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Depression and Risk for Hospitalizations and Rehospitalizations for Ambulatory Care-Sensitive Conditions in Denmark: a Population-Based Cohort Study

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Guarantor: Dr. Vestergaard has had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Data Sharing: Requests for analyses of de-identified data from this study should be directed to Mogens Vestergaard (email: mv@ph.au.dk).

ABSTRACT

Objective: Hospitalizations for ambulatory care-sensitive conditions (ACSCs) and early rehospitalizations are common and costly. We sought to determine whether individuals with depression are at increased risk for hospitalizations for ACSCs, and rehospitalization for the same or another ACSC, within 30 days.

Design: National, population-based cohort study.

Setting: Denmark.

Participants: 5,049,353 individuals ≥ 18 years old between January 1, 2005 and December 31, 2013.

Measurements: Depression was ascertained via psychiatrist diagnoses in the Danish Psychiatric Central Register or antidepressant prescription redemption from the Danish National Prescription Registry. Hospitalizations for ACSCs and rehospitalizations within 30 days were identified using the Danish National Patient Register.

Results: Overall, individuals with depression were 2.35-times more likely to be hospitalized for an ACSC (95% Confidence Interval [95%CI]: 2.32, 2.37) versus those without depression after adjusting for age, sex, and calendar period, and 1.45-times more likely after adjusting for socioeconomic factors, comorbidities, and primary care utilization (95%CI: 1.43, 1.46). After adjusting for ACSC-predisposing comorbidity, depression was associated with significantly greater risk for hospitalizations for all chronic (e.g., angina, diabetes complications, congestive heart failure exacerbation) and acute ACSCs (e.g., pneumonia) compared to those without depression. Compared to those without depression, persons with depression were 1.21-times more likely to be rehospitalized within 30 days for the same ACSC (95%CI: 1.18, 1.24) and

1.19-times more likely to be rehospitalized within 30 days for a different ACSC (95%CI: 1.15, 1.23).

Conclusions: Individuals with depression are at increased risk for hospitalizations for ACSCs, and once discharged are at elevated risk for rehospitalizations within 30 days for ACSCs.

ARTICLE SUMMARY

- A strength of our study is that we followed a nationwide, population-based cohort with nearly no loss to follow-up.
- Our use of data from a country with a national healthcare system with universal access to health care and a relatively homogeneous population may impact generalizability to other countries with more ethnically diverse populations and different healthcare settings.
- Although we lack data on potential mediators of an association between depression and ambulatory care-sensitive condition (ACSC)-related hospitalizations such as health-risk behaviors (e.g., smoking, sedentary lifestyle), previous studies that controlled for health-risk behaviors found that the association between depression and greater risk for ACSC-related hospitalizations was independent of these factors.
- Our data lacks the degree of detail required to determine if adequate treatment for depression could moderate the adverse outcomes seen here.

INTRODUCTION

Hospitalizations for chronic illnesses and their sequelae are a major contributor to rising healthcare costs in Western societies.[1] In the U.S., an estimated 10% of all hospitalizations may be preventable,[2] such as those for ambulatory care-sensitive conditions (ACSCs), a set of chronic and acute illnesses considered not to require inpatient treatment if patients receive timely and appropriate ambulatory care.[3] Hospitalizations for ACSCs have been estimated to cost the U.S. $31.9 billion and £1.4 billion in the U.K. annually.[4,5] Moreover, early rehospitalizations, some of which may be due to ACSCs, are common and costly to health systems.[6] With the advent of accountable care organizations in the U.S. and other efforts to improve healthcare delivery worldwide, health systems are increasingly trying to prevent hospitalizations for ACSCs and early rehospitalizations in an effort to reduce healthcare spending.[7-9]

Depression is highly prevalent worldwide,[10] and is independently associated with more chronic disease sequelae,[11] greater healthcare costs,[12] and increased mortality.[13] Importantly, depression is amenable to treatment and could be a potentially modifiable risk factor for ACSC-related hospitalizations. Depression may increase hospitalizations for ACSCs through factors such as reduced adherence to chronic disease treatments and reduced self-care.[14] While prior studies have found higher risk of hospitalizations for ACSCs and/or early rehospitalizations among persons with depression, they have been limited to single centers,[15,16] specific chronic disease populations,[17] geographically-defined health systems,[16,17] and older adults.[18] Furthermore, previous research on depression and risk of rehospitalizations within 30 days has not focused on potentially preventable rehospitalizations,[15,16,18,19] such as rehospitalizations within 30 days for an ACSC, an outcome that is arguably of particular importance to health systems and health policy makers. Also, it remains unknown whether depressed individuals are

at greater risk of ACSC-related hospitalizations and rehospitalizations simply because they are more likely to have underlying chronic diseases.[20,21]

Utilizing data from a population-based cohort of five million Danish adults, we sought to determine if individuals with depression are at increased risk for hospitalizations for ACSCs after adjusting for demographics, socioeconomic factors, comorbidity (ACSC-predisposing and non-ACSC-predisposing comorbidity), and primary care utilization. Further, we examined whether persons with depression who have been hospitalized for an ACSC are at greater risk for rehospitalization for the same, or another ACSC, within 30 days. We hypothesized that depression would be independently associated with increased risk for hospitalizations for ACSCs as well as rehospitalizations within 30 days for either the same or a different ACSC.

METHODS

Population

We conducted a population-based cohort study of all adults ≥ 18 years old, alive and residing in Denmark at least one day between January 1, 2005 and December 31, 2013. The cohort was constructed using data from the Danish Civil Registration System,[22] which includes data on sex, date of birth, vital status, and emigration since January 1, 1968. In the register, Danish residents are each assigned a unique personal identification number which links to person-level data.[22]

The Danish Data Protection Agency and the Danish Health and Medicine Authority approved the study protocol, and requirement for informed consent was waived.

Primary Independent Variable

Our primary independent variable of interest was depression as identified by either psychiatric diagnosis or filling at least one antidepressant prescription. Depression was treated as a time-dependent variable (i.e., an individual without a recorded depression diagnosis or antidepressant prescription redemption at baseline could be diagnosed with depression or redeem an antidepressant prescription during the follow-up period, moving from the "unexposed" to the "exposed" group). Information on psychiatric diagnoses was obtained from the Danish Psychiatric Central Register[23] (see Appendix 1), which includes diagnostic information on all psychiatric hospitalizations from 1969 onwards and outpatient specialty mental health visits from 1995 onwards.[23] Prescription fills for antidepressant prescriptions (i.e. selective serotonin re-uptake inhibitors, monoamine oxidase inhibitors, and other non-tricyclic (TCA) antidepressants, see Appendix 1) were identified using the Danish National Prescription Registry.[24] This register includes data on all prescriptions dispensed at Danish pharmacies since 1995, including purchase date and classification of drugs according to the Anatomical Therapeutic Chemical Classification.[25] We excluded TCA prescriptions from our depression definition because of their frequent use for insomnia and/or pain. We also excluded bupropion or trazodone prescriptions since neither was approved for treating depression in Denmark during the study period. Individuals with schizophrenia, schizoaffective disorders or bipolar disorder were censored at date of diagnosis (see Appendix 2) and excluded from analyses.

Outcomes of Interest

Our primary outcome of interest was hospitalization for one of 12 ACSCs as defined by the Agency for Healthcare Research and Quality (AHRQ) (see Appendix 3).[2] Prior to December 31, 1993, register-based diagnoses were based on the Danish version of the International Classification of Diseases, 8th Revision (ICD-8).[26] From January 1, 1994 forward, the Danish

version of the ICD-10[27] was used. Since the AHRQ-defined ACSCs were originally derived using ICD-9 diagnoses, we included eight AHRQ-defined ACSCs (i.e., angina without concomitant cardiovascular procedures, chronic obstructive pulmonary disease (COPD) exacerbation, congestive heart failure (CHF) exacerbation, diabetes with short-term complications, diabetes with long-term complications, uncontrolled diabetes, hypertension (HTN), and appendicitis with perforation) that were translated into ICD-10 diagnosis codes and validated in a previous study.[28] We also included four AHRQ-defined ACSCs (i.e., bacterial pneumonia, diabetes-related lower extremity amputations, urinary tract infections (UTIs), and adult asthma exacerbations) based on ICD-10 codes used in prior Danish register-based studies.[29-32] We further divided ACSCs into five "chronic" ACSCs (i.e., angina, CHF exacerbation, HTN, diabetes-related, COPD/adult asthma exacerbation) and three "acute" ACSCs (i.e., appendicitis with perforation, pneumonia, and UTI). We used the Danish National Patient Register,[33] which contains information on all medical hospitalizations since January 1, 1977 and outpatient visits since January 1, 1995,[33] to obtain information on hospitalizations with principal discharge diagnoses for ACSCs occurring between January 1, 2005 and December 31, 2013. If a discharge was followed by an admission within one day, it was considered a transfer and counted as one admission only. We excluded hospitalizations with secondary obstetric diagnoses (ICD-10 codes: O00.0-O99.9).

Our secondary outcome of interest was rehospitalization for an ACSC within 30 days of discharge from the initial ACSC-related hospitalization. We counted rehospitalizations that were for the same ACSC, or for a different ACSC, using data from the Danish National Patient Register.

Socioeconomic Factors, Comorbid Medical Conditions, and Substance Abuse Disorders

Information on marital/partnered status and education was obtained from Statistics Denmark and the Danish Educational Registers, respectively (see Appendix 4).[34,35] We categorized marital/partnered status as living with a partner (i.e., married, registered partnership, or cohabitation) or living alone (i.e., living without a partner, including widows/widowers). We classified maximum educational level attained into the following three categories based on the United Nations Educational, Scientific and Cultural Organization's International Standard Classification of Education: low (<10 years), middle (10–15 years), and high (>15 years).[36]

For the five chronic ACSCs, we defined ACSC-predisposing medical comorbidity specific for each ACSC in question (see Appendix 5). Information on ACSC-predisposing medical comorbidity and non-ACSC predisposing medical comorbidity was obtained from the Danish National Patient Register and based on Charlson Comorbidity Index (CCI) categories[37] (see Appendix 6) (e.g., myocardial infarction as ACSC-predisposing medical comorbidity for angina hospitalization, etc.), with two exceptions. Diabetes diagnoses were obtained from the Danish National Diabetes Register between January 1, 1990 and December 31, 2013 (see Appendix 7).[38] Chronic pulmonary disease was identified as either a diagnosis based on the CCI category obtained from the Danish National Patient Register or ≥ two prescription redemptions within a six month period for medications treating obstructive airway diseases (see Appendix 8) as obtained from the Danish National Prescription Registry. Non-ACSC predisposing medical comorbidity included all remaining CCI diagnostic categories. We did not define ACSC-predisposing medical comorbidity for the three acute ACSCs.

Data on substance abuse (excluding tobacco abuse) was obtained from the Danish Psychiatric Central Register or the Danish National Patient Register (see Appendix 9).

Primary Care Utilization

We obtained information on day-time face-to-face visits with primary care physicians (PCPs) or other primary care staff from the Danish National Health Service Register,[39] which has been collecting primary care administrative data since January 1, 1990. To reduce the chances of including a primary care visit that directly resulted in an ACSC-related hospitalization, we constructed a time-dependent variable counting the number of primary care visits from 10-375 days before any given day. We categorized primary care visits into three equally-sized categories of low, medium, or high utilization based on observed frequencies (i.e., 0-2, 3-9 or ≥10 visits).

Statistical Analysis

We compared individuals with depression to those without depression using Poisson regression models in order to estimate incidence rate ratios (IRRs) for hospitalizations for ACSCs and subsequent rehospitalization within 30 days for an ACSC. We estimated corresponding 95% Confidence Intervals (95%CIs) using cluster robust variance estimation to account for interperson correlation and dichotomy of rehospitalization. In these analyses, our outcomes of interest were a count of the number of hospitalizations for ACSCs. Age and calendar period were adjusted for using two-year and one-year age and time bands, respectively. All variables (including depression status), except sex, were treated as time-dependent. Individuals contributed at-risk time from January 1, 2005 or from their 18th birthday, whichever came last, and were censored at date of death, emigration, date of bipolar disorder or schizophrenia diagnosis, or on December 31, 2013, whichever came first.

For each ACSC-related hospitalization outcome, we fitted five risk models, adjusting sequentially for demographics (i.e., age, sex and calendar period), socioeconomic factors (i.e., marital/partnered status and education), ACSC-predisposing medical comorbidity (with each comorbid condition entered individually), other comorbidity (i.e., non-ACSC-predisposing

medical comorbidity entered individually and substance abuse), and primary care utilization. All model covariates were chosen *a priori* based on prior studies identifying their potential associations with both depression and healthcare utilization outcomes.[12,16,17,40] To address missing data on education, we conducted multiple imputation using five imputed data sets according to methods developed by Rubin.[41]

We performed two pre-specified sub-analyses. First, we examined whether the association between depression and risk for ACSC-related hospitalizations was modified by age. To do so, we repeated our Poisson regressions stratified by three age categories: ≤ 40 years old, 41-64 years old, and ≥ 65 years old. Second, we examined the associated risk for hospitalizations for chronic and acute ACSCs based on time since depression diagnosis in models adjusted for demographics.

In order to determine if an association between depression and risk for hospitalizations for ACSCs was impacted by our depression definition, we performed a pre-specified sensitivity analysis in which we repeated our regressions using three different depression definitions: antidepressant prescription alone, outpatient psychiatric visit-based diagnosis alone or psychiatric hospitalization for depression.

We fitted three models examining risk for rehospitalization within 30 days for an ACSC. The first model adjusted for demographics, the second included adjustment for socioeconomic factors and the third for medical and substance abuse comorbidities. Our outcome of interest in these models was time to rehospitalization for an ACSC within 30 days of discharge from the initial ACSC-related hospitalization. Individuals were at risk for the outcome on the day of discharge from their ACSC-related hospitalization. All variables in these analyses excluding sex were treated as time-dependent.

We used two-sided significance tests for all analyses with statistical significance set at $P < 0.05$. Analyses were performed using STATA 13 (Stata Corporation, College Station, TX).

RESULTS

We followed a cohort of 5,049,353 individuals for a total of 38,674,363 person-years at risk, including 1,319,896 (26.1%) persons diagnosed with depression or who had redeemed an antidepressant prescription during the study period. Of those with depression, 1,182,495 (89.6%) cases were from antidepressant prescription fills while 137,401 (10.4%) cases were diagnosed by mental health specialists in outpatient or inpatient contacts. The mean age at initially registered depression diagnosis was 49.1 (standard deviation: 19.2) years old.

Table 1 displays the characteristics of our cohort by depression status. During the nine year follow-up period, we identified 1,255,640 hospitalizations for ACSCs, including 542,184 (43.2%) among persons with depression. There were 71.4 ACSC-related hospitalizations per 1,000 person-years among those with depression versus 23.0 per 1,000 person-years among those without depression during the study period.

[Please insert Table 1 here]

Compared to those without depression, the IRR for having any ACSC-related hospitalization was 2.35 (95% CI: 2.32, 2.37) for individuals with depression after adjusting for demographics. This association remained robust after adjusting for socioeconomic factors, and decreased though remained significant after adjusting for possible mediators including comorbidities and PCP visits during the previous year (Table 2).

In comparison to persons without depression, depression was associated with increased risk for hospitalizations for all of the chronic ACSCs even after adjusting for specific chronic

ACSC-predisposing medical comorbidity (Table 2), particularly for hospitalizations for angina (IRR: 1.77; 95%CI: 1.73, 1.81), COPD/asthma exacerbations (IRR: 1.88; 95%CI: 1.84, 1.93), and diabetes-related hospitalizations (IRR: 1.83; 95%CI: 1.77, 1.89). Although these results were attenuated by adjusting for additional comorbidity and PCP visits during the previous year, depression remained independently associated with increased risk for hospitalizations for all chronic ACSCs, especially for hospitalizations for COPD/asthma exacerbations (IRR: 1.61; 95%CI: 1.57, 1.65), and diabetes-related hospitalizations (IRR: 1.69; 95%CI: 1.63, 1.75) (Table 2).

Similarly, depression was associated with increased risk for hospitalizations for all three acute ACSCs even after adjusting for medical and substance abuse comorbidity (appendicitis with perforation: IRR: 1.26; 95%CI: 1.21, 1.33; pneumonia: IRR: 1.55; 95%CI: 1.53, 1.56; UTI: 1.74; 95%CI: 1.71, 1.77). These associations remained significant after adjusting for PCP visits during the preceding year.

[Please insert Table 2 here]

When we stratified by age categories, we found that the association between depression and risk for hospitalizations for ACSCs was especially potent for individuals 40 years old or younger (IRR: 2.06; 1.98, 2.13). Depression was also independently associated with increased risk for hospitalizations for ACSCs among middle-aged and older adults (Table 3).

[Please insert Table 3 here]

In the first year after depression diagnosis, the associated risk for hospitalization for a chronic ACSC was nearly 3-times greater than those without depression (IRR: 2.89; 95%CI: 2.83, 2.96) (Figure 1). The associated risk remained nearly 2.4-times greater than for those without depression (IRR: 2.39, 95%CI: 2.34, 2.43) 10 or more years after depression diagnosis.

During the first year after depression diagnosis, the associated risk for hospitalization for an acute ACSC was 3 1/3-times greater than for those without depression (IRR: 3.33, 95%CI: 3.27, 3.40), and the associated risk remained 2 ¼-times higher at ≥ 10 years after depression diagnosis (IRR: 2.25; 95%CI: 2.22, 2.29) (Figure 2).

[Please insert Figure 1 here]

[Please insert Figure 2 here]

In our sensitivity analysis in which we examined whether our results regarding risk for hospitalization for any ACSC were impacted by depression definition, we found that depression defined by antidepressant prescription alone (IRR: 2.31; 95%CI: 2.28, 2.33), outpatient psychiatric visit-based diagnosis alone (IRR: 2.66; 95%CI: 2.56, 2.77) or psychiatric hospitalization for depression (IRR: 2.69; 95%CI: 2.62, 2.77) were all associated increased risk for hospitalization for an ACSC after adjusting for demographics. These associations remained significant after adjusting for socioeconomic factors, comorbidities, and PCP visits in the previous year (antidepressant prescription alone: IRR: 1.44; 95%CI: 1.43, 1.45; outpatient psychiatric visit-based diagnosis: IRR: 1.54; 95%CI: 1.48, 1.60; psychiatric hospitalization for depression: IRR: 1.50; 95%CI: 1.46, 1.54).

Approximately 6.8% of all ACSC-related hospitalizations during the follow-up period were followed by an ACSC-related rehospitalization within 30 days, of which 73.0% were for the same ACSC and 27.0% were for a different ACSC. Of the 85,046 ACSC-related rehospitalizations within 30 days, 42,791 (50.3%) were among those with depression. Compared to those without depression, depression was associated with 1.36-times greater risk for rehospitalization within 30 days for the same ACSC (95%CI: 1.32, 1.39) and 1.44-times greater risk for rehospitalization within 30 days for a different ACSC (95%CI: 1.39, 1.49) after adjusting

for age, sex, and calendar period (Table 4). After adjusting for socioeconomic factors and comorbidities, while attenuated, depression remained independently associated with greater risk for rehospitalization within 30 days for the same ACSC (IRR: 1.21; 95%CI: 1.18, 1.24) or another ACSC (IRR: 1.19; 95%CI: 1.15, 1.23).

[Please insert Table 4 here]

DISCUSSION

In this nationwide, population-based longitudinal study of over 5 million individuals, we found that depression was independently associated with higher risk for hospitalizations for both chronic and acute ACSCs and that the associated risk remained high for at least 10 years. To our knowledge, the present study is the first to show that depression was associated with higher risk of rehospitalization for the same or another ACSC within 30 days of an ACSC-related hospitalization. Importantly, we identified that the associated risk of hospitalizations for ACSCs was greater among persons with depression even when we adjusted for the higher prevalence of predisposing chronic diseases in this population.

An increased risk of hospitalization and subsequent rehospitalization for an ACSC among depressed individuals is troubling in light of evidence that some ACSC-related hospitalizations may have negative effects on long-term functioning, cognition and mental health.[42] Depression in-and-of-itself is known to increase the risk of cognitive decline and functional impairment,[43,44] both of which increase risk of ACSC-related hospitalizations.[18,45] Therefore, depressed individuals could be especially at risk for a vicious cycle of hospitalizations, rehospitalizations, and rapid decline.

This study has important implications for development of interventions to prevent costly ACSC-related hospitalizations and rehospitalizations. A potential explanation for our findings is that depressed individuals may not receive timely and/or appropriate ambulatory care for chronic diseases such as diabetes or cardiovascular disease as well as acute diseases such as pneumonia or UTIs. Yet, we found that depression was independently associated with increased risk for hospitalizations for these conditions even in a country, Denmark, with universal access to primary care. Therefore, it could be reasonable to conclude that simply increasing access to primary care may not ameliorate these problems. This interpretation is supported by recent studies evaluating the impact of health care reform in Massachusetts that found improving access to care was not associated with reductions in ACSC-related hospitalizations or rehospitalizations within 30 days among high-risk populations.[46,47]

If expanding access to primary care by itself is insufficient to prevent hospitalizations for ACSCs among at-risk populations such as those with depression, then additional research is needed to identify cost-effective interventions that could reduce these potentially preventable events. One possibility is through ongoing efforts to integrate psychiatric care into primary care and other ambulatory care medical settings. Collaborative care for depression and comorbid conditions in primary care settings has been proven effective and cost-effective,[48-53] and its cost-effectiveness is in part due to reductions in hospitalizations for comorbid medical conditions.[54] Further studies of sufficient duration and size are needed to determine if collaborative care could prevent ACSC-related hospitalizations among individuals with depression. More research is also needed to ascertain if integrating aspects of collaborative care into existing interventions focusing on improving transitional care from the hospital back to primary care[55,56] could prevent early rehospitalizations for ACSCs. Such research would be of particular interest to accountable

care organizations and health policy makers aiming to reduce healthcare costs while simultaneously improving patient outcomes and overall quality of care.

Our study has several strengths and limitations. We followed a nationwide, population-based cohort with nearly no loss to follow-up. However, our use of data from a country with a national healthcare system with universal access to health care and a relatively homogeneous population may impact generalizability. Yet, these factors may enhance internal validity by decreasing the degree socioeconomic factors play in healthcare-seeking behavior, and potentially suggest that our estimates may be overly conservative. Further, our depression definition was based on a combination of psychiatric diagnoses and antidepressant prescription records, potentially introducing selection bias since patients with more severe depression are more likely to be prescribed antidepressants and/or referred to psychiatrists,[57,58] and is further exacerbated by inability to capture depressed individuals who have not sought treatment.[59] However, our sensitivity analysis examining different depression definitions did not yield differing results, and our primary depression definition has been used in prior related research.[43]

While we lack data on potential mediators of an association between depression and ACSC-related hospitalizations such as health-risk behaviors (e.g., smoking, sedentary lifestyle), previous studies in this area that controlled for health-risk behaviors found that the association between depression and greater risk for ACSC-related hospitalizations was independent of these factors.[17,18] Our data lacks the degree of detail required to determine if adequate treatment for depression could moderate the adverse outcomes seen here. Also, the registers lack detail to sufficiently ascertain illness severity, so we cannot fully exclude the possibility that our findings reflect that when compared to the general population, depressed individuals may present with

higher acuity of medical illnesses and a greater burden of comorbidity, necessitating hospitalization for optimal treatment.

In conclusion, in a nationwide study in Denmark, we found that compared to individuals without depression, depression was associated with increased risk for hospitalizations for ACSCs. Furthermore, once hospitalized for an ACSC, depression was associated with greater risk for rehospitalization within 30 days for the same, or another, ACSC. Further research that clarifies the mechanisms linking depression and ACSC-related hospitalizations, and that develops interventions that prevent ACSC-related hospitalizations in persons with depression, is needed given the burden that recurrent hospitalizations places on individuals and society.

