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Changes in oral corticosteroid use in asthma treatment—A 20-year Danish nationwide drug utilisation study

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Abstract

Oral corticosteroids (OCS) are used in asthma management but can cause serious adverse effects. We aimed to investigate the usage trends in a nationwide asthma cohort in Denmark from 1999 to 2018. Using national registers, we identified young adults (18–45 years) with two or more asthma drug collections within 12 months since the age of 15 years as indicative of active asthma. OCS exposure level was stratified as high use (≥5 mg prednisolone/day/year) and low use (<5 mg/day/year). Lorenz curves were computed to illustrate potential skewness of consumption among the OCS users. We identified 318 950 individuals with a median age of 29 years (IQR 20–38 years) whereof 57% were women. The 1-year prevalence of OCS users was stable at 4.8% (median, IQR 4.7%–4.8%), but with nearly 40% decrease in high-users from 0.54% in 1999 to 0.33% in 2018. The median annual exposure decreased from 500 mg/year (1999) to 250 mg/year (2018). We found a substantial skewness in the distribution of OCS usage with 10% of users accounting for almost 50% of all OCS use. The prevalence of OCS users among young adults with active asthma has been relatively stable from 1999 to 2018, but with a decreasing prevalence of high-users and annual consumption.

KEYWORDS
adults, asthma, drug utilisation, glucocorticoids, pharmacoepidemiology

1 | INTRODUCTION

Asthma is the most common respiratory disease among children and young adults and is estimated to affect over 339 million people globally.[1] It is characterised by considerable heterogeneity in both severity degrees and inflammation types.[2,3] Corticosteroids have constituted the cornerstone in asthma treatment since the 1950s due to the potent anti-inflammatory effects.[4] Though oral corticosteroids (OCS) were largely replaced by inhaled corticosteroids (ICS) during the 1970s–1980s, OCS has remained a crucial treatment option in asthma management as short-term treatment for asthma exacerbations or as last choice opportunity in long-term treatment for severe asthma.[5,6] Unfortunately, OCS use is associated with numerus adverse effects involving cardiovascular, musculoskeletal and endocrine systems.[7] While the adverse effects of long-term OCS are well recognised in

asthma treatment guidelines,[5] a growing amount of evidence indicates that also repeated short-term OCS use can lead to serious adverse effects due to the cumulative exposure.[8–10] This risk increases at cumulative doses as low as 1 g of prednisolone corresponding to only four lifetime courses,[9,11] which calls for an overall increased attention on appropriate OCS use in asthma treatment.[12–14] Although the management of severe asthma has advanced with the access to biological therapies, these treatments are costly and reserved for selected patients, that is, patients with severe asthma and a high degree of type 2 inflammation.[15] Consequently, frequent or long-term OCS use remains prevalent in many cases of severe or uncontrolled asthma.[10] However, OCS use in asthma is an indication of poor disease control, and an overall goal in asthma management should be to minimise the need for OCS as much as possible.[16]

Describing trends and changes in OCS use in asthma is therefore an important aspect in overall asthma management monitoring and central in exploring potential favourable, as well as inappropriate, developments of treatment patterns. Observational studies on drug use may furthermore be instrumental in healthcare planning aiming at changing prescribing practices regarding assessment of the potential need for increased focus and informative interventions promoting rational drug use.

We therefore aimed to explore nationwide utilisation trends of OCS among young adults with asthma in Denmark during a 20-year period.

2 | METHODS

2.1 | Study design and data sources

We conducted a nationwide observational register-based study with annually repeated cross-sectional drug analyses on data from Danish administrative and healthcare registries. We used *the Danish National Prescriptions Registry*,[17] containing data on all pharmacy-collected drug prescriptions since 1995; *the Danish National Patient Register*,[18] providing information on all hospital contacts in Denmark since 1977 including International Classification of Diseases (ICD)-10 codes; and *the Danish Civil Registration System*,[19] providing basic personal information on all Danish citizens. Data from the national registers were linked on a personal level via the unique Civil Personal Registration (CPR) number, assigned to all inhabitants in Denmark at birth or residing longer than 3 months.[19] All CPR numbers were replaced by pseudonymized serial numbers to preserve confidentiality.

