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ORIGINAL RESEARCH

High Use of Antidepressant Medication in Both Mild-to-Modelate and Possible Severe Asthma – A Nationwide Cohort Study

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Purpose: In asthma, increased severity has been linked to depression assessed as assessed by patient-reported outcomes. However, little is known about predictors of antidepressant use in asthma compared to the background population.

Methods: The study consists of 60,534 asthma patients aged 18–45 and a 1:1 age- and sex-matched control group. Using national registries and prescription data, the prevalence of and risk factors for antidepressant use were investigated by logistic regression adjusted for age, sex, workforce and civil status, income- and education-level and comorbidity. Results presented as odds ratio (OR) with 95% confidence intervals (CI).

Results: A total of 16% and 22%, respectively, among patients with mild-to-moderate and possible severe asthma redeemed antidepressant drugs, compared to 10% of controls. Antidepressant use was more prevalent amongst patients with high rescue medication use (>600 annual doses) and those with a history of moderate or severe exacerbation(s). Both mild-to-moderate and possible severe asthma were independent risk factors for antidepressant use (OR 1.40 (95% CI 1.35, 1.46) and OR 1.55 (95% CI 1.41, 1.70), respectively). Female sex, age, being divorced or never married, having only primary education or currently being under education, as well as being on welfare/transfer income increased odds of antidepressant use. Completing higher education and having high income were associated with lower odds.

Conclusion: In asthma, antidepressant use is significantly higher than in the background population. Even after adjusting for known risk factors, asthma remains a predictor of antidepressant use, signalling a psychologic burden related to living with asthma.

Keywords: depression, anxiety, major mood disorders, airway disease, disease burden

Introduction

Asthma, a heterogenous chronic respiratory disease with an increasing prevalence, represents a major public health issue on a global scale.[1] Poor asthma control is the main driver of morbidity and mortality, whereas sufficient treatment with inhaled corticosteroids (ICS) significantly reduces symptoms, exacerbation- and mortality risk.[1] With proper treatment, most asthma patients are without any major day-to-day asthma-related symptoms or limitations,[1] yet sub-optimal – or even poor – asthma control is common[2–4] with potential important consequences for the patients as asthma has been linked to major mood disorders (MMD) such as anxiety and depression.[5]

Psychiatric comorbidity in asthma influences asthma symptom burden, reduces quality of life (QoL) and increases healthcare resource utilization.[6] Estimates of

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anxiety and depression prevalence in asthma vary greatly depending on setting, study design, use of patient-reported or objective diagnostic criteria, and ranges from 2.5% to 48%, compared to 12–17% in the background population.[7,8] While the general risk of MMD in chronic disease exists across all ages,[9,10] the mechanisms behind the increased prevalence of asthma are largely unknown, yet neuroendocrine mechanisms, hyperventilation-induced abnormal carbon dioxide sensitivity or even genetic factors have been proposed.[11–13] However, a correlation between MMD and poor self-rated asthma control has previously been described,[14] indicating that disease severity and asthma control may be primary drivers of increased MMD prevalence rather than the asthma diagnosis itself.

In a previously published large multicentre study, Scott et al found an increased odds ratio (OR) of 1.6 of self-reported MMDs in patients with asthma compared to the background population,[15] yet, little is known about the prevalence of objective markers of MMD, such as antidepressant use, in young adults with asthma, and especially its relation to increasing objective disease severity and disease control markers. As such, we hypothesize that in a nationwide cohort of young adults with asthma, the use of antidepressant is high when compared to the background population, and that antidepressant use increases with objective disease severity and control markers, even after adjusting for common risk factors of MMD.

Methods

Data Collection and Sources

The REASSESS Danish Asthma cohort is a nationwide asthma cohort and corresponding controls, utilizing nationally spanning registries from Statistics Denmark,[16] the Danish National Database of Reimbursed Prescriptions (DNDRP)[17] as well as the Danish National Patient Register and the Danish Clinical Quality Program – Asthma (DrAsthma).[18,19] Further description of the cohort has been published previously.[4]

Ethics and Data Sharing

The present study is approved by the Capital Region of Copenhagen's Data Safety Board (ref. P-2019-142) and the Capital Region of Copenhagen's Scientific Ethics Committee (ref. H-19042597). As per Danish law, access to patient journals does not require informed consent if granted by the Capital Region of Copenhagen's Data Safety Board and the Scientific Ethics Committee. The study was conducted in accordance with the Declaration of Helsinki.

