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Depression and risk of hospitalisations and rehospitalisations for ambulatory care-sensitive conditions in Denmark: a population-based cohort study

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ABSTRACT

Objective: Hospitalisations 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 rehospitalisations are common and costly. We sought to determine whether individuals with depression are at increased risk of hospitalisations for ACSCs, and rehospitalisation for the same or another ACSC, within 30 days.

Design: National, population-based cohort study.

Setting: Denmark.

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

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

Results: Overall, individuals with depression were 2.35 times more likely to be hospitalised for an ACSC (95% CI 2.32 to 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 utilisation (95% CI 1.43 to 1.46). After adjusting for ACSC-predisposing comorbidity, depression was associated with significantly greater risk of hospitalisations for all chronic (eg, angina, diabetes complications, congestive heart failure exacerbation) and acute ACSCs (eg, pneumonia) compared to those without depression. Compared to those without depression, persons with depression were 1.21 times more likely to be rehospitalised within 30 days for the same ACSC (95% CI 1.18 to 1.24) and 1.19 times more likely to be rehospitalised within 30 days for a different ACSC (95% CI 1.15 to 1.23).

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

Strengths and limitations of this study

- 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 healthcare and a relatively homogeneous population may impact generalisability 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 hospitalisations such as health-risk behaviours (eg, smoking, sedentary lifestyle), previous studies that controlled for health-risk behaviours found that the association between depression and greater risk for ACSC-related hospitalisations 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

Hospitalisations for chronic illnesses and their sequelae are a major contributor to rising healthcare costs in Western societies.[1] In the USA, an estimated 10% of all hospitalisations may be preventable,[2] such as those for ambulatory care-sensitive conditions (ACSCs), a set of chronic (eg, diabetes with complications, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD) exacerbation) and acute illnesses (eg, bacterial pneumonia, urinary tract infection (UTI)) considered not to require inpatient treatment if patients receive timely and appropriate ambulatory care.[3] Hospitalisations for ACSCs have been estimated to cost US$31.9 billion and £1.4

billion in the UK annually.[4 5] Moreover, early rehospitalisations, some of which may be due to ACSCs, are common and costly to health systems.[6] With the advent of accountable care organisations in the USA and other efforts to improve healthcare delivery worldwide, health systems are increasingly trying to prevent hospitalisations for ACSCs and early rehospitalisations 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 hospitalisations. Depression may increase hospitalisations 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 hospitalisations for ACSCs and/or early rehospitalisations among persons with depression, they have been limited to single centre,[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 rehospitalisations within 30 days has not focused on potentially preventable rehospitalisations,[15 16 18 19] such as rehospitalisations within 30 days for an ACSC, an outcome that is arguably of particular importance to health systems and health policymakers. Also, it remains unknown whether depressed individuals are at greater risk of ACSC-related hospitalisations and rehospitalisations simply because they are more likely to have underlying chronic diseases.[20 21]

Utilising data from a population-based cohort of 5 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 of hospitalisations for ACSCs after adjusting for demographics, socioeconomic factors, comorbidities (ACSC-predisposing and non-ACSC-predisposing comorbidities), and primary care utilisations. Further, we examined whether persons with depression who have been hospitalised for an ACSC are at greater risk of rehospitalisation for the same, or another ACSC, within 30 days. We hypothesised that depression would be independently associated with increased risk of hospitalisations for ACSCs as well as rehospitalisations 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 of age, alive and residing in Denmark at least 1 day between 1 January 2005 and 31 December 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 1 January 1968. In the register, Danish residents are each assigned a unique personal identification number which links to person-level data.[22]

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 (ie, 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 online supplementary appendix 1), which includes diagnostic information on all psychiatric hospitalisations from 1969 onwards and outpatient specialty mental health visits from 1995 onwards.[23] Prescription fills for antidepressants (ie, selective serotonin re-uptake inhibitors, monoamine oxidase inhibitors, and other non-tricyclic (TCA) antidepressants, see online supplementary 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 online supplementary appendix 2) and excluded from analyses.