2.2 | Study population

In accordance with validated methods,[20,21] we identified all adults aged 18 to 45 years, who had filled at least two asthma drug prescriptions on different occasions within 12 successive months since the age of 15 years during the period of 1995–2018, as indicative of actively treated asthma, henceforth referred to as 'active asthma'. We defined the study period as 1999–2018 to ensure a sufficient run-in period (1995–1998), allowing for better classification of asthma patients. The asthma-related drugs of interest included inhalations of selective β2-agonists (Anatomical Therapeutic Chemical, [ATC] code R03AC), ICS (R03BA), fixed combinations of β2-agonists and ICS (R03AK), leukotriene receptor antagonists (R03DC) and xanthines (R03DA).

The inclusion date was defined as the date of the first of the two redeemed prescriptions with the 18th birthday as the earliest date.

We excluded individuals with any hospital-given diagnoses of chronic obstructive pulmonary diseases (ICD-10 codes J41-44.9, not including J44.8) or cystic fibrosis (ICS-10 code E85), a previous use of roflumilast (ATC code R03DX07), or recent migrations within 2 years prior to inclusion time. Furthermore, we excluded individuals with hospital-given diagnoses of other diseases commonly treated OCS, that is, sarcoidosis (ICD-10 code D86), primary adrenocortical insufficiency (ICD-10 code E271), pneumonitis (ICD-10 code J67-70), inflammatory bowel disease (ICD-10 code K50-51), inflammatory polyarthropathies (ICD-10 code M05-14), systemic connective tissue disorders (ICD-10 code M30-36), inflammatory spondylopathies (ICD-10 code M45-46) and/or malignancy (ICD-10 code C00-99). Individuals with apparent inactive asthma, defined by no redeemed asthma medication for two consecutive years, were censored from the analyses but were permitted to re-enter the cohort upon resumed use.

Individuals were followed until the age of 46 years, death, migration, other disease commonly treated with OCS, or end of study period (31 December 2018).

Study design and study population selection are shown in Figure 1.

2.3 | OCS usage

All OCS prescriptions (ATC code H02AB) were converted into prednisolone-equivalent doses (equivalences available in Table S1) and evaluated by tablet strength. We calculated the number of OCS prescriptions and cumulative exposure per OCS user. All individuals in the study population were classified annually by their respective cumulative OCS consumption within the given calendar

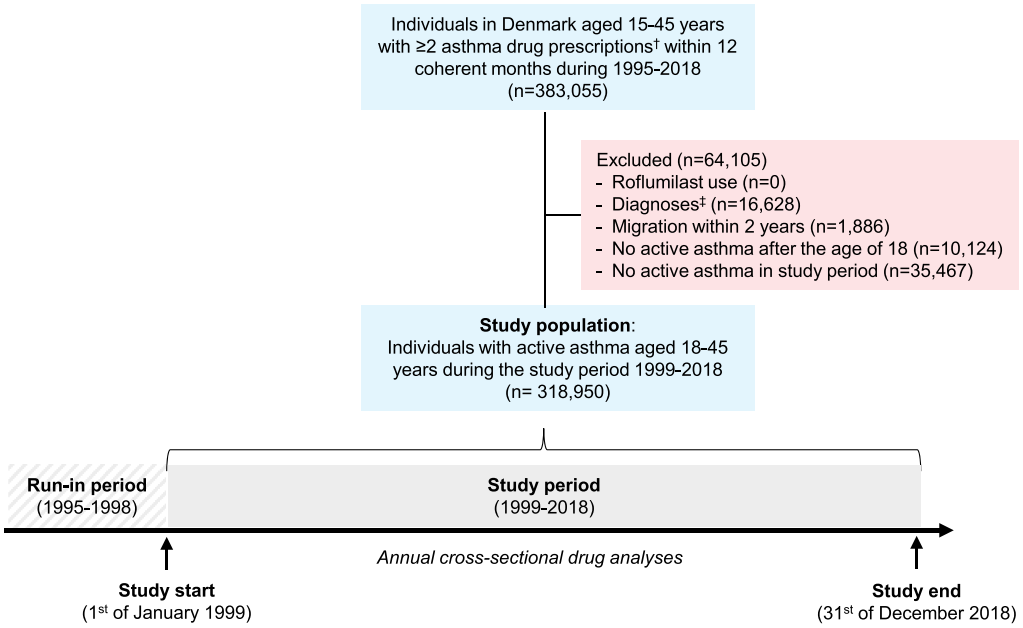

FIGURE 1 Study design and flow chart of the asthma population selection

year, categorised in three exposure groups in accordance with previous literature[22,23]:

(i) a *no-use* group,
(ii) a *low-use* group, defined by use of <1825 mg in the given year, corresponding to <5 mg OCS/day/year (not including non-use) and
(iii) a *high-use* group, corresponding to ≥5 mg OCS/day/year.

