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ORIGINAL RESEARCH

Prevalence, Change and Burden of Systemic Corticosteroid Use in Type 2 Inflammation Associated Diseases Over 25 Years – A Nationwide Danish Study

Kjell Erik Julius Håkansson[1,2], Inge Raadal Skov[3], Steven Arild Wuyts Andersen[4,5], Zarqa Ali[6], Anders Løkke[7,8], Rikke Ibsen[9], Ole Hilberg[7,8], Howraman Meteran[1], Claus R Johnsen[10], Vibeke Backer[4,5], Charlotte Suppli Ulrik[1,5]

[1]Department of Respiratory Medicine, Copenhagen University Hospital - Hvidovre, Hvidovre, Denmark; [2]Department of Respiratory Medicine, Copenhagen University Hospital - Bispebjerg, Copenhagen, Denmark; [3]Department of Medicine, Little Belt Hospital, Kolding, Denmark; [4]Department of Otorhinolaryngology – Head & Neck Surgery and Audiology, Copenhagen University Hospital - RigsHospitalet, Copenhagen, Denmark; [5]Institute of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark; [6]Department of Dermatology, Copenhagen University Hospital - Bispebjerg, Copenhagen, Denmark; [7]Department of Medicine, Lillebælt Hospital, Vejle, Denmark; [8]Department of Regional Health Research, University of Southern Denmark, Odense, Denmark; [9]i2Minds, Aarhus, Denmark; [10]Allergy Clinic, Copenhagen University Hospital - Gentofte, Gentofte, Denmark

Correspondence: Kjell Erik Julius Håkansson, Respiratory Research Unit 237, Copenhagen University Hospital – Hvidovre, Kettegård Allé 30, Hvidovre, 2650, Denmark, Email kjell.erik.julius.haakansson@regionh.dk

Background: Systemic corticosteroid use in type 2 inflammation-associated diseases including asthma, atopic dermatitis, allergic rhinitis, and chronic rhinosinusitis has been associated with adverse outcomes, and corticosteroid-sparing treatments are available.

Objective: Assess temporal changes in systemic corticosteroid use and the impact of type 2 inflammation multimorbidity (eg multiple concurrent type 2 inflammation-associated diseases) and specialist assessment on systemic corticosteroid exposure.

Methods: Using nationwide databases, all Danish adults with asthma, atopic dermatitis, allergic rhinitis, or chronic rhinosinusitis, based on hospital diagnoses or redeemed prescriptions between 1997 and 2021 were included in an open, serial cross-sectional cohort.

Results: Over 25 years, a total of 2,151,209 Danish adults were included. Of those with a single diagnosis (type 2 inflammation monomorbidity),13.9% had asthma, 19.2% allergic rhinitis, 52.9% atopic dermatitis, and 14.0% chronic rhinosinusitis. In terms of type 2 inflammation multimorbidity, 75.1% of included individuals had one, 21.3% two and 3.5% three diagnoses, respectively. Overall, 9.6% of type 2 monomorbid individuals redeemed systemic corticosteroids, with asthma (16.5%) and atopic dermatitis (6.0%) having the highest and lowest prevalence of use. Systemic corticosteroid use peaked in 2006 (10.6%) and was lowest in 2020 (7.2%). Exposure > 5 mg prednisolone/day was constant around 15% overall among users. Type 2 inflammation multimorbidity was associated with increases in systemic corticosteroid use at 9.6%, 16.0% and 20.9% for one, two and three diagnoses, respectively. A median referral delay of 4.1 [8.1] years from first systemic corticosteroid redemption to specialist assessment was seen. Specialist assessment led to a 64.9% reduction in median annual systemic corticosteroid exposure overall.

Conclusion: In type 2 inflammation associated diseases, systemic corticosteroid use remains common despite the introduction of corticosteroid-sparing treatments. Timely referrals to specialist assessment could reduce the overall systemic corticosteroid exposure.

Plain Language Summary: This study looked at how often a type of medicine called systemic corticosteroids is used by people with certain health conditions related to inflammation such as asthma, allergies, atopic eczema and chronic rhinosinusitis, in Denmark over the past 25 years. Systemic corticosteroids (eg *prednisolone*) are strong medications that help reduce inflammation in the body. While they can be very effective towards severe symptoms, long-time use can lead to serious health problems, including weight gain, diabetes, and weakened bones.

The study aimed to determine how many patients with these inflammatory diseases were using systemic corticosteroids and how this has changed over time. They found that overall, about 9.6% of patients with one of these conditions used systemic corticosteroids. Among these patients, asthma patients had the highest usage at 16.8%, while those with atopic eczema had the lowest at 6.0%.

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Overall, the study observed a decrease in the use of these medications since 2006, especially during the COVID-19 pandemic. However, patients with multiple conditions, such as having both asthma and allergies, tended to rely more on systemic corticosteroids. Importantly, the study showed that patients who visited a specialist after starting systemic corticosteroids were able to significantly reduce their use of these medications, but many patients had to wait several years before being seen by a specialist.

In conclusion, even though there are safer treatments available, many people still depend on systemic corticosteroids. Timely help from specialists can assist in reducing the need for these medications and the associated health risks.

Keywords: prednisolone, allergic rhinitis, asthma, chronic rhinosinusitis, atopic dermatitis, corticosteroid sparing

Introduction

Type 2 inflammation and steroid-responsiveness are closely associated[1,2] and diseases with known type 2 inflammation involvement in their pathogenesis such as asthma, atopic dermatitis, allergic rhinitis and chronic rhinosinusitis are typically treated with topical corticosteroids or other anti-inflammatory agents. However, in acute and severe presentations of these diseases, systemic corticosteroids are often used either as short, higher-dose rescue bursts or longer term, low-dose maintenance (maintenance oral corticosteroids).[3–6]

The use of systemic corticosteroids has consistently been associated with corticosteroid-associated diseases or adverse effects such as osteoporosis, type 2 diabetes, cardiovascular disease, infections and even mortality.[7,8] Furthermore, prolonged exposure to high-dose inhaled corticosteroids and topical corticosteroids have been suggested to drive an increased risk of corticosteroid-associated morbidity.[9–11] Considering the risks associated with corticosteroid exposure, the advent of corticosteroid-sparing therapies for Type 2 inflammation-associated diseases such as monoclonal antibodies, Janus kinase inhibitors[5,12] and allergen immunotherapy[4,13] holds promise for reducing the burden of corticosteroid-associated morbidity.

The use of systemic corticosteroids and high-dose topical corticosteroids continue to be frequent,[9,14,15] despite the increased attention to corticosteroid-associated adverse events, changes in expert and guideline recommendations against routine use of systemic corticosteroids and an increasing availability of corticosteroid-sparing therapies. Airway diseases such as asthma often dominate prescription patterns for systemic corticosteroids,[16,17] yet a subset of individuals with Type 2 inflammation-associated diseases suffer from multiple conditions under the type 2 umbrella (eg concurrent asthma and allergic rhinitis, "Type 2 inflammation multimorbidity").[18] For individuals with Type 2 inflammation multimorbidity, it has been speculated that the corticosteroid burden may be even higher than for individuals with a single diagnosis,[18,19] yet real-world evidence supporting this assumption is lacking.