Data are available upon reasonable request. However, approval from the Danish National Scientific Ethics Committee, Statistics Denmark, DrAsthma, DNDRP and the Capital Region of Copenhagen's Data Safety Board may be required as per Danish law.

Study Population

Patients were included in the REASSESS Danish Asthma cohort if they had redeemed ≥2 ICS inhalers during a -calendar year within the study period (2014–2018), as commonly used in Danish asthma cohorts.[2,4,20] To reduce the risk of inclusion of ICS-treated patients with chronic obstructive pulmonary disease, the cohort was limited to individuals aged 18–45 on cohort entry (at 1st ICS redemption).[2]

An age- and sex-matched population serving as controls was supplied by Statistics Denmark. Controls were randomly selected from the general population and matched based on birth-year and sex according to the central person registry (1:1). Cases were excluded from the pool of possible controls and controls were unique, meaning that one individual could not serve as a control for two cases.

Medication Dosage, Asthma Severity and Control Definitions

GINA 2020 Treatment Steps 1–5 were used to define treatment levels.[1] ICS doses were calculated as exposed ICS dose, based on mean daily ICS dose exposure during the study period and reported as standard-particle beclomethasone dipropionate equivalents as follows: below low dose (<200 micrograms daily), low dose (200–599 micrograms daily), moderate dose (600–1200 micrograms daily) and high dose (>1200 micrograms daily).[21] ICS dose equivalents to standard particle, CFC-free beclomethasone (bcm) and other compounds and formulations (comp) were estimated per National Institute for Health and Care Excellence ICS doses using a coefficient calculated as:

$$\frac{\frac{\text{Mean comp.boundry, Low dose}}{\text{Mean bcm.boundry, Low dose}} + \frac{\text{Mean comp.boundry, Medium dose}}{\text{Mean bcm.boundry, Medium dose}} + \frac{\text{Mean comp.boundry, High dose}}{\text{Mean bcm.boundry, High dose}}}{3}$$

Possible severe asthma was defined as GINA 2020 Step 4 with either ≥2 courses of systemic corticosteroids or ≥1 asthma-related hospitalization or GINA Step 5 regardless of exacerbations.[22]

Excessive use of SABA was defined as filled prescriptions for at least 600 doses of SABA per year.[23]

A moderate exacerbation was defined as a prescription of at least 37.5 mg of prednisolone for 5 days or more. A severe exacerbation was defined as an exacerbation requiring hospitalization.

Comorbidities

A modified Charlson Comorbidity Index ("Charlson score"), where the group "Chronic Pulmonary Disease" was removed due to mediator effects, with updated weights by Quan et al[24,25] was used to quantify the comorbidity burden in the cohort. Caution should as such be used when directly comparing Charlson scores from the present study to other studies.

Concomitant Medications

For common comorbidities not accounted for in the Charlson score, patients were classified by concomitant medications if redeeming at least two prescriptions in a -calendar year during the study period:

- Use of decongestants and antiallergics: Nasal antiallergic agents with (ATC code R01AD) or without (R01AC) corticosteroids, ophthalmologic (S01G) or systemic antihistamines (R06)
- Depression: Antidepressants (N06A)
- Proton-pump inhibitor (PPI) use: Proton-pump inhibitors (A02BC).

Specialist Care

Patients registered in the DrAsthma[19] database were considered to be managed in secondary care. The remaining patients were considered to be managed in primary care, as access to private respiratory specialist care is highly limited in Denmark. Patients registered with DrAsthma, but not fulfilling the ICS-criteria for cohort inclusion (n = 5393) were deemed not to be in active treatment and excluded from the present study.