2.4 | Baseline characteristics

The baseline period was defined as the 12 months prior to the inclusion date. The Charlson Comorbidity Index[24] was used as a marker for the overall comorbidity burden based on ICD-10 codes diagnoses recorded from inpatient or outpatient hospital contacts[25] with exclusion of asthma diagnoses (ICD-10 codes J45-J46). Specific asthma-related comorbidities were chosen from the existing literature[5,26–28] and estimated by presence of hospital-given diagnoses or use of relevant medication dispensed from public pharmacies in Denmark. Additional details on baseline comorbidities including specification of applied ICD-10 codes and ATC codes are available in Table S2.

2.5 | Statistical analyses

Continuous variables were presented as number, median and interquartile range (IQR) or mean and standard deviation (SD) and categorical variables as frequencies and percentages. The annual period prevalence proportion of OCS users was defined as the number of individuals filling at least one OCS prescription per calendar year per 100 individuals in the study population and stratified according to OCS exposure group (high-use and low-use) and by sex and age categories (18–25 years, 26–35 years and 36–45 years). Each year, the average daily dose and number of prescriptions per OCS user was calculated, stratified according to OCS exposure groups. All OCS prescriptions dispensed in the given year were assessed according to tablet strength and categorised into two dosage groups (≤10 mg per tablet and >10 mg per tablet). Lorenz curves[29] for the years 1999, 2009 and 2018 were computed to assess trends in the skewness of OCS consumptions among the prevalent OCS users, ranking all users in order by the amount of consumed OCS. The Gini coefficient, where 0 indicates total equality in consumption among users and 1 indicates total inequality, was calculated as a single measure of skewness in consumption of OCS among the users.

We conducted two sensitivity analyses to test our definition of inactive asthma (i.e., censoring after ≥2 years with no filled asthma drug prescriptions). The first analysis was restricted to only include years with concurrent use of other asthma medication. In the second analysis, individuals were allowed up to five successive years of no filled asthma drug prescriptions before being censored.

Two post hoc analyses were conducted exploring the utilisation trends of biological treatment and ICS use in the asthma population. Biological treatment was defined

by hospital procedure codes, as this treatment is exclusively administered in hospital care in Denmark, and included BOHJ19A1 (omalizumab), BOHJ19I2 (mepolizumab), BOHJ19I3 (benralizumab) and BOHJ19I1 (reslizumab). ICS use was stratified by average daily dose and defined as low dose (≤400 mcg/day) and medium/high dose (>400 mcg/day) in budesonide equivalents.[5]

Stata Version 16 (StataCorp, College Station, TX, USA) was used in the analyses.

3 | RESULTS

3.1 | Study population

We included 318 950 unique individuals with asthma during the study period of 1999–2018, contributing with a total of 1 731 632 years of observation time. Demographic characteristics at time of inclusion including frequency of asthma-related comorbidities are summarised in Table 1. Further details on distributions

TABLE 1 Baseline demographic characteristics of Danish adults aged 18–45 years with asthma during 1999–2018

	Asthma population (n = 318 950)
Total time of observation (person-years)	1 731 632
Follow-up per person (years), median (IQR)	3 (2–7)
Sex, *n* (%)	
Women	181 348 (57%)
Men	137 602 (43%)
Age (years), median (IQR)	29 (20–38)
Age, *n* (%)	
18–25 years	128 623 (40%)
26–35 years	88 526 (28%)
36–45 years	101 801 (32%)
Comorbidities (indicated by hospital-given diagnoses and comedication), *n* (%)	
Atopic dermatitis	6045 (1.9%)
Allergies or use of antihistamines	175 383 (55%)
Chronic rhinosinusitis or use of nasal steroids	115 522 (36%)
Food allergy	802 (0.3%)
Obesity or use of anti-obesity drugs	40 192 (13%)
Sleep apnoea	1437 (0.5%)
Anxiety/depression or use of antidepressants	43 862 (14%)
Serious mental disorders or use of antipsychotics	18 233 (5.7%)
Dyspeptic disorders or use of anti-acid drugs	66 389 (21%)
Charlson Comorbidity Index	
0	312 200 (98%)
1	3613 (1.1%)
≥2	3137 (1.0%)
Year of inclusion, *n* (%)	
<1999	97 065 (30%)
1999–2002	51 165 (16%)
2003–2006	46 044 (14%)
2007–2010	46 393 (15%)
2011–2014	41 134 (13%)
2015–2018	37 149 (12%)