Outcomes of interest

Our primary outcome of interest was hospitalisation for 1 of 12 ACSCs as defined by the Agency for Healthcare Research and Quality (AHRQ) (see online supplementary appendix 3).[2] Register-based diagnoses were based on the Danish version of the International Classification of Diseases, 8th Revision (ICD-8) prior to 31 December 1993.[26] From 1 January 1994 onwards, 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 (ie, 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 (ie, 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 (ie, angina, CHF exacerbation, HTN, diabetes related, COPD/adult asthma exacerbation) and three 'acute' ACSCs (ie, appendicitis with perforation, pneumonia and UTI). We used the Danish National Patient Register,[33] which contains information on all medical hospitalisations since 1 January 1977 and outpatient visits since 1 January 1995,[33] to obtain information on hospitalisations with principal discharge diagnoses for ACSCs occurring between 1 January 2005 and 31 December 2013. If a discharge was followed by an admission within 1 day, it was considered a transfer and counted as one admission only. We excluded hospitalisations with secondary obstetric diagnoses (ICD-10 codes: O00.0-O99.9).

Our secondary outcome of interest was rehospitalisation for an ACSC within 30 days of discharge from the initial ACSC-related hospitalisation. We counted rehospitalisations 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 online supplementary appendix 4).[34 35] We categorised marital/partnered status as living with a partner (ie, married, registered partnership or cohabitation) or living alone (ie, 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 Organisation'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 online supplementary 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 online supplementary appendix 6) (eg, myocardial infarction as ACSC-predisposing medical comorbidity for angina hospitalisation, etc), with two exceptions. Diabetes diagnoses were obtained from the Danish National Diabetes Register between 1 January 1990 and 31 December 2013 (see online supplementary 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 ≥2 prescription redemptions within a 6-month period for medications treating obstructive airway diseases (see online supplementary 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 online supplementary appendix 9).

Primary care utilisation

We obtained information on daytime 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 1 January 1990. To reduce the chances of including a primary care visit that directly resulted in an ACSC-related hospitalisation, we constructed a time-dependent variable counting the number of primary care visits from 10 to 375 days before any given day. We categorised primary care visits into three equally sized categories of low, medium or high utilisation based on observed frequencies (ie, 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) of hospitalisations for ACSCs and subsequent rehospitalisation within 30 days for an ACSC. We estimated corresponding 95% CIs using cluster robust variance estimation to account for interperson correlation and dichotomy of rehospitalisation. In these analyses, our outcomes of interest were a count of the number of hospitalisations for ACSCs. Age and calendar period were adjusted for using 2-year and 1-year age and time bands, respectively. All variables (including depression status), except sex, were treated as time-dependent. Individuals contributed at-risk time from 1 January 2005 or from their 18th birthday, whichever came last, in different time bands based on the different covariate combinations they enter with during follow-up. Within each of these combinations, we counted the number of ACSC-related hospitalisations. These methods allowed us to count only ACSC-related hospitalisations 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 31 December 2013, whichever came first.

For each ACSC-related hospitalisation outcome, we fitted five risk models, adjusting sequentially for demographics (ie, age, sex and calendar period), socioeconomic factors (ie, marital/partnered status and education), ACSC-predisposing medical comorbidity (with each comorbid condition entered individually), other comorbidities (ie, non-ACSC-predisposing medical comorbidity entered individually and substance abuse) and primary care utilisation. All model covariates were chosen a priori based on prior studies identifying their

potential associations with both depression and healthcare utilisation 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 subanalyses. First, we examined whether the association between depression and risk of ACSC-related hospitalisations was modified by age. To do so, we repeated our Poisson regressions stratified by three age categories: ≤40, 41–64 and ≥65 years. Second, we examined the associated risk of hospitalisations 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 of hospitalisations for ACSCs was impacted by our depression definition, we performed a prespecified sensitivity analysis in which we repeated our regressions using three different depression definitions: antidepressant prescription alone, outpatient psychiatric visit-based diagnosis alone or psychiatric hospitalisation for depression.

We fitted three models examining risk of rehospitalisation within 30 days for an ACSC. The first model was 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 rehospitalisation for an ACSC within 30 days of discharge from the initial ACSC-related hospitalisation. Individuals were at risk of the outcome on the day of discharge from their ACSC-related hospitalisation. 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 V.13 (Stata Corporation, College Station, Texas, USA).

