (6.6)	8.4	198 (6.9)	9.2	38 (2.6)	-11.2	136 (6.2)	6.8
25%-50% quartile	1,519 (5.4)	803 (5.9)	2.1	203 (7.0)	6.7	114 (7.8)	9.8	163 (7.5)	8.4
50%-75% quartile	1,505 (5.4)	776 (5.7)	1.4	214 (7.4)	8.4	292 (20.1)	45.3	285 (13.1)	26.9
75%-100% quartile	1,046 (3.7)	483 (3.5)	-1.0	133 (4.6)	4.4	690 (47.5)	115.7	508 (23.3)	59.8

Abbreviations: NSAID, Non-Steroidal Anti-inflammatory drug; DKK, Danish kroner.

Table 2. Preadmission patient characteristics by anti-inflammatory drug use in the propensity score matched cohorts.

	Statin			NSAID			Glucocorticoid			Combination		
	No use N=6,088	Use N=6,088		No use N=2,886	Use N=2,886		No use N=1,440	Use N=1,440		No use N=1,743	Use N=1,743	
	N (%)	N (%)	Stand. Diff., %	N (%)	N (%)	Stand. Diff., %	N (%)	N (%)	Stand. Diff., %	N (%)	N (%)	Stand. Diff., %
Sex												
Female	1,506 (24.7)	1,692 (27.8)	-6.9	1,104 (38.3)	1,095 (37.9)	0.6	681 (47.3)	663 (46.0)	2.4	579 (33.2)	589 (33.8)	-1.2
Male	4,582 (75.3)	4,396 (72.2)		1,782 (61.7)	1,791 (62.1)		759 (52.7)	777 (54.0)		1,164 (66.8)	1,154 (66.2)	
Age, years												
18-39	105 (1.7)	47 (0.8)	-8.6	269 (9.3)	240 (8.3)	-3.5	66 (4.6)	62 (4.3)	-1.3	25 (1.4)	18 (1.0)	-3.6
40-64	2,022 (33.2)	2,087 (34.3)	2.3	1,205 (41.8)	1,207 (41.8)	0.1	415 (28.8)	428 (29.7)	1.9	520 (29.8)	500 (28.7)	-2.5
65-79	3,056 (50.2)	3,316 (54.5)	8.6	1,013 (35.1)	1,067 (37.0)	3.9	699 (48.5)	691 (48.0)	-1	916 (52.6)	976 (56.0)	6.9
80+	905 (14.9)	638 (10.5)	-13.2	399 (13.8)	372 (12.9)	-2.7	260 (18.1)	259 (18.0)	-0.1	282 (16.2)	249 (14.3)	-5.3
Educational level												
Primary School	2,496 (41.0)	2,443 (40.1)	-1.8	1,316 (45.6)	1,287 (44.6)	-2	735 (51.0)	696 (48.3)	-5.3	794 (45.6)	798 (45.8)	0.5
High School	2,416 (39.7)	2,378 (39.1)	-1.3	1,085 (37.6)	1,064 (36.9)	-1.5	450 (31.3)	493 (34.2)	6.4	651 (37.3)	658 (37.8)	0.8
Higher Education	981 (16.1)	1,042 (17.1)	2.7	357 (12.4)	378 (13.1)	2.2	194 (13.5)	189 (13.1)	-1	235 (13.5)	225 (12.9)	-1.7
Unknown	195 (3.2)	225 (3.7)	2.7	128 (4.4)	157 (5.4)	4.6	61 (4.2)	62 (4.3)	0	63 (3.6)	62 (3.6)	-0.3
Gross income, DKK												
< 100,000	577 (9.5)	675 (11.1)	5.3	<345 (<12.0)	<325 (<11.2)	-2.5	207 (14.4)	<175 (<12.2)	-6.7	<205 (<11.8)	<210 (<12.0)	0.7
100,000-199,999	2,926 (48.1)	2,833 (46.5)	-3.1	1,454 (50.4)	1,455 (50.4)	0.1	807 (56.0)	822 (57.1)	2.2	938 (53.8)	944 (54.2)	0.7
200,000-299,999	1,197 (19.7)	1,244 (20.4)	1.9	540 (18.7)	571 (19.8)	2.7	227 (15.8)	266 (18.5)	7.2	298 (17.1)	300 (17.2)	0.3
>300,000	1,383 (22.7)	1,323 (21.7)	-2.4	545 (18.9)	535 (18.5)	-0.9	199 (13.8)	177 (12.3)	-4.5	304 (17.4)	292 (16.8)	-1.8
Unknown	5 (0.1)	13 (0.2)	3.4	<5 (<0.2)	<5 (<0.2)	1	0 (0.0)	<5 (<0.3)	0	<5 (<0.3)	<5 (<0.3)	0
Employment status												
Employed or self-employed	1,736 (28.5)	1,783 (29.3)	1.7	903 (31.3)	931 (32.3)	2.1	300 (20.8)	285 (19.8)	-2.6	395 (22.7)	391 (22.4)	-0.5
Retired early	131 (2.2)	132 (2.2)	0.1	<180 (<6.2)	<150 (<5.2)	-4.8	<35 (<2.4)	<50 (<3.5)	4.7	<40 (<2.3)	<35 (<2.0)	-1.7
Unemployed, receiving benefits or student	818 (13.4)	876 (14.4)	2.8	569 (19.7)	556 (19.3)	-1.1	261 (18.1)	243 (16.9)	-3.3	265 (15.2)	258 (14.8)	-1.1
Pensioner	3,398 (55.8)	3,284 (53.9)	-3.8	1,234 (42.8)	1,250 (43.3)	1.1	844 (58.6)	865 (60.1)	3.1	1,046 (60.0)	1,061 (60.9)	1.8
Unknown	5 (0.1)	13 (0.2)	3.4	<5 (<0.2)	<5 (<0.2)	1	<5 (<0.3)	<5 (<0.3)	0	<5 (<0.3)	<5 (<0.3)	0