of comorbidities and comedication are available in Table S2. The annual cohort from 1999 to 2018 consisted of 68 799 individuals with active asthma (median, IQR 67 414–70 277), corresponding to an annual asthma prevalence of 3.4% among 18- to 45-year-olds in Denmark. During follow-up, 2061 individuals died, distributed as 497 OCS users (corresponding to 1.05% of all OCS-users) and 1564 never-users (corresponding to 0.58% of all never-users).

3.2 | OCS use

A total number of 47 389 individuals (14.9% of the total asthma cohort) became OCS users at one point during the study period, whereof 4475 (1.4% of the total asthma cohort) at one point fulfilled the criteria of having a high OCS use corresponding to ≥5 mg OCS/day/year. Women were more frequent among OCS users (*n* 28 735, 60%). The annual prevalence of OCS users in the asthma cohort was 4.8% (median, IQR 4.7%–4.8%) with a slight increase from 4.3% in 1999 to 4.7% in 2018. The annual prevalence of high-users in the asthma cohort decreased from 0.54% in 1999 to 0.33% in 2018 (Figure 2A). OCS use was more prevalent among women and in older age groups as depicted in Figure 2B,C. The majority (56%) of OCS users were one-time users, while 27% filled two to three OCS prescriptions and 16% filled four or more prescriptions during follow-up. The most frequent accumulated dose of OCS during follow-up was 201–300 mg (32% of all OCS users), while 21% of the users were exposed to >1000 mg during the observation period (Tables S3 and S4). Both the median and mean annual OCS dose among users decreased in the period of 1999–2018 from 500 mg/year (IQR 250–750 mg/year) to 250 mg/year (IQR 250–500 mg/year) and from 878 mg/year (SD 1479 mg/year) to 614 mg/year (SD 961 mg/year), respectively (Figure 3). The differences in median and mean OCS use emphasise a notable skewness in the distribution among the users. Table 2 illustrates changes in median daily dose, number of prescriptions per year and tablet dose strength in year 1999, 2009 and 2018. The proportion of prescriptions with tablet doses ≤10 mg/tablet decreases from 76.7% to 18.1% for low-users and from 81.9% to 42.2% for high-users in 1999 and 2018, respectively (Table 2).

3.3 | Lorenz curves

Distribution of the overall consumption among OCS users in 2018 is illustrated in a Lorenz curve in Figure 4. Lorenz curves for the year 1999 and 2009 are available in Figure S1. Overall, we found the top 10% most heavy OCS users accounted for almost 50% of the total OCS consumption, though with a decreasing tendency from 49% in 1999 to 46% in 2018. Correspondingly, we found a decreasing Gini coefficient from 0.60 in 1999 to 0.49 in 2018, confirming a reduced inequality of OCS intake among users.