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 (SD=19.2) years.

Table 1 displays the characteristics of our cohort by depression status. During the 9-year follow-up period, we identified 1 255 640 hospitalisations for ACSCs, including 542 184 (43.2%) among persons with depression. There were 71.4 ACSC-related hospitalisations per 1000 person-years among those with depression versus 23.0 per 1000 person-years among those without depression during the study period.

Compared to those without depression, the IRR for individuals with depression having any ACSC-related hospitalisation was 2.35 (95% CI 2.32 to 2.37) 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 of hospitalisations for all of the chronic ACSCs even after adjusting for specific chronic ACSC-predisposing medical comorbidity (table 2), particularly for hospitalisations for angina (IRR=1.77; 95% CI 1.73 to 1.81), COPD/asthma exacerbations (IRR=1.88; 95% CI 1.84 to 1.93) and diabetes-related hospitalisations (IRR=1.83; 95% CI 1.77 to 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 of hospitalisations for all chronic ACSCs, especially for hospitalisations for COPD/asthma exacerbations (IRR=1.61; 95% CI 1.57 to 1.65), and diabetes-related hospitalisations (IRR=1.69; 95% CI 1.63 to 1.75) (table 2).

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

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

In the first year after depression diagnosis, the associated risk of hospitalisation for a chronic ACSC was nearly three times greater than those without depression (IRR 2.89; 95% CI 2.83 to 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 to 2.43) 10 or more years after depression diagnosis. During the first year after depression diagnosis, the associated risk of hospitalisation for an acute ACSC was 3 1/3 times greater than for those without depression (IRR 3.33, 95% CI 3.27 to 3.40), and the associated risk remained 2¼ times higher at ≥10 years after depression diagnosis (IRR 2.25; 95% CI 2.22 to 2.29) (figure 2).

In our sensitivity analysis in which we examined whether our results regarding risk of hospitalisation for any ACSC were impacted by depression definition, we found that depression defined by antidepressant prescription alone (IRR 2.31; 95% CI 2.28 to 2.33), outpatient psychiatric visit-based diagnosis alone (IRR 2.66;

Table 1 Study cohort characteristics

Measure	Depression (n=1 319 896)			Without depression (n=3 782 713)		
	Number of hospitalisations for ACSCs	Person-years at risk	Risk time spent in category (%)	Number of hospitalisations for ACSCs	Person-years at risk	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	5287	27 978	0.4	3516	34 556	0.1
Paraplegia	7123	31 836	0.4	4893	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	1011	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

ACSC, ambulatory care-sensitive condition; CHF, congestive heart failure; MI, myocardial infarction.

Table 2 The risk of hospitalisations for ACSCs associated with depression compared to individuals without depression

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

*Age, sex and calendar period.
†Educational level and marital status.
‡Charlson comorbidity index diagnoses not previously adjusted for.
§Adjusted for myocardial infarction.
¶Adjusted for chronic pulmonary disease.
**Adjusted for CHF.
††Adjusted for diabetes mellitus.
‡‡Adjusted for myocardial infarction, CHF, cerebrovascular disease and peripheral vascular disease.
‡p<0.001.
ACSC, ambulatory care-sensitive condition; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; HTN, hypertension; PCP, primary care physician; UTI, urinary tract infection.

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

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

‡p<0.001.
PCP, primary care physician.

95% CI 2.56 to 2.77) or psychiatric hospitalisation for depression (IRR 2.69; 95% CI 2.62 to 2.77) were all associated increased risk of hospitalisation 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 to 1.45; outpatient psychiatric visit-based diagnosis: IRR 1.54, 95% CI 1.48 to 1.60; psychiatric hospitalisation for depression: IRR 1.50, 95% CI 1.46 to 1.54).

Approximately 6.8% of all ACSC-related hospitalisations during the follow-up period were followed by an ACSC-related rehospitalisation within 30 days, of which 73% were for the same ACSC and 27% were for a different ACSC. Of the 85 046 ACSC-related rehospitalisations 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 of rehospitalisation within 30 days for the same ACSC (95% CI 1.32 to 1.39) and 1.44 times greater risk of rehospitalisation within 30 days for a different ACSC (95% CI 1.39 to 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 of rehospitalisation within 30 days for the same ACSC (IRR 1.21; 95% CI 1.18 to 1.24) or another ACSC (IRR 1.19; 95% CI 1.15 to 1.23).

