Changes in oral corticosteroid use in asthma treatment – a 20-year nationwide drug utilization study

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Abstract

Background: Oral corticosteroid use in asthma management can lead to serious adverse effects, but knowledge on usage trends are limited. We aimed to investigate this in a nationwide asthma cohort in Denmark from 1999-2018. Methods: By use of Danish nationwide registers, we identified all young adults (18-45 years) with two or more asthma drug collections within 12 months since the age of 15 as indicative of active asthma. Oral corticosteroid use was stratified by exposure level as high use ([?]5 mg prednisolone/day) and low use (<5 mg/day) per year, age groups and gender. Lorenz curves were used to express the skewness of consumption among users. Results: We identified 318,950 unique individuals with active asthma during the study period with a median age of 29 years (interquartile range [IQR] 20-38 years) whereof 57% were women. The 1-year prevalence of oral corticosteroid users was stable at 4.8% (median, IQR 4.7%-4.8%), but with a nearly 40% decrease in high-users from 0.54% in 1999 to 0.33% in 2018. The median annual dose decreased from 500 mg/y in 1999 to 250 mg/y in 2018. We found a substantial skewness in the distribution of oral corticosteroid usage with 10% of users accounting for almost 50% of all oral corticosteroid use. Conclusions: Although the prevalence of oral corticosteroid users among young adults with active asthma in Denmark has been relatively stable from 1999-2018, we observed a decreasing trend in the prevalence of high-users and annual consumption.

TITLE PAGE

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Results : We identified 318,950 unique individuals with active asthma during the study period with a median age of 29 years (interquartile range [IQR] 20-38 years) whereof 57% were women. The 1-year prevalence of oral corticosteroid users was stable at 4.8% (median, IQR 4.7%-4.8%), but with a nearly 40% decrease in high-users from 0.54% in 1999 to 0.33% in 2018. The median annual dose decreased from 500 mg/y in 1999 to 250 mg/y in 2018. We found a substantial skewness in the distribution of oral corticosteroid usage with 10% of users accounting for almost 50% of all oral corticosteroid use.

Conclusions : Although the prevalence of oral corticosteroid users among young adults with active asthma in Denmark has been relatively stable from 1999-2018, we observed a decreasing trend in the prevalence of high-users and annual consumption.

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Introduction

Asthma is the most common respiratory disease among children and adults, estimated to affect over 339 million people globally (1). It is characterized 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 and wide-ranging anti-inflammatory effects (4). Though oral corticosteroids (OCS) were largely replaced by inhaled corticosteroids (ICS) during the 1970-80s, OCS still remain crucial in asthma management guidelines today 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 recognized in asthma treatment guidelines (5), a growing amount of evidence indicate 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 4 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 biologic therapies, these treatments are costly and reserved to selected patients, i.e. patients with severe asthma and a high degree of type 2 inflammation (15). Consequently, frequent or long-term OCS use remain prevalent in many cases of severe or uncontrolled asthma (10).

The monitoring of OCS usage trends is crucial in order to better address and prevent OCS-related adverse effects, as well as to evaluate potential treatment changes at the arrival of biologic treatments. We therefore aimed to explore nationwide and longitudinal utilization trends of OCS among young adults with asthma in Denmark during a 20-year period, which has not previously been done.

Methods

Study design and data sources

We conducted a nationwide observational study with annually repeated cross-sectional drug analyses on data from Danish Health Data. We used *the Danish National Prescriptions Registry* (16), containing data on all pharmacy collected drug prescriptions since 1995; *the Danish National Patient Register* (17), providing information on all hospital contacts in Denmark since 1977 including International Classification of Diseases (ICD)-10 codes; and *the Danish Civil Registration System* (18), 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 three months (18). All CPR-numbers were replaced with pseudomized serial numbers to preserve confidentiality.

Study population

We identified all adults aged 18 to 45, who had filled at least two asthma drug prescriptions on different occasions within 12 successive months since the age of 15 during the period 1995-2018 (19, 20). We defined the study period as 1999-2018 to ensure a sufficient run-in period (1995-1998). Inclusion time was the date for the first of the two redeemed prescription with the 18th birthday as the earliest date. The asthma-related drugs of interest included inhalations of selective b2-agonists, inhaled glucocorticoids, fixed combinations of b2-agonists and glucocorticoids, leukotriene receptor antagonists and xanthines.