Socioeconomic Status

Based on data from Statistics Denmark, patients were classified using the following socioeconomic parameters and definitions as previously described:[4]

1. Education: Basic Education (Primary and Secondary Education, up to approx. 12 years of study); Vocational Education (Basic Education and 2–5 years of vocational school); Higher Education (University studies with at least a bachelor's degree, at least 15 years of study).
2. Occupation: Transfer Income Recipient (registered as receiving disability, unemployment or other direct benefits at the end of the study period); Currently under Education (registered as currently undergoing education (regardless of vocational, primary, secondary or tertiary) by Statistics Denmark at the end of the study period); Employed (registered as employed, self-employed or under current education with more than 950 salaried hours per calendar year).
3. Income: Patients' average taxable income (before tax and labour market contributions) during the study period, divided by quartiles.
4. Metropolitan Residence: Place of residence at study period close was used to classify patients as residing as within or outside the five largest municipalities (Copenhagen, Frederiksberg, Århus, Aalborg and Odense).
5. Civil status: Legal civil status (married, separated, never married) as registered in public records at study period close.

Statistical Analyses

Cohort characterization was performed using demographic statistics presented as median (interquartile range, IQR). For groupwise comparisons, Wilcoxon rank-sum test or Chi-squared test of independence were used depending on continuous or categorical data.

Predictors of antidepressant use were investigated using bi- and multivariable logistic regression. Multivariable analyses were adjusted for sex, age, income, education, workforce status, civil status, use of decongestants and antiallergics, PPI use and a Charlson score ≥2. Results are presented as odds ratio (OR) and 95% confidence intervals (CI).

R 4.0.2 (The R Foundation, AU) was used for statistical analyses. P-values ≤0.05 were considered to be statistically significant.

Results

The REASSESS Danish Asthma cohort consists of 60,534 patients with actively treated asthma and a 1:1 age- and sex-matched control cohort from the background population. Overall, the median age was 38 (IQR 29, 43), with 55% of asthma patients being female. A total of 3475

patients (5.7%) were classified as having possible severe asthma, with the remaining patients being classified as having mild-to-moderate disease. Of the enrolled patients, 18% were managed in secondary care (Table 1).

Comorbidity Burden

In the control population, 10% were treated with antidepressants during the study period. The proportion of individuals treated with antidepressants increased with having actively treated asthma and asthma severity, with mild-to-moderate disease and possible severe asthma showing a prevalence of 16% and 22%, respectively (Table 1). Across the study population, 0.6% were deemed as multimorbid with a Charlson score of 2 or above, with increasing prevalence with actively treated asthma and between asthma severities (Table 1).

Asthma Treatment and Disease Control

When assessing pharmacologic treatment in patients with asthma with or without antidepressant use, patients using antidepressants were slightly overrepresented in GINA 2020 Step 4 and 5. The use of long-acting bronchodilators (beta$_2$-agonists, antimuscarinic, or a combination of both) was more common in patients using antidepressants,

Table 1 Demographics, Prevalence of Antidepressant Use and Comorbidities in 60,534 Patients with Actively Treated Asthma and an Age- and Sex Matched Control Group in a Nationwide Cohort

