Preadmission use of antidepressants and quality of care, intensive care admission and mortality of colorectal cancer surgery – a nationwide population-based cohort study

Research year report

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PREFACE

This research year report is based on a study carried out during my research year at the Department of Clinical Epidemiology at Aarhus University Hospital, from September 2014 to August 2015.

First of all, I would like to express my sincerest gratitude to my supervisors Mette Nørgaard and Christian Fynbo Christiansen, for being very enthusiastic about my project and for guidance throughout the year. They formulated the project idea, introduced me to clinical epidemiology, and shared their extensive research knowledge. Despite at times a very packed schedule, they have always been able to have time for me, commenting on my manuscript, and giving my constructive feedback.

During my research year, I had the pleasure to visit the Department of Epidemiology at University of North Carolina, Gillings School of Public Health, Chapel Hill, for nearly three months. I am very grateful for the opportunity and experience. A special thanks to Jenny Lund for huge engagement in my project and stay. Furthermore, I would like to thank Alan Kinlaw for a warm welcome, pleasant stay, and for introducing me to the American way of living. It was an amazing experience – both educationally and intellectually.

I would also like thank my other colleagues at the Department of Clinical Epidemiology for a learning research year. Last, but not least and most importantly, I owe a special thanks to the other research year students at the Department of Clinical Epidemiology for always creating an inspiring and great work atmosphere. Throughout the year, we have shared many tricks for STATA, knowledge of epidemiology, lunch breaks, and great laughs.

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ABBREVIATIONS

ADs	Antidepressants
aHR	Adjusted hazard ratio
ASA	American Society of Anesthesiologists physical status classification system
ATC	Anatomical Therapeutic Chemical classification system
BMI	Body mass index
CCI	Charlson Comorbidity Index
CI	Confidence interval
CRC	Colorectal cancer
CPR-number	Central Person Register number
DCCG	Danish Colorectal Cancer Group Database
DNRP	Danish National Registry of Patients
HR	Hazard ratio
ICU	Intensive care unit
IQR	Interquartile range
MDT	Multidisciplinary team
MICE	Multiple imputation by chained equations
NIV	Non-invasive ventilation
OR	Odds ratio
SSRI	Selective serotonin reuptake inhibitor
UICC	Union for International Cancer Control

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ABSTRACT

Background: Cancer patients commonly use antidepressants (ADs), and pre-existing psychiatric disorders are associated with increased mortality, lower quality care, and higher risk of intensive care unit (ICU) admission. But data on the association between use of ADs and clinical outcomes are sparse.

Methods: Therefore, we conducted a nationwide population-based cohort study of surgical colorectal cancer (CRC) patients in Denmark using the Danish Colorectal Cancer Group Database (DCCG) from 2005 to 2012. We assessed exposure as AD prescriptions redeemed before surgery categorized into current use, former use, and non-use based on time since redemption of the latest AD prescription (≤90 days, 91-365 days, >365 days, respectively). We assessed quality of care through quality indicators recorded in DCCG and the Danish Intensive Care Database. We followed each patient for up to 30 days after surgery and estimated the cumulative incidence of ICU admission with death treated as competing risk and 30-day mortality. The 30-day ICU admission rate and mortality according to use of ADs was compared by adjusted hazard ratios (aHR) estimated with Cox regression with adjustment for age, gender, comorbidity, lifestyle factors, cancer site and stage, type of admission and surgery.

Results: We identified 26,649 surgical CRC patients of whom 3,167 (11.9%) were users of ADs with 2,366 (74.7%) as current users and 801 (25.3%) as former users. Current and former users were older, had higher level of comorbidity, and had similar cancer stage distribution as non-users. Current users were more likely to be admitted acutely and have palliative surgical procedures than non-users. Quality indicators of care were similar for current, former, and non-users. Compared with non-users, the ICU admission rate was higher among current users, aHR 1.25 (95% CI 1.14-1.36), and former users, aHR 1.12 (95% CI 0.96-1.32). The 30-day mortality was 11.6% among current, 9.3% among former, and 6.3% among non-users with corresponding aHR of 1.27 (95% CI 1.11-1.45) for current and 1.14 (95% CI 0.90-1.44) for former users compared with non-users.

Conclusion: Surgical CRC patients with use of ADs receive similar quality of care, but have increased risk of ICU admission and 30-day mortality than non-users.

DANSK RESUMÉ

Baggrund: Antidepressiva (AD) bruges ofte af kræftpatienter, og kræftpatienter med eksisterende psykiske sygdomme har forhøjet dødelighed, lavere behandlingskvalitet og højere risiko for indlæggelse på intensivafdeling. Men data på sammenhængen mellem brug af AD og kliniske udfald er sparsom.

Metode: Vi lavede derfor et landsdækkende kohorte studie blandt patienter, som blev opereret for tyk- og endetarmskræft, i Danmark ved at benytte Dansk Colorektal Cancer Gruppe Database (DCCG) fra 2005 til 2012. Vi undersøgte eksponering vha. indløste recepter for AD før operationen, og inddelte patienterne som aktuelle, tidligere og ikke-brugere baseret på tiden fra seneste receptindløsning til operation (≤90 dage, 91-365 dage, >365 dage, hhv.). Vi benyttede kvalitetsindikatorer fra DCCG og Dansk Intensiv Database til at vurdere kirurgisk og intensiv behandlingskvalitet. Vi fulgte hver patient i op til 30 dage efter operationen, og i denne periode estimerede vi raten af intensivindlæggelser (med død som competing risk) og dødelighed. Vi sammenlignede intensivindlæggelsesrate og dødeligheden for de tre grupper af AD-brugere vha. Cox regression og justerede hazard ratios (aHR) med justering for alder, køn, komorbiditet, livsstilsfaktorer, kræftplacering og -stadie samt indlæggelses- og kirurgitype

Resultater: Vi fandt 26.649 patienter, som var blevet opereret for tyk- og endetarmskræft. Heraf var 3,167 (11,9%) brugere af AD med 2.366 (74.7%) aktuelle og 801 (25.3%) tidligere brugere. Aktuelle og tidligere brugere var ældre, havde sværere grad af komorbiditet, samt tilsvarende fordeling af kræftstadie som ikke-brugere. Aktuelle brugere blev oftere indlagt akut og fik palliativ kirurgi end ikke-brugere. Der var ingen forskel i behandlingskvaliteten for aktuelle, tidligere og ikke-brugere. Sammenlignet med ikke-brugere, var indlæggelsesraten på intensivafdeling højere for aktuelle brugere, aHR 1,25 (95% CI 1,14-1,36), og tidligere brugere, aHR 1,12 (95% CI 0,96-1,32). Indenfor 30 dage efter operationen døde 11,6% aktuelle brugere, 9,3% tidligere brugere og 6,3% ikke-brugere. Dette svarede til aHR på 1,27 (95% CI 1,11-1,45) for aktuelle og 1,14 (95% CI 0,90-1,44) for tidligere brugere sammenlignet med ikke-brugere.

Konklusion: Patienter, som bliver opereret for tyk- og endetarmskræft, og bruger AD har tilsvarende behandlingskvalitet, men har højere risiko for indlæggelse på intensivafdeling og dødelighed inden for 30 dage efter operationen end ikke-brugere.

MANUSCRIPT

INTRODUCTION

The use of antidepressants (ADs) has increased over the past decades and ADs are frequently used drugs among cancer patients.[1-3] Cancer patients, including colorectal cancer (CRC) patients, with pre-existing psychiatric disorders have higher short- and long-term mortality than patients without psychiatric disorders.[4-8] Explanations for this excess mortality may include delayed cancer diagnosis,[6,7] higher level of somatic comorbidity,[6,9,10] adverse lifestyle,[10] increased risk of critical illness and thereby admission to intensive care unit (ICU).[11,12] However, use of ADs in itself may cause excess mortality by increasing the risk of perioperative bleeding.[13-15]

CRC is one of the most common cancer diagnoses and with surgery being the primary treatment.[16] To our knowledge, no previous studies have examined the impact of AD use on outcome of CRC surgery. However, two studies have examined the relation between psychiatric disorders and quality of care among CRC patients. An American cohort study with more than 80,000 colon cancer patients aged 67 or older found lower frequency of surgery, chemotherapy and elevated cancer stage and mortality regardless of surgery in patients with mood disorder than in non-psychiatric patients.[6] Likewise, a Japanese study among elective surgical CRC patients found higher risk of postoperative complications among psychiatric patients than non-psychiatric patients, whilst the mortality was uninvestigated.[17] The latter study only included 83 patients during a 10 year study period, whereof 27 patients (32.5%) had a psychiatric disorder implying a highly selected population.

We hypothesize that use of ADs and potential underlying psychiatric disorders is associated with lower quality of care and increased risk of ICU admission and death. Therefore, we conducted a cohort study to examine the association between use of ADs and postoperative complications and mortality in CRC patients with particular focus on the quality of surgical care, ICU admission rate and quality of intensive care.