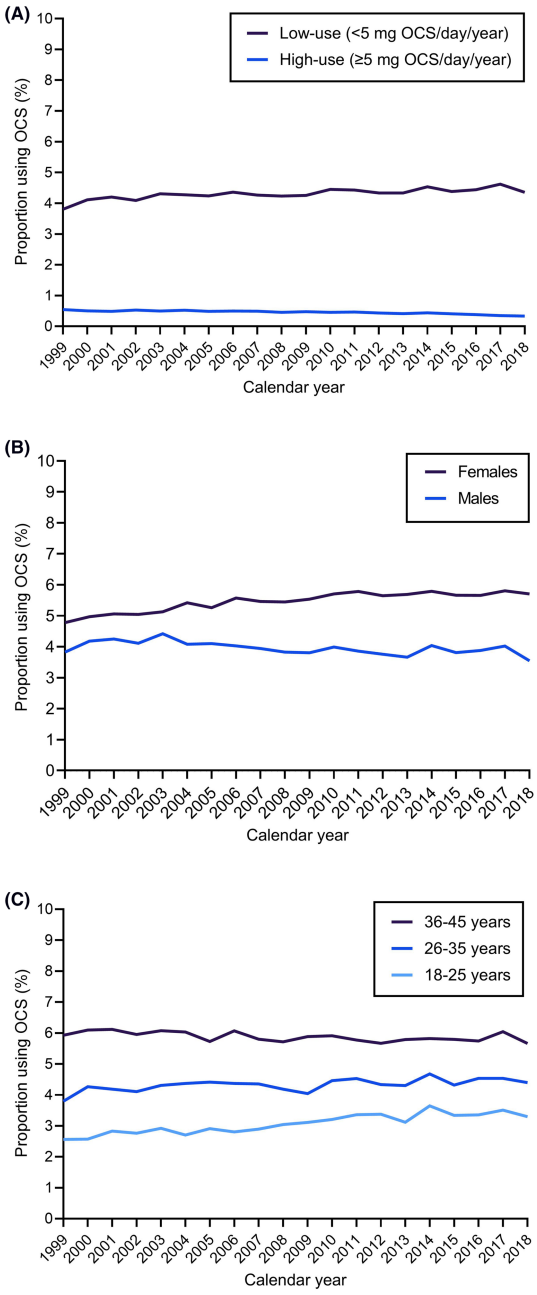

FIGURE 2 Trends in the prevalence of oral corticosteroid (OCS) use among young adults with asthma in Denmark from 1999 to 2018, given as annual prevalence stratified by (A) OCS exposure categories (low-use <5 mg/day/year and high-use ≥5 mg/day/year), (B) by sex and (C) by age categories

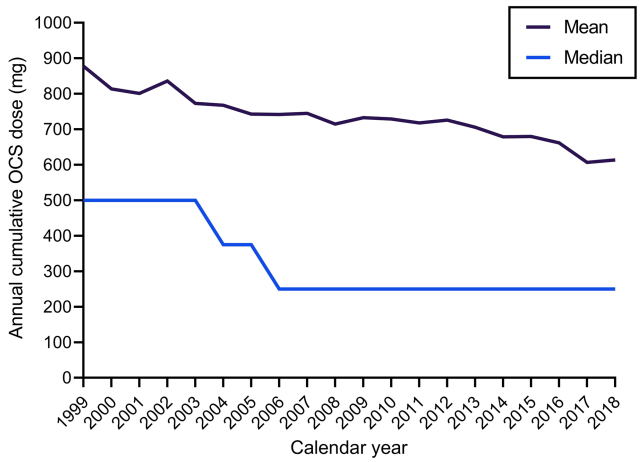

FIGURE 3 Trends in mean and median annual cumulative dose of oral corticosteroids (OCS) in the asthma population

3.4 | Sensitivity analyses

Both of the sensitivity analyses showed the same tendencies as the main analyses: a stable proportion of OCS users throughout the study period, though with an overall slight increase from 1999 to 2018, as well as decreasing proportions of high-users (i.e., use of ≥5 mg/day/year).

When restricting OCS utilisation analyses to include only years with concurrent fills for other asthma medication, the annual prevalence of OCS users was 5.8% (median, IQR 5.7%–5.9%), with 0.79% of the total cohort classified as high-users in 1999 and 0.56% in 2018.

When allowing up to five successive years of no asthma medication prescription fills before being censored, the annual prevalence of OCS users was 3.8% (median, IQR 3.7%–3.9%) with 0.36% and 0.26% of the total cohort classified as high-users in 1999 and 2018, respectively.

3.5 | Post hoc analyses

Results from the post hoc analyses are displayed in Appendix S1. The use of biological treatment increased from 2005 to 2016 (Figure S2). While monotherapy with ICS decreased, the frequency of ICS/LABA combinations increased in all OCS exposure groups (Figure S3). The frequency of individuals not using ICS was markedly higher among individuals not using OCS compared with both low and high use of OCS.