In the present study, utilising the Danish National Prescription Registry, we aimed to conduct a 25-year nationwide analysis of prevalence and temporal changes of systemic corticosteroids use in Type 2 inflammation-associated diseases: asthma, atopic dermatitis, allergic rhinitis, and chronic rhinosinusitis. Furthermore, we aimed to assess the impact of Type 2 inflammation multimorbidity on systemic corticosteroid use as well as the impact of specialist assessment.

Methods

Approvals, Data Sources and Sharing

No informed consent from individuals included is needed for epidemiological research according to Danish law due to the use of anonymized large-scale data. Statistics Denmark approved study data access. Data is available upon reasonable request but is subject to Statistics Denmark's terms and Danish law.

Study Design and Population

The current study is a nationwide Danish open, serial cross-sectional cohort study utilizing the National Patient Registry and the National Prescription Registry, which includes all secondary care contacts and all redeemed prescriptions from all pharmacies, irrespective of prescriber. Data is linked using the Central Person Registry, which allows for individual-level linkage between beforementioned registries as well as socioeconomic and demographic data from Statistics Denmark. All

individuals aged 18 and above were eligible for inclusion, provided they fulfilled one or more Type 2 inflammation-associated disease definitions mentioned below.

Observation Period

This study was designed as an open cohort study. Eligible individuals were followed from their index date (ie date of fulfilling disease definition as defined below) but censored from analyses after 48 months of no active treatment or secondary care contacts, as defined below. The individual follow-up period was extended with another 48 months after each relevant repeated prescription redemption or secondary care contact, as exemplified in Figure 1 and described in detail below. Censored individuals could at any time re-enter the cohort if they re-fulfilled the inclusion criteria. Early censoring occurred if the individual died or emigrated.

A two-year run-in period from data availability in 1995 was utilized to mitigate left-censoring and allow assessment of exclusion criteria for all possible cases. Furthermore, a two-year run-out period was applied to allow for a two-year disease burden assessment for all possible cases.

A graphical overview of the study design is found in Figure 1.

Disease Definitions

In our study, Type 2 inflammation-associated diseases included were asthma, allergic rhinitis, atopic dermatitis and chronic rhinosinusitis. The definition of individual diseases was based on a combination of either a) pharmacy redemptions (at least two within the same disease classification during 12 months) or b) secondary care outpatient clinic's ICD-10 diagnoses. Relevant exclusion criteria were defined per disease, as well as global exclusion criteria for both known systemic corticosteroid-dependent comorbidities and COPD. Inclusion as well as exclusion criteria were based on previously published definitions. An overview is provided below. Full disease definitions and references are available in Supplementary Table 1.

Asthma was defined as either inhaled corticosteroid (ICS)-monotherapy or any combination of ICS and long-acting bronchodilators or secondary care outpatient diagnoses of asthma or status asthmaticus (J45+46). Any individuals with coexisting diagnoses of Chronic obstructive pulmonary disease (COPD) (J41-44, but not J44.8) were excluded.[7,14]

Atopic dermatitis was defined as redemptions of topical dermatitis treatments and corticosteroids and/or a diagnosis of atopic dermatitis (DL20). Exclusion criteria included any other form for dermatitis such as contact, drug phototoxic

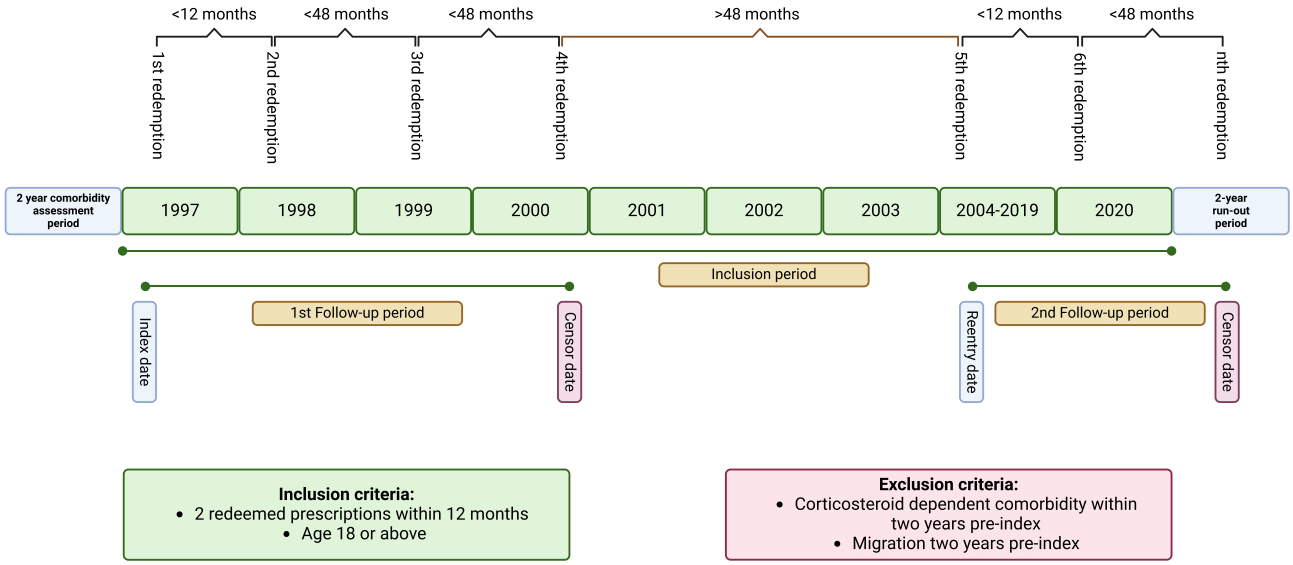

Figure 1 Overview of the study design of a nationwide Danish open, serial cross-sectional cohort study on the prevalence and burden of systemic corticosteroid use in type 2 inflammation associated diseases.

reactions and lupus (L30, 40–45, 53, L55-6, L80, L90, L93), as well as any group IV topical corticosteroid or combination of topical treatments with antifungals and antibacterials.[20]

Allergic rhinitis was defined as redemption of intranasal decongestants or corticosteroids with >50% of redemptions during the Danish pollen season from April through August or a diagnosis of allergic rhinitis (J30.0–30.4) or any recipiency of allergen immunotherapy. Exclusion criteria were a known diagnosis of chronic or acute rhinosinusitis (J33, J01.0–9, J32.0–9), itch (L29) or urticaria (L50).[20]

Chronic rhinosinusitis was defined as redemption of nasal decongestants or corticosteroids not fulfilling the seasonality criterium for allergic rhinitis or a diagnosis of chronic rhinosinusitis with or without nasal polyps (J31-33).[20] Due to overlap between treatments, mutual exclusivity was established between atopic dermatitis and chronic rhinosinusitis and the most likely disease based on a hierarchy of (a) secondary care specialist-supplied diagnosis (allergic rhinitis >chronic rhinosinusitis) OR any allergen immunotherapy and (b) seasonality (seasonal redemption patterns > perennial redemption patterns).

Type 2 Inflammation Mono- and Multimorbidity

Analyses are performed either on individuals fulfilling only one disease definition ("Type 2 inflammation monomorbid") during their entire follow-up period, or on individuals fulfilling two or more definitions (eg asthma and concurrent allergic rhinitis, "Type 2 inflammation multimorbid"). For analyses based on patient years, individuals are assigned mono/multimorbidity burden according to the number of known Type 2 inflammation-associated diseases during each year of follow-up. For analyses based on absolute number of individuals, included individuals had their diagnostic status calculated as either.