METHODS

Study population and design

We conducted a nationwide population-based cohort study in Denmark including all surgical CRC patients from January 1, 2005, to December 31, 2012. The health care system in Denmark is tax-funded and all citizens have equal access to medical care including partial reimbursement of prescriptions. We used the Danish Colorectal Cancer Group Database (DCCG) to define the cohort of all patients with incident CRC undergoing acute or elective CRC surgery.[16] Since 1994, all surgical

departments have reported data on rectum cancer patients and since 2001 on colon cancer patients to DCCG. DCCG has information on date of surgery, hospital, type of admission (acute, elective), cancer stage (classified according to Union for International Cancer Control (UICC)), cancer site (colon, rectum), surgical procedure (see appendix for definitions), intraoperative blood loss and transfusion, postoperative complications, and reoperations due to surgical postoperative complications.

Since 1968, each Danish citizen at birth and to residents at immigration has been assigned a personal civil registration number (CPR-number), which is registered in the Civil Registration System.[18,19] This has information on date of birth, gender, emigration, vital status, and date of vital status. The CPR-number allows us to link data from DCCG, the Civil Registration System, the Danish National Registry of Patients (DNRP), the Danish National Health Service Prescription Database, and the Danish Intensive Care Database.[20-22] Patients with missing follow-up data on vital status in the Civil Registration System were excluded.

Every in- and outpatient hospital contact have been registered in DNRP since 1977 and 1995, respectively, including discharge diagnoses coded according to the International Classification of Disease 10th edition (ICD-10) since 1993. We excluded patients if the registered date of surgery in DCCG did not correspond to a hospital admission recorded in DNRP.

Exposure

Using the Danish National Health Service Prescription Database, we identified all redeemed prescriptions for ADs in the year prior to surgery for the cohort. Each redeemed prescription is registered according to the patient's CPR-number, date of redemption, type and amount of drug prescribed according to the Anatomical Therapeutic Chemical (ATC) classification system. We defined patients who redeemed a prescription of ADs (ATC code N06A) as AD-users. AD users were categorized as current and former users if the date of redemption were ≤90 days or 91-365 days prior to surgery, respectively. The period of 90 days was chosen since ADs are mainly prescribed in packets for 3 months use. Non-users were patients without redeemed prescription of ADs within 365 days prior to surgery. If an effect of ADs exists, we would expect the effect to be greater among current users than former users.

Main outcome measures

Surgical care

The quality of surgical care was assessed by quality indicators from DCCG including 1) whether a multidisciplinary team (MDT) conference was held prior to surgery for rectum cancer patients, 2) whether a surgical specialist performed the colon surgery stratified into acute and elective patients, 3) whether the elective surgical procedure was radical, 4) whether the patients had anastomosis leakage among elective colon and rectum cancer patients. Each indicator had specific variables for inclusion (see appendix for definitions), and patients with missing value for each indicator were excluded.

ICU admission, treatment, and quality of intensive care

Since 2005, the Danish Intensive Care Database has included date and time for ICU admissions and treatments with mechanical ventilation, non-invasive ventilation (NIV), inotropes/vasopressors, and dialysis. Since 2009, the database also includes data on date and time of ICU discharge, and ICU discharge status and destination.

The quality indicators of intensive care are defined by the Danish Intensive Care Database and we included the following two indicators: 1) readmission within 48 hours after discharge to ward, 2) night-time discharge to ward between 10pm and 8am. The variables for these indicators were implemented during 2009 and therefore we restricted the analyses to ICU admission in 2010-2012. Patients were included if they were discharged from ICU to ward, and excluded it they had missing values for each indicator (see appendix for definitions)

30-day mortality

The date of any death within 30 days after surgery was ascertained from the Danish Civil Registration System, which is daily updated and has virtually complete follow-up. The mortality for all patients and patients admitted to ICU is also quality indicators for surgical and intensive care.

Covariates

Data on comorbidity was obtained from in- and outpatient hospital diagnoses recorded in DNRP up to five years prior to surgery. We computed Charlson Comorbidity Index (CCI) scores including 19 conditions weighted between 1 and 6 points (see appendix for definitions).[23] We categorized the CCI score into 1) 0 = low, 2) 1-2 = medium, and 3) 3+ = high comorbidity level. Information on

alcohol-related disease was also ascertained. For adjustment of somatic comorbidity we grouped CCI and alcohol-related disease to 11 somatic conditions (see appendix for definitions). From DCCG we obtained information on smoking status, weekly alcohol intake, height and weight. Body mass index (BMI) was calculated using height and weight, and classified according to underweight (BMI < 18.5 kg/m^2), normal weight (≥ 18.5 kg/m^2 BMI < 25 kg/m^2), overweight (≥ 25 kg/m^2 BMI < 30 kg/m^2), and obese (≥ 30 kg/m^2 BMI). Hospital volume was calculated by the annual number of operations and categorized to <100 patients per year, 100-200 patients per year, and >200 patients per year.

Statistical analysis

We tabulated frequencies of covariates according to use of ADs, i.e. current, former, and non-user. In order to address missing values of smoking status, alcohol intake, and BMI, we imputed the values using multiple imputation by chained equations (MICE).[24]

We estimated the fulfillment frequency of each quality indicator and used a logistic regression model to estimate the quality of surgical and intensive care comparing current and former users of ADs to non-users. The estimates of surgical care were adjusted for age, gender, smoking status, alcohol intake, BMI, each of the 11 somatic comorbidities, type of admission, cancer stage, surgical procedure, and hospital volume. The estimates for intensive care quality were unadjusted due to small number of patients.

All patients were followed from date of surgery to death, emigration, or up to 30 days. The ICU admission rate was assessed within 30 postoperative days and estimated by a cumulative incidence function treating death as a competing risk. We performed Cox regression to compare the ICU admission rates according to user status of ADs. The estimates were adjusted for age, gender, smoking status, alcohol intake, BMI, each of the 11 somatic comorbidities, type of admission, cancer site, cancer stage, blood transfusion, surgical procedure, and hospital volume.

We estimated and plotted 30-day mortality according to use of ADs for all patients using the Kaplan-Meier method as 1 – Kaplan-Meier estimate. We used Cox regression model to compute hazard ratios (HRs) with 95% confidence intervals (95% CI) and compared the rate of death among current and former users of ADs with non-users as the reference. The estimates were adjusted for age, gender, smoking status, alcohol intake, BMI, each of the 11 somatic comorbidities, type of admission, surgical procedure, cancer site, and hospital volume. Additionally, we performed strati-

fied analyses on 30-day mortality according to acute colon surgery, elective colon surgery, elective rectum surgery, cancer stage, CCI score, and patients admitted to ICU.

All statistical analyses were performed using STATA software (v13.0 StataCorp LP, College Station, Texas, USA). The study was approved by the Danish Data Protection Agency (record no. 2007-58-0010 and Central Denmark Region record no. 1-16-02-444-14).

RESULTS

Patient characteristics

We included 26,649 surgical CRC patients after exclusion of patients with missing vital status (*n* = 13) and lacking admission data in DNRP on the day of surgery (*n* = 729). The patient characteristics according to use of ADs are shown in table 1. Within a year prior to surgery, 3,167 patients (11.9%) had redeemed a prescription of ADs, whereof 2,366 (74.7%) were current users and 801 (25.3%) were former users. AD users were older, more likely to be women, and had more comorbidity than non-users, which was more pronounced among current users than former users. Users were less likely to be never smokers and more likely to have no alcohol intake. BMI did not differ according to use of ADs. The distributions of cancer stage were similar, but the prevalence of colon cancer was higher among users of ADs. Current users were more often admitted acutely and had palliative minor procedures in low-volume hospitals instead of curative major procedures in high-volume hospitals compared with former users and non-users. Oncological treatment was less likely among current and former users than non-users. The frequency of intraoperative blood transfusions was higher among current (25.5%) and former users (21.8%) compared with non-users (19.5%). However, there was no clinical relevant difference in estimated blood loss during surgery, which for current users was 180 ml (interquartile range (IQR) 50; 400), for former users 150 ml (IQR 50; 400), and 200 ml (IQR 50; 400) for non-users.

Among current users, 14.8% were reoperated due to surgical postoperative complications compared with 14.0% among former users and 13.7% among non-users (table 2). Reoperation due to postoperative bleeding was similar among current (7.4%), former (6.2%), and non-users (7.4%). The presence of medical complications was higher among current users (15.8%) than among former (10.6%) and non-users (10.2%), which was mainly due to a higher frequency of heart failure and respiratory failure.

Quality of surgical care

The fulfilment of quality indicators of surgical care did not differ much between current, former and non-users of ADs (table 3). However, former users (76.1%) were less likely to have a surgical specialist performing the surgery compared with current (79.0%) and non-users (80.0%), corresponding to an adjusted odds ratio (OR) of 0.80 (95% CI 0.64; 1.01) for former users and 1.01 (95% 0.87; 1.17) for current users, compared with non-users. Anastomosis leakage among elective colon patients was similarly frequent for current (6.4%), former (6.6%), and non-users (6.0%). The frequency of anastomosis leakage among elective rectum patients was slightly lower for current (11.6%) and former (11.9%) users compared with non-users (13.1%), but this small difference vanished after adjustment.

