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Early View

Original research article

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Trends and predictors of specialist assessments in oral corticosteroid treated asthma among young adults

Short title:
Specialist care in asthma management

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Take home message
Repeated use of oral corticosteroids indicates poor asthma control and is associated with adverse effects, why referral for specialist assessment is recommended. However, the majority (70%) of patients are managed exclusively in primary care.

Abstract

Background: Repeated oral corticosteroid use indicates uncontrolled disease among asthma patients and referral for asthma specialist assessment is recommended. We aimed to describe trends and predictors associated with specialist contacts among young adults with asthma and repeated oral corticosteroid use.

Methods: Individuals aged 18-45 years with ≥2 dispensed asthma medication prescriptions and two dispended oral corticosteroid prescriptions (including short-term and long-term treatments) within 12 months during 1999-2018 were identified by use of Danish healthcare registers. The frequency of specialist contacts within one year of follow-up was assessed among individuals without previous specialist contacts within five years of inclusion. Factors associated with specialist contact were identified by logistic regression models. Furthermore, oral corticosteroid prescriber sources were assessed.

Results: For the 11,223 individuals included, 2,444 (22%) had previous specialist contacts care within five years prior of inclusion and additionally 926 (8.3%) within one year of follow-up. Among those without previous specialist contacts (n 8,779), the frequency of incident specialist contacts within one year of follow-up increased from 6.3% in 1999 to 18% in 2017. Factors associated with incident specialist contacts included dispensing ≥12 SABA canisters and previous asthma-related emergency department visits and hospitalisations. The majority of oral corticosteroid prescriptions at baseline (71%) were prescribed by general practitioners, though with decreasing proportions from 1999-2018.

Conclusions: The majority (70%) of young adults with asthma and repeated oral corticosteroid use do not seem to receive specialist assessment in Denmark. This highlights a potential room for improvement in the patient referral pathway for at-risk asthma patients.

Keywords: asthma, oral corticosteroids, referral, specialist care

Abstract word count: **250**

Background

Asthma is a common inflammatory airway disease with an estimated prevalence of 8-10% among adults in Denmark[1,2]. Most patients with asthma are managed in primary care, though with the option of referral for asthma specialist assessment, e.g., in case of uncertain diagnosis, severe or uncontrolled disease. Despite recent decades' advances in asthma understanding and management, poor asthma control is prevalent in more than one in three with severe asthma and one in four with mild-moderate asthma in Scandinavia[3-5] with major consequences for the patients' quality of life as well as societal costs[5-7].

Oral corticosteroids (OCS) are used for treating uncontrolled asthma, either as short-term courses for severe exacerbations or long-term treatments for severe asthma that remains uncontrolled despite otherwise optimised treatment[8]. Though new therapies for controlling asthma have emerged over the years, OCS continues to be frequently used in asthma management[9] with no reduction in the prevalence of OCS users among young adults with asthma in Denmark during the last two decades[10]. Recently, international experts have proposed that a cumulative OCS exposure of 0.5-1 g/year (equivalent to 2-4 OCS exacerbation courses) is indicative of poor asthma control[11] and that patients receiving ≥2 courses within a year should be considered referred for specialist assessment[12]. Similarly, the Global Initiative for Asthma (GINA) has since 2014 recommended referral for expert advice in case of long term or frequent OCS use, e.g. two or more courses a year[13]. Recent studies have mainly focused on the referral pathways among severe asthma populations[3,4,14,15], but if the overall OCS use in asthma management is to be minimised, a focus on general asthma populations is called for. A great deal of inappropriate OCS use occurs in mild–moderate asthma which may be poorly controlled due to underuse of ICS and/or poor adherence[9,16]. The most important problem in suboptimal treated asthma is recurrent exacerbations, decline of pulmonary function, and OCS associated side effects[5,7,16]. A growing amount of evidence suggest that receiving even a few OCS courses is associated with long-term side effects in general asthma populations[9,17-19], emphasising a need of easy-to-recall red flags for the identification of at-risk patients in broader asthma populations who would benefit from a second opinion from a specialist.

We therefore aimed to describe trends and factors associated with specialist assessment in a nationwide cohort of young adults with asthma and repeated oral corticosteroid use over a 20-year period using population-based healthcare registers.

Materials and methods

Design and data sources

We performed a register-based open cohort study with a study period from 1999-2018. Data from nationwide administrative and healthcare registers was provided by the Danish Health and Medicines Authority and included data on basic demographics[24], drug prescriptions filled at community pharmacies[25], procedures and diagnoses from hospitals[26], and services from private practices[27]. Pseudonymised data were linked on an individual level using the civil registration number unique to all Danish citizens[28].

Study population

A study population of young adults with asthma and repeated OCS use was based on validated methods and identified as individuals aged 18-45 years with ≥2 redeemed asthma medication prescriptions (including inhaled corticosteroids (ICS), selective β2 agonists, leukotriene receptor antagonists, and xanthines)[29,30], and two OCS prescriptions within 12 consecutive months[8,12] (i.e., the baseline period) using the second OCS prescription as index date. OCS prescriptions included prednisolone and prednisone (Anatomical Therapeutic Chemical (ATC) codes H02AB06 and H02AB07) independent of dose and duration. Exclusion criteria included hospital-given diagnoses of chronic obstructive pulmonary disease (COPD) or cystic fibrosis, and under five years of available data prior to cohort entry (i.e., recent migrations etc.). Furthermore, individuals with comorbidities often treated with OCS (including sarcoidosis, primary adrenocortical insufficiency, pneumonitis, inflammatory bowel disease, inflammatory polyarthropathies, systemic connective tissue disorders, inflammatory spondylopathies, and/or malignance, as defined in the **Online Supplement, Table S1**) were excluded at index date and censored during follow-up upon incident diagnosis. All individuals were followed for maximum five years after index date, until death, or

migration. Patient selection flowchart is shown in **Figure 1** and the study design in **Figure S1 (Online Supplement)**.

Covariates

Baseline characteristics at index date included sex, age, marital status, and region of residency. Asthma medication use, number of asthma-related emergency department (ED) visits and hospitalisations, and comedication use (including systemic antibiotics, systemic antihistamines, nasal corticosteroids, antidepressants, anti-acid drugs, anti-obesity drugs, antidiabetic drugs excl. insulins, bisphosphonates) were assessed during the baseline period. ICS use was categorised as no use, low dose (≤400 µg/day) or medium/high dose (>400 µg/day) in budesonide equivalents[8]. To enable comparison of short-acting β2-agonists (SABA) canisters, one canister was defined as 200 doses (puffs) irrespective of dosage and strength. SABA use was categorised as low use (0-<3 canisters), increased use (3-<12 canisters), and excessive use (≥12 canisters). OCS prescriber source was categorised as general practitioners, private specialists, hospital physicians, and others. Years since the first asthma medication dispensing from index date was used as an indicator of number of years lived with asthma.

Specialist assessment

Patient contacts to specialised care were defined by presence of an outpatient hospital contact with a relevant asthma-related diagnosis code as defined by the Danish National Database for Asthma (DrAstma)[31] or as a contact with a private specialist with a relevant pulmonary service code as previously described[3] (further specified in **Online Supplement, Table S1**).

The main outcomes of interests were the proportion of individuals with a specialist contact during a five-year period leading up to time of inclusion and the proportion of incident specialist contacts within one year of follow up (i.e., among those without previous specialist contacts).

Baseline characteristics were evaluated for their potential association with incident specialist assessments within one year of follow-up among patients included during 2014-2017. The analysis was restricted to 2014-2017 due to GINA first implementing the recommendation of referral for specialist advice if the patient had used repeated OCS (e.g., two courses or more a

year) in 2014. Furthermore, this was done in order to increase the clinical relevance of the estimates.