Preadmission diseases												
Myocardial infarction	1,361 (22.4)	1,288 (21.2)	-2.9	265 (9.2)	259 (9.0)	-0.7	105 (7.3)	110 (7.6)	1.3	327 (18.8)	330 (18.9)	0.4
Congestive heart failure	539 (8.9)	636 (10.4)	5.4	112 (3.9)	128 (4.4)	2.8	101 (7.0)	99 (6.9)	-0.5	153 (8.8)	137 (7.9)	-3.3
Hypertension	543 (8.9)	533 (8.8)	-0.6	119 (4.1)	132 (4.6)	2.2	79 (5.5)	83 (5.8)	1.2	176 (10.1)	164 (9.4)	-2.3
Atrial fibrillation/atrial flutter	506 (8.3)	572 (9.4)	3.8	148 (5.1)	177 (6.1)	4.4	145 (10.1)	145 (10.1)	0	161 (9.2)	161 (9.2)	0
Chronic pulmonary disease	1,506 (24.7)	1,624 (26.7)	4.4	785 (27.2)	803 (27.8)	1.4	974 (67.6)	935 (64.9)	-5.6	737 (42.3)	709 (40.7)	-3.3
Cancer	675 (11.1)	729 (12.0)	2.8	502 (17.4)	495 (17.2)	-0.6	277 (19.2)	258 (17.9)	-3.4	263 (15.1)	260 (14.9)	-0.5
Diabetes	1,173 (19.3)	1,157 (19.0)	-0.7	274 (9.5)	285 (9.9)	1.3	147 (10.2)	144 (10.0)	-0.7	453 (26.0)	431 (24.7)	-2.9
Connective tissue disease	133 (2.2)	146 (2.4)	1.4	106 (3.7)	127 (4.4)	3.7	236 (16.4)	234 (16.3)	-0.5	184 (10.6)	179 (10.3)	-0.9
Gastrointestinal and liver disease	318 (5.2)	362 (5.9)	3.1	387 (13.4)	422 (14.6)	3.5	134 (9.3)	140 (9.7)	1.4	150 (8.6)	167 (9.6)	3.4
Renal disease	204 (3.4)	245 (4.0)	3.6	36 (1.2)	46 (1.6)	2.9	92 (6.4)	80 (5.6)	-3.8	71 (4.1)	70 (4.0)	-0.3
Dementia	35 (0.6)	38 (0.6)	0.6	18 (0.6)	18 (0.6)	0	5 (0.3)	7 (0.5)	2.2	6 (0.3)	9 (0.5)	2.6
Osteoporosis	122 (2.0)	122 (2.0)	0	79 (2.7)	84 (2.9)	1	117 (8.1)	133 (9.2)	4	92 (5.3)	97 (5.6)	1.3
Alcoholism	172 (2.8)	205 (3.4)	3.1	254 (8.8)	253 (8.8)	-0.1	48 (3.3)	57 (4.0)	3.3	48 (2.8)	50 (2.9)	0.7
Preadmission drug use												
Cardiovascular drugs	5,150 (84.6)	4,806 (78.9)	-14.7	1,242 (43.0)	1,294 (44.8)	3.6	827 (57.4)	831 (57.7)	0.5	1,410 (80.9)	1,376 (78.9)	-4.9
Inhaled respiratory drugs	492 (8.1)	558 (9.2)	3.9	341 (11.8)	343 (11.9)	0.2	729 (50.6)	686 (47.6)	-5.9	369 (21.2)	361 (20.7)	-1.1
Immunosuppresants	38 (0.6)	36 (0.6)	-0.4	34 (1.2)	41 (1.4)	2.1	93 (6.5)	89 (6.2)	-1.4	55 (3.2)	52 (3.0)	-1
Opioids	514 (8.4)	573 (9.4)	3.4	839 (29.1)	855 (29.6)	1.2	294 (20.4)	310 (21.5)	2.8	477 (27.4)	443 (25.4)	-4.4
Prior cumulative use of statins												
No prior use	3,365 (55.3)	2,849 (46.8)	-17	2,549 (88.3)	2,551 (88.4)	0.2	1,258 (87.4)	1,242 (86.3)	-3.3	697 (40.0)	534 (30.6)	-19.7
0-25% quartile	883 (14.5)	1,214 (19.9)	14.4	146 (5.1)	142 (4.9)	-0.6	74 (5.1)	82 (5.7)	2.5	172 (9.9)	269 (15.4)	16.8
25%-50% quartile	759 (12.5)	1,028 (16.9)	12.5	93 (3.2)	91 (3.2)	-0.4	53 (3.7)	46 (3.2)	-2.7	231 (13.3)	374 (21.5)	21.8
50%-75% quartile	616 (10.1)	685 (11.3)	3.7	54 (1.9)	60 (2.1)	1.5	30 (2.1)	48 (3.3)	7.7	295 (16.9)	322 (18.5)	4.1
75%-100% quartile	465 (7.6)	312 (5.1)	-10.3	44 (1.5)	42 (1.5)	-0.6	25 (1.7)	22 (1.5)	-1.6	348 (20.0)	244 (14.0)	-15.9
Prior cumulative use of NSAIDS												
No prior use	2,064 (33.9)	2,056 (33.8)	-0.3	367 (12.7)	415 (14.4)	4.9	472 (32.8)	459 (31.9)	-2	207 (11.9)	269 (15.4)	10.4
0-25% quartile	888 (14.6)	934 (15.3)	2.1	236 (8.2)	248 (8.6)	1.5	206 (14.3)	198 (13.8)	-1.6	147 (8.4)	149 (8.5)	0.4
25%-50% quartile	1,118 (18.4)	1,134 (18.6)	0.7	431 (14.9)	404 (14.0)	-2.7	228 (15.8)	246 (17.1)	3.4	269 (15.4)	218 (12.5)	-8.4

50%-75% quartile	1,088 (17.9)	1,051 (17.3)	-1.6	694 (24.0)	540 (18.7)	-13	276 (19.2)	283 (19.7)	1.3	458 (26.3)	325 (18.6)	-18.4
75%-100% quartile	930 (15.3)	913 (15.0)	-0.8	1,158 (40.1)	1,279 (44.3)	8.5	258 (17.9)	254 (17.6)	-0.7	662 (38.0)	782 (44.9)	14
Prior cumulative use of glucocorticoids												
No prior use	4,847 (79.6)	4,674 (76.8)	-6.9	2,188 (75.8)	2,138 (74.1)	-4	287 (19.9)	320 (22.2)	5.5	908 (52.1)	969 (55.6)	7
0-25% quartile	315 (5.2)	448 (7.4)	9	169 (5.9)	198 (6.9)	4.1	44 (3.1)	38 (2.6)	-2.5	120 (6.9)	119 (6.8)	-0.2
25%-50% quartile	349 (5.7)	365 (6.0)	1.1	183 (6.3)	203 (7.0)	2.8	166 (11.5)	114 (7.9)	-12.2	183 (10.5)	119 (6.8)	-13.1
50%-75% quartile	349 (5.7)	363 (6.0)	1	203 (7.0)	214 (7.4)	1.5	383 (26.6)	292 (20.3)	-14.9	252 (14.5)	198 (11.4)	-9.2
75%-100% quartile	228 (3.7)	238 (3.9)	0.9	143 (5.0)	133 (4.6)	-1.6	560 (38.9)	676 (46.9)	16.4	280 (16.1)	338 (19.4)	8.7

Abbreviations: NSAID, Non-Steroidal Anti-inflammatory drug; DKK, Danish kroner.