1) For monomorbidity: having only one diagnosis during the entire follow-up period (eg individuals fulfilling asthma only fulfilled the asthma criteria during the entire follow-up period)
2) For multimorbidity: index date was set to the date where the highest number of diagnoses during the follow-up period was achieved.

Outcomes

The main outcomes in the present study were the annual prevalence of any systemic corticosteroid users and the annual cumulative corticosteroid exposure for included individuals, stratified by Type 2 inflammation-associated disease or Type 2 inflammation mono/multimorbidity. Secondary outcomes were prevalence of substantial annual corticosteroid exposure (defined as average daily exposure to at least 5 mg prednisolone equivalents) for systemic corticosteroids, time to specialist assessment after the first registered systemic corticosteroid redemption and change in corticosteroid burden after specialist assessment.

Corticosteroid Burden

Corticosteroid burden was calculated as the sum of registered pharmacy-redeemed systemic corticosteroids. Corticosteroid burden includes both oral and parenteral (eg intramuscular) corticosteroids. All doses were calculated as total burden per follow-up year and presented as either annual burden, total burden or average daily burden depending on outcome.

All corticosteroids were converted to estimated prednisolone equivalent doses. For systemic corticosteroids, a simple dose equivalence factor was used.[7] A summary of conversion factors and equivalence calculations is found in Supplementary Table 2.

Specialist Assessment

Time to specialist assessment was performed for individuals with at least one redemption of systemic corticosteroids and a subsequent specialist assessment with a relevant ICD-10 code as defined under "Disease definitions". Individuals with any specialist assessment two years prior to their first systemic corticosteroid redemption and with less than one year of prospective follow-up were excluded from the analysis.

Number of prescriptions of systemic corticosteroids was calculated for the entire period from the index date to the first specialist assessment. Individuals with less than 30 days between systemic corticosteroid redemption and specialist assessment or between specialist assessment and censoring were excluded to reduce overestimation. Average daily systemic corticosteroid exposure was calculated as all redeemed redemptions prior to and after the first registered specialist assessment, divided by the corresponding observation time.

Statistical Analyses

Data are presented as n(%), mean (standard deviation) or median [interquartile range]. Statistical testing between groups was performed using chi-squared tests, pre/post testing was performed using Wilcoxon signed rank tests due to evidence of non-normality. All analyses were performed using SAS 9.4 (SAS Institute, NC, USA). Graphics were generated using ggplot2 and Biorender.com.

Results

The present cohort includes 2,151,209 Danish adults with at least one Type 2 inflammation-associated disease, followed for a total of 12,266,351 person-years. For individuals with monomorbidity (n = 1,616,609), 13.9% had asthma, 19.2% allergic rhinitis, 52.9% atopic dermatitis, and 14.0% chronic rhinosinusitis, respectively (Table 1). In terms of type 2 inflammation multimorbidity, 24.9% had more than two or more concurrent diagnoses (Table 2).

Of the included individuals, 54.7% were female and the mean age at inclusion was 48 (SD 20) years. Individuals with allergic rhinitis were younger with a mean age 40 years (SD 18), compared to asthma, atopic dermatitis and chronic rhinosinusitis at 51 (SD 20), 51 (SD 21) and 48 (SD 18), respectively. Differences in education level at index between diseases were seen (Table 1). For individuals with multimorbidity, fewer differences in demographics were observed. However, individuals with three diagnoses were slightly younger and more often female compared to monomorbid individuals (Supplementary Table 3).

Table 1 Baseline Characteristics of 1,616,609 Danish Adults with Monomorbid, Pharmacologically Treated Type 2-Inflammatory Disease Included in a Nationwide Cohort

	Overall n = 1,616,609	Asthma n = 225,302	Allergic Rhinitis n = 310,050	Atopic Dermatitis n = 855,323	Chronic Rhinosinusitis n = 225,934	p-Value
Age (years), Mean (SD)	49 (20)	51 (20)	40 (18)	51 (21)	48 (18)	<0.0001
Female	864,680 (53.5%)	122,478 (54.4%)	168,112 (54.2%)	458,190 (53.6%)	115,900 (51.3%)	<0.0001
Metropolitan residence	638,862 (39.5%)	81,827 (36.3%)	133,502 (43.0%)	333,352 (39.0%)	90,181 (39.9%)	<0.0001
Cohabiting or married	937,401 (58.0%)	125,583 (55.7%)	176,312 (56.9%)	488,537 (57.1%)	146,969 (65.0%)	<0.0001
Education						<0.0001
Primary or secondary education	682,884 (42,2%)	108,274 (48.0%)	133,627 (43,1%)	360,993 (42,2%)	79,990 (35,4%)	
Vocational education	477,605 (29.5%)	63,499 (28.2%)	87,299 (28.2%)	254,073 (29.7%)	72,734 (32.2%)	
Bachelor's degree or higher	342,421 (21,2%)	38.490 (17,1%)	76,391 (24,7%)	164,119 (19.1%)	63,421 (28.1%)	
Unknown	113,699 (7.0%)	15,039 (6.7%)	12,733 (4.1%)	76,138 (8.9%)	9,789 (4.3%)	
Workforce attachment						<0.0001
Employed	785,434 (48.6%)	91,291 (40.5%)	173,049 (55.8%)	392,567 (45.9%)	128,527 (56.9%)	
Outside the workforce	255,674 (15.9%)	44,833 (19.9%)	40,107 (12.9%)	138,867 (16.2%)	31,867 (14.1%)	
Under education	172,414 (10.7%)	22,897 (10.2%)	53,875 (17.4%)	75,296 (8.8%)	20,346 (9.0%)	
Age pension	362,618 (22.4%)	60,207 (26.7%)	34,597 (11.2%)	228,192 (26.7%)	39,622 (17.5%)	
Other & unknown	40,469 (2.5%)	6,074 (2.7%)	8,422 (2.7%)	20,401 (2.4%)	5,572 (2.5%)	
Inclusion period						<0.0001
2021–2017	257,529 (15.2%)	34,427 (15.4%)	51,973 (16.8%)	121,373 (12.8%)	49,756 (22.0%)	
2016–2012	260,385 (16.2%)	36,748 (16.4%)	49,448 (15.9%)	129,035 (15.1%)	45,154 (20.0%)	
2011–2007	265,733 (16.4%)	41,139 (18,3%)	44,874 (14.4%)	142,478 (16.7%)	37,242 (16.6%)	
2006–2002	298,442 (18.5%)	39,802 (17.7%)	50,826 (16.3%)	172,849 (20.2%)	34,965 (15.4%)	
2001–1997	546,500 (33.8%)	73,185 (32.5%)	112,927 (36.4%)	301,576 (35.2%)	58,812 (26%)	

Table 2 Steroid Burden Prior to and Time to Specialist in Individuals with Monomorbid Type 2-Inflammatory Diseases Without Prior Secondary Care Specialist Contacts