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Table 1. Study cohort characteristics

Measure	Depression (n = 1,319,896)			Without Depression (n = 3,782,713)		
	Number of Hospitalizations for ACSCs	Person-Years at Risk	Percentage risk time spent in category (%)	Number of Hospitalizations for ACSCs	Person-Years at Risk	Percentage risk time spent in category (%)
Total	542,184	7,596,536	100.0	713,456	31,077,828	100.0
Age (years)						
≤ 40	28,434	1,771,769	23.3	69,350	11,940,484	38.4
41-64	158,633	3,697,843	48.7	197,925	13,201,867	42.5
≥ 65	355,117	2,126,924	28.0	446,181	5,935,477	19.1
Sex						
Male	231,216	2,884,303	38.0	393,065	16,114,603	51.8
Female	310,968	4,712,233	62.0	320,391	14,963,225	48.2
Calendar period						
2005	47,853	661,461	8.7	79,756	3,564,097	11.5
2006	57,932	711,984	9.4	90,186	3,523,904	11.3
2007	46,477	761,231	10.0	67,588	3,494,327	11.2
2008	51,896	805,396	10.6	71,465	3,475,920	11.2
2009	63,150	848,956	11.2	83,274	3,452,336	11.1
2010	51,567	895,574	11.8	64,832	3,425,594	11.0
2011	74,991	938,720	12.4	89,372	3,405,029	11.0
2012	74,535	972,971	12.8	85,424	3,378,860	10.9
2013	73,783	1,000,243	13.2	81,559	3,358,761	10.8
Marital status						
Living with partner	226,573	3,585,166	47.2	348,530	15,922,753	51.2
Living alone	315,611	4,011,370	52.8	364,926	15,155,075	48.8
Education (years)						
< 10	265,781	2,751,794	36.2	312,769	8,845,177	28.5

10-15	178,680	3,182,588	41.9	249,363	14,267,047	45.9
≥ 16	47,039	1,284,597	16.9	75,866	6,318,611	20.3
Missing	50,684	377,558	5.0	75,458	1,646,993	5.3
Comorbidity						
MI	89,475	261,404	3.4	109,123	556,446	1.8
CHF	118,101	212,889	2.8	137,507	367,223	1.2
Diabetes	155,739	761,878	10.0	165,161	1,567,720	5.0
Cerebrovascular disease	126,796	615,389	8.1	98,828	834,803	2.7
Peripheral vascular disease	79,566	283,055	3.7	70,493	443,853	1.4
Chronic pulmonary disease	229,594	674,995	8.9	208,423	1,339,308	4.3
Dementia	44,638	217,259	2.9	19,519	110,040	0.3
Connective tissue disease	42,814	269,168	3.5	39,087	514,840	1.7
Peptic ulcer disease	69,733	327,298	4.3	53,974	464,831	1.5
Renal disease	45,769	123,767	1.6	50,315	245,853	0.8
Mild liver disease	19,437	129,645	1.7	11,845	159,553	0.5
Moderate/severe liver disease	5,287	27,978	0.4	3,516	34,556	0.1
Paraplegia	7,123	31,836	0.4	4,893	46,060	0.1
Cancer	102,324	608,120	8.0	118,072	1,430,995	4.6
Metastatic carcinoma	12,338	58,013	0.8	13,715	116,930	0.4
HIV/AIDS	1,011	10,673	0.1	998	22,685	0.1
Substance abuse disorders	87,977	792,810	10.4	42,932	881,074	2.8
Primary care visits in prior year						
0-2	119,055	2,487,888	32.7	196,845	17,355,110	55.8
3-9	223,859	3,739,020	49.2	317,381	11,687,211	37.6
≥ 10	199,270	1,369,628	18.0	199,230	2,035,670	6.5

Abbreviations (in alphabetical order): ACSC = ambulatory care-sensitive condition; AIDS = Acquired Immunodeficiency Syndrome; CHF = congestive heart failure; HIV = Human Immunodeficiency Virus; MI = myocardial infarction.

Table 2. The risk of hospitalizations for ambulatory care-sensitive conditions associated with depression compared to individuals without depression

Outcome	Model 1 Adjusted for demographics[a]	Model 2 Adjusted for variables in Model 1 and socioeconomic factors[b]	Model 3 Adjusted for variables in Model 2 and ACSC-predisposing comorbidity	Model 4 Adjusted for variables in Model 3 and non-ACSC-predisposing comorbidity[h] and substance abuse disorders	Model 5 Adjusted for variables in Model 4 and PCP visits in the previous year
	Incidence Rate Ratio (95% Confidence Interval)				
Any ACSC	2.35 (2.32, 2.37)[‡]	2.27 (2.25, 2.29)[‡]		1.53 (1.51, 1.54)[‡]	1.45 (1.43, 1.46)[‡]
Type of ACSC					
Chronic ACSCs					
Angina	2.03 (1.99, 2.08)[‡]	2.00 (1.96, 2.05)[‡]	1.77 (1.73, 1.81)[c‡]	1.52 (1.49, 1.56)[‡]	1.35 (1.32, 1.38)[‡]
COPD/Asthma exacerbation	3.17 (3.09, 3.24)[‡]	2.97 (2.90, 3.04)[‡]	1.88 (1.84, 1.93)[d‡]	1.66 (1.62, 1.70)[‡]	1.61 (1.57, 1.65)[‡]
CHF exacerbation	1.72 (1.67, 1.76)[‡]	1.67 (1.62, 1.71)[‡]	1.22 (1.19, 1.25)[e‡]	1.09 (1.06, 1.12)[‡]	1.06 (1.03, 1.09)[‡]
Diabetes-related	2.88 (2.79, 2.98)[‡]	2.66 (2.57, 2.75)[‡]	1.83 (1.77, 1.89)[f‡]	1.86 (1.80, 1.93)[‡]	1.69 (1.63, 1.75)[‡]
HTN	1.52 (1.48, 1.57)[‡]	1.48 (1.44, 1.53)[‡]	1.37 (1.33, 1.41)[g‡]	1.30 (1.26, 1.34)[‡]	1.18 (1.14, 1.21)[‡]
Acute ACSCs					
Appendicitis with perforation	1.31 (1.25, 1.37)[‡]	1.31 (1.25, 1.37)[‡]		1.26 (1.21, 1.33)[‡]	1.21 (1.16, 1.27)[‡]
Pneumonia	2.35 (2.33, 2.38)[‡]	2.29 (2.27, 2.32)[‡]		1.55 (1.53, 1.56)[‡]	1.50 (1.48, 1.52)[‡]
UTI	2.38 (2.34, 2.42)[‡]	2.34 (2.31, 2.38)[‡]		1.74 (1.71, 1.77)[‡]	1.63 (1.60, 1.66)[‡]

Abbreviations (in alphabetical order): ACSC = ambulatory care-sensitive condition; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; HTN = hypertension; PCP = primary care physician; UTI = urinary tract infection.

[a] Age, sex and calendar period.

[b] Educational level and marital status.

[c] Adjusted for myocardial infarction.

[d] Adjusted for chronic pulmonary disease.

[e] Adjusted for CHF.

[f] Adjusted for diabetes mellitus.

[g] Adjusted for myocardial infarction, CHF, cerebrovascular disease and peripheral vascular disease.

[h] Charlson Comorbidity Index diagnoses not previously adjusted for.

[‡] $P < 0.001$

Table 3. The effect of age on the association of depression with risk of hospitalization for an ambulatory care-sensitive condition

Age categories	Adjusted for demographics	Adjusted for socioeconomic factors	Adjusted for comorbidities	Adjusted for PCP visits
	Incidence Rate Ratio (95% Confidence Interval)			
≤ 40 years old	2.88 (2.78, 3.00)‡	2.83 (2.72, 2.93)‡	2.34 (2.25, 2.43)‡	2.06 (1.98, 2.13)‡
41 – 64 years old	2.93 (2.88, 2.98)‡	2.74 (2.69, 2.78)‡	1.94 (1.91, 1.97)‡	1.73 (1.70, 1.76)‡
Age ≥ 65 years old	2.30 (2.28, 2.32)‡	2.18 (2.15, 2.20)‡	1.34 (1.33, 1.36)‡	1.31 (1.30, 1.32)‡

Abbreviation: PCP = primary care physician.

‡ $P < 0.001$

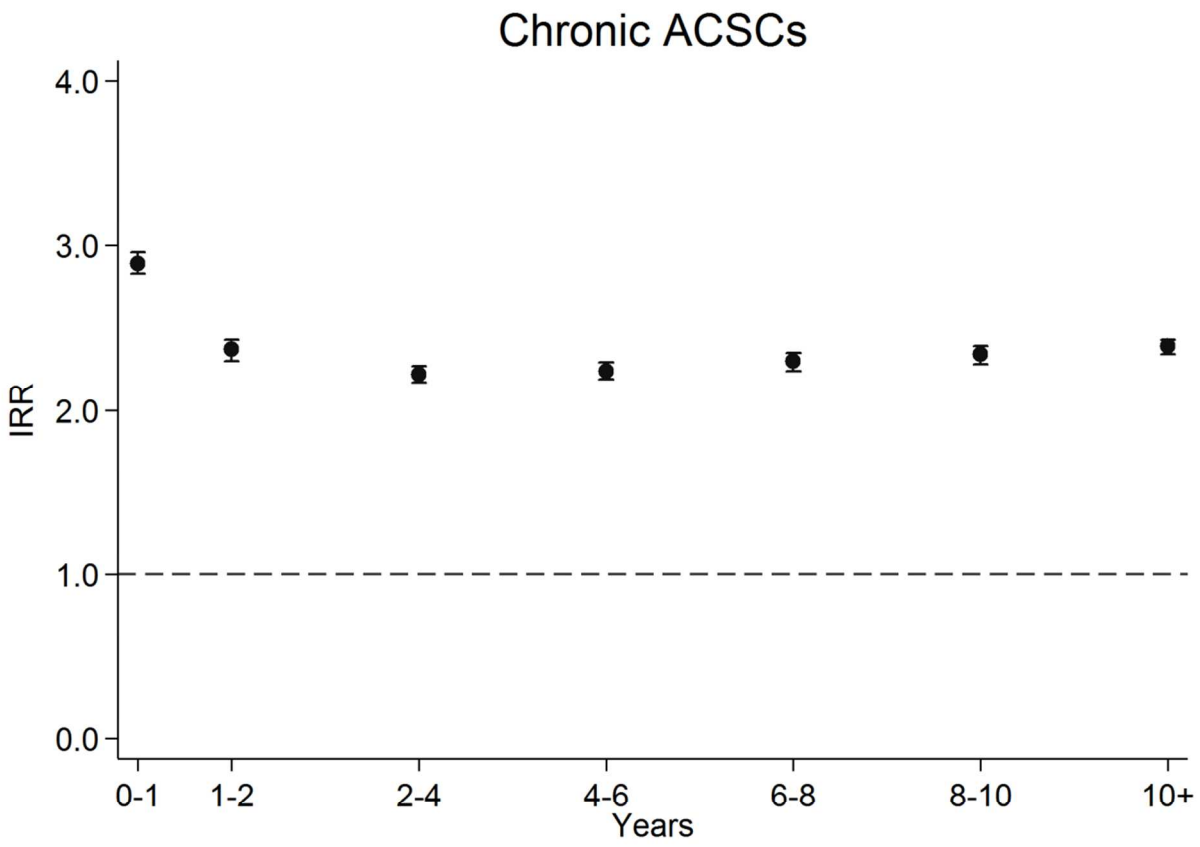
Table 4. The risk of rehospitalization within 30 days for the same or another ambulatory care-sensitive condition among those with depression compared to individuals without depression

Outcome	Model 1 Adjusted for demographics	Model 2 Adjusted for variables in Model 1 and socioeconomic factors	Model 3 Adjusted for variables in Model 2, comorbidity and substance abuse disorders
	Incidence Rate Ratio (95% Confidence Interval)		
Same ACSC	1.36 (1.32, 1.39)‡	1.34 (1.31, 1.38)‡	1.21 (1.18, 1.24)‡
Another ACSC	1.44 (1.39, 1.49)‡	1.42 (1.37, 1.47)‡	1.19 (1.15, 1.23)‡

Abbreviation: ACSC = ambulatory care-sensitive condition.

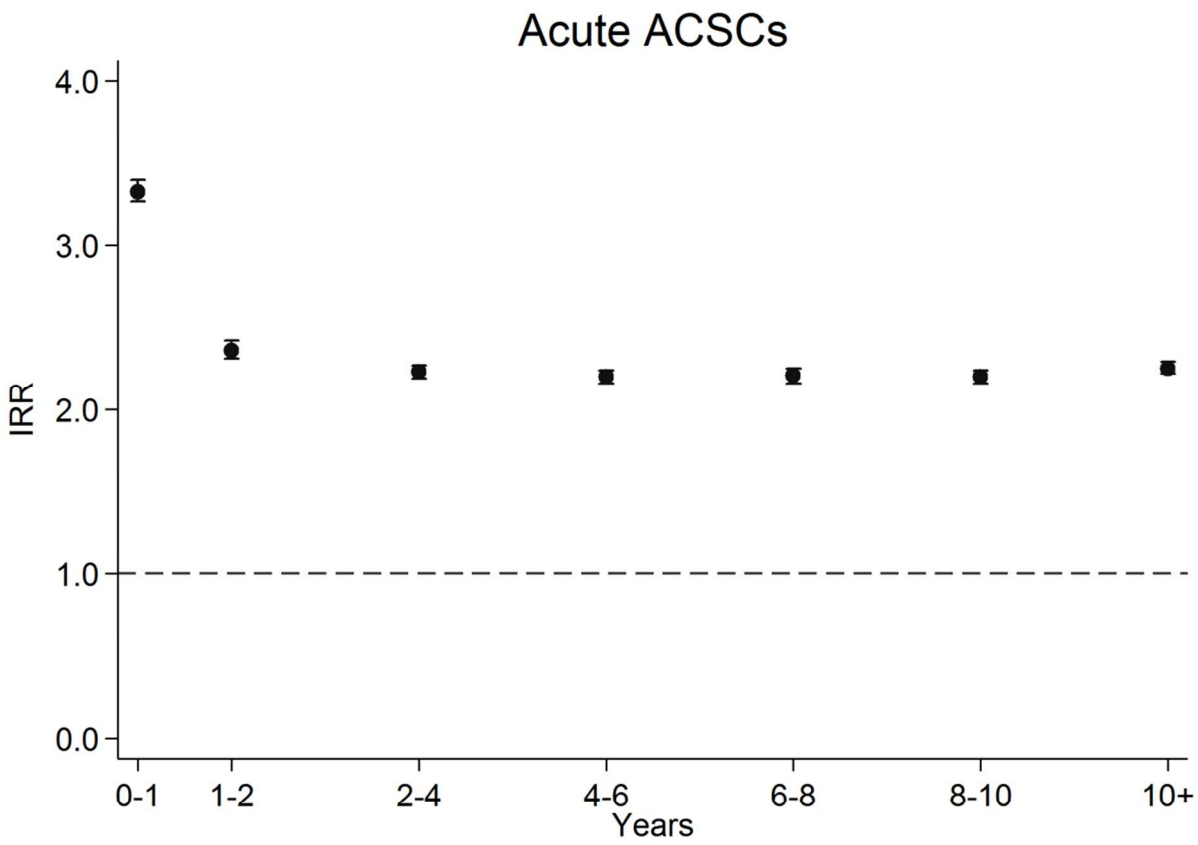
‡ $P < 0.001$

Figure 1. Risk of hospitalization for a chronic ambulatory care-sensitive condition by time since depression diagnosis



Abbreviations (in alphabetical order): ACSCs = ambulatory care-sensitive conditions; IRR = incidence rate ratio.

Figure 2. Risk of hospitalization for an acute ambulatory care-sensitive condition by time since depression diagnosis



Abbreviations (in alphabetical order): ACSCs = ambulatory care-sensitive conditions; IRR = incidence rate ratio.

Supplementary Online Material

APPENDIX 1: Information on depression obtained from the Danish Psychiatric Central Register and the Danish National Prescription Registry

A diagnosis of depression was identified if at least one of the following criteria applied:

1. Registration of a diagnosis of depression in the Danish Psychiatric Central Register.
   And/or
2. Registration of at least one prescription of antidepressants redeemed in the Danish National Prescription Registry

Diagnosis according to a record of depression in the Danish Psychiatric Central Register:

ICD-8	ICD-10
296.09, 296.29, 296.99, 298.09, 300.49, and 300.19	F32, F33

Diagnosis according to a record of prescriptions for antidepressants in the Danish National Prescription Registry:

Name	Drug	ATC-codes
SSRI (Selective serotonin re-uptake inhibitors)	Fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, and escitalopram	N06AB
MAOIs (Monoamine oxidase inhibitors)	Isocarboxazid and moclobemide	N06AF, N06AG
Other antidepressants	Mianserin, nefazodone, mirtazapine, venlafaxine, reboxetine, duloxetine, and agomelatine	N06AX

APPENDIX 2: Information on severe mental illness obtained from the Danish Psychiatric Central Register.

	ICD-8	ICD-10
Schizophrenia	295 (excluding 295.79)	F20
Schizoaffective disorders	295.79, 296.8	F25

Bipolar affective disorders	296.19, 296.39	F30, F31

Appendix 3: Information on Ambulatory Care Sensitive Conditions (ACSCs) obtained from the Danish National Patient Register.

Hospitalizations for 12 of the conditions identified by the Agency for Healthcare Research and Quality as ACSCs in their report on prevention quality indicator

Disease	Description in the AHRQ list	ICD-10
Angina	**Angina Without Procedure Admission Rate** **Numerator:** Discharges with ICD-9-CM principal diagnosis code for angina (see below). All discharges of age 18 years and older. **Exclude:** Discharges with a surgical procedure in any field (010-8699). Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes:** 4111 INTERMED CORONARY SYND 4130 ANGINA DECUBITUS 41181 CORONARY OCCLSN W/O MI 4131 PRINZMETAL ANGINA 41189 AC ISCHEMIC HRT DIS NEC 4139 ANGINA PECTORIS NEC/NOS **Denominator:** Population in MSA or county, age 18 years and older.	I20.0, I20.1, I20.8, I20.9, I24.0, I24.1, I24.8, I24.9 **EXCLUSIONS:** **All surgical procedures (starting with a K in the Danish version of the NCSP, which means surgical)**
COPD (Chronic obstructive pulmonary disorder) exacerbation	**Chronic Obstructive Pulmonary Disease (COPD) Admission Rate** **Numerator:** Discharges with ICD-9-CM principal diagnosis code for COPD (see below). All discharges of age 18 years and older.	J20.0-J20.9*, J40.0-J40.9*, J41.0, J41.1, J42.0-J42.9, J43.8, J43.9, J44.0-J44.9, J47.0-J47.9

	Exclude: Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes**: 4660 AC BRONCHITIS* 4920 EMPHYSEMATOUS BLEB 490 BRONCHITIS NOS* 4928 EMPHYSEMA NEC 4910 SIMPLE CHR BRONCHITIS 494 BRONCHIECTASIS -OCT00 4911 MUCOPURUL CHR BRONCHITIS 4940 BRONCHIECTAS W/O AC EXAC 49120 OBS CHR BRNC W/O ACT EXA OCT00- 49121 OBS CHR BRNC W ACT EXA 4941 BRONCHIECTASIS W AC EXAC 4918 CHRONIC BRONCHITIS NEC OCT00- 4919 CHRONIC BRONCHITIS NOS 496 CHR AIRWAY OBSTRUCT NEC * Qualifies only if accompanied by secondary diagnosis of 491.xx, 492.x, or 496 (i.e., any other code on this list). **Denominator:** Population in MSA or county, age 18 years and older.	***qualify only if accompanied by secondary diagnosis of any of the other codes listed under COPD**
CHF (Congestive heart failure) exacerbation	**Congestive Heart Failure (CHF) Admission Rate Numerator:** Discharges with ICD-9-CM principal diagnosis code for CHF (see below). All discharges of age 18 years and older. **Exclude:** Discharges with cardiac procedure codes (see below) in any field. Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2]	I09.0-I09.9 I11.0, I13.0, I13.2, I13.9, I50.0, I50.1, I50.9, I46.9 **EXCLUSION:** **Cardiac procedures**: **KFNG02, KFNG05, KFNA, KFNC, KFT, KFW, KFQ, BFCA01-BFCA07**

	ICD-9-CM diagnosis codes: 39891 RHEUMATIC HEART FAILURE 40413 BEN HYP HRT/REN W CHF&RF 40201 MAL HYPERT HRT DIS W CHF 40491 HYPER HRT/REN NOS W CHF 40211 BENIGN HYP HRT DIS W CHF 40493 HYP HT/REN NOS W CHF&RF 40291 HYPERTEN HEART DIS W CHF 4280 CONGESTIVE HEART FAILURE 40401 MAL HYPER HRT/REN W CHF 4281 LEFT HEART FAILURE 40403 MAL HYP HRT/REN W CHF&RF 4289 HEART FAILURE NOS 40411 BEN HYPER HRT/REN W CHF Exclude ICD-9-CM procedure codes: 3601 PTCA-1 VESSEL W/O AGENT 3619 HRT REVAS BYPS ANAS NEC 3602 PTCA-1 VESSEL WITH AGNT 375 HEART TRANSPLANTATION 3605 PTCA-MULTIPLE VESSEL 3770 INT INSERT PACEMAK LEAD 3606 INSERT CORONARY ART STENT OCT95- 3771 INT INSERT LEAD IN VENT 3610 AORTOCORONARY BYPASS NOS 3772 INT INSER LEAD ATRI-VENT 3611 AORTOCOR BYPAS-1 COR ART 3773 INT INSER LEAD IN ATRIUM 3612 AORTOCOR BYPAS-2 COR ART 3774 INT OR REPL LEAD EPICAR 3613 AORTOCOR BYPAS-3 COR ART 3775 REVISION OF LEAD 3614 AORTCOR BYPAS-4+ COR ART 3776 REPL TV ATRI-VENT LEAD 3615 1 INT MAM-COR ART BYPASS 3777 REMOVAL OF LEAD W/O REPL 3616 2 INT MAM-COR ART BYPASS 3778 INSER TEMP PACEMAKER SYS 3617 ABD-CORON ART BYPASS OCT96- 3779 REVIS OR RELOCATE POCKET	

	Denominator: Population in MSA or county, age 18 years and older.	
Diabetes (with short-term complications)	**Diabetes Short-term Complications Admission Rate** **Numerator:** Discharges with ICD-9-CM principal diagnosis code for short-term complications (ketoacidosis, hyperosmolarity, coma) (see below). All discharges of age 18 years and older. **Exclude**: Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes:** 25010 DM KETO T2, DM CONT 25022 DM W/ HYPROSM T2, DM UNCNT 25011 DM KETO T1, DM CONT 25023 DM W/ HYPROSM T1, DM UNCNT 25012 DM KETO T2, DM UNCONT 25030 DM COMA NEC T2, DM CONT 25013 DM KETO T1, DM UNCONT 25031 DM COMA NEC T1, DM CONT 25020 DM W/ HYPROSM T2, DM CONT 25032 DM COMA NEC T2, DM UNCONT 25021 DM W/ HYPROSM T1, DM CONT 25033 DM COMA NEC T1, DM UNCONT **Denominator:** Population in MSA or county, age 18 years and older.	E10.0, E10.1, E11.0, E11.1,
Diabetes (uncontrolled (without short-term or long-term complications))	**Uncontrolled Diabetes Admission Rate** **Numerator:** Discharges with ICD-9-CM principal diagnosis code for uncontrolled diabetes, without mention of a short-term or long-term complication (see below).	E10.9, E11.9

	All discharges of age 18 years and older. **Exclude:** Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes:** 25002 DM, T2, UNCONT 25003 DM, T1, UNCONT **Denominator:** Population in MSA or county, age 18 years and older. May be combined with diabetes short-term complications as a single indicator.	
Diabetes (with long-term complications)	**Diabetes Long-term Complications Admission Rate** **Numerator:** Discharges with ICD-9-CM principal diagnosis code for long-term complications (renal, eye, neurological, circulatory, or complications not otherwise specified) (see below). All discharges of age 18 years and older. **Exclude:** Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes:** 25040 DM RENAL COMP T2 CONT 25070 DM CIRCU DIS T2 CONT 25041 DM RENAL COMP T1 CONT 25071 DM CIRCU DIS T1 CONT 25042 DM RENAL COMP T2 UNCNT 25072 DM CIRCU DIS T2 UNCNT 25043 DM RENAL COMP T1 UNCNT 25073 DM	E10.2-E10.8, E11.2-E11.8

	CIRCU DIS T1 UNCNT 25050 DM EYE COMP T2 CONT 25080 DM W COMP NEC T2 CONT 25051 DM EYE COMP T1 CONT 25081 DM W COMP NEC T1 CONT 25052 DM EYE COMP T2 UNCNT 25082 DM W COMP NEC T2 UNCNT 25053 DM EYE COMP T1 UNCNT 25083 DM W COMP NEC T1 UNCNT 25060 DM NEURO COMP T2 CONT 25090 DM W COMPL NOS T2 CONT 25061 DM NEURO COMP T1 CONT 25091 DM W COMPL NOS T1 CONT 25062 DM NEURO COMP T2 UNCNT 25092 DM W COMPL NOS T2 UNCNT 25063 DM NEURO COMP T1 UNCNT 25093 DM W COMPL NOS T1 UNCNT **Denominator:** Population in MSA or county, age 18 years and older.	
HTN (Hypertension)	**Hypertension Admission Rate** **Numerator:** Discharges with ICD-9-CM principal diagnosis code for hypertension (see below). All discharges of age 18 years and older. **Exclude:** Discharges with cardiac procedure codes (see below) in any field. Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes**: 4010 MALIGNANT HYPERTENSION 40310 BENIGN HYP HRT DIS W/OUT RF 4019 HYPERTENSION NOS 40390 HYPERTEN HEART DIS W/OUT RF	I10.0-I10.9, I11.9, I12.9, I13.9 **EXCLUSION:** **Cardiac procedures**: **KFNG02, KFNG05, KFNA, KFNC, KFT, KFW, KFQ, BFCA01-BFCA07**