Demographics & Comorbidities	Overall, N = 121,068	Controls, N = 60,534[1]	Mild-to-Moderate Asthma, N = 57,059[1]	Possible Severe Asthma, N = 3475[1]	p-value[2]
Age	38 (29, 43)	38 (29, 43)[3]	37 (29, 43)	41 (34, 45)	<0.001
Female	66,112 (55%)	33,056 (55%)	31,144 (55%)	1912 (55%)	0.9
Secondary Care Asthma Management	10,694 (18%)[4]	NA	9338 (16%)	1356 (39%)	<0.001
Antidepressant Use	15,854 (13%)	6190 (10%)	8887 (16%)	777 (22%)	<0.001
Charlson Score >1	752 (0.6%)	284 (0.5%)	411 (0.7%)	57 (1.6%)	<0.001
Any Malignancy	1362 (1.1%)	670 (1.1%)	645 (1.1%)	47 (1.1%)	0.4
Cerebrovascular Disease	715 (0.6%)	300 (0.5%)	377 (0.7%)	38 (1.1%)	<0.001
Dementia	7 (<0.1%)	3 (<0.1%)	4 (<0.1%)	0 (0%)	NA
Diabetes with Complications	317 (0.3%)	114 (0.2%)	175 (0.3%)	28 (0.8%)	<0.001
Diabetes without Complications	1240 (1.0%)	475 (0.8%)	688 (1.2%)	77 (2.2%)	<0.001
Heart Failure	187 (0.2%)	53 (<0.1%)	111 (0.2%)	23 (0.7%)	<0.001
Hemi/Tetraplegia	180 (0.1%)	72 (0.1%)	97 (0.2%)	11 (0.3%)	0.003
Leukaemia	32 (<0.1%)	13 (<0.1%)	18 (<0.1%)	1 (<0.1%)	NA
Lymphoma	103 (<0.1%)	49 (<0.1%)	50 (<0.1%)	4 (0.1%)	NA
Liver Disease, Mild	657 (0.5%)	257 (0.4%)	356 (0.6%)	44 (1.3%)	<0.001
Liver Disease, Severe	59 (<0.1%)	27 (<0.1%)	26 (<0.1%)	6 (0.2%)	NA
Myocardial Infarction	341 (0.3%)	135 (0.2%)	179 (0.3%)	27 (0.8%)	<0.001
Peptic Ulcer Disease	322 (0.3%)	120 (0.2%)	184 (0.3%)	18 (0.5%)	<0.001
Peripheral Vascular Disease	200 (0.2%)	89 (0.1%)	99 (0.2%)	12 (0.3%)	0.016
Renal Disease	245 (0.2%)	104 (0.2%)	125 (0.2%)	16 (0.5%)	<0.001
Rheumatic Disease	820 (0.7%)	313 (0.5%)	459 (0.8%)	48 (1.4%)	<0.001

Notes: [1]Statistics presented: n (%); median (IQR). [2]Statistical tests performed: Kruskal–Wallis rank sum test; Pearson's Chi-squared test. P-values correspond to tests across all three subpopulations Controls, Mild-to-Moderate Asthma and Possible Severe Asthma. [3]P-value for Age < 0.9 between Controls and Asthma patients when not stratified by disease severity. [4]Of patients with asthma only. [3]Prevalence based on the asthma subpopulation (n=60,534).

where as no differences in leukotriene receptor antagonist use was seen. Proton-pump inhibitors were more frequently redeemed by those receiving antidepressant therapy (34% vs 14%), but no differences in nasal decongestants and/or antihistamine use was seen (Table 2).

In terms of disease control, annual SABA use was higher in patients using antidepressants (200 (IQR 100, 350) vs 175 (60, 267) annual doses), as was excessive use of rescue medication (>600 annual doses) at 13.0% vs 8.9%. Moderate exacerbations were more common in patients redeeming antidepressants (11% vs 6.6%), but no significant difference in number of exacerbations was seen between antidepressant users and non-users. Patients using antidepressants were more likely to have experienced at least one severe exacerbation (14% vs 8.8%) and had a higher exacerbation rate than non-users (Table 2).

Risk Factors for Antidepressant Use in Asthma

Bivariable logistic regression showed higher odds of antidepressant use in patients with asthma, both in mild-to-moderate disease (OR 1.62 (95% CI 1.56, 1.68), p<0.001) and possible severe asthma (OR 2.53 (95% CI 2.32, 2.75), p<0.001) (Table 3).

In multivariable logistic regression analysis adjusted for age, sex, workforce status, education, income, civil status, presence of multimorbidity (Charlson score ≥2) and redemption of common ocular and/or nasal as well as gastroesophageal relief drugs, asthma remained significantly associated with antidepressant use. Odds of antidepressant use was increased with both asthma disease severities (OR 1.40 (95% CI 1.35, 1.46), p<0.001 and OR 1.56 (95% CI 1.41, 1.71), p<0.001) for mild-to-moderate asthma and possible severe asthma, respectively (Table 3).

Female sex, increasing age, being outside the workforce or under current education, use of decongestants and antiallergics, PPI use, being never- or previously married and multimorbidity were associated with higher odds of antidepressant use, while a high level of education and income were associated with lower odds of antidepressant use (Table 3).