ICU admission, treatment, and quality of intensive care

The rate of ICU admission within 30 days was 24.8% among current users, 20.4% among former and 17.4% among non-users (table 4a). After adjustment, the HR for ICU admission remained higher for current users, HR 1.25 (95% CI 1.14; 1.36) and former users, HR 1.12 (95% CI 0.96; 1.32). During ICU admission, 52.9% of the current and 52.5% of the former users of ADs received any treatment with non-invasive ventilation (NIV), mechanical ventilation, dialysis, or inotropes/vasopressors compared with 46.9% among non-users of ADs (table 4b). The difference was mainly due to more frequent use of NIV, mechanical ventilation, and inotropes/vasopressors.

The quality of intensive care showed no major differences when measured as readmission to ICU within 48 hours after discharge or nighttime discharge (10pm-8am) between current, former, and non-users of ADs (table 4c). However, the reported proportion fulfilling the quality indicators were low and consequently imprecise.

30-day mortality

Within 30 days after surgery, 1,817 patients died (6.8%). The overall 30-day mortality was 11.6% among current users and 9.3% among former users compared with 6.3% among non-users (table 5 and figure 1). This corresponded to crude HRs of 1.90 (95% CI 1.67; 2.16) and 1.49 (95% CI 1.18; 1.89), respectively. After adjustment the overall 30-day mortality rate was 27% higher for current users, aHR = 1.27 (95% CI 1.11; 1.45), and 14% higher for former users, aHR = 1.14 (95% CI 0.90; 1.44). In the stratified analyses for acute colon surgery, elective colon surgery, and elective rectum surgery, the 30-day mortality was higher for current users compared with non-users. The associa-

tion attenuated after confounder adjustment, but remained at least 20% higher. When stratified on type of admission and cancer site, the 30-day mortality for former users was only higher for elective rectum cancer patients, compared with non-users. When we stratified on cancer stage, the 30-day mortality was 20-40% higher for current user than non-users irrespective of cancer stage. Former users had tendency towards higher mortality than non-users. When we stratified on comorbidity level (CCI), the 30-day mortality was 30-50% higher for current and former users compared with non-users for low (0) and medium (1-2) level of comorbidity. However, for the high (3+) level of comorbidity, the adjusted 30-day mortality was similar for current, former, and non-users. The 30-day mortality for patients admitted to ICU was 22.2% among current users, 25.4% among former users, and 16.3% among non-users. After adjustment, the 30-day mortality remained increased for current users, HR 1.22 (95% CI 1.00; 1.49) and for former users, HR 1.52 (95% CI 1.10; 2.11).

DISCUSSION

Key results

In this large population-based cohort study including more than 25,000 CRC patients, we found no difference in quality of surgical and intensive care among AD users compared with non-users. However, use of ADs was associated with higher admission rate to ICU and higher 30-day mortality. The mortality was higher for both current and former users of ADs than for non-users irrespective of cancer stage, level of comorbidity, cancer site (colon vs. rectum), type of admission (acute vs. elective), and transferal to ICU, except for patients with high level of comorbidity. In general, the impact of ADs was higher for current than for former users when compared with non-users, implying a drug effect of ADs.

Other studies

The finding of increased mortality among users of ADs is consistent with former studies comparing patients with CRC and psychiatric disorder with non-psychiatric patients.[6,17] The study by Baillargeon *et al.* found an adjusted HR for death of 1.07 (95% CI 1.03-1.10) comparing CRC patients with mood disorders to patients without psychiatric disorders in the study period from 1993 to 2005.[6] However, they investigated the mortality in all CRC patients and not specifically surgical CRC patients. In the study by Hashimoto *et al.*, 70.4% of 27 surgical CRC patients with psychiatric disorder had postoperative complications, whilst the frequency was 39.3% in the non-psychiatric group. This rate of postoperative complications is much higher than the 10-15% complication and

reoperation rate in our study.[17] Hashimoto *et al.* found psychiatric disorders in 27 of 83 (32.5%) patients, which is substantially higher than our 11.9% of CRC patients using of ADs. Of AD users, approximately 80% have psychiatric diagnosis.[1] Hereby we included patients with less severe psychiatric symptoms, which is associated with lower mortality.[12] In this context, our finding of 20-30% increased 30-day mortality is therefore of concern and warrants further investigation.

Possible mechanisms

Besides the potential effect of underlying psychiatric disorders, a possible explanation of the increased mortality could be a higher risk of bleeding among users of selective serotonin reuptake inhibitors (SSRI).[13-15] This could explain the higher proportion of intraoperative blood transfusions among users of ADs, which is associated with increased mortality.[25-27] But we did not find differences in intraoperative blood loss according to use of ADs. Instead, the higher frequency of intraoperative blood transfusion could be due to preoperative anemia, which also is associated with higher mortality in surgical patients.[28,29] Anemia is more prevalent among older patients undergoing acute surgery and in patients with ASA score ≥ II,[29] which is consistent with our findings of more older patients admitted acutely, higher level of somatic comorbidity and ASA score among AD users than non-users. Unfortunately, we did not have any information on preoperative anemia and therefore we could not examine this any further. Still, anemia, as mentioned, is associated with several of the covariates in our study that we already accounted for in the analyses and any residual effect of anemia is thus expected to be minor.

Another potential explanation is lower socioeconomic status and unhealthy lifestyle among AD users, which increases mortality.[10] Especially low socioeconomic status and smoking is associated with increased mortality among surgical CRC patients.[30-32] We found smoking to be more prevalent among AD users and despite missing values we were able to consider lifestyle factors using a multiple imputation model. Since the impact of socioeconomic status on mortality among CRC patients is correlated with comorbidity and lifestyle,[32] we were partially able to consider socioeconomic status and therefore we expect sparse residual effect of socioeconomic status.

Strengths and limitations

The main strengths of this study include its large size and population-based and nationwide design within a tax supported healthcare system with virtually complete follow-up. This design considerably reduces the likelihood of selection bias. Collecting data from independent medical databases

and registries avoids reliance upon self-reporting and hereby limiting recall bias. The registration completeness of surgical CRC patients in DCCG is >98% in the study period, 2005-2012.[16] In addition, the follow-up for mortality was virtually complete.[18]

Some limitations should be taken into consideration when interpreting our results. We defined our exposure by using redeemed prescriptions for ADs as a proxy for actual drug use. This may not always be entirely correct due to lacking patient adherence. However, the fact that the drug exposure information was based on actual dispensing at pharmacies could suggest high adherence. Any misclassification due to non-adherence would have attenuated our relative estimates.

We aimed to control for confounding by extensive adjustment for known potential confounders, but unmeasured confounding cannot be ruled out. We did not have information on severity of all the conditions included in CCI from DNRP. We estimated the proportion fulfilling several quality indicators in orders to address the quality of surgical and intensive care. But we did not directly investigate differences in treatment of comorbid somatic diseases, which may be lower among psychiatric patients than non-psychiatric patients.[5,33] However, we found higher frequency of postoperative heart failure and respiratory failure and higher level of somatic comorbidity, implying differences in somatic care and need. Unmeasured differences in somatic care of comorbidity could cause bias away from the null. Furthermore, we did not assess other drugs that could influence the bleeding risk or drugs that might interact with the ADs.

Additionally, confounding by indication is important to consider when comparing outcomes of users of ADs with non-users. In this study we are not able to distinguish whether the increased mortality is due to an effect of the drug itself or underlying psychiatric disorders. However, we found more pronounced effect among current users than former users, implying a causal effect of ADs rather than just confounding by indication.

Conclusion

In conclusion, we found no difference in quality of surgical and intensive care among AD users. Still, use of ADs was associated with higher risk of ICU admission and death following surgery for CRC compared with non-users. The mortality was higher for current users than former users of ADs. Our study suggests that the effects of AD use and potential underlying psychiatric disorders need additional attention in perioperative care among CRC patients in order to reduce the mortality.

SUPPLEMENTARY

The following section of the research year report contains general methodological considerations of the study design, missing values, and strengths and limitations, including discussion of bias and confounding. In this section we present additional results of ICU admissions at the date of surgery and within 1-30 and 2-30 days after surgery in order to assess planned and prophylactic ICU admissions and admissions that are more likely due to postoperative complications. Furthermore, considerations of clinical perspectives and future studies are presented.