Table 3. Cumulative incidence and risk ratio of depression and anxiety following intensive care unit admission by anti-inflammatory drug use in the propensity score matched cohorts.

		6 months		1 year		3 years	
		Cumulative incidence (95% CI)	Risk ratio (95% CI)	Cumulative incidence (95% CI)	Risk ratio (95% CI)	Cumulative incidence (95% CI)	Risk ratio (95% CI)
Statins	User	9.1 (8.3-9.8)	0.94 (0.84-1.05)	11.9 (11.1-12.7)	0.94 (0.85-1.04)	18.0 (17.0-19.0)	1.04 (0.96-1.13)
	Non-user	9.7 (8.9-10.4)	1 (ref)	12.6 (11.8-13.5)	1 (ref)	17.2 (16.2-18.2)	1 (ref)
NSAIDs	User	11.5 (10.4-12.7)	0.98 (0.85-1.14)	15.3 (14.0-16.6)	0.99 (0.87-1.12)	21.3 (19.8-22.9)	1.00 (0.90-1.11)
	Non-user	11.7 (10.5-12.9)	1 (ref)	15.4 (14.1-16.8)	1 (ref)	21.3 (19.8-22.9)	1 (ref)
Glucocorticoids	User	9.4 (7.9-11.0)	1.00 (0.79-1.26)	12.2 (10.5-13.9)	0.96 (0.79-1.17)	17.4 (15.4-19.5)	0.97 (0.82-1.14)
	Non-user	9.4 (7.9-11.0)	1 (ref)	12.7 (11.0-14.5)	1 (ref)	18.0 (16.0-20.2)	1 (ref)
Combination	User	10.6 (9.2-12.2)	1.07 (0.88-1.31)	13.5 (11.7-15.0)	1.01 (0.85-1.21)	19.0 (16.3-20.2)	1.05 (0.90-1.21)
	Non-user	9.9 (8.6-11.4)	1 (ref)	13.3 (11.9-15.1)	1 (ref)	18.2 (17.1-21.0)	1 (ref)

Abbreviations: NSAID, Non-Steroidal Anti-inflammatory drug.

Supplemental Table 1. Codes used to define the study population.

Procedure	**Health Care Classification System procedure codes**
Intensive care therapy or observation	NABB or NABE
Mechanical ventilation	BGDA0
Psychiatric diagnosis	***International Classification of Diseases, Tenth Revision* codes**
Schizophrenia	F20
Schizoaffective disorders	F25
Bipolar affective disorder (including manic and mixed episodes)	F30, F31, F38.0
Depression	F32, F33
Neurotic, stress-related and somatoform disorders	F40-F48
Psychopharmacological drugs	**Anatomical Therapeutic Chemical codes**
Antipsychotics	N05A
Anxiolytics	N05B
Antidepressants	N06A

Supplemental Table 2. Codes used to define the exposure.

Drug	Anatomical Therapeutic Chemical codes
Statins	C10AA
NSAIDs	
Non-selective NSAIDs	M01AA, M01AC, M01AE01- M01AE 03, M01AE11, M01AE14, M01AE17, M01AE52, M01AG
Older COX2-inhibitors	M01AB01, M01AB05, M01AB08, M01AB16, M01AB55,
Newer COX2-inhibitors	M01AX01
	M01AH
Glucocorticoids, systemic use	H02AB

Abbreviations: NSAID, Non-Steroidal Anti-inflammatory drug.

Supplemental Table 3. Codes used to define covariates.

Preadmission diseases	***International Classification of Diseases, Tenth Revision* codes / Anatomical Therapeutic Chemical codes**
Myocardial infarction	I21-I23
Congestive heart failure	I11.0, I13.0, I13.2, I50
Hypertension	I10, I15
Atrial fibrillation/atrial flutter	I48
Chronic pulmonary disease	J40 -J67, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2-J98.3 / R03
Cancer	C00-C43, C45-C96
Diabetes	E10-E14, O24 (*except* O24.4), G63.2, H36.0, N08.3 / A10A, A10B
Connective tissue disease	M05-M06, M08-M09, M30-M36, M45, D86
Gastrointestinal and liver disease	K22.1, K25-K28, B15.0, B16.0, B16.2, B18, B19.0, K70-K74, K76.0, K76.6, I85
Renal disease	I12-I13, N00-N05, N07, N11, N14, N18-N19, Q61
Dementia	F00-F03, F05.1, G30
Osteoporosis	M80-M82
Alcoholism	F10.1-F10.9, G31.2, G62.1, G72.1, I42.6, K29.2, K86.0, Z72.1 / N07BB
Preadmission drug use	**Anatomical Therapeutic Chemical codes**
Cardiovascular drugs	B01AA, C01AA, C01DA, C03, C07-C09, N02BA01
Inhaled respiratory medications	R03A
Immunosuppressants	L04
Opioids	N02A

Supplemental Table 4. Codes used to define the outcomes.

Psychiatric diagnosis	***International Classification of Diseases, Tenth Revision* codes**
Depression	F32, F33
Neurotic, stress-related and somatoform disorders	F40-F48
Psychopharmacological drugs	**Anatomical Therapeutic Chemical codes**
Anxiolytics	N05B
Antidepressants	N06A

Supplemental Table 5. Cumulative incidence and risk ratio of depression following intensive care unit admission by anti-inflammatory drug use in the propensity score matched cohorts.