DISCUSSION

In this nationwide, population-based longitudinal study of over 5 million individuals, we found that depression was independently associated with higher risk of hospitalisations for both chronic and acute ACSCs and that the associated risk remained high for at least 10 years. To the best of our knowledge, the present study is the first to show that depression was associated with higher risk of rehospitalisation for the same or another ACSC within 30 days of an ACSC-related hospitalisation. Importantly, we identified that the associated risk of hospitalisations 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 hospitalisation and subsequent rehospitalisation for an ACSC among depressed individuals is troubling in light of evidence that some ACSC-related hospitalisations 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

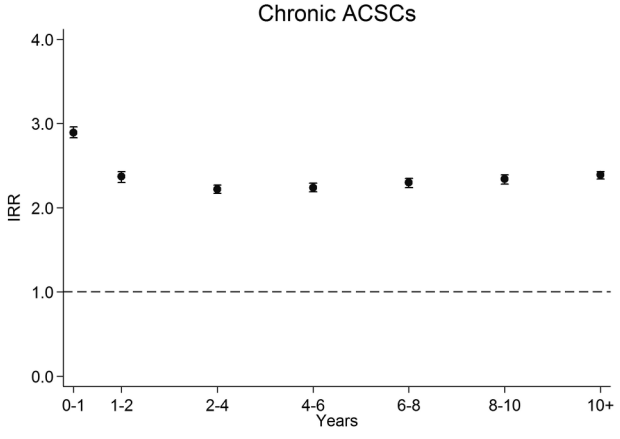

Figure 1 Risk of hospitalisation for a chronic ACSC by time since (ACSC, ambulatory care-sensitive condition; IRR, incidence rate ratio).

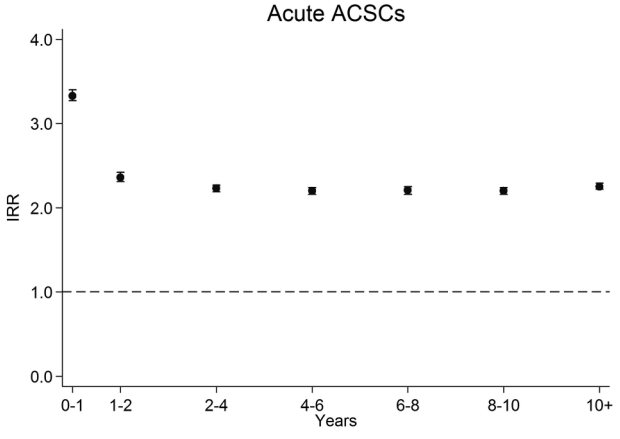

Figure 2 Risk of hospitalisation for an ACSC by time since (ACSC, ambulatory care-sensitive condition; IRR, incidence rate ratio).

Table 4 The risk of rehospitalisation within 30 days for the same or another ACSC among those with depression compared to individuals without depression

Outcome	Incidence rate ratio (95% CI)		
	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
Same ACSC	1.36 (1.32 to 1.39)‡	1.34 (1.31 to 1.38)‡	1.21 (1.18 to 1.24)‡
Another ACSC	1.44 (1.39 to 1.49)‡	1.42 (1.37 to 1.47)‡	1.19 (1.15 to 1.23)‡

‡p<0.001.
ACSC, ambulatory care-sensitive condition.

impairment,[43 44] both of which increase the risk of ACSC-related hospitalisations.[18 45] Therefore, depressed individuals could be especially at risk for a vicious cycle of hospitalisations, rehospitalisations and rapid decline.