Methodological considerations

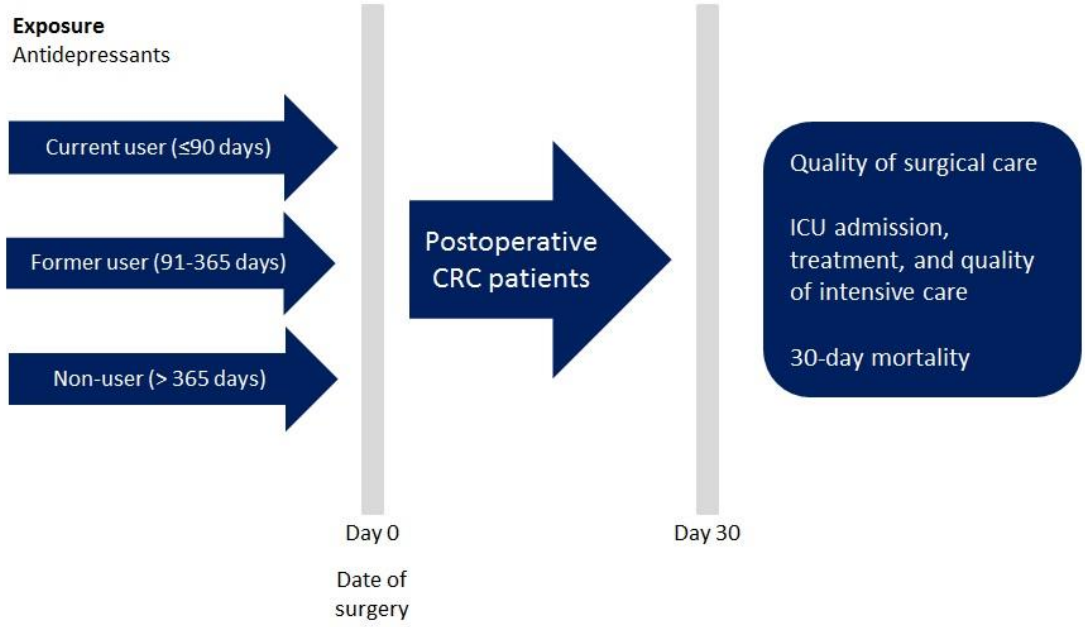
Study design

The present study is an observational study, which is a study where the researcher gathers information by observing, and the researcher has no active role in e.g. assigning exposure to patients.[34] Observational studies of drug effects are useful when ethics and economics restrict experimental studies.[35]

We designed a nationwide cohort study using data from national population-based registries. A cohort is defined by a group of patients who are followed for a period of time and shares a similar condition or other characteristics. Our cohort was defined by patients with CRC who underwent CRC surgery. In a cohort study, subjects are selected to investigate the incidence of an outcome and the subjects are then classified according to exposure status. In order to assess the effect of exposure, the cohort is divided into one or more exposure groups with different level of exposure. The exposed are compared to unexposed or a reference group.[35] In our study, we defined a) current users of ADs as patients who redeemed a prescription within 90 days prior to CRC surgery, b) former users, who had redeemed a prescription within 91-365 days prior to CRC surgery, c) non-users who had no redemption of AD prescriptions within 365 days prior to CRC surgery (Supplemental figure 1). Additionally, this study is population-based, which is when the cohort is defined by a geographical area, here Denmark.[36,37]

The aim of our study was to examine differences among current, former, and non-users of ADs among CRC patients, meaning descriptive differences as well as differences in quality of care, ICU admission rate, and mortality. For the purpose of our study, we found a cohort study most suitable.

Supplemental figure 1. Study design



Multiple imputation for missing values

Missing data are common and practically unavoidable in epidemiological studies. Many researchers choose to include solely complete cases in analyses. However, this can lead to substantial exclusion of patients and can cause bias and loss of precision and power.[38] Multiple imputation is a statistical technique that allows individuals with missing information to be included in the analyses.[38,39] Multiple imputation limits bias if predicted missing values are included in the imputation model.[38]

In the present study, we had missing values of lifestyle factors, i.e. smoking status, weekly alcohol intake, and BMI group. However, in order to use multiple imputation for our missing data, the assumption of data being missing at random needs to be fulfilled. Missing at random is that any systematic differences between the missing values and the observed values can be explained by differences in the observed data.[38] Said in another way, the probability that data are missing does not depend on unobserved data, but may depend on observed data. The assumption cannot be tested directly by observing the data. Instead it can be approximated by including relevant and sufficient variables in the imputation model.[38]

A multiple imputation model uses the distribution of the observed data to create data sets of plausible values for the missing data.[39] Each imputed data set gives different estimated associations and these are combined to an overall estimate by applying Rubin's rule.[38,39] The missing values are hereby replaced with imputed values, which are generated from their predictive distribution based

on the observed data.[38] However, the true values of the missing data are never known. The imputed values are then used in standard statistical methods, e.g. Cox proportional hazards regression.
In our study, the distribution of missing values for smoking status, alcohol intake, and BMI group were as following:

Variable	Frequency of missing values
Smoking	27%
Alcohol intake	28%
BMI group	26%

However, missing values for one of the three covariates was highly correlated to missing values for the two other covariates, as seen in the table below:

Number of missing values per individual	Frequency of total study population
0	69%
1	4%
2	3%
3	24%

One approach is to impute the same number of data sets as the percentage of incomplete cases in the data set.[39] In our study, 31% of the patients had missing values for smoking status, alcohol intake, and BMI group. Therefore, we imputed 31 data sets. We used multiple imputation by chained equations (MICE), which is an approach to generate imputations based on a set of imputation models for each variable with missing values.[39] This approach is suitable for large data sets.[39]
An adequate imputation model should include covariates and outcome from the analysis model, and variables that predict the incomplete variables and missing values of the incomplete variables.[39] We therefore imputed the following variables: smoking status, alcohol intake, and BMI group. We used the following set of predictive variables: age, gender, somatic comorbidity, type of admission, surgical procedure, cancer site and stage, intraoperative blood transfusion, hospital volume, and fulfilled of surgical quality indicators, ICU admission, and death within 30 days.

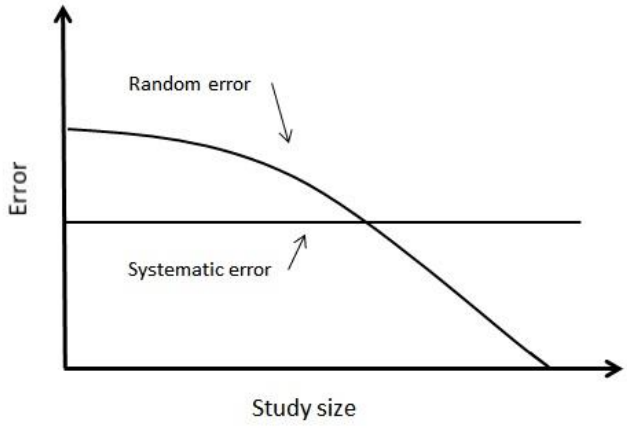
Strengths and limitations

The main strengths of this study are its nationwide and population-based design in a homogenous study population. This is due to a tax-funded health care system, and also by using a well-defined

cohort of surgical CRC patients. We used data from high-quality and complete databases and registries.[16,18,21,23,40]

The large study size with more than 25,000 CRC patients has relevance in relation to random error (chance), since random error decreases with study size (Supplemental figure 2). On the other hand, systematic error remains unaffected by study size. Systematic error is systematic distortion and is another term for bias. Bias causes systematic difference between the association of observed and the actual effect. The systematic errors can be classified as selection bias, information bias, and confounding.[37] Selection and information bias arises from the study design and therefore cannot be corrected by statistical analyses.[35]

Supplemental figure 2. The relation of systematic error and random error to study size (after Rothman, KJ. Epidemiology: An Introduction)



Selection bias

Selection bias is a systematic error that results from the procedures that is used to select patients and factors that influence study participation. It arises when there is a difference between the relation of exposure and disease among patients participating in the study and patients not participating in study, but are eligible.[35]

Our population-based design in a tax-supported health care system largely removed selection bias. The included patients were independent of specific hospitals, health insurance, or age.[36] In addition, the completeness of DCCG in the study period, 2005-2012, was more than 98%, leaving minimal amount of patients that were not included.[16] Moreover, the Civil Registration System allowed virtually complete follow-up.[18]

Information bias

Another way to introduce systematic error is erroneous collection of information. This type of error is called information bias, and misclassification leads to information bias.[37] It is especially important to consider misclassification of exposure and outcome. Misclassification can be classified as either non-differential or differential misclassification. Non-differential misclassification occurs when the misclassification is unrelated to exposure or outcome, whilst differential misclassification arises when the misclassification is related to exposure or outcome.[37]

As previously mentioned, misclassification of exposure is highly relevant to consider in this study, since we used redeemed prescriptions of ADs as a proxy for actual use. Patients, we classified as either current or former users of ADs, might not be actual users and should have been in the non-user group instead. Misclassification due to non-adherence of the ADs causes bias that may attenuate our estimates. However, the fact that the information on drug exposure was based on actual dispensing at pharmacies suggest high adherence. In addition, our use of register data avoided reliance upon self-reporting and hereby recall bias. Recall bias, which is differential misclassification, arises when the exposure information is gathered by interviewing the patients after occurrence of outcome, and the patients are more likely to remember, exaggerate or understate due to their outcome.[35]

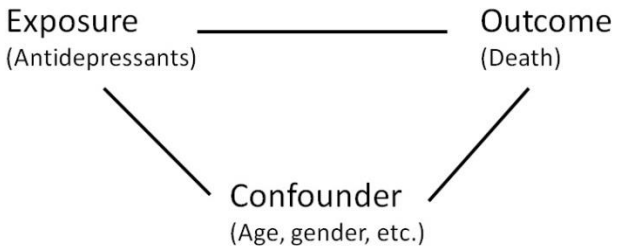
Confounding

Confounding is confusing or mixing of effects, which implies that the effect of exposure on outcome is mixed with the effect of another variable leading to bias.[37] Confounding is essential to consider and discuss in observational studies, since the exposure is not assigned randomly and hereby causing differences between exposed and unexposed patients.