TABLE 2 Daily dosage, number of prescriptions and tablet strength of oral corticosteroid

	1999		2009		2018	
	Low use (<5 mg/day/year)	High use (≥5 mg/day/year)	Low use (<5 mg/day)	High use (≥5 mg/day/year)	Low use (<5 mg/day/year)	High use (≥5 mg/day/year)
	n = 2575	*n* = 368	*n* = 3007	*n* = 334	*n* = 2946	*n* = 223
Daily dose and number of prescriptions per OCS user						
Daily dose (mg/day), median (IQR)	1.37 (0.68–1.37)	8.22 (6.85–11.13)	0.68 (0.68–1.37)	7.53 (6.85–10.96)	0.68 (0.68–1.37)	7.53 (6.85–9.59)
Prescriptions per year, median (IQR)	1 (1–2)	5 (2–5)	1 (1–1)	3 (1–5)	1 (1–1)	2 (1–5)
Tablet dose and distribution of dispensed OCS prescriptions						
Tablet dose (mg), mean	9.6 mg	9.0 mg	18.8 mg	16.8 mg	21.4 mg	18.6 mg
Dispensed prescriptions with ≤10 mg per tablet, *n* (%)	2800 (76.7%)	1602 (81.9%)	1269 (30.9%)	653 (49.0%)	680 (18.1%)	309 (42.4%)
Dispensed prescriptions with >10 mg per tablet, *n* (%)	851 (23.3%)	354 (18.1%)	2832 (69.1%)	680 (51.0%)	3076 (81.9%)	419 (57.6%)

Note: Average daily dosage and number of prescriptions of oral corticosteroid (OCS) per OCS user in the asthma population in the years 1999, 2009 and 2018, as well as average tablet strength and dose distribution of the dispensed OCS prescriptions in the given year, stratified by OCS exposure groups.

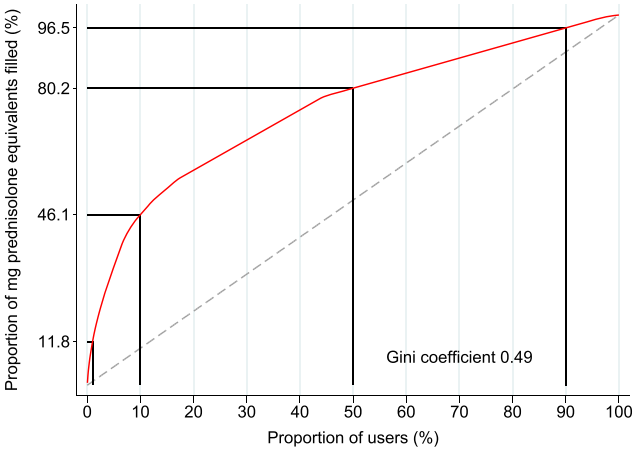

FIGURE 4 Lorenz curve of oral corticosteroid use among asthma patients illustrating the total amount of dispensed oral corticosteroid in the asthma population in 2018 measured in mg (*y* axis), distributed among the users arranged in order of consumption (*x* axis)

4 | DISCUSSION

In this 20-year nationwide utilisation study, we found an annual prevalence of OCS use at 4.8% among young adults with active asthma with a slight increase in the period of 1999–2018. Interestingly, we found an almost 40% decrease in the prevalence of high-users (i.e., use of ≥5 mg/day/year), as well as a halving in the annual median cumulative OCS dose among users. Furthermore, we found a pronounced change in the prescribed OCS tablet strength with a markedly decreasing proportion of prescriptions with ≤10 mg/tablet in both low- and high-use OCS groups, suggesting a shift towards lower proportions of OCS being prescribed as low-dose maintenance treatment. We found that OCS use was associated with older age and female sex in line with previous studies.[10,22,30]