The waiting time for achieving incident specialist assessment was furthermore evaluated within a five year follow up window.

Statistical analyses

Categorical variables were summarised as number and percentage an compared by Chi-square test of independence. Continuous variables were reported as median and interquartile range (IQR) and compared by nonparametric equality-of-medians test. Among individuals included during 2014-2017, associations between baseline characteristics (covariates) and receiving specialist assessment within one year of follow-up (outcome) were evaluated by multivariable logistic regression and reported as crude and adjusted odds ratio (OR) with 95% confidence intervals (CI). The waiting time for first specialist contact within five years of follow-up was illustrated graphically.

Two sensitivity analyses were performed with alternative definitions of 'repeated OCS users' as patients with three and four OCS prescriptions within the baseline year, respectively, in order to explore the impact of choosing other thresholds for a potential guideline recommendation.

A supplemental post hoc analysis was performed on a subpopulation with possible severe asthma defined by GINA step 4-5 (use of medium or high-dose ICS plus $\geq$1 add-on treatment within the baseline period)[8].

All data was analysed using Stata version 17.0 (StataCorp, College Station, TX, USA).

Results

Baseline characteristics

Baseline characteristics are presented in **Table 1**. A total of 11,223 individuals with asthma (62% female, median age 36 years (IQR 29-41 years)) were included in the study population as repeated OCS users whereof 2,444 (22%) had a specialist contact within five years of inclusion. Patients with previous specialist contacts were younger (35 years versus 37 years, p<0.001) and more often

female (67% versus 61%, p<0.001). Furthermore, they were more often treated with medium/high dose ICS and add-on therapies and less often had an excessive use of SABA (see **Table 1**).

Trends in specialist assessment

Among those without previous specialist contacts, a total of 11% (926 of 8,779) had an incident specialist contact within one year of follow-up, resulting in a total of 70% of the total cohort (7,853 of 11,223) not meeting the primary endpoint of specialist assessment either five years prior to or one year after inclusion. Annual cross-sectional analyses showed that the proportion of incident specialist contacts within one year of follow up increased from 6.3% in 1999 to 18% in 2017 (**Figure 2**).

Characteristics associated with specialist assessment

Several characteristics appeared to be associated incident specialist assessment among individuals included during 2014-2017. The strongest associated factors included asthma-related ED visits (OR 3.76, 95% CI 2.14-6.61), asthma-related hospitalisations (OR 3.19, 95% CI 2.16-4.71), medium/high dose ICS (OR 1.80, 95% CI 1.16-2.80), and $\geq$2 add-on controllers (OR 1.72, 95% CI 1.09-2.71). Patients of higher age (36-45 years), the divorced/widowed, and patients residing outside the Capital and Zealand were less likely to receive specialist assessment (see **Table 2**). However, when adjusting for the other factors in the model, only asthma-related ED visits (OR 2.62, 95% 1.42-4.84), hospitalisations (OR 2.59, 95% CI 1.71-3.90), $\geq$12 SABA canisters (OR 1.78, 95% 1.01-3.14), and residence in North Denmark (OR 0.65, 95% 0.44-0.97) achieved statistically significant p-values below 0.05.

Specialist assessment waiting time

Among those without previous specialist contacts, 19% (1,696 of 8,779) received specialist assessment within a five-year follow-up period with a median waiting time of 9 months (IQR 2-28 months). As depicted in **Figure 3**, we observed an increase in incident specialist assessments in the months shortly after inclusion as repeated OCS user. However, this effect declined after six to eight months to a level appearing to be a baseline frequency of incident specialist referrals in the cohort.

Prescriber information

The majority of OCS dispensed during the baseline period was prescribed by general practitioners (71%) with an overall decrease from 79% in 1999 to 66% in 2018 (**Figure 4**). Prescriptions by hospital physicians increased from 17% in 1999 to 26% in 2018 (a total relative increase of 65%). Hospital physicians were more likely to prescribe the second OCS prescription compared to the first prescription (analysis restricted to the years 2014-2018, see **Figure 5**). The amount of OCS prescriptions without prescriber source information reduced from 44% in 1999 to 6.0% in 2018 (not shown).

Sensitivity analyses and post hoc analyses

In the sensitivity analyses of patients with three and four annual OCS prescriptions, we found a slight increase in the proportion of previous specialist contacts from 22% (two OCS prescriptions) to 25% and 26% for three and four OCS prescriptions, respectively. However, the frequency of incident specialist contacts within one year of follow-up decreased slightly from 11% (two OCS prescriptions) to 9.9% (three OCS prescriptions) and 8.8% (four prescriptions).

The post hoc analysis restricted to patients with possible severe asthma showed similar trends of increasing referral for specialist assessment, however with larger fluctuations, which was probably due to the lower population number (**Figure S2**).

Discussion

In this observational nationwide cohort study of young adults with asthma in Denmark, we found that patients with repeated OCS treatments are mainly managed in primary care. Overall, 70% of the patients did not have contacts to specialised care within either five prior to or one year post of inclusion. However, among those without previous specialist contacts, the frequency of incident specialist referrals tripled over the 20-year observation period from 6% to 18% a year. These results illustrate an opportunity for a potential optimisation of the referral pathway for patients with uncontrolled asthma who are in risk of long-term treatment side effects[9,17,19]. While previous studies have mainly focused on specialist referrals among severe asthma populations[3,4,14,15], the aim of this study was to explore trends and tendencies in a general asthma population with a

specific focus on repeated OCS treatments as a 'red flag' for identification of at-risk patients. Patients with repeated OCS use are at risk of both long-term morbidity as well as underestimation of the true severity of the disease. As stated in a recent national report from the United Kingdom, many cases of death due to asthma occurs in seemingly mild to moderate cases, highlighting a potential undertreatment of the disease[23]. Implementation of repeated OCS use as an easy-to-recall criterion and indication of specialist referral would be relevant for both primary care but also for hospital physicians.

Our study parallels findings from previous studies on uncontrolled and severe asthma populations which have also found a potential room for improvement in the overall patient referral pathway. A Danish cross-sectional study from 2014 found that only 14% of patients with low asthma control had contact to a respiratory specialist within 365 days[3]. Among patients with severe asthma and low control, the number was somewhat higher at 36%[3]. A more recent Danish study from 2021 found that 61% of patients with possible severe asthma were exclusively managed in primary care during 2014-2018 with significant differences in socioeconomic parameters compared to those achieving specialist referral[14]. Similar trends have been found in other countries. In Sweden, a register-based study found that only 20% of severe asthma patients were managed in secondary care[4]. Furthermore, only 32% of severe asthma patients had an asthma-related primary care contact within one year of inclusion, which indicates an overall low frequency of asthma-related health care contacts among severe asthma patients[4]. Studies from England have found similar trends with only a minority of patients with uncontrolled and severe asthma being referred for specialist care[15,32,33]. Bloom et al. found that the prevalence of asthma patients receiving ≥3 OCS courses a year had increased from 1% in 2006 to 2% in 2016, and that generally less than 20% of the patients were referred for specialist care[32]. Encouragingly, one interesting finding of the study was that the specialist referral rates of eligible patients continually increased, which is consistent with our findings.

We furthermore found that acute asthma-related hospital visits and dispensing ≥12 SABA canisters were independent predictors of receiving specialist assessment in agreement with previous literature[32]. This indicates that patients with difficult-to-treat and possible severe asthma are being referred to specialist assessments to a greater extent in agreement with current

recommendations[8]. In the crude analysis, older age and residency outside the capital were associated with lower odds of specialist care, as found by a previous Danish study[14].