	Overall n = 43,105	Asthma n = 30,479	Atopic Dermatitis n = 2,262	Allergic Rhinitis n = 3,942	Chronic Rhinosinusitis n = 6,422
Secondary care management[1, 2]					
Time to secondary care management (years, median, IQR)	4.1 [8.1]	4.4 [8.0]	2.3 [5.9]	5.3 [8.4]	3.2 [8.5]
Number of prescriptions prior to secondary care management (median, IQR)[3]	2 [0; 4]	3 [0.5; 5.5]	2 [0; 4]	3 [0.5; 5.5]	2 [0.5; 4.5]
Systemic steroid burden					
Annual systemic steroid burden prior to specialist management (prednisolone eq. mg, median, IQR)[3]	146.1 [438.3]	171.7 [515.0]	255.7 [741.5]	73.1 [102.3]	124.2 [317.8]
Annual systemic burden after specialist management (prednisolone eq. mg, median, IQR)[3]	51.3 [277.6]; p < 0.0001	91.3 [438.3]; p < 0.0001	0.2 [87.7]; p < 0.0001	7.3 [40.2]; p < 0.0001	11.0 [54.8]; p < 0.0001

Notes: [1]Only includes individuals with at least 1 redemption of systemic steroids. [2]Time to specialist management defined as time from first prescription of systemic steroids to first outpatient visit with corresponding ICD-10 codes – excluding individuals with active outpatient codes 2 years prior to the first prescription. [3]Annualised for all follow-up time available for individuals until censored due to right censoring, emigration or death.

The Prevalence of Systemic Corticosteroid Users in Type 2 Inflammation Associated Diseases

Between the years 1997–2021, the average prevalence of systemic corticosteroid users in individuals with Type 2 inflammation monomorbidity was 9.6% among 1,047,446 users over 10,874,875 patient-years. The prevalence of systemic corticosteroid users was highest in 2006 (10.7%) and lowest in 2020 (7.2%). Overall, a trend towards fewer systemic corticosteroid users was seen from 2006 and onwards, with the exception of an increase in prevalence from 7.2% to 8.0% from 2020 to 2021 (Figure 2A). In terms of absolute number of users, a bell-shaped development over time was observed, with 1997 and 2021 having approximately 35,000 active users, with a peak in 2006 with 45,840 users (Figure 2B).

Stratified by disease, asthma had the overall highest prevalence of systemic corticosteroid users, with an average prevalence of 16.8% of individuals exposed. A decrease in prevalence over time was observed, from 19.1% in 2001 to 11.8% in 2020 (Figure 2A). The prevalence of systemic corticosteroid users in asthma was highly dependent on age (Supplementary Figure 1). For allergic rhinitis, atopic dermatitis and chronic rhinosinusitis, average prevalence of systemic corticosteroid users was 8.8%, 6.0% and 6.8%, respectively. In allergic rhinitis and chronic rhinosinusitis, a slight decrease over time was observed, whereas the prevalence of systemic corticosteroid users remained unchanged over time for atopic dermatitis (Figure 2A).

For individuals with Type 2 inflammation multimorbidity, average prevalence of systemic corticosteroid users across the entire follow-up period was 9.6%, 16.0% and 20.9% for individuals with one, two, and three diagnoses, respectively. Over time, a downward trend in prevalence of systemic corticosteroid users was observed. However, a dose-response relationship in prevalence of systemic corticosteroid users and number of Type 2 inflammation-associated diseases was seen, with the highest prevalence of systemic corticosteroid users being observed among individuals with three diagnoses. Additionally, the highest reduction in systemic corticosteroid use over time was observed in individuals with three diagnoses (Figure 3A).

Corticosteroid Exposure Burden in Type 2 Inflammation Associated Diseases

Among individuals with Type 2 inflammation monomorbidity and systemic corticosteroid use, an increase in both mean and median redeemed systemic corticosteroid doses was seen (Figure 4A). When stratified according to disease, the median and mean annual exposures remained relatively stable for asthma, whereas allergic rhinitis, atopic dermatitis and chronic rhinosinusitis all demonstrated increases in annual exposure over time (Figure 4B).

When stratified according to the prevalence of individuals exposed to at least 5 mg prednisolone equivalents on a daily basis, the prevalence slowly increased from 12.5% in 1997 to 15.6% in 2021 (Figure 5A). The relative prevalence

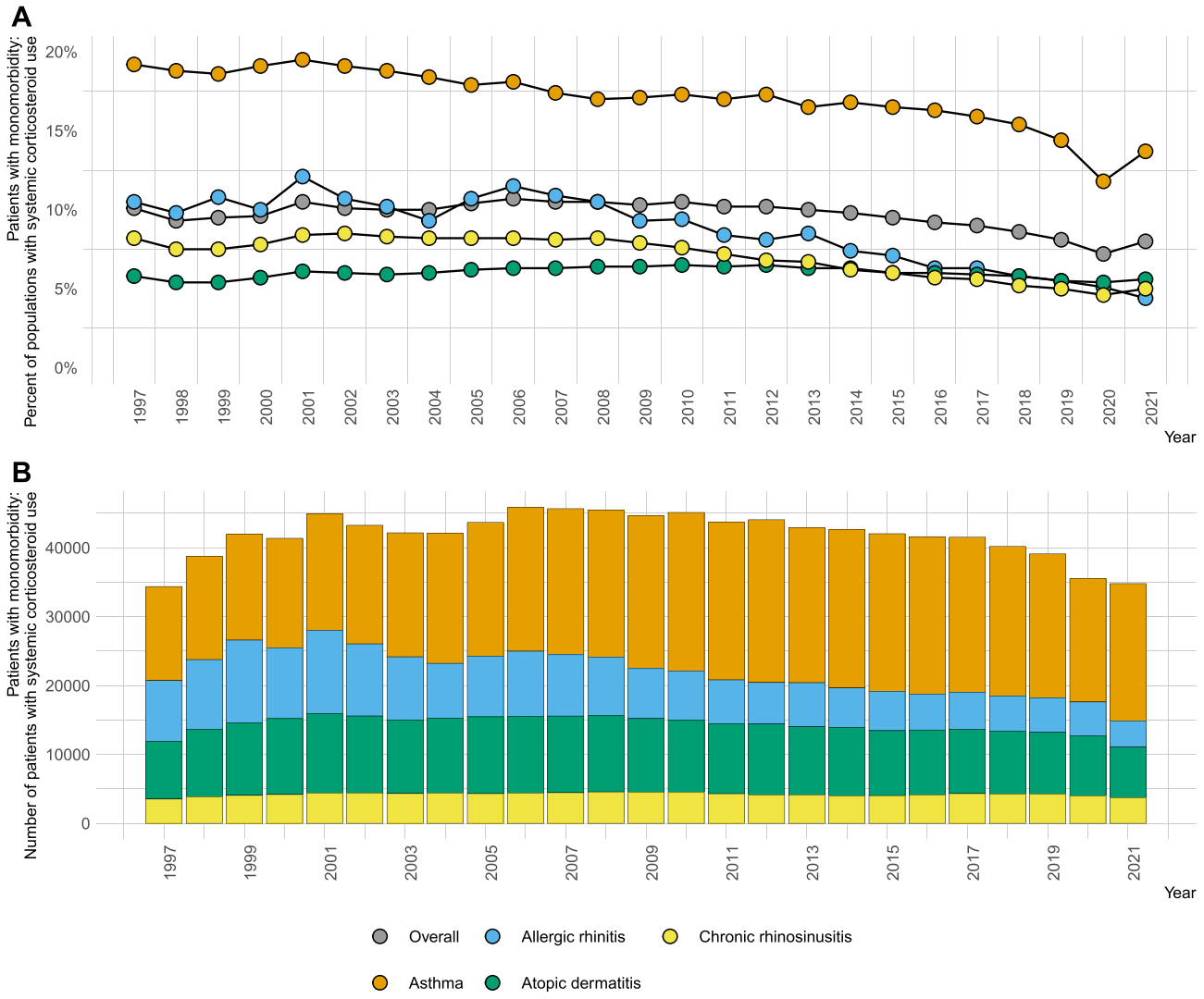

Figure 2 Changes of (**A**) prevalence of systemic corticosteroid (SCS) use and (**B**) absolute number of systemic corticosteroid users in a cohort of 1,616,609 Danish adults with monomorbid type 2 inflammation-associated disease.