The prevalence of OCS use in our asthma population was somewhat lower than other European studies based on patients in secondary health care[22] or on medical record databases.[30] A recent Swedish register study restricted to asthma patients diagnosed in secondary health care found 1.5% of patients to have a high OCS use (≥5 mg/day/year) and 22.9% to have a low OCS use (<5 mg/day/year) within the baseline year.[22] These higher prevalences might reflect a population of patients with more severe asthma compared with our broader cohort of asthma patients, who were not restricted to secondary health care, as well as a higher median age. A newer European multi-country study conducted on asthma populations from medical record databases in France, Germany, Italy, and the United Kingdom found 14–44% of asthma patients to be OCS users.[30] The annual prevalence of high OCS use (defined as ≥5 mg/day in a 90-day window) in this study was stable at approximately 3% in the period of 2011–2018. These overall stable trends in OCS use are supported by a recent systematic review performed on studies published during the period of 2000–2017, which concluded that OCS continues to be commonly used, and overused, in asthma treatment.[10] Authors of this review confirmed a dose–response relationship, where the risk of steroid-induced adverse effects increased with increased cumulative OCS doses. Hence, interestingly, repeated rescue high-dose courses of OCS may induce a higher risk of adverse effects than low-dose maintenance treatment.[9,10] The dose–response relationship between cumulative OCS exposure and increased risk of adverse effects has been shown to begin at exposures as low as 1 g of OCS, corresponding to four exacerbation courses of OCS.[9,11] Of note, more than one in five individuals using OCS in our study were exposed to >1 g of OCS during follow-up.

Other studies have found trends of increased OCS use during the last decades. This includes a French study on national claim data among 18- to 40-year-old asthma medication users[31] and a study on electronic healthcare records from the United Kingdom.[32] The latter study demonstrated that the proportion of asthma patients in the United Kingdom receiving at least three courses of OCS per year doubled from 1% to 2% in the period of 2006–2017. Less than 20% of these patients were referred for specialist care in contrary to national recommendations. This indicates an unmet need for specialist care assessment among frequent OCS users, though similar numbers have not been explored in a Danish asthma population. The differences in the trends of OCS user prevalence between studies might reflect differences in treatment practice patterns across the countries and asthma populations, but also the different OCS quantification methods, data availability and access to asthma specialists, as well as differences in reimbursement to medical expenses as OCS is less expensive than inhaled asthma drugs and thereby easier accessible.

Despite an overall minor increase in the annual prevalence of OCS users, we observed an interesting shift in dosage trends towards lower annual OCS doses, which offers some encouragement. The frequency of high-users decreased by almost 40% from 0.54% in 1999 to 0.33% in 2018, and the average intake of OCS per year decreased throughout the observation period with a halving of the median dose from 500 mg to 250 mg from 1999 to 2018. This shift in OCS usage trends was supported by the Lorenz curves and Gini coefficients, which show the trends have changed towards a more equal distribution of OCS consumption among the users with fewer 'heavy

users'. Still, a substantial skewness in OCS consumption among OCS users persisted throughout the observation period, where 10% of the heaviest users accounted for almost 50% of all consumed OCS, though with overall decreasing tendencies from 1999 to 2018.

This change towards lower cumulative OCS doses might reflect several improvements in asthma treatment during the last two decades, including the introduction of fixed dose combination inhalers with ICS and β2-agonist in Denmark in 2000 and 2001, an overall increase in use of ICS among adults with asthma in Denmark[33] and the availability of biological treatment for severe asthma, which have demonstrated OCS-sparring abilities.[15] A post hoc analysis of our study shows that the use of biological treatment in the asthma cohort has increased in the period of 2005–2016 (available in Figure S2). Omalizumab, an anti-IgE treatment, was the first biological treatment for asthma to be approved in Europe in 2005 and has since been approved for chronic urticaria in 2014, which explains the increased use at this time. The decrease 3 years later might be explained by burn out of some chronic urticaria and a stabilising of urticaria in need of omalizumab (Figure S2). Use of anti-interleukin (IL) therapies, approved in the period of 2015–2018, was more uncommon, as expected. A post hoc analysis on ICS treatment showed a decrease in both low-dose and medium/high-dose ICS but a significant increase in fixed dose ICS/LABA combinations in all OCS groups (Figure S3), which explains the decrease in monotherapy ICS. The proportion of individuals not using any ICS was largest in the group with no OCS use, but a smaller, albeit slightly decreasing, proportion of individuals not using ICS also persisted among the high OCS users. This may be due to poor adherence to maintenance ICS treatment, which is unfortunately common in asthma treatment.[5,34] Individual-level estimates of adherence were, however, beyond the capability of this study, as it would acquire date on individual asthma treatment plans. Still, these results indicate a persistent group of undertreated patients, which emphasises the importance of frequent asthma control visits including evaluation of adherence to maintenance treatment.