In sub-analyses only including patients with asthma and adjusting for previous covariates, as well as being under specialist asthma care, possible severe asthma was associated with higher odds of antidepressant use (OR 1.15 (1.05, 1.26), p 0.004) compared to mild-to-moderate disease irrespective of place of care (Table 4).

Disease Control and Antidepressant Use in Asthma

Exploratory analyses including three different objective disease control markers were performed in the asthma sub-population using the same covariates as in the main analysis. No increase in the odds of antidepressant use was seen in patients with poor disease control measured as >600 annual doses of rescue medication (OR 1.04 (0.96–1.12), p 0.3). A borderline significant increase in odds of antidepressant use in patients with two or more moderate exacerbations (OR 1.11 (0.99–1.24), p 0.071) and a significant increase for patients with severe exacerbations (OR 1.11 (1.04–1.20), p 0.0004) was observed (Table 5).

Discussion

In the present study, we found that antidepressant use was seen in 16–22% of patients with asthma, depending on severity. In logistic regression, both mild-to-moderate and possible severe asthma were independently associated with antidepressant use (OR 1.40–1.55) when adjusted for common demographic and socioeconomic risk factors for anxiety and depression.

Prevalence of Antidepressant Use and Mood Disorders

The present study is supported by earlier findings, both in prevalence and risk of major mood disorders in asthma.[15,26] Furthermore, we have demonstrated that the risk of antidepressant use increases with disease severity, also in accordance with studies showing a decline in quality of life and increasing risk of self-rated poor mental health status with increasing asthma severity.[27]

The World Federation of Societies of Biological Psychiatry estimates the median lifetime prevalence of depression to 16.1% and adds that only one fourth of patients with depressive symptoms classify as having major depressive disease, where antidepressant therapy is typically indicated.[28] Taking the high prevalence of antidepressant use in the present study into account, other indications than major depressive diseases, such as anxiety, must be considered. Indeed, several studies have found a higher prevalence of anxiety than depression,[14,29] suggesting that the present study findings represent a combination of patients with depression, anxiety or a combination of both.

Table 2 Pharmacologic Asthma Treatment and Disease Control Measurements in 60,534 Patients with Actively Treated Asthma in a Nationwide Cohort, Stratified by Antidepressant Use

	Overall, N = 60,534	No Antidepressant Use, N = 50,870[1]	Antidepressant Users, N = 9664[1]	p-value[2]
Population				<0.001
Mild-to-moderate Asthma	57,059 (94%)	48,172 (95%)	8887 (92%)	
Possible Severe Asthma	3475 (5.7%)	2698 (5.3%)	777 (8.0%)	
GINA 2020 Step				<0.001
Step 1	25,497 (42%)	21,476 (42%)	4021 (42%)	
Step 2	13,092 (22%)	11,089 (22%)	2003 (21%)	
Step 3	13,411 (22%)	11,381 (22%)	2030 (21%)	
Step 4	6005 (9.9%)	4939 (9.7%)	1066 (11%)	
Step 5	2529 (4.2%)	1985 (3.9%)	544 (5.6%)	
ICS Dose[3]				<0.001
Below Low	25,497 (42%)	21,476 (42%)	4021 (42%)	
Low	21,911 (36%)	18,590 (37%)	3321 (34%)	
Moderate	9380 (15%)	7833 (15%)	1547 (16%)	
High	3746 (6.2%)	2971 (5.8%)	775 (8.0%)	
Add-on Therapies				
Long-acting Beta-2-agonists (LABA)	23,302 (38%)	19,677 (39%)	3625 (38%)	0.030
Long-acting Antimuscarinics (LAMA)	1574 (2.6%)	1128 (2.2%)	446 (4.6%)	<0.001
Dual Long-acting Bronchodilators (LABA+LAMA)	1031 (1.7%)	760 (1.5%)	271 (2.8%)	<0.001
Leukotriene Receptor Antagonists	3530 (5.8%)	2950 (5.8%)	580 (6.0%)	0.4
Decongestants and Anti-allergic Drugs	6928 (11%)	5807 (11%)	1121 (12%)	0.6
Proton-pump Inhibitors	10,152 (17%)	6903 (14%)	3249 (34%)	<0.001
Annual SABA Doses	195 (60, 280)	175 (60, 267)	200 (100, 350)	<0.001
>600 Annual Doses	5762 (9.5%)	4503 (8.9%)	1259 (13%)	<0.001
Moderate Exacerbation(s)	4380 (7.2%)	3342 (6.6%)	1038 (11%)	<0.001
1 Exacerbation[4]	2276 (52%)	1756 (53%)	520 (50%)	0.3
2 Exacerbations[4]	956 (22%)	729 (22%)	227 (22%)	
3 Exacerbations[4]	519 (12%)	396 (12%)	123 (12%)	
4+ Exacerbations[4]	629 (14%)	461 (14%)	168 (16%)	
Severe Exacerbation(s)	5819 (9.6%)	4455 (8.8%)	1364 (14%)	<0.001
1 Exacerbation[4]	4076 (70%)	3173 (71%)	903 (66%)	<0.001
2 Exacerbations[4]	1057 (18%)	805 (18%)	252 (18%)	
3 Exacerbations[4]	328 (5.6%)	236 (5.3%)	92 (6.7%)	
4+ Exacerbations[4]	358 (6.2%)	241 (5.4%)	117 (8.6%)	