of substantial systemic corticosteroid exposure (at least 5 mg prednisolone equivalents) decreased after 2014 for asthma, remained relatively constant for atopic dermatitis, whereas allergic rhinitis and chronic rhinosinusitis demonstrated an increase over time (Figure 5B).

For individuals with Type 2 inflammation multimorbidity, slight increases in annual SCS exposure were seen, albeit without a clear dose–response pattern for the number of Type 2 inflammation-associated diagnoses (Supplementary Figure 2). When stratified according to substantial daily systemic corticosteroid exposure, a slight increase over time from 12.2% in 1997 to 15.2% in 2021 without a clear pattern when stratified by the number of type 2 inflammatory diagnoses (Figure 3B).

Patients who were exposed to systemic corticosteroids were in general older, were more likely to reside outside of metropolitan areas, were less likely to have attained a bachelor's degree and have a weaker attachment to the workforce (Table 3).

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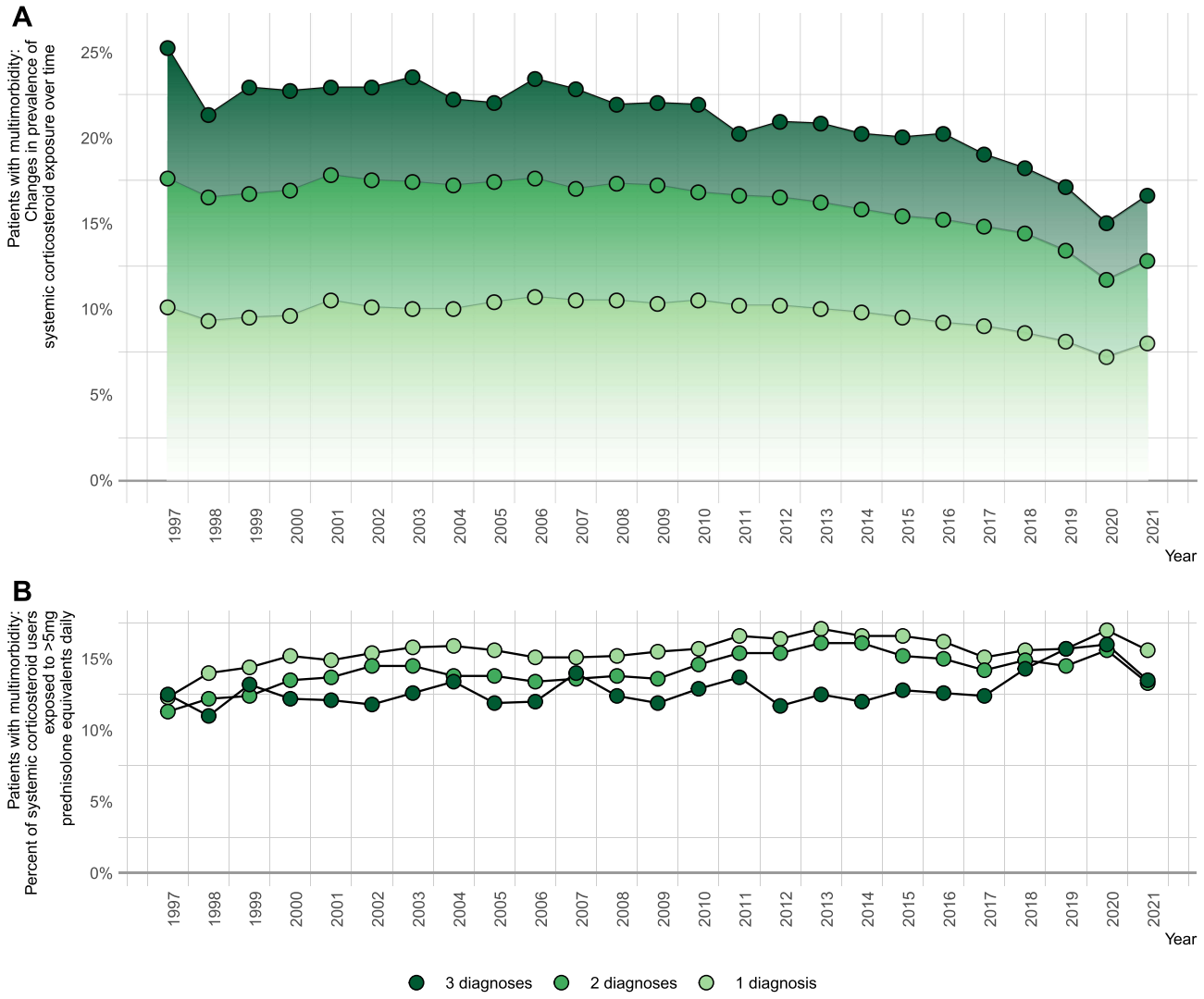

Figure 3 Changes in (**A**) prevalence of systemic corticosteroid (SCS) use and (**B**) prevalence of annual systemic corticosteroid (SCS) exposure of at least 5 mg prednisolone-equivalents in a cohort of 2,151,209 Danish adults with multimorbid type 2-inflammation associated disease, stratified by number of diagnoses.

Specialist Assessment and Its Relation to Systemic Corticosteroid Exposure

For individuals who had no prior specialist visit registered two years before the first systemic corticosteroid redemption (n = 43,105), the median time to specialist assessment was 4.1 years [IQR 8.1]. Time to specialist assessment varied by diagnoses, with atopic dermatitis and allergic rhinitis having the lowest and longest delay at 2.3 [IQR 5.9] and 5.3 [8.4] years, respectively (Table 2).

The overall number of steroid prescriptions prior to specialist assessment was 2 [IQR 4], with a range from 3 [IQR 5] for asthma and allergic rhinitis to 2 [IQR 4] and 2 [IQR 3] for atopic dermatitis and chronic rhinosinusitis, respectively. Median annual exposure for individuals overall was 146.1 mg [IQR 438.3] prior to specialist assessment and subsequently reduced to 51.3 mg [IQR 277.6] after specialist assessment. With the exception of asthma, all T2-associated diseases had their median annual exposures reduced to below 20 mg/year after specialist assessment. Of note, in asthma, specialist assessment reduced annual exposure from 171.7 mg [IQR 515.0] to 91.3 mg [IQR 438.3] and in atopic dermatitis, reductions to close to zero systemic corticosteroid exposure were seen (Table 2).