This study has important implications for development of interventions to prevent costly ACSC-related hospitalisations and rehospitalisations. 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 of hospitalisations 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 healthcare reform in Massachusetts that found improving access to care was not associated with reductions in ACSC-related hospitalisations or rehospitalisations within 30 days among high-risk populations.[46 47]

If expanding access to primary care by itself is insufficient to prevent hospitalisations 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 hospitalisations for comorbid medical conditions.[54] Further studies of sufficient duration and size are needed to determine if collaborative care could prevent ACSC-related hospitalisations 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 rehospitalisations for ACSCs. Such research would be of particular interest to accountable care organisations and health policymakers 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 healthcare and a relatively homogeneous population may impact generalisability. Yet, these factors may enhance internal validity by decreasing the degree socioeconomic factors play in healthcare-seeking behaviour, 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 the data on potential mediators of an association between depression and ACSC-related hospitalisations such as health-risk behaviours (eg, smoking, sedentary lifestyle), previous studies in this area that controlled for health-risk behaviours found that the association between depression and greater risk for ACSC-related hospitalisations 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 when compared to the general population, depressed individuals may present with higher acuity of medical illnesses and a greater burden of comorbidity, necessitating hospitalisation 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 of hospitalisations for ACSCs. Furthermore, once hospitalised for an ACSC, depression was associated with greater risk of rehospitalisation within 30 days for the same, or another, ACSC. Further research that clarifies the mechanisms linking depression and ACSC-related hospitalisations, and that develops interventions that prevent

ACSC-related hospitalisations in persons with depression, is needed given the burden that recurrent hospitalisations places on individuals and society.