		6 months		1 year		3 years	
		Cumulative incidence (95% CI)	Risk ratio (95% CI)	Cumulative incidence (95% CI)	Risk ratio (95% CI)	Cumulative incidence (95% CI)	Risk ratio (95% CI)
Statin	User	6.7 (6.0-7.3)	0.92 (0.81-1.05)	8.8 (8.1-9.6)	0.90 (0.81-1.01)	13.4 (12.5-14.3)	0.98 (0.89-1.08)
	Non-user	7.2 (6.6-7.9)	1 (ref)	9.8 (9.0-10.6)	1 (ref)	13.7 (12.8-14.6)	1 (ref)
NSAID	User	8.4 (7.4-9.5)	1.00 (0.84-1.19)	11.4 (10.3-12.6)	1.00 (0.86-1.15)	16.0 (14.6-17.4)	0.97 (0.86-1.10)
	Non-user	8.4 (7.4-9.5)	1 (ref)	11.4 (10.3-12.7)	1 (ref)	16.5 (15.1-18.0)	1 (ref)
Glucocorticoid	User	6.6 (5.4-7.9)	0.96 (0.73-1.27)	8.8 (7.4-10.4)	0.97 (0.76-1.22)	12.6 (10.9-14.5)	0.97 (0.79-1.18)
	Non-user	6.8 (5.6-8.2)	1 (ref)	9.1 (7.7-10.7)	1 (ref)	13.1 (11.3-15.0)	1 (ref)
Combination	User	8.0 (6.7-9.3)	1.06 (0.84-1.34)	10.1 (8.9-11.8)	0.98 (0.80-1.20)	14.2 (12.8-16.3)	0.98 (0.83-1.17)
	Non-user	7.5 (6.3-8.8)	1 (ref)	10.3 (8.7-11.5)	1 (ref)	14.5 (12.6-16.0)	1 (ref)

Abbreviations: NSAID, Non-Steroidal Anti-inflammatory drug.

Supplemental Table 6. Cumulative incidence and risk ratio of anxiety following intensive care unit admission by anti-inflammatory drug use in the propensity score matched cohorts.

		6 months		1 year		3 years	
		Cumulative incidence (95% CI)	Risk ratio (95% CI)	Cumulative incidence (95% CI)	Risk ratio (95% CI)	Cumulative incidence (95% CI)	Risk ratio (95% CI)
Statin	User	3.3 (2.9-3.8)	0.92 (0.76-1.12)	4.4 (3.9-5.0)	0.93 (0.79-1.10)	7.5 (6.9-8.3)	1.08 (0.95-1.24)
	Non-user	3.6 (3.1-4.1)	1 (ref)	4.8 (4.3-5.3)	1 (ref)	7.0 (6.3-7.7)	1 (ref)
NSAID	User	3.3 (2.9-3.8)	0.92 (0.76-1.12)	4.4 (3.9-5.0)	0.93 (0.79-1.10)	7.5 (6.9-8.3)	1.08 (0.95-1.24)
	Non-user	3.6 (3.1-4.1)	1 (ref)	4.8 (4.3-5.3)	1 (ref)	7.0 (6.3-7.7)	1 (ref)
Glucocorticoid	User	4.0 (3.1-5.1)	1.06 (0.74-1.54)	5.0 (3.9-6.2)	0.91 (0.66-1.25)	7.9 (6.5-9.5)	0.90 (0.70-1.17)
	Non-user	3.8 (2.9-4.8)	1 (ref)	5.5 (4.4-6.8)	1 (ref)	8.7 (7.3-10.4)	1 (ref)
Combination	User	4.0 (3.1-5.0)	1.11 (0.79-1.55)	5.3 (3.8-5.8)	1.12 (0.84-1.51)	8.3 (6.1-8.8)	1.13 (0.89-1.44)
	Non-user	3.6 (2.8-4.5)	1 (ref)	4.7 (4.3-6.5)	1 (ref)	7.4 (7.0-9.7)	1 (ref)

Abbreviations: NSAID, Non-Steroidal Anti-inflammatory drug.

Supplemental Table 7. Comparison of defined daily dose by the World Health Organization and Danish prescription recommendations.

Anatomical Therapeutic Chemical code (International nonproprietary names)	World Health Organization, mg/day[63]	Danish prescription recommendations, mg/day[50]
Statin		
C10AA01 (simvastatin)	30	20-40
C10AA02 (lovastatin)	45	20-80
C10AA03 (pravastatin)	30	20-40
C10AA04 (fluvastatin)	60	20-80
C10AA05 (atorvastatin)	20	10-40
C10AA06 (cerivastatin)	0.2	Unknown
C10AA07 (rosuvastatin)	10	10-20
Non-Steroidal Anti-inflammatory Drug		
M01AA01 (phenylbutazon)	300	100-200
M01AB01 (indometacin)	100	50-100
M01AB05 (diclofenac)	100	50-150
M01AB08 (etodolac)	400	400-600
M01AB16 (aceclofenac)	200	200[64]
M01AB55 (diclofenac comb)	100	150
M01AC01 (piroxicam)	20	10-20
M01AC02 (tenoxicam)	20	20
M01AC05 (lornoxicam)	12	8-16
M01AC06 (meloxicam)	15	7.5-15
M01AE01 (ibuprofen)	1,200	1,200-1,800
M01AE02 (naproxen)	500	500-1,000
M01AE03 (ketoprofen)	150	100-200
M01AE11 (tiaprofenic acid)	600	600
M01AE14 (dexibuprofen)	800	600-900
M01AE17 (dexketoprofen)	75	75
M01AG02 (tolfenamsyre)	300	200-400
M01AH01 (celecoxib)	200	200
M01AH02 (rofecoxib)	25	25-50[65]
M01AH05 (etoricoxib)	60	30-90
M01AX01 (nabumetone)	1,000	1,000
Glucocorticoid		
H02AB01 (bethametasone)	1.5	1.4-14
H02AB02 (dexametasone)	1.5	1-12
H02AB04 (methylprednisolone)	Parenteral: 20 Oral: 7.5	4-80
H02AB06 (prednisolone)	10	7.5-75
H02AB07 (prednisone)	10	7.5-75
H02AB08 (triamsinolone)	7.5	5-80
H02AB09 (hydrocortisone)	30	Oral: 10-30 Parenteral: 100-500

Supplemental Table 8. Cross-tabulation of users and non-users by exposure definition version 1 and exposure definition version 2 by anti-inflammatory drugs.