In average, 71% of the OCS was prescribed by general practitioners, which is lower than the 76% found in an Australian asthma study[34] but higher than the 60% found in a recent German study[35]. Interestingly, this proportion decreased over the study period as a further indication that more patients requiring OCS treatments are being managed in specialised care. This may be due to changes in asthma guidelines or increased implementation hereof, however, exploration of such underlying reasons was beyond the capability of this study.

4.1 Clinical considerations

Our results indicate that many patients with potentially uncontrolled asthma are not referred for specialist assessment. As to date, repeated use of OCS is not considered an independent criterion for referral in e.g., Danish guidelines. It is however recognised by international experts[11,12] and stated in the GINA guidelines[8], as repeated OCS use indicates uncontrolled disease[11] and even a few lifetime courses is associated with significant adverse effects[9].

Uncontrolled asthma might be caused by difficult to treat asthma - i.e., lack of adherence - or severe asthma in need of medicine administered only by hospital specialists. In both cases, to prevent long-term complications of uncontrolled asthma, timely referral of at-risk patients is essential[12,36] and easy-to-recall indicators are warranted. Specialist care for at-risk patients with asthma is associated with improved asthma-related outcomes[37,38]. A national report from the United Kingdom found that 19% of asthma deaths were potentially attributable to a lack of specialist referrals[23]. Specialists might identify treatable traits such type 2 inflammation, and address comorbidities such as bronchiectasis, inducible laryngeal obstruction, heart diseases, allergic bronchopulmonary aspergillosis (ABPA), and eosinophilic granulomatous polyangiitis (EGPA). Also, biological treatment for severe asthma, which has proven able to reduce both exacerbation rates and maintenance OCS use[39], is only available through hospital care in Denmark. While only 800-900 patients receive biological treatment in Denmark, it is estimated by experts that 10,000 may be eligible for this treatment[40] underpinning that more patients with OCS use could benefit from referral. One way to ease this process could be implementation of an easy-to-recall recommendation of referral for patients in need of more than one OCS treatment within a

year. Digital applications and computerised decision support systems may further be of aid, as well as formal collaborations with pharmacists.

4.2 Strengths and limitations

The nationwide Danish registers provide data on all individuals residing in Denmark and are generally of high validity and completeness with the opportunity of data-linkage on an individual level[41]. They provide real-world data, which are collected systematically and independently of the researchers.

There are several important limitations to this study. Firstly, due to the lack of diagnostic data from general practice and the low positive predictive value of asthma diagnoses in the National Patient Register[42], we constructed an asthma cohort based on validated methods using prescription data[29,30]. The approach required a strict upper age of 45 years to limit the inclusion of patients with COPD. This limits the generalisability of the results to older asthma populations. Secondly, relevant clinical information on e.g., smoking, body mass index, spirometry parameters, and indications for prescribed treatment were not available. We sought to limit including OCS use due to other reasons than asthma by censoring patients with potential OCS-treated comorbidities. We can however not account for other potential clinical factors contributing to the OCS use such as allergies. Thirdly, a dispensed prescription is not necessarily equal to the medication amount taken, and we are not able to account for possible stockpiling. The use of dispensed prescriptions did however reduce the risk of misclassification due to primary nonadherence. Fourthly, we did not have information on asthma severity, as dispensed asthma medication is no longer recommended for imputing asthma severity in observational studies[8]. Nor did we have data on asthma endotypes, hence limiting the identification of possible candidates for biological treatment. Finally, our definition of 'specialist assessment' was not restricted to physicians with a speciality in respiratory medicine, as we considered this definition too restrictive for the purpose of this study.

Despite of the noted limitations, we expect that the used definitions and chosen analyses have revealed results which to a high degree reflect actual trends and predictors of specialist assessments among patients with repeated OCS use.

4.3 Conclusion

The proportion of patients being referred for specialist assessment has increased markedly over the last two decades, however only 30% of adults with asthma and repeated OCS use are managed in specialist care overall. Though clarification of underlying reasons and/or barriers for most patients not achieving specialist assessment was beyond the capability of this study, our findings call for focusing on and optimisation of the patient referral pathway for high-risk patients with poor asthma control. Repeated use of OCS may serve as an easy-to-recall red flag for identification of patients with uncontrolled asthma where specialist referral should be considered. Future studies should focus on the feasibility of implementing this recommendation as an intervention in randomised controlled studies to assess whether patients referred to specialists on behalf of a red flag signal may benefit in form of faster assessment and better overall asthma management. In addition, studies should also focus on identifying potential barriers of referral and exploring other instruments for optimising the complex patient pathway.

Ethics

The data extraction was approved by the Data Protection Agency (record no 10.121). Approval from ethics review board is not required for register-based studies in Denmark due to the use of pseudonymised data. Recommendations from The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Initiative were used in conducting and reporting results for this study.

Data availability

Data used in this study was supplied by the Danish Health Data Authority and is accessible to researchers upon relevant application and a data extraction fee at https://sundhedsdatastyrelsen.dk/da/english

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Author contributions

JRD, HM, and IRS conceptualised the study. IRS and AP designed the study. JHA performed the formal analyses. JRD, HM, and IRS acquired the funding. IRS wrote the original draft. JRD was the main supervisor. All authors reviewed and approved the final version.

Declaration of interest

IRS reports grants paid to her institution from AstraZeneca, Teva, Novartis, Odd Fellows Haderslev Denmark, the Region of Southern Denmark, and the University of Southern Denmark; and personal fees for lectures from Roche, Teva, and AstraZeneca outside the submitted work. Anton Pottegård reports participation in research projects funded by Alcon, Almirall, Astellas, AstraZeneca, Boehringer-Ingelheim, Novo Nordisk, Servier and LEO Pharma, all regulator-mandated phase IV-studies, all with funds paid to the institution where he was employed (no personal fees) and with no relation to the work reported in this paper. JRD reports grants and personal fees for advisory board participation and lectures from Roche and Boehringer Ingelheim, and personal fees for lectures from Chiesi, outside the submitted work. HM, DPH and JHA have nothing to disclose.

Tables

Table 1: Baseline characteristics of young adults with asthma and repeated oral corticosteroid use stratified according to previous specialist contacts (within five years of index date)

	All patients	**Previous specialist contacts**	**No previous specialist contacts**	**p-value**
Individuals, n	(n=11,223)	(n=2,444)	(n=8,779)	
Female, n (%)	7003 (62.4%)	1637 (67.0%)	5366 (61.1%)	<0.001
Age, median (IQR)	36 (29-41)	35 (26-41)	37 (30-42)	<0.001
18-25	1761 (15.7%)	555 (22.7%)	1206 (13.7%)	<0.001
26-35	3406 (30.3%)	734 (30.0%)	2672 (30.4%)	0.709
36-45	6056 (54.0%)	1155 (47.3%)	4901 (55.8%)	<0.001
Marital status, n (%)				
Unmarried	3434 (30.6%)	928 (38.0%)	2506 (28.5%)	<0.001
Married/registered partnership	4717 (42.0%)	933 (38.2%)	3784 (43.1%)	<0.001
Divorced/widowed	1242 (11.1%)	223 (9.1%)	1019 (11.6%)	<0.001
Other/missing	14 (0.1%)	5 (0.2%)	9 (0.1%)	0.203
Region of residency, n (%)				
Capital	3262 (29.1%)	888 (36.3%)	2374 (27.0%)	<0.001
Zealand	1734 (15.5%)	236 (9.7%)	1498 (17.1%)	<0.001
North Denmark	1094 (9.7%)	189 (7.7%)	905 (10.3%)	<0.001
Central Denmark	2595 (23.1%)	473 (19.4%)	2122 (24.2%)	<0.001
Southern Denmark	2520 (22.5%)	654 (26.8%)	1866 (21.3%)	<0.001
Missing	18 (0.2%)	(n<5)	-	-
Years since first asthma drug dispensing (any time before index date), median (IQR)	7 (4-13)	9 (4-14)	7 (4-12)	<0.001
Concurrent asthma medication, n (%)				
ICS				
No use	1735 (15.5%)	200 (8.2%)	1535 (17.5%)	<0.001
Low dose	5696 (50.8%)	1208 (49.4%)	4488 (51.1%)	0.143
Medium/high dose	3792 (33.8%)	1036 (42.4%)	2756 (31.4%)	<0.001
LABA	6296 (56.1%)	1790 (73.2%)	4506 (51.3%)	<0.001
LTRA	1876 (16.7%)	732 (30.0%)	1144 (13.0%)	<0.001
LAMA	344 (3.1%)	126 (5.2%)	218 (2.5%)	<0.001
SABA canisters				
0–<3	4690 (41.8%)	978 (40.0%)	3712 (42.3%)	0.046
3–<12	4749 (42.3%)	1145 (46.8%)	3604 (41.1%)	<0.001
≥12	1784 (15.9%)	321 (13.1%)	1463 (16.7%)	<0.001
Co-medication, n (%)				
Antibiotics	8009 (71.4%)	1731 (70.8%)	6278 (71.5%)	0.511