Notes: [1]Statistics presented: n (%); median (IQR). [2]Statistical tests performed: chi-square test of independence; Wilcoxon rank sum test. [3]Based on daily beclomethasone eq. exposure during the study period; below low < 200 daily mcg, low 200–599 daily mcg, moderate 600–1200 daily mcg, high >1200 mcg daily. [4]During the study period.

Table 3 Multivariable Logistic Regression of Antidepressant Treatment in 60,534 Patients with Actively Treated Asthma and 60,534 Age- and Sex-Matched Controls

Logistic Regression	Bivariable			Multivariable		
	OR[1]	95% CI	p-value	OR[1]	95% CI	p-value
Population						
Background Population	1	—		1	—	
Mild-to-Moderate Asthma	1.62	1.56, 1.68	<0.001	1.40	1.35, 1.46	<0.001
Possible Severe Asthma	2.53	2.32, 2.75	<0.001	1.55	1.41, 1.70	<0.001
Female				1.53	1.47, 1.59	<0.001
Age				1.03	1.03, 1.04	<0.001
Workforce Status						
Employed				1	—	
Transfer Income Recipient				3.96	3.76, 4.16	<0.001
Currently Under Education				1.34	1.23, 1.45	<0.001
Level of Education						
Primary and Basic Education				1	—	
Vocational Training				1.01	0.96, 1.06	0.8
Higher Education				0.84	0.80, 0.88	<0.001
Taxable Income Level						
Low (1st Quartile)				1	—	
Middle (2nd + 3rd Quartile)				1.01	0.96, 1.06	0.8
High (4th Quartile)				0.61	0.56, 0.65	<0.001
Civil Status						
Married				1	—	
Separated				1.61	1.52, 1.71	<0.001
Never Married				1.31	1.25, 1.37	<0.001
Metropolitan Residence						
Use of decongestants and antiallergics				1.10	1.03, 1.17	0.007
PPI use				2.26	2.16, 2.36	<0.001
Charlson Score ≥2				1.26	1.06, 1.50	0.008

Abbreviations: [1]CI, confidence interval; OR, odds ratio; PPI, proton-pump inhibitor.

Associations Between Major Mood Disorders and Asthma

In the present study, we adjusted for several risk factors for depression and anxiety in asthma. Female sex, older age, comorbidity burden and increasing asthma severity have all previously been shown to be associated with psychiatric comorbidity in asthma.[5]

A dose–response relationship between socioeconomic markers such as low income, education, civil- and employment status has previously been demonstrated in

Table 4 Multivariable Logistic Regression for Odds of Antidepressant Treatment in 60,534 Patients with Actively Treated Asthma, Stratified by Asthma Severity and Adjusted for Specialist Asthma Care and Common Risk Factors