Statin	Version 2		
Version 1	Non-user	User	Total
Non-user	32,438	242	32,680
User	1,936	13,591	15,527
Total	34,374	13,833	48,207

Non-steroidal Anti-Inflammatory Drugs	Version 2		
Version 1	Non-user	User	Total
Non-user	43,537	182	43,719
User	1,580	2,908	4,488
Total	45,117	3,090	48,207

Glucocorticoid	Version 2		
Version 1	Non-user	User	Total
Non-user	45,498	301	45,799
User	595	1,813	2,408
Total	46,093	2,114	48,207

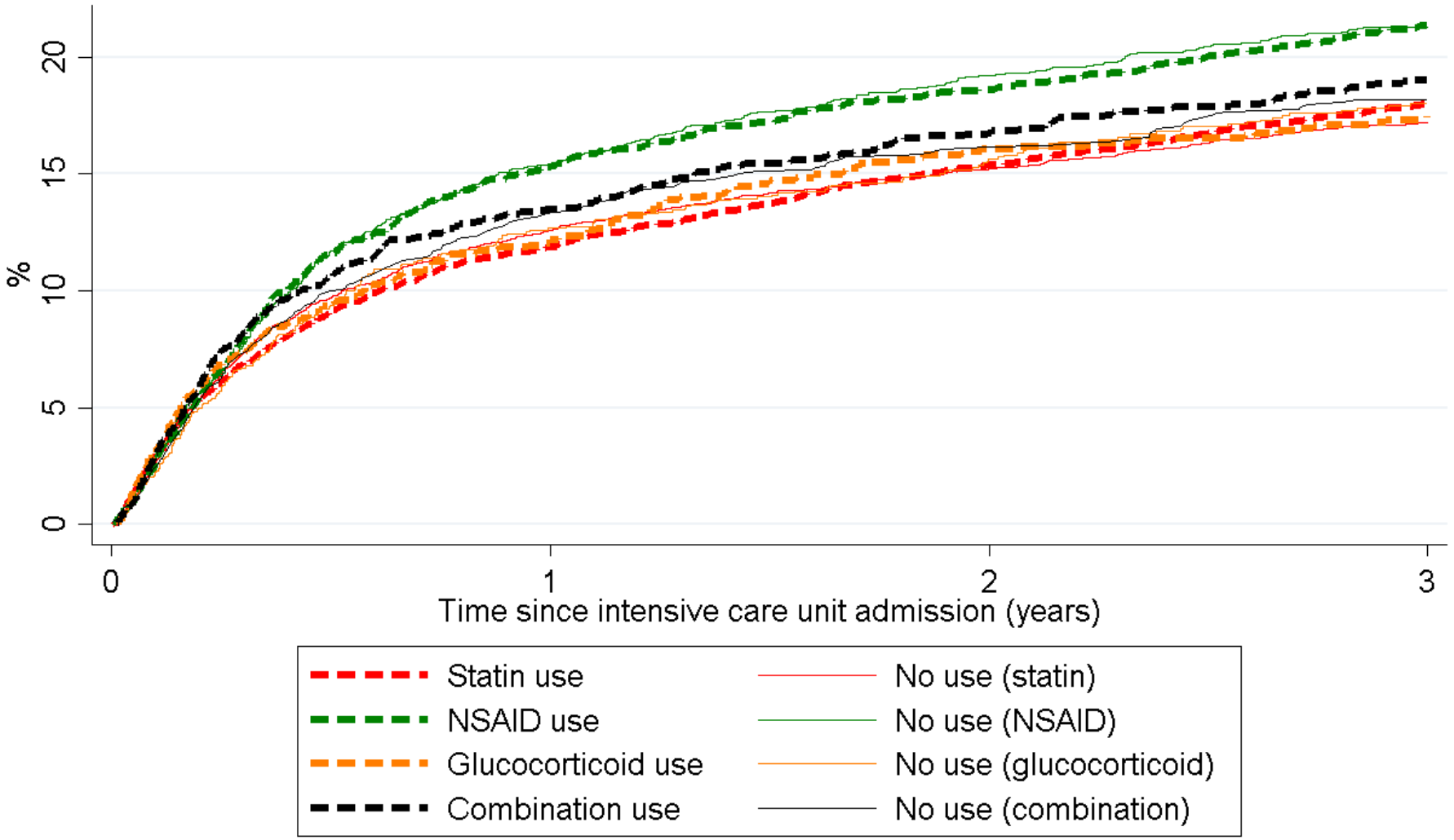
Combination	Version 2		
Version 1	Non-user	User	Total
Non-user	45,855	175	46,030
User	921	1,256	2,177
Total	46,776	1,431	48,207

Supplemental Table 9. The risk ratio of depression and anxiety following intensive care admission by anti-inflammatory drug use by three exposure versions.

	Cohort	6-months risk ratio (95% CI)	1-year risk ratio (95% CI)	3-year risk ratio (95% CI)
Statin	Version 1	0.94 (0.84-1.05)	0.94 (0.85-1.04)	1.04 (0.96-1.13)
	Version 2	0.96 (0.86-1.06)	0.96 (0.87-1.05)	1.02 (0.94-1.10)
	Version 3	0.92 (0.82-1.04)	0.92 (0.83-1.02)	1.03 (0.95-1.13)
Non-Steroidal	Version 1	0.98 (0.85-1.14)	0.99 (0.87-1.12)	1.00 (0.90-1.11)
Anti-inflammatory	Version 2	1.02 (0.86-1.21)	1.04 (0.90-1.21)	1.00 (0.88-1.13)
Drug	Version 3	1.01 (0.84-1.21)	1.01 (0.87-1.18)	1.01 (0.89-1.15)
Glucocorticoid	Version 1	1.00 (0.79-1.26)	0.96 (0.79-1.17)	0.97 (0.82-1.14)
	Version 2	1.03 (0.82-1.29)	0.96 (0.79-1.17)	0.98 (0.83-1.15)
	Version 3	1.07 (0.82-1.38)	1.00 (0.80-1.24)	0.97 (0.81-1.17)
Combination	Version 1	1.07 (0.88-1.31)	1.01 (0.85-1.21)	1.05 (0.90-1.21)
	Version 2	1.07 (0.83-1.37)	1.12 (0.91-1.39)	1.06 (0.88-1.26)
	Version 3	0.95 (0.72-1.25)	0.98 (0.77-1.24)	1.01 (0.83-1.24)