Antihistamines	3655 (32.6%)	1042 (42.6%)	2613 (29.8%)	<0.001
Nasal corticosteroids	2983 (26.6%)	942 (38.5%)	2041 (23.2%)	<0.001
Antidepressants	1628 (14.5%)	299 (12.2%)	1329 (15.1%)	<0.001
Anti-acid drugs	1813 (16.2%)	438 (17.9%)	1375 (15.7%)	0.008
Anti-obesity drugs	355 (3.2%)	57 (2.3%)	298 (3.4%)	0.007
Antidiabetic drugs, excl. insulins	157 (1.4%)	36 (1.5%)	121 (1.4%)	0.698
Bisphosphonates	16 (0.1%)	(n<5)	-	0.762
Asthma-related ED visits, n (%)				
1	431 (3.8%)	147 (6.0%)	284 (3.2%)	<0.001
2	73 (0.7%)	30 (1.2%)	43 (0.5%)	<0.001
≥3	47 (0.4%)	13 (0.5%)	34 (0.4%)	0.374
Asthma-related hospitalisations, n (%)				
1	1097 (9.8%)	336 (13.7%)	761 (8.7%)	<0.001
2	276 (2.5%)	133 (5.4%)	143 (1.6%)	<0.001
≥3	141 (1.3%)	70 (2.9%)	71 (0.8%)	<0.001

ED: emergency department; ICS: inhaled corticosteroids; IQR: interquartile range; LABA: long-acting β2-agonists; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonist; SABA: short-acting β2-agonist

Table 2: Factors associated with specialist assessment among young adults with asthma and repeated oral corticosteroid use included during 2014-2017 (only individuals without previous specialist contacts)

	Crude OR (95% CI)	p-value	Adjusted* OR (95% CI)	p-value
Female (reference)	1.00	-	1.00	-
Male	0.89 (0.67–1.19)	0.443	0.93 (0.69–1.25)	0.638
Age				
18–25 (reference)	1.00	-	1.00	-
26–35	0.87 (0.58–1.29)	0.477	0.94 (0.61–1.45)	0.773
36–45	0.63 (0.44–0.92)	0.015	0.74 (0.47–1.15)	0.181
Marital status				
Unmarried (reference)	1.00	-	1.00	-
Married/registered partnership	0.81 (0.59–1.09)	0.164	0.95 (0.66–1.37)	0.793
Divorced/widowed	0.55 (0.33–0.93)	0.027	0.57 (0.32–1.02)	0.057
Other/missing	0.83 (0.50–1.40)	0.490	0.79 (0.46–1.38)	0.411
Region of residency				
Capital (reference)	1.00	-	1.00	-
Zealand	0.73 (0.49–1.08)	0.119	0.86 (0.57–1.29)	0.457
North Denmark	0.61 (0.42–0.88)	0.009	0.65 (0.44–0.97)	0.036
Central Denmark	0.55 (0.32–0.93)	0.027	0.58 (0.33–1.00)	0.052
Southern Denmark	0.61 (0.40–0.94)	0.024	0.72 (0.46–1.14)	0.160
Concurrent asthma medication				
ICS				
No use (reference)	1.00	-	1.00	-
Low dose	1.75 (1.18–2.59)	0.006	1.52 (0.99–2.35)	0.057
Medium/high dose	1.80 (1.16–2.80)	0.009	1.31 (0.78–2.21)	0.303
Add-on controllers (LABA, LAMA, LTRA)				
0 (reference)	1.00	-	1.00	-
1	1.17 (0.87–1.57)	0.308	1.05 (0.76–1.45)	0.766
≥2	1.72 (1.09–2.71)	0.019	1.62 (0.99–2.66)	0.055
SABA canisters				
0–<3 (reference)	1.00	-	1.00	-
3–<12	1.44 (1.08–1.93)	0.014	1.37 (0.99–1.89)	0.055
≥12	1.65 (0.99–2.75)	0.057	1.78 (1.01–3.14)	0.046
Asthma-related ED visits				
0 (reference)	1.00	-	1.00	-
≥1	3.76 (2.14–6.61)	0.000	2.62 (1.42–4.84)	0.002
Asthma-related hospitalisation				
0 (reference)	1.00	-	1.00	-
≥1	3.19 (2.16–4.71)	0.000	2.59 (1.71–3.90)	0.000

*Adjusted for all other factors in the model.

Estimates tested by multivariable logistic regression analyses and reported as odds ratio (OR) with 95% confidence intervals (CI). ED: emergency department; ICS: inhaled corticosteroids; LABA: long-

acting β2-agonists; LAMA: long-acting muscarinic antagonist; LTRA: leukotriene receptor antagonist; SABA: short-acting β2-agonist

References

1. To T, Stanojevic S, Moores G, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC Public Health.* 2012;12:204. doi:10.1186/1471-2458-12-204
2. Hvidberg MF, Johnsen SP, Davidsen M, Ehlers L. A Nationwide Study of Prevalence Rates and Characteristics of 199 Chronic Conditions in Denmark. *Pharmacoecon Open.* 2020;4(2):361-380. doi:10.1007/s41669-019-0167-7
3. von Bulow A, Kriegbaum M, Backer V, Porsbjerg C. The prevalence of severe asthma and low asthma control among Danish adults. *J Allergy Clin Immunol Pract.* 2014;2(6):759-767. doi:10.1016/j.jaip.2014.05.005
4. Larsson K, Stallberg B, Lisspers K, et al. Prevalence and management of severe asthma in primary care: an observational cohort study in Sweden (PACEHR). *Respir Res.* 2018;19(1):12. doi:10.1186/s12931-018-0719-x
5. Stridsman C, Axelsson M, Warm K, Backman H. Uncontrolled asthma occurs in all GINA treatment steps and is associated with worse physical health - a report from the OLIN adult asthma cohort. *J Asthma.* 2020:1-10. doi:10.1080/02770903.2020.1713150
6. Lee LK, Ramakrishnan K, Safioti G, Ariely R, Schatz M. Asthma control is associated with economic outcomes, work productivity and health-related quality of life in patients with asthma. *BMJ Open Respir Res.* 2020;7(1). doi:10.1136/bmjresp-2019-000534
7. Czira A, Turner M, Martin A, et al. A systematic literature review of burden of illness in adults with uncontrolled moderate/severe asthma. *Respir Med.* 2021;191:106670. doi:10.1016/j.rmed.2021.106670
8. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2021. Available from: www.ginasthma.org.
9. Bleecker ER, Menzies-Gow AN, Price DB, et al. Systematic Literature Review of Systemic Corticosteroid Use for Asthma Management. *Am J Respir Crit Care Med.* 2020;201(3):276-293. doi:10.1164/rccm.201904-0903SO
10. Skov IR, Henriksen DP, Madsen H, Pottegard A, Davidsen JR. Changes in oral corticosteroid use in asthma treatment-A 20-year Danish nationwide drug utilisation study. *Basic Clin Pharmacol Toxicol.* 2022;130(1):122-131. doi:10.1111/bcpt.13680
11. Suehs CM, Menzies-Gow A, Price D, et al. Expert Consensus on the Tapering of Oral Corticosteroids for the Treatment of Asthma. A Delphi Study. *Am J Respir Crit Care Med.* 2021;203(7):871-881. doi:10.1164/rccm.202007-2721OC
12. Humbert M, Bourdin A, Papadopoulos NG, et al. Reducing the hidden burden of severe asthma: recognition and referrals from primary practice. *J Asthma.* 2020:1-6. doi:10.1080/02770903.2020.1759084
13. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2014. Available from: www.ginasthma.org.
14. Håkansson KEJ, Backer V, Suppli Ulrik C. Socioeconomic biases in asthma control and specialist referral of possible severe asthma. *Eur Respir J.* 2021. doi:10.1183/13993003.00741-2021
15. Ryan D, Heatley H, Heaney LG, et al. Potential Severe Asthma Hidden in UK Primary Care. *J Allergy Clin Immunol Pract.* 2020. doi:10.1016/j.jaip.2020.11.053
16. Blakey J, Chung LP, McDonald VM, et al. Oral corticosteroids stewardship for asthma in adults and adolescents: A position paper from the Thoracic Society of Australia and New Zealand. *Respirology.* 2021;26(12):1112-1130. doi:10.1111/resp.14147