	40200 MAL HYPERTEN HRT DIS W/OUT CHF 40400 MAL HYPER HRT/REN W/OUT CHF/RF 40210 BEN HYPERTEN HRT DIS W/OUT CHF 40410 BEN HYPER HRT/REN W/OUT CHF/RF 40290 HYPERTENSIVE HRT DIS W/OUT CHF 40490 HYPER HRT/REN NOS W/OUT CHF/RF 40300 MAL HYPERT HRT DIS W/OUT RF Exclude ICD-9-CM procedure codes: 3601 PTCA-1 VESSEL W/O AGENT 3619 HRT REVAS BYPS ANAS NEC 3602 PTCA-1 VESSEL WITH AGNT 375 HEART TRANSPLANTATION 3605 PTCA-MULTIPLE VESSEL 3770 INT INSERT PACEMAK LEAD 3606 INSERT CORONARY ART STENT OCT95- 3771 INT INSERT LEAD IN VENT 3610 AORTOCORONARY BYPASS NOS 3772 INT INSER LEAD ATRI-VENT 3611 AORTOCOR BYPAS-1 COR ART 3773 INT INSER LEAD IN ATRIUM 3612 AORTOCOR BYPAS-2 COR ART 3774 INT OR REPL LEAD EPICAR 3613 AORTOCOR BYPAS-3 COR ART 3775 REVISION OF LEAD 3614 AORTCOR BYPAS-4+ COR ART 3776 REPL TV ATRI-VENT LEAD 3615 1 INT MAM-COR ART BYPASS 3777 REMOVAL OF LEAD W/O REPL 3616 2 INT MAM-COR ART BYPASS 3778 INSER TEMP PACEMAKER SYS 3617 ABD-CORON ART BYPASS OCT96- 3779 REVIS OR RELOCATE POCKET **Denominator:** Population in MSA or county, age 18 years and older.	
Perforated appendicitis	**Perforated Appendix Admission Rate** **Numerator:** Discharges with ICD-9-CM diagnosis code for perforations or abscesses of appendix (see below)	K35.0, K35.1, K35.2, K35.3

	in any field. All discharges of age 18 years and older. **Exclude:** Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes (outcome of interest):** 5400 AC APPEND W PERITONITIS 5401 ABSCESS OF APPENDIX **ICD-9-CM diagnosis codes (population at risk):** 5400 AC APPEND W PERITONITIS 5409 ACUTE APPENDICITIS NOS 5401 ABSCESS OF APPENDIX 541 APPENDICITIS NOS **Denominator:** Number of discharges with diagnosis code for appendicitis in any field in MSA or county.	
Pneumonia	**Bacterial Pneumonia Admission Rate** **Numerator:** Discharges with ICD-9-CM principal diagnosis code for bacterial pneumonia (see below). All discharges of age 18 years and older. **Exclude:** Discharges with diagnosis code for sickle cell anemia or HB-S disease (see below) in any field. Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes:** 481 PNEUMOCOCCAL PNEUMONIA 48230 STREP PNEUMONIA UNSPEC	J13-J14.9, J15.3-J15.4, J15.7-J15.9, J16.0-J16.9, J18.0-J18.9 **EXCLUSION:** **Sickle cell disorders** **D57.0-D57.9**

	4822 H.INFLUENZAE PNEUMONIA 48231 GRP A STREP PNEUMONIA 4829 BACTERIAL PNEUMONIA NOS 48232 GRP B STREP PNEUMONIA 4830 MYCOPLASMA PNEUMONIA 48239 OTH STREP PNEUMONIA 4831 CHLAMYDIA PNEUMONIA OCT96- 485 BRONCOPNEUMONIA ORG NOS 4838 OTH SPEC ORG PNEUMONIA 486 PNEUMONIA, ORGANISM NOS **Exclude ICD-9-CM diagnosis codes:** 28260 SICKLE-CELL ANEMIA NOS 28263 SICKLE-CELL/HB-C DISEASE 28261 HB-S DISEASE W/O CRISIS 28269 SICKLE-CELL ANEMIA NEC 28262 HB-S DISEASE WITH CRISIS	
UTIs (urinary tract infections)	**Urinary Tract Infection Admission Rate** **Numerator:** Discharges with ICD-9-CM principal diagnosis code of urinary tract infection (see below). **Exclude:** Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes:** 59000 CHR PYELONEPHRITIS NOS 59080 PYELONEPHRITIS NOS 59001 CHR PYELONEPH W MED NECR 59081 PYELONEPHRIT IN OTH DIS 59010 AC PYELONEPHRITIS NOS 5909 INFECTION OF KIDNEY NOS 59011 AC PYELONEPHR W MED NECR 5950 AC CYSTITIS 5902 RENAL/PERIRENAL ABSCESS 5959 CYSTITIS NOS 5903 PYELOURETERITIS CYSTICA 5990 URIN TRACT INFECTION NOS	N10.0-N12.9, N15.1-15.9, N30.0-N30.9, N34.0-N34.9, N39.0

	Denominator: Population in MSA or county.	
Adult Asthma exacerbation	**Adult Asthma Admission Rate** **Numerator:** Discharges with ICD-9-CM principal diagnosis code of asthma (see below). All discharges of age 18 years and older. **Exclude:** Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes:** 49300 EXT ASTHMA W/O STAT ASTH 49320 CH OB ASTH W/O STAT ASTH 49301 EXT ASTHMA W STATUS ASTH 49321 CH OB ASTHMA W STAT ASTH 49302 EXT ASTHMA W STATUS ACEX OCT00- 49322 CH OB ASTHMA W STAT ACEX 49310 INT ASTHMA W/O STAT ASTH OCT00- 49311 INT ASTHMA W STATUS ASTH 49390 ASTHMA W/O STATUS ASTHM 49312 INT ASTHMA W STATUS ACEX OCT00- 49391 ASTHMA W STATUS ASTHMAT 49392 ASTHMA W STATUS AC EXAC OCT00- **Denominator:** Population in MSA or county, age 18 years and older.	J45, J46
Amputations (diabetes-related)	**Rate of Lower-extremity Amputation among Patients with Diabetes** **Numerator:** Discharges with ICD-9-CM procedure code for lower-extremity amputation (see below) in any field and diagnosis code of diabetes in any field (see below). All discharges of age 18 years and older.	Z89.4-Z89.7 ***qualify only if registered with diabetes in the Danish National Diabetes Register or if registered with a diagnosis of diabetes (ICD-10:E10-14, H36.0, O24, excluding O24.4) at the same admission as the ACSC**

	Exclude: Trauma (see below). Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM procedure codes:** 8410 LOWER LIMB AMPUTAT NOS 8415 BELOW KNEE AMPUTAT NEC 8411 TOE AMPUTATION 8416 DISARTICULATION OF KNEE 8412 AMPUTATION THROUGH FOOT 8417 ABOVE KNEE AMPUTATION 8413 DISARTICULATION OF ANKLE 8418 DISARTICULATION OF HIP 8414 AMPUTAT THROUGH MALLEOLI 8419 HINDQUARTER AMPUTATION ICD-9-CM diagnosis codes for diabetes: 25000 DMII WO CMP NT ST UNCNTR 25050 DMII OPHTH NT ST UNCNTRL 25001 DMI WO CMP NT ST UNCNTRL 25051 DMI OPHTH NT ST UNCNTRLD 25002 DMII WO CMP UNCNTRLD 25052 DMII OPHTH UNCNTRLD 25003 DMI WO CMP UNCNTRLD 25053 DMI OPHTH UNCNTRLD 25010 DMII KETO NT ST UNCNTRLD 25060 DMII NEURO NT ST UNCNTRL 25011 DMI KETO NT ST UNCNTRLD 25061 DMI NEURO NT ST UNCNTRLD 25012 DMII KETOACD UNCONTROLD 25062 DMII NEURO UNCNTRLD 25013 DMI KETOACD UNCONTROLD 25063 DMI NEURO UNCNTRLD 25020 DMII HPRSM NT ST UNCNTRL 25070 DMII CIRC NT ST UNCNTRLD 25021 DMI HPRSM NT ST UNCNTRLD 25071 DMI CIRC NT ST UNCNTRLD	**EXCLUSION:** **Traumatic amputations of lower limb** **S78.0-S78.9, S88.0-S88.9, S98.0-S98.4, T05.3-T05.5**

	25022 DMII HPROSMLR UNCONTROLD 25072 DMII CIRC UNCNTRLD 25023 DMI HPROSMLR UNCONTROLD 25073 DMI CIRC UNCNTRLD 25030 DMII O CM NT ST UNCNTRLD 25080 DMII OTH NT ST UNCNTRLD 25031 DMI O CM NT ST UNCNTRL 25081 DMI OTH NT ST UNCNTRLD 25032 DMII OTH COMA UNCONTROLD 25082 DMII OTH UNCNTRLD 25033 DMI OTH COMA UNCONTROLD 25083 DMI OTH UNCNTRLD 25040 DMII RENL NT ST UNCNTRLD 25090 DMII UNSPF NT ST UNCNTRL 25041 DMI RENL NT ST UNCNTRLD 25091 DMI UNSPF NT ST UNCNTRLD 25042 DMII RENAL UNCNTRLD 25092 DMII UNSPF UNCNTRLD 25043 DMI RENAL UNCNTRLD 25093 DMI UNSPF UNCNTRLD **Exclude: Trauma** **ICD-9-CM diagnosis codes:** 8950 AMPUTATION TOE 8971 AMPUTAT BK, UNILAT-COMPL 8951 AMPUTATION TOE-COMPLICAT 8972 AMPUT ABOVE KNEE, UNILAT 8960 AMPUTATION FOOT, UNILAT 8973 AMPUT ABV KN, UNIL-COMPL 8961 AMPUT FOOT, UNILAT-COMPL 8974 AMPUTAT LEG, UNILAT NOS 8962 AMPUTATION FOOT, BILAT 8975 AMPUT LEG, UNIL NOS-COMP 8963 AMPUTAT FOOT, BILAT-COMP 8976 AMPUTATION LEG, BILAT 8970 AMPUT BELOW KNEE, UNILAT 8977 AMPUTAT LEG, BILAT-COMPL **Denominator:** Population in MSA or county, age 18 years and older.	

[1]Transfers imply that if a discharge date is followed by another admission date with an overlap of +/- 1 day this is counted as one admission. [2]The exclusion of obstetric admissions was performed if any diagnostic codes for obstetric diagnoses were present as a secondary diagnosis at the same admission as the ACSC. The obstetric diagnostic codes included: O0.0-O99.9.		

Appendix 4: Information on socioeconomic position (SEP) obtained from Statistics Denmark.
Education level
< 10 years
10-15 years
> 15 years
Civil status
Living alone/single
Cohabitation
Partners
Married

Appendix 5: Information on the ACSC-predisposing medical comorbidity obtained from the Danish National Patient Register, the Danish National Diabetes Register and the Danish National Prescription Registry.

ACSC Outcome	ACSC-predisposing medical comorbidity
Chronic conditions	
Angina	Myocardial infarction[1]
CHF exacerbation	CHF[1]
HTN	Myocardial infarction[1] CHF[1] Cerebrovascular disease[1] Peripheral vascular disease[1]
Diabetes-related ACSCs	Diabetes[2]
COPD exacerbation	Chronic pulmonary disease[1] or Redemption of at least 2 prescriptions of drugs for obstructive airway diseases within 6 months[3]
Adult asthma exacerbation	Chronic pulmonary disease[1] or Redemption of at least 2 prescriptions of drugs for obstructive airway diseases within 6 months[3]
Acute conditions	
Perforated appendicitis	-
Pneumonia	-

UTI	-

[1]Obtained from the Danish National Patient Register using the algorithm defined in the Charlson Comorbidity Index (see appendix 6).
[2]Obtained from the Danish National Diabetes Register (see appendix 7)
[3]Obtained from the Danish National Prescriptions Registry (see appendix 8).

Appendix 6: Information on chronic diseases included in the Charlson Comorbidity Index obtained from the Danish National Patient Register

	ICD-8	ICD-10
Myocardial infarction	410	I21;I22;I23
Congestive heart failure	427.09, 427.10, 427.11, 427.19, 428.99, 782.49	I50; I11.0; I13.0; I13.2
Peripheral vascular disease	440, 441, 442, 443, 444, 445,	I70; I71; I72; I73; I74; I77
Cerebrovascular disease	430-438	I60-I69; G45; G46
Dementia	290.09-290.19, 293.09	F00-F03; F05.1; G30
Chronic pulmonary disease	490-493, 515-518	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3
Connective tissue disease	712, 716, 734, 446, 135.99	M05; M06; M08; M09;M30;M31; M32; M33; M34; M35; M36; D86
Ulcer disease	530.91, 530.98, 531-534,	K22.1; K25-K28
Mild liver disease	571, 573.01, 573.04	B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0
Diabetes mellitus	249.00, 249.06, 249.07, 249.09, 250.00, 250.06,	E10.0, E10.1; E10.9; E11.0; E11.1; E11.9

	250.07, 250.09	
Hemiplegia	344	G81; G82
Moderate/severe renal Disease	403,404,580-583, 584, 590.09, 593.19, 753.10-753.19, 792	I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61
Diabetes mellitus with chronic complications	249.01-249.05, 249.08, 250.01-250.05, 250.08	E10.2-E10.8; E11.2-E11.8
Any tumour	140-194	C00-C75
Leukaemia	204-207	C91-C95
Lymphoma	200-203, 275.59	C81-C85; C88; C90; C96
Moderate/severe liver Disease	070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.00-456.09	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85
Metastatic solid tumour	195-198, 199	C76-C80
AIDS	079.83	B21-B24

Appendix 7: Information on diabetes obtained from the Danish National Diabetes Register.

Algorithm: Individuals were classified as having diabetes on the day where at least one of the following six criteria was met:

1. A diagnosis of diabetes made at any Danish hospital as registered in the Danish National Patient Register (ICD-8:249, 250; ICD-10:E10-14, H36.0, O24, excluding O24.4).
2. A referral to chiropody of diabetic patients as registered in the Danish National Health Service Register.(Andersen *et al.* 2011)
3. Five blood glucose measurements within one year as registered in the Danish National Health Service Register.
4. Two blood glucose measurements per year for five consecutive years as registered in the Danish National Health Service Register.
5. Two redemptions of oral anti-diabetic drugs within six months as registered in the Danish National Prescription Registry.
6. Two redemptions of prescribed insulin as registered in the Danish National Prescription Registry.

Appendix 8: ATC codes for drugs for obstructive airway disease obtained from the Danish National Prescription Registry.	
ATC codes	**Type of drug**
R03	Drugs for obstructive airway diseases
R03A	Adrenergics, inhalants
R03B	Other drugs for obstructive airway diseases, inhalants
R03C	Adrenergics for systemic use
R03D	Other systemic drugs for obstructive airway diseases

Appendix 9: Information on substance abuse disorders obtained from the Danish National Patient Register and the Danish Psychiatric Central Register.		
	ICD-8	ICD-10
Drug related		
Opioids	304.09, 304.19	F11.0–F11.9
Cannabinoids	304.59	F12.0–F12.9
Sedatives/hypnotics	304.29, 304.39	F13.0–F13.9
Cocaine	304.49	F14.0–F14.9
Other stimulants	304.69	F15.0–15.9
Hallucinogens	304.79	F16.0–F16.9
Other and multiple drugs	304.89, 304.99	F18.0–F19.9
Alcohol related		
Alcohol psychosis and abuse syndrome	291.09–291.99 303.09–303.99	F10.0–F10.9
Cirrhosis and steatosis of the liver	571.09, 571.10, 571.19	K70.0–K70.9
Esophageal varices	456.00, 456.01, 456.09	I85.0–I85.9

The risk of ACSCs and rehospitalizations for ACSCs among persons with depression

		Considerations
Study population:	**Depression study** All persons born in Denmark, alive and minimum 18 years of age and still living in Denmark at some time between January 1, 1999 and December 31, 2013. - Sub-analysis: Stratified by age categories: ≤ 40, 41-65, ≥ 65 (i.e., adult, middle-aged, older adults)	
Follow-up:	January 1, 2005-December 31,2013	This enables us to make sure who has a mental disorder between 1995 and 2005
Censor-in	18 years of birthday or study start, whichever comes last.	We do not want to include children. And also, this definition is a part of the AHRQ list. No age maximum.
Censor-out	Emigration, death, SMI diagnosis or study end whichever comes first.	We will censor out persons with SMI!
Dropping individuals	• Out-censored before in-censored (children and young persons dying before their 18th years birthday, or emigration, SMI diagnosis or death before study start).	

Exposure		
	Depression	Time-dependent variable (see Appendix 1): • All cases of depression between 1969 and 2013 (diagnoses-in and outpatient contacts) and between 1995 and 2013 (prescriptions). Remember that depression identified by redemptions need at least 2 prescriptions within 6 months. Sub-analysis Risk of ACSC-related hospitalizations by depression diagnosis-type (i.e., our rough proxy for depression severity): 1) Psychiatric hospitalization for depression 2) Outpatient depression diagnosis only 3) Antidepressant prescriptions only
	Dual diagnosis	If a person has a primary care determined depression it is overruled by a diagnosis from the registers (the secondary health care).
Outcome		
	1. The number of hospitalizations for ACSCs (Ambulatory care sensitive conditions) during follow-up = hospitalization rates for the following categories: Using codes from the Danish ACSC validation paper(Schiotz *et al.* 2011): -Angina -COPD exacerbation -Congestive heart failure exacerbation -Diabetes-short term compl. -Diabetes long-term compl. -Diabetes- uncontrolled	1) The algorithm: We have modified this outcome measure because it is classified according to ICD-9 (and diagnoses in Denmark are according to ICD-8 before 1994 and ICD-10 since 1995). We have used a validated algorithm from a Danish 'translated versions' in a Danish article (Schiotz *et al.* 2011). However, as this version does not include all of the categories of ACSCs from the AHRQ list, we have additionally included for all practical purposes, the rest of the categories (pneumonia, amputations, urinary tract infections, and asthma) (and a translation of the codes from ICD-9 to 10 have been conducted with inspiration

	-Hypertension -Appendicitis <u>Using codes with inspiration from Danish register-based studies (or own algorithms):</u> -Bacterial Pneumonia(Nielsen *et al.* 2012) -Lower extremities amputations (Jorgensen *et al.* 2014) -Urinary tract infections -Adult asthma exacerbation (Andersen *et al.* 2013) combine COPD exacerbation and adult asthma exacerbation into a single category for analyses 2. The number of rehospitalizations within 30 days after the index ACSC hospitalization for the same ACSC or for a different ACSC	from algorithms from previous Danish papers). This means that the only diseases not included in this model (compared to the original AHRQ list) are dehydration, immunizations, and IUGR. 2) <u>Inpatient contacts only:</u> Per definition ACSCs includes ONLY inpatient. 3) <u>Principal discharge diagnosis</u> (see Danish article or Davydow 2013) 4) <u>Appendicitis with perforation</u> 5) <u>Epidemiological considerations</u> One of the major epidemiological considerations for this study is the fact that persons with mental illness have higher rates for chronic diseases and are also more likely to receive poor quality of care treatment. If we show these persons have higher risk of ACSC we will have difficulty disentangling the increased risk of chronic diseases from the increased risk of suboptimal treatment. But the causal mechanism is likely to include both, and it will have to be discussed!! 6) <u>Exclusions:</u> - All transfers: Unfortunately we do not have access to data on transfers between hospitals. If a discharge date is followed by another admission date with an overlap of 1 day then we only count this as 1 admission. See the table for how to count the ACSCs. - Procedures for angina: Exclusions

		of angina cases who has had ANY surgical procedures (NCSP surgical codes) at the SAME admission. - Specific exclusions concerning diabetic amputations and concerning pneumonia
Covariates		
Demographic	Age, gender, calendar period.	We are adjusting for age as a time-dependent variable divided into 2 years age-bands. We are adjusting for calendar period as a time-dependent variable divided into 1 year-time-bands.
Socio-economic position (SEP)	**Depression paper** Marital status (married, registered partners, cohabitant or single). Income (OECD-adjusted household income) Educational level	
Comorbidity		
Medical comorbidity (See Appendices 6-8)	Diagnoses included in the Charlson Comorbidity index except for diabetes, which will come from the Diabetes Register, COPD/asthma exacerbations which will come from the combination of the CCI chronic pulmonary disease category and prescriptions.	Time-dependent We will identify hospital contacts for the chronic somatic diseases included in the CCI. Each diagnosis will be entered into the models as a time-dependent covariate. From 1995 onwards, outpatient contacts are also included. Adjusting for each category of disease from the CCI (instead of using an index).

	Substance abuse	See appendix 10
Health care utilization	Primary care visits (Face-to-Face-contacts=0101 contacts) In the analyses, we will categorize according to the interquartile range of PCP visits in the cohort We will count PCP visits from 10-375 days before any given day.	# of GP visits during the follow-up period for each individual Time-dependent This could be confounded by indication, but reduced contacts to GP and hospitals could also be an intermediate variable between mental illness and ACSC.
Statistical Analyses		
	Poisson regression with variance adjusted for clustering. <u>Outcome measures</u>: -number of hospitalizations per person years (rate measure). -rate ratios, RR	I. The outcome will be the number of these events since we will be using Poisson regression models. The outcome measure is rate ratio which approximates the relative risks. -We make the analysis for any ACSC and subsequently the analyses for each category , dividing into “chronic” ACSCs and “acute” ACSCs. a) <u>Sub-analyses for the time since analyses</u> b) <u>Analyses with adjustments</u> **<u>For depression study</u>** Adjustment: Models 1-5: 1) age, gender and calendar period, 2)SEP, 3) ACSC-predisposing comorbidity for chronic ACSCs, 4) non-ACSC-predisposing comorbidity and substance abuse, 5) GP contacts a) Sub-analysis: Stratified by age categories: ≤ 40, 41-65, ≥ 65 (i.e., adult, middle-aged, older adults),

		adjusted in sequence of Models 1-5 b) Sensitivity analysis: depression diagnosis type analysis (hospitalization for depression vs. outpatient depression vs. prescription alone), adjusted in sequence of Models 1-5 c) Time since depression diagnosis (adjusted for age, sex and calendar period) II. 30-day rehospitalizations for the same or another ACSC adjusted for demographics, then SES and comorbidity

Regarding transfers		
	Second admission	
First admission	ACSC	Non-ACSC
ACSC	Count the second ASCS*	Count the ACSC-admission
Non-ACSC	Count the ACSC-admission	Count as 0

*This means that if the ACSC diagnoses are two different that it will be the second admission that counts.

Appendices

Exposures

EXPOSURES (Appendices 1-3)

APPENDIX 1: Information on depression obtained from the Danish Psychiatric Central Register and the Danish National Prescription Registry

A diagnosis of depression was identified if at least one of the following criteria applied:

1. Registration of a diagnosis of depression in the Danish Psychiatric Central Register.
   And/or
2. Registration of at least one prescription of antidepressants redeemed in the Danish National Prescription Registry

Diagnosis according to a record of depression in the Danish Psychiatric Central Register:

ICD-8	ICD-10
296.09, 296.29, 296.99, 298.09, 300.49, and 300.19	F32, F33

Diagnosis according to a record of prescriptions for antidepressants in the Danish National Prescription Registry:

Name	Drug	ATC-codes
SSRI (Selective serotonin re-uptake inhibitors)	Fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, and escitalopram	N06AB
MAOIs (Monoamine oxidase inhibitors)	Isocarboxazid and moclobemide	N06AF,

		N06AG
Other antidepressants	Mianserin, nefazodone, mirtazapine, venlafaxine, reboxetine, duloxetine, and agomelatine	N06AX

APPENDIX 2: Information on severe mental illness obtained from the Danish Psychiatric Central Register.