For a variable to be a confounder, three criteria must be met (Supplemental figure 3):[35]

1. The confounder must be associated with exposure (unevenly distributed across exposure categories)
2. A confounder must be associated with the outcome (either as a cause or a proxy for a cause, but not as an effect of the outcome)
3. The confounder must not be an intermediate step of the causal pathway

Supplemental figure 3. General correlation of exposure, outcome, and confounder. In the parentheses are presented examples of correlations in the current study (after Rothman, KJ. Epidemiology – An Introduction)



In epidemiological studies with drugs, i.e. pharmacoepidemiology, a specific type of confounding is central – confounding by indication. Confounding by indication arises from the fact that patients who take a drug usually differ from patients who do not take a drug according to the medical indication for which the drug was prescribed.[37] The indication for the treatment is linked to the outcome. Typically, there are differences between populations who receive different treatments even for the same disease.[37]

In our analyses, we incorporated an extensive number of confounding covariates. The correlation of exposure and the confounding covariates is shown in the descriptive table 1. For confounding to occur, the covariates must be imbalanced across exposure categories.[37] In general, bias and confounding can be controlled by the study design through randomizing, restriction, and matching, and by statistical analyses through stratification, standardization or by multivariable regression.[35] In this study, we aimed to control for confounding in our analyses by using stratification and adjustment by multivariable regression models. Stratification is division of data into subgroups of variables. This way it is possible to identify data differences, and assess confounding and interaction.[35] We made stratification of the 30-day mortality with different type of admissions, cancer site and stage, level of comorbidity (Charlson Comorbidity Index), and patients admitted to ICU. Additionally, we also used multivariable models to control for confounding in our estimates.

Additional results

We performed additional restricted analyses of ICU admission and treatment at the date of surgery (day 0) and within 1-30 and 2-30 days after surgery. The additional analyses were performed in order to address differences in ICU admission at day 0, where we expect a high prevalence of planned and prophylactic ICU admissions, and at 1-30 and 2-30 days after surgery, where we expect ICU admissions more likely due to postoperative complications.

Methods

We calculated the frequencies of ICU admissions at day 0 according to use of ADs. The admission rates at 1-30 and 2-30 days after surgery were estimated with a cumulative incidence function treating death as competing risk for current, former, and non-users of ADs.

Results

At the date of surgery (day 0), 9.0% of the patients were admitted to ICU, correlating to 12.8% among current users, 10.0% among former users, and 8.6% among on-users of ADs (Supplemental table 1a). The results for ICU admission rate at 1-30 and 2-30 days surgery showed the same trend as the results of day 0 with higher admission rates for current users of ADs than former and non-users. These results of the additional analyses show the same pattern as the main analysis of 0-30 days.

Patients admitted to ICU on the date of surgery (day 0) were less likely to receive any treatment in ICU compared to patients admitted with 1-30 and 2-30 days after surgery (Supplemental table 1b). At day 0, 38.9-50.7% of the patients received treatment, whilst it was 54.7-63.4% at 1-30 days, and 64.5-70.7% at 2-30 days after surgery. The elevation of frequency of treatment in ICU was due to rise in all types of treatment, including non-invasive ventilation, mechanical ventilation, inotropes or vasopressors, and to lesser extent dialyses. At day 0, current users were more likely to receive treatment in ICU compared to former and non-users. On the contrary, current and non-users had similar frequency of treatment at 1-30 and 2-30 days after surgery, whilst the treatment frequency was higher for former users.

Conclusion

In conclusion, a considerable amount of patients are admitted to ICU on the same date as surgery, which nearly accounts for half of the patients admitted to ICU within 30 days after surgery. The proportion of ICU admissions decreased with time from surgery, whilst the frequency of treatment in ICU rose. This rise was possibly due to postoperative complications. As in the main analysis, the ICU admission rate was higher for users of ADs as than non-users and with highest rates for current users.

Clinical perspectives and future studies

In the extract we showed that use of ADs prior to CRC surgery was associated with increased ICU admission rate and mortality. The results suggest that CRC patients with use of ADs need additional attention in perioperative care. However, we investigated surgical and intensive care and we did not find any major differences in quality of surgical and intensive care explaining the increased mortality.

In this present study, we were not able to distinguish whether the association of increased ICU admission and mortality was due to ADs in itself, psychiatric disorders or a combination. However, current users had in general higher ICU admission rate and mortality than former users, implying some effect of ADs. To investigate this further, it would be interesting to include psychiatric diagnosis of depression, anxiety, and bipolar disorders in future studies to more closely assess the effect of psychiatric disorders. The effect of ADs and particular the increased use of intraoperative blood transfusions among users of ADs than non-users could also be investigated further by including preoperative hemoglobin level to assess preoperative anemia, since preoperative anemia is associated with increased mortality among surgical patients.[28,29] In addition, we could include other drugs that influences the bleeding risk profile, e.g. acetylsalicylic acid and clopidogrel.

Another clinical relevant result of our study was a relative substantial higher frequency of acute admissions among current users compared to non- and former users. 17.2% of current users of ADs were admitted acute, whilst 13.9% among former and 12.6% among non-users were admitted acute. This could be due to misinterpretation or negligence of non-specific cancer symptoms among users of ADs, e.g. tiredness and abdominal pain, even though users of ADs to some extent are in close contact with the health care system of psychiatrists and general practitioners.[41] The closer contact with the health care system among users of ADs could lead to earlier detection of cancer. However, we found similar cancer stage among surgical CRC patients.

Our results contribute with knowledge of a sparse investigated area among surgical CRC patients with preadmission use of ADs. To our knowledge, no previous studies have examined the effect of ADs on postoperative complications and mortality in CRC patients with focus on quality of surgical care, ICU admission rate, and quality of intensive care.

In general, this area of research – the impact of ADs – is important due to the increasing use of ADs during the past decades and rising amount of comorbid patients with use of several types of drugs.

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TABLES

Table 1. Characteristics of 26,649 colorectal cancer patients who underwent surgery in the period 2005-2012 in Denmark according current, former, and non-use of antidepressants.

	Antidepressants, n=3,167 (11.9%)				Non-users, n=23,482 (88.1%)	
	Current user		Former user			
	n	%	n	%	n	%
Total	2,366	(100)	801	(100)	23,482	(100)
Median age (IQR)	74.3	(66.1; 81.0)	73.8	(63.9; 81.0)	71.0	(63.2; 78.6)
Age group						
18-49	66	(2.8)	42	(5.2)	1,117	(4.8)
50-59	225	(9.5)	91	(11.4)	2,945	(12.5)
60-69	543	(23.0)	185	(23.1)	6,882	(29.3)
70-79	860	(36.4)	248	(31.0)	7,593	(32.3)
80-	672	(28.4)	235	(29.3)	4,945	(21.1)
Gender						
Female	1,439	(60.8)	458	(57.2)	10,735	(45.7)
Male	927	(39.2)	343	(42.8)	12,747	(54.3)
Charlson Comorbidity Index						
Low (0)	890	(37.6)	318	(39.7)	12,771	(54.4)
Medium (1-2)	933	(39.4)	304	(38.0)	6,827	(29.1)
High (3+)	543	(23.0)	179	(22.4)	3,884	(16.5)
Comorbidity						
Myocardial infarction	77	(3.2)	28	(3.5)	650	(2.8)
Congestive heart failure	157	(6.6)	61	(7.6)	1,093	(4.6)
Peripheral vascular disease	150	(6.3)	44	(5.5)	923	(3.9)
Stroke	391	(16.5)	116	(14.5)	1,498	(6.4)
Dementia	132	(5.6)	30	(3.8)	220	(0.9)
Chronic pulmonary disease	495	(20.9)	181	(22.6)	3,073	(13.1)
Liver disease	126	(5.3)	50	(6.2)	561	(2.4)
Diabetes	371	(15.7)	109	(13.6)	2,637	(11.2)
Moderate to severe renal disease	81	(3.4)	17	(2.1)	540	(2.3)
Solid tumor (except colon and rectum)	208	(8.8)	62	(7.7)	1,772	(7.6)
Metastatic tumor (except colon and rectum)	176	(7.4)	62	(7.7)	1,786	(7.6)
ASA						
I	178	(7.5)	92	(11.5)	4,802	(20.4)
II	1,116	(47.2)	391	(48.8)	12,423	(52.9)
III	821	(34.7)	244	(30.5)	4,752	(20.2)
IV	115	(4.9)	32	(4.0)	411	(1.8)
V	7	(0.3)	-	-	19	(0.1)
Unknown	129	(5.4)	41	(5.1)	1,075	(4.6)
Smoking						
Smoker	423	(17.9)	145	(18.1)	3,530	(15.0)
Former smoker	652	(27.6)	247	(30.8)	7,412	(31.6)
Never	504	(21.3)	165	(20.6)	6,287	(26.8)
Unknown	787	(33.3)	244	(30.5)	6,253	(26.6)
Alcohol intake						
No intake	646	(27.3)	208	(26.0)	4,793	(20.4)
Recommended†	792	(33.5)	291	(36.3)	10,682	(45.5)
Above	137	(5.8)	55	(6.9)	1,715	(7.3)
Unknown	791	(33.4)	247	(30.8)	6,292	(26.8)
Body mass index (BMI), kg/m^2						
Underweight, < 18.5	71	(3.0)	34	(4.2)	664	(2.8)
Normal weight, ≥ 18.5 < 25	762	(32.3)	254	(31.7)	8,202	(34.9)
Overweight, ≥ 25 < 30	504	(21.3)	192	(24.0)	6,123	(26.1)
Obese, ≥ 30	270	(11.4)	100	(12.5)	2,520	(10.7)
Unknown	759	(32.1)	221	(27.6)	5,973	(25.4)
Cancer stage (UICC)						
I	321	(13.6)	123	(15.4)	3,460	(14.7)
II	793	(33.5)	286	(35.7)	7,790	(33.2)
III	601	(25.4)	211	(26.3)	6,521	(27.8)