17. Price DB, Trudo F, Voorham J, et al. Adverse outcomes from initiation of systemic corticosteroids for asthma: long-term observational study. *J Asthma Allergy*. 2018;11:193-204. doi:10.2147/JAA.S176026
18. Sullivan PW, Ghushchyan VH, Globe G, Schatz M. Oral corticosteroid exposure and adverse effects in asthmatic patients. *J Allergy Clin Immunol*. 2018;141(1):110-116 e117. doi:10.1016/j.jaci.2017.04.009
19. Skov IR, Madsen H, Henriksen DP, Andersen JH, Pottegård A, Davidsen JR. Low dose oral corticosteroids in asthma associates with increased morbidity and mortality. *Eur Respir J*. 2022. doi:10.1183/13993003.03054-2021
20. McBrien CN, Menzies-Gow A. Time to FOCUS on oral corticosteroid stewardship in asthma management. *Respirology*. 2019;24(4):304-305. doi:10.1111/resp.13494
21. Watchorn D, Menzies-Gow A. Oral corticosteroid stewardship for asthma: Time to move from theory to routine clinical practice. *Respirology*. 2021;26(12):1094-1095. doi:10.1111/resp.14171
22. Price D, Castro M, Bourdin A, Fucile S, Altman P. Short-course systemic corticosteroids in asthma: striking the balance between efficacy and safety. *Eur Respir Rev*. 2020;29(155). doi:10.1183/16000617.0151-2019
23. Levy M, Andrews R, Buckingham R, et al. Why asthma still kills national review of asthma deaths (NRAD). *Eur Respir J*. 2014;44.
24. Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol*. 2014;29(8):541-549. doi:10.1007/s10654-014-9930-3
25. Pottegard A, Schmidt SAJ, Wallach-Kildemoes H, Sorensen HT, Hallas J, Schmidt M. Data Resource Profile: The Danish National Prescription Registry. *Int J Epidemiol*. 2017;46(3):798-798f. doi:10.1093/ije/dyw213
26. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449-490. doi:10.2147/CLEP.S91125
27. Andersen JS, Olivarius Nde F, Krasnik A. The Danish National Health Service Register. *Scandinavian journal of public health*. 2011;39(7 Suppl):34-37. doi:10.1177/1403494810394718
28. Schmidt M, Schmidt SAJ, Adelborg K, et al. The Danish health care system and epidemiological research: from health care contacts to database records. *Clin Epidemiol*. 2019;11:563-591. doi:10.2147/CLEP.S179083
29. Pont LG, van der Werf GT, Denig P, Haaijer-Ruskamp FM. Identifying general practice patients diagnosed with asthma and their exacerbation episodes from prescribing data. *Eur J Clin Pharmacol*. 2002;57(11):819-825. doi:10.1007/s00228-001-0395-4
30. Ortqvist AK, Lundholm C, Wettermark B, Ludvigsson JF, Ye W, Almqvist C. Validation of asthma and eczema in population-based Swedish drug and patient registers. *Pharmacoepidemiol Drug Saf*. 2013;22(8):850-860. doi:10.1002/pds.3465
31. The Danish National Database for Asthma. National årsrapport 2018 [Internet]. 2018. Available from: www.sundhed.dk (Danish).
32. Bloom CI, Walker S, Quint JK. Inadequate specialist care referrals for high-risk asthma patients in the UK: an adult population-based cohort 2006-2017. *J Asthma*. 2021;58(1):19-25. doi:10.1080/02770903.2019.1672723
33. Blakey JD, Gayle A, Slater MG, Jones GH, Baldwin M. Observational cohort study to investigate the unmet need and time waiting for referral for specialist opinion in adult asthma in England (UNTWIST asthma). *BMJ Open*. 2019;9(11):e031740. doi:10.1136/bmjopen-2019-031740

34. Hew M, McDonald VM, Bardin PG, et al. Cumulative dispensing of high oral corticosteroid doses for treating asthma in Australia. *Med J Aust.* 2020;213(7):316-320. doi:10.5694/mja2.50758
35. Nan C, Schmidt O, Lindner R, et al. German regional variation of acute and high oral corticosteroid use for asthma. *J Asthma*. 2021:1-10. doi:10.1080/02770903.2021.1878532
36. Price D, Bjermer L, Bergin DA, Martinez R. Asthma referrals: a key component of asthma management that needs to be addressed. *J Asthma Allergy*. 2017;10:209-223. doi:10.2147/JAA.S134300
37. Gibeon D, Heaney LG, Brightling CE, et al. Dedicated severe asthma services improve health-care use and quality of life. *Chest.* 2015;148(4):870-876. doi:10.1378/chest.14-3056
38. Schatz M, Zeiger RS, Mosen D, et al. Improved asthma outcomes from allergy specialist care: a population-based cross-sectional analysis. *J Allergy Clin Immunol.* 2005;116(6):1307-1313. doi:10.1016/j.jaci.2005.09.027
39. Tan R, Liew MF, Lim HF, Leung BP, Wong WSF. Promises and challenges of biologics for severe asthma. *Biochem Pharmacol.* 2020;179:114012. doi:10.1016/j.bcp.2020.114012
40. Semple B, Porsbjerg C, Coleman C. Balancing treatment and side-effects in severe asthma: a patient and professional perspective. *Breathe (Sheff).* 2021;17(2):210045. doi:10.1183/20734735.0045-2021
41. Thygesen LC, Daasnes C, Thaulow I, Bronnum-Hansen H. Introduction to Danish (nationwide) registers on health and social issues: structure, access, legislation, and archiving. *Scandinavian journal of public health.* 2011;39(7 Suppl):12-16. doi:10.1177/1403494811399956
42. Jensen AO, Nielsen GL, Ehrenstein V. Validity of asthma diagnoses in the Danish National Registry of Patients, including an assessment of impact of misclassification on risk estimates in an actual dataset. *Clin Epidemiol.* 2010;2:67-72. doi:10.2147/clep.s6875