Logistic Regression			
	OR[1]	**95% CI**	**p-value**
Population			
Mild-to-Moderate Asthma	1		
Possible Severe Asthma	1.15	1.05, 1.26	0.004
Specialist Asthma Care	0.90	0.84, 0.96	<0.001
Female	1.52	1.44, 1.60	<0.001
Age	1.03	1.03, 1.04	<0.001
Workforce Status			
Employed	1		
Transfer Income Recipient	4.02	3.76, 4.30	<0.001
Currently Under Education	1.32	1.19, 1.47	<0.001
Level of Education			
Primary and Basic Education	1		
Vocational Training	1.04	0.97, 1.11	0.3
Higher Education	0.87	0.82, 0.93	<0.001
Taxable Income Level			
Low (1st Quartile)	1		
Middle (2nd + 3rd Quartile)	0.97	0.91, 1.04	0.5
High (4th Quartile)	0.58	0.53, 0.64	<0.001
Civil Status			
Married	1		
Separated	1.63	1.51, 1.76	<0.001
Never Married	1.34	1.26, 1.42	<0.001
Metropolitan Residence	0.87	0.82, 0.92	<0.001
Use of decongestants and antiallergics	1.03	0.96, 1.11	0.4
PPI use	2.12	2.00, 2.23	<0.001
Charlson Score ≥2	1.33	1.07, 1.64	0.008

Abbreviations: [1]CI, confidence interval; OR, odds ratio; PPI, proton-pump inhibitor.

depression,[30] and the present study confirms that this is present even in patients with asthma. While socioeconomic status (SES) can be defined in a plethora of ways, it often includes income and education.[31] It is debatable whether lower SES is a cause of depression, or depression is a cause of lower SES,[32] but a strong correlation between SES and asthma control,[4,33,34] as well as asthma control and depression,[7,14] exists. The complex interplay between risk factors warrants further clinical attention, as the vicious circle between psychiatric comorbidity and asthma suggested by DiMatteo et al[35] is a difficult one to break for at-risk patients without healthcare professional support.

Disease Control and Major Mood Disorders

In the present study, severe exacerbations were the only objective measure of loss of disease control associated with increased odds of antidepressant use after controlling for other risk factors, despite patients receiving antidepressant having a higher use of rescue medication and a higher prevalence of exacerbations overall. Whether these findings are due to differences in healthcare seeking behaviours and sociodemographic factors amongst patients with severe asthma exacerbations,[36] the impact of severe exacerbations on QoL[37] or whether antidepressant use is a risk marker for patients less likely to be adherent to controller medication[35] remains to be elucidated. Furthermore, the use of antidepressant use as a proxy for MMD symptoms could lead to an underestimation of certain risk factors such as rescue medication use, which has been shown to correlate to poor QoL and depressive symptoms[38] – but perhaps not enough to warrant antidepressant therapy.

As interventions specifically for MMDs in asthma have been unconvincing in terms of reducing MMD symptoms,[39,40] it can be argued that healthcare providers should prioritize reducing the overall disease burden to reduce the prevalence of antidepressant-requiring MMD in asthma. Indeed, impressive gains in QoL can be seen with the use of biologics in severe asthma,[41] but it is unknown whether these translate to a lower prevalence of antidepressant requiring MMD. Alas, both for possible severe asthma and patients with mild-to-moderate disease ineligible for biologic therapy, a patient-centered qualitative approach should be considered in future studies to help untangle the web between asthma, disease control and MMD across all disease severities.

Table 5 Multivariable Logistic Regression for Odds of Antidepressant Treatment in 60,534 Patients with Actively Treated Asthma, Using Three Different Measures of Asthma Control