IV	509	(21.5)	142	(17.7)	4,847	(20.6)
Unknown	142	(6.0)	39	(4.9)	864	(3.7)
Cancer type						
Colon	1,707	(72.2)	572	(71.4)	15,721	(67.0)
Rectum	659	(27.8)	229	(28.6)	7,761	(33.0)
Hospital volume (patients per year)						
<100	156	(6.6)	48	(6.0)	1,293	(5.5)
100-200	1,150	(48.6)	356	(44.4)	10,509	(44.8)
>200	1,060	(44.8)	397	(49.6)	11,680	(49.7)
Type of admission						
Elective	1,880	(79.5)	674	(84.1)	19,817	(84.4)
Acute	406	(17.2)	111	(13.9)	2,953	(12.6)
Unknown	80	(3.4)	16	(2.0)	712	(3.0)
Intension of treatment						
Curative	1,919	(81.1)	675	(84.3)	19,870	(84.6)
Palliative	367	(15.5)	110	(13.7)	2,902	(12.4)
Unknown	80	(3.4)	16	(2.0)	710	(3.0)
Course of treatment						
Only surgery	1,497	(63.3)	493	(61.6)	12,518	(53.3)
Surgery and oncology	789	(33.4)	292	(36.4)	10,251	(43.6)
Surgical procedure						
Major	2,063	(87.2)	710	(88.6)	21,124	(90.0)
Minor	269	(11.4)	81	(10.1)	2,035	(8.7)
Unknown	34	(1.4)	10	(1.2)	323	(1.4)
Intraoperative blood loss, Median ml (IQR)	180	(50; 400)	150	(50; 400)	200	(50; 400)
Intraoperative blood transfusion	603	(25.5)	175	(21.8)	4,586	(19.5)

† 1-14 units per week for women and 1-21 units per week for men
IQR: Interquartile range

Table 2. Distribution of reoperations due to postoperative surgical complications and postoperative medical complications according to use of antidepressants. The frequency of each complication is related to the total number of reoperations or postoperative medical complications.

	Antidepressants				**Non-users**	
	Current user		Former user			
	n	%	n	%	n	%
Total	2,366		801		23,482	
Reoperation due postoperative surgical complications	349	(14.8)	112	(14.0)	3,226	(13.7)
Bleeding	26	(7.4)	7	(6.2)	238	(7.4)
Wound rupture	84	(24.1)	20	(18.9)	619	(19.2)
Ileus	36	(10.3)	15	(13.4)	348	(10.8)
Wound abscess	91	(26.1)	28	(25.0)	808	(25.0)
Intra-abdominal abscess	39	(11.2)	6	(5.4)	389	(12.1)
Stoma complications	21	(6.0)	9	(8.0)	252	(7.8)
Postoperative medical complications	373	(15.8)	85	(10.6)	2,388	(10.2)
Stroke	13	(3.5)	4	(4.7)	131	(5.5)
Acute myocardial infarction	50	(13.4)	13	(15.3)	373	(15.6)
Heart failure	57	(15.3)	17	(20.0)	273	(11.4)
Aspiration	30	(8.0)	8	(9.4)	175	(7.3)
Pneumonia	138	(37.0)	33	(38.8)	911	(38.2)
Respiratory failure	113	(30.3)	31	(36.5)	582	(24.4)
Renal failure	40	(10.7)	10	(11.8)	259	(10.8)
Sepsis	108	(29.0)	27	(31.8)	709	(29.7)
Deep venous thrombosis	4	(1.1)	-	-	28	(1.2)
Pulmonary embolism	9	(2.4)	-	-	68	(2.8)
Arterial embolism	-	-	-	-	19	(0.8)

Table 3. Frequency of events of quality indicators from Danish Colorectal Cancer Group Database and relative estimates comparing the quality of surgical care according to current, former, and non-use of antidepressants. Patients with unknown value for the quality indicators were excluded in the analyses.

	Total	Eligible	Indicator fulfilled	Crude OR (95% CI)	Adjusted OR (95% CI)*
	n	n	n (%)		
MDT conference					
Non-acute rectum cancer patients	8394	3,192			
Current user	640	223	204 (91.5)	0.98 (0.60; 1.60)	1.36 (0.80; 2.32)
Former user	223	97	86 (88.7)	0.71 (0.38; 1.35)	0.99 (0.49; 1.98)
Non-user	7,531	2,872	2,632 (91.6)	1.0 (ref.)	1.0 (ref.)
Surgical specialist					
Acute colon surgery	3,206	3,206			
Current user	386	386	219 (56.7)	0.97 (0.78; 1.20)	0.95 (0.76; 1.19)
Former user	104	104	60 (57.7)	1.01 (0.68; 1.50)	0.96 (0.64; 1.44)
Non-user	2,716	2,716	1,503 (57.4)	1.0 (ref.)	1.0 (ref.)
Elective colon surgery	14,165	14,165			
Current user	1,251	1,251	988 (79.0)	0.94 (0.82; 1.08)	1.01 (0.87; 1.17)
Former user	452	452	344 (76.1)	0.80 (0.64, 0.99)	0.80 (0.64; 1.01)
Non-user	12,462	12,462	9,967 (80.0)	1.0 (ref.)	1.0 (ref.)
Radical surgery					
Elective major surgery	17,647	17,197			
Current user	1,441	1,401	1,349 (96.3)	0.92 (0.69; 1.23)	0.88 (0.65; 1.18)
Former user	542	532	517 (97.2)	1.22 (0.73; 2.06)	1.17 (0.69; 1.98)
Non-user	15,664	15,264	14,741 (96.6)	1.0 (ref.)	1.0 (ref.)
Anastomosis leakage					
Elective colon surgery	13,114	13,109			
Current user	1,148	1,148	73 (6.4)	1.05 (0.82; 1.35)	1.16 (0.90; 1.49)
Former user	406	406	27 (6.6)	1.11 (0.74; 1.65)	1.22 (0.82; 1.82)
Non-user	11,560	11,555	699 (6.0)	1.0 (ref.)	1.0 (ref.)
Elective rectum surgery	4,086	4,085			
Current user	242	242	28 (11.6)	0.87 (0.58; 1.30)	0.96 (0.64; 1.45)
Former user	84	84	10 (11.9)	0.90 (0.46; 1.75)	1.01 (0.51; 1.97)
Non-user	3,760	3,759	492 (13.1)	1.0 (ref.)	1.0 (ref.)

MDT: multidisciplinary team

*Adjustments:

- MDT conference, surgical specialist, and radical surgery: age, gender, smoking, alcohol intake, BMI, somatic comorbidity, type of admission, cancer stage, surgical procedure, and hospital size
- Anastomosis leakage: age, gender, and cancer stage

Table 4a. Rates of ICU admissions within 0-30 days after colorectal cancer surgery for patients with current, former and non-use of antidepressants.

ICU admissions				
	Total	**ICU-admission**	**Crude HR (95% CI)**	**Adjusted HR (95% CI)***
	n	n (%)		
0-30 postoperative days	26,649	4,810 (18.2)		
Current user	2,366	580 (24.8)	1.47 (1.35; 1.60)	1.25 (1.14; 1.36)
Former user	801	162 (20.4)	1.18 (1.01; 1.38)	1.12 (0.96; 1.32)
Non-user	23,482	4,068 (17.4)	1.0 (ref.)	1.0 (ref.)

* Adjusted for age, gender, BMI, smoking status, alcohol intake, somatic comorbidity, type of admission, type of cancer, cancer stage, blood transfusion, surgical procedure, and hospital volume.

Table 4b. Frequencies of treatments in ICU for patients admitted to ICU within 0-30 days after surgery for colorectal cancer for patients according to current, former, or non-use of antidepressants.