	ICD-8	ICD-10
Schizophrenia	295 (excluding 295.79)	F20
Schizoaffective disorders	295.79, 296.8	F25
Bipolar affective disorders	296.19, 296.39	F30, F31

Outcome

Definition of outcome measures for the ACSC (see Appendix 4)	
	Categories
Any ACSC	Any of the categories
Type of ACSC	
Angina	
COPD/adult asthma exacerbation	
CHF exacerbation	
Diabetes-related ACSC	The 3 diabetes categories + amputations
HTN	
Perforated appendicitis	
Pneumonia	
UTI	

Appendix 4: Information on Ambulatory Care Sensitive Conditions (ACSCs) obtained from the Danish National Patient

Register. Hospitalizations for 12 of the conditions identified by the Agency for Healthcare Research and Quality as ACSCs in their report on prevention quality indicator		
Disease	**Description in the AHRQ list**	**ICD-10**
Angina	**Angina Without Procedure Admission Rate** **Numerator:** Discharges with ICD-9-CM principal diagnosis code for angina (see below). All discharges of age 18 years and older. **Exclude:** Discharges with a surgical procedure in any field (010-8699). Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes:** 4111 INTERMED CORONARY SYND 4130 ANGINA DECUBITUS 41181 CORONARY OCCLSN W/O MI 4131 PRINZMETAL ANGINA 41189 AC ISCHEMIC HRT DIS NEC 4139 ANGINA PECTORIS NEC/NOS **Denominator:** Population in MSA or county, age 18 years and older.	I20.0, I20.1, I20.8, I20.9, I24.0, I24.1, I24.8, I24.9 **EXCLUSIONS:** **All surgical procedures (starting with a K in the Danish version of the NCSP, which means surgical)**
COPD (Chronic obstructive pulmonary disorder) exacerbation	**Chronic Obstructive Pulmonary Disease (COPD) Admission Rate** **Numerator:** Discharges with ICD-9-CM principal diagnosis code for COPD (see below). All discharges of age 18 years and older. **Exclude:**	J20.0-J20.9*, J40.0-J40.9*, J41.0, J41.1, J42.0-J42.9, J43.8, J43.9, J44.0-J44.9, J47.0-J47.9 ***qualify only if accompanied by**

	Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes**: 4660 AC BRONCHITIS* 4920 EMPHYSEMATOUS BLEB 490 BRONCHITIS NOS* 4928 EMPHYSEMA NEC 4910 SIMPLE CHR BRONCHITIS 494 BRONCHIECTASIS -OCT00 4911 MUCOPURUL CHR BRONCHITIS 4940 BRONCHIECTAS W/O AC EXAC 49120 OBS CHR BRNC W/O ACT EXA OCT00- 49121 OBS CHR BRNC W ACT EXA 4941 BRONCHIECTASIS W AC EXAC 4918 CHRONIC BRONCHITIS NEC OCT00- 4919 CHRONIC BRONCHITIS NOS 496 CHR AIRWAY OBSTRUCT NEC * Qualifies only if accompanied by secondary diagnosis of 491.xx, 492.x, or 496 (i.e., any other code on this list). **Denominator:** Population in MSA or county, age 18 years and older.	**secondary diagnosis of any of the other codes listed under COPD**
CHF (Congestive heart failure) exacerbation	**Congestive Heart Failure (CHF) Admission Rate** **Numerator:** Discharges with ICD-9-CM principal diagnosis code for CHF (see below). All discharges of age 18 years and older. **Exclude:** Discharges with cardiac procedure codes (see below) in any field. Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2]	I09.0-I09.9 I11.0, I13.0, I13.2, I13.9, I50.0, I50.1, I50.9, I46.9 **EXCLUSION:** **Cardiac procedures**: **KFNG02, KFNG05, KFNA, KFNC, KFT, KFW, KFQ, BFCA01-BFCA07**

	ICD-9-CM diagnosis codes: 39891 RHEUMATIC HEART FAILURE 40413 BEN HYP HRT/REN W CHF&RF 40201 MAL HYPERT HRT DIS W CHF 40491 HYPER HRT/REN NOS W CHF 40211 BENIGN HYP HRT DIS W CHF 40493 HYP HT/REN NOS W CHF&RF 40291 HYPERTEN HEART DIS W CHF 4280 CONGESTIVE HEART FAILURE 40401 MAL HYPER HRT/REN W CHF 4281 LEFT HEART FAILURE 40403 MAL HYP HRT/REN W CHF&RF 4289 HEART FAILURE NOS 40411 BEN HYPER HRT/REN W CHF Exclude ICD-9-CM procedure codes: 3601 PTCA-1 VESSEL W/O AGENT 3619 HRT REVAS BYPS ANAS NEC 3602 PTCA-1 VESSEL WITH AGNT 375 HEART TRANSPLANTATION 3605 PTCA-MULTIPLE VESSEL 3770 INT INSERT PACEMAK LEAD 3606 INSERT CORONARY ART STENT OCT95- 3771 INT INSERT LEAD IN VENT 3610 AORTOCORONARY BYPASS NOS 3772 INT INSER LEAD ATRI-VENT 3611 AORTOCOR BYPAS-1 COR ART 3773 INT INSER LEAD IN ATRIUM 3612 AORTOCOR BYPAS-2 COR ART 3774 INT OR REPL LEAD EPICAR 3613 AORTOCOR BYPAS-3 COR ART 3775 REVISION OF LEAD 3614 AORTCOR BYPAS-4+ COR ART 3776 REPL TV ATRI-VENT LEAD 3615 1 INT MAM-COR ART BYPASS 3777 REMOVAL OF LEAD W/O REPL 3616 2 INT MAM-COR ART BYPASS 3778 INSER TEMP PACEMAKER SYS 3617 ABD-CORON ART BYPASS OCT96- 3779 REVIS OR RELOCATE POCKET	

	Denominator: Population in MSA or county, age 18 years and older.	
Diabetes (with short-term complications)	**Diabetes Short-term Complications Admission Rate** **Numerator:** Discharges with ICD-9-CM principal diagnosis code for short-term complications (ketoacidosis, hyperosmolarity, coma) (see below). All discharges of age 18 years and older. **Exclude**: Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes:** 25010 DM KETO T2, DM CONT 25022 DM W/ HYPROSM T2, DM UNCNT 25011 DM KETO T1, DM CONT 25023 DM W/ HYPROSM T1, DM UNCNT 25012 DM KETO T2, DM UNCONT 25030 DM COMA NEC T2, DM CONT 25013 DM KETO T1, DM UNCONT 25031 DM COMA NEC T1, DM CONT 25020 DM W/ HYPROSM T2, DM CONT 25032 DM COMA NEC T2, DM UNCONT 25021 DM W/ HYPROSM T1, DM CONT 25033 DM COMA NEC T1, DM UNCONT **Denominator:** Population in MSA or county, age 18 years and older.	E10.0, E10.1, E11.0, E11.1,
Diabetes (uncontrolled (without short-term or long-term complications))	**Uncontrolled Diabetes Admission Rate** **Numerator:** Discharges with ICD-9-CM principal diagnosis code for uncontrolled diabetes, without mention of a short-term or long-term complication (see below).	E10.9, E11.9

	All discharges of age 18 years and older. **Exclude:** Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes:** 25002 DM, T2, UNCONT 25003 DM, T1, UNCONT **Denominator:** Population in MSA or county, age 18 years and older. May be combined with diabetes short-term complications as a single indicator.	
Diabetes (with long-term complications)	**Diabetes Long-term Complications Admission Rate** **Numerator:** Discharges with ICD-9-CM principal diagnosis code for long-term complications (renal, eye, neurological, circulatory, or complications not otherwise specified) (see below). All discharges of age 18 years and older. **Exclude:** Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes:** 25040 DM RENAL COMP T2 CONT 25070 DM CIRCU DIS T2 CONT 25041 DM RENAL COMP T1 CONT 25071 DM CIRCU DIS T1 CONT 25042 DM RENAL COMP T2 UNCNT 25072 DM CIRCU DIS T2 UNCNT 25043 DM RENAL COMP T1 UNCNT 25073 DM CIRCU DIS T1 UNCNT	E10.2-E10.8, E11.2-E11.8

	25050 DM EYE COMP T2 CONT 25080 DM W COMP NEC T2 CONT 25051 DM EYE COMP T1 CONT 25081 DM W COMP NEC T1 CONT 25052 DM EYE COMP T2 UNCNT 25082 DM W COMP NEC T2 UNCNT 25053 DM EYE COMP T1 UNCNT 25083 DM W COMP NEC T1 UNCNT 25060 DM NEURO COMP T2 CONT 25090 DM W COMPL NOS T2 CONT 25061 DM NEURO COMP T1 CONT 25091 DM W COMPL NOS T1 CONT 25062 DM NEURO COMP T2 UNCNT 25092 DM W COMPL NOS T2 UNCNT 25063 DM NEURO COMP T1 UNCNT 25093 DM W COMPL NOS T1 UNCNT **Denominator:** Population in MSA or county, age 18 years and older.	
HTN (Hypertension)	**Hypertension Admission Rate** **Numerator:** Discharges with ICD-9-CM principal diagnosis code for hypertension (see below). All discharges of age 18 years and older. **Exclude:** Discharges with cardiac procedure codes (see below) in any field. Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes**: 4010 MALIGNANT HYPERTENSION 40310 BENIGN HYP HRT DIS W/OUT RF 4019 HYPERTENSION NOS 40390 HYPERTEN HEART DIS W/OUT RF 40200 MAL HYPERTEN HRT DIS W/OUT CHF	I10.0-I10.9, I11.9, I12.9, I13.9 **<u>EXCLUSION:</u>** **Cardiac procedures**: **KFNG02, KFNG05, KFNA, KFNC, KFT, KFW, KFQ, BFCA01-BFCA07**

	40400 MAL HYPER HRT/REN W/OUT CHF/RF 40210 BEN HYPERTEN HRT DIS W/OUT CHF 40410 BEN HYPER HRT/REN W/OUT CHF/RF 40290 HYPERTENSIVE HRT DIS W/OUT CHF 40490 HYPER HRT/REN NOS W/OUT CHF/RF 40300 MAL HYPERT HRT DIS W/OUT RF Exclude ICD-9-CM procedure codes: 3601 PTCA-1 VESSEL W/O AGENT 3619 HRT REVAS BYPS ANAS NEC 3602 PTCA-1 VESSEL WITH AGNT 375 HEART TRANSPLANTATION 3605 PTCA-MULTIPLE VESSEL 3770 INT INSERT PACEMAK LEAD 3606 INSERT CORONARY ART STENT OCT95- 3771 INT INSERT LEAD IN VENT 3610 AORTOCORONARY BYPASS NOS 3772 INT INSER LEAD ATRI-VENT 3611 AORTOCOR BYPAS-1 COR ART 3773 INT INSER LEAD IN ATRIUM 3612 AORTOCOR BYPAS-2 COR ART 3774 INT OR REPL LEAD EPICAR 3613 AORTOCOR BYPAS-3 COR ART 3775 REVISION OF LEAD 3614 AORTCOR BYPAS-4+ COR ART 3776 REPL TV ATRI-VENT LEAD 3615 1 INT MAM-COR ART BYPASS 3777 REMOVAL OF LEAD W/O REPL 3616 2 INT MAM-COR ART BYPASS 3778 INSER TEMP PACEMAKER SYS 3617 ABD-CORON ART BYPASS OCT96- 3779 REVIS OR RELOCATE POCKET **Denominator:** Population in MSA or county, age 18 years and older.	
Perforated appendicitis	**Perforated Appendix Admission Rate** **Numerator:** Discharges with ICD-9-CM diagnosis code for perforations or abscesses of appendix (see below) in any field.	K35.0, K35.1, K35.2, K35.3

	All discharges of age 18 years and older. **Exclude:** Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes (outcome of interest):** 5400 AC APPEND W PERITONITIS 5401 ABSCESS OF APPENDIX **ICD-9-CM diagnosis codes (population at risk):** 5400 AC APPEND W PERITONITIS 5409 ACUTE APPENDICITIS NOS 5401 ABSCESS OF APPENDIX 541 APPENDICITIS NOS **Denominator:** Number of discharges with diagnosis code for appendicitis in any field in MSA or county.	
Pneumonia	**Bacterial Pneumonia Admission Rate** **Numerator:** Discharges with ICD-9-CM principal diagnosis code for bacterial pneumonia (see below). All discharges of age 18 years and older. **Exclude:** Discharges with diagnosis code for sickle cell anemia or HB-S disease (see below) in any field. Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes:** 481 PNEUMOCOCCAL PNEUMONIA 48230 STREP PNEUMONIA UNSPEC 4822 H.INFLUENZAE PNEUMONIA 48231 GRP	J13-J14.9, J15.3-J15.4, J15.7-J15.9, J16.0-J16.9, J18.0-J18.9 **EXCLUSION:** **Sickle cell disorders** **D57.0-D57.9**

	A STREP PNEUMONIA 4829 BACTERIAL PNEUMONIA NOS 48232 GRP B STREP PNEUMONIA 4830 MYCOPLASMA PNEUMONIA 48239 OTH STREP PNEUMONIA 4831 CHLAMYDIA PNEUMONIA OCT96- 485 BRONCOPNEUMONIA ORG NOS 4838 OTH SPEC ORG PNEUMONIA 486 PNEUMONIA, ORGANISM NOS **Exclude ICD-9-CM diagnosis codes:** 28260 SICKLE-CELL ANEMIA NOS 28263 SICKLE-CELL/HB-C DISEASE 28261 HB-S DISEASE W/O CRISIS 28269 SICKLE-CELL ANEMIA NEC 28262 HB-S DISEASE WITH CRISIS	
UTIs (urinary tract infections)	**Urinary Tract Infection Admission Rate Numerator:** Discharges with ICD-9-CM principal diagnosis code of urinary tract infection (see below). **Exclude:** Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes:** 59000 CHR PYELONEPHRITIS NOS 59080 PYELONEPHRITIS NOS 59001 CHR PYELONEPH W MED NECR 59081 PYELONEPHRIT IN OTH DIS 59010 AC PYELONEPHRITIS NOS 5909 INFECTION OF KIDNEY NOS 59011 AC PYELONEPHR W MED NECR 5950 AC CYSTITIS 5902 RENAL/PERIRENAL ABSCESS 5959 CYSTITIS NOS 5903 PYELOURETERITIS CYSTICA 5990 URIN TRACT INFECTION NOS	N10.0-N12.9, N15.1-15.9, N30.0-N30.9, N34.0-N34.9, N39.0

	Denominator: Population in MSA or county.	
Adult Asthma exacerbation	**Adult Asthma Admission Rate** **Numerator:** Discharges with ICD-9-CM principal diagnosis code of asthma (see below). All discharges of age 18 years and older. **Exclude:** Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes:** 49300 EXT ASTHMA W/O STAT ASTH 49320 CH OB ASTH W/O STAT ASTH 49301 EXT ASTHMA W STATUS ASTH 49321 CH OB ASTHMA W STAT ASTH 49302 EXT ASTHMA W STATUS ACEX OCT00- 49322 CH OB ASTHMA W STAT ACEX 49310 INT ASTHMA W/O STAT ASTH OCT00- 49311 INT ASTHMA W STATUS ASTH 49390 ASTHMA W/O STATUS ASTHM 49312 INT ASTHMA W STATUS ACEX OCT00- 49391 ASTHMA W STATUS ASTHMAT 49392 ASTHMA W STATUS AC EXAC OCT00- **Denominator:** Population in MSA or county, age 18 years and older.	J45, J46
Amputations (diabetes-related)	**Rate of Lower-extremity Amputation among Patients with Diabetes** **Numerator:** Discharges with ICD-9-CM procedure code for lower-extremity amputation (see below) in any field and diagnosis code of diabetes in any field (see below). All discharges of age 18 years and older.	Z89.4-Z89.7 ***qualify only if registered with diabetes in the Danish National Diabetes Register or if registered with a diagnosis of diabetes (ICD-10:E10-14, H36.0, O24, excluding O24.4) at the same admission as the ACSC**

	Exclude: Trauma (see below). Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM procedure codes:** 8410 LOWER LIMB AMPUTAT NOS 8415 BELOW KNEE AMPUTAT NEC 8411 TOE AMPUTATION 8416 DISARTICULATION OF KNEE 8412 AMPUTATION THROUGH FOOT 8417 ABOVE KNEE AMPUTATION 8413 DISARTICULATION OF ANKLE 8418 DISARTICULATION OF HIP 8414 AMPUTAT THROUGH MALLEOLI 8419 HINDQUARTER AMPUTATION ICD-9-CM diagnosis codes for diabetes: 25000 DMII WO CMP NT ST UNCNTR 25050 DMII OPHTH NT ST UNCNTRL 25001 DMI WO CMP NT ST UNCNTRL 25051 DMI OPHTH NT ST UNCNTRLD 25002 DMII WO CMP UNCNTRLD 25052 DMII OPHTH UNCNTRLD 25003 DMI WO CMP UNCNTRLD 25053 DMI OPHTH UNCNTRLD 25010 DMII KETO NT ST UNCNTRLD 25060 DMII NEURO NT ST UNCNTRL 25011 DMI KETO NT ST UNCNTRLD 25061 DMI NEURO NT ST UNCNTRLD 25012 DMII KETOACD UNCONTROLD 25062 DMII NEURO UNCNTRLD 25013 DMI KETOACD UNCONTROLD 25063 DMI NEURO UNCNTRLD 25020 DMII HPRSM NT ST UNCNTRL 25070 DMII CIRC NT ST UNCNTRLD 25021 DMI HPRSM NT ST UNCNTRLD 25071 DMI CIRC NT ST UNCNTRLD 25022 DMII HPROSMLR UNCONTROLD 25072	**<u>EXCLUSION:</u>** **Traumatic amputations of lower limb** **S78.0-S78.9, S88.0-S88.9, S98.0-S98.4, T05.3-T05.5**

	DMII CIRC UNCNTRLD 25023 DMI HPROSMLR UNCONTROLD 25073 DMI CIRC UNCNTRLD 25030 DMII O CM NT ST UNCNTRLD 25080 DMII OTH NT ST UNCNTRLD 25031 DMI O CM NT ST UNCNTRL 25081 DMI OTH NT ST UNCNTRLD 25032 DMII OTH COMA UNCONTROLD 25082 DMII OTH UNCNTRLD 25033 DMI OTH COMA UNCONTROLD 25083 DMI OTH UNCNTRLD 25040 DMII RENL NT ST UNCNTRLD 25090 DMII UNSPF NT ST UNCNTRL 25041 DMI RENL NT ST UNCNTRLD 25091 DMI UNSPF NT ST UNCNTRLD 25042 DMII RENAL UNCNTRLD 25092 DMII UNSPF UNCNTRLD 25043 DMI RENAL UNCNTRLD 25093 DMI UNSPF UNCNTRLD **Exclude: Trauma** **ICD-9-CM diagnosis codes:** 8950 AMPUTATION TOE 8971 AMPUTAT BK, UNILAT-COMPL 8951 AMPUTATION TOE-COMPLICAT 8972 AMPUT ABOVE KNEE, UNILAT 8960 AMPUTATION FOOT, UNILAT 8973 AMPUT ABV KN, UNIL-COMPL 8961 AMPUT FOOT, UNILAT-COMPL 8974 AMPUTAT LEG, UNILAT NOS 8962 AMPUTATION FOOT, BILAT 8975 AMPUT LEG, UNIL NOS-COMP 8963 AMPUTAT FOOT, BILAT-COMP 8976 AMPUTATION LEG, BILAT 8970 AMPUT BELOW KNEE, UNILAT 8977 AMPUTAT LEG, BILAT-COMPL **Denominator:** Population in MSA or county, age 18 years and older.	

[1]Transfers imply that if a discharge date is followed by another admission date with an overlap of +/- 1 day this is counted as one admission. [2]The exclusion of obstetric admissions was performed if any diagnostic codes for obstetric diagnoses were present as a secondary diagnosis at the same admission as the ACSC. The obstetric diagnostic codes included: O0.0-O99.9.

Covariates

Appendix 5: Information on socioeconomic position (SEP) obtained from Statistics Denmark.
Education level
< 10 years
10-15 years
> 15 years
Civil status
Living alone/single
Cohabitation
Partners
Married

Appendix 6: Information on chronic diseases included in the Charlson Comorbidity Index obtained from the Danish National Patient Register		
	ICD-8	ICD-10
Myocardial infarction	410	I21;I22;I23
Congestive heart failure	427.09, 427.10, 427.11, 427.19, 428.99, 782.49	I50; I11.0; I13.0; I13.2
Peripheral vascular disease	440, 441, 442, 443, 444, 445,	I70; I71; I72; I73; I74; I77
Cerebrovascular disease	430-438	I60-I69; G45; G46
Dementia	290.09-290.19, 293.09	F00-F03; F05.1; G30
Chronic pulmonary disease	490-493, 515-518	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3
Connective tissue disease	712, 716, 734, 446, 135.99	M05; M06; M08; M09;M30;M31; M32; M33; M34; M35; M36; D86
Ulcer disease	530.91, 530.98, 531-534,	K22.1; K25-K28
Mild liver disease	571, 573.01, 573.04	B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0
Diabetes mellitus	249.00, 249.06, 249.07, 249.09, 250.00, 250.06, 250.07, 250.09	E10.0, E10.1; E10.9; E11.0; E11.1; E11.9
Hemiplegia	344	G81; G82
Moderate/severe renal Disease	403,404,580-583, 584, 590.09, 593.19, 753.10-753.19, 792	I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61
Diabetes mellitus with chronic complications	249.01-249.05, 249.08, 250.01-250.05, 250.08	E10.2-E10.8; E11.2-E11.8
Any tumour	140-194	C00-C75
Leukaemia	204-207	C91-C95
Lymphoma	200-203, 275.59	C81-C85; C88; C90; C96
Moderate/severe liver Disease	070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.00-456.09	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85
Metastatic solid tumour	195-198, 199	C76-C80

AIDS	079.83	B21-B24

Appendix 7: Information on the ACSC-predisposing medical comorbidity obtained from the Danish National Patient Register, the Danish National Diabetes Register and the Danish National Prescription Registry.

ACSC Outcome	ACSC-predisposing medical comorbidity
Chronic conditions	
Angina	Myocardial infarction[1]
CHF exacerbation	CHF[1]
HTN	Myocardial infarction[1] CHF[1] Cerebrovascular disease[1] Peripheral vascular disease[1]
Diabetes-related ACSCs	Diabetes[2]
COPD exacerbation	Chronic pulmonary disease[1] or Redemption of at least 2 prescriptions of drugs for obstructive airway diseases within 6 months[3]
Adult asthma exacerbation	Chronic pulmonary disease[1] or Redemption of at least 2 prescriptions of drugs for obstructive airway diseases within 6 months[3]
Acute conditions	
Perforated appendicitis	-
Pneumonia	-
UTI	-

[1]Obtained from the Danish National Patient Register using the algorithm defined in the Charlson Comorbidity Index (see appendix 6).
[2]Obtained from the Danish National Diabetes Register (see appendix 8)
[3]Obtained from the Danish National Prescriptions Registry (see appendix 9).

Appendix 8: Information on diabetes obtained from the Danish National Diabetes Register.

Algoritm: Individuals were classified as having diabetes on the day where at least one of the following six criteria was met:

1. A diagnosis of diabetes made at any Danish hospital as registered in the Danish National Patient Register (ICD-8:249, 250; ICD-10:E10-14, H36.0, O24, excluding O24.4).
2. A referral to chiropody of diabetic patients as registered in the Danish National Health Service Register.(Andersen *et al.* 2011)
3. Five blood glucose measurements within one year as registered in the Danish National Health Service Register.
4. Two blood glucose measurements per year for five consecutive years as registered in the Danish National Health Service Register.
5. Two redemptions of oral anti-diabetic drugs within six months as registered in the Danish National Prescription Registry.
6. Two redemptions of prescribed insulin as registered in the Danish National Prescription Registry.

Appendix 9: ATC codes for drugs for obstructive airway disease obtained from the Danish National Prescription Registry.

ATC codes	**Type of drug**
R03	Drugs for obstructive airway diseases
R03A	Adrenergics, inhalants
R03B	Other drugs for obstructive airway diseases, inhalants
R03C	Adrenergics for systemic use
R03D	Other systemic drugs for obstructive airway diseases

Appendix 10: Information on substance abuse disorders obtained from the Danish National Patient Register and the Danish Psychiatric Central Register.

	ICD-8	ICD-10
Drug related		
Opioids	304.09, 304.19	F11.0–F11.9
Cannabinoids	304.59	F12.0–F12.9
Sedatives/hypnotics	304.29, 304.39	F13.0–F13.9
Cocaine	304.49	F14.0–F14.9
Other stimulants	304.69	F15.0–15.9
Hallucinogens	304.79	F16.0–F16.9
Other and multiple drugs	304.89, 304.99	F18.0–F19.9
Alcohol related		
Alcohol psychosis and abuse syndrome	291.09–291.99 303.09–303.99	F10.0–F10.9
Cirrhosis and steatosis of the liver	571.09, 571.10, 571.19	K70.0–K70.9
Esophageal varices	456.00, 456.01, 456.09	I85.0–I85.9

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Corresponding Manuscript Page Number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **X**	**1**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **X**	**2-3**
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **X**	**4**
Objectives	3	State specific objectives, including any prespecified hypotheses **X**	**5**
Methods			
Study design	4	Present key elements of study design early in the paper **X**	**5**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **X**	**5**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **X** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	**5-6**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	**N/A**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **X**	**6-9**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **X**	**6-9**
Bias	9	Describe any efforts to address potential sources of bias **X**	**9**
Study size	10	Explain how the study size was arrived at **N/A**	**N/A**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **X**	**8-10**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **X**	**9-10**
		(*b*) Describe any methods used to examine subgroups and	**10**

interactions **X**	
(*c*) Explain how missing data were addressed **X**	**9**
(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed **N/A** *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	**N/A**
(*e*) Describe any sensitivity analyses **X**	**10**

Continued on next page

Results			Corresponding Manuscript Page Number
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **X**	**10-11**
		(b) Give reasons for non-participation at each stage **N/A**	**N/A**
		(c) Consider use of a flow diagram	**N/A**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **X**	**11, 27-28 (Table 1)**
		(b) Indicate number of participants with missing data for each variable of interest **X**	**27-28 (Table 1)**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) **X**	**11**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **X**	**11**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	**N/A**
		Cross-sectional study—Report numbers of outcome events or summary measures	**N/A**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **X**	**11, 13, 30-31 (Table 2), 33 (Table 4)**
		(*b*) Report category boundaries when continuous variables were categorized **X**	**8-10**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **N/A**	**N/A**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **X**	**12-13, 32 (Table 3), 34-35 (Figures 1 and 2)**
Discussion			
Key results	18	Summarise key results with reference to study objectives **X**	**14**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **X**	**15-16**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **X**	**15-16**
Generalisability	21	Discuss the generalisability (external validity) of the study results **X**	**15-16**
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **X**	**1, 10**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Depression and Risk for Hospitalizations and Rehospitalizations for Ambulatory Care-Sensitive Conditions in Denmark: a Population-Based Cohort Study

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Depression and Risk for Hospitalizations and Rehospitalizations for Ambulatory Care-Sensitive Conditions in Denmark: a Population-Based Cohort Study

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ABSTRACT

Objective: Hospitalizations for ambulatory care-sensitive conditions (ACSCs), a group of chronic and acute illnesses considered not to require inpatient treatment if timely and appropriate ambulatory care is received, and early rehospitalizations are common and costly. We sought to determine whether individuals with depression are at increased risk for hospitalizations for ACSCs, and rehospitalization for the same or another ACSC, within 30 days.