We excluded individuals with diagnoses of chronic obstructive pulmonary diseases or cystic fibrosis, use of roflumilast, or recent migrations within two years prior of inclusion time. Furthermore, we excluded individuals with other diseases commonly treated OCS, i.e. sarcoidosis, primary adrenocortical insufficiency, pneumonitis, inflammatory bowel disease, inflammatory polyarthropathies, systemic connective tissue disorders, inflammatory and/or malignancy. Individuals with apparent inactive asthma, defined by no redeemed asthma-medication for two consecutive years, were censored but were permitted to re-enter the cohort upon resumed use.

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

The study design and study population selection are shown in**Figure 1** .

OCS usage

All OCS prescriptions were converted into prednisolone-equivalent doses (equivalences available in **Online Supplement Table E1**). We calculated the number of OCS prescriptions and accumulated daily dose per OCS-user. All individuals in the study population were classified annually by their respective cumulative OCS consumption within the given calendar year, categorized in three exposure groups (21);

1. a *no-use* group
2. a *low-use* group, defined by use of <1825 mg in the given year, corresponding to <5 mg OCS/day (not including 0 use), and
3. a *high-use* group, corresponding to [?]5 mg OCS/day

Baseline characteristics

The Charlson Comorbidity Index (22) was used as a marker for the overall comorbidity burden based on International Classification of Diseases (ICD)-10 codes diagnoses recorded from in- or outpatient hospital contacts (23) with exclusion of asthma diagnoses (ICD10 J45-J46). Specific asthma-related comorbidities were chosen from the existing literature (5, 24-26) 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 Anatomical Therapeutic Chemical (ATC)-codes are available in **Online Supplement Table E2** .

Statistical analyses

Descriptive statistics were presented as number, median and interquartile range (IQR) for continuous variables, and as frequencies and percentages for categorical variables. 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, stratified according to OCS-usage groups (high-use and low-use), and by sex and age categories (18-25 years, 26-35 years, 36-45 years). Lorenz curves (27) for the years 1999, 2009 and 2018 were computed to assess 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.

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

Sensitivity analyses

We conducted two sensitivity analyses in order 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 analyses, individuals were allowed up to five successive years of no filled asthma drug prescriptions before being censored.

Results

Study population

We included 318,950 unique individuals with asthma during the study period 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 summarized in **Table 1** . The majority were women (57%) and the median age at cohort entry was 29 years (IQR 20-38 years). The annual asthma cohort from 1999-2018 consisted of 68,799 individuals with active asthma (median, IQR 67,414-70,277), corresponding to an annual asthma prevalence of 3.4% among 18-45-year-olds in Denmark.

OCS use

A total number of 47,389 individuals (14.9%) became OCS users during the study period, whereof 4,475 (1.4% of the total cohort) at one point fulfilled the criteria of having a high OCS use corresponding to [?]5 mg OCS/day within a calendar year. The annual prevalence of OCS users was 4.8% (median, IQR 4.7%-4.8%) with a slight increase from 4.3% in 1999 to 4.7% in 2018. The prevalence of high-users 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 and C** . The majority (56%) of OCS users was one-time users, while 27% filled 2-3 OCS prescriptions and 16% filled [?]4 prescriptions during their follow up time. The most frequent accumulated dose of OCS was 201-300 mg (32% of all users), while 21% of the users were exposed to >1000 mg during the observation period (**Online Supplement Table E3**). Both the median and mean annual OCS dose among users decreased in the period 1999-2018 from 500 mg/y (IQR 250-750 mg/y) to 250 mg/y (IQR 250-500 mg/y), and from 878 mg/y (SD 1479 mg/y) to 614 mg/y (SD 961 mg/y), respectively (**Figure 3**). The differences in median and mean illustrates a skewness in the distribution of OCS use.