Treatment during ICU admissions						
	ICU admissions	**Any treatment**	**NIV**	**Mechanical ventilation**	**Dialysis**	**Inotropes and/or vasopressors**
	n	n (%)	n (%)	n (%)	n (%)	n (%)
Total	4,810					
Current user	580	307 (52.9)	55 (9.5)	186 (32.1)	28 (4.8)	218 (37.6)
Former user	162	85 (52.5)	11 (6.8)	46 (28.4)	6 (3.7)	63 (38.9)
Non-user	4,068	1,908 (46.9)	283 (7.0)	1,222 (30.0)	208 (5.1)	1,445 (35.5)

NIV: non-invasive ventilation

Table 4c. Number and proportion fulfilling quality indicator of intensive care for patients admitted to ICU within 0-30 days after surgery for colorectal cancer and with discharge to ward in 2010-2012. Patients with missing value for the quality indicators were excluded from the analyses.

Quality of intensive care				
	Total	**Eligible**	**Indicator fulfilled**	**Crude OR (95% CI)**
	n	n	n (%)	
ICU-admissions (2010-2012)	1,292			
Readmission within 48 hours after discharge to ward				
Current user	163	163	6 (3.7)	1.18 (0.49; 2.85)
Former user	46	46	3 (6.5)	2.15 (0.64; 7.28)
Non-user	1,083	1,083	34 (3.1)	1.0 (ref.)
Nighttime discharge (10pm-8am) to ward				
Current user	163	154	11 (7.1)	0.85 (0.44; 1.64)
Former user	46	43	3 (7.0)	0.83 (0.25; 2.74)
Non-user	1,083	1,040	86 (8.3)	1.0 (ref.)

Table 5. 30-day mortality after colorectal cancer surgery according to current, former and non-use of antidepressants. Stratified analyses according to acute colon procedures, elective colon procedures, elective rectum procedure, cancer stage, Charlson Comorbidity Index (CCI), and for patients admitted to ICU

	Total, n	Deaths, n (%)	Crude HR (95% CI)	Adjusted HR (95% CI)*
Over-all	26,649	1,817 (6.8)		
Current user	2,366	274 (11.6)	1.90 (1.67; 2.16)	1.27 (1.11; 1.45)
Former user	801	74 (9.3)	1.49 (1.18; 1.89)	1.14 (0.90; 1.44)
Non-user	23,482	1,469 (6.3)	1.0 (ref.)	1.0 (ref.)
Acute colon	3,215			
Current user	387	107 (27.7)	1.60 (1.30; 1.97)	1.20 (0.96; 1.50)
Former user	105	23 (22.1)	1.20 (0.79; 1.82)	0.93 (0.60; 1.43)
Non-user	2,723	499 (18.4)	1.0 (ref.)	1.0 (ref.)
Elective colon	14,272			
Current user	1,267	105 (8.3)	1.77 (1.44; 2.17)	1.29 (1.04; 1.60)
Former user	456	29 (6.4)	1.34 (0.92; 1.95)	0.94 (0.65; 1.38)
Non-user	12,549	600 (4.8)	1.0 (ref.)	1.0 (ref.)
Elective rectum	8,099			
Current user	613	44 (7.2)	2.32 (1.68; 3.20)	1.53 (1.09; 2.16)
Former user	218	15 (6.9)	2.23 (1.32; 3.76)	1.94 (1.14; 3.29)
Non-user	7,268	228 (3.1)	1.0 (ref.)	1.0 (ref.)
Cancer stage (UICC)				
I	3,904			
Current user	321	15 (4.7)	1.84 (1.06; 3.17)	-
Former user	123	5 (4.1)	1.60 (0.65; 3.95)	-
Non-user	3,460	89 (2.6)	1.0 (ref.)	1.0 (ref.)
II	8,869			
Current user	793	81 (10.2)	2.08 (1.64; 2.65)	1.22 (0.95; 1.58)
Former user	286	21 (7.4)	1.48 (0.95; 2.30)	1.14 (0.73; 1.78)
Non-user	7,790	390 (5.0)	1.0 (ref.)	1.0 (ref.)
III	7,333			
Current user	601	54 (9.0)	2.04 (1.53; 2.73)	1.44 (1.06; 1.95)
Former user	211	16 (7.6)	1.72 (1.04; 2.85)	1.22 (0.73; 2.05)
Non-user	6,521	292 (4.5)	1.0 (ref.)	1.0 (ref.)
IV	5,498			
Current user	509	96 (18.9)	1.76 (1.42; 2.19)	1.35 (1.07; 1.69)
Former user	142	21 (14.8)	1.30 (0.84; 2.01)	0.93 (0.60; 1.46)
Non-user	4,847	549 (11.4)	1.0 (ref.)	1.0 (ref.)
Charlson Comorbidity Index				
Low (0)	13,979			
Current user	890	58 (6.5)	1.96 (1.49; 2.57)	1.55 (1.17; 2.05)
Former user	318	20 (6.3)	1.88 (1.20; 2.95)	1.49 (0.94; 2.34)
Non-user	12,771	431 (3.4)	1.0 (ref.)	1.0 (ref.)
Medium (1-2)	8,064			
Current user	933	128 (13.7)	1.74 (1.44; 2.11)	1.47 (1.20; 1.79)
Former user	304	34 (11.2)	1.40 (0.99; 1.99)	1.30 (0.91; 1.85)
Non-user	6,827	552 (8.1)	1.0 (ref.)	1.0 (ref.)
High (3+)	4,606			
Current user	543	88 (16.3)	1.34 (1.06; 1.68)	0.95 (0.75; 1.20)
Former user	179	20 (11.2)	0.88 (0.56; 1.38)	0.73 (0.47; 1.16)
Non-user	3,884	486 (12.6)	1.0 (ref.)	1.0 (ref.)
Patients admitted to ICU	4,714			
Current user	572	127 (22.2)	1.41 (1.17; 1.71)	1.22 (1.00; 1.49)
Former user	158	40 (25.4)	1.63 (1.18; 2.24)	1.52 (1.10; 2.11)
Non-user	3,984	649 (16.3)	1.0 (ref.)	1.0 (ref.)

* Adjusted for age group, gender, BMI, smoking, weekly alcohol intake, somatic comorbidity, type of admission, surgical procedure, type of cancer, and hospital size

Supplemental table 1a. Frequency and rates of ICU admissions at day of surgery (day 0), and 1-30 and 2-30 days after colorectal cancer surgery according to current, former, and non-use of antidepressants.

ICU admissions		
	Total	**ICU-admission**
	n	n (%)
Day 0	26,649	2,405 (9.0)
Current user	2,366	302 (12.8)
Former user	801	80 (10.0)
Non-user	23,482	2,023 (8.6)
Day 1-30	24,213	2,405 (10.0)
Current user	2,060	278 (13.8)
Former user	721	82 (11.5)
Non-user	21,432	2,045 (9.6)
Day 2-30	23,343	1,600 (7.0)
Current user	1,947	174 (9.2)
Former user	696	58 (8.5)
Non-user	20,700	1,368 (6.7)