Design: National, population-based cohort study.

Setting: Denmark.

Participants: 5,049,353 individuals ≥ 18 years old between January 1, 2005 and December 31, 2013.

Measurements: Depression was ascertained via psychiatrist diagnoses in the Danish Psychiatric Central Register or antidepressant prescription redemption from the Danish National Prescription Registry. Hospitalizations for ACSCs and rehospitalizations within 30 days were identified using the Danish National Patient Register.

Results: Overall, individuals with depression were 2.35-times more likely to be hospitalized for an ACSC (95% Confidence Interval [95%CI]: 2.32, 2.37) versus those without depression after adjusting for age, sex, and calendar period, and 1.45-times more likely after adjusting for socioeconomic factors, comorbidities, and primary care utilization (95%CI: 1.43, 1.46). After adjusting for ACSC-predisposing comorbidity, depression was associated with significantly greater risk for hospitalizations for all chronic (e.g., angina, diabetes complications, congestive heart failure exacerbation) and acute ACSCs (e.g., pneumonia) compared to those without depression. Compared to those without depression, persons with depression were 1.21-times more likely to be rehospitalized within 30 days for the same ACSC (95%CI: 1.18, 1.24) and

1.19-times more likely to be rehospitalized within 30 days for a different ACSC (95%CI: 1.15, 1.23).

Conclusions: Individuals with depression are at increased risk for hospitalizations for ACSCs, and once discharged are at elevated risk for rehospitalizations within 30 days for ACSCs.

ARTICLE SUMMARY

- A strength of our study is that we followed a nationwide, population-based cohort with nearly no loss to follow-up.
- Our use of data from a country with a national healthcare system with universal access to health care and a relatively homogeneous population may impact generalizability to other countries with more ethnically diverse populations and different healthcare settings.
- Although we lack data on potential mediators of an association between depression and ambulatory care-sensitive condition (ACSC)-related hospitalizations such as health-risk behaviors (e.g., smoking, sedentary lifestyle), previous studies that controlled for health-risk behaviors found that the association between depression and greater risk for ACSC-related hospitalizations was independent of these factors.
- Our data lacks the degree of detail required to determine if adequate treatment for depression could moderate the adverse outcomes seen here.

INTRODUCTION

Hospitalizations for chronic illnesses and their sequelae are a major contributor to rising healthcare costs in Western societies.[1] In the U.S., an estimated 10% of all hospitalizations may be preventable,[2] such as those for ambulatory care-sensitive conditions (ACSCs), a set of chronic (e.g., diabetes with complications, congestive heart failure [CHF], chronic obstructive pulmonary disease [COPD] exacerbation) and acute illnesses (e.g., bacterial pneumonia, urinary tract infection [UTI]) considered not to require inpatient treatment if patients receive timely and appropriate ambulatory care.[3] Hospitalizations for ACSCs have been estimated to cost the U.S. $31.9 billion and £1.4 billion in the U.K. annually.[4,5] Moreover, early rehospitalizations, some of which may be due to ACSCs, are common and costly to health systems.[6] With the advent of accountable care organizations in the U.S. and other efforts to improve healthcare delivery worldwide, health systems are increasingly trying to prevent hospitalizations for ACSCs and early rehospitalizations in an effort to reduce healthcare spending.[7-9]

Depression is highly prevalent worldwide,[10] and is independently associated with more chronic disease sequelae,[11] greater healthcare costs,[12] and increased mortality.[13] Importantly, depression is amenable to treatment and could be a potentially modifiable risk factor for ACSC-related hospitalizations. Depression may increase hospitalizations for ACSCs through factors such as reduced adherence to chronic disease treatments and reduced self-care.[14] While prior studies have found higher risk of hospitalizations for ACSCs and/or early rehospitalizations among persons with depression, they have been limited to single centers,[15,16] specific chronic disease populations,[17] geographically-defined health systems,[16,17] and older adults.[18] Furthermore, previous research on depression and risk of rehospitalizations within 30 days has not focused on potentially preventable rehospitalizations,[15,16,18,19] such as rehospitalizations

within 30 days for an ACSC, an outcome that is arguably of particular importance to health systems and health policy makers. Also, it remains unknown whether depressed individuals are at greater risk of ACSC-related hospitalizations and rehospitalizations simply because they are more likely to have underlying chronic diseases.[20,21]

Utilizing data from a population-based cohort of five million Danish adults, we sought to determine if individuals with depression, defined by a clinical diagnosis and/or receiving antidepressant treatment, are at increased risk for hospitalizations for ACSCs after adjusting for demographics, socioeconomic factors, comorbidity (ACSC-predisposing and non-ACSC-predisposing comorbidity), and primary care utilization. Further, we examined whether persons with depression who have been hospitalized for an ACSC are at greater risk for rehospitalization for the same, or another ACSC, within 30 days. We hypothesized that depression would be independently associated with increased risk for hospitalizations for ACSCs as well as rehospitalizations within 30 days for either the same or a different ACSC.

METHODS

Population

We conducted a population-based cohort study of all adults ≥ 18 years old, alive and residing in Denmark at least one day between January 1, 2005 and December 31, 2013. The cohort was constructed using data from the Danish Civil Registration System,[22] which includes data on sex, date of birth, vital status, and emigration since January 1, 1968. In the register, Danish residents are each assigned a unique personal identification number which links to person-level data.[22]

The Danish Data Protection Agency and the Danish Health and Medicine Authority approved the study protocol, and requirement for informed consent was waived.

Primary Independent Variable

Our primary independent variable of interest was depression as identified by either psychiatric diagnosis or filling at least one antidepressant prescription. Depression was treated as a time-dependent variable (i.e., an individual without a recorded depression diagnosis or antidepressant prescription redemption at baseline could be diagnosed with depression or redeem an antidepressant prescription during the follow-up period, moving from the "unexposed" to the "exposed" group). Information on psychiatric diagnoses was obtained from the Danish Psychiatric Central Register[23] (see Appendix 1), which includes diagnostic information on all psychiatric hospitalizations from 1969 onwards and outpatient specialty mental health visits from 1995 onwards.[23] Prescription fills for antidepressant prescriptions (i.e. selective serotonin re-uptake inhibitors, monoamine oxidase inhibitors, and other non-tricyclic (TCA) antidepressants, see Appendix 1) were identified using the Danish National Prescription Registry.[24] This register includes data on all prescriptions dispensed at Danish pharmacies since 1995, including purchase date and classification of drugs according to the Anatomical Therapeutic Chemical Classification.[25] We excluded TCA prescriptions from our depression definition because of their frequent use for insomnia and/or pain. We also excluded bupropion or trazodone prescriptions since neither was approved for treating depression in Denmark during the study period. Individuals with schizophrenia, schizoaffective disorders or bipolar disorder were censored at date of diagnosis (see Appendix 2) and excluded from analyses.

Outcomes of Interest

Our primary outcome of interest was hospitalization for one of 12 ACSCs as defined by the Agency for Healthcare Research and Quality (AHRQ) (see Appendix 3).[2] Prior to December 31, 1993, register-based diagnoses were based on the Danish version of the International Classification of Diseases, 8th Revision (ICD-8).[26] From January 1, 1994 forward, the Danish version of the ICD-10[27] was used. Since the AHRQ-defined ACSCs were originally derived using ICD-9 diagnoses, we included eight AHRQ-defined ACSCs (i.e., angina without concomitant cardiovascular procedures, COPD exacerbation, CHF exacerbation, diabetes with short-term complications, diabetes with long-term complications, uncontrolled diabetes, hypertension (HTN), and appendicitis with perforation) that were translated into ICD-10 diagnosis codes and validated in a previous study.[28] We also included four AHRQ-defined ACSCs (i.e., bacterial pneumonia, diabetes-related lower extremity amputations, UTIs, and adult asthma exacerbations) based on ICD-10 codes used in prior Danish register-based studies.[29-32] We further divided ACSCs into five "chronic" ACSCs (i.e., angina, CHF exacerbation, HTN, diabetes-related, COPD/adult asthma exacerbation) and three "acute" ACSCs (i.e., appendicitis with perforation, pneumonia, and UTI). We used the Danish National Patient Register,[33] which contains information on all medical hospitalizations since January 1, 1977 and outpatient visits since January 1, 1995,[33] to obtain information on hospitalizations with principal discharge diagnoses for ACSCs occurring between January 1, 2005 and December 31, 2013. If a discharge was followed by an admission within one day, it was considered a transfer and counted as one admission only. We excluded hospitalizations with secondary obstetric diagnoses (ICD-10 codes: O00.0-O99.9).

Our secondary outcome of interest was rehospitalization for an ACSC within 30 days of discharge from the initial ACSC-related hospitalization. We counted rehospitalizations that were

for the same ACSC, or for a different ACSC, using data from the Danish National Patient Register.

Socioeconomic Factors, Comorbid Medical Conditions, and Substance Abuse Disorders

Information on marital/partnered status and education was obtained from Statistics Denmark and the Danish Educational Registers, respectively (see Appendix 4).[34,35] We categorized marital/partnered status as living with a partner (i.e., married, registered partnership, or cohabitation) or living alone (i.e., living without a partner, including widows/widowers). We classified maximum educational level attained into the following three categories based on the United Nations Educational, Scientific and Cultural Organization's International Standard Classification of Education: low (<10 years), middle (10–15 years), and high (>15 years).[36]

For the five chronic ACSCs, we defined ACSC-predisposing medical comorbidity specific for each ACSC in question (see Appendix 5). Information on ACSC-predisposing medical comorbidity and non-ACSC predisposing medical comorbidity was obtained from the Danish National Patient Register and based on Charlson Comorbidity Index (CCI) categories[37] (see Appendix 6) (e.g., myocardial infarction as ACSC-predisposing medical comorbidity for angina hospitalization, etc.), with two exceptions. Diabetes diagnoses were obtained from the Danish National Diabetes Register between January 1, 1990 and December 31, 2013 (see Appendix 7).[38] Chronic pulmonary disease was identified as either a diagnosis based on the CCI category obtained from the Danish National Patient Register or ≥ two prescription redemptions within a six month period for medications treating obstructive airway diseases (see Appendix 8) as obtained from the Danish National Prescription Registry. Non-ACSC predisposing medical comorbidity included all remaining CCI diagnostic categories. We did not define ACSC-predisposing medical comorbidity for the three acute ACSCs.

Data on substance abuse (excluding tobacco abuse) was obtained from the Danish Psychiatric Central Register or the Danish National Patient Register (see Appendix 9).

Primary Care Utilization

We obtained information on day-time face-to-face visits with primary care physicians (PCPs) or other primary care staff from the Danish National Health Service Register,[39] which has been collecting primary care administrative data since January 1, 1990. To reduce the chances of including a primary care visit that directly resulted in an ACSC-related hospitalization, we constructed a time-dependent variable counting the number of primary care visits from 10-375 days before any given day. We categorized primary care visits into three equally-sized categories of low, medium, or high utilization based on observed frequencies (i.e., 0-2, 3-9 or ≥10 visits).

Statistical Analysis

We compared individuals with depression to those without depression using Poisson regression models in order to estimate incidence rate ratios (IRRs) for hospitalizations for ACSCs and subsequent rehospitalization within 30 days for an ACSC. We estimated corresponding 95% Confidence Intervals (95%CIs) using cluster robust variance estimation to account for interperson correlation and dichotomy of rehospitalization. In these analyses, our outcomes of interest were a count of the number of hospitalizations for ACSCs. Age and calendar period were adjusted for using two-year and one-year age and time bands, respectively. All variables (including depression status), except sex, were treated as time-dependent. Individuals contributed at-risk time from January 1, 2005 or from their 18th birthday, whichever came last, in different time bands based upon the different covariate combinations they enter with during follow-up. Within each of these combinations, we counted the number of ACSC-related hospitalizations. These methods allowed for us to count only ACSC-related

hospitalizations that occurred after registration of a depression diagnosis and/or redemption of an antidepressant prescription. Censoring occurred at date of death, emigration, date of bipolar disorder or schizophrenia diagnosis, or on December 31, 2013, whichever came first.

For each ACSC-related hospitalization outcome, we fitted five risk models, adjusting sequentially for demographics (i.e., age, sex and calendar period), socioeconomic factors (i.e., marital/partnered status and education), ACSC-predisposing medical comorbidity (with each comorbid condition entered individually), other comorbidity (i.e., non-ACSC-predisposing medical comorbidity entered individually and substance abuse), and primary care utilization. All model covariates were chosen *a priori* based on prior studies identifying their potential associations with both depression and healthcare utilization outcomes.[12,16,17,40] To address missing data on education, we conducted multiple imputation using five imputed data sets according to methods developed by Rubin.[41]

We performed two pre-specified sub-analyses. First, we examined whether the association between depression and risk for ACSC-related hospitalizations was modified by age. To do so, we repeated our Poisson regressions stratified by three age categories: ≤ 40 years old, 41-64 years old, and ≥ 65 years old. Second, we examined the associated risk for hospitalizations for chronic and acute ACSCs based on time since depression diagnosis in models adjusted for demographics.

In order to determine if an association between depression and risk for hospitalizations for ACSCs was impacted by our depression definition, we performed a pre-specified sensitivity analysis in which we repeated our regressions using three different depression definitions: antidepressant prescription alone, outpatient psychiatric visit-based diagnosis alone or psychiatric hospitalization for depression.

We fitted three models examining risk for rehospitalization within 30 days for an ACSC. The first model adjusted for demographics, the second included adjustment for socioeconomic factors and the third for medical and substance abuse comorbidities. Our outcome of interest in these models was time to rehospitalization for an ACSC within 30 days of discharge from the initial ACSC-related hospitalization. Individuals were at risk for the outcome on the day of discharge from their ACSC-related hospitalization. All variables in these analyses excluding sex were treated as time-dependent.

We used two-sided significance tests for all analyses with statistical significance set at $P < 0.05$. Analyses were performed using STATA 13 (Stata Corporation, College Station, TX).

RESULTS

We followed a cohort of 5,049,353 individuals for a total of 38,674,363 person-years at risk, including 1,319,896 (26.1%) persons diagnosed with depression or who had redeemed an antidepressant prescription during the study period. Of those with depression, 1,182,495 (89.6%) cases were from antidepressant prescription fills while 137,401 (10.4%) cases were diagnosed by mental health specialists in outpatient or inpatient contacts. The mean age at initially registered depression diagnosis was 49.1 (standard deviation: 19.2) years old.

Table 1 displays the characteristics of our cohort by depression status. During the nine year follow-up period, we identified 1,255,640 hospitalizations for ACSCs, including 542,184 (43.2%) among persons with depression. There were 71.4 ACSC-related hospitalizations per 1,000 person-years among those with depression versus 23.0 per 1,000 person-years among those without depression during the study period.

[Please insert Table 1 here]

Compared to those without depression, the IRR for having any ACSC-related hospitalization was 2.35 (95% CI: 2.32, 2.37) for individuals with depression after adjusting for demographics. This association remained robust after adjusting for socioeconomic factors, and decreased though remained significant after adjusting for possible mediators including comorbidities and PCP visits during the previous year (Table 2).

In comparison to persons without depression, depression was associated with increased risk for hospitalizations for all of the chronic ACSCs even after adjusting for specific chronic ACSC-predisposing medical comorbidity (Table 2), particularly for hospitalizations for angina (IRR: 1.77; 95%CI: 1.73, 1.81), COPD/asthma exacerbations (IRR: 1.88; 95%CI: 1.84, 1.93), and diabetes-related hospitalizations (IRR: 1.83; 95%CI: 1.77, 1.89). Although these results were attenuated by adjusting for additional comorbidity and PCP visits during the previous year, depression remained independently associated with increased risk for hospitalizations for all chronic ACSCs, especially for hospitalizations for COPD/asthma exacerbations (IRR: 1.61; 95%CI: 1.57, 1.65), and diabetes-related hospitalizations (IRR: 1.69; 95%CI: 1.63, 1.75) (Table 2).

Similarly, depression was associated with increased risk for hospitalizations for all three acute ACSCs even after adjusting for medical and substance abuse comorbidity (appendicitis with perforation: IRR: 1.26; 95%CI: 1.21, 1.33; pneumonia: IRR: 1.55; 95%CI: 1.53, 1.56; UTI: 1.74; 95%CI: 1.71, 1.77). These associations remained significant after adjusting for PCP visits during the preceding year.

[Please insert Table 2 here]

When we stratified by age categories, we found that the association between depression and risk for hospitalizations for ACSCs was especially potent for individuals 40 years old or

younger (IRR: 2.06; 1.98, 2.13). Depression was also independently associated with increased risk for hospitalizations for ACSCs among middle-aged and older adults (Table 3).

[Please insert Table 3 here]

In the first year after depression diagnosis, the associated risk for hospitalization for a chronic ACSC was nearly 3-times greater than those without depression (IRR: 2.89; 95%CI: 2.83, 2.96) (Figure 1). The associated risk remained nearly 2.4-times greater than for those without depression (IRR: 2.39, 95%CI: 2.34, 2.43) 10 or more years after depression diagnosis. During the first year after depression diagnosis, the associated risk for hospitalization for an acute ACSC was 3 1/3-times greater than for those without depression (IRR: 3.33, 95%CI: 3.27, 3.40), and the associated risk remained 2 ¼-times higher at ≥ 10 years after depression diagnosis (IRR: 2.25; 95%CI: 2.22, 2.29) (Figure 2).

[Please insert Figure 1 here]

[Please insert Figure 2 here]

In our sensitivity analysis in which we examined whether our results regarding risk for hospitalization for any ACSC were impacted by depression definition, we found that depression defined by antidepressant prescription alone (IRR: 2.31; 95%CI: 2.28, 2.33), outpatient psychiatric visit-based diagnosis alone (IRR: 2.66; 95%CI: 2.56, 2.77) or psychiatric hospitalization for depression (IRR: 2.69; 95%CI: 2.62, 2.77) were all associated increased risk for hospitalization for an ACSC after adjusting for demographics. These associations remained significant after adjusting for socioeconomic factors, comorbidities, and PCP visits in the previous year (antidepressant prescription alone: IRR: 1.44; 95%CI: 1.43, 1.45; outpatient psychiatric visit-based diagnosis: IRR: 1.54; 95%CI: 1.48, 1.60; psychiatric hospitalization for depression: IRR: 1.50; 95%CI: 1.46, 1.54).

Approximately 6.8% of all ACSC-related hospitalizations during the follow-up period were followed by an ACSC-related rehospitalization within 30 days, of which 73.0% were for the same ACSC and 27.0% were for a different ACSC. Of the 85,046 ACSC-related rehospitalizations within 30 days, 42,791 (50.3%) were among those with depression. Compared to those without depression, depression was associated with 1.36-times greater risk for rehospitalization within 30 days for the same ACSC (95%CI: 1.32, 1.39) and 1.44-times greater risk for rehospitalization within 30 days for a different ACSC (95%CI: 1.39, 1.49) after adjusting for age, sex, and calendar period (Table 4). After adjusting for socioeconomic factors and comorbidities, while attenuated, depression remained independently associated with greater risk for rehospitalization within 30 days for the same ACSC (IRR: 1.21; 95%CI: 1.18, 1.24) or another ACSC (IRR: 1.19; 95%CI: 1.15, 1.23).

[Please insert Table 4 here]

DISCUSSION

In this nationwide, population-based longitudinal study of over 5 million individuals, we found that depression was independently associated with higher risk for hospitalizations for both chronic and acute ACSCs and that the associated risk remained high for at least 10 years. To our knowledge, the present study is the first to show that depression was associated with higher risk of rehospitalization for the same or another ACSC within 30 days of an ACSC-related hospitalization. Importantly, we identified that the associated risk of hospitalizations for ACSCs was greater among persons with depression even when we adjusted for the higher prevalence of predisposing chronic diseases in this population.

An increased risk of hospitalization and subsequent rehospitalization for an ACSC among depressed individuals is troubling in light of evidence that some ACSC-related hospitalizations may have negative effects on long-term functioning, cognition and mental health.[42] Depression in-and-of-itself is known to increase the risk of cognitive decline and functional impairment,[43,44] both of which increase risk of ACSC-related hospitalizations.[18,45] Therefore, depressed individuals could be especially at risk for a vicious cycle of hospitalizations, rehospitalizations, and rapid decline.

This study has important implications for development of interventions to prevent costly ACSC-related hospitalizations and rehospitalizations. A potential explanation for our findings is that depressed individuals may not receive timely and/or appropriate ambulatory care for chronic diseases such as diabetes or cardiovascular disease as well as acute diseases such as pneumonia or UTIs. Yet, we found that depression was independently associated with increased risk for hospitalizations for these conditions even in a country, Denmark, with universal access to primary care. Therefore, it could be reasonable to conclude that simply increasing access to primary care may not ameliorate these problems. This interpretation is supported by recent studies evaluating the impact of health care reform in Massachusetts that found improving access to care was not associated with reductions in ACSC-related hospitalizations or rehospitalizations within 30 days among high-risk populations.[46,47]

If expanding access to primary care by itself is insufficient to prevent hospitalizations for ACSCs among at-risk populations such as those with depression, then additional research is needed to identify cost-effective interventions that could reduce these potentially preventable events. One possibility is through ongoing efforts to integrate psychiatric care into primary care and other ambulatory care medical settings. Collaborative care for depression and comorbid

conditions in primary care settings has been proven effective and cost-effective,[48-53] and its cost-effectiveness is in part due to reductions in hospitalizations for comorbid medical conditions.[54] Further studies of sufficient duration and size are needed to determine if collaborative care could prevent ACSC-related hospitalizations among individuals with depression. More research is also needed to ascertain if integrating aspects of collaborative care into existing interventions focusing on improving transitional care from the hospital back to primary care[55,56] could prevent early rehospitalizations for ACSCs. Such research would be of particular interest to accountable care organizations and health policy makers aiming to reduce healthcare costs while simultaneously improving patient outcomes and overall quality of care.

Our study has several strengths and limitations. We followed a nationwide, population-based cohort with nearly no loss to follow-up. However, our use of data from a country with a national healthcare system with universal access to health care and a relatively homogeneous population may impact generalizability. Yet, these factors may enhance internal validity by decreasing the degree socioeconomic factors play in healthcare-seeking behavior, and potentially suggest that our estimates may be overly conservative. Further, our depression definition was based on a combination of psychiatric diagnoses and antidepressant prescription records, potentially introducing selection bias since patients with more severe depression are more likely to be prescribed antidepressants and/or referred to psychiatrists,[57,58] and is further exacerbated by inability to capture depressed individuals who have not sought treatment.[59] However, our sensitivity analysis examining different depression definitions did not yield differing results, and our primary depression definition has been used in prior related research.[43]

While we lack data on potential mediators of an association between depression and ACSC-related hospitalizations such as health-risk behaviors (e.g., smoking, sedentary lifestyle),

previous studies in this area that controlled for health-risk behaviors found that the association between depression and greater risk for ACSC-related hospitalizations was independent of these factors.[17,18] Our data lacks the degree of detail required to determine if adequate treatment for depression could moderate the adverse outcomes seen here. Also, the registers lack detail to sufficiently ascertain illness severity, so we cannot fully exclude the possibility that our findings reflect that when compared to the general population, depressed individuals may present with higher acuity of medical illnesses and a greater burden of comorbidity, necessitating hospitalization for optimal treatment.

In conclusion, in a nationwide study in Denmark, we found that compared to individuals without depression, depression was associated with increased risk for hospitalizations for ACSCs. Furthermore, once hospitalized for an ACSC, depression was associated with greater risk for rehospitalization within 30 days for the same, or another, ACSC. Further research that clarifies the mechanisms linking depression and ACSC-related hospitalizations, and that develops interventions that prevent ACSC-related hospitalizations in persons with depression, is needed given the burden that recurrent hospitalizations places on individuals and society.

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Authorship: Drs. Davydow, Ribe, Pedersen, Prior, Vedsted, Unützer and Vestergaard, and Messrs. Fenger-Grøn and Pedersen fulfill all three of the ICJME criteria for authorship, including: 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, 2) drafting the article or revising it critically for important intellectual content, and 3) final approval of the version to be published.