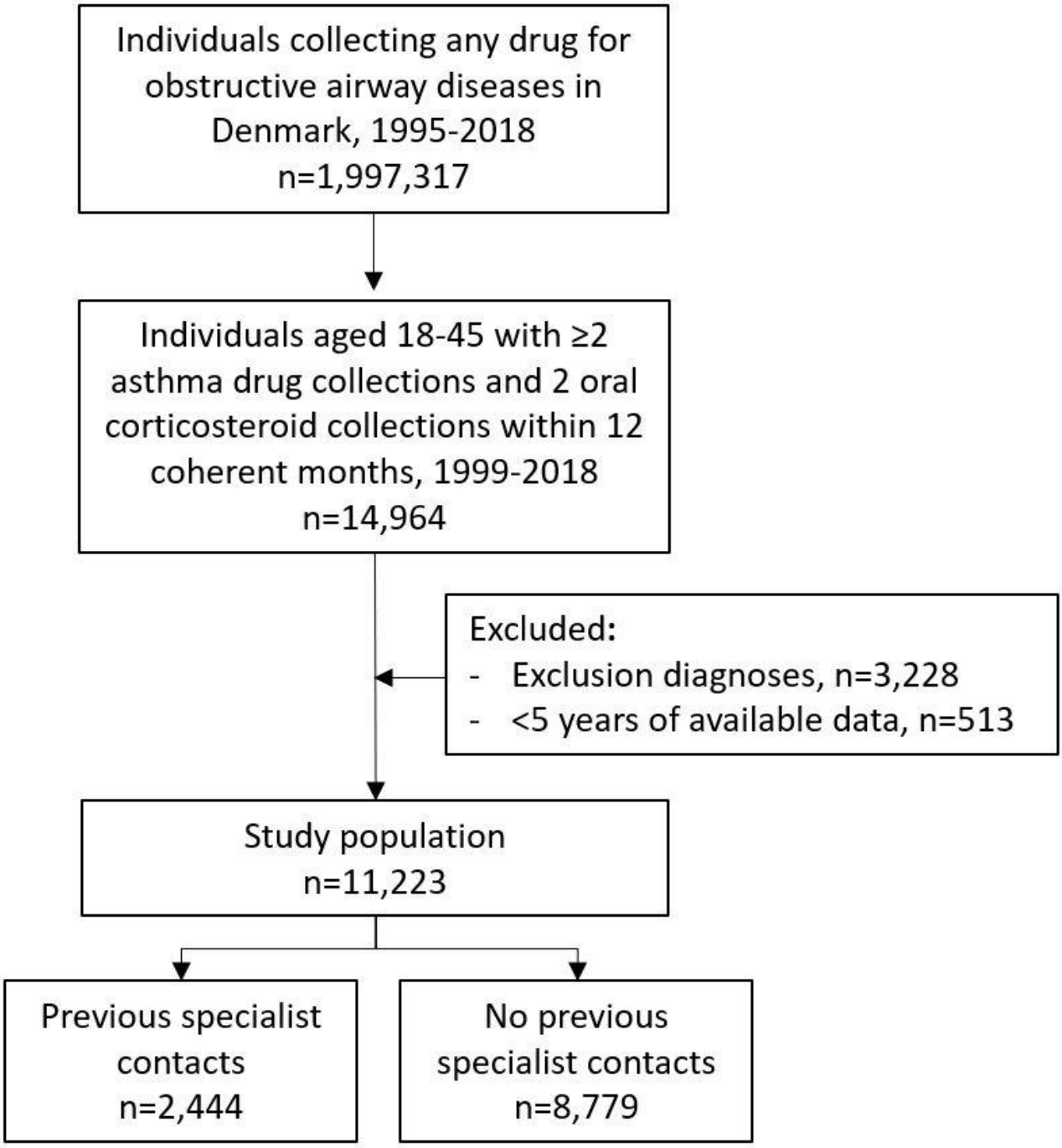

Figure 1: Flowchart of patient selection

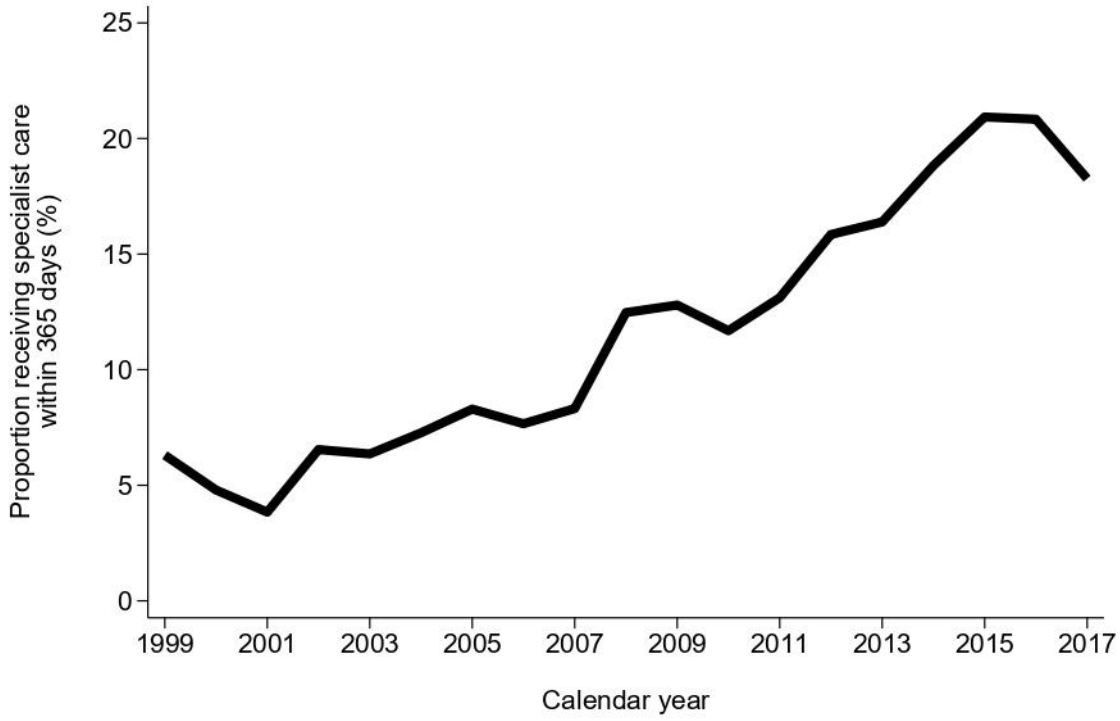

Figure 2: Frequency of incident specialist assessments within one year of follow up