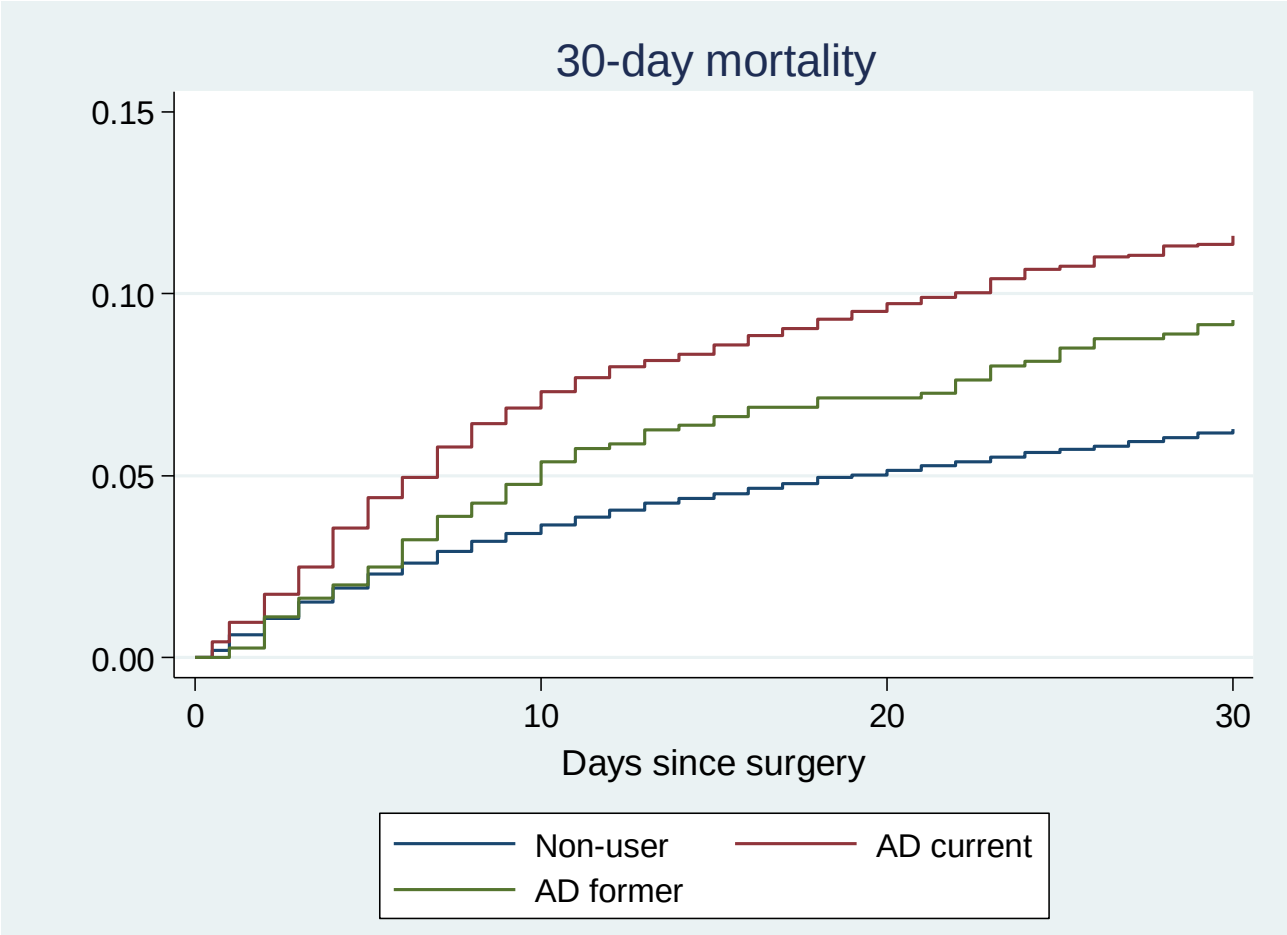
Supplemental table 1b. Frequencies of treatment during ICU admissions at day of surgery (day 0), and 1-30 and 2-30 days after colorectal cancer surgery according to current, former, and non-use of antidepressants.

Treatment during ICU admissions						
	ICU admissions	**Any treatment**	**NIV**	**Mechanical ventilation**	**Dialysis**	**Inotropes and/or vasopressors**
	n	n (%)	n (%)	n (%)	n (%)	n (%)
Day 0	2,405					
Current user	302	153 (50.7)	17 (5.6)	89 (29.5)	5 (1.7)	111 (36.8)
Former user	80	33 (41.2)	-	17 (21.2)	-	23 (28.8)
Non-user	2,023	787 (38.9)	66 (3.3)	430 (21.3)	35 (1.7)	606 (30.0)
1-30 days	2,405					
Current user	278	154 (55.4)	38 (13.7)	97 (34.9)	23 (8.3)	107 (38.5)
Former user	82	52 (63.4)	9 (11.0)	29 (35.4)	4 (4.9)	40 (48.8)
Non-user	2,049	1,121 (54.7)	217 (10.6)	792 (38.6)	173 (8.4)	839 (41.0)
2-30 days	1,600					
Current user	174	118 (67.8)	33 (19.0)	77 (44.2)	22 (12.6)	82 (47.1)
Former user	58	41 (70.7)	9 (15.5)	24 (41.4)	4 (6.9)	32 (55.2)
Non-user	1,368	885 (64.5)	186 (13.6)	667 (48.6)	154 (11.2)	660 (48.1)

NIV: non-invasive ventilation

FIGURES

Figure 1. Kaplan-Meier curve (1 – Kaplan-Meier estimate) for overall 30-day mortality



APPENDIX
Surgical procedures

Major surgical procedure	Rectal resection
	Rectal resection with colostomy
	Abdominoperineal resection (APR) a.m. Holm
	Abdominoperineal resection (APR) conventional
	Ileocecal resection
	Right hemicolectomy
	Transverse colectomy
	Left hemicolectomy
	Sigmoidectomy
	Sigmoidectomy with colostomy
	Other resection of colon and small intestine
	Colectomy and ileorectostomy
	Colectomy and ileostomy
	Proctocolectomy and ileostomy
Minor surgical procedure	Temporary ileostomy or internal shunt (only)
	Exploratory surgery (only)
	Transanal endoscopic microsurgery (TEM)
	Other local resections, incl. polyp removal/endoscopic mucosal resection (EMR)
	Rectal stent
	Colonic stent
Unknown	Unknown

Definitions of surgical quality indicators from the Danish Colorectal Cancer Group Database

Quality indicator	Inclusion	Exclusion
Multidisciplinary team (MDT) conference	Cancer site: rectum Type of admission: all, except acute	Missing status of MDT conference
Surgical specialist – acute colon surgery	Cancer site: colon Surgical procedure: all except other local resections Type of admission: acute	Missing status of surgical specialist
Surgical specialist – elective colon surgery	Cancer site: colon Surgical procedure: all except other local resections Type of admission: elective	Missing status of surgical specialist
Radical after elective surgery	Surgical procedure: all except temporary ileostomy or internal shunt (only), exploratory surgery (only), transanal endoscopic microsurgery (TEM), other local resections, rectal stent, colonic stent Cancer stage (UICC): I, II, III Type of admission: elective Intension of treatment: curative	Missing status of radical surgery
Anastomosis leakage – elective colon surgery	Cancer site: colon Surgical procedure: ileocecal resection, right hemicolectomy, transverse colectomy, left hemicolectomy, Sigmoidectomy, other resection of colon and small intestine, colectomy and ileorectostomy, rectal resection, temporary ileostomy or internal shunt (only) Type of admission: elective	Missing status of anastomosis leakage
Anastomosis leakage – elective rectum surgery	Cancer site: rectum Surgical procedure: rectal resection Type of admission: elective	Missing status of anastomosis leakage

Definitions of intensive care quality indicators from the Danish Intensive Care Database

The study period is restricted to January 1 2010 to December 31 2012 due to implementation of the quality indicators in 2009.

Quality indicator	Inclusion	Exclusion
Readmission within 48 hours after discharge from ICU	Discharge destination: transferred to ward, transferred to ward due to capacity problems at ICU	Missing status of discharge destination
Nighttime discharge	Discharge destination: transferred to ward, transferred to ward due to capacity problems at ICU	Missing status of nighttime discharge

Comorbidity

Charlson Comorbidity Index			
Charlson comorbidity category	**ICD-10**	**ATC-code**	**Charlson Score**
Myocardial infarction	I21; I22; I23		1
Congestive heart failure	I50; I11.0; I13.0; I13.2		1
Peripheral vascular disease	I70; I71; I72; I73; I74; I77		1
Cerebrovascular disease	I60-69; G45; G46		1
Dementia	F00-03; F05.1; G30		1
Chronic pulmonary disease	J40-47; J60-67; J68.4; J70.1; J70.3; J84.1; J92.0; J 98.2; J 98.3	R03	1
Connective tissue disease	M06; M08; M09; M30; M31; M32; M33; M34; M35; M36; D86		1
Ulcer disease	K22.1; K25-28		1
Mild liver disease	B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0		1
Diabetes	E10.0; E10.1; E10.9; E11.0; E11.1; E11.0; E12.0; E12.1; E12.0; E13.0; E13.1; E13.9; E14.0; E14.1; E14.9; O24 (except O24.4)	A10A; A10B	1
Hemiplegia	G81; G82		1
Moderate to severe renal disease	I12; I13; N00-05; N07; N11; N14; N17.19; Q61		2
Diabetes with end organ damage	E10.2-E10.8; E11.2-E11.8; E12.2-E12.8; E13.2-E13.8; E14.2-E14.8; G63.2; H36.0; N08.3		2
Any tumor (non-metastatic)	C00-75 (except C18-C20)		2
Leukemia	C91-95		2
Lymphoma	C81-C85; C88; C90; C96		2
Moderate to severe liver disease	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85		3
Metastatic solid tumor	C76-C80 (except C78.5)		6
AIDS	B21-B24		6
Additional comorbidity	**ICD-10**	**ATC-code**	
Alcohol-related disease	F10 (except F10.0); K86.0; K70.0; K29.2; G62.1; G72.1; G31.2; I42.6; Z72.1	N07BB01	

Classification of each somatic comorbidity condition for adjustments

Each somatic condition	Disease(s) from Charlson and additional comorbidity
Myocardial infarction	Myocardial infarction
Congestive heart failure	Congestive heart failure
Peripheral vascular disease	Peripheral vascular disease
Stroke	Cerebrovascular disease
	Hemiplegia
Dementia	Dementia
Chronic pulmonary disease	Chronic pulmonary disease
Liver disease	Mild liver disease
	Moderate to severe liver disease
	Alcohol-related disease
Diabetes	Diabetes
	Diabetes with end organ damage
Moderate to severe renal disease	Moderate to severe renal disease
Solid tumor (except colon and rectum)	Any tumor (non-metastatic)
	Leukemia
	Lymphoma
Metastatic solid tumor (except colon and rectum)	Metastatic solid tumor