Transparency Declaration: Dr. Davydow affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Guarantor: Dr. Vestergaard has had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1. Study cohort characteristics

Measure	Depression (n = 1,319,896)			Without Depression (n = 3,782,713)		
	Number of Hospitalizations for ACSCs	Person-Years at Risk	Percentage risk time spent in category (%)	Number of Hospitalizations for ACSCs	Person-Years at Risk	Percentage risk time spent in category (%)
Total	542,184	7,596,536	100.0	713,456	31,077,828	100.0
Age (years)						
≤ 40	28,434	1,771,769	23.3	69,350	11,940,484	38.4
41-64	158,633	3,697,843	48.7	197,925	13,201,867	42.5
≥ 65	355,117	2,126,924	28.0	446,181	5,935,477	19.1
Sex						
Male	231,216	2,884,303	38.0	393,065	16,114,603	51.8
Female	310,968	4,712,233	62.0	320,391	14,963,225	48.2
Calendar period						
2005	47,853	661,461	8.7	79,756	3,564,097	11.5
2006	57,932	711,984	9.4	90,186	3,523,904	11.3
2007	46,477	761,231	10.0	67,588	3,494,327	11.2
2008	51,896	805,396	10.6	71,465	3,475,920	11.2
2009	63,150	848,956	11.2	83,274	3,452,336	11.1
2010	51,567	895,574	11.8	64,832	3,425,594	11.0
2011	74,991	938,720	12.4	89,372	3,405,029	11.0
2012	74,535	972,971	12.8	85,424	3,378,860	10.9
2013	73,783	1,000,243	13.2	81,559	3,358,761	10.8
Marital status						
Living with partner	226,573	3,585,166	47.2	348,530	15,922,753	51.2
Living alone	315,611	4,011,370	52.8	364,926	15,155,075	48.8
Education (years)						
< 10	265,781	2,751,794	36.2	312,769	8,845,177	28.5

10-15	178,680	3,182,588	41.9	249,363	14,267,047	45.9
≥ 16	47,039	1,284,597	16.9	75,866	6,318,611	20.3
Missing	50,684	377,558	5.0	75,458	1,646,993	5.3
Comorbidity						
MI	89,475	261,404	3.4	109,123	556,446	1.8
CHF	118,101	212,889	2.8	137,507	367,223	1.2
Diabetes	155,739	761,878	10.0	165,161	1,567,720	5.0
Cerebrovascular disease	126,796	615,389	8.1	98,828	834,803	2.7
Peripheral vascular disease	79,566	283,055	3.7	70,493	443,853	1.4
Chronic pulmonary disease	229,594	674,995	8.9	208,423	1,339,308	4.3
Dementia	44,638	217,259	2.9	19,519	110,040	0.3
Connective tissue disease	42,814	269,168	3.5	39,087	514,840	1.7
Peptic ulcer disease	69,733	327,298	4.3	53,974	464,831	1.5
Renal disease	45,769	123,767	1.6	50,315	245,853	0.8
Mild liver disease	19,437	129,645	1.7	11,845	159,553	0.5
Moderate/severe liver disease	5,287	27,978	0.4	3,516	34,556	0.1
Paraplegia	7,123	31,836	0.4	4,893	46,060	0.1
Cancer	102,324	608,120	8.0	118,072	1,430,995	4.6
Metastatic carcinoma	12,338	58,013	0.8	13,715	116,930	0.4
HIV/AIDS	1,011	10,673	0.1	998	22,685	0.1
Substance abuse disorders	87,977	792,810	10.4	42,932	881,074	2.8
Primary care visits in prior year						
0-2	119,055	2,487,888	32.7	196,845	17,355,110	55.8
3-9	223,859	3,739,020	49.2	317,381	11,687,211	37.6
≥ 10	199,270	1,369,628	18.0	199,230	2,035,670	6.5

Abbreviations (in alphabetical order): ACSC = ambulatory care-sensitive condition; AIDS = Acquired Immunodeficiency Syndrome; CHF = congestive heart failure; HIV = Human Immunodeficiency Virus; MI = myocardial infarction.

Table 2. The risk of hospitalizations for ambulatory care-sensitive conditions associated with depression compared to individuals without depression

Outcome	Model 1 Adjusted for demographics[a]	Model 2 Adjusted for variables in Model 1 and socioeconomic factors[b]	Model 3 Adjusted for variables in Model 2 and ACSC-predisposing comorbidity	Model 4 Adjusted for variables in Model 3 and non-ACSC-predisposing comorbidity[h] and substance abuse disorders	Model 5 Adjusted for variables in Model 4 and PCP visits in the previous year
	Incidence Rate Ratio (95% Confidence Interval)				
Any ACSC	2.35 (2.32, 2.37)[‡]	2.27 (2.25, 2.29)[‡]		1.53 (1.51, 1.54)[‡]	1.45 (1.43, 1.46)[‡]
Type of ACSC					
Chronic ACSCs					
Angina	2.03 (1.99, 2.08)[‡]	2.00 (1.96, 2.05)[‡]	1.77 (1.73, 1.81)[c‡]	1.52 (1.49, 1.56)[‡]	1.35 (1.32, 1.38)[‡]
COPD/Asthma exacerbation	3.17 (3.09, 3.24)[‡]	2.97 (2.90, 3.04)[‡]	1.88 (1.84, 1.93)[d‡]	1.66 (1.62, 1.70)[‡]	1.61 (1.57, 1.65)[‡]
CHF exacerbation	1.72 (1.67, 1.76)[‡]	1.67 (1.62, 1.71)[‡]	1.22 (1.19, 1.25)[e‡]	1.09 (1.06, 1.12)[‡]	1.06 (1.03, 1.09)[‡]
Diabetes-related	2.88 (2.79, 2.98)[‡]	2.66 (2.57, 2.75)[‡]	1.83 (1.77, 1.89)[f‡]	1.86 (1.80, 1.93)[‡]	1.69 (1.63, 1.75)[‡]
HTN	1.52 (1.48, 1.57)[‡]	1.48 (1.44, 1.53)[‡]	1.37 (1.33, 1.41)[g‡]	1.30 (1.26, 1.34)[‡]	1.18 (1.14, 1.21)[‡]
Acute ACSCs					
Appendicitis with perforation	1.31 (1.25, 1.37)[‡]	1.31 (1.25, 1.37)[‡]		1.26 (1.21, 1.33)[‡]	1.21 (1.16, 1.27)[‡]
Pneumonia	2.35 (2.33, 2.38)[‡]	2.29 (2.27, 2.32)[‡]		1.55 (1.53, 1.56)[‡]	1.50 (1.48, 1.52)[‡]
UTI	2.38 (2.34, 2.42)[‡]	2.34 (2.31, 2.38)[‡]		1.74 (1.71, 1.77)[‡]	1.63 (1.60, 1.66)[‡]

Abbreviations (in alphabetical order): ACSC = ambulatory care-sensitive condition; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; HTN = hypertension; PCP = primary care physician; UTI = urinary tract infection.

[a] Age, sex and calendar period.

[b] Educational level and marital status.

[c] Adjusted for myocardial infarction.

[d] Adjusted for chronic pulmonary disease.

[e] Adjusted for CHF.

[f] Adjusted for diabetes mellitus.

[g] Adjusted for myocardial infarction, CHF, cerebrovascular disease and peripheral vascular disease.

[h] Charlson Comorbidity Index diagnoses not previously adjusted for.

[‡] $P < 0.001$

Table 3. The effect of age on the association of depression with risk of hospitalization for an ambulatory care-sensitive condition

Age categories	Adjusted for demographics	Adjusted for socioeconomic factors	Adjusted for comorbidities	Adjusted for PCP visits
	Incidence Rate Ratio (95% Confidence Interval)			
≤ 40 years old	2.88 (2.78, 3.00)‡	2.83 (2.72, 2.93)‡	2.34 (2.25, 2.43)‡	2.06 (1.98, 2.13)‡
41 – 64 years old	2.93 (2.88, 2.98)‡	2.74 (2.69, 2.78)‡	1.94 (1.91, 1.97)‡	1.73 (1.70, 1.76)‡
Age ≥ 65 years old	2.30 (2.28, 2.32)‡	2.18 (2.15, 2.20)‡	1.34 (1.33, 1.36)‡	1.31 (1.30, 1.32)‡

Abbreviation: PCP = primary care physician.

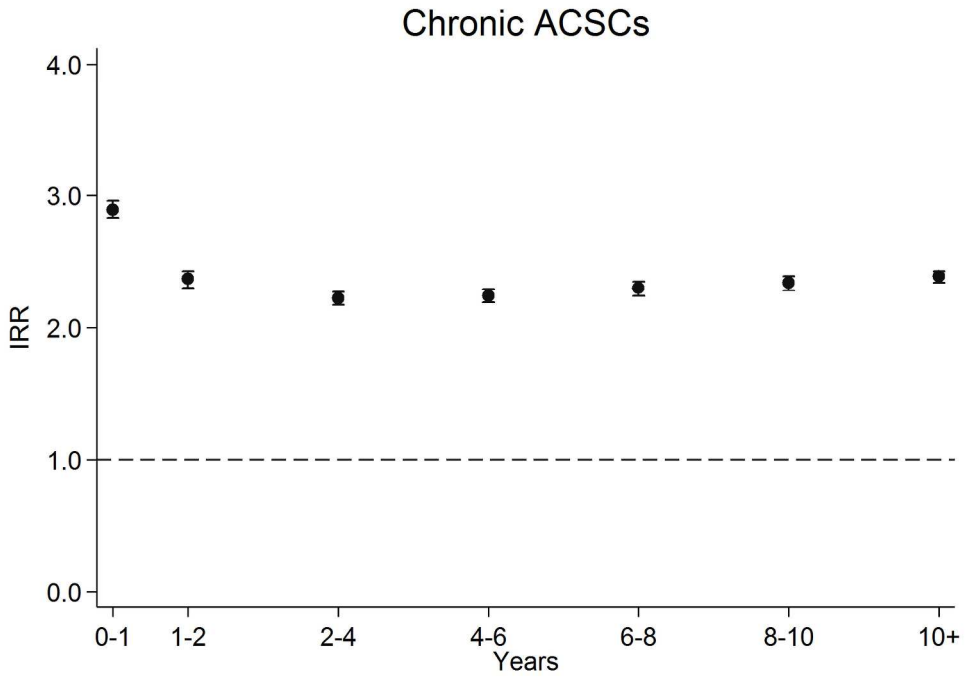
‡ $P < 0.001$

Table 4. The risk of rehospitalization within 30 days for the same or another ambulatory care-sensitive condition among those with depression compared to individuals without depression

Outcome	Model 1 Adjusted for demographics	Model 2 Adjusted for variables in Model 1 and socioeconomic factors	Model 3 Adjusted for variables in Model 2, comorbidity and substance abuse disorders
	Incidence Rate Ratio (95% Confidence Interval)		
Same ACSC	1.36 (1.32, 1.39)‡	1.34 (1.31, 1.38)‡	1.21 (1.18, 1.24)‡
Another ACSC	1.44 (1.39, 1.49)‡	1.42 (1.37, 1.47)‡	1.19 (1.15, 1.23)‡

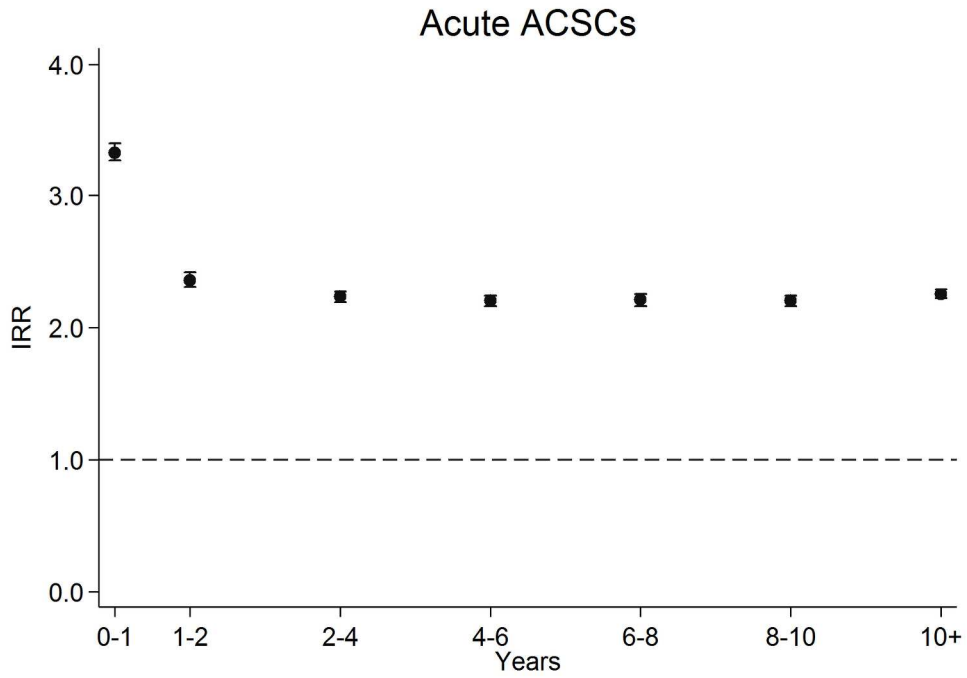
Abbreviation: ACSC = ambulatory care-sensitive condition.

‡ $P < 0.001$



Legend: Figure 1. Risk of hospitalization for a chronic ambulatory care-sensitive condition by time since depression diagnosis

Caption: Abbreviations (in alphabetical order): ACSCs = ambulatory care-sensitive conditions; IRR = incidence rate ratio.
529x384mm (300 x 300 DPI)



Legend: Figure 2. Risk of hospitalization for an acute ambulatory care-sensitive condition by time since depression diagnosis

Caption: Abbreviations (in alphabetical order): ACSCs = ambulatory care-sensitive conditions; IRR = incidence rate ratio.
529x384mm (300 x 300 DPI)

Supplementary Online Material

APPENDIX 1: Information on depression obtained from the Danish Psychiatric Central Register and the Danish National Prescription Registry

A diagnosis of depression was identified if at least one of the following criteria applied:

1. Registration of a diagnosis of depression in the Danish Psychiatric Central Register.
   And/or
2. Registration of at least one prescription of antidepressants redeemed in the Danish National Prescription Registry

Diagnosis according to a record of depression in the Danish Psychiatric Central Register:

ICD-8	ICD-10
296.09, 296.29, 296.99, 298.09, 300.49, and 300.19	F32, F33

Diagnosis according to a record of prescriptions for antidepressants in the Danish National Prescription Registry:

Name	Drug	ATC-codes
SSRI (Selective serotonin re-uptake inhibitors)	Fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, and escitalopram	N06AB
MAOIs (Monoamine oxidase inhibitors)	Isocarboxazid and moclobemide	N06AF, N06AG
Other antidepressants	Mianserin, nefazodone, mirtazapine, venlafaxine, reboxetine, duloxetine, and agomelatine	N06AX

APPENDIX 2: Information on severe mental illness obtained from the Danish Psychiatric Central Register.

	ICD-8	ICD-10
Schizophrenia	295 (excluding 295.79)	F20
Schizoaffective disorders	295.79, 296.8	F25

Bipolar affective disorders	296.19, 296.39	F30, F31

Appendix 3: Information on Ambulatory Care Sensitive Conditions (ACSCs) obtained from the Danish National Patient Register.

Hospitalizations for 12 of the conditions identified by the Agency for Healthcare Research and Quality as ACSCs in their report on prevention quality indicator

Disease	Description in the AHRQ list	ICD-10
Angina	**Angina Without Procedure Admission Rate** **Numerator:** Discharges with ICD-9-CM principal diagnosis code for angina (see below). All discharges of age 18 years and older. **Exclude:** Discharges with a surgical procedure in any field (010-8699). Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes:** 4111 INTERMED CORONARY SYND 4130 ANGINA DECUBITUS 41181 CORONARY OCCLSN W/O MI 4131 PRINZMETAL ANGINA 41189 AC ISCHEMIC HRT DIS NEC 4139 ANGINA PECTORIS NEC/NOS **Denominator:** Population in MSA or county, age 18 years and older.	I20.0, I20.1, I20.8, I20.9, I24.0, I24.1, I24.8, I24.9 **EXCLUSIONS:** **All surgical procedures (starting with a K in the Danish version of the NCSP, which means surgical)**
COPD (Chronic obstructive pulmonary disorder) exacerbation	**Chronic Obstructive Pulmonary Disease (COPD) Admission Rate** **Numerator:** Discharges with ICD-9-CM principal diagnosis code for COPD (see below). All discharges of age 18 years and older.	J20.0-J20.9*, J40.0-J40.9*, J41.0, J41.1, J42.0-J42.9, J43.8, J43.9, J44.0-J44.9, J47.0-J47.9

	Exclude: Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes**: 4660 AC BRONCHITIS* 4920 EMPHYSEMATOUS BLEB 490 BRONCHITIS NOS* 4928 EMPHYSEMA NEC 4910 SIMPLE CHR BRONCHITIS 494 BRONCHIECTASIS -OCT00 4911 MUCOPURUL CHR BRONCHITIS 4940 BRONCHIECTAS W/O AC EXAC 49120 OBS CHR BRNC W/O ACT EXA OCT00- 49121 OBS CHR BRNC W ACT EXA 4941 BRONCHIECTASIS W AC EXAC 4918 CHRONIC BRONCHITIS NEC OCT00- 4919 CHRONIC BRONCHITIS NOS 496 CHR AIRWAY OBSTRUCT NEC * Qualifies only if accompanied by secondary diagnosis of 491.xx, 492.x, or 496 (i.e., any other code on this list). **Denominator:** Population in MSA or county, age 18 years and older.	***qualify only if accompanied by secondary diagnosis of any of the other codes listed under COPD**
CHF (Congestive heart failure) exacerbation	**Congestive Heart Failure (CHF) Admission Rate Numerator:** Discharges with ICD-9-CM principal diagnosis code for CHF (see below). All discharges of age 18 years and older. **Exclude:** Discharges with cardiac procedure codes (see below) in any field. Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2]	I09.0-I09.9 I11.0, I13.0, I13.2, I13.9, I50.0, I50.1, I50.9, I46.9 **<u>EXCLUSION:</u>** **Cardiac procedures**: **KFNG02, KFNG05, KFNA, KFNC, KFT, KFW, KFQ, BFCA01-BFCA07**

	ICD-9-CM diagnosis codes: 39891 RHEUMATIC HEART FAILURE 40413 BEN HYP HRT/REN W CHF&RF 40201 MAL HYPERT HRT DIS W CHF 40491 HYPER HRT/REN NOS W CHF 40211 BENIGN HYP HRT DIS W CHF 40493 HYP HT/REN NOS W CHF&RF 40291 HYPERTEN HEART DIS W CHF 4280 CONGESTIVE HEART FAILURE 40401 MAL HYPER HRT/REN W CHF 4281 LEFT HEART FAILURE 40403 MAL HYP HRT/REN W CHF&RF 4289 HEART FAILURE NOS 40411 BEN HYPER HRT/REN W CHF Exclude ICD-9-CM procedure codes: 3601 PTCA-1 VESSEL W/O AGENT 3619 HRT REVAS BYPS ANAS NEC 3602 PTCA-1 VESSEL WITH AGNT 375 HEART TRANSPLANTATION 3605 PTCA-MULTIPLE VESSEL 3770 INT INSERT PACEMAK LEAD 3606 INSERT CORONARY ART STENT OCT95- 3771 INT INSERT LEAD IN VENT 3610 AORTOCORONARY BYPASS NOS 3772 INT INSER LEAD ATRI-VENT 3611 AORTOCOR BYPAS-1 COR ART 3773 INT INSER LEAD IN ATRIUM 3612 AORTOCOR BYPAS-2 COR ART 3774 INT OR REPL LEAD EPICAR 3613 AORTOCOR BYPAS-3 COR ART 3775 REVISION OF LEAD 3614 AORTCOR BYPAS-4+ COR ART 3776 REPL TV ATRI-VENT LEAD 3615 1 INT MAM-COR ART BYPASS 3777 REMOVAL OF LEAD W/O REPL 3616 2 INT MAM-COR ART BYPASS 3778 INSER TEMP PACEMAKER SYS 3617 ABD-CORON ART BYPASS OCT96- 3779 REVIS OR RELOCATE POCKET	

	Denominator: Population in MSA or county, age 18 years and older.	
Diabetes (with short-term complications)	**Diabetes Short-term Complications Admission Rate** **Numerator:** Discharges with ICD-9-CM principal diagnosis code for short-term complications (ketoacidosis, hyperosmolarity, coma) (see below). All discharges of age 18 years and older. **Exclude**: Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes:** 25010 DM KETO T2, DM CONT 25022 DM W/ HYPROSM T2, DM UNCNT 25011 DM KETO T1, DM CONT 25023 DM W/ HYPROSM T1, DM UNCNT 25012 DM KETO T2, DM UNCONT 25030 DM COMA NEC T2, DM CONT 25013 DM KETO T1, DM UNCONT 25031 DM COMA NEC T1, DM CONT 25020 DM W/ HYPROSM T2, DM CONT 25032 DM COMA NEC T2, DM UNCONT 25021 DM W/ HYPROSM T1, DM CONT 25033 DM COMA NEC T1, DM UNCONT **Denominator:** Population in MSA or county, age 18 years and older.	E10.0, E10.1, E11.0, E11.1,
Diabetes (uncontrolled (without short-term or long-term complications))	**Uncontrolled Diabetes Admission Rate** **Numerator:** Discharges with ICD-9-CM principal diagnosis code for uncontrolled diabetes, without mention of a short-term or long-term complication (see below).	E10.9, E11.9

	All discharges of age 18 years and older. **Exclude:** Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes:** 25002 DM, T2, UNCONT 25003 DM, T1, UNCONT **Denominator:** Population in MSA or county, age 18 years and older. May be combined with diabetes short-term complications as a single indicator.	
Diabetes (with long-term complications)	**Diabetes Long-term Complications Admission Rate** **Numerator:** Discharges with ICD-9-CM principal diagnosis code for long-term complications (renal, eye, neurological, circulatory, or complications not otherwise specified) (see below). All discharges of age 18 years and older. **Exclude:** Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes:** 25040 DM RENAL COMP T2 CONT 25070 DM CIRCU DIS T2 CONT 25041 DM RENAL COMP T1 CONT 25071 DM CIRCU DIS T1 CONT 25042 DM RENAL COMP T2 UNCNT 25072 DM CIRCU DIS T2 UNCNT 25043 DM RENAL COMP T1 UNCNT 25073 DM	E10.2-E10.8, E11.2-E11.8

	CIRCU DIS T1 UNCNT 25050 DM EYE COMP T2 CONT 25080 DM W COMP NEC T2 CONT 25051 DM EYE COMP T1 CONT 25081 DM W COMP NEC T1 CONT 25052 DM EYE COMP T2 UNCNT 25082 DM W COMP NEC T2 UNCNT 25053 DM EYE COMP T1 UNCNT 25083 DM W COMP NEC T1 UNCNT 25060 DM NEURO COMP T2 CONT 25090 DM W COMPL NOS T2 CONT 25061 DM NEURO COMP T1 CONT 25091 DM W COMPL NOS T1 CONT 25062 DM NEURO COMP T2 UNCNT 25092 DM W COMPL NOS T2 UNCNT 25063 DM NEURO COMP T1 UNCNT 25093 DM W COMPL NOS T1 UNCNT **Denominator:** Population in MSA or county, age 18 years and older.	
HTN (Hypertension)	**Hypertension Admission Rate** **Numerator:** Discharges with ICD-9-CM principal diagnosis code for hypertension (see below). All discharges of age 18 years and older. **Exclude:** Discharges with cardiac procedure codes (see below) in any field. Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes**: 4010 MALIGNANT HYPERTENSION 40310 BENIGN HYP HRT DIS W/OUT RF 4019 HYPERTENSION NOS 40390 HYPERTEN HEART DIS W/OUT RF	I10.0-I10.9, I11.9, I12.9, I13.9 **EXCLUSION:** **Cardiac procedures**: **KFNG02, KFNG05, KFNA, KFNC, KFT, KFW, KFQ, BFCA01-BFCA07**