Lorenz curves

Distribution of the overall consumption among OCS users in 2018 is illustrated in a Lorenz curve (27) in **Figure 4** . Lorenz curves for the year 1999 and 2009 are available in the **Online Supplement** . 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.

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, tough with an overall slight increase from 1999-2018, as well as decreasing proportions of high-users (i.e. use of [?]5 mg per day).

When restricting OCS-utilization 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.

Discussion

In this 20-year nationwide utilization study, we found an annual OCS use prevalence at 4.8% among young adults with active asthma with a slight increase in the period 1999 to 2018. Interestingly, we found an almost 40% decrease in the prevalence of high-users (i.e. use of [?]5 mg per day), as well as a halving in the annual median cumulative OCS dose among users. We found that OCS use was associated with older age and female sex in line with previous studies (10, 21, 28).

The prevalence of OCS use in our asthma population was somewhat lower than other European studies based on patients in secondary care (21) or on medical record databases (28). A recent Swedish register study restricted to asthma patients diagnosed in secondary care found 1.5% of patients to have a high OCS use ([?]5 mg/y) and 22.9% to have a low OCS use (<5 mg/y) within the baseline year (21). These higher prevalences might reflect a population of patients with more severe asthma compared to our broader cohort of asthma patients, not restricted to secondary care. In addition, patients in this study were generally older with a median age of 33 years. The authors confirmed a stable proportion at 15% of asthma patients using OCS over the 10-year study period. 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 (28). The annual prevalence of high OCS use (defined as [?]5 mg OCS/d in a 90-day window) was stable at approximately 3% in the period 2011-2018. The findings of overall stable OCS user trends during the last decades are supported by a recent systematic review performed on studies published in the period 2000-2017, which concluded that OCS continues to be commonly used and overused in asthma

treatment (10). Authors from 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 4 lifetime 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.

Other studies have found trends of increased OCS use during the last decades. This includes a French study on national claim data among 18-40-year-old asthma medication users (29) and a study on electronic healthcare records from the United Kingdom (UK) (30). The latter study demonstrated that the proportion of asthma patients in the UK receiving at least 3 courses of OCS per year doubled from 1% to 2% in the period 2006-2017. Less than 20% of these patients were referred for specialist care in contrary to national recommendations. Though similar numbers have not been explored on a Danish asthma population, this indicates an unmet need for specialist care assessment among frequent OCS users.

The differences in the trends of OCS user prevalence between studies might reflect the different OCS-quantification methods, data availability, differences in treatment practice patterns across the countries and asthma populations, 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, i.e. individuals using [?]1825 mg OCS per year, corresponding to [?]5 mg OCS/day, 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 1999-2018.

This change towards lower 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 2000 (31) and the availability of biological treatment (15). The first biological treatment for asthma treatment approved in Europe in 2005 was anti-IgE therapy (Omalizumab), which has since been followed by several other biologic therapies targeting type 2 inflammatory pathways. These treatments have launched a new era in severe asthma treatment and demonstrated the ability to reduce the use of OCS (15).

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 emphasized by the finding that 54% had a previous use of anti-histamines and 36% had a use of nasal corticosteroids, as proxies for treatment-requiring allergies and chronic rhinosinusitis, respectively (see **Online Supplement Table E2**). In Denmark, many antihistamines are available as over-the-counter medication, which was not included in our analyses, thereby likely underestimating the 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 (26), and severe mental disorders such as schizophrenia and bipolar disorder increase the risk of hospitalization for asthma (25).

Strengths and limitations

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 (32). 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 (32). Due to OCS and other asthma drugs being prescription-only medication, no potential over-the-counter exchanges were neglected.