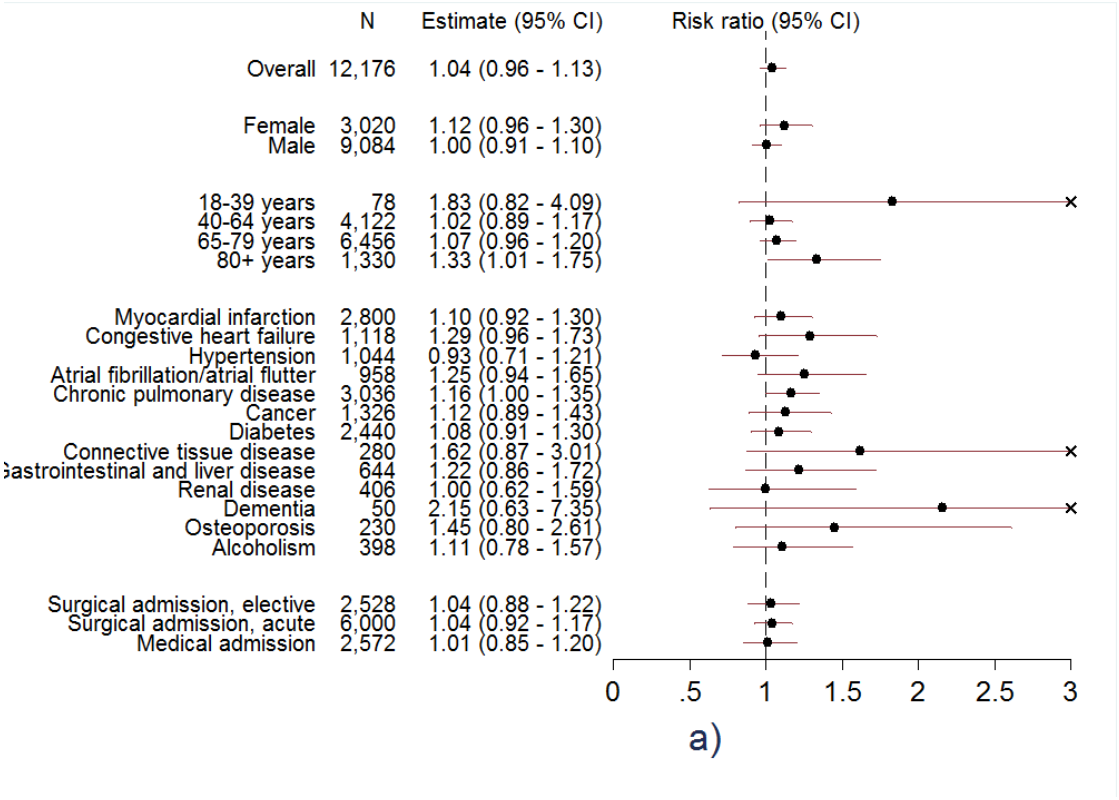
FIGURES

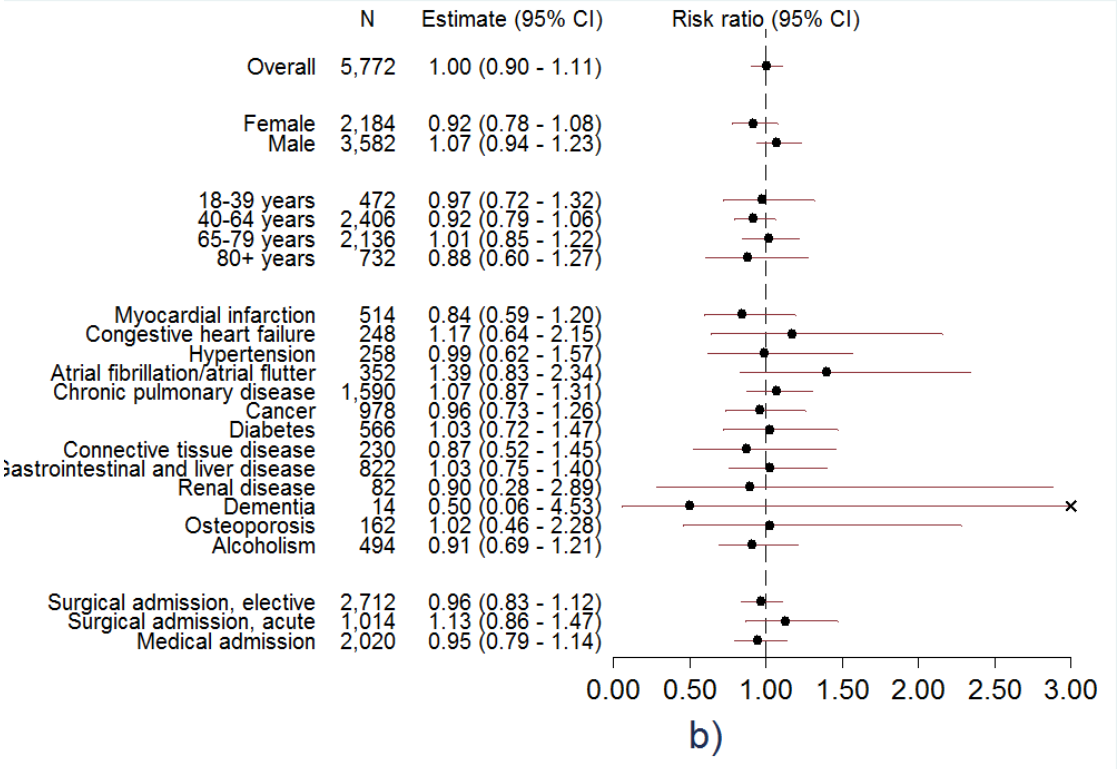
Figure 1. Cumulative incidence of anxiety and depression by use of anti-inflammatory drug in the propensity score matched cohorts.