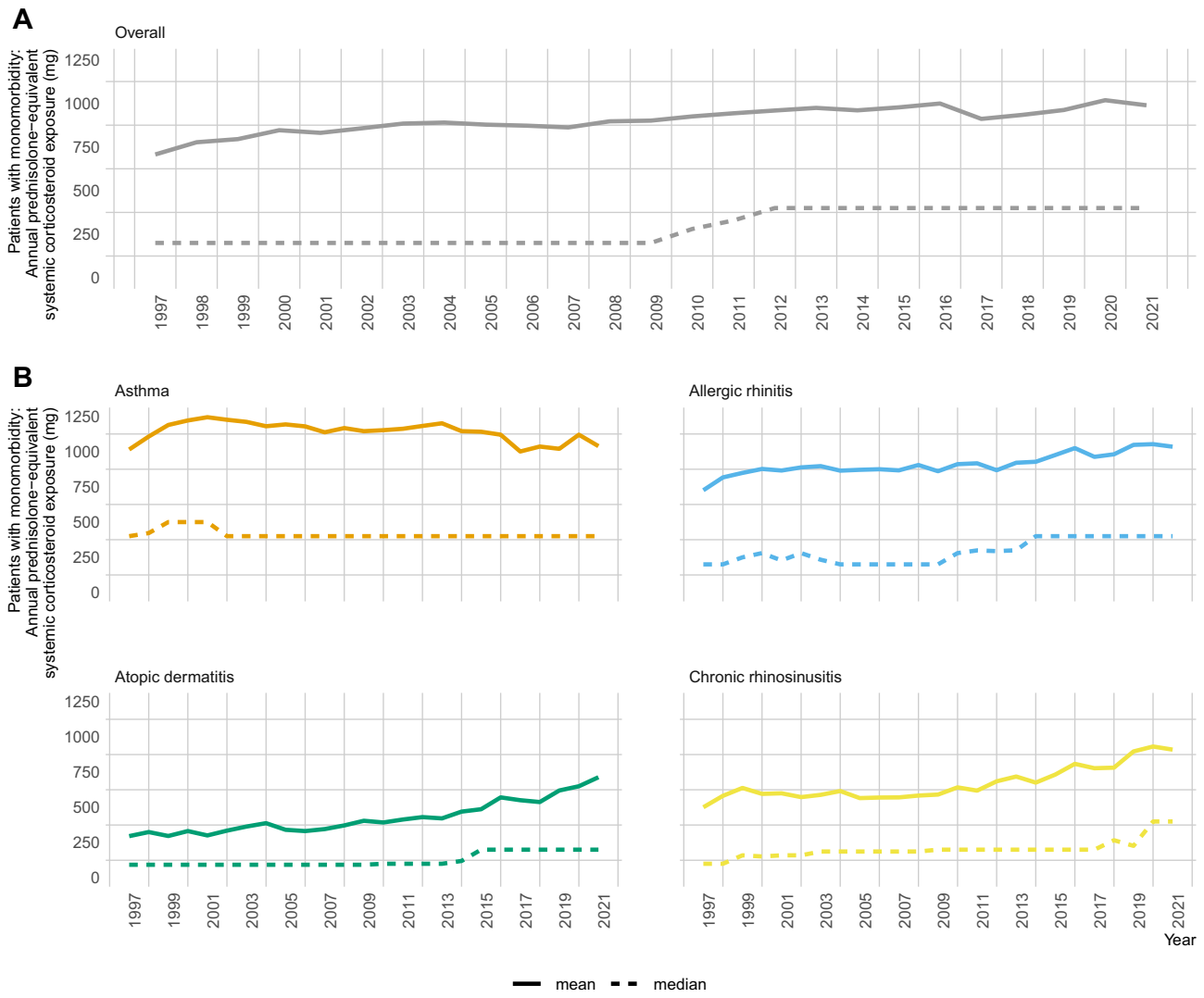

Figure 4 Changes in mean and median annual systemic corticosteroid (SCS) exposure in a nationwide cohort of 1,616,609 Danish adults with monomorbid type 2 inflammation-associated disease (**A**), stratified by disease (**B**).

Discussion

The present cohort includes 2,151,209 Danish adults with at least one type 2 inflammation-associated disease, followed for a total of 12,266,351 person-years. Over the course of 25 years, we found the overall use of systemic corticosteroids to decline, driven primarily by a reduced use in asthma. Type 2 inflammation multimorbidity was found to increase the prevalence of use but not systemic corticosteroid exposure. Finally, we found a referral delay of approximately 4 years from the first systemic corticosteroid prescription to specialist assessment, yet specialist assessment led to reductions in annual systemic corticosteroid exposure of approximately two-thirds.

Several temporal trends were identified in our present study, including a general decline in the prevalence of systemic corticosteroid use. This has been demonstrated in several earlier cohorts, both disease-specific and general cohorts on systemic corticosteroid use across the US, UK and the Europe.[16,17,21,22] For studies focusing on asthma, some hallmark events would be expected to influence systemic corticosteroid use patterns due to the assumed increase in disease control. Events of interest would, among others, be the introduction of fixed-dose ICS/long-acting beta$_2$-agonists coinciding with the (off-label until 2021) adoption of long-acting anti-muscarinics in the early 2000's[23] and the introduction of anti-Interleukin 5 biologics around 2016,[24] yet an accelerated decline in systemic corticosteroid use is mainly observable after the latter. Additionally, the COVID-19 pandemic and its sudden change in behaviour, number of daily contacts with peers