Besides describing the OCS usage in asthma treatment, this study also investigated baseline characteristics for a general population of Danish young adults with asthma. Women were more frequent, which is common among adults with asthma.[5] Concurrent treatment of asthma-related comorbidities such as allergy and chronic rhinosinusitis was common. This was emphasised by the finding that 54% used prescription antihistamines and 36% used nasal corticosteroids, as proxies for treatment-requiring allergies and chronic rhinosinusitis, respectively (Table S2). Because diagnostic information from general practice was not available, we used a combined estimate based on hospital-given ICD-10 diagnoses and pharmacy-dispensed medication as indicative of these common conditions. Many antihistamines are available as over-the-counter medication in Denmark, thus not included in our analyses and thereby likely underestimating an actual use. Less common comorbidities were dyspeptic disorders, anxiety or depression, obesity, sleep apnoea and food allergies, though these prevalences might have been underestimated due to the lack of diagnostic information from general practice. The GINA strategy recommends active management of these comorbidities as they may be associated to or contribute to the symptom burden in patients with asthma.[5] Furthermore, Danish studies have found associations between having asthma and schizophrenia,[28] and severe mental disorders such as schizophrenia and bipolar disorder increase the risk of hospitalisation for asthma.[27]

A major strength of this study is the use of routinely collected prescription and healthcare information in nationwide registers with high completeness and data validity.[35] Denmark has a longstanding tradition for public registers and a universally tax-funded healthcare system, which ensures coverage of the entire Danish population regardless of differences in socioeconomic class or insurance status.[35] While public health care services are free of charge, prescriptions redeemed at community pharmacies require patient co-payment with a percentage of the cost reimbursed according to the total expenditures. Due to OCS and other asthma drugs being prescription-only medication, no potential over-the-counter drug purchases were neglected.

However, several limitations must be acknowledged. In lack of access to diagnostic data from primary health care and due to the low positive predictive value of hospital-given asthma diagnoses in Denmark,[36] we used medical prescription data as a proxy for active asthma. Identifying asthma patients from prescription data has been validated as a reliable method by several European studies.[20,21] This is, however, at the expense of a conservative upper age cut-off of 45 years in order to minimise the inclusion of COPD patients, which limits the generalisability to older asthma populations. The mildest cases of asthma, requiring less than two asthma drugs per year at any time, were not identified. The restrictions of the study design might make our estimates more conservative, reflected in our finding of a prevalence of active asthma at 3.4%. Data on the underlying indications for the prescribed OCS as well as treatment duration were not available, thereby making an exact distinction between rescue courses and maintenance treatment beyond the capability of this study. To increase the probability of the OCS use being due to asthma, we excluded individuals

with hospital-given diagnoses of diseases commonly treated with OCS. Furthermore, we only included OCS prescriptions filled during periods of active asthma as defined in the study design, which may underestimate the total cumulative exposure per individual. Use of prescription data may on the other hand overestimate the actual drug use as a dispensed prescription is not synonymous to the medication being consumed. However, the use of dispensed prescriptions reduces the risk of misclassification due to primary non-adherence. Due to the study design with annual cross-sectional drug analyses, the prevalence of OCS users exposed to ≥1825 mg OCS (i.e., ≥5 mg/day in average) in any 12-month period will inherently be underestimated. We did not have information on individual clinical data, for example, smoking history, BMI, pulmonary function tests and asthma control assessments. Information on medication given during hospitalisations and socioeconomical status was not available. However, medication during hospitalisations has only a minor impact in the total medication exposure, as hospitalisations due to asthma are rare and only affect 1.7–2.4% of the population.[37] Associations to OCS-related complications was beyond the scope of this study, but a significant focus in future studies.

In conclusion, during 1999–2018, the annual prevalence of OCS use among adults aged 18–45 years with asthma in Denmark was almost 5%, and more frequent among women. Though the proportion of OCS users has increased slightly during this period, we observed an interesting shift towards lower annual cumulative OCS exposure per individual. We found that high OCS use was rare and decreasing over time. Awareness of such trends is crucial when evaluating the development in asthma management and informative for focused healthcare interventions to continuously improve prescribing practices towards OCS sparing strategies.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

The regulations of data sharing defined by standard terms for research projects and Danish Act on Processing of Personal Data will be followed (https://www.datatilsynet.dk/english/).

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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