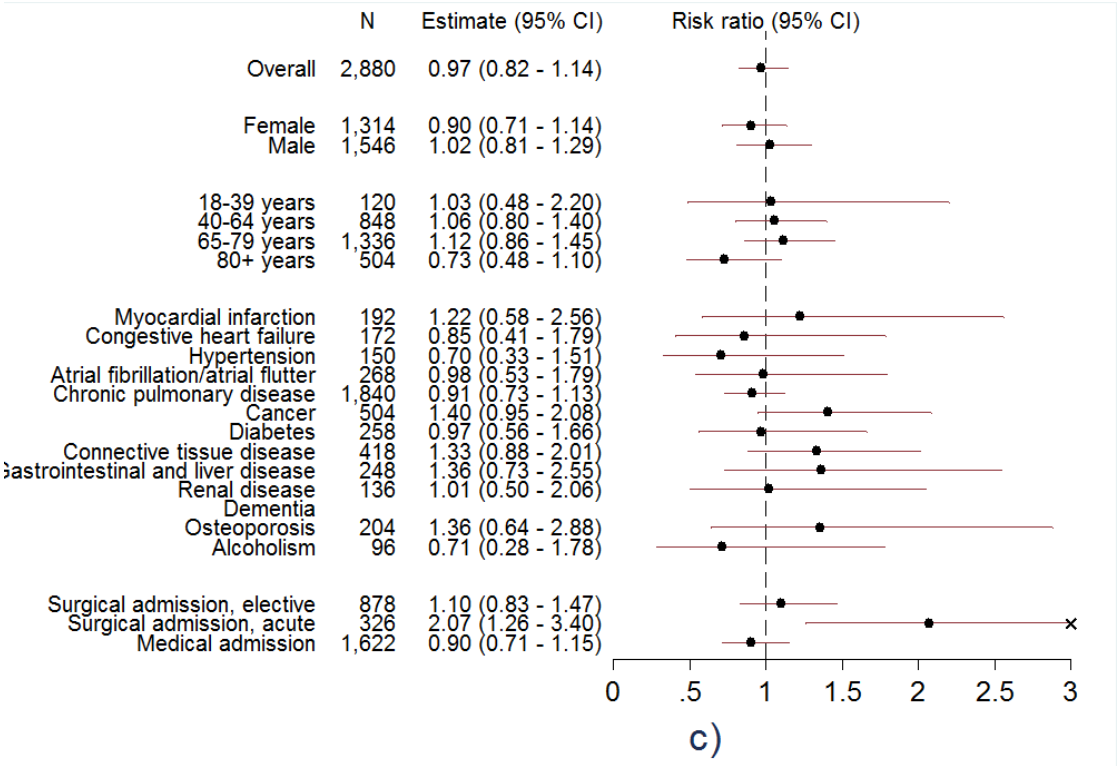


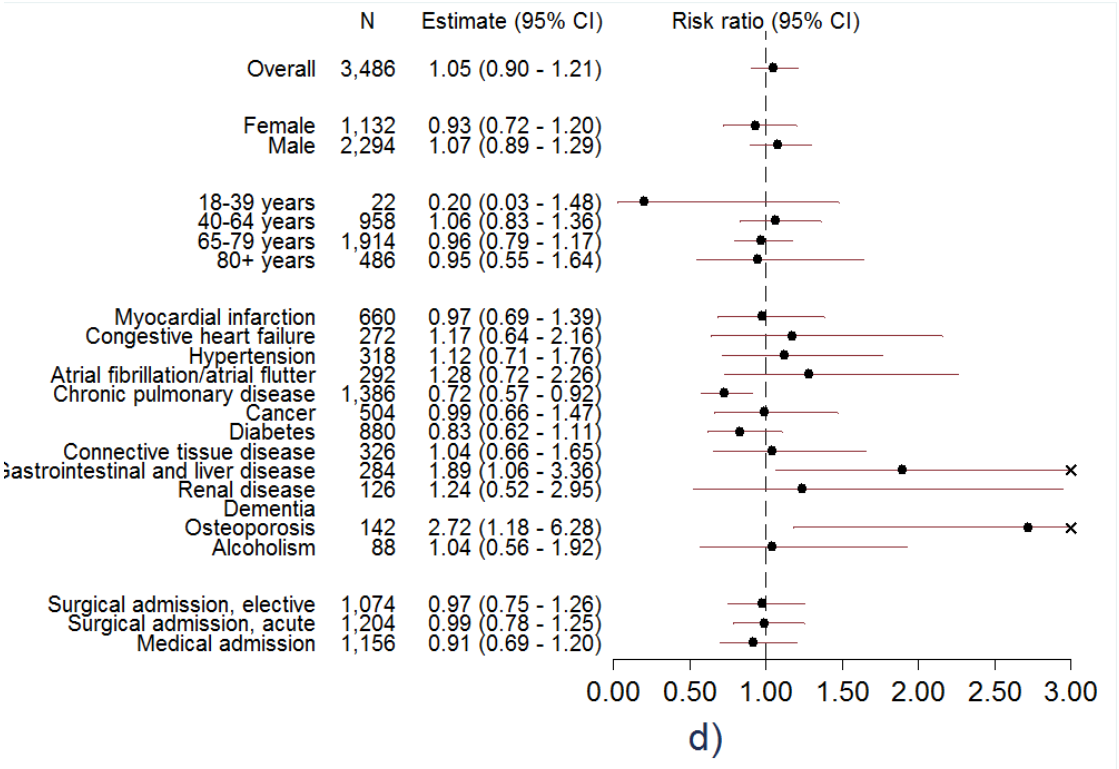
Abbreviations: NSAID, Non-Steroidal Anti-inflammatory drug.

Figure 2. Risk ratio of anxiety and depression within three years after intensive care unit admission by use of anti-inflammatory drugs in the propensity score matched cohorts. Stratified according to subgroups. a) Statin cohort, b) NSAID cohort, c) glucocorticoid cohort and d) combination cohort.