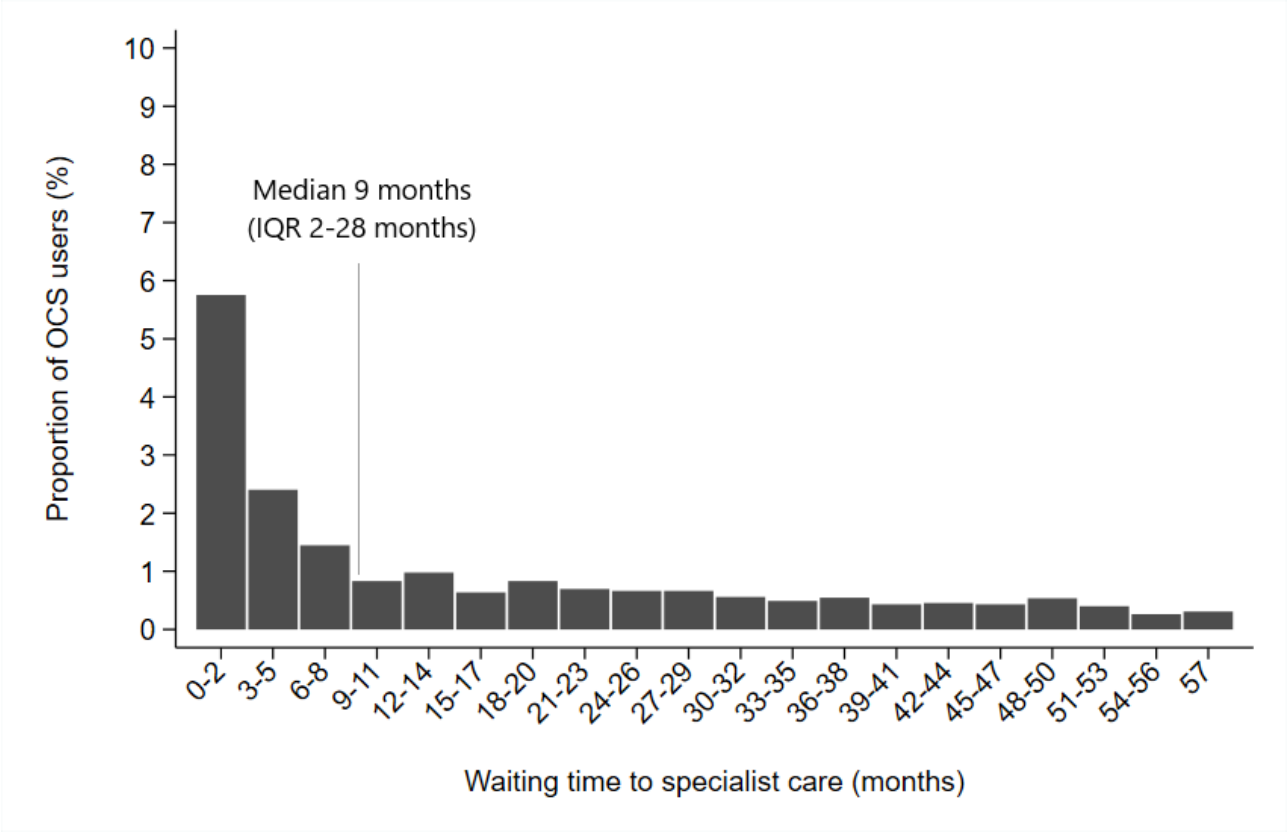

Figure 3: Waiting time distribution for incident specialist assessment within five years of follow-up

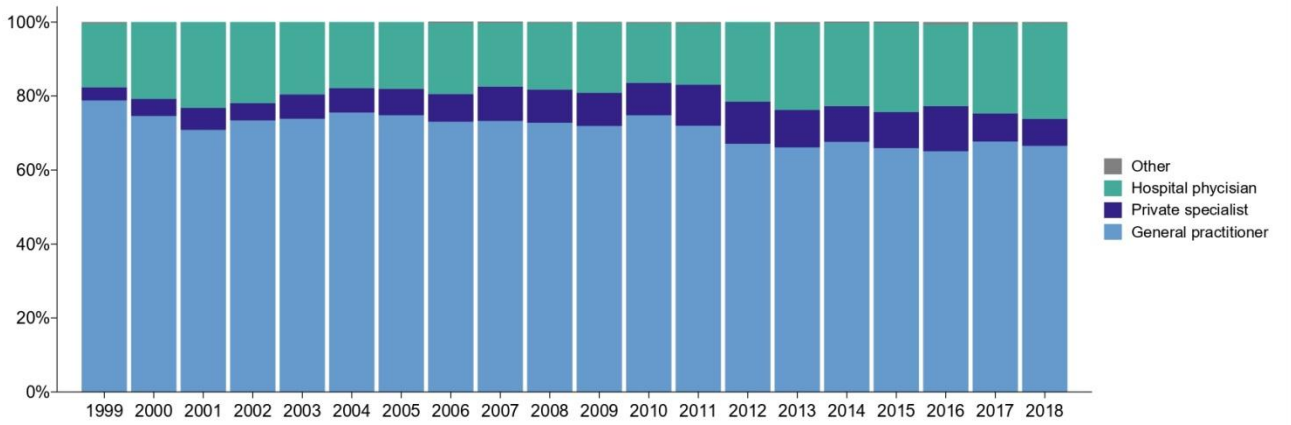

Figure 4: Prescriber source information on oral corticosteroid prescriptions dispensed during the baseline period

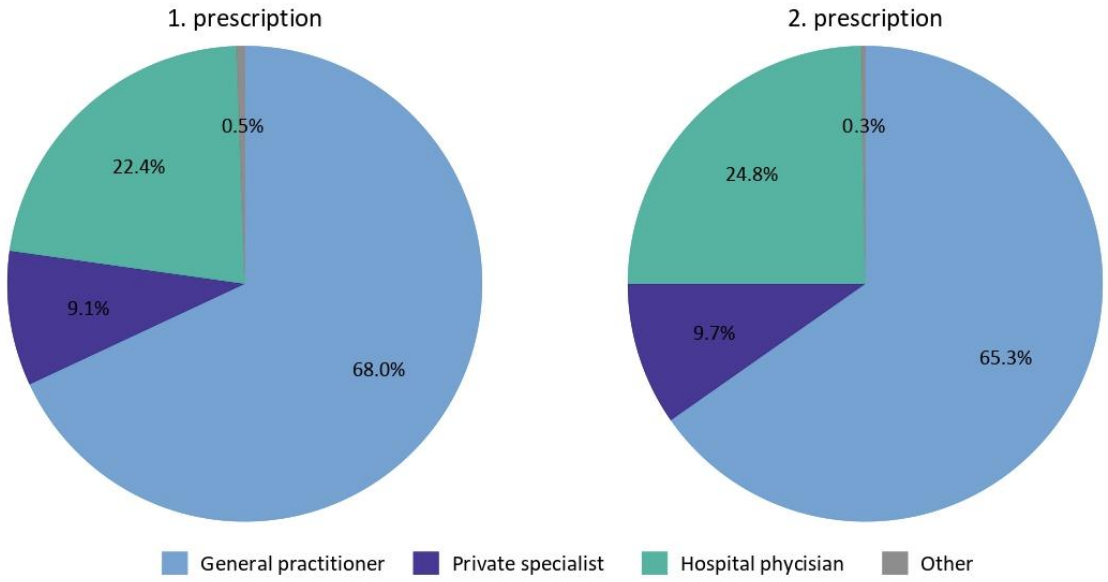

Figure 5: Prescriber source information distributed by first and second oral corticosteroid prescription, restricted to 2014-2018

Supplemental material

Trends and predictors of specialist assessments in oral corticosteroid treated asthma among young adults

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Table S1 Variable definitions

Definition of study variables with specification of Anatomic Therapeutic Chemical Index (ATC) codes obtained from The Danish National Prescription Registry (DNPR), International Classification of Diseases (ICD)-10 codes obtained from The Danish National Patient Register (NPR), and service codes obtained from National Health Insurance Service Registry (NHSR), and the Danish Civil Registration System (CPR)