However, several limitations much be acknowledged. In lack of access to diagnostic data from primary care, we used medical prescription data as proxies for asthma diagnoses. The method of identifying asthma patients from prescribing data has been validated as a reliable method by several European studies (19, 20). We chose a conservative upper age cut-off of 45 years to minimize the presence of COPD patients. We furthermore excluded individuals diagnosed with COPD, cystic fibrosis or diseases commonly treated with OCS in order to increase the probability of the OCS use being attributed to asthma. The study design's restrictions might make our estimates more conservative, reflected in our finding of a prevalence of active asthma at 3.4%. Also, the mildest cases of asthma, requiring less than two asthma drugs per year, were not identified. Due to the use of prescription data, we might have overestimated the actual OCS use, as a dispensed prescription is not synonymous to the medication being consumed. The use of dispensed prescriptions, however, reduce the risk of misclassification due to primary non-adherence. We were not able to account for possible stockpiling. Data on the underlying indications for the prescribed OCS were not available, and although we sought to describe only the OCS usage in asthma treatment, OCS prescriptions for asthma patients are often prescribed for other conditions (31). We sought to accommodate this by excluding patients with several comorbidities likely treated with OCS. In addition, we did not include OCS prescriptions filled during periods of apparent inactive asthma as defined in the study design, which possibly have led to an underestimation of the total OCS exposure per individual.

Conclusion

The annual prevalence of OCS use among young adults with asthma in Denmark is almost 5%. Though the proportion of OCS users has increased slightly in the years 1999-2018, we observed an interesting shift towards use of lower overall OCS doses. We found that OCS use at [?]5 mg per day was rare and decreasing. These findings may aid as an evidence-based foundation in the ongoing discussion of asthma management and OCS sparing initiatives.

Data availability : 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/

Conflict of interest :

IRS reports grants paid to her institution from AstraZeneca, Teva, the Odd Fellow Lodge of Haderslev Denmark, the Region of Southern Denmark, and the University of Southern Denmark during the conduct of the study; and personal fees for lectures from Roche and grants from Novartis, outside the submitted work.

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Author contribution : All authors participated in the study design. IRS wrote the first draft of the paper. All authors interpreted the data and revised the paper with approval of the final version. JRD was the head supervisor of the project.

Ethical approval : Register-based studies do not require approval from ethical boards in Denmark due to the use of pseudomized data. The study was approved by the Danish Data Protection Agency.

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Tables

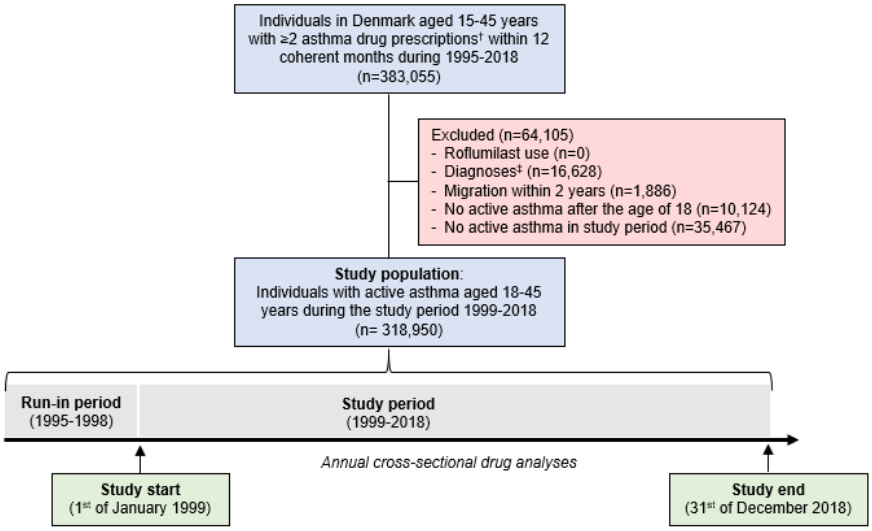
Table 1: Baseline demographic characteristics of young Danish adults aged 18-45 with asthma in 1999-2018

	Asthma population (n=318,950)
Total time of observation (person-years)	1,731,632
Median 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 and comedication, n(%)	
Atopic dermatitis^{+}	6045 (1.9%)
Allergies^{++}	175,383 (55%)
Chronic rhinosinusitis^{++}	115,522 (36%)
Food allergy^{+}	802 (0.3%)
Obesity^{++}	40,192 (13%)
Sleep apnea^{+}	1437 (0.5%)
Anxiety or depression^{++}	43,862 (14%)
Serious mental disorders^{++}	18,233 (5.7%)
Dyspeptic disorders^{++}	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%)

*+identified by hospital-given diagnosis, ++identified by hospital-given diagnosis or dispensed prescriptions of relevant specific medication (see **Online Supplement Table E2** for specifications)*

Figures

Figure 1: Study design and flow chart of the asthma population selection.