	40200 MAL HYPERTEN HRT DIS W/OUT CHF 40400 MAL HYPER HRT/REN W/OUT CHF/RF 40210 BEN HYPERTEN HRT DIS W/OUT CHF 40410 BEN HYPER HRT/REN W/OUT CHF/RF 40290 HYPERTENSIVE HRT DIS W/OUT CHF 40490 HYPER HRT/REN NOS W/OUT CHF/RF 40300 MAL HYPERT HRT DIS W/OUT RF Exclude ICD-9-CM procedure codes: 3601 PTCA-1 VESSEL W/O AGENT 3619 HRT REVAS BYPS ANAS NEC 3602 PTCA-1 VESSEL WITH AGNT 375 HEART TRANSPLANTATION 3605 PTCA-MULTIPLE VESSEL 3770 INT INSERT PACEMAK LEAD 3606 INSERT CORONARY ART STENT OCT95- 3771 INT INSERT LEAD IN VENT 3610 AORTOCORONARY BYPASS NOS 3772 INT INSER LEAD ATRI-VENT 3611 AORTOCOR BYPAS-1 COR ART 3773 INT INSER LEAD IN ATRIUM 3612 AORTOCOR BYPAS-2 COR ART 3774 INT OR REPL LEAD EPICAR 3613 AORTOCOR BYPAS-3 COR ART 3775 REVISION OF LEAD 3614 AORTCOR BYPAS-4+ COR ART 3776 REPL TV ATRI-VENT LEAD 3615 1 INT MAM-COR ART BYPASS 3777 REMOVAL OF LEAD W/O REPL 3616 2 INT MAM-COR ART BYPASS 3778 INSER TEMP PACEMAKER SYS 3617 ABD-CORON ART BYPASS OCT96- 3779 REVIS OR RELOCATE POCKET **Denominator:** Population in MSA or county, age 18 years and older.	
Perforated appendicitis	**Perforated Appendix Admission Rate** **Numerator:** Discharges with ICD-9-CM diagnosis code for perforations or abscesses of appendix (see below)	K35.0, K35.1, K35.2, K35.3

	in any field. All discharges of age 18 years and older. **Exclude:** Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes (outcome of interest):** 5400 AC APPEND W PERITONITIS 5401 ABSCESS OF APPENDIX **ICD-9-CM diagnosis codes (population at risk):** 5400 AC APPEND W PERITONITIS 5409 ACUTE APPENDICITIS NOS 5401 ABSCESS OF APPENDIX 541 APPENDICITIS NOS **Denominator:** Number of discharges with diagnosis code for appendicitis in any field in MSA or county.	
Pneumonia	**Bacterial Pneumonia Admission Rate** **Numerator:** Discharges with ICD-9-CM principal diagnosis code for bacterial pneumonia (see below). All discharges of age 18 years and older. **Exclude:** Discharges with diagnosis code for sickle cell anemia or HB-S disease (see below) in any field. Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes:** 481 PNEUMOCOCCAL PNEUMONIA 48230 STREP PNEUMONIA UNSPEC	J13-J14.9, J15.3-J15.4, J15.7-J15.9, J16.0-J16.9, J18.0-J18.9 **EXCLUSION:** **Sickle cell disorders** **D57.0-D57.9**

	4822 H.INFLUENZAE PNEUMONIA 48231 GRP A STREP PNEUMONIA 4829 BACTERIAL PNEUMONIA NOS 48232 GRP B STREP PNEUMONIA 4830 MYCOPLASMA PNEUMONIA 48239 OTH STREP PNEUMONIA 4831 CHLAMYDIA PNEUMONIA OCT96- 485 BRONCOPNEUMONIA ORG NOS 4838 OTH SPEC ORG PNEUMONIA 486 PNEUMONIA, ORGANISM NOS **Exclude ICD-9-CM diagnosis codes:** 28260 SICKLE-CELL ANEMIA NOS 28263 SICKLE-CELL/HB-C DISEASE 28261 HB-S DISEASE W/O CRISIS 28269 SICKLE-CELL ANEMIA NEC 28262 HB-S DISEASE WITH CRISIS	
UTIs (urinary tract infections)	**Urinary Tract Infection Admission Rate** **Numerator:** Discharges with ICD-9-CM principal diagnosis code of urinary tract infection (see below). **Exclude:** Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes:** 59000 CHR PYELONEPHRITIS NOS 59080 PYELONEPHRITIS NOS 59001 CHR PYELONEPH W MED NECR 59081 PYELONEPHRIT IN OTH DIS 59010 AC PYELONEPHRITIS NOS 5909 INFECTION OF KIDNEY NOS 59011 AC PYELONEPHR W MED NECR 5950 AC CYSTITIS 5902 RENAL/PERIRENAL ABSCESS 5959 CYSTITIS NOS 5903 PYELOURETERITIS CYSTICA 5990 URIN TRACT INFECTION NOS	N10.0-N12.9, N15.1-15.9, N30.0-N30.9, N34.0-N34.9, N39.0

	Denominator: Population in MSA or county.	
Adult Asthma exacerbation	**Adult Asthma Admission Rate** **Numerator:** Discharges with ICD-9-CM principal diagnosis code of asthma (see below). All discharges of age 18 years and older. **Exclude:** Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes:** 49300 EXT ASTHMA W/O STAT ASTH 49320 CH OB ASTH W/O STAT ASTH 49301 EXT ASTHMA W STATUS ASTH 49321 CH OB ASTHMA W STAT ASTH 49302 EXT ASTHMA W STATUS ACEX OCT00- 49322 CH OB ASTHMA W STAT ACEX 49310 INT ASTHMA W/O STAT ASTH OCT00- 49311 INT ASTHMA W STATUS ASTH 49390 ASTHMA W/O STATUS ASTHM 49312 INT ASTHMA W STATUS ACEX OCT00- 49391 ASTHMA W STATUS ASTHMAT 49392 ASTHMA W STATUS AC EXAC OCT00- **Denominator:** Population in MSA or county, age 18 years and older.	J45, J46
Amputations (diabetes-related)	**Rate of Lower-extremity Amputation among Patients with Diabetes** **Numerator:** Discharges with ICD-9-CM procedure code for lower-extremity amputation (see below) in any field and diagnosis code of diabetes in any field (see below). All discharges of age 18 years and older.	Z89.4-Z89.7 ***qualify only if registered with diabetes in the Danish National Diabetes Register or if registered with a diagnosis of diabetes (ICD-10:E10-14, H36.0, O24, excluding O24.4) at the same admission as the ACSC**

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	Exclude: Trauma (see below). Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM procedure codes:** 8410 LOWER LIMB AMPUTAT NOS 8415 BELOW KNEE AMPUTAT NEC 8411 TOE AMPUTATION 8416 DISARTICULATION OF KNEE 8412 AMPUTATION THROUGH FOOT 8417 ABOVE KNEE AMPUTATION 8413 DISARTICULATION OF ANKLE 8418 DISARTICULATION OF HIP 8414 AMPUTAT THROUGH MALLEOLI 8419 HINDQUARTER AMPUTATION ICD-9-CM diagnosis codes for diabetes: 25000 DMII WO CMP NT ST UNCNTR 25050 DMII OPHTH NT ST UNCNTRL 25001 DMI WO CMP NT ST UNCNTRL 25051 DMI OPHTH NT ST UNCNTRLD 25002 DMII WO CMP UNCNTRLD 25052 DMII OPHTH UNCNTRLD 25003 DMI WO CMP UNCNTRLD 25053 DMI OPHTH UNCNTRLD 25010 DMII KETO NT ST UNCNTRLD 25060 DMII NEURO NT ST UNCNTRL 25011 DMI KETO NT ST UNCNTRLD 25061 DMI NEURO NT ST UNCNTRLD 25012 DMII KETOACD UNCONTROLD 25062 DMII NEURO UNCNTRLD 25013 DMI KETOACD UNCONTROLD 25063 DMI NEURO UNCNTRLD 25020 DMII HPRSM NT ST UNCNTRL 25070 DMII CIRC NT ST UNCNTRLD 25021 DMI HPRSM NT ST UNCNTRLD 25071 DMI CIRC NT ST UNCNTRLD	**EXCLUSION:** **Traumatic amputations of lower limb** **S78.0-S78.9, S88.0-S88.9, S98.0-S98.4, T05.3-T05.5**

	25022 DMII HPROSMLR UNCONTROLD 25072 DMII CIRC UNCNTRLD 25023 DMI HPROSMLR UNCONTROLD 25073 DMI CIRC UNCNTRLD 25030 DMII O CM NT ST UNCNTRLD 25080 DMII OTH NT ST UNCNTRLD 25031 DMI O CM NT ST UNCNTRL 25081 DMI OTH NT ST UNCNTRLD 25032 DMII OTH COMA UNCONTROLD 25082 DMII OTH UNCNTRLD 25033 DMI OTH COMA UNCONTROLD 25083 DMI OTH UNCNTRLD 25040 DMII RENL NT ST UNCNTRLD 25090 DMII UNSPF NT ST UNCNTRL 25041 DMI RENL NT ST UNCNTRLD 25091 DMI UNSPF NT ST UNCNTRLD 25042 DMII RENAL UNCNTRLD 25092 DMII UNSPF UNCNTRLD 25043 DMI RENAL UNCNTRLD 25093 DMI UNSPF UNCNTRLD **Exclude: Trauma** **ICD-9-CM diagnosis codes:** 8950 AMPUTATION TOE 8971 AMPUTAT BK, UNILAT-COMPL 8951 AMPUTATION TOE-COMPLICAT 8972 AMPUT ABOVE KNEE, UNILAT 8960 AMPUTATION FOOT, UNILAT 8973 AMPUT ABV KN, UNIL-COMPL 8961 AMPUT FOOT, UNILAT-COMPL 8974 AMPUTAT LEG, UNILAT NOS 8962 AMPUTATION FOOT, BILAT 8975 AMPUT LEG, UNIL NOS-COMP 8963 AMPUTAT FOOT, BILAT-COMP 8976 AMPUTATION LEG, BILAT 8970 AMPUT BELOW KNEE, UNILAT 8977 AMPUTAT LEG, BILAT-COMPL **Denominator:** Population in MSA or county, age 18 years and older.	

[1]Transfers imply that if a discharge date is followed by another admission date with an overlap of +/- 1 day this is counted as one admission. [2]The exclusion of obstetric admissions was performed if any diagnostic codes for obstetric diagnoses were present as a secondary diagnosis at the same admission as the ACSC. The obstetric diagnostic codes included: O0.0-O99.9.		

Appendix 4: Information on socioeconomic position (SEP) obtained from Statistics Denmark.
Education level
< 10 years
10-15 years
> 15 years
Civil status
Living alone/single
Cohabitation
Partners
Married

Appendix 5: Information on the ACSC-predisposing medical comorbidity obtained from the Danish National Patient Register, the Danish National Diabetes Register and the Danish National Prescription Registry.

ACSC Outcome	ACSC-predisposing medical comorbidity
Chronic conditions	
Angina	Myocardial infarction[1]
CHF exacerbation	CHF[1]
HTN	Myocardial infarction[1] CHF[1] Cerebrovascular disease[1] Peripheral vascular disease[1]
Diabetes-related ACSCs	Diabetes[2]
COPD exacerbation	Chronic pulmonary disease[1] or Redemption of at least 2 prescriptions of drugs for obstructive airway diseases within 6 months[3]
Adult asthma exacerbation	Chronic pulmonary disease[1] or Redemption of at least 2 prescriptions of drugs for obstructive airway diseases within 6 months[3]
Acute conditions	
Perforated appendicitis	-
Pneumonia	-

UTI	-

[1]Obtained from the Danish National Patient Register using the algorithm defined in the Charlson Comorbidity Index (see appendix 6).
[2]Obtained from the Danish National Diabetes Register (see appendix 7)
[3]Obtained from the Danish National Prescriptions Registry (see appendix 8).

Appendix 6: Information on chronic diseases included in the Charlson Comorbidity Index obtained from the Danish National Patient Register

	ICD-8	ICD-10
Myocardial infarction	410	I21;I22;I23
Congestive heart failure	427.09, 427.10, 427.11, 427.19, 428.99, 782.49	I50; I11.0; I13.0; I13.2
Peripheral vascular disease	440, 441, 442, 443, 444, 445,	I70; I71; I72; I73; I74; I77
Cerebrovascular disease	430-438	I60-I69; G45; G46
Dementia	290.09-290.19, 293.09	F00-F03; F05.1; G30
Chronic pulmonary disease	490-493, 515-518	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3
Connective tissue disease	712, 716, 734, 446, 135.99	M05; M06; M08; M09;M30;M31; M32; M33; M34; M35; M36; D86
Ulcer disease	530.91, 530.98, 531-534,	K22.1; K25-K28
Mild liver disease	571, 573.01, 573.04	B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0
Diabetes mellitus	249.00, 249.06, 249.07, 249.09, 250.00, 250.06,	E10.0, E10.1; E10.9; E11.0; E11.1; E11.9

	250.07, 250.09	
Hemiplegia	344	G81; G82
Moderate/severe renal Disease	403,404,580-583, 584, 590.09, 593.19, 753.10-753.19, 792	I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61
Diabetes mellitus with chronic complications	249.01-249.05, 249.08, 250.01-250.05, 250.08	E10.2-E10.8; E11.2-E11.8
Any tumour	140-194	C00-C75
Leukaemia	204-207	C91-C95
Lymphoma	200-203, 275.59	C81-C85; C88; C90; C96
Moderate/severe liver Disease	070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.00-456.09	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85
Metastatic solid tumour	195-198, 199	C76-C80
AIDS	079.83	B21-B24

Appendix 7: Information on diabetes obtained from the Danish National Diabetes Register.

Algorithm: Individuals were classified as having diabetes on the day where at least one of the following six criteria was met:

1. A diagnosis of diabetes made at any Danish hospital as registered in the Danish National Patient Register (ICD-8:249, 250; ICD-10:E10-14, H36.0, O24, excluding O24.4).
2. A referral to chiropody of diabetic patients as registered in the Danish National Health Service Register.(Andersen *et al.* 2011)
3. Five blood glucose measurements within one year as registered in the Danish National Health Service Register.
4. Two blood glucose measurements per year for five consecutive years as registered in the Danish National Health Service Register.
5. Two redemptions of oral anti-diabetic drugs within six months as registered in the Danish National Prescription Registry.
6. Two redemptions of prescribed insulin as registered in the Danish National Prescription Registry.

Appendix 8: ATC codes for drugs for obstructive airway disease obtained from the Danish National Prescription Registry.	
ATC codes	**Type of drug**
R03	Drugs for obstructive airway diseases
R03A	Adrenergics, inhalants
R03B	Other drugs for obstructive airway diseases, inhalants
R03C	Adrenergics for systemic use
R03D	Other systemic drugs for obstructive airway diseases

Appendix 9: Information on substance abuse disorders obtained from the Danish National Patient Register and the Danish Psychiatric Central Register.		
	ICD-8	ICD-10
Drug related		
Opioids	304.09, 304.19	F11.0–F11.9
Cannabinoids	304.59	F12.0–F12.9
Sedatives/hypnotics	304.29, 304.39	F13.0–F13.9
Cocaine	304.49	F14.0–F14.9
Other stimulants	304.69	F15.0–15.9
Hallucinogens	304.79	F16.0–F16.9
Other and multiple drugs	304.89, 304.99	F18.0–F19.9
Alcohol related		
Alcohol psychosis and abuse syndrome	291.09–291.99 303.09–303.99	F10.0–F10.9
Cirrhosis and steatosis of the liver	571.09, 571.10, 571.19	K70.0–K70.9
Esophageal varices	456.00, 456.01, 456.09	I85.0–I85.9

The risk of ACSCs and rehospitalizations for ACSCs among persons with depression

		Considerations
Study population:	**Depression study** All persons born in Denmark, alive and minimum 18 years of age and still living in Denmark at some time between January 1, 1999 and December 31, 2013. - Sub-analysis: Stratified by age categories: ≤ 40, 41-65, ≥ 65 (i.e., adult, middle-aged, older adults)	
Follow-up:	January 1, 2005-December 31,2013	This enables us to make sure who has a mental disorder between 1995 and 2005
Censor-in	18 years of birthday or study start, whichever comes last.	We do not want to include children. And also, this definition is a part of the AHRQ list. No age maximum.
Censor-out	Emigration, death, SMI diagnosis or study end whichever comes first.	We will censor out persons with SMI!
Dropping individuals	• Out-censored before in-censored (children and young persons dying before their 18th years birthday, or emigration, SMI diagnosis or death before study start).	

Exposure		
	Depression	Time-dependent variable (see Appendix 1): • All cases of depression between 1969 and 2013 (diagnoses-in and outpatient contacts) and between 1995 and 2013 (prescriptions). Remember that depression identified by redemptions need at least 2 prescriptions within 6 months. Sub-analysis Risk of ACSC-related hospitalizations by depression diagnosis-type (i.e., our rough proxy for depression severity): 1) Psychiatric hospitalization for depression 2) Outpatient depression diagnosis only 3) Antidepressant prescriptions only
	Dual diagnosis	If a person has a primary care determined depression it is overruled by a diagnosis from the registers (the secondary health care).
Outcome		
	1. The number of hospitalizations for ACSCs (Ambulatory care sensitive conditions) during follow-up = hospitalization rates for the following categories: Using codes from the Danish ACSC validation paper(Schiotz *et al.* 2011): -Angina -COPD exacerbation -Congestive heart failure exacerbation -Diabetes-short term compl. -Diabetes long-term compl. -Diabetes- uncontrolled	1) The algorithm: We have modified this outcome measure because it is classified according to ICD-9 (and diagnoses in Denmark are according to ICD-8 before 1994 and ICD-10 since 1995). We have used a validated algorithm from a Danish 'translated versions' in a Danish article (Schiotz *et al.* 2011). However, as this version does not include all of the categories of ACSCs from the AHRQ list, we have additionally included for all practical purposes, the rest of the categories (pneumonia, amputations, urinary tract infections, and asthma) (and a translation of the codes from ICD-9 to 10 have been conducted with inspiration

	-Hypertension -Appendicitis <u>Using codes with inspiration from Danish register-based studies (or own algorithms):</u> -Bacterial Pneumonia(Nielsen *et al.* 2012) -Lower extremities amputations (Jorgensen *et al.* 2014) -Urinary tract infections -Adult asthma exacerbation (Andersen *et al.* 2013) combine COPD exacerbation and adult asthma exacerbation into a single category for analyses 2. The number of rehospitalizations within 30 days after the index ACSC hospitalization for the same ACSC or for a different ACSC	from algorithms from previous Danish papers). This means that the only diseases not included in this model (compared to the original AHRQ list) are dehydration, immunizations, and IUGR. 2) <u>Inpatient contacts only:</u> Per definition ACSCs includes ONLY inpatient. 3) <u>Principal discharge diagnosis</u> (see Danish article or Davydow 2013) 4) <u>Appendicitis with perforation</u> 5) <u>Epidemiological considerations</u> One of the major epidemiological considerations for this study is the fact that persons with mental illness have higher rates for chronic diseases and are also more likely to receive poor quality of care treatment. If we show these persons have higher risk of ACSC we will have difficulty disentangling the increased risk of chronic diseases from the increased risk of suboptimal treatment. But the causal mechanism is likely to include both, and it will have to be discussed!! 6) <u>Exclusions:</u> - All transfers: Unfortunately we do not have access to data on transfers between hospitals. If a discharge date is followed by another admission date with an overlap of 1 day then we only count this as 1 admission. See the table for how to count the ACSCs. - Procedures for angina: Exclusions

		of angina cases who has had ANY surgical procedures (NCSP surgical codes) at the SAME admission. - Specific exclusions concerning diabetic amputations and concerning pneumonia
Covariates		
Demographic	Age, gender, calendar period.	We are adjusting for age as a time-dependent variable divided into 2 years age-bands. We are adjusting for calendar period as a time-dependent variable divided into 1 year-time-bands.
Socio-economic position (SEP)	**Depression paper** Marital status (married, registered partners, cohabitant or single). Income (OECD-adjusted household income) Educational level	
Comorbidity		
Medical comorbidity (See Appendices 6-8)	Diagnoses included in the Charlson Comorbidity index except for diabetes, which will come from the Diabetes Register, COPD/asthma exacerbations which will come from the combination of the CCI chronic pulmonary disease category and prescriptions.	Time-dependent We will identify hospital contacts for the chronic somatic diseases included in the CCI. Each diagnosis will be entered into the models as a time-dependent covariate. From 1995 onwards, outpatient contacts are also included. Adjusting for each category of disease from the CCI (instead of using an index).

	Substance abuse	See appendix 10
Health care utilization	Primary care visits (Face-to-Face-contacts=0101 contacts) In the analyses, we will categorize according to the interquartile range of PCP visits in the cohort We will count PCP visits from 10-375 days before any given day.	# of GP visits during the follow-up period for each individual Time-dependent This could be confounded by indication, but reduced contacts to GP and hospitals could also be an intermediate variable between mental illness and ACSC.
Statistical Analyses		
	Poisson regression with variance adjusted for clustering. <u>Outcome measures</u>: -number of hospitalizations per person years (rate measure). -rate ratios, RR	I. The outcome will be the number of these events since we will be using Poisson regression models. The outcome measure is rate ratio which approximates the relative risks. -We make the analysis for any ACSC and subsequently the analyses for each category , dividing into “chronic” ACSCs and “acute” ACSCs. a) <u>Sub-analyses for the time since analyses</u> b) <u>Analyses with adjustments</u> **<u>For depression study</u>** Adjustment: Models 1-5: 1) age, gender and calendar period, 2)SEP, 3) ACSC-predisposing comorbidity for chronic ACSCs, 4) non-ACSC-predisposing comorbidity and substance abuse, 5) GP contacts a) Sub-analysis: Stratified by age categories: ≤ 40, 41-65, ≥ 65 (i.e., adult, middle-aged, older adults),

		adjusted in sequence of Models 1-5 b) Sensitivity analysis: depression diagnosis type analysis (hospitalization for depression vs. outpatient depression vs. prescription alone), adjusted in sequence of Models 1-5 c) Time since depression diagnosis (adjusted for age, sex and calendar period) II. 30-day rehospitalizations for the same or another ACSC adjusted for demographics, then SES and comorbidity

Regarding transfers		
	Second admission	
First admission	ACSC	Non-ACSC
ACSC	Count the second ASCS*	Count the ACSC-admission
Non-ACSC	Count the ACSC-admission	Count as 0

*This means that if the ACSC diagnoses are two different that it will be the second admission that counts.

Appendices

Exposures

EXPOSURES (Appendices 1-3)

APPENDIX 1: Information on depression obtained from the Danish Psychiatric Central Register and the Danish National Prescription Registry

A diagnosis of depression was identified if at least one of the following criteria applied:

1. Registration of a diagnosis of depression in the Danish Psychiatric Central Register.
   And/or
2. Registration of at least one prescription of antidepressants redeemed in the Danish National Prescription Registry

Diagnosis according to a record of depression in the Danish Psychiatric Central Register:

ICD-8	ICD-10
296.09, 296.29, 296.99, 298.09, 300.49, and 300.19	F32, F33

Diagnosis according to a record of prescriptions for antidepressants in the Danish National Prescription Registry:

Name	Drug	ATC-codes
SSRI (Selective serotonin re-uptake inhibitors)	Fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, and escitalopram	N06AB
MAOIs (Monoamine oxidase inhibitors)	Isocarboxazid and moclobemide	N06AF,

		N06AG
Other antidepressants	Mianserin, nefazodone, mirtazapine, venlafaxine, reboxetine, duloxetine, and agomelatine	N06AX

APPENDIX 2: Information on severe mental illness obtained from the Danish Psychiatric Central Register.