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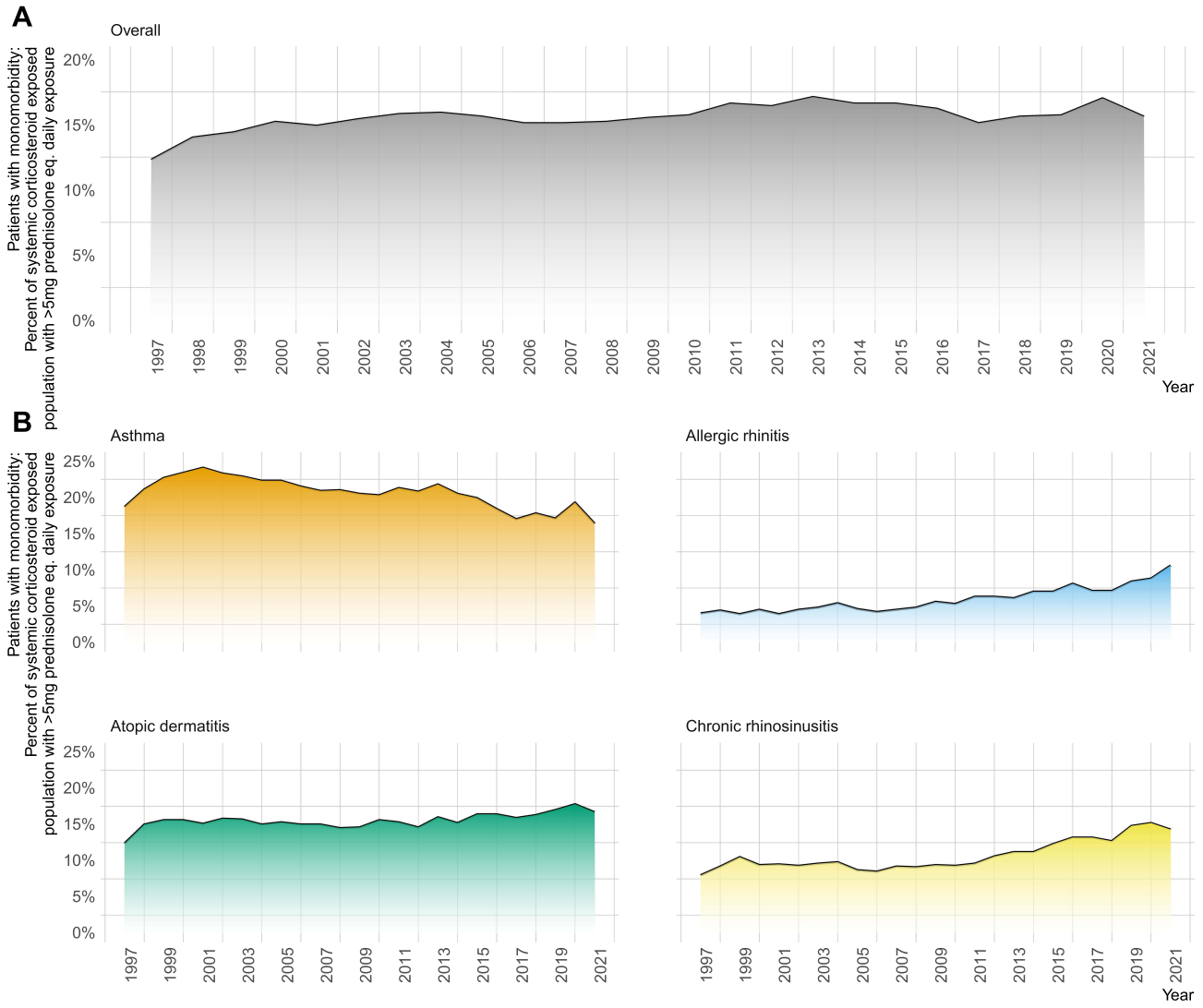

Figure 5 Prevalence of substantial daily systemic corticosteroid (SCS) exposure of 5 mg prednisolone equivalents in a nationwide cohort of 1,616,609 Danish adults with monomorbid type 2 inflammation-associated disease (**A**), stratified by disease (**B**).

and transmission of respiratory viruses led to a marked reduction in asthma exacerbations over time,[25] visible as a sharp decline in systemic corticosteroid use in 2020 and subsequent rebound after the pandemic. In terms of allergen immunotherapy, pioneering trials began in the early 1900s,[26] however, a decline in systemic corticosteroid use for

Table 3 Baseline Characteristics of 2,151,209 Danish Adults with Pharmacologically Treated Type 2-Inflammatory Diseases Included in a Nationwide Cohort, Stratified by Their Exposure to Systemic Corticosteroids

	Not Exposed to Systemic Corticosteroids (n = 1,974,941)	Exposed to <5 Prednisolone eq. Daily (n = 157,369)	Exposed to >5 mg Prednisolone eq. Daily (n = 18,899)	p-Value
Age (years), Mean (SD)	47 (20)	52 (20)	66 (17)	<0.0001
Female	1,080,785 (54.7%)	85,524 (54.3%)	9,822 (52.0%)	<0.0001
Metropolitan residence	795,685 (40.3%)	51,916 (33.0%)	5,998 (31.7%)	<0.0001
Cohabiting or married	1,155,450 (58.5%)	95,615 (60.8%)	10,219 (54.1%)	<0.0001

(*Continued*)

Table 3 (Continued).

	Not Exposed to Systemic Corticosteroids (n = 1,974,941)	Exposed to <5 Prednisolone eq. Daily (n = 157,369)	Exposed to >5 mg Prednisolone eq. Daily (n = 18,899)	p-Value
Education				<0.0001
Primary or secondary education	847,617 (49.6%)	69,073 (43.9%)	8,088 (42.8%)	
Vocational education	583,039 (29.5%)	48,863 (31.0%)	4,779 (25.3%)	
Bachelor's degree or higher	421,031 (21.3%)	27,344 (17.4%)	2,257 (11.9%)	
Unknown	123,254 (2.5%)	12,089 (7.7%)	3,775 (20.0%)	
Workforce attachment				<0.0001
Employed	978,929 (49.6%)	72,539 (46.1%)	3,914 (20.7%)	
Outside the workforce	329,682 (16.7%)	29,908 (19.0%)	3,998 (21.2%)	
Under education	222,900 (11.3%)	10,891 (6.9%)	306 (1.6%)	
Age pension	393,110 (19.9%)	40,653 (25.8%)	10,432 (55.2%)	
Other & unknown	50,320 (2.5%)	3,378 (2.1%)	249 (1.3%)	
Disease burden[1]				<0.0001
One type 2 inflammation-associated disease (%)	1,496,562 (75.8%; 92.6%)	105,114 (66.8%; 6.5%)	14,933 (79.0%; 0.9%)	
Of which Asthma (%)	190,911 (12.8%; 84.7%)	28,712 (27.3%; 12.7%)	5,679 (38.0%; 2.5%)	
Of which Allergic rhinitis (%)	282,995 (18.9%; 91.3%)	25,425 (23.2%; 8.2%)	1,630 (10.9%; 0.5%)	
Of which Atopic dermatitis (%)	811,090 (54.2%; 94.8%)	37,905 (36.1%; 4.4%)	6,328 (42.4%; 0.7%)	
Of which Chronic rhinosinusitis (%)	211,566 (14.1%; 93.6%)	13,072 (12.4%; 5.8%)	1,296 (8.7%; 0.6%)	
Two type 2 inflammation-associated diseases (%)	412,472 (20.9%; 89.9%)	43,187 (27.4%; 9.4%)	3,380 (17.9%; 0.7%)	
Three type 2 inflammation-associated diseases (%)	65,907 (3.3%; 87.2%)	9,068 (5.8%; 12.0%)	586 (3.1%; 0.8%)	

Notes: [1]Percentages presented as column-wise; row-wise.

allergic rhinitis was seen in the present study after 2006, coinciding with the introduction of sublingual therapy in 2007 and its subsequent uptake into national guidelines after demonstrating reductions in the need of systemic corticosteroids.[27] For atopic dermatitis and chronic rhinosinusitis, relatively stable prescription patterns were seen, hovering around 5–7%. However, corticosteroid-sparing biologic therapies became relatively recently available for both diseases (eg 2018 for atopic dermatitis and 2022 for chronic rhinosinusitis with nasal polyps), and the use of systemic corticosteroids is thus expected to decline.

Our present study demonstrated referral inertia for individuals with Type 2 inflammation-associated diseases exposed to systemic corticosteroids, with several years passing from first systemic corticosteroid redemption to specialist assessment and a significant number of individuals receiving repeated bursts prior to specialist assessment. The initial decision to prescribe systemic corticosteroids is often appropriate in acute presentations of type 2 inflammation associated diseases to regain disease control and is most commonly prescribed in primary- or emergency care settings.[28] However, guidelines such as GINA also mandate prompt subsequent referral for specialist assessment after acute exacerbations requiring systemic corticosteroids.[6] Referral inertia, or inappropriate referral delay, has previously been described within several of the included diseases (eg asthma and atopic dermatitis).[29,30] Considering the large impact on steroid exposure observed after specialist care observed in the present study and strengthened by previous work,[31] enabling better access to specialist advice in primary care settings, improving shared care and ensuring timely referral to specialists are key elements to reducing both systemic corticosteroid exposure and the consequences here of in individuals with T2-inflammatory diseases.