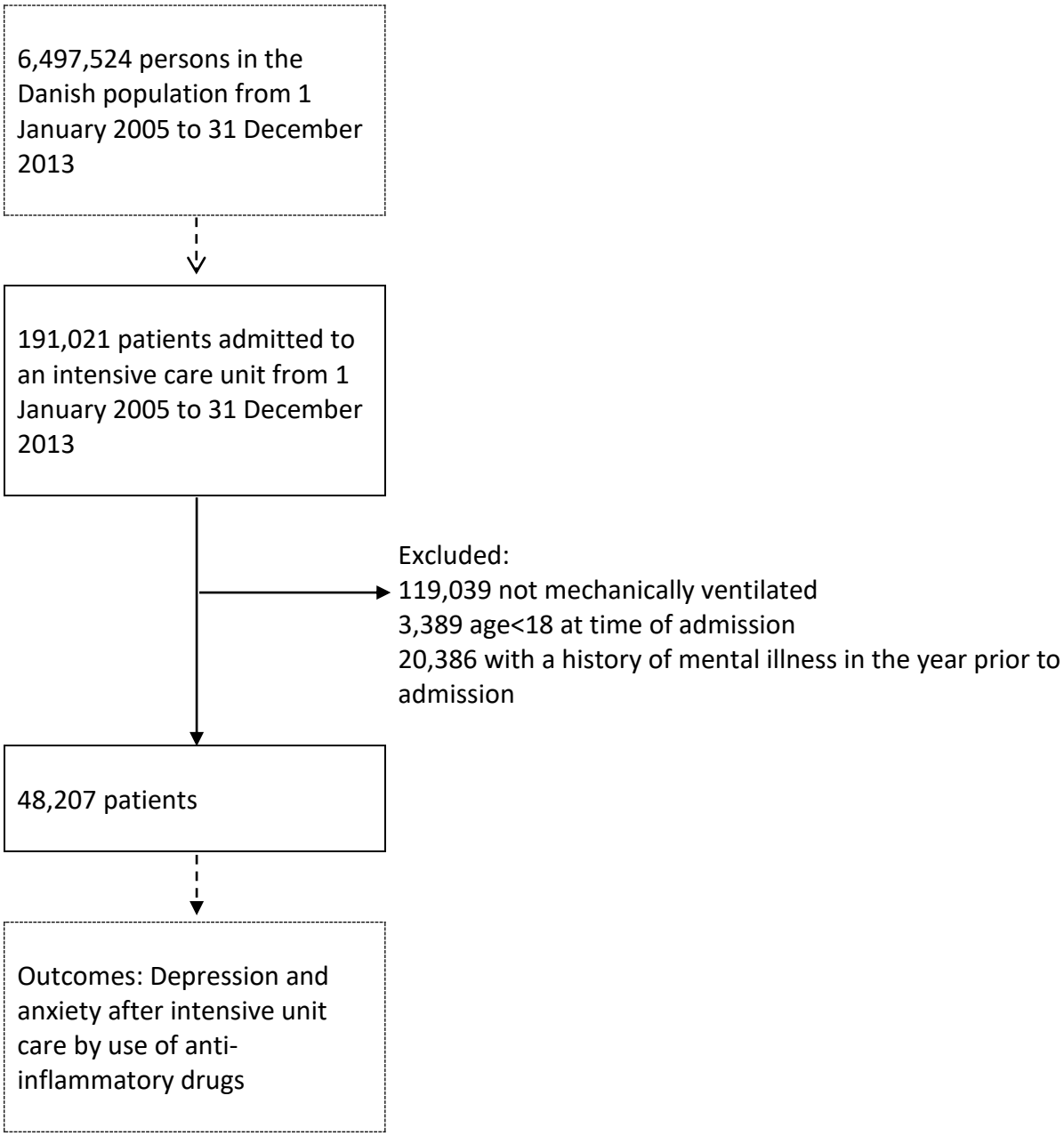




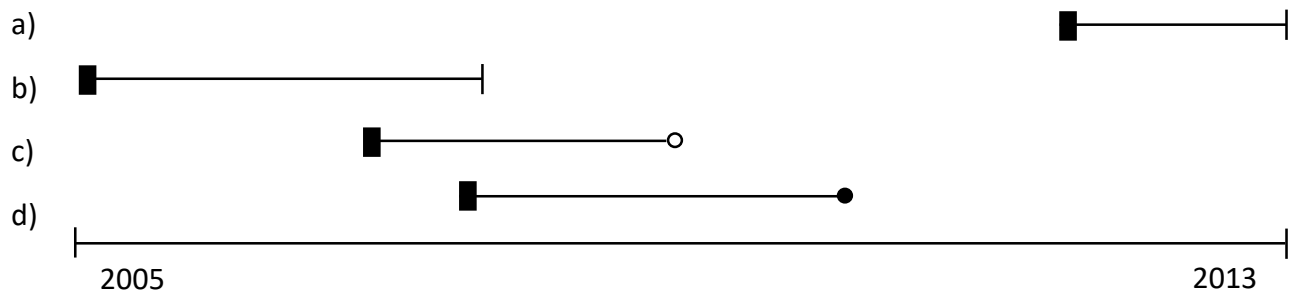


Abbreviations: NSAID, Non-Steroidal Anti-inflammatory drug.

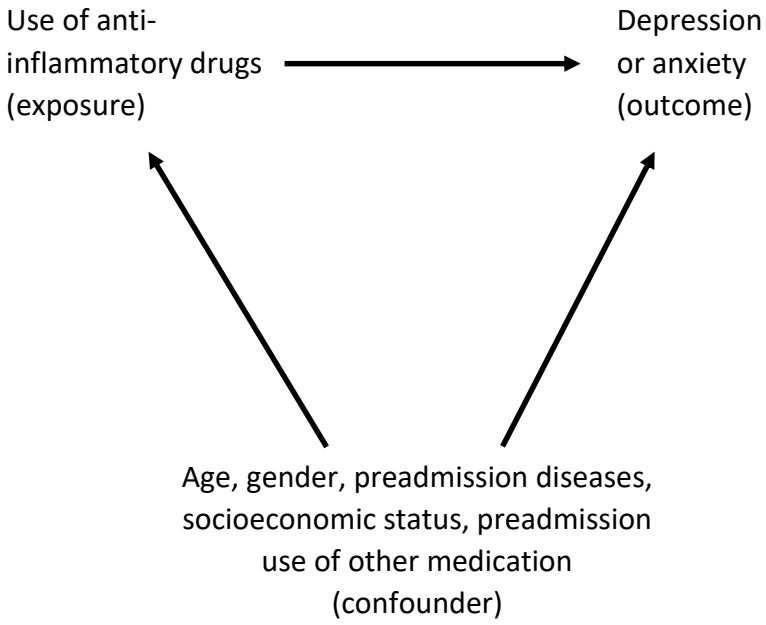
Supplemental Figure 1. Flowchart of the study population.



Supplemental Figure 2. Different trajectories of follow-up. a) Censored due to end of study period. b) Censored after 3-years of follow-up (full follow-up). c) Outcome. d) Death. ▮ = Date of admission.



Supplemental Figure 3. Confounding. The relationship between use of anti-inflammatory drugs and risk of depression and anxiety is potentially confounded by patient characteristics and behaviors related to both use of anti-inflammatory drugs and risk of depression and anxiety.



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