Variable	**Data source**	**Code format**	**Inclusion codes**	**Exclusion codes**
Study population definition				
Asthma case definition	DNPR	ATC	R03BA, R03AC, R03AK, R03DC, R03DA Prescriptions dispensed on ≥2 occasions within 12 coherent months between the ages 18-45 years (1,2)	
	NPR	ICD-10		J41-44.9 (not including J44.8), E84, D86, E271, J67-J70, K50, K51, M05-M14, M30-M36, M45, M46, C00-C99.
Frequent OCS users	DNPR	ATC	H02AB06, H02AB07 (≥2 prescriptions in baseline year)	
Primary endpoint (specialist care)				
Specialist care, hospital (3) *(only including contacts from departments of respiratory medicine, internal medicine, paediatric, or occupational medicine)*	NPR	ICD10	J45-J46 as primary (A-) diagnosis of ambulatory contact, or as secondary (B-) diagnosis in combination with J00-99 (diseases of the respiratory system), R06 (dyspnoea), T781 (adverse food reaction), K522 (allergic gastroenteritis), L20 (atopic dermatitis) as	

			primary diagnosis.	
Specialist care, private practitioner (4) *(only including physician specialty 08 internal medicine)*	NHSR	Service codes	One or more specific pulmonary service codes, including: lung function test (2204, 2206, 2207), breath test (2214), bronchial provocation test (2322), total lung capacity test (2324), peak expiratory flow (7213, 7230).	
Covariates				
Sex	CPR	N/A		
Age	CPR	N/A		
Marital status (married, unmarried/widow/divorced, other/missing)	CPR	N/A		
Region of residence (Capital, Zealand, Northern, Central, Southern)	CPR	N/A		
Asthma medication				
Inhaled corticosteroids (ICS)	DNPR	ATC	R03BA01-08, R03AK06-13, R03AL08-09	
Long-acting beta-agonists (LABA)	DNPR	ATC	R03AC11-19, R03AL03-09, R03AK06-13	
Leukotriene receptor antagonists (LTRA)	DNPR	ATC	R03DC	
Long-acting muscarinic antagonists (LAMA)	DNPR	ATC	R03BB01-07, R03AL03-07, R03AL08-09	
Short-acting beta-agonist (SABA)	DNPR	ATC	R03AC02-10, R03AL01-02	
Unscheduled asthma visits				
Emergency department visits	NPR	ICD10	J45-J46 as primary (A) diagnoses, or as secondary (B) diagnosis if primary diagnosis is R04-R09.	
Hospitalisation	NPR	ICD10	J45-J46 as primary (A) diagnoses, or as secondary (B) diagnosis if primary diagnosis is R04-R09.	

Co-medication				
Systemic antibiotics	DNPR	ATC	J01	
Systemic antihistamines	DNPR	ATC	R06	
Nasal corticosteroids	DNPR	ATC	R01AD	
Antidepressants	DNPR	ATC	N06A	
Anti-acid drugs	DNPR	ATC	A02	
Anti-obesity drugs	DNPR	ATC	A08A	
Antidiabetic drugs excl. insulins	DNPR	ATC	A10B	
Bisphosphonates	DNPR	ATC	M05BA	

(1) Pont LG, van der Werf GT, Denig P, Haaijer-Ruskamp FM. Identifying general practice patients diagnosed with asthma and their exacerbation episodes from prescribing data. Eur J Clin Pharmacol. 2002;57(11):819-25

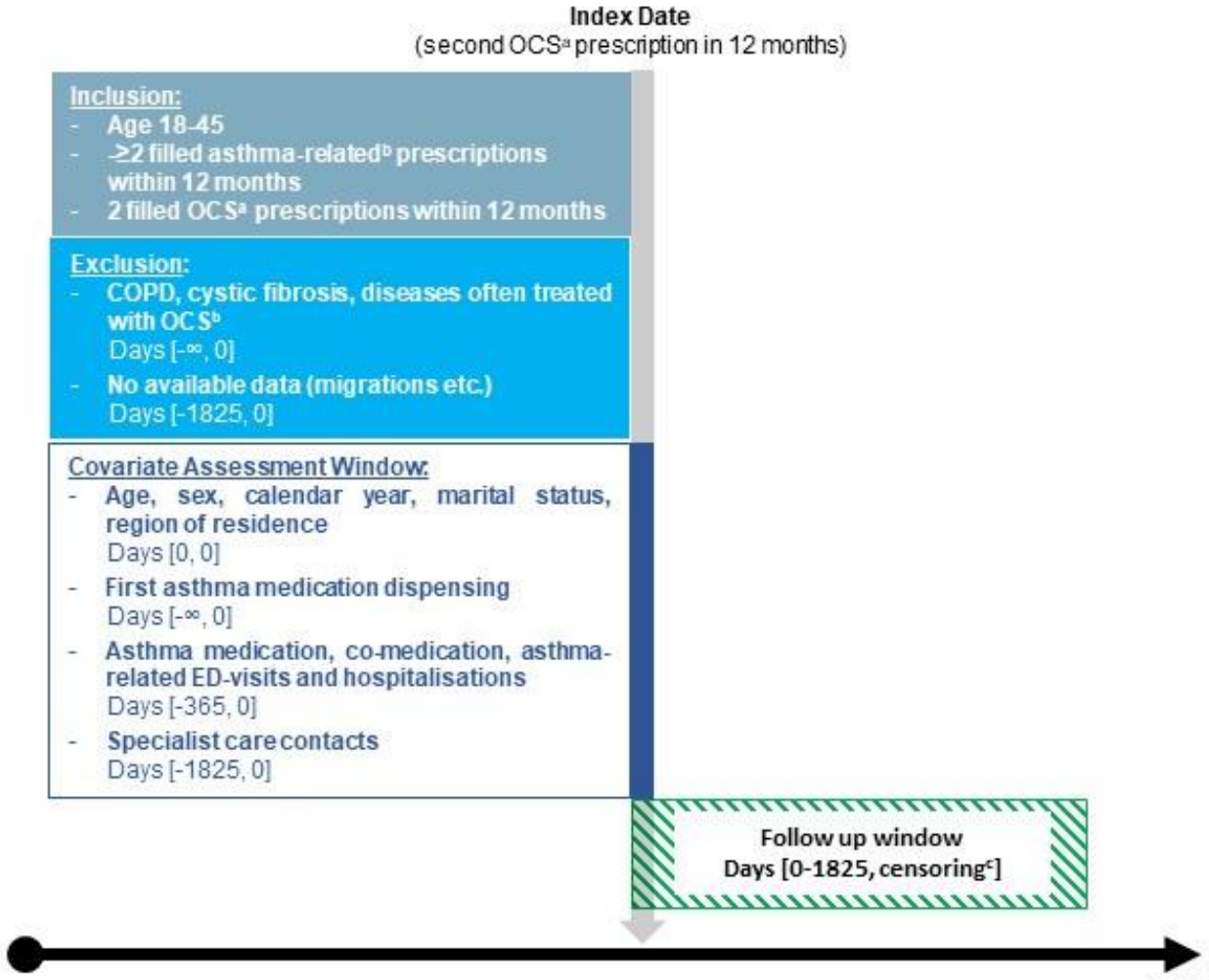
(2) Ortqvist AK, Lundholm C, Wettermark B, Ludvigsson JF, Ye W, Almqvist C. Validation of asthma and eczema in population-based Swedish drug and patient registers. Pharmacoepidemiol Drug Saf. 2013;22(8):850-60

(3) The Danish National Database for Asthma. National årsrapport 2018 [Internet]. 2018. Available from: www.sundhed.dk (Danish). Accessed June 2021.

(4) von Bulow A, Kriegbaum M, Backer V, Porsbjerg C. The prevalence of severe asthma and low asthma control among Danish adults. J Allergy Clin Immunol Pract. 2014;2(6):759-67

(5) Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2018. Available from: www.ginasthma.org Accessed October 30, 2020

Figure S1 Study design



a. Oral corticosteroids, including prednisolone and prednisone
b. Including selective b2-adrenoreceptor agonists, inhaled glucocorticoids, fixed combinations of b2-agonists and inhaled glucocorticoids, leukotriene receptor antagonists and theophylline/methylxanthine.
c. Diagnoses of sarcoidosis, primary adrenocortical insufficiency, pneumonitis, inflammatory bowel disease, inflammatory polyarthropathies, systemic connective tissue disorders, inflammatory spondylopathies and/or malignancy

Figure S2: Frequency of incident specialist assessments among repeated OCS users within one year of follow up restricted to patients with possible severe asthma (medium or high-dose ICS plus ≥1 add-on treatment)