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REFERENCES

1. Muka T, Imo D, Jaspers L, *et al*. The global impact of non-communicable diseases on healthcare spending and national income: a systematic review. *Eur J Epidemiol* 2015;30:251–77.
2. Stranges E, Stocks C. *Potentially preventable hospitalizations for acute and chronic conditions, 2008*. HCUP Statistical Brief #99. Rockville, MD: Agency for Healthcare Research and Quality, 2010.
3. Agency for Healthcare Research and Quality. *AHRQ quality indicators—guide to prevention quality indicators: hospital admission for ambulatory care sensitive conditions*. Rockville, MD: Agency for Healthcare Research and Quality, 2001. AHRQ Pub No. 02-R0203.
4. Torio CM, Elixhauser A, Andrews RM. *Trends in potentially preventable hospital admissions among adults and children, 2005–2010*. HCUP Statistical Brief #151. Rockville, MD: Agency for Healthcare Research and Quality, 2013.
5. The King's Fund. Emergency hospital admissions for ambulatory care-sensitive conditions: identifying the potential for reductions. http://www.kingsfund.org.uk/sites/files/kf/field/field_publication_file/data-briefing-emergency-hospital-admissions-for-ambulatory-care-sensitive-conditions-apr-2012.pdf (accessed 20 Jun 2015).
6. Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. *N Engl J Med* 2009;360:1418–28.
7. Harrison MJ, Dusheiko M, Sutton M, *et al*. Effect of a national primary care pay for performance scheme on emergency hospital admissions for ambulatory care-sensitive conditions: controlled longitudinal study. *BMJ* 2014;349:g6423.
8. Nelson KM, Helfrich C, Sun H, *et al*. Implementation of the patient-centered medical care home in the Veterans Health Administration: associations with patient satisfaction, quality of care, staff burnout and hospital and emergency department use. *JAMA Intern Med* 2014;174:1350–8.
9. Centers for Medicare and Medicaid Services. Readmissions Reduction Program. http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/AcuteInpatientPPS/Readmissions-Reduction-Program.html (accessed 15 Jun 2015).
10. Global Burden of Disease Study Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015;386:743–800.
11. Lin EH, Rutter CM, Katon W, *et al*. Depression and advanced complications of diabetes: a prospective cohort study. *Diabetes Care* 2010;33:264–9.
12. Katon WJ, Lin E, Russo JE, *et al*. Increased medical costs of a population-based sample of depressed elderly patients. *Arch Gen Psychiatry* 2003;60:897–903.
13. Sullivan MD, O'Connor P, Feeney P, *et al*. Depression predicts all-cause mortality: epidemiological evaluation from the ACCORD HRQL substudy. *Diabetes Care* 2012;35:1708–15.
14. Katon WJ. Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. *Biol Psychiatry* 2003;54:216–26.
15. Mitchell SE, Paasche-Orlow MK, Forsythe SR, *et al*. Post-discharge hospital utilization among adult medical inpatients with depressive symptoms. *J Hosp Med* 2010;5:378–84.
16. Burke RE, Donzé J, Schnipper JL. Contribution of psychiatric illness and substance abuse to 30-day readmission risk. *J Hosp Med* 2013;8:450–5.
17. Davydow DS, Katon WJ, Lin EH, *et al*. Depression and risk of hospitalizations for ambulatory care-sensitive conditions in patients with diabetes. *J Gen Intern Med* 2013;28:921–9.
18. Davydow DS, Zivin K, Katon WJ, *et al*. Neuropsychiatric disorders and potentially preventable hospitalizations in a prospective cohort study of older Americans. *J Gen Intern Med* 2014;29:1362–71.
19. Ahmedani BK, Solberg LI, Copeland LA, *et al*. Psychiatric comorbidity and 30-day readmissions after hospitalization for heart failure, AMI, and pneumonia. *Psychiatr Serv* 2015;66:134–40.
20. Mezuk B, Eaton WW, Albrecht S, *et al*. Depression and type 2 diabetes over the lifespan: a meta-analysis. *Diabetes Care* 2008;31:2383–90.
21. Cooper DC, Trivedi RB, Nelson KM, *et al*. Antidepressant adherence and risk of coronary artery disease hospitalizations in older and younger adults with depression. *J Am Geriatr Soc* 2014;62:1238–45.
22. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011;39(7 Suppl):22–5.
23. Mors O, Perto GP, Mortensen PB. The Danish Psychiatric Central Research Register. *Scand J Public Health* 2011;39(7 Suppl):54–7.
24. Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health* 2011;39(7 Suppl):38–41.
25. Skrbo A, Zulic I, Hadzic S, *et al*. [Anatomic-therapeutic-chemical classification of drugs]. *Med Arh* 1999;53:57–60.
26. World Health Organization. *Manual of the International Classification of Diseases, Eighth Revision (ICD-8)*. Geneva, Switzerland: World Health Organization, 1967.
27. World Health Organization. *Manual of the International Classification of Diseases, Tenth Revision (ICD-10)*. Geneva, Switzerland: World Health Organization, 1992.
28. Schiøtz M, Price M, Frølich A, *et al*. Something is amiss in Denmark: a comparison of preventable hospitalisations and readmissions for chronic medical conditions in the Danish Healthcare system and Kaiser Permanente. *BMC Health Serv Res* 2011;11:347.
29. Nielsen AG, Nielsen RB, Riis AH, *et al*. The impact of statin use on pneumonia risk and outcome: a combined population-based case-control and cohort study. *Crit Care* 2012;16:R122.
30. Jørgensen ME, Almdal TP, Faerch K. Reduced incidence of lower-extremity amputations in a Danish diabetes population from 2000 to 2011. *Diabet Med* 2014;31:443–7.
31. Ribe AR, Vestergaard M, Katon W, *et al*. Thirty-day mortality after infection among persons with severe mental illness: a population-based cohort study in Denmark. *Am J Psychiatry* 2015;172:776–83.
32. Andersen AB, Ehrenstein V, Erichsen R, *et al*. Parental inflammatory bowel disease and risk of asthma in offspring: a nationwide cohort study in Denmark. *Clin Transl Gastroenterol* 2013;4:e41.
33. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011;39(7 Suppl):30–3.
34. Statistics Denmark. http://www.dst.dk/en/Statistik/dokumentation/Declarations.aspx (accessed 19 Mar 2015).
35. Jensen VM, Rasmussen AW. Danish Education Registers. *Scand J Public Health* 2011;39(7 Suppl):91–4.
36. United Nations Educational, Scientific and Cultural Organization. ISCED: International Standard Classification of Education. http://www.uis.unesco.org/Education/Pages/international-standard-classification-of-education.aspx (accessed 19 Mar 2015).
37. Charlson ME, Pompei P, Ales KL. A new method for classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chron Dis* 1987;40:373–83.
38. Carstensen B, Kristensen JK, Marcussen MM, *et al*. The National Diabetes Register. *Scand J Public Health* 2011;39(7 Suppl):58–61.
39. Andersen JS, Olivarius NF, Krasnik A. The Danish National Health Service Register. *Scand J Public Health* 2011;39(7 Suppl):34–7.
40. Bindman AB, Chattopadhyay A, Auerback GM. Interruptions in Medicaid coverage and risk for hospitalizations for ambulatory care-sensitive conditions. *Ann Intern Med* 2008;149:854–60.
41. Rubin DB. *Multiple imputation for non-response in surveys*. New York, NY: Wiley, 1987.
42. Davydow DS, Hough CL, Levine DA, *et al*. Functional disability, cognitive impairment, and depression after hospitalization for pneumonia. *Am J Med* 2013;126:615–24.