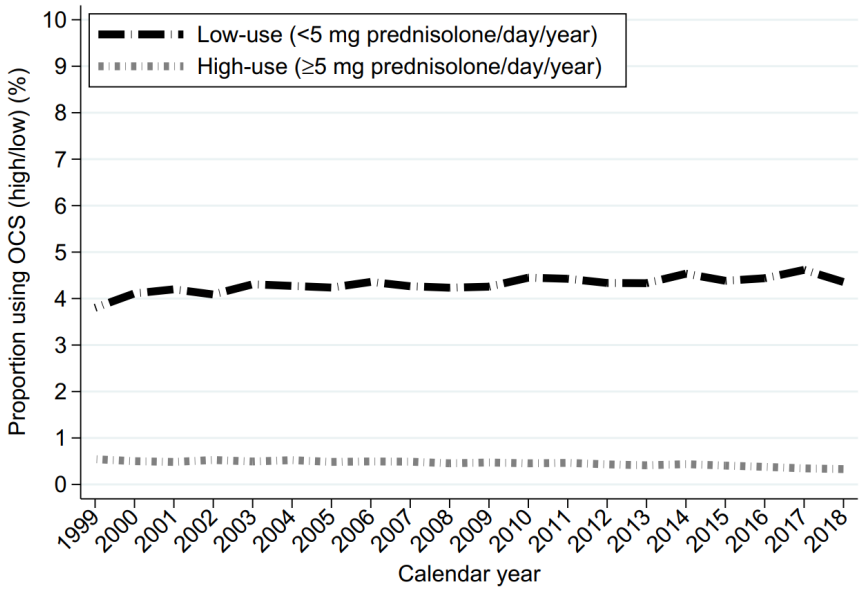
Footnote:

+Including inhalations of selective β2-agonists, inhaled glucocorticoids, fixed combinations of β2-agonists and glucocorticoids, leukotriene receptor antagonists and xanthines.

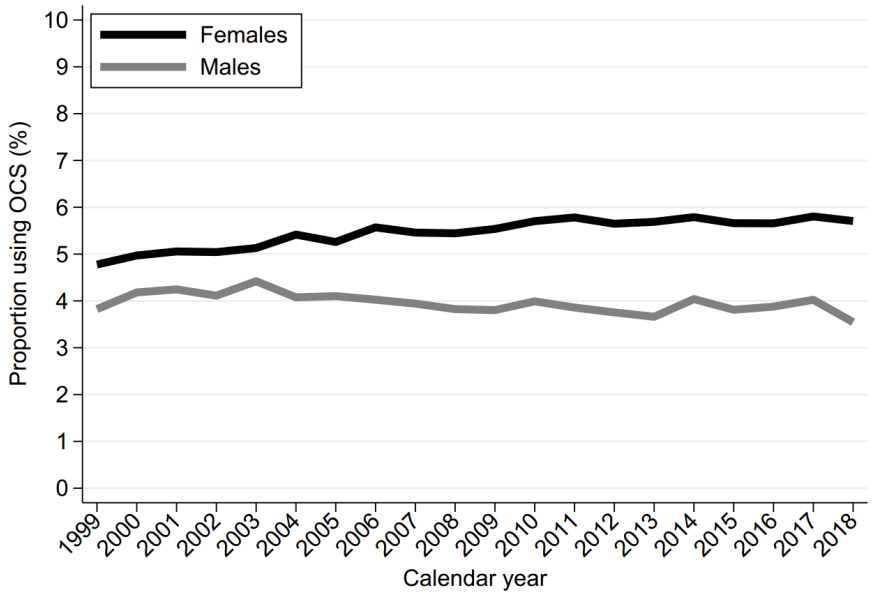
++Including chronic obstructive pulmonary disease, cystic fibrosis, sarcoidosis, primary adrenocortical insufficiency, pneumonitis due to external agents, inflammatory bowel disease, inflammatory polyarthropathies, systemic connective tissue disorders, inflammatory spondylopathies, and/or malignancy