	ICD-8	ICD-10
Schizophrenia	295 (excluding 295.79)	F20
Schizoaffective disorders	295.79, 296.8	F25
Bipolar affective disorders	296.19, 296.39	F30, F31

Outcome

Definition of outcome measures for the ACSC (see Appendix 4)	
	Categories
Any ACSC	Any of the categories
Type of ACSC	
Angina	
COPD/adult asthma exacerbation	
CHF exacerbation	
Diabetes-related ACSC	The 3 diabetes categories + amputations
HTN	
Perforated appendicitis	
Pneumonia	
UTI	

Appendix 4: Information on Ambulatory Care Sensitive Conditions (ACSCs) obtained from the Danish National Patient

Register. Hospitalizations for 12 of the conditions identified by the Agency for Healthcare Research and Quality as ACSCs in their report on prevention quality indicator		
Disease	**Description in the AHRQ list**	**ICD-10**
Angina	**Angina Without Procedure Admission Rate** **Numerator:** Discharges with ICD-9-CM principal diagnosis code for angina (see below). All discharges of age 18 years and older. **Exclude:** Discharges with a surgical procedure in any field (010-8699). Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes:** 4111 INTERMED CORONARY SYND 4130 ANGINA DECUBITUS 41181 CORONARY OCCLSN W/O MI 4131 PRINZMETAL ANGINA 41189 AC ISCHEMIC HRT DIS NEC 4139 ANGINA PECTORIS NEC/NOS **Denominator:** Population in MSA or county, age 18 years and older.	I20.0, I20.1, I20.8, I20.9, I24.0, I24.1, I24.8, I24.9 **EXCLUSIONS:** **All surgical procedures (starting with a K in the Danish version of the NCSP, which means surgical)**
COPD (Chronic obstructive pulmonary disorder) exacerbation	**Chronic Obstructive Pulmonary Disease (COPD) Admission Rate** **Numerator:** Discharges with ICD-9-CM principal diagnosis code for COPD (see below). All discharges of age 18 years and older. **Exclude:**	J20.0-J20.9*, J40.0-J40.9*, J41.0, J41.1, J42.0-J42.9, J43.8, J43.9, J44.0-J44.9, J47.0-J47.9 ***qualify only if accompanied by**

	Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes**: 4660 AC BRONCHITIS* 4920 EMPHYSEMATOUS BLEB 490 BRONCHITIS NOS* 4928 EMPHYSEMA NEC 4910 SIMPLE CHR BRONCHITIS 494 BRONCHIECTASIS -OCT00 4911 MUCOPURUL CHR BRONCHITIS 4940 BRONCHIECTAS W/O AC EXAC 49120 OBS CHR BRNC W/O ACT EXA OCT00- 49121 OBS CHR BRNC W ACT EXA 4941 BRONCHIECTASIS W AC EXAC 4918 CHRONIC BRONCHITIS NEC OCT00- 4919 CHRONIC BRONCHITIS NOS 496 CHR AIRWAY OBSTRUCT NEC * Qualifies only if accompanied by secondary diagnosis of 491.xx, 492.x, or 496 (i.e., any other code on this list). **Denominator:** Population in MSA or county, age 18 years and older.	**secondary diagnosis of any of the other codes listed under COPD**
CHF (Congestive heart failure) exacerbation	**Congestive Heart Failure (CHF) Admission Rate Numerator:** Discharges with ICD-9-CM principal diagnosis code for CHF (see below). All discharges of age 18 years and older. **Exclude:** Discharges with cardiac procedure codes (see below) in any field. Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2]	I09.0-I09.9 I11.0, I13.0, I13.2, I13.9, I50.0, I50.1, I50.9, I46.9 **<u>EXCLUSION:</u>** **Cardiac procedures**: **KFNG02, KFNG05, KFNA, KFNC, KFT, KFW, KFQ, BFCA01-BFCA07**

	ICD-9-CM diagnosis codes: 39891 RHEUMATIC HEART FAILURE 40413 BEN HYP HRT/REN W CHF&RF 40201 MAL HYPERT HRT DIS W CHF 40491 HYPER HRT/REN NOS W CHF 40211 BENIGN HYP HRT DIS W CHF 40493 HYP HT/REN NOS W CHF&RF 40291 HYPERTEN HEART DIS W CHF 4280 CONGESTIVE HEART FAILURE 40401 MAL HYPER HRT/REN W CHF 4281 LEFT HEART FAILURE 40403 MAL HYP HRT/REN W CHF&RF 4289 HEART FAILURE NOS 40411 BEN HYPER HRT/REN W CHF Exclude ICD-9-CM procedure codes: 3601 PTCA-1 VESSEL W/O AGENT 3619 HRT REVAS BYPS ANAS NEC 3602 PTCA-1 VESSEL WITH AGNT 375 HEART TRANSPLANTATION 3605 PTCA-MULTIPLE VESSEL 3770 INT INSERT PACEMAK LEAD 3606 INSERT CORONARY ART STENT OCT95- 3771 INT INSERT LEAD IN VENT 3610 AORTOCORONARY BYPASS NOS 3772 INT INSER LEAD ATRI-VENT 3611 AORTOCOR BYPAS-1 COR ART 3773 INT INSER LEAD IN ATRIUM 3612 AORTOCOR BYPAS-2 COR ART 3774 INT OR REPL LEAD EPICAR 3613 AORTOCOR BYPAS-3 COR ART 3775 REVISION OF LEAD 3614 AORTCOR BYPAS-4+ COR ART 3776 REPL TV ATRI-VENT LEAD 3615 1 INT MAM-COR ART BYPASS 3777 REMOVAL OF LEAD W/O REPL 3616 2 INT MAM-COR ART BYPASS 3778 INSER TEMP PACEMAKER SYS 3617 ABD-CORON ART BYPASS OCT96- 3779 REVIS OR RELOCATE POCKET	

	Denominator: Population in MSA or county, age 18 years and older.	
Diabetes (with short-term complications)	**Diabetes Short-term Complications Admission Rate** **Numerator:** Discharges with ICD-9-CM principal diagnosis code for short-term complications (ketoacidosis, hyperosmolarity, coma) (see below). All discharges of age 18 years and older. **Exclude**: Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes:** 25010 DM KETO T2, DM CONT 25022 DM W/ HYPROSM T2, DM UNCNT 25011 DM KETO T1, DM CONT 25023 DM W/ HYPROSM T1, DM UNCNT 25012 DM KETO T2, DM UNCONT 25030 DM COMA NEC T2, DM CONT 25013 DM KETO T1, DM UNCONT 25031 DM COMA NEC T1, DM CONT 25020 DM W/ HYPROSM T2, DM CONT 25032 DM COMA NEC T2, DM UNCONT 25021 DM W/ HYPROSM T1, DM CONT 25033 DM COMA NEC T1, DM UNCONT **Denominator:** Population in MSA or county, age 18 years and older.	E10.0, E10.1, E11.0, E11.1,
Diabetes (uncontrolled (without short-term or long-term complications))	**Uncontrolled Diabetes Admission Rate** **Numerator:** Discharges with ICD-9-CM principal diagnosis code for uncontrolled diabetes, without mention of a short-term or long-term complication (see below).	E10.9, E11.9

	All discharges of age 18 years and older. **Exclude:** Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes:** 25002 DM, T2, UNCONT 25003 DM, T1, UNCONT **Denominator:** Population in MSA or county, age 18 years and older. May be combined with diabetes short-term complications as a single indicator.	
Diabetes (with long-term complications)	**Diabetes Long-term Complications Admission Rate** **Numerator:** Discharges with ICD-9-CM principal diagnosis code for long-term complications (renal, eye, neurological, circulatory, or complications not otherwise specified) (see below). All discharges of age 18 years and older. **Exclude:** Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes:** 25040 DM RENAL COMP T2 CONT 25070 DM CIRCU DIS T2 CONT 25041 DM RENAL COMP T1 CONT 25071 DM CIRCU DIS T1 CONT 25042 DM RENAL COMP T2 UNCNT 25072 DM CIRCU DIS T2 UNCNT 25043 DM RENAL COMP T1 UNCNT 25073 DM CIRCU DIS T1 UNCNT	E10.2-E10.8, E11.2-E11.8

	25050 DM EYE COMP T2 CONT 25080 DM W COMP NEC T2 CONT 25051 DM EYE COMP T1 CONT 25081 DM W COMP NEC T1 CONT 25052 DM EYE COMP T2 UNCNT 25082 DM W COMP NEC T2 UNCNT 25053 DM EYE COMP T1 UNCNT 25083 DM W COMP NEC T1 UNCNT 25060 DM NEURO COMP T2 CONT 25090 DM W COMPL NOS T2 CONT 25061 DM NEURO COMP T1 CONT 25091 DM W COMPL NOS T1 CONT 25062 DM NEURO COMP T2 UNCNT 25092 DM W COMPL NOS T2 UNCNT 25063 DM NEURO COMP T1 UNCNT 25093 DM W COMPL NOS T1 UNCNT **Denominator:** Population in MSA or county, age 18 years and older.	
HTN (Hypertension)	**Hypertension Admission Rate** **Numerator:** Discharges with ICD-9-CM principal diagnosis code for hypertension (see below). All discharges of age 18 years and older. **Exclude:** Discharges with cardiac procedure codes (see below) in any field. Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes**: 4010 MALIGNANT HYPERTENSION 40310 BENIGN HYP HRT DIS W/OUT RF 4019 HYPERTENSION NOS 40390 HYPERTEN HEART DIS W/OUT RF 40200 MAL HYPERTEN HRT DIS W/OUT CHF	I10.0-I10.9, I11.9, I12.9, I13.9 **EXCLUSION:** **Cardiac procedures**: **KFNG02, KFNG05, KFNA, KFNC, KFT, KFW, KFQ, BFCA01-BFCA07**

	40400 MAL HYPER HRT/REN W/OUT CHF/RF 40210 BEN HYPERTEN HRT DIS W/OUT CHF 40410 BEN HYPER HRT/REN W/OUT CHF/RF 40290 HYPERTENSIVE HRT DIS W/OUT CHF 40490 HYPER HRT/REN NOS W/OUT CHF/RF 40300 MAL HYPERT HRT DIS W/OUT RF Exclude ICD-9-CM procedure codes: 3601 PTCA-1 VESSEL W/O AGENT 3619 HRT REVAS BYPS ANAS NEC 3602 PTCA-1 VESSEL WITH AGNT 375 HEART TRANSPLANTATION 3605 PTCA-MULTIPLE VESSEL 3770 INT INSERT PACEMAK LEAD 3606 INSERT CORONARY ART STENT OCT95-3771 INT INSERT LEAD IN VENT 3610 AORTOCORONARY BYPASS NOS 3772 INT INSER LEAD ATRI-VENT 3611 AORTOCOR BYPAS-1 COR ART 3773 INT INSER LEAD IN ATRIUM 3612 AORTOCOR BYPAS-2 COR ART 3774 INT OR REPL LEAD EPICAR 3613 AORTOCOR BYPAS-3 COR ART 3775 REVISION OF LEAD 3614 AORTCOR BYPAS-4+ COR ART 3776 REPL TV ATRI-VENT LEAD 3615 1 INT MAM-COR ART BYPASS 3777 REMOVAL OF LEAD W/O REPL 3616 2 INT MAM-COR ART BYPASS 3778 INSER TEMP PACEMAKER SYS 3617 ABD-CORON ART BYPASS OCT96- 3779 REVIS OR RELOCATE POCKET **Denominator:** Population in MSA or county, age 18 years and older.	
Perforated appendicitis	**Perforated Appendix Admission Rate** **Numerator:** Discharges with ICD-9-CM diagnosis code for perforations or abscesses of appendix (see below) in any field.	K35.0, K35.1, K35.2, K35.3

	All discharges of age 18 years and older. **Exclude:** Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes (outcome of interest):** 5400 AC APPEND W PERITONITIS 5401 ABSCESS OF APPENDIX **ICD-9-CM diagnosis codes (population at risk):** 5400 AC APPEND W PERITONITIS 5409 ACUTE APPENDICITIS NOS 5401 ABSCESS OF APPENDIX 541 APPENDICITIS NOS **Denominator:** Number of discharges with diagnosis code for appendicitis in any field in MSA or county.	
Pneumonia	**Bacterial Pneumonia Admission Rate** **Numerator:** Discharges with ICD-9-CM principal diagnosis code for bacterial pneumonia (see below). All discharges of age 18 years and older. **Exclude:** Discharges with diagnosis code for sickle cell anemia or HB-S disease (see below) in any field. Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes:** 481 PNEUMOCOCCAL PNEUMONIA 48230 STREP PNEUMONIA UNSPEC 4822 H.INFLUENZAE PNEUMONIA 48231 GRP	J13-J14.9, J15.3-J15.4, J15.7-J15.9, J16.0-J16.9, J18.0-J18.9 **EXCLUSION:** **Sickle cell disorders** **D57.0-D57.9**

	A STREP PNEUMONIA 4829 BACTERIAL PNEUMONIA NOS 48232 GRP B STREP PNEUMONIA 4830 MYCOPLASMA PNEUMONIA 48239 OTH STREP PNEUMONIA 4831 CHLAMYDIA PNEUMONIA OCT96- 485 BRONCOPNEUMONIA ORG NOS 4838 OTH SPEC ORG PNEUMONIA 486 PNEUMONIA, ORGANISM NOS **Exclude ICD-9-CM diagnosis codes:** 28260 SICKLE-CELL ANEMIA NOS 28263 SICKLE-CELL/HB-C DISEASE 28261 HB-S DISEASE W/O CRISIS 28269 SICKLE-CELL ANEMIA NEC 28262 HB-S DISEASE WITH CRISIS	
UTIs (urinary tract infections)	**Urinary Tract Infection Admission Rate** **Numerator:** Discharges with ICD-9-CM principal diagnosis code of urinary tract infection (see below). **Exclude:** Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes:** 59000 CHR PYELONEPHRITIS NOS 59080 PYELONEPHRITIS NOS 59001 CHR PYELONEPH W MED NECR 59081 PYELONEPHRIT IN OTH DIS 59010 AC PYELONEPHRITIS NOS 5909 INFECTION OF KIDNEY NOS 59011 AC PYELONEPHR W MED NECR 5950 AC CYSTITIS 5902 RENAL/PERIRENAL ABSCESS 5959 CYSTITIS NOS 5903 PYELOURETERITIS CYSTICA 5990 URIN TRACT INFECTION NOS	N10.0-N12.9, N15.1-15.9, N30.0-N30.9, N34.0-N34.9, N39.0

	Denominator: Population in MSA or county.	
Adult Asthma exacerbation	**Adult Asthma Admission Rate** **Numerator:** Discharges with ICD-9-CM principal diagnosis code of asthma (see below). All discharges of age 18 years and older. **Exclude:** Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM diagnosis codes:** 49300 EXT ASTHMA W/O STAT ASTH 49320 CH OB ASTH W/O STAT ASTH 49301 EXT ASTHMA W STATUS ASTH 49321 CH OB ASTHMA W STAT ASTH 49302 EXT ASTHMA W STATUS ACEX OCT00- 49322 CH OB ASTHMA W STAT ACEX 49310 INT ASTHMA W/O STAT ASTH OCT00- 49311 INT ASTHMA W STATUS ASTH 49390 ASTHMA W/O STATUS ASTHM 49312 INT ASTHMA W STATUS ACEX OCT00- 49391 ASTHMA W STATUS ASTHMAT 49392 ASTHMA W STATUS AC EXAC OCT00- **Denominator:** Population in MSA or county, age 18 years and older.	J45, J46
Amputations (diabetes-related)	**Rate of Lower-extremity Amputation among Patients with Diabetes** **Numerator:** Discharges with ICD-9-CM procedure code for lower-extremity amputation (see below) in any field and diagnosis code of diabetes in any field (see below). All discharges of age 18 years and older.	Z89.4-Z89.7 ***qualify only if registered with diabetes in the Danish National Diabetes Register or if registered with a diagnosis of diabetes (ICD-10:E10-14, H36.0, O24, excluding O24.4) at the same admission as the ACSC**

	Exclude: Trauma (see below). Transfers[1]. MDC 14 (pregnancy, childbirth, and puerperium)[2] **ICD-9-CM procedure codes:** 8410 LOWER LIMB AMPUTAT NOS 8415 BELOW KNEE AMPUTAT NEC 8411 TOE AMPUTATION 8416 DISARTICULATION OF KNEE 8412 AMPUTATION THROUGH FOOT 8417 ABOVE KNEE AMPUTATION 8413 DISARTICULATION OF ANKLE 8418 DISARTICULATION OF HIP 8414 AMPUTAT THROUGH MALLEOLI 8419 HINDQUARTER AMPUTATION ICD-9-CM diagnosis codes for diabetes: 25000 DMII WO CMP NT ST UNCNTR 25050 DMII OPHTH NT ST UNCNTRL 25001 DMI WO CMP NT ST UNCNTRL 25051 DMI OPHTH NT ST UNCNTRLD 25002 DMII WO CMP UNCNTRLD 25052 DMII OPHTH UNCNTRLD 25003 DMI WO CMP UNCNTRLD 25053 DMI OPHTH UNCNTRLD 25010 DMII KETO NT ST UNCNTRLD 25060 DMII NEURO NT ST UNCNTRL 25011 DMI KETO NT ST UNCNTRLD 25061 DMI NEURO NT ST UNCNTRLD 25012 DMII KETOACD UNCONTROLD 25062 DMII NEURO UNCNTRLD 25013 DMI KETOACD UNCONTROLD 25063 DMI NEURO UNCNTRLD 25020 DMII HPRSM NT ST UNCNTRL 25070 DMII CIRC NT ST UNCNTRLD 25021 DMI HPRSM NT ST UNCNTRLD 25071 DMI CIRC NT ST UNCNTRLD 25022 DMII HPROSMLR UNCONTROLD 25072	**EXCLUSION:** **Traumatic amputations of lower limb** **S78.0-S78.9, S88.0-S88.9, S98.0-S98.4, T05.3-T05.5**

	DMII CIRC UNCNTRLD 25023 DMI HPROSMLR UNCONTROLD 25073 DMI CIRC UNCNTRLD 25030 DMII O CM NT ST UNCNTRLD 25080 DMII OTH NT ST UNCNTRLD 25031 DMI O CM NT ST UNCNTRL 25081 DMI OTH NT ST UNCNTRLD 25032 DMII OTH COMA UNCONTROLD 25082 DMII OTH UNCNTRLD 25033 DMI OTH COMA UNCONTROLD 25083 DMI OTH UNCNTRLD 25040 DMII RENL NT ST UNCNTRLD 25090 DMII UNSPF NT ST UNCNTRL 25041 DMI RENL NT ST UNCNTRLD 25091 DMI UNSPF NT ST UNCNTRLD 25042 DMII RENAL UNCNTRLD 25092 DMII UNSPF UNCNTRLD 25043 DMI RENAL UNCNTRLD 25093 DMI UNSPF UNCNTRLD **Exclude: Trauma** **ICD-9-CM diagnosis codes:** 8950 AMPUTATION TOE 8971 AMPUTAT BK, UNILAT-COMPL 8951 AMPUTATION TOE-COMPLICAT 8972 AMPUT ABOVE KNEE, UNILAT 8960 AMPUTATION FOOT, UNILAT 8973 AMPUT ABV KN, UNIL-COMPL 8961 AMPUT FOOT, UNILAT-COMPL 8974 AMPUTAT LEG, UNILAT NOS 8962 AMPUTATION FOOT, BILAT 8975 AMPUT LEG, UNIL NOS-COMP 8963 AMPUTAT FOOT, BILAT-COMP 8976 AMPUTATION LEG, BILAT 8970 AMPUT BELOW KNEE, UNILAT 8977 AMPUTAT LEG, BILAT-COMPL **Denominator:** Population in MSA or county, age 18 years and older.	

[1]Transfers imply that if a discharge date is followed by another admission date with an overlap of +/- 1 day this is counted as one admission. [2]The exclusion of obstetric admissions was performed if any diagnostic codes for obstetric diagnoses were present as a secondary diagnosis at the same admission as the ACSC. The obstetric diagnostic codes included: O0.0-O99.9.

Covariates

Appendix 5: Information on socioeconomic position (SEP) obtained from Statistics Denmark.
Education level
< 10 years
10-15 years
> 15 years
Civil status
Living alone/single
Cohabitation
Partners
Married

Appendix 6: Information on chronic diseases included in the Charlson Comorbidity Index obtained from the Danish National Patient Register		
	ICD-8	ICD-10
Myocardial infarction	410	I21;I22;I23
Congestive heart failure	427.09, 427.10, 427.11, 427.19, 428.99, 782.49	I50; I11.0; I13.0; I13.2
Peripheral vascular disease	440, 441, 442, 443, 444, 445,	I70; I71; I72; I73; I74; I77
Cerebrovascular disease	430-438	I60-I69; G45; G46
Dementia	290.09-290.19, 293.09	F00-F03; F05.1; G30
Chronic pulmonary disease	490-493, 515-518	J40-J47; J60-J67; J68.4; J70.1; J70.3; J84.1; J92.0; J96.1; J98.2; J98.3
Connective tissue disease	712, 716, 734, 446, 135.99	M05; M06; M08; M09;M30;M31; M32; M33; M34; M35; M36; D86
Ulcer disease	530.91, 530.98, 531-534,	K22.1; K25-K28
Mild liver disease	571, 573.01, 573.04	B18; K70.0-K70.3; K70.9; K71; K73; K74; K76.0
Diabetes mellitus	249.00, 249.06, 249.07, 249.09, 250.00, 250.06, 250.07, 250.09	E10.0, E10.1; E10.9; E11.0; E11.1; E11.9
Hemiplegia	344	G81; G82
Moderate/severe renal Disease	403,404,580-583, 584, 590.09, 593.19, 753.10-753.19, 792	I12; I13; N00-N05; N07; N11; N14; N17-N19; Q61
Diabetes mellitus with chronic complications	249.01-249.05, 249.08, 250.01-250.05, 250.08	E10.2-E10.8; E11.2-E11.8
Any tumour	140-194	C00-C75
Leukaemia	204-207	C91-C95
Lymphoma	200-203, 275.59	C81-C85; C88; C90; C96
Moderate/severe liver Disease	070.00, 070.02, 070.04, 070.06, 070.08, 573.00, 456.00-456.09	B15.0; B16.0; B16.2; B19.0; K70.4; K72; K76.6; I85
Metastatic solid tumour	195-198, 199	C76-C80

AIDS	079.83	B21-B24

Appendix 7: Information on the ACSC-predisposing medical comorbidity obtained from the Danish National Patient Register, the Danish National Diabetes Register and the Danish National Prescription Registry.

ACSC Outcome	ACSC-predisposing medical comorbidity
Chronic conditions	
Angina	Myocardial infarction[1]
CHF exacerbation	CHF[1]
HTN	Myocardial infarction[1] CHF[1] Cerebrovascular disease[1] Peripheral vascular disease[1]
Diabetes-related ACSCs	Diabetes[2]
COPD exacerbation	Chronic pulmonary disease[1] or Redemption of at least 2 prescriptions of drugs for obstructive airway diseases within 6 months[3]
Adult asthma exacerbation	Chronic pulmonary disease[1] or Redemption of at least 2 prescriptions of drugs for obstructive airway diseases within 6 months[3]
Acute conditions	
Perforated appendicitis	-
Pneumonia	-
UTI	-

[1]Obtained from the Danish National Patient Register using the algorithm defined in the Charlson Comorbidity Index (see appendix 6).
[2]Obtained from the Danish National Diabetes Register (see appendix 8)
[3]Obtained from the Danish National Prescriptions Registry (see appendix 9).

Appendix 8: Information on diabetes obtained from the Danish National Diabetes Register.

Algoritm: Individuals were classified as having diabetes on the day where at least one of the following six criteria was met:

1. A diagnosis of diabetes made at any Danish hospital as registered in the Danish National Patient Register (ICD-8:249, 250; ICD-10:E10-14, H36.0, O24, excluding O24.4).
2. A referral to chiropody of diabetic patients as registered in the Danish National Health Service Register.(Andersen *et al.* 2011)
3. Five blood glucose measurements within one year as registered in the Danish National Health Service Register.
4. Two blood glucose measurements per year for five consecutive years as registered in the Danish National Health Service Register.
5. Two redemptions of oral anti-diabetic drugs within six months as registered in the Danish National Prescription Registry.
6. Two redemptions of prescribed insulin as registered in the Danish National Prescription Registry.

Appendix 9: ATC codes for drugs for obstructive airway disease obtained from the Danish National Prescription Registry.

ATC codes	**Type of drug**
R03	Drugs for obstructive airway diseases
R03A	Adrenergics, inhalants
R03B	Other drugs for obstructive airway diseases, inhalants
R03C	Adrenergics for systemic use
R03D	Other systemic drugs for obstructive airway diseases

Appendix 10: Information on substance abuse disorders obtained from the Danish National Patient Register and the Danish Psychiatric Central Register.

	ICD-8	ICD-10
Drug related		
Opioids	304.09, 304.19	F11.0–F11.9
Cannabinoids	304.59	F12.0–F12.9
Sedatives/hypnotics	304.29, 304.39	F13.0–F13.9
Cocaine	304.49	F14.0–F14.9
Other stimulants	304.69	F15.0–15.9
Hallucinogens	304.79	F16.0–F16.9
Other and multiple drugs	304.89, 304.99	F18.0–F19.9
Alcohol related		
Alcohol psychosis and abuse syndrome	291.09–291.99 303.09–303.99	F10.0–F10.9
Cirrhosis and steatosis of the liver	571.09, 571.10, 571.19	K70.0–K70.9
Esophageal varices	456.00, 456.01, 456.09	I85.0–I85.9

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Corresponding Manuscript Page Number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **X**	**1**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **X**	**2-3**
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **X**	**4**
Objectives	3	State specific objectives, including any prespecified hypotheses **X**	**5**
Methods			
Study design	4	Present key elements of study design early in the paper **X**	**5**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **X**	**5**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **X** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	**5-6**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	**N/A**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **X**	**6-9**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **X**	**6-9**
Bias	9	Describe any efforts to address potential sources of bias **X**	**9**
Study size	10	Explain how the study size was arrived at **N/A**	**N/A**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **X**	**8-10**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **X**	**9-10**
		(*b*) Describe any methods used to examine subgroups and	**10**

interactions **X**	
(*c*) Explain how missing data were addressed **X**	**9**
(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed **N/A** *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	**N/A**
(*e*) Describe any sensitivity analyses **X**	**10**

Continued on next page

Results			Corresponding Manuscript Page Number
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **X**	**10-11**
		(b) Give reasons for non-participation at each stage **N/A**	**N/A**
		(c) Consider use of a flow diagram	**N/A**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **X**	**11, 27-28 (Table 1)**
		(b) Indicate number of participants with missing data for each variable of interest **X**	**27-28 (Table 1)**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) **X**	**11**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **X**	**11**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	**N/A**
		Cross-sectional study—Report numbers of outcome events or summary measures	**N/A**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **X**	**11, 13, 30-31 (Table 2), 33 (Table 4)**
		(*b*) Report category boundaries when continuous variables were categorized **X**	**8-10**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **N/A**	**N/A**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **X**	**12-13, 32 (Table 3), 34-35 (Figures 1 and 2)**
Discussion			
Key results	18	Summarise key results with reference to study objectives **X**	**14**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **X**	**15-16**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **X**	**15-16**
Generalisability	21	Discuss the generalisability (external validity) of the study results **X**	**15-16**
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **X**	**1, 10**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.