	>600 Annual SABA Doses			≥2 Moderate Exacerbations[1]			≥1 Severe Exacerbation(s)[2]		
	OR[3]	95% CI	p-value	OR[1]	95% CI	p-value	OR[1]	95% CI	p-value
Asthma Control Measure[4]	1.04	0.96, 1.12	0.3	1.11	0.99, 1.24	0.071	1.11	1.04, 1.20	0.004
Female	1.51	1.44, 1.59	<0.001	1.51	1.43, 1.59	<0.001	1.51	1.43, 1.58	<0.001
Age	1.03	1.03, 1.04	<0.001	1.03	1.03, 1.04	<0.001	1.03	1.03, 1.04	<0.001
Workforce Status									
Employed	1			1			1		
Transfer Income Recipient	4.01	3.76, 4.29	<0.001	4.01	3.75, 4.29	<0.001	4.00	3.74, 4.28	<0.001
Currently Under Education	1.32	1.19, 1.47	<0.001	1.32	1.19, 1.47	<0.001	1.32	1.19, 1.47	<0.001
Level of Education									
Primary and Basic Education	1			1			1		
Vocational Training	1.04	0.97, 1.11	0.3	1.04	0.97, 1.11	0.3	1.04	0.97, 1.11	0.2
Higher Education	0.87	0.82, 0.93	<0.001	0.87	0.82, 0.93	<0.001	0.87	0.82, 0.93	<0.001
Taxable Income Level									
Low (1st Quartile)	1			1			1		
Middle (2nd + 3rd Quartile)	0.97	0.91, 1.04	0.4	0.97	0.91, 1.04	0.4	0.97	0.91, 1.04	0.5
High (4th Quartile)	0.58	0.53, 0.64	<0.001	0.58	0.52, 0.64	<0.001	0.58	0.53, 0.64	<0.001
Civil Status									
Married	1			1			1		
Separated	1.63	1.51, 1.76	<0.001	1.63	1.51, 1.76	<0.001	1.63	1.51, 1.76	<0.001
Never Married	1.34	1.27, 1.42	<0.001	1.34	1.27, 1.43	<0.001	1.34	1.27, 1.43	<0.001
Metropolitan Residence	0.87	0.82, 0.92	<0.001	0.87	0.82, 0.92	<0.001	0.87	0.82, 0.92	<0.001
Use of decongestants and antiallergics	1.03	0.96, 1.11	0.4	1.03	0.96, 1.11	0.4	1.04	0.96, 1.12	0.4
PPI use	2.11	2.00, 2.23	<0.001	2.11	1.99, 2.23	<0.001	2.10	1.99, 2.22	<0.001
Charlson Score ≥2	1.32	1.07, 1.64	0.010	1.32	1.07, 1.63	0.010	1.30	1.05, 1.61	0.015

Notes: [1]Defined as at least two redeemed prescriptions for oral corticosteroids. [2]Defined as at least one asthma-related hospitalization. [4]As defined in table header.
Abbreviations: [3]CI, confidence interval; OR, odds ratio; PPI, proton-pump inhibitor.

Limitations

The present study has several weaknesses that should be considered. First, the study is a cross-sectional retrospective study and is thus limited by inherent flaws due to study designs, such as limited ability to establish causation. Second, the use of antidepressants should be extrapolated to a real-world prevalence of depression with caution as non-pharmacologic treatment is considered first-in-line and is not accounted for in the present study. Third, important confounders such as smoking status and alcohol consumption are not registered in national registries and are thus unaccounted for. Fourth, the present study uses a daily ICS exposure measurement to establish ICS dose based on NICE cut-offs, instead of prescribed dose as typically used when determining GINA treatment steps.[1] However, the classic approach fails to account for adherence to ICS treatment, and due to the increasing use of as needed ICS/LABA treatment,[1] we believe that ICS exposure provides a more accurate depiction of the inhaler therapy used on an

individual basis. Finally, as no universal dose equivalence charts between ICS compounds and formulations exist,[42] estimations that might differ from real-world efficacy have been used. Differences in cut-offs between NICE and GINA guidelines might lead to differential classifications depending on the definition used, yet ramifications are assumed to be minor due to the large number of assumptions already used in estimating daily doses from long-term redemption data.

Conclusion

In the present nationwide study, antidepressant use was common in asthma with 16–22% of patients redeeming prescriptions during the study period and the use increased with increasing disease severity. When compared to the background populations, asthma was associated with antidepressant use (ORs 1.40 to 1.55) even after adjusting for common risk factors, suggesting a substantial psychological burden of an asthma diagnosis. Continued and increased attention to the psychological effects of asthma is warranted.

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