Across all included Type 2 inflammation-associated diseases, evidence of systemic steroid-related morbidity has been established previously and range from osteoporosis, diabetes mellitus, fractures, obesity and cataracts.[7,8,13,32,33] While an exact threshold for safe use of systemic corticosteroid remains to be identified, some studies suggest that longer-term exposure is the main driver of poor outcomes compared to shorter (and more recent) bursts.[8,33,34] In asthma, cumulative doses of redeemed corticosteroids of 1000 mg have previously been suggested as an "acceptable upper limit",[35] yet Skov et al found that cumulative doses as low as 500 mg in young adults aged 18–45 were associated with adverse corticosteroid-related outcomes compared to matched never-users.[7] Whether these cutoffs translate to other Type 2

inflammation-associated diseases remains to be elucidated, especially considering asthma's position as a main driver of systemic corticosteroid use, yet differing results would be surprising considering the many shared traits among individuals and diseases under the Type 2 inflammation umbrella.

In our present study, we found Type 2 inflammation multimorbidity to associate with increased prevalence of systemic corticosteroid use but not with an increase in annual exposure measured in milligrams. Due to our study design, firm causation cannot be established, yet it can be hypothesised that Type 2 inflammation multimorbidity reflects an increase in underlying inflammatory activity, as co-morbid asthma, chronic rhinosinusitis, allergic rhinitis and atopic dermatitis has been shown to influence one another in terms of disease severity.[18,36] The numerous shared pathways among various manifestations of type 2 inflammation-associated diseases suggest that a heightened inflammatory response can affect multiple organs. This may lead to additional symptoms and potentially create self-amplifying cycles of uncontrolled inflammation.[37] Consequently, this phenomenon may contribute to the increased reliance on systemic corticosteroids seen in type 2 inflammation multimorbidity to regain control over the diseases and their symptoms. Further studies including type 2 inflammatory markers such as blood eosinophil counts, fractional exhaled nitrogen oxide or total and/or specific immunoglobulin E levels could help in solidifying this relationship. Another disease where type 2 inflammation has gained traction is COPD, where the presence of type 2 inflammation has been associated with increased disease activity and/or exacerbation risk,[38] analogous to asthma and chronic rhinosinusitis with nasal polyps[18] where steroid-sparing biologic therapies have recently become available.[39] Taken together, the current body of research speaks towards treating type 2 inflammation as a trait, rather than observing singular disease entities.[18,38]

While the present study has chosen the moniker "Type 2 inflammation-associated" diseases, it should be noted that many of the included diseases are associated with multiple inflammatory pathways. For chronic rhinosinusitis, nasal polyposis has indeed been strongly correlated with type 2 inflammation, whereas chronic rhinosinusitis without nasal polyps has less type 2 inflammation.[40] The same pattern is seen in asthma, where type 2 inflammation is present in many, yet "type 2 low" asthma driven by type 1 or type 3-inflammatory pathways is seen in up to 50% of patients.[41] For patients with type 2 low disease, whether chronic rhinosinusitis or asthma, a common trait is relative corticosteroid resistance, eg a need for higher corticosteroid exposure to achieve disease control.[41] As such, it can be hypothesized that users with less type 2 inflammation can be, in part, drivers of systemic corticosteroid use due to their relative resistance to topical corticosteroids. Furthermore, the decline of systemic corticosteroid use in asthma may level out due to the relative paucity of "type 2 low" corticosteroid-sparing therapies,[41] as known "type 2 high" patients are eligible for steroid-sparing therapies.

While the present study is nationwide, covering a large population of patients and suggests that the total burden of type 2 inflammation is important for disease activity and thus the need for systemic corticosteroid therapy, it is mainly hypothesis generating. Future studies should in greater detail pheno- and endotype patients according to their inflammatory biomarkers, clinical data and objective confirmation of included physician-treated diagnoses to further our understanding and elucidate the full clinical impact of type 2 inflammation and type 2 inflammation multimorbidity.

Limitations

The present study is strengthened by its nationwide design, complete data availability of all pharmacy redemptions and its 25-year follow-up. However, there are several limitations that should be addressed. First, the study uses pharmacy redemptions, and any steroids administered at a hospital during emergency care and admissions are thus not included resulting in some underestimation of exposure. Conversely, overestimation due to systemic corticosteroids redeemed but not administered is also possible. Second, some diagnoses such as (perennial) allergic rhinitis and chronic rhinosinusitis may be underestimated or conflated due to the lack of inclusion of individuals utilising over-the-counter treatments or other anti-inflammatory agents such as leukotriene receptor antagonists in monotherapy. Third, due to the use of registry data, information on smoking status, point-of-care FeNO and other clinical data on type 2 inflammation (eg blood eosinophil counts) are not available. Fourth, due to the exclusion of other systemic corticosteroid treated diseases, we are unable to assess the impact of "type 2 low" comorbidities such as inflammatory bowel diseases. Fifth, ICS use as a marker for asthma may, despite relevant exclusion criteria, lead to some erroneous inclusion of COPD as systemic

corticosteroid use in asthma was dependent on age. While Danish nationwide registries are validated[42,43] and criteria used have been previously published, the diagnostic validity of pharmacoepidemiologic studies can be discussed.

Conclusion

In type 2 inflammation-associated diseases, systemic corticosteroid use remains common despite the introduction of corticosteroid-sparing treatments. Timely referrals to specialist assessment could reduce the overall systemic corticosteroid exposure.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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IRS, RI, ZA and CRJ has no conflicts to declare. KEJH has received personal fees from AstraZeneca, Chiesi, GSK, Sanofi and TEVA outside of the submitted work. AL has received personal fees from AstraZeneca, GSK, TEVA, Chiesi, Sanofi Genzyme, Boehringer-Ingelheim, Orion Pharma, Novartis, ALK-Abello, Mundipharma and Pfizer outside of the submitted work. OH has received personal fees from AstraZeneca, GSK, TEVA, Chiesi, Sanofi Genzyme, Boehringer-Ingelheim outside of the submitted work. HM has received personal fees from GSK, Teva, AstraZeneca, Novartis, Sanofi-Aventis, Airsonett AB, and ALK-Abelló A/S outside of the submitted work, and has received a research grant from ALK-Abelló A/S. VB has received personal fees from GSK, Sanofi Genzyme, AstraZeneca, TEVA, Chiesi, Boehringer-Ingelheim, Novartis, ALK-Abello, Mundipharma Menarini, Birk and Pfizer outside of the submitted work. SA has consulted for Ambu A/S outside of the submitted work. CSU has received personal fees from AstraZeneca, GSK, Sanofi, Chiesi, Boehringer Ingelheim, Mundipharma, Pfizer, Berlin Chemie, Menarini, Hikma Pharmaceuticals, TEVA, Orion Pharma, Novartis, TFF Pharmaceuticals and Actelion outside the submitted work. The authors report no other conflicts of interest in this work.

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