43. Katon W, Pedersen HS, Ribe AR, *et al*. Effect of depression and diabetes mellitus on the risk for dementia: a national population-based cohort study. *JAMA Psychiatry* 2015;72:612–19.
44. Mezuk B, Edwards L, Lohman M, *et al*. Depression and frailty in later life: a synthetic review. *Int J Geriatr Psychiatry* 2012;27:879–92.
45. Phelan EA, Borson S, Grothaus L, *et al*. Association of incident dementia with hospitalizations. *JAMA* 2012;307:165–72.
46. McCormick D, Hanchate AD, Lasser KE, *et al*. Effect of Massachusetts healthcare reform on racial and ethnic disparities in admissions to hospital for ambulatory care sensitive conditions: retrospective analysis of hospital episode statistics. *BMJ* 2015;350:h1480.
47. Lasser KE, Hanchate AD, McCormick D, *et al*. The effect of Massachusetts health reform on 30 day hospital readmissions: retrospective analysis of hospital episode statistics. *BMJ* 2014;348:g2329.
48. Unützer J, Katon W, Callahan CM, *et al*, IMPACT Investigators. Improving Mood-Promoting Access to Collaborative Treatment. Collaborative care management of late-life depression in the primary care setting: a randomized controlled trial. *JAMA* 2002;288:2836–45.
49. Lin EH, Katon W, Von Korff M, *et al*, IMPACT Investigators. Effect of improving depression care on pain and functional outcomes among older adults with arthritis: a randomized controlled trial. *JAMA* 2003;290:2428–34.
50. Katon WJ, Schoenbaum M, Fan MY, *et al*. Cost-effectiveness of improving primary care treatment of late-life depression. *Arch Gen Psychiatry* 2005;62:1313–20.
51. Gilbody S, Bower P, Fletcher J, *et al*. Collaborative care for depression: a cumulative meta-analysis and review of longer-term outcomes. *Arch Intern Med* 2006;166:2314–21.
52. Katon WJ, Lin EH, Von Korff M, *et al*. Collaborative care for patients with depression and chronic illness. *N Engl J Med* 2010;363:2611–20.
53. Katon W, Russo J, Lin EH, *et al*. Cost-effectiveness of a multicondition collaborative intervention: a randomized controlled trial. *Arch Gen Psychiatry* 2012;69:506–14.
54. Unützer J, Katon WJ, Fan MY, *et al*. Long-term cost effects of collaborative care for late-life depression. *Am J Manag Care* 2008;14:95–100.
55. Coleman EA, Parry C, Chalmers S, *et al*. The care transitions intervention: results of a randomized controlled trial. *Arch Intern Med* 2006;166:1822–8.
56. Jack BW, Chetty VK, Anthony D, *et al*. A reengineered hospital discharge program to decrease rehospitalization: a randomized trial. *Ann Intern Med* 2009;150:178–87.
57. Gaynes BN, Rush AJ, Trivedi M, *et al*. A direct comparison of presenting characteristics of depressed outpatients from primary vs. specialty care settings: preliminary findings from the STAR*D clinical trial. *Gen Hosp Psychiatry* 2005;27:87–96.
58. Cooper-Patrick L, Crum RM, Ford DE. Characteristics of patients with major depression who received care in general medical and specialty mental health settings. *Med Care* 1994;32:15–24.
59. Bet PM, Hugtenburg JG, Penninx BW, *et al*. Treatment inadequacy in primary and specialized care patients with depressive and/or anxiety disorders. *Psychiatry Res* 2013;210:594–600.

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 **<u>EXCLUSIONS:</u>** **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 **<u>EXCLUSION:</u>** **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	**<u>EXCLUSION:</u>** **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