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

A



B



C

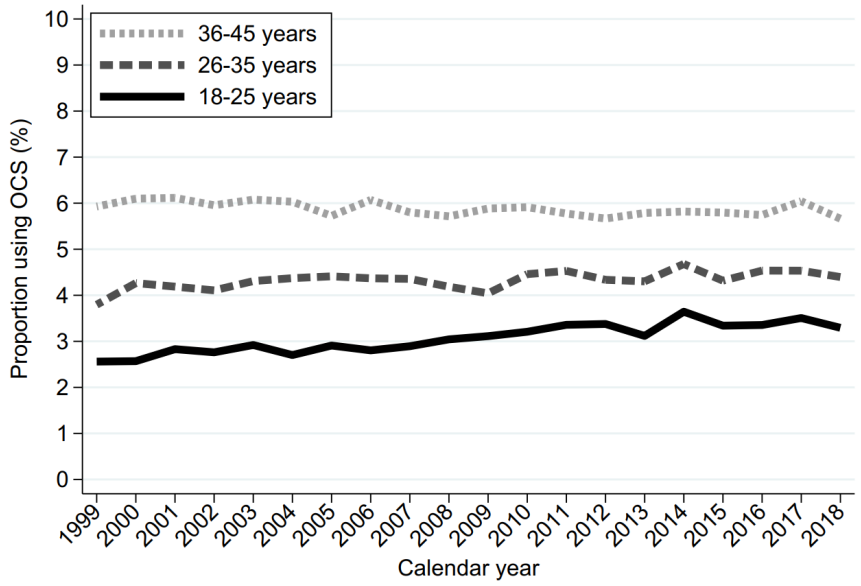


Figure 3: Trends in mean and median annual cummulative dose of oral corticosteroids (OCS, in prednisolone equivalent doses) among young adults with active asthma using OCS in Denmark from 1999-2018.

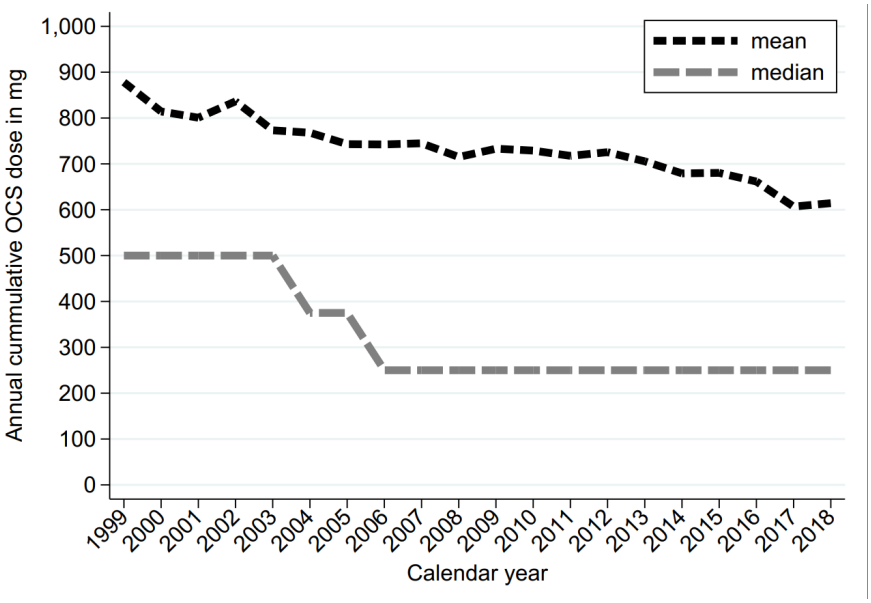


Figure 4: Lorenz curve of oral corticosteroid use among asthma patients (25). The graph illustrates the total amount of dispensed oral corticosteroid in the asthma population in 2018 measured in mg (y-axis), distributed among the users arranged in order of consumption (x-axis). The top 1% most heavy users account for 12% of the drug use, the top 10% for 46% of the drug use, and the top 50% for 80% of the drug use. The Gini coefficient was 0.49.